Chronic congestive heart failure

The right clinical information, right where it's needed
# Table of Contents

## Summary

## Basics
- Definition 4
- Epidemiology 4
- Aetiology 5
- Pathophysiology 6
- Classification 6

## Prevention
- Primary prevention 8
- Screening 8

## Diagnosis
- Case history 9
- Step-by-step diagnostic approach 9
- Risk factors 11
- History & examination factors 16
- Diagnostic tests 18
- Differential diagnosis 22
- Diagnostic criteria 24

## Treatment
- Step-by-step treatment approach 25
- Treatment details overview 31
- Treatment options 34
- Emerging 63

## Follow up
- Recommendations 65
- Complications 66
- Prognosis 67

## Guidelines
- Diagnostic guidelines 68
- Treatment guidelines 69

## Online resources

## References

## Disclaimer
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.

It is a major and growing public health problem. It is the only cardiovascular disease that is increasing in incidence and prevalence, partly because the population is ageing, but also because of improved cardiovascular interventions for disease processes that reduce early mortality but may result in cardiac changes that lead to heart failure.

The key manifestations are dyspnoea and fatigue, which may limit exercise tolerance, and fluid retention, which may lead to pulmonary congestion and peripheral oedema.

Diagnosis is largely clinical; a thorough history and physical examination should be obtained to identify cardiac and non-cardiac disorders or behaviours that might cause congestive heart failure or accelerate progression.

The single most useful diagnostic test in the evaluation of patients is the comprehensive 2-dimensional echocardiogram coupled with Doppler flow studies. Measurement of B-type natriuretic peptide can be useful in the evaluation of patients at initial presentation.

Interventions that have a proven beneficial impact on patient survival include ACE inhibitors, angiotensin receptor blockers, beta-blockers, aldosterone antagonists, hydralazine and nitrates, cardiac re-synchronisation therapy, and implantable cardioverter defibrillators.
Definition

Heart failure is a condition in which the heart is unable to generate a cardiac output sufficient to meet the demands of the body without increasing diastolic pressure. It can result from any cardiac disease that compromises ventricular systolic or diastolic function or both. The term 'congestive heart failure' (CHF) is reserved for patients with breathlessness and abnormal sodium and water retention resulting in oedema.

Heart failure comprises a wide range of clinical scenarios, from patients with normal left ventricular ejection fraction (LVEF) >50% to those with reduced myocardial contractility (LVEF <40%).

Based on LVEF, heart failure is defined as follows.[1]

1. Heart failure with reduced ejection fraction (HFrEF): symptoms and signs with LVEF <40%.

2. Heart failure with mid-range ejection fraction (HFmrEF): symptoms and signs with LVEF 40% to 49%. Other features include elevated natriuretic peptides (B-type natriuretic peptide [BNP] >35 nanograms/L [>35 picograms/mL] or N-terminal pro-brain natriuretic peptide [NT-pro-BNP] >125 nanograms/L [>125 picograms/mL]) and at least one additional criterion: (a) relevant structural heart disease (e.g., left ventricular hypertrophy [LVH] or left atrial enlargement), (b) diastolic dysfunction.

3. Heart failure with preserved ejection fraction (HFpEF): symptoms and signs with LVEF >50%. Other features include elevated natriuretic peptides (BNP >35 nanograms/L [>35 picograms/mL] or NT-pro-BNP >125 nanograms/L [>125 picograms/mL]) and at least one additional criteria: (a) relevant structural heart disease (e.g., LVH or left atrial enlargement), (b) diastolic dysfunction.

Epidemiology

The prevalence of CHF in the western world has been estimated at 1% to 2%, and the incidence is thought to approach 5 to 10 per 1000 people per year.[4] In the UK, CHF is thought to account for a total of 1 million inpatient bed days and 5% of all emergency admissions. These figures are projected to rise by as much as 50% in the next 25 years.[5] A major heart study conducted in Australia in 2006 found that 6.3% of the population of Canberra had overt symptomatic heart failure and there was an even higher proportion of people with subclinical heart failure.[6]

Heart failure is a global disease. The prevalence of heart disease is about 1.3% in China, 6.7% in Malaysia, 1.0% in Japan, 4.5% in Singapore, 0.12% to 0.44% in India, 1.0% in South America, and 1.0% to 2.0% in Australia.[7]

From 2011 to 2014, an estimated 6.5 million adults ≥20 years of age had heart failure in the US.[8] In 2014 there were 1 million new cases in patients >55 years of age.[8] Heart failure is the primary reason for 12 to 15 million clinic visits and 6.5 million hospital-days each year.[9] Recurrent hospitalisation is a major quality of life and cost issue: for example, from 1990 to 1999, the annual number of hospitalisations increased from approximately 810,000 to over 1 million for primary diagnosis and from 2.4 million to 3.6 million for primary or secondary diagnosis.[11] Patients are particularly prone to re-admission, with reported rates as high as 50% within 6 months of discharge. In 2001, nearly 53,000 patients died of heart failure as a primary cause. The number of deaths is increasing steadily despite advances in treatment, in part because of increasing numbers of patients with heart failure, due to better treatment and reduced mortality of patients with acute myocardial infarctions earlier in life. Heart failure is primarily a condition of older people, and thus the widely recognised 'ageing of the population' also contributes to its increasing incidence.
The prevalence of heart failure increases with increasing age. In the US, among patients aged 40 to 59 years the prevalence of heart failure is about 1.4% in males and 1.9% in females, whereas among patients aged >80 years the prevalence of heart failure is about 14.1% in males and 13.4% in females.[8] The total prevalence of heart failure in the US is between 1.5% and 1.9%.[7]

**Aetiology**

There are numerous and varied causes of heart failure.

Common causes of chronic heart failure include:

- Coronary artery disease
- Hypertension
- Valvular disease
- Myocarditis.

Other causes include:

- Infiltrative diseases: amyloidosis, haemochromatosis, sarcoid
- Congenital heart diseases
- Pericardial disease
- Toxin-induced: heroin, alcohol, cocaine, amphetamines, lead, arsenic, cobalt, phosphorus
- Infection: bacterial, fungal, viral (HIV), *Borrelia burgdorferi* (Lyme disease), parasite (e.g., *Trypanosoma cruzi* [Chagas disease])
- Endocrine disorders: diabetes mellitus, thyroid disease, hypoparathyroidism with hypocalcaemia, phaeochromocytoma, acromegaly, growth hormone deficiency
- Systemic collagen vascular diseases: lupus, rheumatoid arthritis, systemic sclerosis, polyarteritis nodosa, hypersensitivity vasculitis, Takayasu syndrome, polymyositis, reactive arthritis
- Chemotherapy-induced: for example, adriamycin, trastuzumab
- Nutritional deficiencies: thiamine, protein, selenium, L-carnitine
- Pregnancy: peripartum cardiomyopathy
- Familial cardiomyopathy
- Tachycardia-induced cardiomyopathy.

Although Chagas disease is an uncommon cause of congestive heart failure in Europe and North America, it is an important cause of heart failure in Central and South America.

Some of these conditions tend to increase metabolic demand, which may not be matched by a sufficient increase in cardiac output by the failing heart. Tachyarrhythmias also decrease the diastolic ventricular filling time and increase myocardial oxygen demand. Uncontrolled hypertension depresses systolic function by increasing the afterload against which the failing ventricle must pump blood, and may be the first clinical manifestation. It should be emphasised that many of these causes may be completely reversible given appropriate and timely treatment/intervention (e.g., revascularisation for stunned or hibernating myocardium; standard therapy for peripartum or hypertensive cardiomyopathy; valvuloplasty or valve replacement for valvular heart disease; standard treatment and adjunctive rate control therapy for tachycardia-induced cardiomyopathy). Other causes, such as scarred myocardium or dilated cardiomyopathy, are currently considered irreversible.
Pathophysiology

The understanding of the pathophysiology of heart failure has evolved significantly over the last decades, from the haemodynamic model to the neurohormonal paradigm. Heart failure represents a complex syndrome in which an initial myocardial insult results in the over-expression of multiple peptides with different short- and long-term effects on the cardiovascular system. Neurohormonal activation is recognised to play a pivotal role in the development as well as the progression of heart failure. In the acute phase, neurohormonal activation seems to be beneficial in terms of maintaining adequate cardiac output and peripheral perfusion. Sustained neurohormonal activation, however, eventually results in increased wall stress, dilation, and ventricular remodelling, which contribute to disease progression in the failing myocardium, which eventually leads to further neurohormonal activation. Left ventricular remodelling is the process by which mechanical, neurohormonal, and possibly genetic factors alter ventricular size, shape, and function. Remodelling occurs in several clinical conditions, including myocardial infarction, cardiomyopathy, hypertension, and valvular heart disease; its hallmarks include hypertrophy, loss of myocytes, and increased interstitial fibrosis. One potential deleterious outcome of remodelling, as the left ventricle dilates and the heart assumes a more globular shape, is the development of mitral regurgitation. Mitral regurgitation results in an increasing volume overload on the overburdened left ventricle that further contributes to remodelling and progression of disease and symptoms.

Classification

American College of Cardiology/American Heart Association stages of heart failure[2]

This staged classification underscores the fact that established risk factors and structural abnormalities are necessary for the development of heart failure, recognises its progressive nature, and superimposes treatment strategies on the fundamentals of preventative efforts. Heart failure may progress from stage A to stage D in a given patient, but generally does not follow the path in reverse.

- Stage A: patients at high risk of developing heart failure because of the presence of conditions that are strongly associated with the development of heart failure (for example, hypertension, diabetes, or coronary disease); however, such patients have no identified structural or functional abnormalities of the pericardium, myocardium, or cardiac valves and have never shown signs or symptoms of heart failure.
- Stage B: patients who have developed structural heart disease that is strongly associated with the development of heart failure but who have never shown signs or symptoms of heart failure (for example, asymptomatic post-infarction left ventricular dysfunction).
- Stage C: patients who have current or prior symptoms of heart failure associated with underlying structural heart disease.
- Stage D: patients with advanced structural heart disease and marked symptoms of heart failure at rest despite maximal medical therapy and who require specialised interventions (for example, heart transplant or left ventricular assist devices).

Framingham criteria for the diagnosis of CHF[3]

Heart failure is essentially a clinical diagnosis. Clinical criteria for diagnosing heart failure, the Framingham criteria for the diagnosis of CHF, were established before the widespread use of echocardiographic
assessment of systolic and diastolic dysfunction. The Framingham clinical criteria, listed below, have been extremely useful for identifying heart failure patients, both in clinical practice and in epidemiological studies, for more than 40 years. However, because their specificity is greater than their sensitivity, it is recognised that they probably miss mild cases of heart failure. In order to come up with a definite diagnosis of CHF, one needs to have either 2 major criteria or the combination of 1 major and 2 minor criteria.

Major criteria:

- Neck vein distension
- Rales
- Acute pulmonary oedema
- S3 gallop
- Increased venous pressure >16 cm of water
- Circulation time >25 seconds
- Hepatojugular reflux
- Cardiomegaly
- Paroxysmal nocturnal dyspnoea or orthopnoea.

Minor criteria:

- Ankle oedema
- Night cough
- Dyspnoea on exertion
- Hepatomegaly
- Pleural effusion
- Less than one third maximum vital capacity
- Tachycardia (heart rate >120 bpm).

Major or minor criteria:

- Weight loss greater than 4.5 kg in 5 days in response to treatment.
Primary prevention

Heart failure is the final pathway for a wide array of pathophysiological processes. Interventions that reduce the risk of development of any cardiovascular disease will ultimately reduce the incidence. Thus, key public health targets are prevention of development of hypertension, diabetes, dyslipidaemia, obesity (i.e., metabolic syndrome), and ischaemic heart disease. Lifestyle modifications, such as increasing physical activity, reducing tobacco, alcohol, and recreational drug use, and reducing daily salt intake, and proper medical treatment of established diseases such as hypertension, diabetes, and coronary artery disease, are expected to help reduce incident heart failure.[71] [72]

Screening

There is no single test for screening the asymptomatic population. Heart failure is a clinical diagnosis and as such could simply rely on a thorough history and careful physical examination of the population to be tested.

B-type natriuretic peptide (BNP) has recently been used as a screening tool for identifying structural heart disease in the general population. In one study, the sensitivity and specificity of BNP testing for identification of structural heart disease were 61% and 92%, respectively.[89] When sex-specific analyses were performed, sensitivity and specificity were 61% and 91% in men, and 50% and 95% in women, respectively. Although the performance of BNP testing on the basis of these figures might seem suboptimal for the population as a whole, efficacy was improved in subgroups with a high prevalence of heart disease, such as the cohort aged 65 years and older, as well as the cohort having cardiovascular risk factors such as hypertension or diabetes. In another trial, blood N-terminal pro-brain natriuretic peptide concentrations were found to play an important role in stratifying older people into left ventricular dysfunction risk groups. The neurohormone was an independent marker for death or admission for heart failure in the medium term.[90] These results suggest that BNP testing for structural heart disease screening in community-based populations might only be useful for cohorts with a high prevalence of heart disease. The American College of Cardiology/American Heart Association/Heart Failure Society guidelines recommend that for patients at risk of developing heart failure (identified by the presence of hypertension, diabetes mellitus, or known vascular disease), natriuretic peptide biomarker-based screening followed by team-based care, including a cardiovascular specialist optimising guideline-directed management and therapy, can be useful to prevent the development of left ventricular dysfunction (systolic or diastolic) or new-onset heart failure. However, further studies are needed to determine cost-effectiveness, its impact on quality of life, and mortality rate.[73]
Case history

Case history #1

A 67-year-old woman presents to her primary care physician complaining of increasing shortness of breath, especially when trying to sleep. She has a history of hypertension and hyperlipidaemia, and is being treated with a beta-blocker and statin therapy. She does not smoke and drinks alcohol in moderation. On examination, her blood pressure is 148/83 mmHg and heart rate is 126 beats per minute. There is an audible S4 and the jugular venous pressure is elevated 3 cm above normal.

Case history #2

A 60-year-old man presents to the accident and emergency department. He reports being progressively short of breath. He has a history of uncontrolled hypertension, non-insulin-dependent diabetes mellitus, and has been a heavy smoker for more than 40 years. He underwent a successful primary angioplasty for a large acute anterior myocardial infarction 2 months ago. His blood pressure is 75/40 mmHg, his heart rate 110 beats per minute, and his respiratory rate 30. He has elevated neck veins and a prominent S3. His ECG shows sinus tachycardia, and a transthoracic echocardiogram performed in the A&E department reveals impaired systolic function, with an ejection fraction of 20%.

Other presentations

Many patients remain asymptomatic for extended time periods because mild impairment in cardiac function is balanced by compensatory mechanisms. Often, clinical manifestations occur only in the presence of precipitating factors that increase the cardiac workload and tip the balanced state into one of decompensation. Thus, the first symptoms and signs may be those of the underlying precipitating condition, such as atrial flutter or fibrillation, anaemia, fever, infection, hyperthyroidism, or even pregnancy. A large pulmonary embolism can also lead to the first presentation of symptoms, or to exacerbation of known chronic CHF, by causing hypoxaemia, decreased myocardial oxygen supply, and increased right ventricular afterload. An acute ischaemic insult (i.e., an acute coronary syndrome or an myocardial infarction) or the initiation of a negative inotropic medicine for another reason (e.g., large doses of beta-blockers and certain calcium channel blockers for hypertension) can acutely depress myocardial contractility and precipitate symptoms in an otherwise compensated patient.

Step-by-step diagnostic approach

Identification of the condition responsible for the cardiac structural and/or functional abnormalities may be important, because some conditions that lead to left ventricular dysfunction are potentially treatable and/or reversible.[2] Efforts to identify a cause frequently allow the detection of co-existent conditions that may contribute to or exacerbate the severity of symptoms. However, it may not be possible to discern the cause of heart failure in many patients presenting with this syndrome, and in others, the underlying condition may not be amenable to treatment.
**Patient characteristics**

Heart failure is primarily a condition of older people. The incidence and prevalence of heart failure increases with increasing age. In 2014 there were 1 million new cases in patients aged >55 years.[8]

Among patients aged >80 years, the prevalence of heart failure is 14.1% in males and 13.4% in females.[8] Increasing age has been consistently linked to a higher risk.[3] [12] [13] [14] [15] [16] [25] Male sex has also been linked to a higher risk of developing heart failure.[3] [12] [13] [14] [15] [16] [17]

Excess body weight is an established risk factor.[46]

A number of precipitating factors may lead to impaired cardiac function, potentially leading to an episode of acute heart failure. Detection and treatment of precipitating factors plays an important role in patient management. Precipitating factors include excessive salt intake, lack of adherence (with respect to medication and diet), myocardial infarction, pulmonary embolism, uncontrolled hypertension, cardiac arrhythmias, infection, hypothyroidism, hyperthyroidism, renal dysfunction, and alcohol and drug abuse.[1]

**Patient history**

The complexity and variety of potential causative factors means that a multitude of patient historical factors may be relevant. A history of hypertension; diabetes mellitus; dyslipidaemia; tobacco use; coronary, valvular, or peripheral vascular disease; rheumatic fever; heart murmur or congenital heart disease; personal or family history of myopathy; mediastinal irradiation; and sleep-disturbed breathing should be enquired about. The drug history should record the past or current use of illicit drugs; alcohol; ephedra; or antineoplastic agents such as anthracyclines, trastuzumab, or high-dose cyclophosphamide, because heart failure may occur years after exposure to doxorubicin or cyclophosphamide. The history and physical evaluation should include specific consideration of non-cardiac diseases such as collagen vascular disease, bacterial or parasitic infection, obesity, thyroid excess or deficiency, amyloidosis, and phaeochromocytoma.

A detailed family history should be obtained, not only to determine whether there is a familial predisposition to atherosclerotic disease but also to identify relatives with cardiomyopathy, sudden unexplained death, conduction system disease, and skeletal myopathies.

Dyspnoea on exertion or at rest is the most common symptom of left-sided heart failure. With increasing failure patient may develop leg oedema and abdominal distension due to ascites.

**Physical examination**

Particular attention should be paid to the cardinal signs and symptoms of heart failure. Their presence (and degree) may depend on severity of heart failure and associated comorbid disease.

General examination may reveal tachycardia and cyanosis. A focused cardiovascular examination may reveal elevated jugular venous pressure, ankle oedema, and a displaced apex beat, which suggests cardiomegaly. On auscultation, besides presence of pulmonary rales or crepitation, an S3 gallop may be present, which has prognostic significance.

Particular attention should be paid to factors like pallor (which may reflect anaemia), irregularly irregular pulse (reflecting atrial fibrillation), systolic murmur of aortic stenosis and mid diastolic murmur of mitral stenosis, or overt signs of thyrotoxicosis. In dialysis patients, a large arteriovenous fistula may occasionally be the precipitating factor.
**Investigations**

For all patients, initial investigations should include ECG, chest x-ray, transthoracic echocardiogram, and baseline haematology and blood chemistry, including full blood count, serum electrolytes (including calcium and magnesium), serum urea and creatinine, liver function tests, and B-type natriuretic peptide/N-terminal pro-brain natriuretic peptide levels. Anaemia and high lymphocyte percentage are strong risk factors and prognostic markers of poor survival. In patients presenting with dyspnoea, measurement of natriuretic peptide biomarkers is useful to support a diagnosis or exclude heart failure. However, elevated plasma levels of natriuretic peptides can occur with a wide variety of cardiac and non-cardiac causes; therefore, clinical judgement is necessary.

Blood glucose, thyroid function tests and blood lipids are useful to assess for commonly associated comorbid disease.

Subsequent investigations that help in assessing severity of heart failure and functional status include standard exercise stress testing (bicycle or treadmill), cardiopulmonary exercise testing with VO₂ max, 6-minute walking test exercise, right heart catheterisation, and endomyocardial biopsy. Based on clinical history, HIV screening and measurement of iron levels and fasting transferrin saturation to screen for haemochromatosis may also be performed. A cardiac magnetic resonance imaging scan is particularly useful in the investigation of myocarditis and infiltrative cardiomyopathy.

**Risk factors**

**Strong**

**myocardial infarction (MI)**

- The link between MI and risk of heart failure development is strongly and consistently supported by the literature. MI, which confers at least a 15-fold increased risk, is the single most potent risk factor for developing heart failure.[12] [13] [14] [15] [16] [17]

**diabetes mellitus**

- Diabetes mellitus has been associated with a 3- to 5-fold increase in the risk of developing heart failure,[13] [14] [15] [17] [18] [19] with the highest increase in relative risk found among women[13] [17] and people with asymptomatic left ventricular dysfunction.[18] Even a slight increase of 1% in haemoglobin A1C has been linked to a greater than 10% risk of hospitalisation for heart failure or death.[20]

**dyslipidaemia**

- Lipid abnormalities have been linked to increased risk for heart failure.[21] [22] [23] Compared with men with ratios of total cholesterol:HDL cholesterol of less than 5, in one study men with ratios of 5 to 9.9 had a 1.5-times greater incidence of heart failure, and men with ratios of greater than 10 had a nearly 5-times greater incidence of heart failure.[21] In the same study, women with ratios greater than 10 had more than 6-times greater incidence of heart failure than women with ratios less than 5.[21]
In one clinical trial of patients with coronary artery disease, lipid lowering was associated with a 21% reduction in the risk of developing heart failure.[24]

old age

- Increasing age has been consistently linked to a higher risk of developing heart failure.[3] [12] [13] [14] [15] [16] [25] In the Framingham cohort, the incidence of heart failure increased steadily with increasing age.[13] In a cohort of people over age 65 years, every 5-year incremental increase in age was associated with a hazard ratio of 1.37.[15] In another study, the incidence rate of heart failure among the oldest people (age >80 years) was double that of the youngest people (age 65 to 69 years).[25]

male

- Male sex has been consistently linked to a higher risk of developing heart failure.[3] [12] [13] [14] [15] [16] [17] [25] In the Framingham cohort, women had a one third lower incidence of heart failure than men, and male sex was associated with a hazard ratio of 1.34.[13] [15] [17] In other studies the incidence among males is 2 to 4 times that of females.[12] [25] In the National Health and Nutrition Examination Survey (NHANES I) study, which followed a cohort of 13,643 people for an average of 19 years, being male was associated with a relative risk of heart failure of 1.24.[26]

hypertension

- Hypertension has consistently been linked to an increased risk of heart failure in the literature and confers a 2- to 3-fold increase in risk of developing heart failure.[12] [13] [14] [15] [16] [17] [27] Elevated systolic blood pressure, elevated diastolic blood pressure, and elevated pulse pressure have all been associated with increased risk for heart failure.[28] [29] Among the Framingham cohort, a 1 standard deviation (20 mmHg) increase in systolic blood pressure was associated with a 56% increased risk for heart failure, a 1 standard deviation (10 mmHg) increase in diastolic blood pressure was associated with 24% increased risk, and a 1 standard deviation (16 mmHg) increase in pulse pressure was associated with a 55% increase in risk.[28]

left ventricular dysfunction

- Moderate-to-severe asymptomatic left ventricular dysfunction (ejection fraction [EF] less than 40%) has been associated with a hazard ratio of heart failure of 7.8, while mild asymptomatic left ventricular dysfunction (EF 40% to 50%) has been associated with a hazard ratio of 3.3.[30]

cocaine abuse

- Cocaine abuse has been strongly associated with the development of heart failure in a variety of care settings.[31] [32] [33]

exposure to cardiotoxic agents

- Doxorubicin and cyclophosphamide can cause myocardial damage leading to left ventricular dysfunction and heart failure.[41] [42] These chemotherapeutic agents increase risk for heart failure both during acute treatment and for several months after treatment has ended, with increasing risk with increasing cumulative dose.[43] [44] In addition, trastuzumab, a recombinant DNA-derived humanised monoclonal antibody used widely in the treatment of breast cancer, is also associated with the development of cardiomyopathy. The antihypertensive medicine doxazosin has been linked to an increased risk of heart failure. Thiazolidinediones (a class of drug used for the treatment of diabetes) have been associated with an increased risk of heart failure.
• Mediastinal irradiation can cause direct myocardial damage leading to left ventricular dysfunction and heart failure both during acute treatment and for several years after treatment has ended.

**left ventricular hypertrophy**

• Left ventricular hypertrophy on ECG has been associated with a higher risk of heart failure, with highest relative risk among younger people.[45]

**renal insufficiency**

• Renal insufficiency, defined by elevated serum creatinine (over 133 micromols/L [1.5 mg/dL] in men and 115 micromols/L [1.3 mg/dL] in women) or reduced creatinine clearance less than 1 mL/s/m² (60 mL/minute), has been linked to increased risk for development of heart failure. Compared with subjects with creatine of less than 97 micromols/L (<1.1 mg/dL), subjects with creatinine of 115 to 132 micromols/L (1.3 to 1.49 mg/dL) had almost double the risk of developing CHF, subjects with creatine of 133 to 149 micromols/L (1.5 to 1.69 mg/dL) had almost triple the risk, and those with creatine above 150 micromols/L (>1.7 mg/dL) had almost quadruple the risk.[47] [48]

**valvular heart disease**

• Cardiac valvular abnormality was associated with an odds ratio of heart disease of 2.43 among men and 3.47 among women in a multi-variate profile based on the Framingham cohort.[49] Valvular abnormalities create pressure overload (e.g., aortic stenosis, mitral stenosis) or volume overload (e.g., mitral regurgitation), which are initially compensated for by mechanisms such as ventricular hypertrophy or ventricular dilation.[50] Ventricular remodelling alters cardiac contractility and increases the risk of heart failure.

**sleep apnoea**

• Sleep-disordered breathing has been linked with increased risk of heart failure in multiple studies.[51] [52] [53]

**elevated homocysteine**

• In the Framingham cohort, elevated plasma homocysteine levels were linked with a roughly three quarter increased risk for developing heart failure.[57]

**elevated tumour necrosis factor-alpha (TNF-alpha) and interleukin-6 (IL-6)**

• TNF-alpha is a pro-inflammatory cytokine associated with myocyte death and cardiac dysfunction.[58] IL-6 is a similar pro-inflammatory cytokine.[59]

**elevated C-reactive protein (CRP)**

• Among the Framingham cohort, an increase of 48 nanomols/L (5 mg/dL) in CRP level was associated with over a 2-fold increase in risk of heart failure.[59] People who also had elevated serum IL-6 and TNF-alpha values had a 4-fold increase in risk of heart failure.[59]

**decreased insulin-like growth factor-1 (IGF-1)**

• IGF-1 has been shown to have positive inotropic effects and to decrease the rate of cellular apoptosis.[60] [61] IGF-1 has also been tentatively linked to vasodilation, which may improve cardiac emptying.[62] Among the Framingham cohort, patients with a serum IGF-1 level below 18 nanomols/L (140 mg/L) had double the risk of developing heart failure.[63]
Chronic congestive heart failure

**Diagnosis**

- **Elevated natriuretic peptides**
  - In the Framingham cohort, increased levels of plasma B-type natriuretic peptide (BNP) and N-terminus of the atrial natriuretic peptide pro-hormone (N-ANP) were associated with an increased risk of heart failure. BNP levels above the 80th percentile (20 nanograms/L [20 picograms/mL] for men and 23.3 nanograms/L [23.3 picograms/mL] for women) were associated with a 3-fold increase in heart failure risk.[64]

- **Dilation of the left ventricle**
  - The risk-factor-adjusted hazard ratio for heart failure in an asymptomatic population was 1.47 per 1 standard deviation increase in left ventricular end-diastolic diameter and 1.43 per 1 standard deviation increase in left ventricular end-systolic dimension.[30]

- **Increased left ventricular mass**
  - In one cohort, those who developed heart failure had an initial average left ventricular mass/height of 106 g/m versus 88 g/m among those who did not develop heart failure.[30] [65] [66]

- **Abnormal left ventricular diastolic filling**
  - Alternations in the E to A wave ratio, both low and high, have been associated with heart failure risk, with those with the lowest E to A wave ratio (<0.7) having a relative risk of 1.88 and those with the highest E to A wave ratio (>1.5) having a relative risk of 3.50.[30] [66]

- **Family history of heart failure**
  - Several polymorphisms have been linked with an increased risk of developing heart failure: for example, a deletion of 4 amino acids in position 322 to 325 of the gene coding for a2C-adrenergic receptors (a2C Del322-325) in sympathetic nerve endings in the heart has been studied as a possible link to the development of heart failure. A second polymorphism that was evaluated as a candidate for developing heart failure is a change in position 389 of the gene for beta1-adrenergic receptors (b1Arg389) on myocytes. In the same study, patients who were homozygous for this deletion had a 10-fold increase in risk of developing heart failure.[67]

- **Atrial fibrillation**
  - Atrial fibrillation increases the risk of thrombo-embolic events (e.g., stroke) and may lead to a worsening of symptoms. Atrial fibrillation may also serve as a predictor of mortality, or lead to tachycardiomyopathy, though evidence is less clear.[1]

- **Thyroid disorders**
  - For example, thyrotoxicosis and hypothyroidism. Thyroid disorders are treatable, but are linked to sinus tachycardia, bradycardia, and atrial tachycardia/flutter/fibrillation.[1]

- **Anaemia**
  - Anaemia is a strong risk factor and prognostic marker of poor survival. A high prevalence of iron deficiency has been reported in heart failure.[68] Iron deficiency in heart failure is due to gastrointestinal or genitourinary blood loss related to the use of antiplatelet drugs and/or oral anticoagulation, impaired nutrition, malabsorption, and reduced intracellular uptake of iron.[69] [70]

**Weak**
Chronic congestive heart failure

**Diagnosis**

- The National Health and Nutrition Examination Survey (NHANES I) study found that low socio-economic status (as indicated by less than high school education) was associated with a relative risk of heart failure of 1.22 (population attributable risk 8.9%).[26]

**tobacco consumption**

- In contrast to the strong influence of cocaine abuse on the development of heart failure, the literature on the importance of smoking independent of other factors is conflicting.[13] [26] [34] [35] In the Framingham cohort, cigarette smoking was not linked with increased incidence of heart failure except among men over age 64 years.[13] In other studies, tobacco use has been associated with a relative risk of heart failure of 1.59 and of 1.51 (smoking <15 cigarettes a day) to 2.31 (smoking 15 or more cigarettes a day).[26] [34]

**excess alcohol consumption**

- Current data strongly support a relationship between excess alcohol consumption and the development of heart failure.[36] [37] [38] This may be related to both direct myocardial toxicity of alcohol and the higher risk of hypertension development. However, the data also suggest a possible weakly protective effect of moderate alcohol consumption.[39] This may be related to lower risk of diabetes and myocardial infarction, and favourable changes in the lipid profile, platelet function, and blood clotting associated with moderate alcohol intake.

**excess sodium intake**

- The National Health and Nutrition Examination Survey (NHANES) found the relative risk for a 100-mmols/day increase in sodium intake was 1.26.[40]

**excess coffee consumption**

- Consumption of 5 or more cups of coffee a day has been associated with a relative risk of heart failure of 1.11.[34]

**obesity**

- Excess body weight is now an established risk factor for the development of heart failure. Among a subset of the Framingham cohort, the risk of heart failure increased by 5% for men and 7% for women with each increase of 1 in body mass index; obese subjects (body mass index 30 or above) had a risk of heart failure double that of non-obese subjects.[46]

**tachycardia**

- Tachycardia-induced cardiomyopathy has been well described in the literature. Among the Framingham cohort, an increase in heart rate of 10 beats per minute was linked with a greater than 10% increased risk of developing heart failure.[49]

**depression/stress**

- Risk is double among depressed compared with non-depressed older people.[54] [55]

**microalbuminuria**

- Although no link between microalbuminuria and the development of heart failure has been established, microalbuminuria was linked with a 3-fold increased risk of heart failure hospitalisation in the Heart Outcomes Prevention Evaluation study.[56]
History & examination factors

Key diagnostic factors

presence of risk factors (common)
- Key risk factors include: history of myocardial infarction; diabetes mellitus; dyslipidaemia; old age; male sex; hypertension; left ventricular dysfunction; cocaine abuse; exposure to cardiotoxic agents; left ventricular hypertrophy; renal insufficiency; valvular heart disease; sleep apnoea; elevated serum homocysteine; elevated serum tumour necrosis factor-alpha and interleukin-6; elevated serum C-reactive protein; decreased serum insulin-like growth factor-1; elevated natriuretic peptides; dilation of the left ventricle; increased left ventricular mass; abnormal left ventricular diastolic filling; and family history of heart failure.

dyspnoea (common)
- The most common symptom of left-sided heart failure. May occur with exertion (New York Heart Association [NYHA] II-III) or, in more severe cases, at rest (NYHA IV). This is considered a minor criterion for the diagnosis of heart failure (Framingham criteria).

neck vein distension (common)
- A major Framingham criterion for the diagnosis of heart failure.

S3 gallop (common)
- A major Framingham criterion for the diagnosis of heart failure.

cardiomegaly (common)
- Cardiomegaly is a major Framingham criterion for the diagnosis of heart failure. Left ventricular dilation or hypertrophy are common findings.

hepatojugular reflux (common)
- A major Framingham criterion for the diagnosis of heart failure.

rales (common)
- A major Framingham criterion for the diagnosis of heart failure.

orthopnoea and paroxysmal nocturnal dyspnoea (uncommon)
- Orthopnoea worsens immediately after lying down, because of a sudden increase in venous return (i.e., pre-load). Paroxysmal nocturnal dyspnoea occurs several hours after the patient lies down to sleep; it results from the central re-distribution of extravascular fluid that progressively increases the venous return.

nocturia (uncommon)
- Increased frequency of uresis occurs several hours after the patient lies down to sleep; it also results from the central re-distribution of extravascular fluid that augments the amount of circulating blood cleared from the kidneys.

Other diagnostic factors

tachycardia (heart rate >120 beats per minute) (common)
• A minor Framingham criterion for the diagnosis of heart failure.

**chest discomfort (common)**
• A symptom of poor coronary perfusion.

**hepatomegaly (common)**
• A minor Framingham criterion for the diagnosis of heart failure; may cause abdominal discomfort/distension and nausea.

**ankle oedema (common)**
• A minor Framingham criterion for the diagnosis of heart failure.

**night cough (common)**
• A minor Framingham criterion for the diagnosis of heart failure.

**signs of pleural effusion (common)**
• A minor Framingham criterion for the diagnosis of heart failure.

**fatigue, muscle weakness, or tiredness (common)**
• Symptom of poor tissue (muscle) perfusion.

**palpitations, pre-syncope, or syncope (uncommon)**
• This may be the result of frequent ectopic supraventricular or ventricular beats or may reflect paroxysms of atrial flutter/fibrillation; permanent atrial fibrillation may or may not cause palpitations.

**lethargy/confusion (uncommon)**
• Symptom of poor tissue (brain) perfusion.
## Diagnostic tests

### 1st test to order

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>transthoracic echocardiogram</td>
<td>systolic heart failure: depressed and dilated left and/or right ventricle with low ejection fraction; diastolic heart failure: LVEF normal but LVH and abnormal diastolic filling patterns</td>
</tr>
<tr>
<td>• Allows for the accurate determination of biventricular systolic and diastolic function. With systolic heart failure, echo usually demonstrates a dilated left and/or right ventricle with low ejection fraction. With pure diastolic heart failure left ventricular ejection fraction (LVEF) is normal but there is evidence of left ventricular hypertrophy (LVH) and of abnormal diastolic filling patterns on Doppler evaluation. Echo can also identify valvular or pericardial disease or may reveal evidence of underlying coronary artery disease (regional wall motion/thickness abnormalities). It should be performed in every patient presenting with heart failure symptoms.</td>
<td></td>
</tr>
<tr>
<td>ECG</td>
<td>evidence of underlying coronary artery disease, left ventricular hypertrophy, or atrial enlargement; may be conduction abnormalities and abnormal QRS duration</td>
</tr>
<tr>
<td>• QRS duration above 120 ms should always raise the question of ventricular dyssynchrony.</td>
<td></td>
</tr>
<tr>
<td>CXR</td>
<td>abnormal</td>
</tr>
<tr>
<td>• May reveal pulmonary vascular congestion (vascular redistribution, Kerley B lines), cardiomegaly (increased cardiothoracic ratio), or pleural effusion (usually right-sided but often bilateral).</td>
<td></td>
</tr>
<tr>
<td>B-type natriuretic peptide (BNP)/N-terminal pro-brain natriuretic peptide (NT-pro-BNP) levels</td>
<td>elevated</td>
</tr>
<tr>
<td>• Elevated plasma BNP levels have been associated with reduced left ventricular ejection fraction,[74] left ventricular hypertrophy, elevated left ventricular filling pressures, and acute myocardial infarction and ischaemia, although they can occur in other settings, such as pulmonary embolism and chronic obstructive pulmonary disease.[74][75][76] They are sensitive to other biological factors, such as age, sex, weight, and renal function. Elevated levels lend support to a diagnosis of abnormal ventricular function or haemodynamics causing symptomatic heart failure.[77][78][79] A low plasma BNP level (&lt;100 nanograms/L or &lt;100 picograms/mL) can rapidly rule out decompensated heart failure and point to a pulmonary cause. A high plasma BNP level (&gt;400 nanograms/L or &gt;400 picograms/mL) strongly supports the diagnosis of abnormal ventricular function (i.e., heart failure). Intermediate values (100 to 400 nanograms/L or 100 to 400 picograms/mL) fall into the so-called 'grey zone' and should spur a search for a potential non-cardiac cause of dyspnoea: for example, COPD. In patients presenting with dyspnoea, measurement of natriuretic peptide biomarkers is useful to support a diagnosis or exclude heart failure. However, elevated plasma levels of natriuretic peptides can occur with a wide variety of cardiac and non-cardiac causes; therefore, clinical judgement is necessary.[73] • Trials with this diagnostic marker suggest that its use may reduce both the time to hospital discharge and the cost of treatment.[80]</td>
<td></td>
</tr>
</tbody>
</table>
### Chronic congestive heart failure

#### Diagnosis

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>[81] [82] <strong>BNP</strong> levels tend to be less elevated in heart failure with preserved ejection fraction than in heart failure with low ejection fraction and are lower in obese patients. [83] Levels of BNP may be elevated meaningfully in women and in people over 60 years of age who do not have heart failure, and thus BNP levels should be interpreted cautiously in such individuals. [84] [85]</td>
<td>laboratory testing may reveal important heart failure aetiologies, the presence of disorders or conditions that can lead to or exacerbate heart failure; laboratory testing could also reveal important modulators of therapy</td>
</tr>
<tr>
<td><strong>FBC</strong></td>
<td>laboratory testing may reveal important heart failure aetiologies, the presence of disorders or conditions that can lead to or exacerbate heart failure; laboratory testing could also reveal important modulators of therapy</td>
</tr>
<tr>
<td>• Anaemia and high lymphocyte percentage are strong risk factors and prognostic markers of poor survival.</td>
<td>laboratory testing may reveal important heart failure aetiologies, the presence of disorders or conditions that can lead to or exacerbate heart failure; laboratory testing could also reveal important modulators of therapy</td>
</tr>
<tr>
<td><strong>serum electrolytes (including calcium and magnesium)</strong></td>
<td>decreased sodium (usually &lt;135 millimols/L), altered potassium</td>
</tr>
<tr>
<td>• Baseline electrolytes should be obtained in all patients.</td>
<td>decreased sodium (usually &lt;135 millimols/L), altered potassium</td>
</tr>
<tr>
<td><strong>serum creatinine, blood urea nitrogen</strong></td>
<td>normal to elevated</td>
</tr>
<tr>
<td>• Reflects tissue perfusion, fluid status, rules out renal disease.</td>
<td>normal to elevated</td>
</tr>
<tr>
<td><strong>blood glucose</strong></td>
<td>elevated in diabetes</td>
</tr>
<tr>
<td>• Screening for diabetes mellitus as a comorbid condition. Diabetes mellitus has been associated with a 3- to 5-fold increase in the risk of developing heart failure. [13] [14] [15] [17] [18] [19]</td>
<td>elevated in diabetes</td>
</tr>
<tr>
<td><strong>LFT</strong></td>
<td>primary hypothyroidism: elevated TSH, decreased free thyroxine (FT4); hyperthyroidism: decreased TSH, elevated free triiodothyronine, elevated FT4</td>
</tr>
<tr>
<td>• Reflects abdominal congestion.</td>
<td>primary hypothyroidism: elevated TSH, decreased free thyroxine (FT4); hyperthyroidism: decreased TSH, elevated free triiodothyronine, elevated FT4</td>
</tr>
<tr>
<td><strong>thyroid function tests (especially thyroid-stimulating hormone [TSH])</strong></td>
<td>primary hypothyroidism: elevated TSH, decreased free thyroxine (FT4); hyperthyroidism: decreased TSH, elevated free triiodothyronine, elevated FT4</td>
</tr>
<tr>
<td>• Screening for hypo- or hyperthyroidism. Both can be a primary or contributory cause of heart failure.</td>
<td>primary hypothyroidism: elevated TSH, decreased free thyroxine (FT4); hyperthyroidism: decreased TSH, elevated free triiodothyronine, elevated FT4</td>
</tr>
<tr>
<td><strong>blood lipids</strong></td>
<td>elevated in dyslipidaemia, decreased in end-stage heart failure, especially in the presence of cardiac cachexia</td>
</tr>
<tr>
<td>• Screening for dyslipoproteinaemias/metabolic syndrome.</td>
<td>elevated in dyslipidaemia, decreased in end-stage heart failure, especially in the presence of cardiac cachexia</td>
</tr>
<tr>
<td><strong>serum ferritin</strong></td>
<td>elevated (normal value 22-449 picomol/L [10-200 nanograms/mL])</td>
</tr>
<tr>
<td>• For evaluation of cardiomyopathy due to iron overload cardiomyopathy/haemochromatosis.</td>
<td>elevated (normal value 22-449 picomol/L [10-200 nanograms/mL])</td>
</tr>
<tr>
<td><strong>transferrin saturation</strong></td>
<td>elevated level of transferrin saturation; complete or almost complete transferrin saturation (normal transferrin saturation 22% to 46%)</td>
</tr>
<tr>
<td>• For evaluation of cardiomyopathy due to iron overload cardiomyopathy/haemochromatosis.</td>
<td>elevated level of transferrin saturation; complete or almost complete transferrin saturation (normal transferrin saturation 22% to 46%)</td>
</tr>
</tbody>
</table>
## Other tests to consider

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>standard exercise stress testing (bicycle or treadmill)</strong></td>
<td>• Provides an objective assessment of the patient’s functional exercise limitation and haemodynamic response to exercise. Test is ordered when exercise-induced arrhythmias or ischaemia are suspected. Caution should be taken if there is a high likelihood for aortic stenosis or hypertrophic obstructive cardiomyopathy.</td>
</tr>
<tr>
<td></td>
<td>usually reduced exercise capacity in idiopathic dilated cardiomyopathy; reduced exercise capacity and signs of impaired myocardial perfusion in ischaemic cardiomyopathy; however, functional capacity may be completely normal in patients with low left ventricular systolic function</td>
</tr>
<tr>
<td><strong>cardiopulmonary exercise testing with VO₂ max</strong></td>
<td>reduced VO₂ max</td>
</tr>
<tr>
<td></td>
<td>• Provides the most objective assessment of the patient’s functional status.</td>
</tr>
<tr>
<td><strong>6-minute walking test exercise</strong></td>
<td>as an alternative to cardiopulmonary exercise testing it may provide an objective assessment of the patient’s functional status</td>
</tr>
<tr>
<td></td>
<td>• A patient with heart failure who cannot walk more than 300 m in 6 minutes has a substantially greater annual risk of death than one who can walk 450 m or more.</td>
</tr>
<tr>
<td><strong>right heart catheterisation</strong></td>
<td>provides objective haemodynamic assessment of left ventricular filling pressure and direct measures of cardiac output and pulmonary and systemic resistance</td>
</tr>
<tr>
<td></td>
<td>• Considered in patients intolerant to standard medical therapy, in whom medical therapy has failed to achieve symptomatic relief, before initiation of IV inotrope or inodilator therapy and in candidates for heart transplantation.</td>
</tr>
<tr>
<td><strong>endomyocardial biopsy</strong></td>
<td>rarely necessary to establish the aetiology of heart failure; provides definitive pathological evidence of cardiac and systemic disease</td>
</tr>
<tr>
<td></td>
<td>• Ordered if acute myocarditis (giant cell or eosinophilic) or primary infiltrative diseases of the heart (amyloidosis, active cardiac sarcoidosis) suspected.</td>
</tr>
<tr>
<td><strong>serum HIV enzyme-linked immunosorbent assay</strong></td>
<td>positive or negative</td>
</tr>
<tr>
<td></td>
<td>• The majority of patients who have cardiomyopathy due to HIV do not present with symptoms of heart failure until other clinical signs of HIV infection are apparent.</td>
</tr>
<tr>
<td><strong>cardiac MRI</strong></td>
<td>myocarditis: subepicardial delayed enhancement in myocardium, high signal in myocardium in T2-weighted imaging; infiltrative cardiomyopathy: amyloid (global sub-</td>
</tr>
<tr>
<td></td>
<td>• Particularly useful in evaluation of conditions like myocarditis, constrictive pericarditis, and infiltrative cardiomyopathy.</td>
</tr>
</tbody>
</table>
### Diagnosis

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>endocardial delayed enhancement</td>
<td>sarcoïd: (delayed enhancement); no sub-endocardial delayed enhancement; constrictive pericarditis: thick pericardium as well as diastolic septal bounce with inspiration</td>
</tr>
</tbody>
</table>

### Emerging tests

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>biomarkers</td>
<td>borderline to minimally elevated</td>
</tr>
<tr>
<td>• Troponin is helpful in further risk stratification in chronic heart failure, as elevated level is associated with progressive left ventricular dysfunction and increased mortality.</td>
<td></td>
</tr>
<tr>
<td>• Soluble ST2 and galectin-3 (biomarkers for myocardial fibrosis) are predictive of death and hospitalisation in patients with heart failure and are additive to natriuretic peptide in their prognostic value.</td>
<td></td>
</tr>
<tr>
<td>multi-slice computed tomography (MSCT)</td>
<td>quantifies LVEF and coronary artery disease</td>
</tr>
<tr>
<td>• A new method for left ventricular ejection fraction (LVEF) estimation. There appears to be no significant difference in LVEF estimation between MSCT and MRI, and also between MSCT and transthoracic echocardiogram.</td>
<td></td>
</tr>
<tr>
<td>• May offer additional benefit as it provides a combined evaluation of LVEF and coronary artery disease.</td>
<td></td>
</tr>
</tbody>
</table>
## Differential diagnosis

<table>
<thead>
<tr>
<th>Condition</th>
<th>Differentiating signs / symptoms</th>
<th>Differentiating tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ageing/physical inactivity</td>
<td>• Ageing, deconditioning, and/or obesity may cause a reduction in effort tolerance due to dyspnoea and/or fatigue, but without the additional major and minor criteria for diagnosing heart failure.</td>
<td>• Elucidation of the precise reason for exercise intolerance can be difficult because several disorders may co-exist in the same patient. Echocardiography in heart failure shows characteristic signs of heart failure. However, a clear distinction can sometimes be made only by measurements of gas exchange or blood oxygen saturation or by invasive haemodynamic measurements during graded levels of exercise (i.e., cardiopulmonary exercise test with VO₂ max).</td>
</tr>
<tr>
<td>COPD/pulmonary fibrosis</td>
<td>• Dyspnoea may be episodic, with or without environmental triggers, and is usually accompanied by cough, wheezing, sputum, and a history of smoking or industrial exposure.</td>
<td>• Pulmonary function tests will give definite diagnosis of an obstructive pulmonary disease. Plasma B-type natriuretic peptide levels may be intermediate (100 to 400 nanograms/L or 100 to 400 picograms/mL) in COPD.</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>• Patients may present with fever, cough, and productive sputum, with focal signs of consolidation (increased vocal fremitus and bronchial breathing).</td>
<td>• CXR may show signs of consolidation. FBC may show elevated WBC, and blood cultures may be positive for aetiological organism.</td>
</tr>
</tbody>
</table>
| Pulmonary embolism (PE)          | • Sudden onset of chest pain, dyspnoea, and haemoptysis, especially after childbirth,[87] are suggestive of PE. | • ECG is abnormal in the majority of patients with PE and may show a deep S wave in lead I and a deep Q wave and T-wave inversion in lead III (S1-Q3-T3). Other common changes include sinus tachycardia, complete or incomplete right bundle-branch block, and T-wave inversion in the inferior (II, III, aVF) or the anterior leads (V1 to V4).  
• Normal levels of D-dimers can help to exclude PE, but elevated levels occur in other conditions (e.g., aortic
<table>
<thead>
<tr>
<th>Condition</th>
<th>Differentiating signs / symptoms</th>
<th>Differentiating tests</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Post-partum cardiomyopathy (PPCM)</strong></td>
<td>• Patients most commonly present with dyspnoea, but other frequent complaints include cough, orthopnoea, paroxysmal nocturnal dyspnoea, haemoptysis, and chest discomfort, which are also common symptoms of pulmonary embolism.[87] PPCM is defined on the basis of 4 criteria: 1) development of cardiac failure in the last month of pregnancy or within 5 months of delivery; 2) absence of an identifiable cause for the cardiac failure; 3) absence of recognisable heart disease before the last month of pregnancy; 4) left ventricular systolic dysfunction shown on echocardiograph. A number of potential risk factors may point to the diagnosis of PPCM, including age &gt;30 years, multiparity, women of African descent, pregnancy with multiple fetuses, a history of pre-eclampsia/eclampsia/post-partum hypertension, and maternal cocaine misuse.</td>
<td>• In the presence of raised D-dimers (commonplace in pregnancy) and positive risk factors for thromboembolic events, echocardiography will identify the underlying left ventricular systolic dysfunction and point to the diagnosis of PPCM. It usually shows left ventricular enlargement and significant global reduction in ejection fraction. Other findings may include left atrial enlargement, mitral and tricuspid regurgitation, and a small pericardial effusion.</td>
</tr>
<tr>
<td><strong>Cirrhosis</strong></td>
<td>• Typically causes jaundice, fatigue, nausea, peripheral oedema, ascites, bruising and prolonged bleeding, gynaecomastia, and haematemesis.</td>
<td>• LFTs are abnormal. Ultrasound or CT scan may detect ascites and liver abnormalities. Liver biopsy shows characteristic cirrhotic changes and may reveal the underlying cause.</td>
</tr>
<tr>
<td><strong>Nephrotic syndrome</strong></td>
<td>• Typically causes peripheral oedema, fatigue, dyspnoea, and loss of appetite.</td>
<td>• Urinalysis shows proteinuria, and serum albumin is reduced. Twenty-four-hour urine collection shows &gt;3.5 g protein. Serum urea and creatinine clearance may be abnormal in later stages. Serum cholesterol and triglyceride levels may be raised. Kidney ultrasound...</td>
</tr>
<tr>
<td>Condition</td>
<td>Differentiating signs / symptoms</td>
<td>Differentiating tests</td>
</tr>
<tr>
<td>-------------------------</td>
<td>-------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Pericardial disease</td>
<td>• May present with chest pain, typically worse on lying down, swallowing or coughing; tachycardia; dyspnoea; cough; oedema; fatigue; and low-grade fever. Pericardial friction rub may be heard at the left sternal border or apex.</td>
<td>• ECG may show electrical alternans or ST elevation and T wave flattening or inversion. Echocardiography may detect pericardial effusion, tamponade, and pericardial fibrosis. CT scan or MRI may show thickened pericardium. Pericardial biopsy may reveal underlying cause.</td>
</tr>
<tr>
<td>Venous stasis</td>
<td>• Oedema affects lower limbs only, and varicose veins may be present. Skin over the lower legs may be darkened, with ulceration.</td>
<td>• Doppler examination may detect incompetent valves in varicose veins.</td>
</tr>
<tr>
<td>Deep venous thrombosis</td>
<td>• Typically causes pain, swelling, and tenderness of one calf, which becomes red and warm.</td>
<td>• D-dimer test may be positive. Ultrasound scan or contrast venography may detect an area of thrombosis.</td>
</tr>
</tbody>
</table>

### Diagnostic criteria

#### New York Heart Association (NYHA) classification[88]

This classification is symptom-based and has primarily been used as shorthand to describe functional limitations. Heart failure symptoms may progress from one class to the next in a given patient, but can also follow the path in reverse; for example, a patient with NYHA class IV symptoms might have quick improvement to class III with diuretic therapy alone.

- **Class I:** Mild. No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitations, or dyspnoea.
- **Class II:** Mild. Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitations, or dyspnoea.
- **Class III:** Moderate. Marked limitation of physical activity. Comfortable at rest, but gentle activity causes fatigue, palpitations, or dyspnoea.
- **Class IV:** Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.
Step-by-step treatment approach

Goals of treatment of chronic CHF are to:

• Alleviate symptoms
• Delay progression
• Reduce mortality.

General principles of therapy

• In newly diagnosed patients with CHF, congestion and volume overload should be promptly treated with diuretics, which may be given intravenously in the initial phase. Loop diuretics used for the treatment of heart failure and congestion include furosemide, bumetanide, and torasemide.
• In patients with low left ventricular ejection fraction (LVEF), in addition to diuretics, ACE inhibitors, beta-blockers, and aldosterone antagonists (e.g., spironolactone, eplerenone) should be added.
• In unstable patients, beta-blockers should be initiated only after stabilisation, optimisation of volume status, and discontinuation of inotropes. Beta-blockers should be initiated at a low dose.
• In patients with CHF and reduced LVEF who are hospitalised with exacerbation of heart failure, unless there is evidence of low cardiac output or haemodynamic instability or contraindication, both ACE-inhibitors and beta-blockers should be continued.

Lifestyle changes

The success of pharmacological therapy is strongly related to, and greatly enhanced by, encouraging the patient and his/her family to participate in various complementary non-pharmacological management strategies. These mainly include lifestyle changes, dietary and nutritional modifications, exercise training,[91] [92] [93] and health maintenance.

Initial drug treatments

Diuretics:

• All patients with symptoms and signs of congestion should receive diuretics, irrespective of the LVEF. In patients with reduced LVEF, diuretics should always be used in combination with an ACE inhibitor (or angiotensin-II receptor antagonist), a beta-blocker, and an aldosterone antagonist. Loop diuretics used for the treatment of heart failure and congestion include furosemide, bumetanide, and torasemide. The most commonly used agent appears to be furosemide, but some patients may respond more favourably to another loop diuretic. In resistant cases, loop diuretics should be combined with a thiazide diuretic (e.g., chlorothiazide, hydrochlorothiazide) or a thiazide-like diuretic (e.g., metolazone, indapamide).
• Loop diuretics and thiazide diuretics differ in their pharmacological actions. Loop diuretics increase excretion of up to 20% to 25% of the filtered load of sodium, enhance free-water clearance, and maintain their efficacy unless renal function is severely impaired. In contrast, thiazide diuretics increase the fractional excretion of sodium to only 5% to 10% of the filtered load, tend to decrease free-water clearance, and lose their effectiveness in patients with impaired renal function (i.e., creatinine clearance less than 40 mL/minute). Consequently, loop diuretics have emerged as the preferred diuretic agents for use in most patients with heart failure; however, thiazide diuretics
TREATMENT

Chronic congestive heart failure may be preferred in patients with hypertension, heart failure, and mild fluid retention because they confer more persistent antihypertensive effects.

- Careful monitoring of renal function and electrolytes is essential. The minimum dose of diuretic should be used to relieve congestion, keep the patient asymptomatic, and maintain a dry weight.

ACE inhibitors or beta-blockers:

ACE inhibitors

- ACE inhibitors or beta-blockers may be used as first-line treatment. Both are equally important in terms of survival benefit. It has not been shown that starting with an ACE inhibitor is better than starting with a beta-blocker, but in practice most physicians start an ACE inhibitor first; the origin of this practice is historical, as the benefits of ACE inhibitors were demonstrated 10 years before those of beta-blockers. Also, most large-scale studies of beta-blockers were conducted using ACE-inhibitor therapy as comparator or standard. If a patient cannot tolerate target doses of both an ACE inhibitor and a beta-blocker when these drugs are co-administered, it is preferable to co-administer lower doses of both drugs than to reach the target dose in one class and not be able to initiate the other.
- ACE inhibitors have been shown to decrease the morbidity and mortality associated with heart failure,[2] [5] [94] and should be given to all patients with left ventricular (LV) dysfunction, symptomatic or otherwise, unless there is a contraindication or prior intolerance to therapy.

Beta-blockers

- Beta-blockers have also been shown to decrease the morbidity and mortality associated with heart failure.[2] [5] [94] They are initiated at low doses and titrated to target dosage.[2] [95] [96] [97] [98] One meta-analysis found that irrespective of pre-treatment heart rate, beta-blockers reduced mortality in patients with heart failure with reduced ejection fraction (HFrEF) in sinus rhythm.[99] Achieving a lower heart rate is associated with better prognosis for patients in sinus rhythm but not those with atrial fibrillation. Mortality was lower for patients in sinus rhythm randomised to beta-blockers (hazard ratio: 0.73 vs. placebo; 95% confidence interval [CI] 0.67 to 0.79; P <0.001), regardless of baseline heart rate (interaction P = 0.35). Beta-blockers had no effect on mortality in patients with atrial fibrillation (hazard ratio: 0.96; 95% CI 0.81 to 1.12; P = 0.58) at any heart rate (interaction P = 0.48).[99] However, this was a retrospective analysis and authors commented that background therapy, including devices, may have changed since these trials were conducted and that the heart rate was not measured in a standardised fashion across the trials. In a randomised trial of patients with atrial fibrillation and HFrEF, during a median follow-up of 37 months, beta-blockers were associated with significantly lower all-cause mortality (hazard ratio: 0.721; 95% CI 0.549 to 0.945; P = 0.0180) but not hospitalisation (hazard ratio: 0.886; 95% CI 0.715 to 1.100; P = 0.2232).[100] The result of this study supports the evidence-based recommendations for beta-blockers in patients with HFrEF, whether or not they have associated atrial fibrillation.
- Although side effects can include bradycardia, worsening of reactive airway disease, and worsening heart failure, these can often be avoided by careful patient selection, dose titration, and close monitoring. Clinical improvement may be delayed and may take 2 to 3 months to become apparent. However, long-term treatment with beta-blockers can lessen the symptoms of heart failure and improve clinical status.

Angiotensin-II receptor antagonists:
Angiotensin-II receptor antagonists are considered a reasonable alternative to ACE inhibitors in patients with preserved or decreased LVEF who are intolerant of ACE inhibitors because of cough or angio-oedema.[2] [101] Experience with these drugs in controlled clinical trials of patients with heart failure is considerably less than that with ACE inhibitors. Nevertheless, valsartan and candesartan have demonstrated benefit by reducing hospitalisations and mortality.[2] [102] In patients with evidence of left ventricular dysfunction early after myocardial infarction, angiotensin-II receptor antagonists may be no more effective than ACE inhibitors and may be no better tolerated. The combination of an ACE inhibitor and an angiotensin-II receptor antagonist may produce more reduction of left ventricular size[103] and may reduce the need for hospitalisation than either agent alone, although whether or not combination therapy further reduces mortality remains unclear.[103] [104] [105] As an alternative to ACE inhibitors, angiotensin-II receptor antagonists should be initiated in patients early post-infarct, but caution should be used in patients in cardiogenic shock or with marginal renal output.[102]

Addition of an angiotensin-II receptor antagonist may be considered in persistently symptomatic patients with heart failure and reduced LVEF who are already being treated with an ACE inhibitor and beta-blockers and in whom an aldosterone antagonist is not indicated or tolerated.[2] Routine combined use of ACE inhibitors with an aldosterone antagonist and an angiotensin-II receptor antagonist is potentially harmful for patients with heart failure and is not recommended.[2] Combined use should be instigated by a specialist and continued only with specialist supervision. Concomitant administration of an ACE inhibitor, a beta-blocker, and an angiotensin-II receptor antagonist should be used with great caution and perhaps initiated only in hospital under continuous blood pressure and renal function monitoring, because it may provoke life-threatening hypotension and acute renal insufficiency. The CHARM trial showed that this combination may confer added benefit with acceptable risk, but further studies are required.[106] In one study, addition of olmesartan (an angiotensin-II receptor antagonist) to patients with New York Heart Association (NYHA) class II to IV heart failure who had a history of hypertension or who had been treated with antihypertensive medications and were already on ACE inhibitor and beta-blocker therapy did not improve the clinical outcome and led to worsening of renal function.[107] In this study, subgroup analysis showed that the addition of olmesartan to a combination of an ACE inhibitor and a beta-blocker was associated with an increased incidence of primary end point, all-cause death, and renal dysfunction. The routine combined use of all three inhibitors of the renin-angiotensin system cannot be recommended at present. The European Medicines Agency's Pharmacovigilance Risk Assessment Committee has advised that combining drugs that act on the renin-angiotensin system (e.g., ACE inhibitors, angiotensin-II receptor antagonists) is not recommended, particularly in patients with diabetes-related kidney problems. Where such a combination is considered absolutely necessary, it should be carried out under strict specialist supervision with close monitoring.[108]

Renin inhibitors (e.g., aliskiren) should also not be combined with ACE inhibitors. In a study of patients with chronic heart failure (NYHA class II to IV, ejection fraction of 35% or less) addition of aliskiren to enalapril compared with enalapril alone led to more adverse events (hypotension and elevated creatinine) without any benefit or difference in primary outcome of death from cardiovascular causes or hospitalisation for heart failure.[109]

Angiotensin-II receptor antagonist plus neprilysin inhibitor:

In HFrEF (NYHA class II to IV) and ejection fraction of 40% or less, which was later changed to an ejection fraction of 35% or less, a combination of sacubitril, a neprilysin inhibitor, and valsartan, an angiotensin-II receptor antagonist, was superior to enalapril in reducing mortality and heart failure hospitalisation.[110] The drug combination has been approved in the US and in Europe for the treatment
of heart failure. In this study the ejection fraction was 29 ± 6.1% in the sacubitril/valsartan group and 29.4 ± 6.3% in the enalapril group.[110]

Sacubitril/valsartan has been found to improve a patient’s physical and social activities compared with enalapril.[111]

Sacubitril/valsartan is recommended as a replacement for an ACE inhibitor in patients who remain symptomatic despite optimal treatment with an ACE inhibitor, a beta-blocker, and a mineralocorticoid-receptor antagonist.[1] It is recommended for patients who fit the profile of the study showing beneficial effects of this combination (i.e., patients in NYHA class II to IV with LVEF of 35% or <35%).[110] The American Heart Association/American College of Cardiology/Heart Failure Society of America guidelines recommend that, in patients with chronic NYHA class II or III who tolerate an ACE inhibitor or angiotensin-II receptor antagonist, these drugs should be replaced by an angiotensin-II receptor antagonist plus neprilysin inhibitor to further reduce morbidity and mortality.[73] Concomitant administration of an angiotensin-II receptor antagonist plus a neprilysin inhibitor with an ACE inhibitor, or within 36 hours of the last dose of an ACE inhibitor, is not recommended.[73]

Treatment with sacubitril/valsartan reduces cardiovascular death by reducing both worsening heart failure and sudden cardiac death.[112]

Hydralazine and nitrates:

The addition of a combination of hydralazine and a nitrate is reasonable for patients with reduced LVEF who are already taking an ACE inhibitor and beta-blocker for symptomatic heart failure and who have persistent symptoms,[2] and has demonstrated benefit in black patients with heart failure.[113] [114] The combined use of hydralazine and isosorbide dinitrate may also be considered as a therapeutic option in patients who are intolerant of ACE inhibitors.[2] This combination may be a useful alternative in patients intolerant to both ACE inhibitors and angiotensin-II receptor antagonists.[2]

A combination of hydralazine and isosorbide dinitrate can be useful to reduce morbidity or mortality in patients with current or prior symptomatic HFrEF who cannot be given an ACE inhibitor or angiotensin-II receptor antagonist because of drug intolerance, hypotension, or renal insufficiency, unless contraindicated.[2] The American College of Cardiology Foundation/American Heart Association guidelines recommend the combination of hydralazine and isosorbide dinitrate to "reduce morbidity and mortality in patients self-described as African Americans with NYHA class III to IV HFrEF receiving optimal therapy with ACE inhibitors and beta blockers, unless contraindicated".[2]

Anticoagulants:

At present there is little evidence from long-term studies to recommend antiplatelet therapy or oral anticoagulation in patients with heart failure in sinus rhythm, and antiplatelet agents versus control or anticoagulation for heart failure in sinus rhythm.[115]

- A study comparing warfarin and aspirin in patients with heart failure and sinus rhythm showed no significant difference in the combined outcomes of stroke, intracerebral haemorrhage, and death. Warfarin reduced ischaemic stroke at the expense of an increased bleeding risk.[116]
- Although oral anticoagulants are indicated in certain groups of patients with heart failure (e.g., patients with atrial fibrillation), the available data do not support their routine use in heart failure patients who remain in sinus rhythm.[115]
**Digoxin for patients with heart failure**

Digoxin can be beneficial in patients with current or prior symptoms of heart failure or reduced LVEF, especially those with atrial fibrillation. When added to ACE inhibitors, beta-blockers, and diuretics, digoxin can reduce symptoms, prevent hospitalisation, control rhythm, and enhance exercise tolerance.[117] Digoxin reduces the composite end point of mortality or hospitalisations in ambulatory patients with chronic heart failure with NYHA class III or IV symptoms, LVEF <25%, or cardiothoracic ratio of >55% and should be considered in these patients.[118]

Digoxin reduces the composite end point of mortality or hospitalisations, but does not reduce all-cause mortality.[118] Digoxin should be used cautiously with plasma level monitoring. One meta-analysis suggests that digoxin use in patients with heart failure is associated with a higher risk of all-cause mortality.[119]

One systematic review and meta-analysis of observational and controlled trial data showed that digoxin has a neutral effect on mortality in randomised trials and reduces hospital admissions.[120]

**Aldosterone antagonists in moderate-to-severe heart failure**

Aldosterone antagonists (also known as mineralocorticoid receptor antagonists) decrease the morbidity and mortality associated with symptomatic chronic heart failure.

Aldosterone antagonists (spironolactone and eplerenone) are recommended in patients with NYHA class II to IV heart failure who have LVEF of 35% or less, unless contraindicated.[2] They are also recommended to reduce mortality and morbidity following acute myocardial infarction in patients with LVEF of 40% or less who develop symptoms of heart failure or have a history of diabetes mellitus, unless contraindicated.[2] [121]

Aldosterone antagonists should be initiated after titration of standard medical therapy. Spironolactone and eplerenone can both cause hyperkalaemia, and precautions should be taken to minimise the risk. In the EPHESUS trial, the addition of eplerenone to standard care did not increase the risk of hyperkalaemia when potassium was regularly monitored.[122]

**Ivabradine**

Ivabradine is approved for use in patients with heart failure and symptoms in spite of drug therapy. The UK National Institute for Health and Care Excellence has approved it for patients with NYHA class II to IV heart failure, sinus rate of over 75 bpm, and ejection fraction <35%. [123] In the US, the Food and Drug Administration (FDA) has approved it to reduce the risk of hospitalisation for worsening heart failure in patients with stable, symptomatic chronic heart failure, with LVEF ≤35%, who are in sinus rhythm with a resting heart rate ≥70 beats per minute, and are either on a maximum dose of beta-blockers or have a contraindication to beta-blockers.

In a randomised, double-blind, placebo-controlled trial, addition of ivabradine to standard background therapy in patients with stable coronary artery disease without clinical heart failure (no evidence of left ventricular systolic dysfunction in the overall study population, mean ejection fraction was 56.4%) did not improve the outcome. In the subgroup analysis of this study, ivabradine was associated with an increase in the incidence of the primary end point (death from cardiovascular causes or non-fatal myocardial infarction) among patients who had angina of Canadian Cardiovascular Society class II or higher but not among patients without angina or those who had angina of class I. Ivabradine was associated with an increased incidence of bradycardia, QT prolongation, and atrial fibrillation.[121]
Vasopressin antagonists

Use of vasopressin antagonists such as tolvaptan can be considered for patients with symptomatic or severe hyponatraemia (<130 mmol/L) and persistent congestion despite standard therapy, to correct hyponatraemia and related symptoms.[2] [124]

Heart transplant and medical devices

Cardiac transplantation is currently the only established surgical approach, but it is available to fewer than 2500 patients in the US each year.[125] [126] [127] Current indications for cardiac transplantation focus on the identification of patients with severe functional impairment, dependence on intravenous inotropic agents, recurrent life-threatening ventricular arrhythmias, or angina that is refractory to all currently available treatments.[2] [126] [127] [128]

Implantable defibrillators have been shown to decrease mortality in patients with heart failure, both ischaemic and non-ischaemic. The SCD-Heft trial enrolled patients who had left ventricular dysfunction and no prior history of syncope or sustained ventricular tachycardia, and included patients with a prior myocardial infarction and no prior coronary artery disease. Use of implantable defibrillators led to a 23% relative mortality risk reduction at 5 years.[129]

It has been estimated that one quarter to one third of patients with heart failure have left bundle-branch block: that is, manifest a QRS duration greater than 120 milliseconds (ms).[130] Patients with heart failure who have left bundle-branch block, known as ventricular dyssynchrony, have a poorer prognosis than those without left bundle-branch block.[2] Studies have shown that, in these patients, cardiac resynchronisation therapy (CRT) decreases hospitalisation and, when combined with an implantable defibrillator, significantly reduces mortality.[131] [132] [133] [134] [135] [136] In patients who have conduction delay and left ventricular dysfunction, biventricular pacemakers have been shown to improve exercise tolerance and quality of life while decreasing morbidity and mortality.[131] [132] [133] [134] [136] [137] [138] [139] The CARE-HF study randomised patients with a widened QRS, LVEF of 35% or less, and persistent moderate or severe symptoms of heart failure despite pharmacological therapy, to implantation of a CRT device or not.[140] The main study observed substantial benefits on morbidity and mortality that persisted or increased with longer follow-up.[141] [142] [143] [144] [145] [146] [147] [148] [149] [150] [151] Reduction in mortality was due to fewer deaths from heart failure and from reduced sudden death.[141]

The FDA approved the use of CRT devices for patients in NYHA class II heart failure, an LVEF <30%, left bundle-branch block, and QRS width >130 ms. Long-term data from the REVERSE study suggest that improvements in left ventricular function and remodelling can be sustained for over 5 years.[152] [153]

According to the American College of Cardiology Foundation/American Heart Association guidelines, the recommendations for the use of CRT devices in heart failure are as follows.[2]

1. CRT is indicated in patients who have LVEF of 35% or less; sinus rhythm; left bundle-branch block (LBBB) with a QRS duration of 150 ms or greater; NYHA class II, III, or ambulatory IV symptoms on guideline-directed medical therapy.
2. CRT can be useful in patients who have LVEF of 35% or less; sinus rhythm; a non-LBBB with a QRS duration of 150 ms or greater; NYHA class III/ambulatory IV symptoms on guideline-directed medical therapy.
3. CRT can be useful in patients who have LVEF of 35% or less; sinus rhythm; LBBB with a QRS duration of 120 to 149 ms; NYHA class II, III, or ambulatory IV symptoms on guideline-directed medical therapy.

4. CRT can be useful in patients with atrial fibrillation and LVEF of 35% or less on guideline-directed medical therapy if (a) the patient requires pacing or otherwise meets the CRT criteria; and (b) atrioventricular nodal ablation or pharmacological rate control will allow near 100% ventricular pacing with CRT.

5. CRT can be useful for patients on guideline-directed medical therapy who have LVEF of 35% or less and are undergoing device implantation with anticipated requirement for significant (>40%) ventricular pacing.

American Heart Association guidance outlines the indication and evidence behind the use of mechanical circulatory support in patients with heart failure.[154] Mechanical circulatory support, which includes ventricular assist devices, is beneficial in carefully selected patients with end-stage D heart failure in whom definite management (e.g., cardiac transplantation) or cardiac recovery is anticipated.[2]

**Treatment details overview**

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer.
## Chronic congestive heart failure

### Treatment

#### (summary)

<table>
<thead>
<tr>
<th>Acute</th>
<th>1st</th>
<th>plus</th>
<th>adjunct</th>
<th>adjunct</th>
<th>adjunct</th>
<th>adjunct</th>
<th>adjunct</th>
<th>adjunct</th>
</tr>
</thead>
<tbody>
<tr>
<td>tolerance to ACE inhibitors</td>
<td>ACE inhibitor or sacubitril/valsartan</td>
<td>lifestyle changes</td>
<td>beta-blocker</td>
<td>diuretic</td>
<td>aldosterone antagonist</td>
<td>hydralazine + isosorbide dinitrate</td>
<td>digoxin</td>
<td>ivabradine</td>
</tr>
<tr>
<td>2nd</td>
<td>hydralazine + isosorbide dinitrate</td>
<td>beta-blocker</td>
<td>lifestyle changes</td>
<td>diuretic</td>
<td>aldosterone antagonist</td>
<td>hydralazine + isosorbide dinitrate</td>
<td>digoxin</td>
<td>ivabradine</td>
</tr>
<tr>
<td>3rd</td>
<td>hydralazine + isosorbide dinitrate</td>
<td>beta-blocker</td>
<td>lifestyle changes</td>
<td>diuretic</td>
<td>aldosterone antagonist</td>
<td>hydralazine + isosorbide dinitrate</td>
<td>digoxin</td>
<td>ivabradine</td>
</tr>
</tbody>
</table>
### Ongoing

refractory to optimal medical treatment

<table>
<thead>
<tr>
<th>LVEF &lt;35%: no left bundle-branch block</th>
<th>1st</th>
<th>implantable cardiac defibrillator (ICD)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2nd</td>
<td>cardiac transplantation</td>
</tr>
<tr>
<td>LVEF &lt;30%: left bundle-branch block</td>
<td>1st</td>
<td>cardiac re-synchronisation therapy (CRT) with biventricular pacemaker</td>
</tr>
<tr>
<td></td>
<td>2nd</td>
<td>cardiac transplantation</td>
</tr>
</tbody>
</table>
Treatment options

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer.
### Acute tolerance to ACE inhibitors

<table>
<thead>
<tr>
<th>1st</th>
<th>ACE inhibitor or sacubitril/valsartan</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary options</strong></td>
<td></td>
</tr>
<tr>
<td>» captopril:</td>
<td>6.25 to 50 mg orally three times daily</td>
</tr>
<tr>
<td>OR</td>
<td></td>
</tr>
<tr>
<td>» enalapril:</td>
<td>2.5 to 20 mg orally twice daily</td>
</tr>
<tr>
<td>OR</td>
<td></td>
</tr>
<tr>
<td>» fosinopril:</td>
<td>5-40 mg orally once daily</td>
</tr>
<tr>
<td>OR</td>
<td></td>
</tr>
<tr>
<td>» lisinopril:</td>
<td>2.5 to 40 mg orally once daily</td>
</tr>
<tr>
<td>OR</td>
<td></td>
</tr>
<tr>
<td>» perindopril:</td>
<td>2-16 mg orally once daily</td>
</tr>
<tr>
<td>OR</td>
<td></td>
</tr>
<tr>
<td>» quinapril:</td>
<td>5-20 mg orally twice daily</td>
</tr>
<tr>
<td>OR</td>
<td></td>
</tr>
<tr>
<td>» ramipril:</td>
<td>1.25 to 10 mg orally once daily</td>
</tr>
<tr>
<td>OR</td>
<td></td>
</tr>
<tr>
<td>» trandolapril:</td>
<td>1-4 mg orally once daily</td>
</tr>
<tr>
<td>OR</td>
<td></td>
</tr>
<tr>
<td>» sacubitril/valsartan:</td>
<td>treatment-naive patients: 24 mg (sacubitril)/26 mg (valsartan) orally twice daily initially, increase gradually according to response, maximum 97 mg (sacubitril)/103 mg (valsartan); treatment-experienced: 49 mg (sacubitril)/51 mg (valsartan) orally twice daily initially, increase gradually according to response, maximum 97 mg (sacubitril)/103 mg (valsartan) Patients not taking an ACE inhibitor or angiotensin-II receptor antagonist should be started on a lower dose. Patients who were being treated with an ACE inhibitor or angiotensin-II receptor antagonist should be started on a higher dose. Allow 36 hours</td>
</tr>
</tbody>
</table>

Patients not taking an ACE inhibitor or angiotensin-II receptor antagonist should be started on a lower dose. Patients who were being treated with an ACE inhibitor or angiotensin-II receptor antagonist should be started on a higher dose. Allow 36 hours.
### Acute

between stopping an ACE inhibitor and starting this drug.

- ACE inhibitors have been shown to decrease the morbidity and mortality associated with heart failure,[2] [5] [94] and should be given to all patients with left ventricular dysfunction, symptomatic or otherwise, unless there is a contraindication or prior intolerance to therapy.

- ACE inhibitors should be used with caution in patients in cardiogenic shock, with marginal renal output or hyperkalaemia.

- If patients have an idiosyncratic reaction, with angio-oedema, ACE inhibitors should not be rechallenged.

- However, in heart failure with reduced ejection fraction (New York Heart Association [NYHA] class II to IV and ejection fraction of 35% or less) a combination of sacubitril, a neprilysin inhibitor, and valsartan, an angiotensin-II receptor antagonist, is superior to enalapril in reducing mortality and heart failure hospitalisation.[110] The drug combination has been approved in the US and in Europe for the treatment of heart failure. The American Heart Association/ American College of Cardiology/Heart Failure Society of America guidelines recommend that, in patients with chronic NYHA class II or III who tolerate an ACE inhibitor or angiotensin-II receptor antagonist, these drugs should be replaced by an angiotensin-II receptor antagonist plus neprilysin inhibitor to further reduce morbidity and mortality.[73] Concomitant administration of an angiotensin-II receptor antagonist plus neprilysin with an ACE inhibitor, or within 36 hours of the last dose of an ACE inhibitor, is not recommended.[73]

### Lifestyle changes

<table>
<thead>
<tr>
<th>Primary options</th>
</tr>
</thead>
<tbody>
<tr>
<td>- sodium restriction</td>
</tr>
<tr>
<td>- fluid restriction</td>
</tr>
<tr>
<td>- weight monitoring</td>
</tr>
<tr>
<td>- continuous health screening</td>
</tr>
<tr>
<td>- exercise training</td>
</tr>
</tbody>
</table>

Treatment recommended for ALL patients in selected patient group
Chronic congestive heart failure

**Acute**

» Dietary sodium intake is an easily modifiable factor that complements pharmacological therapy for heart failure. For stage A and B heart failure (stage A: at high risk for heart failure but without structural heart disease or symptoms of heart failure; stage B: structural heart disease but without signs or symptoms of heart failure), the recommendation is to limit sodium intake to 1.5 g/day. For stage C and D heart failure (stage C: structural heart disease with prior or current symptoms of heart failure; stage D: refractory heart failure requiring specialised interventions), the recommendation is to limit sodium intake to at least 3 g/day.[2]

» Fluid restriction is mostly used as an in-hospital complementary measure in cases of acute exacerbations. In addition, fluid restriction may be warranted in cases of severe hyponatraemia. However, it would be of importance to advise the patient to keep a daily intake/output balance at home. Patients are advised to monitor their weight daily and to immediately contact their healthcare provider if a specified change in weight occurs.

» Heart failure patients need continuous and close monitoring of their health. A variety of programmes have been shown to decrease morbidity and re-hospitalisation in this context, including home nursing, telephone advice/triage, telemedicine services, and specialised heart failure clinic-based care.[155]

» Exercise training has also been shown to be beneficial.[91] [92] [93]

**Treatment recommended for ALL patients in selected patient group**

**Primary options**

» carvedilol: 3.125 mg orally (immediate-release) twice daily initially, increase according to response, maximum 50 mg/day (body weight ≤85 kg) or 100 mg/day (body weight >85 kg)

**Secondary options**

» metoprolol: 12.5 to 200 mg orally (extended-release) once daily

**plus beta-blocker**

This PDF of the BMJ Best Practice topic is based on the web version that was last updated: Jan 08, 2019.

BMJ Best Practice topics are regularly updated and the most recent version of the topics can be found on bestpractice.bmj.com. Use of this content is subject to our disclaimer. © BMJ Publishing Group Ltd 2020. All rights reserved.
TREATMENT

### Acute

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>bisoprolol</strong></td>
<td>1.25 mg orally once daily initially, increase according to response, maximum 10 mg/day</td>
</tr>
<tr>
<td><strong>nebivolol</strong></td>
<td>1.25 mg orally once daily initially, increase according to response, maximum 10 mg/day</td>
</tr>
</tbody>
</table>

**All patients with chronic heart failure receive a beta-blocker once established on an ACE inhibitor, unless there is a contraindication based on bradycardia, reactive airway disease, and unstable or low-output heart failure.**[2] [5] [94]

**Carvedilol seems superior to metoprolol,**[156] although there is no evidence of superiority to other beta-blockers. In the SENIORS study, nebivolol, a cardioselective beta-blocker with nitric oxide-mediated vasodilating properties, was found to be an effective and well-tolerated treatment for heart failure in patients aged 70 years or more.[157] Data suggest that initiation with moderate doses of nebivolol is not associated with the adverse haemodynamic effects usually observed with other beta-blockers in patients with heart failure; therefore, a long up-titration period may not be necessary with nebivolol.[158]

**Beta-blockers have been shown to decrease the morbidity and mortality associated with heart failure.**[2] [5] [94] They are initiated at low doses and titrated to target dosage.[2] [95] [96] [97] [98] One meta-analysis found that irrespective of pre-treatment heart rate, beta-blockers reduced mortality in patients with heart failure with reduced ejection fraction in sinus rhythm.[99]

**adjunct diuretic**

Treatment recommended for SOME patients in selected patient group

**Primary options**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>furosemide</strong></td>
<td>20-80 mg/dose orally initially, increase by 20-40 mg/dose increments every 6-8 hours according to response, maximum 600 mg/day</td>
</tr>
<tr>
<td><strong>bumetanide</strong></td>
<td>0.5 to 1 mg orally once or twice daily initially, increase according to response, maximum 10 mg/day</td>
</tr>
</tbody>
</table>
## Chronic Congestive Heart Failure

### Treatment

<table>
<thead>
<tr>
<th>Acute</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>OR</td>
<td></td>
</tr>
<tr>
<td>- torasemide: 5-20 mg orally once daily initially, increase according to response, maximum 40 mg/day</td>
<td></td>
</tr>
<tr>
<td>OR</td>
<td></td>
</tr>
<tr>
<td>- chlorothiazide: 250-500 mg orally once or twice daily, maximum 1000 mg/day</td>
<td></td>
</tr>
<tr>
<td>OR</td>
<td></td>
</tr>
<tr>
<td>- hydrochlorothiazide: 25 mg orally once or twice daily, increase according to response, maximum 200 mg/day</td>
<td></td>
</tr>
<tr>
<td>OR</td>
<td></td>
</tr>
<tr>
<td>- indapamide: 2.5 to 5 mg orally once daily</td>
<td></td>
</tr>
<tr>
<td>OR</td>
<td></td>
</tr>
<tr>
<td>- metolazone: 2.5 to 20 mg orally once daily</td>
<td></td>
</tr>
</tbody>
</table>

### Secondary Options

- amiloride: 5-20 mg orally once daily

- triamterene: 50-100 mg orally twice daily initially, increase according to response, maximum 300 mg/day

Diuretics should be considered for patients who have evidence of, or a prior history of, fluid retention.[2] They should generally be combined with an ACE inhibitor and a beta-blocker. All patients with symptoms and signs of congestion should receive diuretics, irrespective of the left ventricular ejection fraction (LVEF).

Loop diuretics used for the treatment of heart failure and congestion include furosemide, bumetanide, and torasemide. The most commonly used agent appears to be furosemide, but some patients may respond more favourably to another loop diuretic. In resistant cases, loop diuretics should be combined with a thiazide diuretic (e.g., chlorothiazide, hydrochlorothiazide) or a thiazide-like diuretic (e.g., metolazone, indapamide). Careful monitoring of renal function and electrolytes is essential in these patients.
### Acute

» The minimum dose of diuretic should be used to relieve congestion, keep the patient asymptomatic, and maintain a dry weight. In patients with stable congestive heart failure, loop diuretics are the preferred agent. In patients with hypertension and only mild fluid retention, a thiazide diuretic may be considered.

» Diuretics produce symptomatic benefits more rapidly than any other drug for heart failure. They can relieve pulmonary and peripheral oedema within hours or days. Few patients with heart failure and fluid retention can maintain sodium balance without the use of diuretic drugs.\[159\]

» Diuretics alone are unable to maintain the clinical stability of patients with heart failure for long periods of time,\[159\] but the risk of clinical decompensation can be reduced when they are combined with an ACE inhibitor and a beta-blocker.\[160\] Diuretics should be used only in combination with an ACE inhibitor (or angiotensin-II receptor antagonist), a beta-blocker, and an aldosterone antagonist in patients with reduced LVEF.

» In intermediate-term studies, diuretics have been shown to improve cardiac function, symptoms, and exercise tolerance in patients with heart failure.\[159\] \[161\] There have been no long-term studies of diuretic therapy in heart failure, and thus their effects on morbidity and mortality are not known.

» Amiloride and triamterene (potassium-sparing diuretics) should be used with caution with aldosterone antagonists, because of the increased risk of developing hyperkalaemia. Close monitoring of serum potassium levels is suggested in this situation.

<table>
<thead>
<tr>
<th>Primary options</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>spironolactone</strong>: 25-100 mg orally once daily</td>
</tr>
</tbody>
</table>

**OR**

<table>
<thead>
<tr>
<th>Primary options</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>eplerenone</strong>: 25-50 mg orally once daily</td>
</tr>
</tbody>
</table>

**Aldosterone antagonists, also known as mineralocorticoid receptor antagonists (e.g., spironolactone and eplerenone), decrease the morbidity and mortality associated with symptomatic chronic heart failure.**
Acute

- Aldosterone antagonists are recommended in patients with New York Heart Association class II to IV heart failure who have left ventricular ejection fraction (LVEF) of 35% or less, unless contraindicated.[2] They are also recommended to reduce mortality and morbidity following acute myocardial infarction in patients with LVEF of 40% or less who develop symptoms of heart failure or have a history of diabetes mellitus, unless contraindicated.

- Aldosterone antagonists should be initiated after titration of standard medical therapy. Spironolactone and eplerenone can both cause hyperkalaemia, and precautions should be taken to minimise the risk.

- These agents should be used with caution in patients with renal dysfunction and hyperkalaemia. They should not be initiated in patients with a serum creatinine above 221 micromols/L (>2.5 mg/dL) or a serum potassium above 5.0 millimols/L (>5.0 mEq/dL) and should be used with caution in patients with serum creatinine below 221 micromols/L (<2.5 mg/dL) plus a serum potassium above 5.0 millimols/L (>5.0 mEq/dL). Patients should discontinue potassium repletion.

- Adherence to intensive monitoring of renal function and potassium levels has been shown to prevent hyperkalaemia, which is as likely to occur with eplerenone therapy as it is with spironolactone therapy.

- Amiloride and triamterene (potassium-sparing diuretics) should be used with caution with aldosterone antagonists, because of the increased risk of developing hyperkalaemia. Close monitoring of serum potassium levels is suggested in this situation.

**adjunct hydralazine + isosorbide dinitrate**

Treatment recommended for SOME patients in selected patient group

**Primary options**

- **isosorbide dinitrate**: 20-40 mg orally (immediate-release) three times daily
  -and-
  - **hydralazine**: 10-100 mg orally three times daily

  **OR**

- **isosorbide dinitrate/hydralazine**: 20 mg (isosorbide dinitrate)/37.5 mg (hydralazine)
### Chronic Congestive Heart Failure: Treatment

#### Acute

<table>
<thead>
<tr>
<th>Adjunct</th>
<th>Primary options</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>digoxin</strong></td>
<td>- <strong>digoxin</strong>: 0.125 to 0.5 mg orally once daily</td>
</tr>
</tbody>
</table>

- A combination of hydralazine and isosorbide dinitrate can be useful to reduce morbidity or mortality in patients with current or prior symptomatic heart failure with reduced ejection fraction (HFrEF) who cannot be given an ACE inhibitor or angiotensin-II receptor antagonist because of drug intolerance, hypotension, or renal insufficiency, unless contraindicated.[2]

The American College of Cardiology Foundation/American Heart Association guidelines recommend the combination of hydralazine and isosorbide dinitrate to "reduce morbidity and mortality in patients self-described as African Americans with NYHA class III to IV HFrEF receiving optimal therapy with ACE inhibitors and beta blockers, unless contraindicated".[2]

- Nitrate therapy may decrease symptoms of dyspnoea at night and during exercise and may improve exercise tolerance in patients who have persistent limitations despite optimisation of other therapies.[162] [163]

- Development of nitrate tolerance seems to be minimised by prescription of a nitrate-free interval of at least 10 hours.[2] Carvedilol use has been shown to prevent nitrate tolerance in patients with CHF.[164] [165]

- Hydralazine may interfere with the biochemical and molecular mechanisms responsible for the development of nitrate tolerance.[166] [167]

- A combination pill containing 37.5 mg hydralazine and 20 mg isosorbide dinitrate is available, approved specifically for self-identified black patients with CHF.
Chronic congestive heart failure

**Treatment**

**Acute**

- Digoxin reduces the composite end point of mortality or hospitalisations in ambulatory patients with chronic heart failure with New York Heart Association class III or IV symptoms, LVEF <25%, or cardiothoracic ratio of >55% and should be considered in these patients.[118]

- Digoxin reduces the composite end point of mortality or hospitalisations, but does not reduce all-cause mortality.[118] Digoxin should be used cautiously with plasma level monitoring; one meta-analysis suggests that digoxin use in patients with heart failure is associated with a higher risk of all-cause mortality.[119]

- Overt digitalis toxicity is commonly associated with serum digoxin levels >2.6 nanomols/L (2 nanograms/mL). However, toxicity may occur with lower levels, especially if hypokalaemia, hypomagnesaemia, or hypothyroidism co-exists.[168] [169]

- Low doses (0.125 mg/day or every other day) should be used initially if the patient is over 70 years old, has impaired renal function, or has a low lean body mass.[170]

- Higher doses (e.g., 0.375 to 0.5 mg/day) are rarely used or needed.

- There is no reason to use loading doses of digoxin to initiate therapy.

**adjunct ivabradine**

Treatment recommended for SOME patients in selected patient group

**Primary options**

- **ivabradine**: 5 mg orally twice daily initially, may increase to 7.5 mg twice daily after 2 weeks if necessary; adjust dose according to heart rate

- Ivabradine may be an option for patients with New York Heart Association class II, III, or IV heart failure who have a sinus rate >75 beats per minute and an ejection fraction <35%, and who remain symptomatic despite optimal therapy. It can also be used in patients who are unable to take beta-blockers.

- Its use should be initiated by a specialist cardiologist and only after a stabilisation period of 4 weeks on optimised standard therapy.[123]

- In a randomised, double-blind, placebo-controlled trial, addition of ivabradine to standard background therapy in patients with stable
Chronic congestive heart failure

<table>
<thead>
<tr>
<th>TREATMENT</th>
<th>Adjunct vasopressin antagonist</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute coronary artery disease without clinical heart failure (no evidence of left ventricular systolic dysfunction in the overall study population, mean ejection fraction was 56.4%) did not improve the outcome. In the subgroup analysis of this study, ivabradine was associated with an increase in the incidence of the primary end point (death from cardiovascular causes or non-fatal myocardial infarction) among patients who had angina of Canadian Cardiovascular Society class II or higher but not among patients without angina or those who had angina of class I. Ivabradine was associated with an increased incidence of bradycardia, QT prolongation, and atrial fibrillation.[121]</td>
<td></td>
</tr>
</tbody>
</table>

| Intolerance to ACE inhibitors |
|---|---|
| 1st beta-blocker + angiotensin-II receptor antagonist |
| **Primary options** |
| → tolvaptan: 15 mg orally once daily initially, increase gradually according to response, maximum 60 mg/day for up to 30 days |
| → Considered for patients with symptomatic or severe hyponatraemia (<130 mmol/L) and persistent congestion despite standard therapy, to correct hyponatraemia and related symptoms.[2] [124] |
| **Secondary options** |
| → metoprolol: 12.5 to 200 mg orally (extended-release) once daily |

This PDF of the BMJ Best Practice topic is based on the web version that was last updated: Jan 08, 2019. BMJ Best Practice topics are regularly updated and the most recent version of the topics can be found on bestpractice.bmj.com. Use of this content is subject to our disclaimer. © BMJ Publishing Group Ltd 2020. All rights reserved.
### Acute

<table>
<thead>
<tr>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>» bisoprolol</strong>: 1.25 mg orally once daily initially, increase according to response, maximum 10 mg/day</td>
</tr>
<tr>
<td><strong>-or-</strong></td>
</tr>
<tr>
<td><strong>» nebivolol</strong>: 1.25 mg orally once daily initially, increase according to response, maximum 10 mg/day</td>
</tr>
<tr>
<td><strong>--AND--</strong></td>
</tr>
<tr>
<td><strong>» candesartan</strong>: 4-32 mg orally once daily</td>
</tr>
<tr>
<td><strong>-or-</strong></td>
</tr>
<tr>
<td><strong>» losartan</strong>: 25-100 mg orally once daily</td>
</tr>
<tr>
<td><strong>-or-</strong></td>
</tr>
<tr>
<td><strong>» valsartan</strong>: 40-160 mg orally twice daily</td>
</tr>
</tbody>
</table>

» All patients with chronic heart failure receive a beta-blocker, unless there is a contraindication based on bradycardia, reactive airway disease, and unstable or low-output heart failure.[2] [5] [94]

» Carvedilol seems superior to metoprolol,[156] although there is no evidence of superiority to other beta-blockers. In the SENIORS study, nebivolol, a cardioselective beta-blocker with nitric oxide-mediated vasodilating properties, was found to be an effective and well-tolerated treatment for heart failure in patients aged 70 years or more.[157] Data suggest that initiation with moderate doses of nebivolol is not associated with the adverse haemodynamic effects usually observed with other beta-blockers in patients with heart failure; therefore, a long up-titration period may not be necessary with nebivolol.[158]

» Angiotensin-II receptor antagonists should be added instead of ACE inhibitors in all patients who are intolerant of ACE inhibitors because of cough or angio-oedema.[2] Valsartan and candesartan have demonstrated benefit by reducing hospitalisations and mortality.[102]

» Angiotensin-II receptor antagonists are as likely to produce hypotension, worsening renal function, and hyperkalaemia as ACE inhibitors. Although angio-oedema is much less frequent, there are cases of patients who developed angio-oedema to both ACE inhibitors and later to angiotensin-II receptor antagonists.

**plus**  
**lifestyle changes**

Treatment recommended for ALL patients in selected patient group

**Primary options**

<table>
<thead>
<tr>
<th>sodium restriction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>-and-</strong></td>
</tr>
</tbody>
</table>
Chronic congestive heart failure

Treatment

TREATMENT

Acute

- fluid restriction
- and-
- weight monitoring
- and-
- continuous health screening
- and-
- exercise training

Dietary sodium intake is an easily modifiable factor that complements pharmacological therapy for heart failure. Thus the patient and family are advised to follow a daily dietary sodium intake between 2 and 3 g. Further restriction to 1 to 2 g/day may be necessary for patients with advanced symptoms refractory to therapy.

Fluid restriction is mostly used as an in-hospital complementary measure in cases of acute exacerbations. In addition, fluid restriction may be warranted in cases of severe hyponatraemia. However, it would be of importance to advise the patient to keep a daily intake/output balance at home. Patients are advised to monitor their weight daily and to immediately contact their healthcare provider if a specified change in weight occurs.

Heart failure patients need continuous and close monitoring of their health. A variety of programmes have been shown to decrease morbidity and re-hospitalisation in this context, including home nursing, telephone advice/triage, telemedicine services, and specialised heart failure-clinic-based care.

Exercise training has also been shown to be beneficial.[91] [92] [93]

adjunct diuretic

Treatment recommended for SOME patients in selected patient group

Primary options

- furosemide: 20-80 mg/dose orally initially, increase by 20-40 mg/dose increments every 6-8 hours according to response, maximum 600 mg/day

OR

- bumetanide: 0.5 to 1 mg orally once or twice daily initially, increase according to response, maximum 10 mg/day

OR

This PDF of the BMJ Best Practice topic is based on the web version that was last updated: Jan 08, 2019. BMJ Best Practice topics are regularly updated and the most recent version of the topics can be found on bestpractice.bmj.com. Use of this content is subject to our disclaimer © BMJ Publishing Group Ltd 2020. All rights reserved.
### Acute

- **torasemide**: 5-20 mg orally once daily initially, increase according to response, maximum 40 mg/day

  OR

- **chlorothiazide**: 250-500 mg orally once or twice daily, maximum 1000 mg/day

  OR

- **hydrochlorothiazide**: 25 mg orally once or twice daily, increase according to response, maximum 200 mg/day

  OR

- **indapamide**: 2.5 to 5 mg orally once daily

  OR

- **metolazone**: 2.5 to 20 mg orally once daily

### Secondary options

- **amiloride**: 5-20 mg orally once daily

  OR

- **triamterene**: 50-100 mg orally twice daily initially, increase according to response, maximum 300 mg/day

**Diuretics should be considered for patients who have evidence of, or a prior history of, fluid retention.**[2] They should generally be combined with an ACE inhibitor and a beta-blocker. All patients with symptoms and signs of congestion should receive diuretics, irrespective of the left ventricular ejection fraction (LVEF).

**Loop diuretics used for the treatment of heart failure and congestion include furosemide, bumetanide, and torasemide. The most commonly used agent appears to be furosemide, but some patients may respond more favourably to other loop diuretics. In resistant cases, loop diuretics should be combined with a thiazide diuretic (e.g., chlorothiazide, hydrochlorothiazide) or a thiazide-like diuretic (e.g., metolazone, indapamide). Careful monitoring of renal function and electrolytes is essential in these patients.**

**The minimum dose of diuretic should be used to relieve congestion, keep the patient...**
### Acute

asymptomatic, and maintain a dry weight. In patients with stable congestive heart failure, loop diuretics are the preferred agent. In patients with hypertension and only mild fluid retention, a thiazide diuretic may be considered.

» Diuretics produce symptomatic benefits more rapidly than any other drug for heart failure. They can relieve pulmonary and peripheral oedema within hours or days. Few patients with heart failure and fluid retention can maintain sodium balance without the use of diuretic drugs.[159]

» Diuretics alone are unable to maintain the clinical stability of patients with heart failure for long periods of time,[159] but the risk of clinical decompensation can be reduced when they are combined with an ACE inhibitor and a beta-blocker.[160] Diuretics should be used only in combination with an ACE inhibitor (or an angiotensin-II receptor antagonist), a beta-blocker, and an aldosterone antagonist in patients with reduced LVEF.

» In intermediate-term studies, diuretics have been shown to improve cardiac function, symptoms, and exercise tolerance in patients with heart failure.[159] [161]

» There have been no long-term studies of diuretic therapy in heart failure; therefore, their effects on morbidity and mortality are not known.

» Amiloride and triamterene (potassium-sparing diuretics) should be used with caution with aldosterone antagonists, because of the increased risk of developing hyperkalaemia. Close monitoring of serum potassium levels is suggested in this situation.

<table>
<thead>
<tr>
<th>adjunct</th>
<th>aldosterone antagonist</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment recommended for SOME patients in selected patient group</td>
<td></td>
</tr>
</tbody>
</table>

### Primary options

- **spironolactone**: 25-100 mg orally once daily

OR

- **eplerenone**: 25-50 mg orally once daily

» Aldosterone antagonists, also known as mineralocorticoid receptor antagonists (e.g., spironolactone and eplerenone), decrease the morbidity and mortality associated with symptomatic chronic heart failure.
Chronic congestive heart failure

**Acute**

» Aldosterone antagonists are recommended in patients with New York Heart Association class II to IV heart failure who have left ventricular ejection fraction (LVEF) of 35% or less, unless contraindicated. They are also recommended to reduce mortality and morbidity following acute myocardial infarction in patients with LVEF of 40% or less who develop symptoms of heart failure or have a history of diabetes mellitus, unless contraindicated.

» Aldosterone antagonists should be initiated after titration of standard medical therapy. Spironolactone and eplerenone can both cause hyperkalaemia, and precautions should be taken to minimise the risk.

» These agents should be used with caution in patients with renal dysfunction and hyperkalaemia. They should not be initiated in patients with a serum creatinine above 221 micromols/L (>2.5 mg/dL) or a serum potassium above 5.0 millimols/L (>5.0 mEq/dL) and should be used with caution in patients with serum creatinine below 221 micromols/L (<2.5 mg/dL) plus a serum potassium above 5.0 millimols/L (>5.0 mEq/dL). Patients should discontinue potassium repletion.

» Adherence to intensive monitoring of renal function and potassium levels has been shown to prevent hyperkalaemia, which is as likely to occur with eplerenone therapy as it is with spironolactone therapy.

» Amiloride and triamterene (potassium-sparing diuretics) should be used with caution with aldosterone antagonists, because of the increased risk of developing hyperkalaemia. Close monitoring of serum potassium levels is suggested in this situation.

**adjunct hydralazine + isosorbide dinitrate**

Treatment recommended for SOME patients in selected patient group

**Primary options**

» **isosorbide dinitrate**: 20-40 mg orally (immediate-release) three times daily
  -and-
  » **hydralazine**: 10-100 mg orally three times daily

OR

» **isosorbide dinitrate/hydralazine**: 20 mg (isosorbide dinitrate)/37.5 mg (hydralazine)
### Acute

<table>
<thead>
<tr>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute orally three times daily, maximum 40 mg (isosorbide dinitrate)/75 mg (hydralazine) three times daily</td>
</tr>
</tbody>
</table>

» The combined use of hydralazine and isosorbide dinitrate may be considered as a therapeutic option in patients who are intolerant of ACE inhibitors and angiotensin-II receptor antagonists. A combination of hydralazine and isosorbide dinitrate can be useful to reduce morbidity or mortality in patients with current or prior symptomatic heart failure with reduced ejection fraction (HFrEF) who cannot be given an ACE inhibitor or angiotensin-II receptor antagonist because of drug intolerance, hypotension, or renal insufficiency, unless contraindicated. The American College of Cardiology Foundation/American Heart Association guidelines recommend the combination of hydralazine and isosorbide dinitrate to “reduce morbidity and mortality in patients self-described as African Americans with NYHA class III to IV HFrEF receiving optimal therapy with ACE inhibitors and beta blockers, unless contraindicated”.

» Nitrate therapy may decrease symptoms of dyspnoea at night and during exercise and may improve exercise tolerance in patients who have persistent limitations despite optimisation of other therapies.

» Development of nitrate tolerance seems to be minimised by prescription of a nitrate-free interval of at least 10 hours. Carvedilol use has been shown to prevent nitrate tolerance in patients with CHF.

» Hydralazine may interfere with the biochemical and molecular mechanisms responsible for the development of nitrate tolerance.

» A combination pill containing 37.5 mg hydralazine and 20 mg isosorbide dinitrate is available, approved specifically for self-identified black patients with CHF.

**adjunct** digoxin

Treatment recommended for SOME patients in selected patient group

**Primary options**

» **digoxin**: 0.125 to 0.5 mg orally once daily

» Digoxin can be beneficial in patients with reduced left ventricular ejection fraction (LVEF), especially those with atrial fibrillation.
### Acute

- When added to ACE inhibitors, beta-blockers, and diuretics, digoxin can reduce symptoms, prevent hospitalisation, control rhythm, and enhance exercise tolerance.

- Digoxin reduces the composite end point of mortality or hospitalisations in ambulatory patients with chronic heart failure with New York Heart Association class III or IV symptoms, LVEF <25%, or cardiothoracic ratio of >55% and should be considered in these patients.[118]

- Digoxin reduces the composite end point of mortality or hospitalisations, but does not reduce all-cause mortality.[118] Digoxin should be used cautiously with plasma level monitoring. One meta-analysis suggests that digoxin use in patients with heart failure is associated with a higher risk of all-cause mortality.[119]

- Overt digitalis toxicity is commonly associated with serum digoxin levels >2.6 nanomols/L (2 nanograms/mL). However, toxicity may occur with lower levels, especially if hypokalaemia, hypomagnesaemia, or hypothyroidism co-exists.[168] [169]

- Low doses (0.125 mg/day or every other day) should be used initially if the patient is over 70 years old, has impaired renal function, or has a low lean body mass.[170]

- Higher doses (e.g., 0.375 to 0.5 mg/day) are rarely used or needed.

- There is no reason to use loading doses of digoxin to initiate therapy.

### adjunct ivabradine

Treatment recommended for SOME patients in selected patient group

#### Primary options

- **ivabradine**: 5 mg orally twice daily initially, may increase to 7.5 mg twice daily after 2 weeks if necessary; adjust dose according to heart rate

- Ivabradine may be an option for patients with New York Heart Association class II, III, or IV heart failure who have a sinus rate >75 beats per minute and an ejection fraction <35%, and who remain symptomatic despite optimal therapy. It can also be used in patients who are unable to take beta-blockers.
### Acute

- Its use should be initiated by a specialist cardiologist and only after a stabilisation period of 4 weeks on optimised standard therapy.[123]

- In a randomised, double-blind, placebo-controlled trial, addition of ivabradine to standard background therapy in patients with stable coronary artery disease without clinical heart failure (no evidence of left ventricular systolic dysfunction in the overall study population, mean ejection fraction was 56.4%) did not improve the outcome. In the subgroup analysis of this study, ivabradine was associated with an increase in the incidence of the primary end point (death from cardiovascular causes or non-fatal myocardial infarction) among patients who had angina of Canadian Cardiovascular Society class II or higher but not among patients without angina or those who had angina of class I. Ivabradine was associated with an increased incidence of bradycardia, QT prolongation, and atrial fibrillation.[121]

**adjunct vasopressin antagonist**

Treatment recommended for SOME patients in selected patient group

**Primary options**

- **tolvaptan**: 15 mg orally once daily initially, increase gradually according to response, maximum 60 mg/day for up to 30 days

- Considered for patients with symptomatic or severe hyponatraemia (<130 mmol/L) and persistent congestion despite standard therapy, to correct hyponatraemia and related symptoms.[2] [124]

**2nd hydralazine + isosorbide dinitrate**

**Primary options**

- **isosorbide dinitrate**: 20-40 mg orally (immediate-release) three times daily

- **hydralazine**: 10-100 mg orally three times daily

- **OR**

  - **isosorbide dinitrate/hydralazine**: 20 mg (isosorbide dinitrate)/37.5 mg (hydralazine) orally three times daily, maximum 40 mg (isosorbide dinitrate)/75 mg (hydralazine) three times daily

- The combined use of hydralazine and isosorbide dinitrate may be considered as a
Chronic congestive heart failure

### Treatment

**Acute**

A therapeutic option in patients who are intolerant of ACE inhibitors and angiotensin-II receptor antagonists.[171] [172] A combination of hydralazine and isosorbide dinitrate can be useful to reduce morbidity or mortality in patients with current or prior symptomatic heart failure with reduced ejection fraction (HFrEF) who cannot be given an ACE inhibitor or angiotensin-II receptor antagonist because of drug intolerance, hypotension, or renal insufficiency, unless contraindicated.[2] The American College of Cardiology Foundation/American Heart Association guidelines recommend the combination of hydralazine and isosorbide dinitrate to “reduce morbidity and mortality in patients self-described as African Americans with NYHA class III to IV HFrEF receiving optimal therapy with ACE inhibitors and beta blockers, unless contraindicated”. [2]

- Nitrate therapy may decrease symptoms of dyspnoea at night and during exercise and may improve exercise tolerance in patients who have persistent limitations despite optimisation of other therapies.[162] [163]
- Development of nitrate tolerance seems to be minimised by prescription of a nitrate-free interval of at least 10 hours.[2] Carvedilol use has been shown to prevent nitrate tolerance in patients with CHF.[164] [165]
- Hydralazine may interfere with the biochemical and molecular mechanisms responsible for the development of nitrate tolerance.[166] [167]

**plus beta-blocker**

Treatment recommended for ALL patients in selected patient group

**Primary options**

- carvedilol: 3.125 mg orally (immediate-release) twice daily initially, increase according to response, maximum 50 mg/day (body weight ≤85 kg) or 100 mg/day (body weight >85 kg)

**Secondary options**

- metoprolol: 12.5 to 200 mg orally (extended-release) once daily

**OR**

- bisoprolol: 1.25 mg orally once daily initially, increase according to response, maximum 10 mg/day
Chronic congestive heart failure

**Treatment**

**Acute**

<table>
<thead>
<tr>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>» nebivolol: 1.25 mg orally once daily initially, increase according to response, maximum 10 mg/day</td>
</tr>
<tr>
<td>» All patients with chronic heart failure receive a beta-blocker, unless there is a contraindication based on bradycardia, reactive airway disease, and unstable or low-output heart failure. [2] [5] [94]</td>
</tr>
<tr>
<td>» Carvedilol seems superior to metoprolol, [156] although there is no evidence of superiority to other beta-blockers. In the SENIORS study, nebivolol, a cardioselective beta-blocker with nitric oxide-mediated vasodilating properties, was found to be an effective and well-tolerated treatment for heart failure in patients aged 70 years or more. [157] Data suggest that initiation with moderate doses of nebivolol is not associated with the adverse haemodynamic effects usually observed with other beta-blockers in patients with heart failure; therefore, a long up-titration period may not be necessary with nebivolol. [158]</td>
</tr>
</tbody>
</table>

**plus** **lifestyle changes**

Treatment recommended for ALL patients in selected patient group

**Primary options**

| » sodium restriction  
| -and-  
| » fluid restriction  
| -and-  
| » weight monitoring  
| -and-  
| » continuous health screening  
| -and-  
| » exercise training |

| Dietary sodium intake is an easily modifiable factor that complements pharmacological therapy for heart failure. Thus the patient and family are advised to follow a daily dietary sodium intake between 2 and 3 g. Further restriction to 1 to 2 g/day may be necessary for patients with advanced symptoms refractory to therapy. |
| Fluid restriction is mostly used as an in-hospital complementary measure in cases of acute exacerbations. In addition, fluid restriction may be warranted in cases of severe hyponatraemia. However, it would be of importance to advise the patient to keep a
### Chronic congestive heart failure

#### Treatment

**Acute**

Daily intake/output balance at home. Patients are advised to monitor their weight daily and to immediately contact their healthcare provider if a specified change in weight occurs.

- Heart failure patients need continuous and close monitoring of their health. A variety of programmes have been shown to decrease morbidity and re-hospitalisation in this context, including home nursing, telephone advice/triage, telemedicine services, and specialised heart failure-clinic-based care.

- Exercise training has also been shown to be beneficial.\[91\] [\[92\] [\[93\]

<table>
<thead>
<tr>
<th>Adjunct</th>
<th>Diuretic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment recommended for SOME patients in selected patient group</td>
<td></td>
</tr>
</tbody>
</table>

**Primary options**

- **Furosemide**: 20-80 mg/dose orally initially, increase by 20-40 mg/dose increments every 6-8 hours according to response, maximum 600 mg/day

  OR

- **Bumetanide**: 0.5 to 1 mg orally once or twice daily initially, increase according to response, maximum 10 mg/day

  OR

- **Torasemide**: 5-20 mg orally once daily initially, increase according to response, maximum 40 mg/day

  OR

- **Chlorothiazide**: 250-500 mg orally once or twice daily, maximum 1000 mg/day

  OR

- **Hydrochlorothiazide**: 25 mg orally once or twice daily, increase according to response, maximum 200 mg/day

  OR

- **Indapamide**: 2.5 to 5 mg orally once daily

  OR
Chronic congestive heart failure

**Treatment**

**Acute**

- **metolazone**: 2.5 to 20 mg orally once daily

**Secondary options**

- **amiloride**: 5-20 mg orally once daily

OR

- **triamterene**: 50-100 mg orally twice daily initially, increase according to response, maximum 300 mg/day

Diuretics should be considered for patients who have evidence of, or a prior history of, fluid retention.[2] They should generally be combined with an ACE inhibitor and a beta-blocker. All patients with symptoms and signs of congestion should receive diuretics, irrespective of the left ventricular ejection fraction (LVEF).

Loop diuretics used for the treatment of heart failure and congestion include furosemide, bumetanide, and torasemide. The most commonly used agent appears to be furosemide, but some patients may respond more favourably to other loop diuretics. In resistant cases, loop diuretics should be combined with a thiazide diuretic (e.g., chlorothiazide, hydrochlorothiazide) or a thiazide-like diuretic (e.g., metolazone, indapamide). Careful monitoring of renal function and electrolytes is essential in these patients.

The minimum dose of diuretic should be used to relieve congestion, keep the patient asymptomatic and maintain a dry weight. In patients with stable congestive heart failure, loop diuretics are the preferred agent. In patients with hypertension and only mild fluid retention, a thiazide diuretic may be considered.

Diuretics produce symptomatic benefits more rapidly than any other drug for heart failure. They can relieve pulmonary and peripheral oedema within hours or days. Few patients with heart failure and fluid retention can maintain sodium balance without the use of diuretic drugs.[159]

Diuretics alone are unable to maintain the clinical stability of patients with heart failure for long periods of time,[159] but the risk of clinical decompensation can be reduced when they are combined with an ACE inhibitor and a beta-blocker.[160] Diuretics should be used only in combination with an ACE inhibitor (or an angiotensin-II receptor antagonist), a beta-blocker, and an aldosterone antagonist in patients with reduced LVEF.
**Acute**

<table>
<thead>
<tr>
<th>adjunc</th>
<th>aldosterone antagonist</th>
</tr>
</thead>
</table>

Treatment recommended for SOME patients in selected patient group

**Primary options**

- **spironolactone**: 25-100 mg orally once daily

**OR**

- **eplerenone**: 25-50 mg orally once daily

**Aldosterone antagonists**, also known as mineralocorticoid receptor antagonists (e.g., spironolactone and eplerenone), decrease the morbidity and mortality associated with symptomatic chronic heart failure.

Aldosterone antagonists are recommended in patients with New York Heart Association class II to IV heart failure who have left ventricular ejection fraction (LVEF) of 35% or less, unless contraindicated.[2] They are also recommended to reduce mortality and morbidity following acute myocardial infarction in patients with LVEF of 40% or less who develop symptoms of heart failure or have a history of diabetes mellitus, unless contraindicated.[2]

Aldosterone antagonists should be initiated after titration of standard medical therapy. Spironolactone and eplerenone can both cause hyperkalaemia, and precautions should be taken to minimise the risk.

These agents should be used with caution in patients with renal dysfunction and hyperkalaemia. They should not be initiated in patients with a serum creatinine above 221 micromols/L (>2.5 mg/dL) or a serum potassium above 5.0 millimols/L (>5.0 mEq/dL) and should be used with caution in patients with serum
**Acute**

Creatinine below 221 micromols/L (<2.5 mg/dL) plus a serum potassium above 5.0 millimols/L (>5.0 mEq/dL). Patients should discontinue potassium repletion.

- Adherence to intensive monitoring of renal function and potassium levels has been shown to prevent hyperkalaemia, which is as likely to occur with eplerenone therapy as it is with spironolactone therapy.

- Amiloride and triamterene (potassium-sparing diuretics) should be used with caution with aldosterone antagonists, because of the increased risk of developing hyperkalaemia. Close monitoring of serum potassium levels is suggested in this situation.

adjunct **digoxin**

Treatment recommended for some patients in selected patient group

**Primary options**

- **digoxin**: 0.125 to 0.5 mg orally once daily

- Digoxin can be beneficial in patients with reduced left ventricular ejection fraction (LVEF), especially those with atrial fibrillation.

- When added to ACE inhibitors, beta-blockers, and diuretics, digoxin can reduce symptoms, prevent hospitalisation, control rhythm, and enhance exercise tolerance.

- Digoxin reduces the composite end point of mortality or hospitalisations in ambulatory patients with chronic heart failure with New York Heart Association class III or IV symptoms, LVEF <25%, or cardiothoracic ratio of >55% and should be considered in these patients.[118]

- Digoxin reduces the composite end point of mortality or hospitalisations, but does not reduce all-cause mortality.[118] One meta-analysis suggests that digoxin use in patients with heart failure is associated with a higher risk of all-cause mortality.[119]

- Overt digitalis toxicity is commonly associated with serum digoxin levels >2.6 nanomols/L (2 nanograms/mL). However, toxicity may occur with lower levels, especially if hypokalaemia, hypomagnesaemia, or hypothyroidism co-exists.[168] [169]

- Low doses (0.125 mg/day or every other day) should be used initially if the patient is over 70
Chronic congestive heart failure

**Treatment**

### Acute

<table>
<thead>
<tr>
<th>Primary options</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>adjunct</strong> ivabradine</td>
</tr>
<tr>
<td>Treatment recommended for SOME patients in selected patient group</td>
</tr>
<tr>
<td><strong>Primary options</strong></td>
</tr>
<tr>
<td>» <strong>ivabradine</strong>: 5 mg orally twice daily initially, may increase to 7.5 mg twice daily after 2 weeks if necessary; adjust dose according to heart rate</td>
</tr>
</tbody>
</table>

- Higher doses (e.g., 0.375 to 0.5 mg/day) are rarely used or needed.
- There is no reason to use loading doses of digoxin to initiate therapy.

<table>
<thead>
<tr>
<th>Primary options</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>adjunct</strong> vasopressin antagonist</td>
</tr>
<tr>
<td>Treatment recommended for SOME patients in selected patient group</td>
</tr>
</tbody>
</table>

- Its use should be initiated by a specialist cardiologist and only after a stabilisation period of 4 weeks on optimised standard therapy.[123]

- In a randomised, double-blind, placebo-controlled trial, addition of ivabradine to standard background therapy in patients with stable coronary artery disease without clinical heart failure (no evidence of left ventricular systolic dysfunction in the overall study population, mean ejection fraction was 56.4%) did not improve the outcome. In the subgroup analysis of this study, ivabradine was associated with an increase in the incidence of the primary end point (death from cardiovascular causes or non-fatal myocardial infarction) among patients who had angina of Canadian Cardiovascular Society class II or higher but not among patients without angina or those who had angina of class I. Ivabradine was associated with an increased incidence of bradycardia, QT prolongation, and atrial fibrillation.[121]
### Acute

<table>
<thead>
<tr>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>tolvaptan</strong>: 15 mg orally once daily initially, increase gradually according to response, maximum 60 mg/day for up to 30 days</td>
</tr>
</tbody>
</table>

» Considered for patients with symptomatic or severe hyponatraemia (<130 mmol/L) and persistent congestion despite standard therapy, to correct hyponatraemia and related symptoms. [2] [124]
Chronic congestive heart failure

### Treatment

**Ongoing refractory to optimal medical treatment**

- **LVEF <35%: no left bundle-branch block**
  - 1st implantable cardiac defibrillator (ICD)
    - An ICD is recommended in the following cases:[2]
      - 1) For primary prevention of sudden cardiac death in selected patients with both non-ischaemic and ischaemic heart failure, at least 40 days post myocardial infarction, New York Heart Association (NYHA) class II or III symptoms on guideline-directed medical therapy, and expected to live for >1 year
      - 2) As secondary prevention to prolong survival in patients with current or prior symptoms of heart failure and reduced left ventricular ejection fraction (LVEF) who have a history of cardiac arrest, ventricular fibrillation, or haemodynamically destabilising ventricular tachycardia
      - 3) Asymptomatic patients with an LVEF less than or equal to 30% who are in NYHA functional class I with chronic optimal medical therapy and who have a reasonable expectation of survival with good functional status for more than 1 year.
    - Patients with refractory end-stage disease who already carry an ICD may want to receive information about the option to inactivate defibrillation.
  - 2nd cardiac transplantation
    - Cardiac transplantation is an option for refractory end-stage disease. Before a patient is considered to have refractory end-stage disease, the accuracy of the diagnosis should be confirmed, any contributing conditions should be identified, and all conventional medical strategies should have been optimally employed.

- **LVEF <30%: left bundle-branch block**
  - 1st cardiac re-synchronisation therapy (CRT) with biventricular pacemaker
    - CRT is a therapeutic approach in which simultaneous electrical activation of both the right and left ventricles with a biventricular pacemaker device decreases dyssynchronous contraction. This approach enhances ventricular contraction and reduces the degree of functional mitral regurgitation.
Ongoing

- The US Food and Drug Administration approved the use of CRT devices for patients with New York Heart Association class II heart failure, a left ventricular ejection fraction (LVEF) <30%, left bundle-branch block, and QRS width >130 milliseconds. Long-term data from the REVERSE study suggest that improvements in left ventricular function and remodelling can be sustained for over 5 years.[152] [153]

- CRT decreases hospitalisation and, when combined with an implantable defibrillator, significantly reduces mortality.[131] [132] [133] [134] [135] [136]

- In patients who have conduction delay and left ventricular dysfunction, biventricular pacemakers have been shown to improve exercise tolerance and quality of life while decreasing morbidity and mortality.[131] [132] [133] [134] [136] [137] [138] [139]

- Recommendations for the use of CRT devices in heart failure are detailed in the 2013 American College of Cardiology/American Heart Association guidelines.[2]

2nd cardiac transplantation

- Cardiac transplantation is an option for refractory end-stage disease. Before a patient is considered to have refractory end-stage disease, the accuracy of the diagnosis should be confirmed, any contributing conditions should be identified, and all conventional medical strategies should have been optimally employed.
**Emerging**

**Calcium-sensitising agents**

Levosimendan, a novel calcium sensitisier, improves myocardial contractility without causing an increase in myocardial oxygen demand. Its role in acute, decompensated heart failure is more established than in chronic heart failure, but it may reduce overall mortality and time in hospital.\(^{[173]}\) In the LIDO study, levosimendan improved survival and haemodynamic performance more effectively than dobutamine, in patients with severe, low-output heart failure.\(^{[174]}\) The superiority of levosimendan over dobutamine in improving central haemodynamics and left ventricular performance seems in part to be related to its anti-inflammatory and anti-apoptotic effects.\(^{[175]}\)

**n-3 polyunsaturated fatty acids (n3-PUFA)**

The GISSI-HF trial showed that the addition of n3-PUFA produced a small improvement in mortality and hospital admissions in patients with heart failure.\(^{[176]}\) However, a 2012 meta-analysis has shown insufficient evidence of a secondary preventive effect of omega-3 fatty acid supplements against overall cardiovascular events among patients with a history of cardiovascular disease.\(^{[177]}\) Omega-3 PUFA supplementation is reasonable to use as adjunctive therapy in patients with New York Heart Association class II to IV symptoms and heart failure, unless contraindicated, to reduce mortality and cardiovascular hospitalisations.

**Statins**

Statins are not beneficial as adjunctive therapy when prescribed solely for treatment of heart failure in the absence of other indications for their use.\(^{[2]}\) Statin therapy has been broadly implicated in prevention of adverse cardiovascular events, including new-onset heart failure. Originally designed to lower cholesterol in patients with cardiovascular disease, statins are known to have beneficial effects on inflammation, oxidative stress, and vascular performance. To date, a sufficient body of evidence does not exist to support the primary prescribing of statins for the treatment of heart failure to improve clinical outcomes.\(^{[2]}\)

**Non-specific immunomodulation therapy**

Inflammatory mediators are proposed to play a role in heart failure development and progression. In the ACCLAIM trial, non-specific immunomodulation therapy reduced the risk of hospitalisation or death, suggesting that this therapy may be of benefit in heart failure patients.\(^{[178]}\)

**Recombinant human growth hormone**

Preliminary studies suggest that recombinant human growth hormone may have beneficial effects in patients with left ventricular dysfunction, although it may produce an increased risk of arrhythmias.\(^{[179]}\)\(^{[180]}\) Further studies are required to determine the safety and efficacy of this treatment.

**Trimetazidine**

In a meta-analysis, trimetazidine, which shifts energy production from fatty acid oxidation to glucose oxidation, was shown to have no effect on mortality, but it improves left ventricular ejection fraction (LVEF) and functional class.\(^{[181]}\)

**Stem-cell therapy**

Some trials of stem-cell therapy in both ischaemic and non-ischaemic heart failure have shown some potential benefit.\(^{[182]}\) A systematic review on the use of stem-cell therapy for chronic ischaemic heart disease and congestive heart failure suggests that at both short- and long-term follow-up (≥12 months) the use of autologous bone marrow stem-cell treatment reduces all-cause mortality, although the quality of evidence is low.\(^{[183]}\)

**Gene therapy**
Chronic congestive heart failure

TREATMENT

An attractive strategy for treatment of heart failure is by gene therapy.[184] In a small randomised study of patients (n=56) with heart failure and LVEF <40%, intracoronary delivery of adenovirus 5 encoding adenyl cyclase 6 (Ad5.hAC6), increased the LVEF at 4 weeks, with no increase in exercise duration.[185] In a larger double-blind placebo-controlled study (n=250), intracoronary infusion of $1 \times 10^{13}$ DNase-resistant particle of adeno-associated virus 1 (AAV1) / sarcoplasmic endoplasmic reticulum Ca2-ATPase (SERCA2a) did not improve the clinical course of patients with heart failure and reduced ejection fraction (ejection fraction ≤35%).[186]

Supportive mechanical assist devices

The use of mechanical circulatory assist devices in end-stage heart failure is an area of intense investigation. In patients with severe heart failure, prolonged unloading of the myocardium with the use of a left ventricular assist device has been reported to lead to myocardial recovery in small numbers of patients for varying periods of time. Extracorporeal devices can be used for short-term circulatory support in patients who are expected to recover from a major cardiac insult (e.g., myocardial ischaemia, post-cardiotomy shock, or fulminant myocarditis). Left ventricular assist devices provide similar degrees of haemodynamic support; many are implantable and thus allow for long-term support, patient ambulation, and hospital discharge.[187] Most clinical experience with these devices has been derived from their use as a ‘bridge-to-transplantation therapy’.[187] [188] [189] [190] [191] [192] [193] [194] [195] [196] [197] The REMATCH trial established the efficacy of device therapy as permanent or ‘destination’ therapy in selected non-transplant-eligible patients.[198] However, device-related adverse events are numerous, including bleeding, infection, thromboembolic events, and device failure.[199] [200] [201] In the US, the Food and Drug Administration issued an alert about serious adverse events associated with left ventricular assist devices. These adverse events include an increased rate of pump thrombosis (blood clots inside the pump) and a high rate of stroke. Improvements in newer generations of devices will hopefully permit even further prolongation of survival. Presently, destination device therapy is anticipated to benefit those patients predicted to have a 1-year survival of less than 50%, such as those not eligible for transplant, requiring continuous intravenous inotropic infusions. Some reports have suggested that prolonged mechanical decompression of the failing heart may occasionally be followed by sufficient recovery of myocardial function to allow explantation of the device.[202] [203] The use of continuous haemodynamic monitoring to guide care has also been investigated but requires further evaluation.[204] [205]

Surgical strategies

There have been numerous reports of alternate surgical approaches for the treatment of end-stage heart failure.[206] Mitral valve repair or replacement has been shown to improve clinical status in patients who have a clinically important degree of mitral regurgitation that is secondary to left ventricular dilation.[207] However, no controlled studies have evaluated the effects of this procedure on ventricular function, re-hospitalisations, or survival. One single-centre study designed to assess the effects of mitral valve annuloplasty on mortality in patients with mitral regurgitation and left ventricular systolic dysfunction failed to demonstrate any clear survival benefit.[208] A variant of the aneurysmectomy procedure is now being developed for the management of patients with ischaemic cardiomyopathy, but its role in the management of heart failure remains to be defined.[209] None of the current surgical reconstruction techniques offer ‘rescue therapy’ to patients with critical haemodynamic compromise.
Monitoring

Patients benefit from frequent formal evaluation in a specialised centre or monitoring in a management programme.[2] Assessment should be made at each visit of the ability of a patient to perform routine and desired activities of daily living. Assessment should be also made of the fluid status and weight of the patient. Careful history of current use of alcohol, tobacco, illicit drugs, alternative therapies, and chemotherapy drugs, as well as diet and sodium intake, should be obtained at each visit. Repeat measurement of ejection fraction and assessment of the severity of structural remodelling can provide useful information in patients with heart failure who have had a change in clinical status, or who have experienced or recovered from a clinical event, or received treatment that might have had a significant effect on cardiac function. The value of serial measurements of B-type natriuretic peptide to guide therapy for patients is still not well established. Data suggest that natriuretic-guided therapy reduces hospitalisation due to heart failure and that in patients younger than 75 years of age, it also provides a survival benefit.[238] However, one randomised trial found that in high-risk patients with heart failure, natriuretic-guided therapy was not more effective than optimal medical therapy alone in improving outcomes.[239] The use of telemonitoring to monitor patients remotely is an emerging strategy but requires further evaluation.[240] [241] [242]

Wireless pulmonary haemodynamic monitoring in patients with chronic heart failure results in significant reduction in heart failure hospitalisations.[243]

Structured telephone support and non-invasive home telemonitoring can reduce the risk of mortality and heart failure-related hospitalisations.[244]

Invasive haemodynamic monitoring, however, is not routinely used in clinical practice, but may be of use in individual patients, particularly those with recurrent heart failure.

In one study of patients with New York Heart Association class III heart failure, wireless implantable haemodynamic monitoring compared with control led to a significant reduction of heart failure-related hospitalisations.[243]

Exercise training and rehabilitation

• In patients with heart failure, cardiac rehabilitation and exercise training improves exercise tolerance and quality of life with decreased morbidity and mortality.[245] Patients with stable heart failure are therefore encouraged to do regular aerobic exercise and it is recommended that they are enrolled in a multidisciplinary care management programme.[1] One consensus paper provides a detailed description of exercise training in heart failure.[246]

Patient instructions

On discharge from hospital, patients should be instructed on:

• Daily home weight monitoring
• Sodium restriction (2 g to 3 g daily) and fluid restriction when necessary
• Tobacco and alcohol discontinuation
• Aggressive control of hypertension and diabetes (e.g., provide patients with blood pressure and HbA1c goal)
• Lipid management (e.g., provide leaflets and show website links for diet, exercise, and healthy lifestyle)
• Regular, symptom-limited exercise
• Routine health-care maintenance.
Complications

<table>
<thead>
<tr>
<th>Complications</th>
<th>Timeframe</th>
<th>Likelihood</th>
</tr>
</thead>
<tbody>
<tr>
<td>pleural effusion</td>
<td>long term</td>
<td>high</td>
</tr>
<tr>
<td>chronic renal insufficiency</td>
<td>long term</td>
<td>medium</td>
</tr>
<tr>
<td>anaemia</td>
<td>long term</td>
<td>medium</td>
</tr>
<tr>
<td>acute decompensation of chronic heart failure</td>
<td>variable</td>
<td>high</td>
</tr>
</tbody>
</table>

Pleural effusions are a common complication of chronic congestive heart failure.

A common reason for refractory symptoms is the cardiorenal syndrome, in which renal function declines progressively as a result of therapy aimed at reducing congestive symptoms of heart failure. These patients show an impaired response to diuretics and ACE inhibitors and are at increased risk of adverse effects during treatment with digoxin.[221] [222] [223] Persistent or progressive renal functional impairment has been associated with a poor prognosis.[224] [225] The symptoms of heart failure in patients with end-stage renal disease may be exacerbated by an increase in loading conditions produced both by anaemia and by fistulas implanted to permit dialysis.[226] Most patients will tolerate mild-to-moderate degrees of functional renal impairment without difficulty. However, if the serum creatinine increases to more than 265 micromols/L (>3 mg/dL), the renal insufficiency can severely limit the efficacy and enhance the toxicity of established treatments.[221] [227] Impaired renal function may exclude the therapeutic use of ACE inhibitors and angiotensin-II receptor antagonists. In patients with a serum creatinine greater than 442 micromols/L (>5 mg/dL), haemofiltration or dialysis may be needed to control fluid retention, minimise the risk of uraemia, and allow the patient to respond to and tolerate the drugs routinely used for the management of heart failure.[228] [229] [230] [231]

Patients with heart failure frequently have anaemia for a variety of reasons, which may worsen heart failure symptoms. Several studies have demonstrated worse outcomes in patients with heart failure and anaemia, such as a 1.027 higher risk for mortality associated with a 1% lower haematocrit, after adjustment for other factors.[232] [233] It is unclear whether anaemia is the cause of decreased survival or a marker of more severe disease. Several small studies have suggested benefit from use of erythropoietin and iron for treatment of mild anaemia in heart failure, although at the cost of increased risk of thromboembolic events.[234] [235] [236] However, a larger study showed no clinical benefit of darbepoietin alfa treatment.[237]

Despite optimal treatment, many precipitating factors or even new events may cause acute decompensation of a previously stable patient, thus leading to pulmonary oedema (backward failure) or cardiogenic shock (forward failure). Common causes include myocardial infarction and its mechanical complications (papillary muscle rupture with new-onset acute mitral regurgitation, ventricular septal defect, and ventricular rupture), arrhythmias, pulmonary embolism, infection, anaemia, tamponade, myocarditis, acute renal failure or even increased salt intake, inappropriate drug therapy, or patient non-compliance.

Patients with acute decompensation require urgent haemodynamic stabilisation and diagnosis of the precipitating cause. Pharmacological therapy includes intravenous diuretics (furosemide, torasemide, bumetanide), intravenous positive inotropic agents (dobutamine, milrinone, enoximone), intravenous vasodilators (nitroprusside, glyceryl trinitrate, nesiritide), and intravenous vasopressors (dopamine, vasopressin). Non-pharmacological treatment modalities will be necessary - these include oxygenation, balloon counterpulsation, pacing, urgent catheterisation or urgent cardiac surgery, or mechanical support with ventricular assist devices.
Complications | Timeframe | Likelihood
---|---|---
acute renal failure | variable | high

Patients have a high risk of developing acute renal insufficiency at any point of their clinical course as a result of either poor renal perfusion (low cardiac output state) or drug overuse to treat heart failure (diuretics, ACE inhibitors, aldosterone antagonists, angiotensin-II receptor antagonists). In addition, the use of carvedilol requires close monitoring of the renal function as it could contribute, with other agents, to the development of acute renal injury. Inability to maintain adequate renal perfusion on oral therapy may eventually necessitate IV inotropic infusion or urgent ultrafiltration and haemodialysis.

sudden cardiac death | variable | medium

Sudden cardiac death is common in heart failure patients and accounts for approximately 30% to 40% of the deaths among these patients. It can be the consequence of both ventricular fibrillation and electromechanical dissociation, and can occur any time in the course of the disease, even in the asymptomatic patient.

In patients who survive an episode of cardiac arrest, prophylactic insertion of an implantable cardioverter defibrillator and initiation of appropriate anti-arrhythmic therapy is indicated.

Prognosis

The evaluation of a patient would be incomplete without an initial and periodic assessment of short- and long-term prognosis. However, the likelihood of survival can be determined reliably only in populations and not in individual patients. Numerous factors have been used as prognostic indicators, including demographics (age, sex, race), symptoms (New York Heart Association [NYHA] classification), comorbidities (hypertension, diabetes, cachexia, anaemia, and renal and hepatic dysfunction), and objective clinical parameters (e.g., ejection fraction, left ventricular size, volume, mass and shape, exercise capacity, and serum levels of sodium, noradrenaline [norepinephrine], renin, B-type natriuretic peptide, uric acid, angiotensin II, aldosterone, tumour necrosis factor-alpha, endothelin). Multi-variate analysis of these variables has helped to identify the most significant predictors of survival, and prognostic models have been developed and validated.[210] [211] [212] [213] [214] [215] [216] [217] However, all existing models to predict the risk of death or need for urgent transplantation have features that may limit their applicability. Haemoglobin A1c was also found to be an independent progressive risk factor for cardiovascular death, hospitalisation, and mortality, even in non-diabetic patients.[218]

The most comprehensive prognostic model is the Seattle Heart Failure Model. [The Seattle Heart Failure Model] This model has been implemented as an interactive programme that employs the Seattle Heart Failure Score to estimate mean, 1-, 2-, and 5-year survival and the benefit of adding medicines and/or devices for an individual patient.[212]

Despite standard medical therapy the survival for patients with end-stage heart failure is poor.

Despite optimal medical therapy including cardiac re-synchronisation therapy, only 65% of patients in NYHA class 4 are alive at a mean follow-up of 17 months.[219]

The 5-year survival in patients with stage D heart failure is only 20%. [220]
## Diagnostic guidelines

### Europe

**Chronic heart failure in adults: diagnosis and management**

*Published by:* National Institute for Health and Care Excellence  
*Last published:* 2018

**Management of chronic heart failure**

*Published by:* Scottish Intercollegiate Guidelines Network  
*Last published:* 2016

**2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure**

*Published by:* European Society of Cardiology  
*Last published:* 2016

### North America

**2017 comprehensive update of the Canadian Cardiovascular Society guidelines for the management of heart failure**

*Published by:* Canadian Cardiovascular Society  
*Last published:* 2017

**2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure**

*Published by:* American College of Cardiology; American Heart Association; Heart Failure Society of America  
*Last published:* 2017

**2013 ACCF/AHA guideline for the management of heart failure**

*Published by:* American College of Cardiology Foundation; American Heart Association  
*Last published:* 2013

**National Academy of Clinical Biochemistry Laboratory Medicine practice guidelines: clinical utilization of cardiac biomarker testing in heart failure**

*Published by:* National Academy of Clinical Biochemistry  
*Last published:* 2007

**Detection of chronic kidney disease in patients with or at increased risk of cardiovascular disease**

*Published by:* American Heart Association  
*Last published:* 2006

### Oceania

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

*Published by:* National Heart Foundation of Australia; Cardiac Society of Australia and New Zealand  
*Last published:* 2018
## Treatment guidelines

### Europe

<table>
<thead>
<tr>
<th>Topic</th>
<th>Published by</th>
<th>Last published</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chronic heart failure in adults: diagnosis and management</strong></td>
<td>National Institute for Health and Care Excellence</td>
<td>2018</td>
</tr>
<tr>
<td><strong>Cardiac arrythmias in coronary heart disease</strong></td>
<td>Scottish Intercollegiate Guidelines Network</td>
<td>2018</td>
</tr>
<tr>
<td><strong>2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure</strong></td>
<td>European Society of Cardiology</td>
<td>2016</td>
</tr>
<tr>
<td><strong>Management of chronic heart failure</strong></td>
<td>Scottish Intercollegiate Guidelines Network</td>
<td>2016</td>
</tr>
<tr>
<td><strong>European Resuscitation Council guidelines for resuscitation 2015</strong></td>
<td>European Resuscitation Council</td>
<td>2015</td>
</tr>
<tr>
<td><strong>Implantable cardioverter defibrillators and cardiac resynchronisation therapy for arrhythmias and heart failure</strong></td>
<td>National Institute for Health and Care Excellence</td>
<td>2014</td>
</tr>
</tbody>
</table>
## North America

### Physical activity guidelines for Americans
*Published by:* US Department of Health and Human Services  
*Last published:* 2018

### 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure
*Published by:* American College of Cardiology; American Heart Association; Heart Failure Society of America  
*Last published:* 2017

### ACC/AATS/AHA/ASE/ASNC/SCAI/SCCT/STS 2017 appropriate use criteria for coronary revascularization in patients with stable ischemic heart disease
*Published by:* American College of Cardiology; American Association for Thoracic Surgery; American Heart Association; American Society of Echocardiography; American Society of Nuclear Cardiology; Society for Cardiovascular Angiography and Interventions; Society of Cardiovascular Computed Tomography; Society of Thoracic Surgeons  
*Last published:* 2017

### 2017 comprehensive update of the Canadian Cardiovascular Society guidelines for the management of heart failure
*Published by:* Canadian Cardiovascular Society  
*Last published:* 2017

### Heart failure evidence-based nutrition practice guideline
*Published by:* Academy of Nutrition and Dietetics  
*Last published:* 2017

### ACC/AATS/AHA/ASE/ASNC/SCAI/SCCT/STS 2016 appropriate use criteria for coronary revascularization in patients with acute coronary syndromes
*Published by:* American College of Cardiology; American Association for Thoracic Surgery; American Heart Association; American Society of Echocardiography; American Society of Nuclear Cardiology; Society for Cardiovascular Angiography and Interventions; Society of Cardiovascular Computed Tomography; Society of Thoracic Surgeons  
*Last published:* 2016

### Chronic heart failure - diagnosis and management

#### 2013 ACCF/AHA guideline for the management of heart failure
*Published by:* American College of Cardiology Foundation; American Heart Association  
*Last published:* 2013

#### 2012 ACCF/AHA/HRS focused update incorporated into the ACCF/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities
*Published by:* American College of Cardiology Foundation; American Heart Association  
*Last published:* 2012

### Indications for cardiac resynchronization therapy
*Published by:* Heart Failure Society of America Guideline Committee  
*Last published:* 2012
### North America

**Task force 8: training in heart failure**

*Published by:* Heart Failure Society of America  
*Last published:* 2008

### Oceania

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

*Published by:* National Heart Foundation of Australia; Cardiac Society of Australia and New Zealand  
*Last published:* 2018

**Physical activity in patients with cardiovascular disease: management algorithm and information for general practice**

*Published by:* National Heart Foundation of Australia  
*Last published:* 2006
Online resources

1. The Seattle Heart Failure Model (external link)
Key articles


References


108. European Medicines Agency. PRAC recommends against combined use of medicines affecting the renin-angiotensin (RAS) system. Apr 2014 [internet publication]. Full text


Chronic congestive heart failure


Chronic congestive heart failure

References


Abstract
Disclaimer

This content is meant for medical professionals situated outside of the United States and Canada. The BMJ Publishing Group Ltd ("BMJ Group") tries to ensure that the information provided is accurate and up-to-date, but we do not warrant that it is nor do our licensors who supply certain content linked to or otherwise accessible from our content. The BMJ Group does not advocate or endorse the use of any drug or therapy contained within nor does it diagnose patients. Medical professionals should use their own professional judgement in using this information and caring for their patients and the information herein should not be considered a substitute for that.

This information is not intended to cover all possible diagnosis methods, treatments, follow up, drugs and any contraindications or side effects. In addition such standards and practices in medicine change as new data become available, and you should consult a variety of sources. We strongly recommend that users independently verify specified diagnosis, treatments and follow up and ensure it is appropriate for your patient within your region. In addition, with respect to prescription medication, you are advised to check the product information sheet accompanying each drug to verify conditions of use and identify any changes in dosage schedule or contraindications, particularly if the agent to be administered is new, infrequently used, or has a narrow therapeutic range. You must always check that drugs referenced are licensed for the specified use and at the specified doses in your region. This information is provided on an "as is" basis and to the fullest extent permitted by law the BMJ Group and its licensors assume no responsibility for any aspect of healthcare administered with the aid of this information or any other use of this information.

View our full Website Terms and Conditions.

Contact us
+ 44 (0) 207 111 1105
support@bmj.com

BMJ
BMA House
Tavistock Square
London
WC1H 9JR
UK
Contributors:

// Authors:

Syed Wamique Yusuf, FACC, FRCPI
Professor of Medicine
Department of Cardiology, University of Texas MD Anderson Cancer Center, Houston, TX
DISCLOSURES: SWY is co-director of the American College of Cardiology annual board review course and in this capacity delivers educational lectures for the board review course.

// Acknowledgements:

Dr Syed Wamique Yusuf would like to gratefully acknowledge Dr Andrew R.J. Mitchell, Dr Grigoris Giamouzis, Dr Sonjoy Raja Laskar, and Dr Javed Butler, the previous contributors to this topic. ARJM, GG, SRL, and JB declare that they have no competing interests.

// Peer Reviewers:

David Leaf, MD, MPH
Professor of Medicine
VA Greater Los Angeles Healthcare System, UCLA School of Medicine, Los Angeles, CA
DISCLOSURES: DL declares that he has no competing interests.

Brian Griffin, MD
Director
Cardiovascular Training Program, Cleveland Clinic, Cleveland, OH
DISCLOSURES: BG declares that he has no competing interests.

Abdallah Al-Mohammad, MD, FRCP(Edin.), FRCP(Lond.)
Consultant Cardiologist and Heart Failure Lead
Sheffield Teaching Hospitals NHS Foundation Trust (Northern General Hospital), Sheffield, UK
DISCLOSURES: AAM has accepted hospitality by NOVARTIS in 2008 to attend the American College of Cardiology meeting in Chicago, and had received honoraria for delivering educational talks before 2008. AAM is the co-author of the NICE chronic heart failure partial update of the guideline in 2010, and of several related articles.