

Heart failure

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Although heart failure is common, disabling, and deadly, there are now many effective treatments, at least for patients with low left-ventricular ejection fraction. For all, angiotensin-converting-enzyme inhibitors and β blockers are the essential disease-modifying treatments, improving symptoms, reducing hospital admissions, and increasing survival. Implantable cardioverter defibrillators also improve survival. For patients with persistent symptoms, angiotensin-receptor blockers and aldosterone antagonists have additional benefits. These treatments are now preferred to digoxin, although this drug can still be useful at an earlier stage in patients with atrial fibrillation. In some patients with persistently severe symptoms and a wide QRS on the electrocardiogram, cardiac resynchronisation therapy also reduces mortality and morbidity. The role of other markers of ventricular dyssynchrony is under investigation. There is growing evidence that left-ventricular assist devices are indicated in some patients with end-stage heart failure. Organised delivery of care also improves outcome. However, there is still no firmly evidence-based treatment for heart failure with preserved ejection fraction. Many new pharmacological, device, and surgical treatments for heart failure are currently under evaluation in clinical trials, and other approaches, including stem-cell treatment, are at an earlier stage of investigation.

Heart failure remains one of the most common, costly, disabling, and deadly medical conditions encountered by a wide range of physicians and surgeons in both primary and secondary care. Understanding of its epidemiology, pathophysiology, diagnosis, and, especially, treatment has advanced greatly during the past 20 years and continues to develop rapidly.

Epidemiology

The epidemiology of symptomatic heart failure in more developed countries is well understood (figure 1).^{1–9} Between 1% and 2% of the adult population have heart failure, although it mainly affects elderly people; 6–10% of people over the age of 65 years have the disorder.^{1–10} The lifetime risk of developing heart failure is roughly one in five for a person aged 40 years.^{11,12} The age-adjusted incidence of heart failure has remained stable over the past 20 years,^{13,14} but prevalence is thought to be increasing.¹⁵ Each year, about two individuals per thousand of the adult population are discharged from hospital with heart failure, which accounts for about 5% of all medical and geriatric admissions and is the single most common cause of such admissions in people aged over 65 years.^{16–22} Age at admission (and at death) seems to be increasing, which suggests that preventive treatments are delaying the development of heart failure.^{16–22} Patients discharged from hospital include those who developed heart failure suddenly, de novo, as a consequence of another cardiac event (myocardial infarction in most cases), those presenting for the first time with decompensation of previously unrecognised cardiac dysfunction, and those with established, chronic, heart failure who have suffered worsening of severity sufficient to necessitate hospital admission. Some of these admissions reflect the unavoidable natural progression of heart failure, whereas others might be avoidable (eg, as a result of non-adherence to treatment).²³ After years of steady increase, age-adjusted rates of admission for heart failure seem to have reached a plateau, or even decreased,

though absolute numbers of admissions continue to increase and heart failure is still an enormous burden on health services and cost to society, accounting for about 2% of all health-care spending.^{16–22,24} Even in primary care, heart failure accounts for more consultations than angina, reflecting the limiting symptoms and reduction in well-being experienced by patients with heart failure.²⁵ Indeed, a consistent finding is that quality of life is reduced more by heart failure than by other chronic illnesses.²⁶ Heart failure is deadly as well as disabling. **Community-based surveys show that 30–40% of patients die within a year of diagnosis and 60–70% die within 5 years,** most from worsening heart failure or suddenly (probably because of a ventricular **arrhythmia**).^{10,12,14,27} Thus, a person **living to age 40 years has a one in five risk of developing heart failure** and, once the disorder is apparent, a **one in three chance of dying within a year of diagnosis. Mortality is even higher in patients who need hospital admission, exceeding that of most cancers,** though several recent studies have suggested that prognosis is **improving**.^{17–22,28,29}

Left-ventricular function has also been measured in several population-based echocardiographic studies, permitting estimates of the prevalence of symptomatic heart failure with reduced and preserved systolic function, as well as the prevalence of asymptomatic left-ventricular systolic and diastolic dysfunction (figure 1).^{30–38}

Search strategy and selection criteria

This Seminar is based on a PubMed search for articles with “heart failure” or “cardiac failure” in their titles, as well as reading of other review articles, major guidelines, and book chapters. We prioritised more recently published papers and those published in journals with high impact factors. Owing to space constraints, we could not cite all articles that support statements made. There was no restriction on language or date of publication.

Lancet 2005; 365: 1877–89

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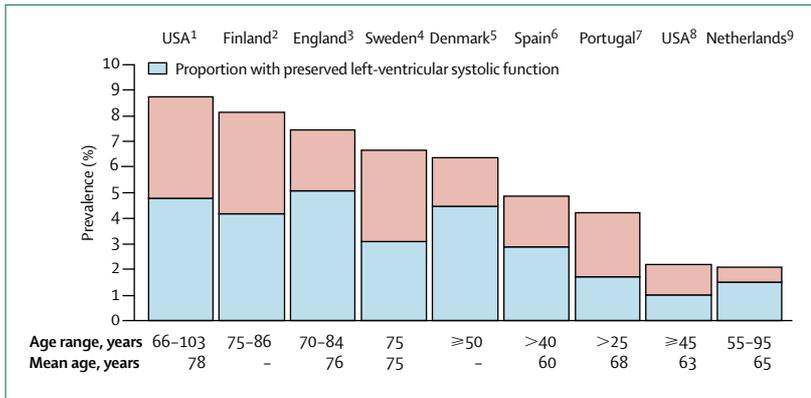


Figure 1: Prevalence of heart failure in cross-sectional population echocardiographic studies and proportion of patients with preserved left-ventricular systolic function

This emerging epidemiological information suggests that roughly half of patients with symptomatic heart failure in the community have reduced systolic function, and half have preserved function.³⁰ The epidemiology of symptomatic heart failure with reduced systolic function differs from that of heart failure with preserved systolic function; patients with preserved function are, on average, older, higher proportions are women or have comorbidity, and they have better age-adjusted survival.^{30–38} The causes of heart failure in patients with preserved systolic function also differ from those with reduced systolic function.^{30–38}

About half of cases of left-ventricular systolic dysfunction are asymptomatic, which raises questions about screening for symptomless cases.³⁹ Recent studies

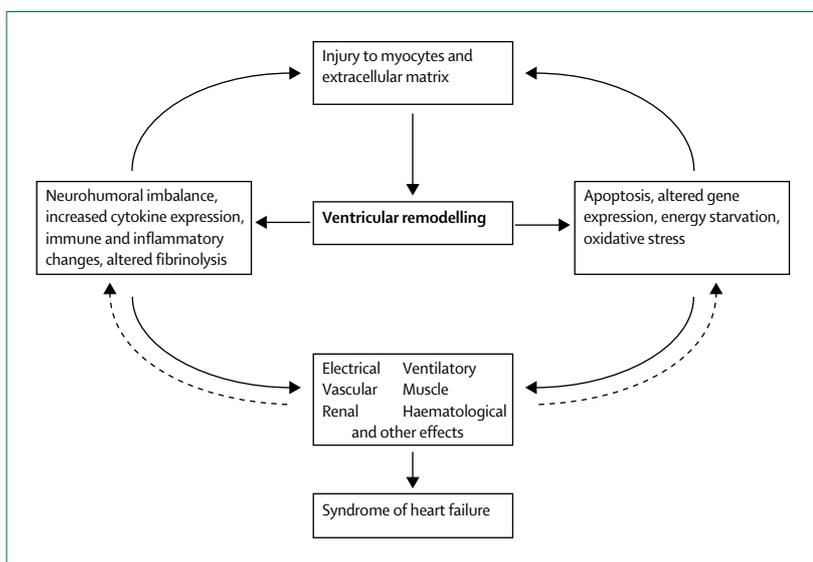


Figure 2: Pathophysiology of heart failure due to left-ventricular systolic dysfunction

Damage to the myocytes and extracellular matrix leads to changes in the size, shape, and function of the left ventricle and heart more generally (“remodelling”). These changes, in turn, lead to electrical instability, systemic processes resulting in many effects on other organs and tissues, and further damage to the heart. These vicious cycles, along with intercurrent events, such as myocardial infarction, are believed to cause progressive worsening of the heart-failure syndrome over time.

have reported varying rates of diastolic dysfunction and proportions of individuals with and without symptoms, and no conclusions can yet be drawn about the epidemiology of asymptomatic diastolic dysfunction.^{30–38,40}

Aetiology and pathophysiology

The syndrome of heart failure arises as a consequence of an abnormality in cardiac structure, function, rhythm, or conduction. In more developed countries, ventricular dysfunction is the commonest underlying problem. It results mainly from myocardial infarction (systolic dysfunction), hypertension (diastolic and systolic dysfunction), or in many cases both. Degenerative valve disease is becoming more common. Other common causes include “idiopathic” dilated cardiomyopathy, some cases of which could have a genetic basis, and alcoholic cardiomyopathy. In other parts of the world, rheumatic valve disease, Chagas’ disease, and endomyocardial fibrosis can cause heart failure.^{41–44} Patients with the rarer and most challenging causes of heart failure to treat are generally excluded from clinical trials.

Whether persisting systolic dysfunction is caused by coronary-artery disease in the absence of infarction is uncertain, as is the corollary—ie, whether reversal of ischaemia and “hibernation” improves systolic function.⁴⁵ The contribution of diabetes to systolic and diastolic dysfunction needs to be elucidated more fully, as does the relation between atrial fibrillation and both types of heart failure.^{46,47} The progression of left-ventricular systolic dysfunction, and the heart-failure syndrome, owing to “remodelling” (as a result of loss of myocytes and maladaptive changes in the surviving myocytes and extracellular matrix), probably occurs in two main ways.^{48–51} One is as a consequence of intercurrent cardiac events (eg, myocardial infarction), and the other as a consequence of the systemic processes activated because systolic function is reduced (eg, neurohumoral pathways).^{52–54} These systemic processes also have detrimental effects on the functioning of the lungs, blood vessels, kidneys, muscles, and probably other organs (eg, the liver) and contribute to a pathophysiological vicious cycle (figure 2).⁵⁴ The molecular, structural, and functional changes in the heart and these systemic processes, coupled with electrolyte imbalances, result in electrical as well as mechanical dysfunction of the heart.^{55,56} Atrial function, synchronised contraction of the left ventricle, and normal interaction between right and left ventricles are also important in preserving stroke volume.^{55,56}

The pathophysiological basis of heart failure with preserved left-ventricular systolic function is not well understood.^{57–60} Many or most of these patients probably have diastolic dysfunction, though this assumption is disputed.^{61,62} Abnormal ventriculoarterial coupling could also be important.⁶³ Whether neurohumoral activation is important is not known, and the part played by reversible myocardial ischaemia and mitral

regurgitation is unclear. The hypothesis that severe hypertension induces transient systolic dysfunction in patients admitted to hospital with this type of heart failure has lately been refuted.⁶⁴

Comorbidity

Heart failure does not occur in isolation. It is caused by an underlying cardiac defect, generally in elderly individuals, many of whom are being treated for other medical problems. Consequently, many patients with heart failure have comorbidity related to the underlying cardiac problem or its cause (eg, angina, hypertension, diabetes, smoking-related lung disease) and age (eg, osteoarthritis), as well as a consequence of heart failure (eg, arrhythmias) and its treatment (eg, gout from diuretics).⁶⁵ Some common comorbidities have many causes (eg, renal dysfunction), whereas others are not fully explained (eg, anaemia, depression, disorders of breathing, and cachexia).⁶⁵⁻⁶⁹ The existence of many comorbidities creates the potential for drug intolerance (eg, inhibitors of angiotensin-converting enzyme [ACE] and renal dysfunction) and drug interactions (eg, non-steroidal anti-inflammatory drugs and ACE inhibitors) and makes the management of heart failure very complex.^{65,70-73} As more patients with heart failure survive longer and progress to more advanced stages, renal failure is becoming one of the most common and difficult to manage comorbidities. Such patients are commonly described as having developed a “cardiorenal syndrome”.

Comorbidity, the key pathophysiological processes in heart failure—left-ventricular remodelling and activation of systemic pathways—and age are the main determinants of prognosis.

Diagnosis

Heart failure can present suddenly, as the consequence of an acute cardiac event such as myocardial infarction, chronically, in most cases in the community to a primary-care physician, or in an acute-on-chronic fashion, when a period of worsening symptoms and signs is followed by an emergency presentation with decompensation. Most of the cardinal symptoms (dyspnoea and fatigue) and signs (peripheral oedema) of heart failure are non-specific, especially in elderly patients, and could be due to other problems, such as chronic lung disease, anaemia, venous insufficiency, renal dysfunction, and hypothyroidism, or concomitant treatments, such as calcium-channel blockers or glitazones.⁷⁴⁻⁷⁶ Other signs, such as raised jugular-venous pressure, cardiomegaly, and a third heart sound, are more specific but much less common and harder to detect.⁷⁴⁻⁷⁶ Even if heart failure is correctly diagnosed on the basis of symptoms and signs, differentiation between preserved and reduced left-ventricular systolic function is still difficult.⁷⁶ Consequently, the diagnosis of heart failure requires investigation. The key

investigations are: echocardiography to demonstrate structural heart disease; electrocardiography (ECG) to show rhythm, rate, and conduction; chest radiography to exclude primary pulmonary disease and identify oedema; blood chemistry; and haematology. As well as providing diagnostic information, each investigation helps to guide treatment—such as surgery for aortic stenosis, anticoagulation for atrial fibrillation, and caution in using an ACE inhibitor in renal dysfunction.⁷⁷⁻⁸¹ There is growing interest in use of MRI in heart failure.⁸²

Heart failure caused by a rhythm or conduction disorder, a valve lesion, or left-ventricular systolic dysfunction is easier to diagnose. Heart failure with preserved systolic function is more difficult; it remains a diagnosis of exclusion owing to lack of agreement on generally applicable, non-invasive measures of diastolic dysfunction.⁸³⁻⁸⁵ Tissue doppler imaging might offer advantages over conventional doppler indices of diastolic function. An underlying cardiac lesion is, however, expected—notably left-ventricular hypertrophy, left-atrial enlargement, or both.

Measurement of the blood concentration of natriuretic peptides secreted by the heart can also help in the diagnosis of heart failure, especially in the acute setting, though there is not absolute agreement on this issue.⁸⁶⁻⁹⁰ Heart failure is an unlikely cause of dyspnoea in an untreated patient with normal concentrations of natriuretic peptides, so echocardiography is unnecessary—ie, these peptides are used as a “rule-out” test. Treatment can return peptide concentrations to normal in some patients. B-type natriuretic peptide (BNP) and N-terminal pro-BNP are more useful than the A-type natriuretic peptides. Other investigations, such as ambulatory ECG monitoring and coronary angiography are generally used selectively to help with the diagnosis and treatment of specific problems such as syncope and angina. Patients for whom devices or surgery (including transplantation) are being considered need additional specialist assessments.

Treatment

An understanding of the pathophysiology and natural history of heart failure underpins the therapeutic approaches used to achieve the goals of treatment, which are to relieve symptoms, to avoid hospital admission, and to prolong life. On the basis of a large number of randomised controlled trials (table 1), drugs are the mainstay of treatment of all patients with heart failure and reduced left-ventricular systolic function. How care is organised and delivered can also influence outcome,⁹¹ and there is some evidence that exercise is beneficial.⁹²⁻⁹⁴ There has lately been intense interest in implantable devices and surgery for selected patients with this type of heart failure. The evidence base for treatments other than drugs, devices, and surgery is poor.

Treatment, trial, and year published	n	Severity of heart failure	Estimated first-year mortality in placebo or control group	Background treatment*	Treatment added	Trial duration (years)	Primary endpoint	Relative risk reduction (%) in primary endpoint	Events prevented per 1000 patients treated†			
									Death	Hospital admission for heart failure	Death or hospital admission for heart failure	
ACE inhibitors												
CONSENSUS 1987	253	End-stage	52.0	Spironolactone	Enalapril 20 mg twice daily	0.54‡	Death	40	146	
SOLVD-T 1991	2569	Mild to severe	15.7	None	Enalapril 10 mg twice daily	3.5	Death	16	45	96	108	
β blockers												
CIBIS-2 1999	2647	Moderate to severe	13.2	ACE-I	Bisoprolol 10 mg once daily	1.3‡	Death	34	55	56	..	
MERIT-HF 1999	3991	Mild to severe	11.0	ACE-I	Metoprolol CR/XL 200 mg once daily	1.0‡	Death	34	36	46	63	
COPERNICUS 2001	2289	Severe	19.7	ACE-I	Carvedilol 25 mg twice daily	0.87‡	Death	35	55	65	81	
Angiotensin-receptor blockers												
Val-HeFT 2001	5010	Mild to severe	~8.0	ACE-I	Valsartan 160 mg twice daily	1.9	Death or morbidity	13	0	35	33§	
CHARM-Alternative 2003	2028	Mild to severe	12.6	BB	Candesartan 32 mg once daily	2.8	Cardiovascular death or hospital admission for heart failure	23	30	78	60	
CHARM-Added 2003	2548	Moderate to severe	10.6	ACE-I+BB	Candesartan 32 mg once daily	3.4	Cardiovascular death or hospital admission for heart failure	15	28	47	39	
Aldosterone blockade												
RALES 1999	1663	Severe	~25	ACE-I	Spironolactone 25–50 mg once daily	2.0‡	Death	30	113	95	..	
Hydralazine and isosorbide dinitrate												
V-HeFT-1 1986	459	Mild to severe	26.4	..	Hydralazine 75 mg three or four times daily; isosorbide dinitrate 40 mg four times daily	2.3	Death	34	52	0	..	
A-HeFT 2004	1050	Moderate to severe	~9.0	ACE-I+BB+spironolactone	Hydralazine 75 mg three times daily; isosorbide dinitrate 40 mg three times daily	0.83‡	Composite	..	40	80	..	
Digitalis glycosides												
DIG 1997	6800	Mild to severe	~11.0	ACE-I	Digoxin	3.1	Death	0	0	79	73	
Cardiac resynchronisation therapy (biventricular pacing)												
COMPANION 2004	925	Moderate to severe	19.0	ACE-I+BB+spironolactone	CRT	1.35‡	Death or any hospital admission	19	38	..	87	
CARE-HF 2005	813	Moderate to severe	12.6	ACE-I+BB+spironolactone	CRT	2.45	Death or cardiovascular hospital admission	37	97	151	184	
Cardiac resynchronisation therapy with device that also defibrillates												
COMPANION 2004	903	Moderate to severe	19.0	ACE-I+BB+spironolactone	CRT-ICD	1.35‡	Death or any hospital admission	20	74	..	114	
Implantable cardioverter defibrillator												
SCD-HeFT 2005	1676	Mild to severe	~7.0	ACE-I+BB	ICD	3.8	Death	23	
Ventricular assist device												
REMATCH 2001	129	End-stage	75	ACE-I+spironolactone	Left-ventricular assist device	1.8	Death	48	282	

Active controlled trials are excluded. ACE-I=ACE inhibitor; BB=β blocker; CRT=cardiac resynchronisation therapy; ICD=implantable cardioverter defibrillator. *In at least a third of patients: ACE-I+BB means ACE inhibitors used in almost all patients and β blockers in the majority. Most patients were also taking diuretics and many digoxin (except in DIG). Spironolactone was used at baseline in 5% Val-HeFT, 8% MERIT-HF, 17% CHARM-Added, 19% SCD-HeFT, 20% COPERNICUS, and 24% in CHARM-Alternative. †Individual trials might not have been designed or powered to assess effect of treatment on these outcomes. Hospital admission means at least one admission for worsening heart failure; some patients had several admissions. ‡Stopped early owing to proven benefit. §Primary endpoint which also included treatment of heart failure with intravenous drugs for 4 h or longer without admission and resuscitated cardiac arrest (both added small numbers).

Table 1: Controlled trials in symptomatic heart failure with reduced systolic function

By contrast, for heart failure with preserved systolic function, to date there have been few clinical trials, so there is no accepted, evidence-based, treatment for patients with this form.^{30–33}

Pharmacological treatment: reduced left-ventricular systolic function

Diuretics are essential for relief of dyspnoea and signs of sodium and water retention; they are needed in virtually all patients with symptomatic heart failure.⁹⁵ They are

best used flexibly and in the minimum dose needed to maintain “dry weight”, to avoid electrolyte disorders (hypokalaemia and hyponatraemia), gout, and renal dysfunction.⁹⁶ In advanced heart failure, high doses of loop diuretics and even the combination of a loop diuretic and a thiazide or thiazide-like diuretic (metolazone) can be needed to maintain dry weight.

ACE inhibitors, by reducing the production of angiotensin II and, possibly, by increasing bradykinin production, exert many biological effects that lead to

improvement in symptoms, fewer admissions to hospital, and prolonged survival in heart failure; as a consequence, they are recommended for all patients with systolic dysfunction (figure 3).^{97–99} The main causes of intolerance are cough, symptomatic hypotension, and renal dysfunction, which is exacerbated by over-diuresis and non-steroidal anti-inflammatory drugs. The specific agents shown to improve outcome in large randomised trials are listed in table 2. For all treatments, including ACE inhibitors, we believe that the best approach is to try to use proven agents in their proven dosing regimen and not to assume a “class effect”.

β blockers probably act to protect the heart from the harmful effects of norepinephrine and epinephrine. The greatest advance in the treatment of heart failure since ACE inhibitors has been the demonstration that the addition of a β blocker, initiated in a low dose and carefully uptitrated—the so-called “start low, go slow” approach—leads to a further and substantial reduction in mortality (by about a third) and morbidity (hospital admissions), as well as an improvement in symptoms and the patient’s well-being.^{100–105} Consequently, the combination of an ACE inhibitor and a β blocker is now the cornerstone of the treatment of patients with reduced left-ventricular systolic function (figure 3, table 2). Intolerance of β blockers is rare and in most cases due to dizziness and bradycardia. Rarely, early worsening of heart failure can occur, but it can generally be managed by reduction in β -blocker dose and temporary increase in diuretic dose.⁹⁶

Angiotensin-receptor blockers (ARB) prevent binding of angiotensin II to its type 1 receptor and are broadly similar to ACE inhibitors in terms of tolerability (with the exception of cough) and clinical outcomes in heart failure. These conclusions are supported by similar findings from a study in patients with heart failure, left-ventricular systolic dysfunction, or both after myocardial infarction.^{106–112} Consequently, a patient with an intolerable cough induced by an ACE inhibitor should be given an ARB instead. Although ARB are also beneficial in patients with other causes of ACE-inhibitor intolerance, use of an ARB in patients with previous hypotension and, especially, hyperkalaemia or renal dysfunction necessitates very careful monitoring.¹⁰⁸

Of more importance, when added to ACE inhibitors in recommended doses (and other treatments for heart failure), an ARB leads to further neurohumoral suppression and greater reverse remodelling of the left ventricle, possibly because blood angiotensin II concentrations remain high or increase despite ACE inhibition.^{113–116} The addition of an ARB to an ACE inhibitor also reduces cardiovascular mortality and hospital admissions for heart failure and improves symptoms and well-being.^{106,109,111,117} Consequently, the recommended approach is to add an ARB to treatment with an ACE inhibitor and β blocker in patients with symptomatic heart failure (figure 3, table 2). Intolerance

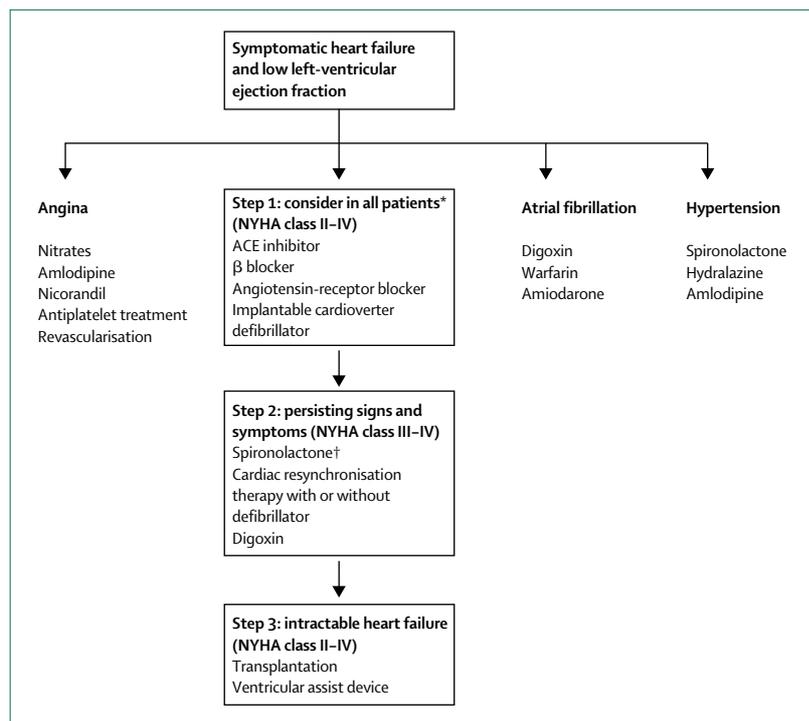


Figure 3: Treatment algorithm for patients with heart failure and reduced left-ventricular systolic function
The starting and target doses of “evidence-based” agents are given in table 2. For other detailed guidance on the use of these drugs, see reference 96. *These treatments are generally added to existing diuretic treatment dosed flexibly to maintain dry weight; hydralazine plus isosorbide dinitrate can also be considered in black patients. †The safety and efficacy of the combination of an ACE inhibitor, an ARB, and an aldosterone antagonist are not known. NYHA=New York Heart Association.

is infrequent and is generally due to hypotension and renal dysfunction. Use of the combination of an ACE inhibitor and an ARB necessitates careful monitoring of blood chemistry.

Aldosterone, the second effector hormone in the renin-angiotensin-aldosterone cascade, seems to have adverse cardiac, vascular, renal, and other actions when produced in excess in heart failure. Whereas ACE inhibitors, β blockers, and ARB have been studied across the range of severity of heart failure (and ARB added to background treatment with both an ACE inhibitor and a β blocker across this range), aldosterone blockade has been tested only in patients with severe symptomatic heart failure, most of whom were receiving an ACE inhibitor but few of whom were treated with a β blocker (because the trial¹¹⁸ was completed before the evidence supporting use of β blockers in patients with this severity of heart failure became available). In these patients, spironolactone led to substantial reductions in mortality and morbidity and improved symptoms.¹¹⁸ These findings were supported by similar, though smaller, benefits with eplerenone in patients with heart failure and reduced left-ventricular systolic function after acute myocardial infarction (in most of whom treatment was an ACE inhibitor and a β blocker).¹¹⁹ Aldosterone blockade is, therefore, recommended for

	Starting dose (mg)	Target total daily dose (mg)*	Doses per day*	Mean total daily dose achieved in outcome studies (mg)
ACE inhibitors				
Captopril	6-25	150	3	121
Enalapril	2-5	20-40	2	16-6
Lisinopril	2.5-5-0	20-35	1	--†
Ramipril	2-5	10	1 or 2	8-7‡
Trandolapril	1-0	4	1	3
β blockers				
Bisoprolol	1-25	10	1	6-2
Carvedilol	3-125	50-100	2	37§
Metoprolol CR/XL	12.5 or 25	200	1	159
Angiotensin-receptor blockers				
Candesartan	4	32	1	24¶
Valsartan	40	320	2	254
Aldosterone blockers				
Eplerenone	25	50	1	43
Spironolactone	25	50	1	26
Hydralazine and isosorbide dinitrate**				
Hydralazine	37-5	225	3	143
Isosorbide dinitrate	20	120	3	60

Based on randomised controlled trials in patients with chronic heart failure or with heart failure, left-ventricular systolic dysfunction, or both after myocardial infarction. *Total daily dose taken once daily or split into two or three equal portions: eg, target total daily dose of captopril is 150 mg, taken as 50 mg three times a day (based on SAVE study). †The ATLAS trial compared high-dose (32.5–35.0 mg) with low-dose (2.5–5.0 mg) lisinopril; guidelines recommend 20 mg daily as a single dose. ‡Based on the AIRE study in which ramipril was prescribed twice daily (target total daily dose 10 mg). §In the COPERNICUS study in which the target total daily dose was 50 mg. ||Metoprolol succinate; the COMET trial showed that low doses of metoprolol tartrate are inferior to carvedilol. ¶In CHARM-Added. **Based on A-HeFT; this combination was given four times daily in V-HeFT I.

Table 2: Evidence-based pharmacological treatment of heart failure

patients with heart failure remaining in New York Heart Association class III and IV despite treatment with an ACE inhibitor and a β blocker (figure 3, table 2). Whether aldosterone blockade is advantageous in milder heart failure is unknown. The main causes of intolerance are renal dysfunction, hyperkalaemia (necessitating careful biochemical monitoring¹²⁰), and, with spironolactone, antiandrogenic side-effects, especially gynaecomastia in men.

In a patient with symptomatic heart failure and low left-ventricular ejection fraction, addition of either an ARB or an aldosterone blocker should be considered, with the caveat that extra biochemical monitoring is essential. An unresolved issue is whether an ARB and an aldosterone blocker can and should be combined (in addition to an ACE inhibitor and a β blocker).¹²¹

The combination of hydralazine and isosorbide dinitrate was the first treatment shown to improve survival in heart failure, but a subsequent study showed that it was less effective than an ACE inhibitor in a direct comparisons.^{99,122–124} A strategy of adding the vasodilator combination to conventional treatment, including an ACE inhibitor, a β blocker, and spironolactone was shown to reduce mortality (and admissions to hospital for heart failure) in African-American patients, although this conclusion was based

on small numbers of events.^{99,122–124} Whether this drug combination is an effective addition in other patients is unknown. Intolerance is generally due to headache and dizziness.

Though generally thought of as an inotrope, digoxin has autonomic, neurohumoral, and diuretic actions. In patients with atrial fibrillation, if a β blocker alone fails to control the ventricular rate (ideally <70/min at rest and <100/min during exercise), digoxin can be added.¹²⁵ This drug can be used first to control the ventricular rate when β-blocker treatment is being initiated or uptitrated. It has a limited role in patients in sinus rhythm. Though digoxin was not associated with a survival benefit when added to an ACE inhibitor, it did reduce the risk of admission to hospital with worsening heart failure in one large clinical trial and it might also have a modest benefit in terms of symptoms.¹²⁶ Consequently, it is recommended only in patients with persisting symptoms and signs, despite use of the more effective treatments mentioned above (figure 3). There is evidence that withdrawal of digoxin can lead to worsening of heart failure.¹²⁷ Intolerance is mostly due to nausea, although conduction disturbances and arrhythmias are also a concern. Toxicity is more likely with higher doses and is increased by hypokalaemia (careful biochemical monitoring is needed), and measurement of blood digoxin concentrations is advisable.

In patients with heart failure and reduced left-ventricular systolic function who have angina (figure 3), nitrates, amlodipine, and, probably, nicorandil can be used safely to prevent and relieve angina when it continues despite use of a β blocker or can be used while β-blocker treatment is being initiated or uptitrated. Antiplatelet treatment should also be considered.

For atrial fibrillation, amiodarone is safer than other antiarrhythmic drugs in heart failure and can help maintain sinus rhythm. Patients with heart failure and atrial fibrillation are at high risk of thromboembolism and should be considered for anticoagulation.

In patients who remain hypertensive despite treatment with an ACE inhibitor and a β blocker, spironolactone or hydralazine should be considered. Amlodipine is also safe.

Pharmacological treatment: preserved left-ventricular systolic function

Treatment of underlying cardiovascular and other disorders that might be contributing to the development of heart failure, such as hypertension, myocardial ischaemia, atrial fibrillation, and diabetes, is important.^{58,128} Diuretics are used, empirically and according to the same principles as in heart failure with reduced systolic function.⁹⁶

The CHARM-Preserved trial¹²⁹ did not show a significant reduction in the risk of the primary composite endpoint (adjudicated death from cardiovascular causes

or admission with heart failure) with addition of ARB, but it did show a substantial reduction in the risk of investigator-reported admissions for heart failure. Current trials are investigating the effect of irbesartan (I-PRESERVE) on mortality and cardiovascular morbidity in these patients, and the ACE inhibitor perindopril (PEP-CHF).¹³⁰

By reducing heart rate and increasing relaxation, β blockers should increase diastolic filling. The anti-ischaemic antihypertensive actions might also be beneficial in heart failure with preserved systolic function. SENIORS assessed the effect of nebivolol in elderly patients with heart failure, a proportion of whom had preserved systolic function. A full analysis of outcomes in this subgroup is awaited.¹⁰⁵

Verapamil shares the pharmacological effects of β blockers, which are theoretically attractive in heart failure with preserved systolic function. Several small trials have suggested that verapamil improves symptoms and exercise tolerance in patients with heart failure and preserved systolic function. There are no trials with mortality or morbidity outcomes with this drug.^{131,132}

Aldosterone is believed to promote extracellular matrix growth and ventricular hypertrophy, effects likely to reduce ventricular relaxation and diastolic filling.¹³³ A large outcome trial (TOPCAT) is planned with an aldosterone blocker in heart failure and preserved systolic function.

Other pharmacological treatments

Vaccination against influenza and pneumococcal infection is recommended in vulnerable individuals, including patients with heart failure in whom these infections can precipitate worsening of their cardiac function and lead to hospital admission. Some patients with heart failure have thiamine deficiency.^{134,135} The choice of treatment for comorbidity might be influenced by heart failure (figure 3). Antiplatelet treatment is generally recommended in patients with arterial disease, although the role of aspirin is still debated.¹³⁶ Trials of statins generally excluded patients with symptomatic heart failure, but two studies with morbidity and mortality outcomes in heart failure are now under way.^{137,138} Nicotine replacement therapy can help with smoking cessation, though it has not been studied extensively in heart failure. Many drugs should be avoided in heart failure, including antiarrhythmic agents, calcium-channel blockers, antipsychotics, antihistamines, corticosteroids, and non-steroidal anti-inflammatory drugs, where possible.¹³⁹ Metformin and thiazolidinediones (glitazones) should be used with caution in heart failure with diabetes.^{140,141} Some salt substitutes contain a lot of potassium and can cause hyperkalaemia. Some dietary supplements can interact with drugs taken by patients with heart failure, such as St John's wort with warfarin and digoxin.¹⁴² There is growing interest in use of erythropoietic agents to treat

anaemia in heart failure, and outcome trials are planned.^{143,144}

Non-pharmacological, non-device, non-surgical treatments

Though there is no evidence that restriction of sodium and fluid is beneficial in heart failure, such restriction is widely advocated. There is no evidence that alcohol in moderation is harmful, although patients with alcoholic cardiomyopathy should clearly abstain.¹⁴⁵ Smoking and obesity should be avoided by all, although substantial involuntary weight loss indicates a bad prognosis.^{67,146} We do not know how to treat cachexia. Regular exercise seems to improve well-being; its effect on prognosis is unclear but is being studied.^{92-94,147,148} Practical advice on exercise prescription for patients with heart failure has been published, although the optimum exercise regimen remains uncertain.⁹³ The role of psychological interventions is also uncertain.¹⁴⁹

Acute "decompensated" heart failure

The management of this heterogeneous group of patients is complex and changing and is beyond the scope of this seminar. New guidelines have been published.¹⁵⁰ The major goal of treatment is relief of symptoms (most commonly extreme dyspnoea); in more critically ill patients, the aim is pharmacological or mechanical haemodynamic support either to recovery or an operative procedure (eg, transplantation). For most patients, a combination of oxygen and intravenous opioid, diuretic, and nitrate is sufficient. Continuous positive airways pressure can also be helpful.¹⁵¹ Hypotension or other severe systemic underperfusion might necessitate an inotropic agent (in most cases a catecholamine such as dobutamine).¹⁵¹ Phosphodiesterase inhibitors do not improve outcome.¹⁵² The calcium-sensitising "inodilator" levosimendan¹⁵³ and nesiritide (BNP) have shown some promise, but more convincing efficacy and safety data are needed.¹⁵⁴ Antagonists of arginine vasopressin receptor are also under investigation.¹⁵⁵ Discharge planning and subsequent management to reduce the risk of readmission are important.¹⁵⁶

Organisation of care

A substantial number of studies have shown that organised, multidisciplinary care led by a specialist nurse can improve outcomes in patients with heart failure, particularly by reducing recurrent admission to hospital.⁹¹ The most successful approach seems to involve education of patients and carers about heart failure and its treatment, including flexible diuretic dosing and reinforcing the importance of adherence; recognising and acting upon early deterioration; and optimising proven pharmacological treatments. A home-based rather than clinic-based approach may be best, though trials are needed to compare types of intervention directly.¹⁵⁷

Panel: Surgical and other interventional treatments for heart failure**Conventional**

Surgical coronary revascularisation
 on pump
 off pump
 Percutaneous coronary revascularisation
 Mitral-valve repair/annuloplasty
 Surgical left-ventricular remodelling (eg, Dor procedure)

Transplantation

Orthotopic/heterotopic
 Xenotransplantation

Ventricular assist devices/mechanical pumps

Bridge to transplantation
 Destination therapy

Other left-ventricular surgery

External compression
 Splinting

Total artificial heart**Cell and gene therapy**

(can be delivered at the time of conventional surgery)
 Skeletal muscle myoblasts
 Stem cells
 Bone marrow
 Embryonic
 Gene delivery (can also be percutaneous)

Devices and surgery

About half of patients with heart failure die suddenly, mostly as a result of ventricular arrhythmias. Antiarrhythmic drugs do not improve survival in heart failure. A recent study (SCD-HeFT) showed that an implantable cardioverter defibrillator (ICD) reduced the risk of death by 23% in patients with mild to severe symptomatic heart failure and a reduced left-ventricular ejection fraction who were receiving optimum medical treatment.¹⁵⁸ These findings are supported by similarly large reductions in death with a cardiac resynchronisation-defibrillator device (CRT-D) in patients with severe symptomatic heart failure and a low left-ventricular ejection fraction in COMPANION¹⁵⁹ (see below) and with an ICD in survivors of myocardial infarction with a reduced left-ventricular ejection fraction in MADIT-2.¹⁶⁰ Consequently, these devices will become more widely used in heart failure (figure 3). There is much debate about the selection of suitable recipients and recognition that patients with truly advanced heart failure will die despite an ICD.

About 25% of patients with heart failure have abnormal electrical activation of the left ventricle (generally reflected by a long QRS duration on the surface ECG), leading to dys-synchronous contraction

between the walls of the left ventricle, resulting in less efficient ventricular emptying and, in many cases, mitral regurgitation.^{56,161} Atrioventricular coupling might also be abnormal (reflected by a long PR interval), as might interventricular synchrony. Atrioventricular or multisite pacing resynchronises cardiac contraction, improves pump function, reduces symptoms, and increases exercise tolerance in patients with severe heart failure.¹⁶²⁻¹⁶⁵ Two trials with morbidity and mortality outcomes have recently been completed.^{159,166} In COMPANION,¹⁵⁹ cardiac resynchronisation therapy (CRT) reduced the composite of death or hospital admission (both for any cause and for heart failure) in patients with severe heart failure (table 1). There was a strong trend to a reduction in death alone. In CARE-heart failure, CRT not only reduced by 37% the risk of the primary outcome of death or hospital admission for a cardiovascular reason but also reduced by 36% the risk of death from any cause (table 1). The absolute risk reductions were large and were obtained despite excellent evidence-based background medical treatment. Many other outcome measures, including quality of life, were also improved. There remains debate about how best to select patients for CRT.¹⁶²⁻¹⁶⁷ Most existing trials selected on the basis of pronounced prolongation of the QRS duration, generally manifest as left bundle-branch block and a QRS duration of longer than 120 ms; CARE-heart failure used additional echocardiographic criteria for patients with a QRS duration between 120 ms and 149 ms. Tissue doppler echocardiography and other imaging techniques might be better at identifying patients likely to benefit, although this idea remains to be proved and the approach used in the large outcome trials mentioned above remains the only evidence-based one.¹⁶⁸ Whether patients with right bundle-branch block, atrial fibrillation, dys-synchrony without pronounced QRS prolongation, and milder heart failure are helped by CRT is uncertain.¹⁶⁰⁻¹⁶⁸ There is no consensus yet about whether, or in whom, CRT alone or a CRT-D device should be used.

Surgical treatments for heart failure are outlined in the panel. Few of these are of proven benefit and none are widely used in patients with heart failure, with the exception of coronary revascularisation (much of which is carried out percutaneously). Two large outcome trials are presently assessing the value of conventional surgery, including coronary bypass grafting, mitral-valve or annulus repair, and reconstruction of the left ventricle.^{169,170} The role of revascularisation in patients without angina but with ischaemia, viability or "hibernation", or both, is particularly interesting, but identification of appropriate patients continues to be a challenge.^{45,171} Orthotopic (or heterotopic) transplantation remains the treatment of last resort in selected patients, but the limited supply of donor organs means interest in xenotransplantation continues.^{172,173} Ventricular assist devices can be used as a bridge to transplantation, but

there is also growing interest in, and evidence for (table 1), their use as destination therapy.^{174,175} Development of total artificial hearts and of novel ventricular splinting and compressive devices also continues.^{176–179} Cell and gene therapy, delivered at the time of conventional surgery, as a primary surgical procedure, or percutaneously are also under evaluation.^{180–182}

Palliative care

The treatments described here might not be tolerated by, or could be inappropriate for, the very elderly patients with many comorbidities who present with, or progress to, end-stage heart failure. End-of-life care has not been as adequately assessed in advanced heart failure as it has for other terminal disorders.^{183,184}

Further challenges and directions

Despite the impressive number of effective treatments available, patients with heart failure continue to experience progressively worsening symptoms, frequent admission to hospital, and premature death. Better treatments are needed, although additional drugs will exacerbate the problem of polypharmacy; there is increasing interest in finding better options rather than in simply adding extra treatments. Comorbidity seems to be an increasing problem, which in many cases limits the use of proven treatments. Indeed, comorbidities are now a therapeutic target in their own right: for example, erythropoietic agents for anaemia;^{143,144} selective A₁ adenosine agonists for patients with cardiorenal syndrome;^{155,185} various treatments for atrial fibrillation;^{186,187} and continuous positive airways pressure for ventilatory abnormalities.¹⁸⁸ Tailoring pharmacological treatment—for example, to normalise concentrations of natriuretic peptides—and targeting treatment on the basis of biological mechanisms or genetic composition are attractive but unproven approaches.^{189,190} Other experimental approaches to treatment are exploring completely novel pathophysiological processes.¹⁹¹ Another topic that remains under-researched is that of monitoring patients during follow-up to detect deterioration in the hope of reversing it and preventing an adverse outcome. Current approaches such as asking the patient to measure his or her weight daily seem crude; there are intriguing new approaches, such as home telemonitoring and implantable devices measuring right heart pressures and devices using bioimpedance to make serial measurements of cardiac function and detect fluid overload, as well as an interest in using natriuretic peptides for this purpose. Advances in technology and surgery will lead to more widespread use of mechanical support, although these treatments are likely to remain restricted to selected, younger patients with little comorbidity. The ultimate goal of repairing or replacing dead or damaged myocytes seems hypothetically possible with cell and gene therapy but only time will tell whether it is really attainable.¹⁸²

Conflict of interest statement

JJVMcM has received research grants, consultancy fees, and honoraria for lectures from Astra-Zeneca, Bristol-Myers-Squibb/Sanofi, GlaxoSmithKline, Novartis, Pfizer, and Roche Pharmaceuticals in relation to clinical trials in heart failure with candesartan, irbesartan, nesiritide, bisoprolol, valsartan, eplerenone, and carvedilol. MAP has received honoraria and educational or research grants, or serves as a consultant for: Novartis, Amgen, Astra-Zeneca, Atherogenics, Bristol-Myers-Squibb, Genzyme, Guidant, Mitsubishi Pharma Corporation, and Pfizer. He is named as co-inventor on a patent awarded to the Brigham and Women's Hospital in relation to the use of inhibitors of the renin-angiotensin system in selected survivors of myocardial infarction; there is a licensing agreement between Novartis and the Brigham and Women's Hospital, which is not linked to any sales. We received no payment in relation to preparation of this Seminar.

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