Heart failure

John J V McMurray, Marc A Pfeffer

Lancet 2005; 365: 1877–89

Department of Cardiology, Western Infirmary, Glasgow, UK (Prof J J V McMurray MD) **and Cardiovascular Division, Brigham and Women's Hospital, Boston, MA, USA** (Prof M A Pfeffer MD)

Correspondence to:
Prof John J V McMurray, Department of Cardiology, Western Infirmary Level 4, Glasgow G11 6NT, UK
j.mcmurray@bio.gla.ac.uk

or

Prof Marc A Pfeffer, Department of Medicine, Brigham and Women's Hospital, 75 Francis Street, Boston, MA 02115, USA
mpfeffer@rics.bwh.harvard.edu

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.

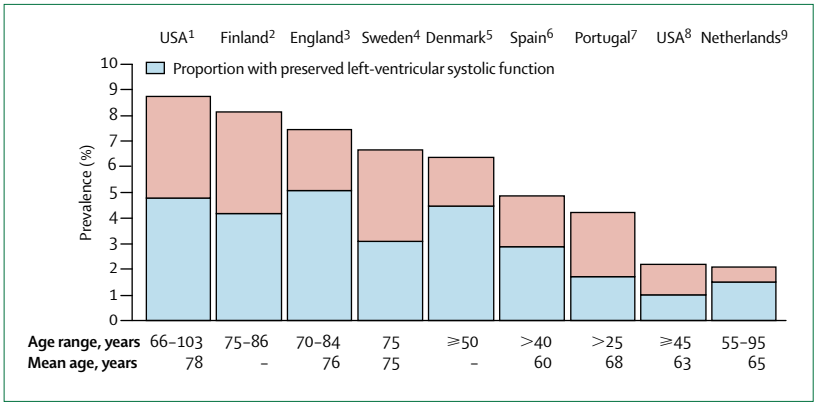

Figure 1: **Prevalence of heart failure in cross-sectional population echocardiographic studies and proportion of patients with preserved left-ventricular systolic function**

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 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]

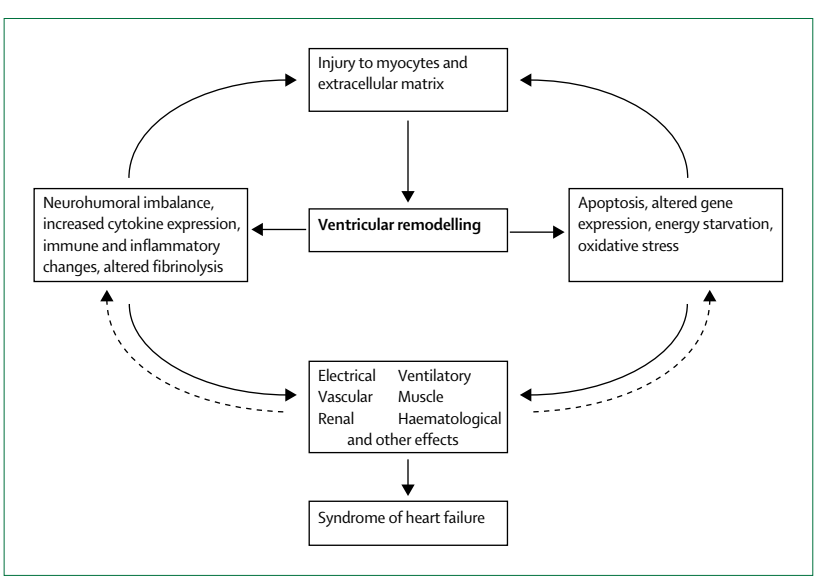

Figure 2: **Pathophysiology of heart failure due to left-ventricular systolic dysfunction**
Damage to the myocytes and extracellular matrix leads to changes in the size, shape, and function of the left ventricle and heart more generally ("remodelling"). These changes, in turn, lead to electrical instability, 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.

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 ventriculovascular 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 admisssion 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 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.

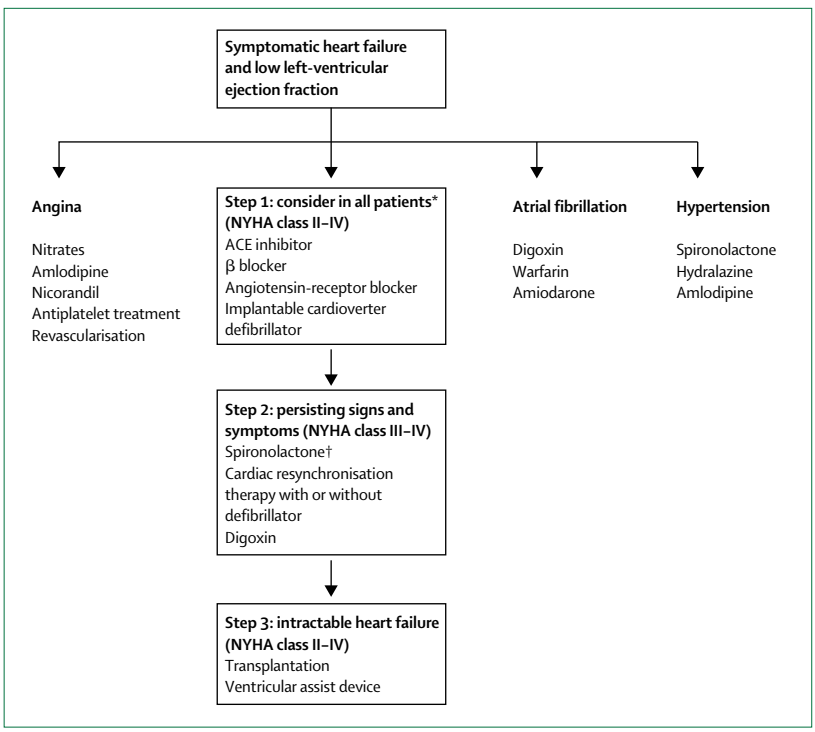

Figure 3: **Treatment algorithm for patients with heart failure and reduced left-ventricular systolic function**
The starting and target doses of "evidence-based" agents are given in table 2. For other detailed guidance on the use of these drugs, see reference 96. *These treatments are generally added 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.

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 trial[118] 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 monitoring[120]), 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 trial[129] 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, corticosteriods, 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" levosimendan[153] 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 COMPANION[159] (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. Atriobiventricular 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-sychrony 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 A_1 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, eperlenone, 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 agreeement 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.

References

1 Gardin JM, Siscovick D, Anton Culver H, et al. Sex, age, and disease affect echocardiographic left ventricular mass and systolic function in the free-living elderly: the Cardiovascular Health Study. *Circulation* 1995; **91:** 1739–48.

2 Kupari M, Lindroos M, Livanainen AM, et al. Congestive heart failure in old age: prevalence, mechanisms and 4-year prognosis in the Helsinki Ageing Study. *J Intern Med* 1997; **241:** 387–94.

3 Morgan S, Smith H, Simpson I, et al. Prevalence and clinical characteristics of left ventricular dysfunction among elderly patients in general practice setting: cross sectional survey. *BMJ* 1999; **318:** 368–72.

4 Hedberg P, Lonnberg I, Jonasson T, et al. Left ventricular systolic dysfunction in 75-year old men and women: a population-based study. *Eur Heart J* 2001; **22:** 676–83.

5 Nielsen OW, Hilden J, Larsen CT, et al. Cross sectional study estimating prevalence of heart failure and left ventricular systolic dysfunction in community patients at risk. *Heart* 2001; **86:** 172–78.

6 Cortina A, Reguero J, Segovia E, et al. Prevalence of heart failure in Asturias (a region in the north of Spain). *Am J Cardiol* 2001; **87:** 1417–19.

7 Ceia F, Fonseca C, Mota T, et al. Prevalence of chronic heart failure in South Western Europe: EPICA study. *Eur J Heart Fail* 2002; **4:** 531–39.

8 Redfield MM, Jacobsen SJ, Burnett JC Jr, et al. Burden of systolic and diastolic ventricular dysfunction in the community: appreciating the scope of the heart failure epidemic. *JAMA* 2003; **289:** 194–202.

9 Mosterd A, Hoes AW, de Bruyne MC, et al. Prevalence of heart failure and left ventricular dysfunction in the general population; the Rotterdam Study. *Eur Heart J* 1999; **20:** 447–55.

10 Ho KK, Pinsky JL, Kannel WB, Levy D. The epidemiology of heart failure: the Framingham Study. *J Am Coll Cardiol* 1993; **22:** 6A–13A.

11 Lloyd-Jones DM, Larson MG, Leip EP, et al. Lifetime risk for developing congestive heart failure: the Framingham Heart Study. *Circulation* 2002; **106:** 3068–72.

12 Bleumink GS, Knetsch AM, Sturkenboom MC, et al. Quantifying the heart failure epidemic: prevalence, incidence rate, lifetime risk and prognosis of heart failure. *Eur Heart J* 2004; **25:** 1614–19.

13 Levy D, Kenchaiah S, Larson MG, et al. Long-term trends in the incidence of and survival with heart failure. *N Engl J Med* 2002; **347:** 1397–402.

14 Roger VL, Weston SA, Redfield MM, et al. Trends in heart failure incidence and survival in a community-based population. *JAMA* 2004; **292:** 344–50.

15 Stewart S, MacIntyre K, Capewell S, McMurray JJ. Heart failure and the aging population: an increasing burden in the 21st century? *Heart* 2003; **89:** 49–53.

16 Stewart S, MacIntyre K, MacLeod MM, et al. Trends in hospitalization for heart failure in Scotland, 1990–1996: an epidemic that has reached its peak? *Eur Heart J* 2001; **22:** 209–17.

17 Schaufelberger M, Swedberg K, Koster M, et al. Decreasing one-year mortality and hospitalization rates for heart failure in Sweden: data from the Swedish Hospital Discharge Registry 1988 to 2000. *Eur Heart J* 2004; **25:** 300–07.

18 Mosterd A, Reitsma JB, Grobbee DE. Angiotensin converting enzyme inhibition and hospitalisation rates for heart failure in the Netherlands, 1980 to 1999: the end of an epidemic? *Heart* 2002; **87:** 75–76.

19 Cowie MR, Fox KF, Wood DA, et al. Hospitalization of patients with heart failure: a population-based study. *Eur Heart J* 2002; **23:** 877–85.

20 Blackledge HM, Tomlinson J, Squire IB. Prognosis for patients newly admitted to hospital with heart failure: survival trends in 12 220 index admissions in Leicestershire 1993–2001. *Heart* 2003; **89:** 615–20.

21 Lee DS, Mamdani MM, Austin PC, et al. Trends in heart failure outcomes and pharmacotherapy: 1992 to 2000. *Am J Med* 2004; **116:** 581–89.

22 Baker DW, Einstadter D, Thomas C, Cebul RD. Mortality trends for 23,505 Medicare patients hospitalized with heart failure in Northeast Ohio, 1991 to 1997. *Am Heart J* 2003; **146:** 258–64.

23 Stewart S, Horowitz JD. Detecting early clinical deterioration in chronic heart failure patients post-acute hospitalisation: a critical component of multidisciplinary, home-based intervention? *Eur J Heart Fail* 2002; **4:** 345–51.

24 Stewart S, Jenkins A, Buchan S, et al. The current cost of heart failure to the National Health Service in the UK. *Eur J Heart Fail* 2002; **4:** 361–71.

25 Murphy NF, Simpson CR, McAlister FA, et al. National survey of the prevalence, incidence, primary care burden, and treatment of heart failure in Scotland. *Heart* 2004; **90:** 1129–36.

26 Hobbs FD, Kenkre JE, Roalfe AK, et al. Impact of heart failure and left ventricular systolic dysfunction on quality of life: a cross-sectional study comparing common chronic cardiac and medical disorders and a representative adult population. *Eur Heart J* 2002; **23:** 1867–76.

27 Cowie MR, Wood DA, Coats AJ, et al. Survival of patients with a new diagnosis of heart failure: a population based study. *Heart* 2000; **83:** 505–10.

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

29 Stewart S, MacIntyre K, Hole DJ, et al. More 'malignant' than cancer? Five-year survival following a first admission for heart failure. *Eur J Heart Fail* 2001; **3:** 315–22.

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

31 Thomas MD, Fox KF, Coats AJ, Sutton GC. The epidemiological enigma of heart failure with preserved systolic function. *Eur J Heart Fail* 2004; **6:** 125–36.

32 Senni M, Redfield MM. Heart failure with preserved systolic function. A different natural history? *J Am Coll Cardiol* 2001; **38:** 1277–82.

33 Banerjee P, Banerjee T, Khand A, et al. Diastolic heart failure: neglected or misdiagnosed? *J Am Coll Cardiol* 2002; **39:** 138–41.

34 Gottdiener JS, McClelland RL, Marshall R, et al. Outcome of congestive heart failure in elderly persons: influence of left ventricular systolic function: the Cardiovascular Health Study. *Ann Intern Med* 2002; **137:** 631–39.

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

36 Fischer M, Baessler A, Hense HW, et al. Prevalence of left ventricular diastolic dysfunction in the community: results from a Doppler echocardiographic-based survey of a population sample. *Eur Heart J* 2003; **24:** 320–28.

37 Pedersen F, Raymond I, Mehlsen J, et al. Prevalence of diastolic dysfunction as a possible cause of dyspnea in the elderly. *Am J Med* 2005; **118:** 25–31.

38 Badano LP, Albanese MC, De Biaggio P, et al. Prevalence, clinical characteristics, quality of life, and prognosis of patients with congestive heart failure and isolated left ventricular diastolic dysfunction. *J Am Soc Echocardiogr* 2004; **17:** 253–61.

39 Wang TJ, Levy D, Benjamin EJ, Vasan RS. The epidemiology of "asymptomatic" left ventricular systolic dysfunction: implications for screening. *Ann Intern Med* 2003; **138:** 907–16.

40 Pedersen F, Raymond I, Madsen LH, et al. Echocardiographic indices of left ventricular diastolic dysfunction in 647 individuals with preserved left ventricular systolic function. *Eur J Heart Fail* 2004; **6:** 439–47.

41 Mendez GF, Cowie MR. The epidemiological features of heart failure in developing countries: a review of the literature. *Int J Cardiol* 2001; **80:** 213–19.

42 Agarwal AK, Venugopalan P, de Bono D. Prevalence and aetiology of heart failure in an Arab population. *Eur J Heart Fail* 2001; **3:** 301–05.

43 Cubillos-Garzon LA, Casas JP, Morillo CA, Bautista LE. Congestive heart failure in Latin America: the next epidemic. *Am Heart J* 2004; **147:** 412–17.

44 Ventura HO, Mehra MR. The growing burden of heart failure: the "syndemic" is reaching Latin America. *Am Heart J* 2004; **147:** 386–89.

45 Camici PG. Hibernation and heart failure. *Heart* 2004; **90:** 141–43.

46 Tang WH, Young JB. Cardiomyopathy and heart failure in diabetes. *Endocrinol Metab Clin North Am* 2001; **30:** 1031–46.

47 Wang TJ, Larson MG, Levy D, et al. Temporal relations of atrial fibrillation and congestive heart failure and their joint influence on mortality: the Framingham Heart Study. *Circulation* 2003; **107:** 2920–25.

48 Konstam MA, Udelson JE, Anand IS, Cohn JN. Ventricular remodeling in heart failure: a credible surrogate endpoint. *J Card Fail* 2003; **9:** 350–53.

49 Hwang JJ, Dzau VJ, Liew CC. Genomics and the pathophysiology of heart failure. *Curr Cardiol Rep* 2001; **3:** 198–207.

50 Feldman AM, Li YY, McTiernan CF. Matrix metalloproteinases in pathophysiology and treatment of heart failure. *Lancet* 2001; **357:** 654–55.

51 Marshall D, Sack MN. Apoptosis: a pivotal event or an epiphenomenon in the pathophysiology of heart failure? *Heart* 2000; **84:** 355–56.

52 Swedberg K. Importance of neuroendocrine activation in chronic heart failure: impact on treatment strategies. *Eur J Heart Fail* 2000; **2:** 229–33.

53 Anker SD, von Haehling S. Inflammatory mediators in chronic heart failure: an overview. *Heart* 2004; **90:** 464–70.

54 Francis GS. Pathophysiology of chronic heart failure. *Am J Med* 2001; **110:** 37S–46S.

55 Daubert JC. Introduction to atrial fibrillation and heart failure: a mutually noxious association. *Europace* 2004; **5:** S1–4.

56 Bleasdale RA, Frenneaux MP. Cardiac resynchronisation therapy: when the drugs don't work. *Heart* 2004; **90:** vi2–4.

57 Zile MR, Brutsaert DL. New concepts in diastolic dysfunction and diastolic heart failure: part I, diagnosis, prognosis, and measurements of diastolic function. *Circulation* 2002; **105:** 1387–93.

58 Zile MR, Brutsaert DL. New concepts in diastolic dysfunction and diastolic heart failure: part II, causal mechanisms and treatment. *Circulation* 2002; **105:** 1503–08.

59 Zile MR, Baicu CF, Gaasch WH. Diastolic heart failure: abnormalities in active relaxation and passive stiffness of the left ventricle. *N Engl J Med* 2004; **350:** 1953–59.

60 Kitzman DW, Little WC, Brubaker PH, et al. Pathophysiological characterization of isolated diastolic heart failure in comparison to systolic heart failure. *JAMA* 2002; **288:** 2144–50.

61 Zile MR, Gaasch WH, Carroll JD, et al. Heart failure with a normal ejection fraction: is measurement of diastolic function necessary to make the diagnosis of diastolic heart failure? *Circulation* 2001; **104:** 779–82.

62 Petrie MC, Hogg K, Caruana L, McMurray JJ. Poor concordance of commonly used echocardiographic measures of left ventricular diastolic function in patients with suspected heart failure but preserved systolic function: is there a reliable echocardiographic measure of diastolic dysfunction? *Heart* 2004; **90:** 511–17.

63 Burkhoff D, Maurer MS, Packer M. Heart failure with a normal ejection fraction: is it really a disorder of diastolic function? *Circulation* 2003; **107:** 656–58.

64 Gandhi SK, Powers JC, Nomeir AM, et al. The pathogenesis of acute pulmonary edema associated with hypertension. *N Engl J Med* 2001; **344:** 17–22.

65 Braunstein JB, Anderson GF, Gerstenblith G, et al. Noncardiac comorbidity increases preventable hospitalizations and mortality among Medicare beneficiaries with chronic heart failure. *J Am Coll Cardiol* 2003; **42:** 1226–33.

66 Anand I, McMurray JJ, Whitmore J, et al. Anemia and its relationship to clinical outcome in heart failure. *Circulation* 2004; **110:** 149–54.

67 Anker SD, Negassa A, Coats AJ, et al. Prognostic importance of weight loss in chronic heart failure and the effect of treatment with angiotensin-converting-enzyme inhibitors: an observational study. *Lancet* 2003; **361:** 1077–83.

68 O'Connor CM, Joynt KE. Depression: are we ignoring an important comorbidity in heart failure? *J Am Coll Cardiol* 2004; **43:** 1550–52.

69 McAlister FA, Ezekowitz J, Tonelli M, Armstrong PW. Renal insufficiency and heart failure: prognostic and therapeutic implications from a prospective cohort study. *Circulation* 2004; **109:** 1004–09.

70 Aronow WS. Treatment of heart failure in older persons. Dilemmas with coexisting conditions: diabetes mellitus, chronic obstructive pulmonary disease, and arthritis. *Congest Heart Fail* 2003; **9:** 142–47.

71 Sirak TE, Jelic S, Le Jemtel TH. Therapeutic update: non-selective beta- and alpha-adrenergic blockade in patients with coexistent chronic obstructive pulmonary disease and chronic heart failure. *J Am Coll Cardiol* 2004; **44:** 497–502.

72 Wolfe F, Michaud K. Heart failure in rheumatoid arthritis: rates, predictors, and the effect of anti-tumor necrosis factor therapy. *Am J Med* 2004; **116:** 305–11.

73 Shlipak MG. Pharmacotherapy for heart failure in patients with renal insufficiency. *Ann Intern Med* 2003; **138:** 917–24.

74 Davie AP, Francis CM, Caruana L, et al. Assessing diagnosis in heart failure: which features are any use? *QJM* 1997; **90:** 335–39.

75 Khunti K, Baker R, Grimshaw G. Diagnosis of patients with chronic heart failure in primary care: usefulness of history, examination, and investigations. *Br J Gen Pract* 2000; **50:** 50–54.

76 Thomas JT, Kelly RF, Thomas SJ, et al. Utility of history, physical examination, electrocardiogram, and chest radiograph for differentiating normal from decreased systolic function in patients with heart failure. *Am J Med* 2002; **112:** 437–45.

77 Heart Failure Society of America. HFSA guidelines for the management of patients with heart failure due to left ventricular systolic dysfunction: pharmacological approaches. *Congest Heart Fail* 2000; **6:** 11–39.

78 Hunt SA, Baker DW, Chin MH, et al. ACC/AHA guidelines for the evaluation and management of chronic heart failure in the adult: executive summary a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1995 Guidelines for the Evaluation and Management of Heart Failure): developed in collaboration with the International Society for Heart and Lung Transplantation; endorsed by the Heart Failure Society of America. *Circulation* 2001; **104:** 2996–3007.

79 National Heart Foundation of New Zealand Cardiac Society of Australia and New Zealand and the Royal New Zealand College of General Practitioners Working Party. New Zealand guidelines for the management of chronic heart failure. *N Z Med J* 1997; **110:** 99–107.

80 Krum H, National Heart Foundation of Australia and Cardiac Society of Australia & New Zealand Chronic Heart Failure Clinical Practice Guidelines Writing Panel. Guidelines for management of patients with chronic heart failure in Australia. *Med J Aust* 2001; **174:** 459–66.

81 Swedberg K, Cleland J, Dargie H, et al. Guidelines for the diagnosis and treatment of chronic heart failure: executive summary (update 2005). *Eur Heart J* (DOI:10.1093/eurheartj/ehi204).

82 Nikitin NP, de Silva R, Cleland JG. The utility of a comprehensive cardiac magnetic resonance examination for the evaluation of patients with heart failure. *Heart* 2004; **90:** 1166.

83 Vasan RS, Levy D. Defining diastolic heart failure: a call for standardized diagnostic criteria. *Circulation* 2000; **101:** 2118–21.

84 Rakowski H, Appleton C, Chan KL, et al. Canadian consensus recommendations for the measurement and reporting of diastolic dysfunction by echocardiography: from the Investigators of Consensus on Diastolic Dysfunction by Echocardiography. *J Am Soc Echocardiogr* 1996; **9:** 736–60.

85 Sim MF, Ho SF, O'Mahony MS, et al. European reference values for Doppler indices of left ventricular diastolic filling. *Eur J Heart Fail* 2004; **6:** 433–38.

86 McDonagh TA, Holmer S, Raymond I, et al. NT-proBNP and the diagnosis of heart failure: a pooled analysis of three European epidemiological studies. *Eur J Heart Fail* 2004; **6:** 269–73.

87 Maisel AS, Krishnaswamy P, Nowak RM, et al. Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure. *N Engl J Med* 2002; **347:** 161–67.

88 McCullough PA, Nowak RM, McCord J, et al. B-type natriuretic peptide and clinical judgment in emergency diagnosis of heart failure: analysis from Breathing Not Properly (BNP) Multinational Study. *Circulation* 2002; **106:** 416–22.

89 Redfield MM, Rodeheffer RJ, Jacobsen SJ, et al. Plasma brain natriuretic peptide concentration: impact of age and gender. *J Am Coll Cardiol* 2002; **40:** 976–82.

90 Packer M. Should B-type natriuretic peptide be measured routinely to guide the diagnosis and management of chronic heart failure? *Circulation* 2003; **108:** 2950–53.

91 McAlister FA, Stewart S, Ferrua S, McMurray JJ. Multidisciplinary strategies for the management of heart failure patients at high risk for admission: a systematic review of randomized trials. *J Am Coll Cardiol* 2004; **44:** 810–19.

92 Piepoli MF, Davos C, Francis DP, Coats AJ, ExTraMATCH Collaborative. Exercise training meta-analysis of trials in patients with chronic heart failure (ExTraMATCH). *BMJ* 2004; **328:** 189.

93 Smart N, Fang ZY, Marwick TH. A practical guide to exercise training for heart failure patients. *J Card Fail* 2003; **9:** 49–58.

94 Giannuzzi P, Temporelli PL, Corra U, Tavazzi L, ELVD-CHF Study Group. Antiremodeling effect of long-term exercise training in patients with stable chronic heart failure: results of the Exercise in Left Ventricular Dysfunction and Chronic Heart Failure (ELVD-CHF) Trial. *Circulation* 2003; **108:** 554–59.

95 Faris R, Flather M, Purcell H, et al. Current evidence supporting the role of diuretics in heart failure: a meta analysis of randomised controlled trials. *Int J Cardiol* 2002; **82:** 149–58.

96 McMurray J, Cohen-Solal A, Dietz R, et al. Practical recommendations for the use of ACE inhibitors, beta-blockers and spironolactone in heart failure: putting guidelines into practice. *Eur J Heart Fail* 2001; **3:** 495–502.

97 CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure: results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). *N Engl J Med* 1987; **316:** 1429–35.

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

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

100 CIBIS investigators. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. *Lancet* 1999; **353:** 9–13.

101 MERIT-HF investigators. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). *Lancet* 1999; **353:** 2001–07.

102 Hjalmarson A, Goldstein S, Fagerberg B, et al. Effects of controlled-release metoprolol on total mortality, hospitalizations, and well-being in patients with heart failure: the Metoprolol CR/XL Randomized Intervention Trial in congestive heart failure (MERIT-HF). *JAMA* 2000; **283:** 1295–302.

103 Packer M, Coats AJ, Fowler MB, et al. Effect of carvedilol on survival in severe chronic heart failure. *N Engl J Med* 2001; **344:** 1651–58.

104 Packer M, Fowler MB, Roecker EB, et al. Effect of carvedilol on the morbidity of patients with severe chronic heart failure: results of the Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) study. *Circulation* 2002; **106:** 2194–99.

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

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

107 Maggioni AP, Anand I, Gottlieb SO, et al. Effects of valsartan on morbidity and mortality in patients with heart failure not receiving angiotensin-converting enzyme inhibitors. *J Am Coll Cardiol* 2002; **40:** 1414–21.

108 Granger CB, McMurray JJ, Yusuf S, et al. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function intolerant to angiotensin-converting-enzyme inhibitors: the CHARM-Alternative trial. *Lancet* 2003; **362:** 772–76.

109 McMurray JJ, Ostergren J, Swedberg K, et al. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function taking angiotensin-converting-enzyme inhibitors: the CHARM-Added trial. *Lancet* 2003; **362:** 767–71.

110 Young JB, Dunlap ME, Pfeffer MA, et al. Mortality and morbidity reduction with candesartan in patients with chronic heart failure and left ventricular systolic dysfunction: results of the CHARM low-left ventricular ejection fraction trials. *Circulation* 2004; **110:** 2618–26.

111 O'Meara E, Solomon S, McMurray J, et al. Effect of candesartan on New York Heart Association functional class: results of the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM) programme. *Eur Heart J* 2004; **25:** 1920–26.

112 Pfeffer MA, McMurray JJ, Velazquez EJ, et al. Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. *N Engl J Med* 2003; **349:** 1893–906.

113 McKelvie RS, Yusuf S, Pericak D, et al. Comparison of candesartan, enalapril, and their combination in congestive heart failure: randomized evaluation of strategies for left ventricular dysfunction (RESOLVD) pilot study. *Circulation* 1999; **100:** 1056–64.

114 McKelvie RS, Rouleau JL, White M, et al. Comparative impact of enalapril, candesartan or metoprolol alone or in combination on ventricular remodelling in patients with congestive heart failure. *Eur Heart J* 2003; **24:** 1727–34.

115 Cohn JN, Anand IS, Latini R, et al. Sustained reduction of aldosterone in response to the angiotensin receptor blocker valsartan in patients with chronic heart failure: results from the Valsartan Heart Failure Trial. *Circulation* 2003; **108:** 1306–09.

116 Krum H, Carson P, Farsang C, et al. Effect of valsartan added to background ACE inhibitor therapy in patients with heart failure: results from Val-HeFT. *Eur J Heart Fail* 2004; **6:** 937–45.

117 Carson P, Tognoni G, Cohn JN. Effect of Valsartan on hospitalization: results from Val-HeFT. *J Card Fail* 2003; **9:** 164–71.

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

119 Pitt B, Remme W, Zannad F, et al. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med* 2003; **348:** 1309–21.

120 Juurlink DN, Mamdani MM, Lee DS, et al. Rates of hyperkalemia after publication of the Randomized Aldactone Evaluation Study. *N Engl J Med* 2004; **351:** 543–51.

121 McMurray JJ, Pfeffer MA, Swedberg K, Dzau VJ. Which inhibitor of the renin-angiotensin system should be used in chronic heart failure and acute myocardial infarction? *Circulation* 2004; **110:** 3281–88.

122 Cohn JN, Johnson G, Ziesche S, et al. Effect of vasodilator therapy on mortality in chronic congestive heart failure. *N Engl J Med* 1986; **314:** 1547–52.

123 Taylor AL, Ziesche S, Yancy C, et al. Combination of isosorbide dinitrate and hydralazine in blacks with heart failure. *N Engl J Med* 2004; **351:** 2049–57.

124 Loeb HS, Johnson G, Henrick A, et al. Effect of enalapril, hydralazine plus isosorbide dinitrate, and prazosin on hospitalization in patients with chronic congestive heart failure. *Circulation* 1993; **87:** VI78–87.

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

126 Hood WB Jr, Dans AL, Guyatt GH, et al. Digitalis for treatment of congestive heart failure in patients in sinus rhythm: a systematic review and meta-analysis. *J Card Fail* 2004; **10:** 155–64.

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

128 Aurigemma GP, Gaasch WH. Clinical practice: diastolic heart failure. *N Engl J Med* 2004; **351:** 1097–105.

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

130 Cleland JG, Tendera M, Adamus J, et al. Perindopril for elderly people with chronic heart failure: the PEP-CHF study. *Eur J Heart Fail* 1999; **1:** 211–17.

131 Setaro JF, Zaret BL, Schulman DS, et al. Usefulness of verapamil for congestive heart failure associated with abnormal left ventricular diastolic filling and normal left ventricular systolic performance. *Am J Cardiol* 1990; **66:** 981–86.

132 Hung MJ, Cherng WJ, Kuo LT, Wang CH. Effect of verapamil in elderly patients with left ventricular diastolic dysfunction as a cause of congestive heart failure. *Int J Clin Pract* 2002; **56:** 57–62.

133 Struthers AD. Aldosterone blockade in cardiovascular disease. *Heart* 2004; **90:** 1229–34.

134 Shapiro ED, Berg AT, Austrian R, et al. The protective efficacy of polyvalent pneumococcal polysaccharide vaccine. *N Engl J Med* 1991; **325:** 1453–60.

135 Nichol KL, Margolis KL, Wuorenma J, Von Sternberg T. The efficacy and cost effectiveness of vaccination against influenza among elderly persons living in the community. *N Engl J Med* 1994; **331:** 778–84.

136 Cleland JG, Findlay I, Jafri S, et al. The Warfarin/Aspirin Study in Heart failure (WASH): a randomized trial comparing antithrombotic strategies for patients with heart failure. *Am Heart J* 2004; **148:** 157–64.

137 Tavazzi L, Tognoni G, Franzosi MG, et al. Rationale and design of the GISSI heart failure trial: a large trial to assess the effects of n-3 polyunsaturated fatty acids and rosuvastatin in symptomatic congestive heart failure. *Eur J Heart Fail* 2004; **6:** 635–41.

138 Dunselman P, Hjalmarson A, Kjekshus J, et al. The statin wars. *Lancet* 2003; **362:** 1854.

139 Amabile CM, Spencer AP. Keeping your patient with heart failure safe: a review of potentially dangerous medications. *Arch Intern Med* 2004; **164:** 709–20.

140 Tang WH, Francis GS, Hoogwerf BJ, Young JB. Fluid retention after initiation of thiazolidinedione therapy in diabetic patients with established chronic heart failure. *J Am Coll Cardiol* 2003; **41:** 1394–98.

141 Nesto RW, Bell D, Bonow RO, et al. Thiazolidinedione use, fluid retention, and congestive heart failure: a consensus statement from the American Heart Association and American Diabetes Association. *Circulation* 2003; **108:** 2941–48.

142 Chagan L, Ioselovich A, Asherova L, Cheng JW. Use of alternative pharmacotherapy in management of cardiovascular diseases. *Am J Manag Care* 2002; **8:** 270–85.

143 Silverberg DS, Wexler D, Sheps D, et al. The effect of correction of mild anemia in severe, resistant congestive heart failure using subcutaneous erythropoietin and intravenous iron: a randomised controlled study. *J Am Coll Cardiol* 2001; **37:** 1775–80.

144 Katz SD. Mechanisms and treatment of anemia in chronic heart failure. *Congest Heart Fail* 2004; **10:** 243–47.

145 Cooper HA, Exner DV, Domanski MJ. Light-to-moderate alcohol consumption and prognosis in patients with left ventricular systolic dysfunction. *J Am Coll Cardiol* 2000; **35:** 1753–59.

146 Suskin N, Sheth T, Negassa A, Yusuf S. Relationship of current and past smoking to mortality and morbidity in patients with left ventricular dysfunction. *J Am Coll Cardiol* 2001; **37:** 1677–82.

147 McKelvie RS, Teo KK, Roberts R, et al. Effects of exercise training in patients with heart failure: the Exercise Rehabilitation Trial (EXERT). *Am Heart J* 2002; **144:** 23–30.

148 Smart N, Marwick TH. Exercise training for patients with heart failure: a systematic review of factors that improve mortality and morbidity. *Am J Med* 2004; **116:** 693–706.

149 MacMahon KM, Lip GY. Psychological factors in heart failure: a review of the literature. *Arch Intern Med* 2002; **162:** 509–16.

150 Nieminen MS, Böhm M, Cowie MR, et al. Executive summary of the guidelines on the diagnosis and treatment of acute heart failure: the Task Force on Acute Heart Failure of the European Society of Cardiology. *Eur Heart J* 2005; **26:** 384–416.

151 Kelly CA, Newby DE, McDonagh TA, et al. Randomised controlled trial of continuous positive airway pressure and standard oxygen therapy in acute pulmonary oedema; effects on plasma brain natriuretic peptide concentrations. *Eur Heart J* 2002; **23:** 1379–86.

152 Cuffe MS, Califf RM, Adams KF Jr, et al. Short-term intravenous milrinone for acute exacerbation of chronic heart failure: a randomized controlled trial (OPTIME-CHF). *JAMA* 2002; **287:** 1541–47.

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

154 Publication Committee for the VMAC Investigators (Vasodilatation in the Management of Acute CHF). Intravenous nesiritide vs nitroglycerin for treatment of decompensated congestive heart failure: a randomized controlled trial. *JAMA* 2002; **287:** 1531–40.

155 Tang WH, Hobbs RE. Novel strategies for the management of acute decompensated heart failure. *Curr Cardiol Rev* 2005; **1:** 1–5.

156 Koelling TM, Johnson ML, Cody RJ, Aaronson KD. Discharge education improves clinical outcomes in patients with chronic heart failure. *Circulation* 2005; **111:** 179–85.

157 Jaarsma T, Van Der Wal MH, Hogenhuis J, et al. Design and methodology of the COACH study: a multicenter randomised coordinating study evaluating outcomes of advising and counselling in heart failure. *Eur J Heart Fail* 2004; **6:** 227–33.

158 Bardy GH, Lee KL, Mark DB, et al. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. *N Engl J Med* 2005; **352:** 225–37.

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

160 Moss AJ, Zareba W, Hall WJ, et al. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. *N Engl J Med* 2002; **346:** 877–83.

161 Leclercq C, Kass DA. Retiming the failing heart: principles and current clinical status of cardiac resynchronization. *J Am Coll Cardiol* 2002; **39:** 194–201.

162 St John Sutton MG, Plappert T, Abraham WT, et al. Effect of cardiac resynchronization therapy on left ventricular size and function in chronic heart failure. *Circulation* 2003; **107:** 1985–90.

163 McAlister FA, Ezekowitz JA, Wiebe N, et al. Systematic review: cardiac resynchronization in patients with symptomatic heart failure. *Ann Intern Med* 2004; **141:** 381–90.

164 Mehra MR, Greenberg BH. Cardiac resynchronization therapy: caveat medicus! *J Am Coll Cardiol* 2004; **43:** 1145–48.

165 Trohman RG, Kim MH, Pinski SL. Cardiac pacing: the state of the art. *Lancet* 2004; **364:** 1701–19.

166 Cleland JG, Daubert JC, Erdmann E, et al. The effect of cardiac resynchronization on morbidity and mortality in heart failure. *N Engl J Med* 2005 Mar 7 [Epub ahead of print].

167 Strickberger SA, Conti J, Daoud EG, et al. Patient selection for cardiac resynchronization therapy. *Circulation* 2005; **111:** 2146–50.

168 Nesser HJ, Breithardt OA, Khandheria BK. Established and evolving indications for cardiac resynchronisation. *Heart* 2004; **90:** vi5–9.

169 Jones RH. Is it time for a randomized trial of surgical treatment of ischemic heart failure? *J Am Coll Cardiol* 2001; **37:** 1210–13.

170 Cleland JG, Freemantle N, Ball SG, et al. The heart failure revascularisation trial (HEART): rationale, design and methodology. *Eur J Heart Fa*il 2003; **5:** 295–303.

171 Cleland JG, John J, Dhawan J, Clark A. What is the optimal medical management of ischaemic heart failure? *Br Med Bull* 2001; **59:** 135–58.

172 Trulock EP, Edwards LB, Taylor DO, et al. The Registry of the International Society for Heart and Lung Transplantation: twenty-first official adult heart transplant report–2004. *J Heart Lung Transplant* 2004; **23:** 804–15.

173 Ogata K, Platt JL. Potential applications and prospects for cardiac xenotransplantation. *J Heart Lung Transplant* 2004; **23:** 515–26.

174 Rose EA, Gelijns AC, Moskowitz AJ, et al. Long-term mechanical left ventricular assistance for end-stage heart failure. *N Engl J Med* 2001; **345:** 1435–43.

175 Park SJ, Tector A, Piccioni W, et al. Left ventricular assist devices as destination therapy: a new look at survival. *J Thorac Cardiovasc Surg* 2005; **129:** 9–17.

176 Copeland JG, Smith RG, Arabia FA, et al. Cardiac replacement with a total artificial heart as a bridge to transplantation. *N Engl J Med* 2004; **351:** 859–67.

177 Raman JS, Byrne MJ, Power JM, Alferness CA. Ventricular constraint in severe heart failure halts decline in cardiovascular function associated with experimental dilated cardiomyopathy. *Ann Thorac Surg* 2003; **76:** 141–47.

178 Chaudhry PA, Anagnostopouls PV, Mishima T, et al. Acute ventricular reduction with the acorn cardiac support device: effect on progressive left ventricular dysfunction and dilation in dogs with chronic heart failure. *J Card Surg* 2001; **16:** 118–26.

179 Guccione JM, Salahieh A, Moonly SM, et al. Myosplint decreases wall stress without depressing function in the failing heart: a finite element model study. *Ann Thorac Surg* 2003; **76:** 1171–80.

180 Menasche P. Myoblast transfer in heart failure. *Surg Clin North Am* 2004; **84:** 125–39.

181 Sesti C, Kloner RA. Gene therapy in congestive heart failure. *Circulation* 2004; **110:** 242–43.

182 Melo LG, Pachori AS, Kong D, et al. Gene and cell-based therapies for heart disease. *FASEB J* 2004; **18:** 648–63.

183 Goodlin SJ, Hauptman PJ, Arnold R, et al. Consensus statement: palliative and supportive care in advanced heart failure. *J Card Fail* 2004; **10:** 200–09.

184 Pantilat SZ, Steimle AE. Palliative care for patients with heart failure. *JAMA* 2004; **291:** 2476–82.

185 Gottlieb SS, Skettino SL, Wolff A, et al. Effects of BG9719 (CVT-124), an A1-adenosine receptor antagonist, and furosemide on glomerular filtration rate and natriuresis in patients with congestive heart failure. *J Am Coll Cardiol* 2000; **35:** 56–59.

186 Hsu LF, Jais P, Sander P, et al. Catheter ablation for atrial fibrillation in congestive heart failure. *N Engl J Med* 2004; **35:** 2373–83.

187 Atrial Fibrillation and Congestive Heart Failure (AF-CHF) Trial investigators. Rationale and design of a study assessing treatment strategies of atrial fibrillation in patients with heart failure: *Am Heart J* 2002; **144:** 597–607.

188 Sin DD, Logan AG, Fitzgerald TS, et al. Effects of continuous positive airway pressure on cardiovascular outcomes in hear failure patients with and without Cheyne-Stokes respiration. *Circulation* 2000; **102:** 61–66.

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

190 del Monte F, Harding SE, Dec GW, et al. Targeting phospholamban by gene transfer in human heart failure. *Circulation* 2002; **105:** 904–07.

191 Freudenberger RS, Schwarz RP Jr, Brown J, et al. Rationale, design and organisation of an efficacy and safety study of oxypurinol added to standard therapy in patients with NYHA class III-IV congestive heart failure. *Expert Opin Investig Drugs* 2004; **13:** 1509–16.