Heart failure

Henry Krum, William T Abraham

Despite advances in management of heart failure, the condition remains a major public-health issue, with high prevalence, poor clinical outcomes, and large health-care costs. Risk factors are well known and, thus, preventive strategies should have a positive effect on disease burden. Treatment of established systolic chronic heart failure includes use of agents that block the renin-angiotensin-aldosterone and sympathetic nervous systems to prevent adverse remodelling, to reduce symptoms and prolong survival. Diuretics are used to achieve and maintain euvolaemia. Devices have a key role in management of advanced heart failure and include cardiac resynchronisation in patients with evidence of cardiac dyssynchrony and implantation of a cardioverter defibrillator in individuals with low ejection fraction. Approaches for treatment of acute heart failure and heart failure with preserved ejection fraction are supported by little clinical evidence. Emerging strategies for heart failure management include individualisation of treatment, novel approaches to diagnosis and tracking of therapeutic response, pharmacological agents aimed at new targets, and cell-based and gene-based methods for cardiac regeneration.

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Centre of Cardiovascular Research and Education in Therapeutics, School of Public Health and Preventive Medicine, Monash University, Melbourne, VIC, Australia (Prof H Krum FRACP); **and Division of Cardiovascular Medicine, Davis Heart and Lung Research Institute, Ohio State University, Columbus, OH, USA** (Prof W T Abraham MD)

Correspondence to:
Prof Henry Krum, Centre of Cardiovascular Research and Education in Therapeutics, School of Public Health and Preventive Medicine, Monash University and Alfred Hospital, Melbourne, VIC 3004, Australia
henry.krum@med.monash.edu.au

Introduction

Considerable advances have been made in management of heart failure over the past few decades. In outpatient-based clinical trials, mortality has more than halved in people with established systolic chronic heart failure; moreover, admissions have fallen and patients' quality of life has risen. Nevertheless, heart failure remains a major public-health issue, with high prevalence and poor outcomes. Management of this condition includes appropriate non-pharmacological strategies, use of drugs (particularly those that inhibit key activated neurohormonal systems), and implantation of devices in appropriate patients. Surgery and transplantation are also options for selected individuals with highly advanced disease.

Despite the promise of new drugs, cell-based therapeutic approaches, and novel devices, a reduction of disease burden is likely to come from preventive strategies. The antecedents to heart failure are well known; enhanced diagnostic precision coupled with early intervention could lessen the burden of disease. In this Seminar we will review recent and emerging data for epidemiology and diagnosis and current and future management techniques to ameliorate heart failure.

Epidemiology

Heart failure is a clinical syndrome and, thus, definitions are imprecise. Most include references to typical symptoms and objective evidence of abnormal ventricular function.[1] Estimates of heart failure prevalence and incidence vary greatly because of non-uniformity in the definition, absence of a gold-standard measure for the disorder, and paucity of adequate and true epidemiological surveys. Furthermore, such data are confined largely to developed countries, although heart failure seems to be growing in developing nations.[2]

Prevalence of heart failure rises steeply with increasing decades of life, particularly from age 50 years;[3] the condition is rare in individuals younger than this age. In a cross-sectional survey of residents of Olmsted County, MN, USA, older than 45 years, overall prevalence was 2·2%, falling to 0·7% in those aged 45–54 years and rising to 8·4% for those 75 years or older.[4] Findings of previous studies in similar populations support these frequencies.[3,5] Asymptomatic systolic left-ventricular dysfunction occurs in about half of patients with impaired left-ventricular systolic function.[6]

Prevalence of heart failure with preserved ejection fraction is highly dependent on how this syndrome is defined, which in itself is a complex and controversial issue.[7] Abnormalities of diastolic function rise more steeply with increasing decade of life than does left-ventricular systolic dysfunction, with prevalence up to 15·8% in people older than 65 years, on the basis of European echocardiographic criteria.[8] In the Olmsted County study, researchers assessed echocardiographic variables for diastolic dysfunction and noted that 44% of people with heart failure had an ejection fraction higher than 50%.[4] Furthermore, 7·3% of individuals older than 45 years had moderate or severe diastolic dysfunction, based on their meeting two or more predefined echocardiographic criteria for severity.[4]

Assessments of incidence of heart failure are scarce. In the Hillingdon West London study, incidence in a population aged 45–55 years was 0·2 per 1000 person-years, rising to 12·4 per 1000 person-years in people older than 85 years.[9] This rate was based on new admissions and clinical referrals for suspected heart failure, with diagnosis confirmed by a panel of cardiologists. In the Rotterdam study, incidence was slightly higher (44 per

Search strategy and selection criteria

We searched the Cochrane library, Medline, and EmBase with the search terms "heart failure", "cardiac failure", and "cardiac dysfunction". We largely selected publications from the past 5 years but did not exclude earlier reports that might have been of relevance. We also searched guideline documents, governmental reports, and chapters of relevant books. Since this Seminar is an update of a similar Review published in *The Lancet* in 2005, we focused mainly on data and references reported since that time.

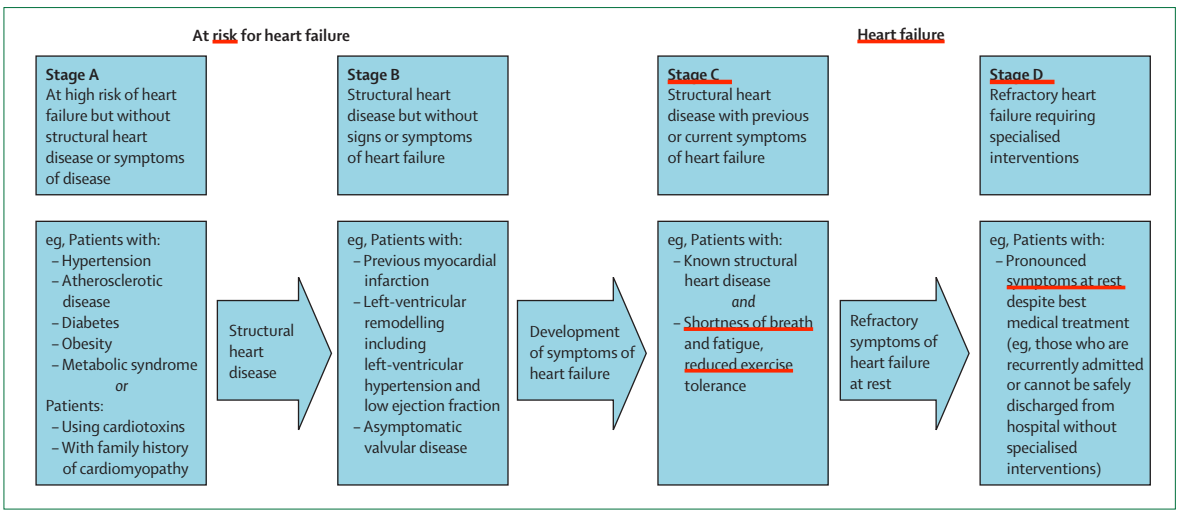

Figure 1: **Stages of heart failure**
Adapted from reference 30, with permission of the American Heart Association.

1000 person-years in individuals 85 years or older) than in the Hillingdon study and was ascertained from symptoms, signs, and relevant drug use.[10]

Age-adjusted incidence of heart failure has not declined substantially in the past 20–30 years,[11,12] despite enhanced control of causal factors including myocardial infarction, coronary artery disease, and hypertension. Potential reasons for this absence of reduction in incidence include a rise in frequency of heart failure risk factors, such as diabetes and obesity.[12] In view of the ageing of the population, non-age-adjusted incidence is likely to increase in the future. Indeed, lifetime risk of developing heart failure at the age of 40 years is close to 20% in both men and women.[13]

Admissions for heart failure have risen greatly over the past few decades, but could have now peaked.[14] The cause of the plateau in heart failure admissions might relate to improvements in pharmacological treatments and the advent of heart failure clinics and specific disease-management programmes. However, a growth in the proportion of patients admitted with heart failure with preserved ejection fraction has been noted;[15] again almost certainly on the basis of increasing prevalence of risk factors for this condition, such as hypertension, atrial fibrillation, and diabetes mellitus.

About two-thirds of the economic burden of heart failure is accounted for by admissions to hospital.[16] In one study, 44% of patients admitted with a primary discharge diagnosis of heart failure were readmitted within 6 months, every admission costing in excess of US$7000 per patient.[17] In Australia, with a population of just over 20 000 000, heart failure consumes AU$1000 million of the health-care budget every year.[18]

Demographic characteristics of patients with chronic heart failure have been derived from data of community-based studies supplemented by information from randomised controlled trials of new therapeutic strategies. In general, findings of community-based assessments show that affected individuals are most likely to be old, female, and have associated comorbidity.[19]

Comorbidities include either causal factors underlying heart failure or diseases that might affect prognosis or treatment. Systemic hypertension is the most frequent and well described comorbidity, relevant to both systolic heart failure and heart failure with preserved ejection fraction. Compared with data of epidemiological studies such as Framingham,[20] findings of intervention studies in heart failure[21] have underestimated the contribution of hypertension,[19] perhaps because this diagnosis is usually embedded within ischaemic and other causes.

Coronary artery disease can lead to heart failure through various mechanisms. Extensive myocardial necrosis can result in pump failure. Infarction of small areas can cause regional contractile dysfunction and adverse remodelling with myocyte hypertrophy, apoptosis, and deposition of extracellular matrix. Furthermore, transient reversible ischaemia can arise with episodic dysfunction, even in the presence of typical resting left-ventricular function.[22]

Diabetes mellitus is an important and sometimes overlooked comorbidity in patients with heart failure.[23] People with diabetes are at strikingly higher risk of heart failure than are those without the disease,[24] and they have higher mortality.[25] The existence of a specific diabetic cardiomyopathy, independent of concomitant hypertension and large-vessel coronary artery disease, has been much debated. In support of this possibility, asymptomatic diastolic dysfunction is a frequent finding on echocardiographic investigation of individuals with diabetes.[26] Furthermore, altered autonomic and endothelial function, advanced glycation end-product deposition,[27] and disordered energy metabolism are shared traits of both diabetes and heart failure.[23]

Both ventricular and atrial arrhythmias are typical associated disorders and can be implicated as causes of heart failure. Many factors contribute to the high rate of arrhythmias in chronic heart failure, including ischaemic heart disease, electrophysiological abnormalities, myocardial hypertrophy, and activation of several key neurohormonal systems.[28] Moreover, patients might be taking proarrhythmic drugs. Furthermore, many heart failure agents cause electrolyte abnormalities that could exacerbate the underlying risk.

Other important comorbidities include respiratory disorders such as chronic airflow obstruction and sleep apnoea, cognitive dysfunction, depression, anaemia, chronic kidney disease, and arthritis.[29] All comorbid disorders add considerable complexity to diagnosis and management.

Pathophysiology

Heart failure has been described variously as: (1) an oedematous disorder, whereby abnormalities in renal haemodynamics and excretory capacity lead to salt and water retention; (2) a haemodynamic disorder, characterised by peripheral vasoconstriction and reduced cardiac output; (3) a neurohormonal disorder, predominated by activation of the renin-angiotensin-aldosterone system (RAAS) and adrenergic nervous system; (4) an inflammatory syndrome, associated with increased local and circulating proinflammatory cytokines; and (5) a myocardial disease, initiated by injury to the heart followed by pathological ventricular remodelling. In fact, these descriptions of heart failure pathophysiology are not mutually exclusive and all factor in the onset and progression of the clinical syndrome of heart failure. Moreover, development of heart failure generally proceeds in stages, from risk factors to end-stage or refractory disease (figure 1).[30]

Heart failure is usually associated with a structural abnormality of the heart. The initial injury might be sudden and obvious (eg, myocardial infarction) or insidious (eg, longstanding hypertension). In some instances, such as idiopathic dilated cardiomyopathy, it is unknown. Once the injury happens, a series of initially compensatory but subsequently maladaptive mechanisms ensue (figure 2).

Compensatory mechanisms that are activated in heart failure include: increased ventricular preload, or the Frank-Starling mechanism, by ventricular dilatation and volume expansion;[31] peripheral vasoconstriction, which initially maintains perfusion to vital organs; myocardial hypertrophy to preserve wall stress as the heart dilates; renal sodium and water retention to enhance ventricular preload; and initiation of the adrenergic nervous system, which raises heart rate and contractile function.[32] These processes are controlled mainly by activation of various neurohormonal vasoconstrictor systems, including RAAS, the adrenergic nervous system, and non-osmotic release of arginine-vasopressin.[33] These and other mechanisms contribute to the symptoms, signs, and poor natural history of heart failure. In particular, an increase in wall stress along with neurohormonal activation facilitates pathological ventricular remodelling; this process has been closely linked to heart failure disease progression.[34] Management of chronic heart failure targets these mechanisms and, in some instances, results in reverse remodelling of the failing heart.

Diagnosis

Heart failure is a clinical syndrome, with diagnosis based on a combination of typical symptoms and signs together with appropriate clinical tests. Presentation can be non-specific and mimicked by many other disease states, especially in elderly people. Unsurprisingly, sensitivity and specificity of frequent presenting symptoms of heart failure are rather poor. Signs of heart failure—such as raised jugular venous pulse, a third heart sound, basal pulmonary crackles, and sinus tachycardia—have somewhat greater specificity for a heart failure diagnosis than do symptoms, at least in some assessments.[35]

Routine objective testing methods, such as electrocardiograms (ECGs) and chest radiographs, are also fairly non-specific. The ECG is, however, a reasonable rule-out test for systolic dysfunction—ie, this diagnosis is somewhat unlikely if the ECG is entirely normal.[36]

Laboratory testing can provide useful information about cause of heart failure, disease severity, and prognosis. Such data are especially valuable if important comorbid disorders (eg, anaemia, hyponatraemia, renal dysfunction, and diabetes) are also present.

Echocardiography is a useful method to assist in diagnosis of heart failure. This modality can provide

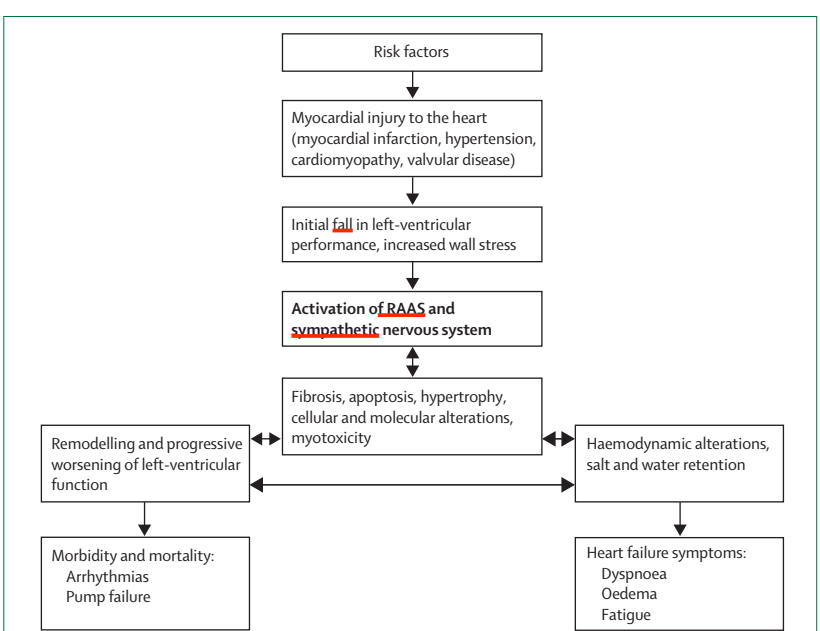

Figure 2: **Simplified view of heart failure pathophysiology**

important information about left-ventricular dimensions and geometry, extent of systolic dysfunction, whether dysfunction is global or segmental, the status of valve apparatus, and estimates of pulmonary pressures. Echocardiography is most specific for diagnosis of left-ventricular systolic dysfunction. Conversely, assessment of diastolic dysfunction remains elusive, even with the advent of tissue doppler imaging, a technique that provides important information on patterns of diastolic relaxation and filling. Tissue doppler imaging can also provide data on ventricular dyssynchrony.

New imaging modalities such as MRI, especially with gadolinium contrast, provide great precision for assessment of ventricular structure and function.[37] However, use of MRI to measure progression of established heart failure is limited by presence of device hardware in many patients.

Measurement of amounts in plasma of either B-type natriuretic peptide (BNP) or its precursor, N terminal-proBNP, has aided diagnosis of heart failure. In patients presenting with acute dyspnoea, area under the receiver-operating characteristic curve is 0·90, indicating relatively high sensitivity and specificity for this peptide compared with the gold standard of diagnosis by a cardiologist on the basis of available clinical information.[38] Low BNP has very high negative predictive value, making it a useful rule-out test, particularly in populations in which frequency of heart failure is expected to be high.[38] By contrast, use of BNP for community-based screening of presence of left-ventricular dysfunction can be complicated by low background disease prevalence.[39]

Clinical use of BNP for diagnosis of heart failure has been criticised,[40] in that patients with high concentrations of this peptide typically have classic signs, symptoms, and laboratory values greatly indicative of the disorder—ie, an accurate diagnosis can be made on clinical grounds. For individuals in whom a diagnosis of heart failure is less clear, BNP amounts often fall within an uncertain grey zone. The usefulness of this peptide is lessened by the fact that amounts are raised with advanced age, female sex, and renal impairment and are lowered with obesity.[41] Nevertheless, plasma BNP testing is emerging as a useful aid for diagnosis of heart failure.

Non-pharmacological treatment

Physical activity is recommended for people with stabilised, non-decompensated chronic heart failure.[42] Findings of several controlled studies of both aerobic and resistance exercise regimens have indicated improvements in surrogate measures of ventricular function[43] and patient's wellbeing.[42] A definitive role in prolonging survival has, however, not been shown as yet, although studies are ongoing.[44]

Salt restriction has been recommended even for patients without overt clinical signs of salt and water overload. This guideline is based on limited clinical data; indeed, some findings suggest that a salt-restricted diet could be detrimental for people with heart failure.[45] This possibility needs further clinical investigation. Other dietary recommendations include ensuring adequate nutrient and micronutrient status in heart failure patients. Studies of nutritional supplementation such as with coenzyme Q10[46] and micronutrient supplementation have yielded variable results.[47] However, much of the data in this area are of low quality, with a need for adequately powered randomised controlled trials.

The issue of weight loss and obesity is complex. Heart failure is a condition of catabolic excess, and even though obesity is an antecedent risk factor for subsequent heart failure, once the disease is established there seems to be so-called reverse epidemiology, whereby patients with the greatest body-mass index are those with better survival.[48] This situation could be related to the syndrome of cardiac cachexia, which in turn is affected by activation of several important proinflammatory cytokines, including tumour necrosis factor α and interleukin 2.[49] In view of these complexities, nutritional advice from a dietician is important.

Psychosocial support is another recommended[29] component of heart failure management because of high rates of comorbid depression and complexity in the treatment of the heart failure patient with depression. A strategy might include use of cognitive behavioural therapy, antidepressants, or both,[50] although specific trials in heart failure populations are scarce.

Other guideline recommendations—sometimes without a strong evidence base—include alcohol restriction (especially if heart failure has an alcoholic cause), smoking cessation, vaccination against influenza and pneumococcus (*Streptococcus pneumoniae*), avoidance of high-altitude destinations, and bed rest for individuals who are acutely decompensated.[29,30,51]

Management strategies that might include use of drugs, devices, and surgery are generally underpinned by the non-pharmacological treatments. Multidisciplinary approaches have yielded impressive reductions in readmission rates in randomised trials.[52]

Drug treatment

Antecedent risk factors for development of left-ventricular systolic dysfunction and heart failure are well recognised and typically include hypertension, ischaemic heart disease, and diabetes mellitus. Aggressive treatment via blood pressure control and adequate monitoring of the lipid profile and glycaemic status is important for prevention.[53,54] However, management of glycaemic status with agents such as thiazolidenediones could exacerbate heart failure.[55] Other frequent causes of left-ventricular dysfunction and heart failure include alcohol abuse and use of cardiotoxic drugs—both prescription (eg, anthracyclines, trastuzumab) and illicit (eg, cocaine).

Preventive treatment with an angiotensin-converting-enzyme (ACE) inhibitor is recommended for individuals at high risk of—but without known—ventricular

dysfunction, on the basis of data from studies such as HOPE.[56] In asymptomatic patients with known left-ventricular systolic dysfunction, ACE inhibitors unequivocally prevent progression of disease and major clinical events.[57] Reduced mortality was also noted with ACE inhibition in people with recent myocardial infarction and left-ventricular systolic dysfunction, but without heart failure symptoms.[58] Treatment with a β blocker should be commenced early after a myocardial infarction if patients have systolic left-ventricular dysfunction, even if they are asymptomatic.[59]

Drug treatment of systolic heart failure is focused on relief of symptoms and prolongation of survival. Symptom relief is attained mainly with diuretics, to achieve and maintain euvolaemia in patients with volume overload. At present, no evidence exists to show that these agents prolong survival, and their use could activate key neurohormonal systems such as RAAS.[60] Increased mortality has been observed with potassium-depleting versus potassium-sparing diuretics in retrospective analyses of major trials.[61]

RAAS is important for progression of the heart failure disease process; conversely, attenuation of this system has yielded considerable benefit in management of systolic heart failure. Indeed, ACE inhibitors are beneficial across the entire range of disease severity.[62,63] Angiotensin-receptor blockers (ARBs) seem to be a reasonable alternative for patients unable to tolerate ACE inhibitors—

	Population	Aim	Active drug/class	Comparator	n	Primary endpoint	Relative risk ratio in primary endpoint	Trial conclusions
Prevention of left-ventricular dysfunction and heart failure								
HOPE (2000)[56]	Previous and at high risk for CVD (no heart failure) and risk factors	ACE inhibitor in CVD prevention	Ramipril/ACE inhibitor	Placebo	9297	Myocardial infarction, stroke, cardiovascular death	0·22	ACE inhibitor lowered new heart failure development
SOLVD Prevention (1992)[57]	Asymptomatic left-ventricular systolic dysfunction (LVEF <35%)	ACE inhibitor in asymptomatic left-ventricular systolic dysfunction	Enalapril/ACE inhibitor	Placebo	4228	Total mortality, cardiovascular mortality	0·08/0·12	ACE inhibitor lowered new heart failure development and non-significantly reduced mortality
Treatment of systolic heart failure: mild-to-moderate								
DIG (1997)[76]	LVEF <45%, NYHA III–IV	Digoxin in symptomatic systolic heart failure	Digoxin/digitalis glycoside	Placebo	6800	Total mortality	0·00	No mortality benefit for digoxin
SOLVD-Treatment (1991)[62]	LVEF <35%, NYHA II–IV	ACE inhibitor in symptomatic systolic heart failure	Enalapril/ACE inhibitor	Placebo	2569	Total mortality	0·16	ACE inhibitor lowered mortality
CIBIS-II (1999)[70]	LVEF <35%, NYHA III–IV	β blocker in symptomatic systolic heart failure	Bisoprolol/β blocker	Placebo	2647	Total mortality	0·34	β blocker lowered mortality in moderate-to-severe systolic heart failure
MERIT-HF (1999)[71]	LVEF ≤40%, NYHA II–IV	β blocker in symptomatic systolic heart failure	Metoprolol succinate/β blocker	Placebo	3951	Total mortality	0·34	β blocker lowered mortality in mild-to-severe systolic heart failure
CIBIS-III (2005)[75]	LVEF <35%, NYHA II–III	β blocker *vs* ACE inhibitor first in systolic heart failure	Bisoprolol/β blocker	Enalapril/ACE inhibitor	1110	Total mortality or admission	0·03	β blocker or ACE inhibitor can be considered first in systolic heart failure
Val-HeFT (2001)[65]	LVEF <40%, NYHA II–III	ARB in symptomatic systolic heart failure	Valsartan/ARB	Placebo	5010	Total mortality, morbidity	0·00/0·13	ARB lowered morbidity
COMET (2003)[74]	LVEF <35%, NYHA II–IV	β1 selective *vs* non-selective β blocker in systolic heart failure	Carvedilol/selective β blocker	Metoprolol tartrate/β blocker	3029	Total mortality	0·17	Reduced mortality with carvedilol
CHARM-Added (2003)[66]	LVEF ≤40%, NYHA II–IV	ARB in symptomatic systolic heart failure	Candesartan/ARB	Placebo	2548	Cardiovascular mortality or chronic heart failure admission	0·15	Combined morbidity and mortality benefit of adding ARB
ATLAS (1999)[88]	LVEF ≤30%, NYHA II–IV	High-dose *vs* low-dose ACE inhibitor in systolic heart failure	Lisinopril/ACE inhibitor 2·5–5·0 mg/day	Lisinopril/ACE inhibitor 32·5–35 mg/day	3164	Total mortality/total mortality and NEP	0·08/0·12	Little mortality reduced with high-dose ACE inhibitor
SENIORS (2005)[73]	NYHA II–IV, age >70 years	β blocker in elderly heart failure	Nebivolol/β blocker	Placebo	2128	Total mortality and cardiovascular admission	0·14	Combined morbidity and mortality benefit of β blocker
CORONA (2007)[86]	LVEF ≤40% (NYHA III–IV), LVEF ≤35% (NYHA II), age >60 years	Statin in ischaemic heart failure	Rosuvastatin/statin	Placebo	5011	Cardiovascular death, non-fatal myocardial infarction, non-fatal stroke	0·08	No significant reduction in heart failure or major cardiovascular events

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	Population	Aim	Active drug/ class	Comparator	n	Primary endpoint	Relative risk ratio in primary endpoint	Trial conclusions
(Continued from previous page)								
Treatment of systolic heart failure: severe								
RALES (1999)[68]	LVEF <35%, NYHA IIIB and IV	Aldosterone blocker in severe heart failure	Spironolactone/ aldosterone blocker	Placebo	1663	Total mortality	0·30	Reduced mortality with aldosterone blocker
CONSENSUS (1987)[63]	NYHA IV	ACE inhibitor in severe heart failure	Enalapril/ACE inhibitor	Placebo	253	Total mortality	0·40	Lowered mortality with ACE inhibitor in end-stage heart failure
COPERNICUS (2001)[72]	LVEF <25%, severe heart failure	β blocker in severe heart failure	Carvedilol/ β blocker	Placebo	2289	Total mortality	0·35	Reduced mortality with β blocker in severe chronic heart failure
Treatment of heart failure with preserved ejection fraction								
CHARM-Preserved (2003)[89]	LVEF >40%, NYHA II–IV	ARB in heart failure with preserved ejection fraction	Candesartan/ ARB	Placebo	3023	Cardiovascular mortality on chronic heart failure admission	0·11	Non-significant reduction in combined mortality and morbidity
PEP-CHF (2006)[90]	Age >70 years, heart failure, WMI >1·4	ACE inhibitor in heart failure with preserved ejection fraction	Perindopril/ ACE inhibitor	Placebo	850	Total mortality or chronic heart failure admission	0·09	Non-significant reduction in combined mortality and morbidity
Treatment of comorbidities in heart failure								
ANDROMEDA (2008)[91]	NYHA II–IV, WMI ≤1·2	Antiarrhythmic in systolic heart failure	Dronedarone	Placebo	627	Total mortality or chronic heart failure admission	0·38 increased risk	Increased early mortality in systolic heart failure with dronedarone
AF-CHF (2008)[92]	LVEF <35%, atrial fibrillation, NYHA III–IV	Rhythm *vs* rate control in atrial fibrillation and systolic heart failure	Increased β blocker or digoxin with or without atrioventricular node ablation and permanent pacemaker	Antiarrhythmic drug with or without electrical cardioversion Amiodarone (with or without sotalol, dofetilide for maintenance)	1376	Cardiovascular death	0·06 increased risk	No difference in rhythm *vs* rate control on major events

CVD=coronary vascular disease. LVEF=left-ventricular ejection fraction. WMI=wall-motion index.

Table: **Summary of key pharmacological studies in heart failure prevention and treatment**

eg, because of cough.[64] Use of ACE inhibitors additional to ARBs is somewhat uncertain. A combined morbidity and mortality benefit was recorded in both Val-HeFT[65] and CHARM-Added studies,[66] although findings of neither study could show a clearcut survival benefit over placebo when ARBs were added to ACE inhibitors in individuals with mild-to-moderate heart failure.

By contrast, use of the aldosterone-receptor antagonist, spironolactone, in patients with advanced disease (class III–IV systolic heart failure) yielded clearcut survival benefits additional to background ACE inhibition,[67] although only a few people were receiving β blockers. Furthermore, the selective aldosterone-receptor antagonist eplerenone was of benefit in individuals with systolic heart failure early after myocardial infarction.[68] The role of aldosterone-receptor-blocking drugs in less severe forms of systolic heart failure is uncertain but under investigation in a large clinical outcome study.[69]

β blockers are a cornerstone of systolic heart failure management. Chronic activation of the sympathetic nervous system—the cardiac effects of which are attenuated by β blockers—has a key role in heart failure disease progression, including fibrosis, necrosis, apoptosis, and arrythmogenesis. The beneficial effects of β blockers have largely been seen additional to background ACE inhibition and, therefore, both are judged mandatory treatment. These effects have been shown in patients with stable systolic heart failure across a broad range of disease severities, with bisoprolol, carvedilol, and extended-release metoprolol.[70–72] A combined morbidity and mortality benefit has been reported with nebivolol, specifically within an elderly population.[73]

Since β blockers are a heterogeneous class of drugs, choice of agent can be important. In the COMET study,[74] the β1 β2 α1-blocking agent, carvedilol, was superior on mortality outcomes compared with the β1-selective agent, immediate-release metoprolol. Researchers on the CIBIS III study[75] raised the hypothesis that the order of initiation of ACE inhibitors and β blockers might not be vital to outcomes provided that, eventually, the patient is receiving appropriate doses of both classes of drug in a timely manner.

Several other pharmacological agents can be useful in systolic heart failure but have been relegated to second-

line status because reports of survival benefit are scarce. Digoxin still has an important role in patients with systolic heart failure and concomitant atrial fibrillation. Its use in patients with systolic heart failure in sinus rhythm is confined largely to reduction of hospital admissions,[76] without evidence of any overall survival benefit. However, in a retrospective analysis of attained plasma concentrations of the drug, a steady state amount of 0·5–0·8 μg/L achieved the best outcomes.[77]

Hydralazine and nitrates were marginally superior to placebo with respect to survival in the Ve-HeFT-I study;[78] however, they were clearly inferior to ACE inhibitors in VeHeFT-II.[79] In a major study of African-American heart failure patients (who generally have low plasma renin concentrations and, thus, are theoretically less responsive to RAAS blockade), hydralazine and nitrates did seem to be of clinical use.[80] Dihydropyridine calcium-channel blockers such as amlodipine[81] and felodipine[82] have a neutral effect in systolic heart failure and, therefore, can be safely used in individuals who need these agents for other indications—eg, systemic hypertension and angina pectoris.

Taken together, use of ACE inhibitors, β blockers, and aldosterone-receptor antagonists or ARBs have had a major effect on chronic heart failure mortality rates compared with the pre-neurohormonal therapy era.[83] In this context, demonstration of further incremental benefits with new agents on survival or clinically relevant endpoints such as heart failure admission has been difficult. Drugs targeting inhibition of tumour necrosis factor α, endothelin, and vasopressin, and those that additionally augment natriuretic peptides, have not shown superiority over conventional treatments.[84] Other agents have been studied in large-scale trials. Statins are frequently used in patients with heart failure[85] but there is equipoise about their use in this setting. In the CORONA trial,[86] workers assessed rosuvastatin in ischaemic systolic heart failure but did not note a significant reduction in the primary combined morbidity and mortality endpoint compared with placebo. Researchers are soon to report data on statin therapy in patients with both systolic heart failure and heart failure with preserved ejection fraction and ischaemic and non-ischaemic causes.[87]

The table summarises key pharmacological trials of prevention and treatment of heart failure. In addition to drugs that are indicated in systolic heart failure, many agents are contraindicated (panel).[29] These include compounds that might be implicated in the underlying cause of heart failure or those that exacerbate established disease.

Use of devices

Three types of device have proven safe and effective for treatment of systolic heart failure: (1) atrial-synchronised biventricular pacing (also called cardiac resynchronisation therapy); (2) implantable cardioverter defibrillators; and (3) in highly selected patients, left-ventricular assist devices. The rationale for cardiac resynchronisation therapy is based on the presence of ventricular dyssynchrony, which is currently defined as a QRS duration of at least 120 ms on the surface ECG.[30] Dyssynchrony can arise between the left and right ventricles and within the left ventricle, impairing the ability of the heart to function as a pump. This disorder can be improved by biventricular pacing, which is accomplished through simultaneous pacing of both the left and right ventricles.

More than 4000 patients have been assessed in randomised controlled trials of cardiac resynchronisation therapy.[93–102] Taken together, data for this technique show consistently enhanced quality of life, functional status, exercise capacity, and ventricular structure and function, and reductions in morbidity and mortality. As noted in the CARE HF study,[100] cardiac resynchronisation therapy without an implantable cardioverter defibrillator and with best medical treatment lowered all-cause mortality by 36% compared with best medical treatment alone. In terms of clinical outcomes and remodelling, no predictors of responsiveness to cardiac resynchronisation therapy have emerged. Although the reverse remodelling effect of this device method is quantitatively greater in non-ischaemic than in ischaemic patients, diminished morbidity and mortality seen with cardiac resynchronisation therapy is the same in these two subgroups of individuals.

***Panel:* Contraindicated drugs in heart failure**

Antiarrhythmic agents
Proarrhythmic potential, negative inotropic effects, associated increased mortality

Non-dihydropyridine calcium antagonists
Direct negative inotropic agents, such as verapamil and diltiazem, are contraindicated in patients with systolic chronic heart failure

Tricyclic antidepressants
Proarrhythmic potential

Non-steroidal anti-inflammatory drugs
Inhibit the effects of diuretics and ACE inhibitors, cause salt and water retention, can worsen both cardiac and renal function

Cyclo-oxygenase 2 inhibitors
Similar adverse effects on salt and water retention as non-selective non-steroidal anti-inflammatory drugs

Corticosteroids
Adverse effects on salt and water retention

Doxorubicin and trastuzumab
Dose-dependent toxic effects with anthracyclines, dose-independent toxic effects with trastuzumab

Thiazolidinediones
Fluid retention, mechanism contentious

Data of the COMPANION trial suggested an incremental mortality reduction with a combined device strategy of cardiac resynchronisation therapy and an implantable cardioverter defibrillator.[102] However, this observation remains somewhat controversial, and selection of cardiac resynchronisation therapy versus a combined device depends on the separate indications for these two device methods. At present, patients with left-ventricular ejection fraction less than or equal to 35%, normal sinus rhythm, and New York Heart Association (NYHA) functional class III or ambulatory class IV symptoms despite best medical treatment who have ventricular dyssynchrony should receive cardiac resynchronisation therapy, unless contraindicated. Few contraindications to this method exist but could include comorbidity expected to limit the success of the procedure and excessive risk in patients who are too ill to undergo device implantation.

Implantable cardioverter defibrillators were initially given to survivors of sudden cardiac death to treat recurrent episodes of ventricular tachycardia or ventricular fibrillation. People with left-ventricular dysfunction, either from ischaemic or non-ischaemic causes, are at increased risk for sudden cardiac death[103,104]. Thus, the notion that implantable cardioverter defibrillators might be useful for primary prevention of sudden cardiac death in heart failure patients was tested in a series of randomised controlled trials. This idea was proven in patients with a previous (older than 1 month) myocardial infarction with left-ventricular systolic dysfunction with or without symptomatic heart failure[105] and in individuals with either an ischaemic or a non-ischaemic cause of chronic systolic heart failure.[106] Although underpowered to show a significant difference for its primary endpoint, data of the DEFINITE trial provided evidence to support prophylactic intervention with an implantable cardioverter defibrillator for management of non-ischaemic heart failure.[107] In these three trials, a 23–31% reduction in all-cause mortality was attributable to diminished risk for sudden cardiac death in patients randomly allocated an implantable cardioverter defibrillator and best medical treatment versus those assigned best medical care alone.

On the basis of these findings, the indication for an implantable cardioverter defibrillator has been extended to NYHA class II and III heart failure patients with reduced ejection fractions less than or equal to 35% who have a reasonable expectation of survival with good functional status for more than 1 year. People meeting criteria for both cardiac resynchronisation therapy and an implantable cardioverter defibrillator could receive a combined device strategy.

Technical difficulties associated with combined device treatment are generally the same as those encountered with pacemakers—eg, poor capture thresholds, programming errors, and lead fractures. Biventricular capture and adequate delivery of cardiac resynchronisation therapy are essential for this method. With implantable cardioverter defibrillators, occasional absence of discrimination between ventricular and supraventricular tachyarrhythmias could lead to inappropriate shocks.

Ventricular assist devices are blood pumps used to support the failing heart in patients with end-stage heart failure. Left-ventricular assist devices are used in three clinical situations: (1) in individuals listed for transplantation but who need support before a suitable donor heart becomes available; (2) as a bridge to recovery in people with potentially reversible forms of heart failure, such as myocarditis or post-partum cardiomyopathy; and (3) as so-called destination therapy for patients not judged candidates for transplantation. People awaiting transplantation who receive a left-ventricular assist device have good survival to transplantation, and post-transplant survival is equal to that seen with unsupported patients.[108] Researchers on the REMATCH trial compared best medical treatment alone (including use of continuous intravenous inotropes) with implantation of a left-ventricular assist device in a few people with ultra-end-stage heart failure.[109] Individuals randomly allocated the device benefited from enhanced survival and quality of life compared with the medically treated group. However, outcome was limited in patients assigned the implant by the pulsatile device technology available at the time. The US Food and Drug Administration has approved a new generation axial flow pump for the bridge-to-transplant indication; this device is undergoing assessment for destination therapy.

Other devices used to treat heart failure include provision of continuous positive airways pressure to individuals with comorbid sleep apnoea[110] and ultrafiltration for people with severe volume overload.[111] In a study of 200 patients,[111] greater fluid and weight loss was noted with ultrafiltration than with intravenous diuretics.

Surgical approaches

Although cardiac transplantation remains the ultimate surgical strategy for heart failure, the poor availability of suitable donor organs renders this option epidemiologically insignificant. For the few patients receiving a transplanted heart, 1-year survival approaches 85%, 5-year survival is about 75%, and 50% of adult recipients will be alive at 10 years.[112] Functional status of transplant recipients is very good: 80–85% have no activity limitations for up to 7 years after transplantation and fewer than 5% need total assistance at any time.

Other surgical approaches to heart failure include revascularisation for ischaemic heart failure, mitral valve repair to address functional mitral regurgitation associated with pathological ventricular remodelling, and surgical reconstruction of the size and shape of the failing left ventricle to render it a more effective pump. None of these surgical techniques has been tested

satisfactorily in adequately powered, randomised controlled trials.

Revascularisation strategies, either percutaneous or surgical, may reduce the frequency of heart failure in patients with atherosclerotic vascular disease. Coronary revascularisation can relieve symptoms of myocardial ischaemia, and coronary-artery bypass surgery lessens angina and diminishes risk of death in people who have multi-vessel disease, decreased left-ventricular ejection fractions, and stable angina.[113] Researchers on the STICH trial are assessing whether or not surgical revascularisation slows the natural history of ischaemic heart disease in association with established symptomatic heart failure. At the present time, key factors affecting the decision to revascularise the myocardium in heart failure include medically refractory angina pectoris associated with demonstration of viable myocardium and surgically acceptable target vessels.

Functional mitral regurgitation is typical in patients with left-ventricular dysfunction irrespective of cause, and it has been associated with poor long-term outcome. Data of single-centre experience and observational studies with historical controls suggest that correction of mitral regurgitation results in partial reversal of left-ventricular remodelling, symptomatic improvement, and enhanced outcomes.[114,115] However, the benefit of this procedure remains to be shown in randomised trials. In addition to functional mitral regurgitation, primary valvular heart disease could be a cause or contributor to heart failure. In some cases—eg, aortic stenosis and mitral stenosis—heart failure can be reversible after surgical or percutaneous treatment of valvular disease.

Surgical ventricular reconstruction or restoration has emerged as a promising approach to dilated cardiomyopathy in patients with previous myocardial infarction. The aim of this procedure is to reduce left-ventricular volume and create geometrically the best possible chamber by exclusion of scar in either akinetic or dyskinetic anteroapical and septal segments. Findings of a worldwide, 11-centre, observational study in 1198 post-infarction patients[116] have led to inclusion of surgical ventricular reconstruction in the STICH trial. Thus, we should know more about the role of non-transplant surgery for treatment of heart failure in the near future.

Acute heart failure

Most patients with chronic heart failure will at one time or another develop worsening symptoms associated with fluid retention, low cardiac output syndrome, or both, and they will need to be admitted for intravenous diuretic or vasoactive treatment. Few randomised controlled trials have been done to guide management of acute heart failure. The only guideline to assessment and management comes from the European Society of Cardiology.[117] About 90% of individuals admitted with worsening heart failure show excessive total-body fluid volume. Thus, intravenous diuretic treatment represents a mainstay for acute heart failure. In general, the goals for management of decompensated heart failure include alleviation of symptoms, reduction of extracellular fluid volume excess, enhancement of haemodynamics, and maintenance of perfusion to vital organs.

Treatment of acute heart failure begins with appropriate triage, prompt stabilisation of respiratory and haemodynamic status, and rapid exclusion or management of immediately reversible disorders (eg, myocardial ischaemia). Simultaneous assessment and empirical treatment starts with supplemental oxygen for patients with hypoxaemia, cardiac monitoring, intravenous access, and a 12-lead ECG. Precipitating factors such as infection, arrhythmias, and uncontrolled hypertension should be sought and treated aggressively.

The general pharmacological approach to management of acute heart failure includes one or more of the following intravenous drug strategies: diuretics to reduce extracellular fluid volume excess; vasodilators to lower ventricular filling pressures and systemic vascular resistance; and positive inotropic agents to increase cardiac output in low-flow states. Ancillary treatments such as morphine, oxygen, and non-invasive ventilation are no less important than these major strategies. Although non-invasive ventilation might help patients feel better more quickly compared with standard oxygen treatment alone, it does not alter outcomes such as the course of admission or short-term mortality.[118]

The most frequent strategy for inpatient treatment of heart failure is an intravenous loop diuretic, in view of its greater potency compared with other agents. Traditional bolus dosing versus continuous infusion has been shown to be related to high rates of ototoxicity and less efficient diuresis.

Intravenous vasodilators used in acute heart failure include nitroglycerin, nitroprusside, and, in some countries, synthetic human BNP or nesiritide. Nitroglycerin can be started at 0·3–0·5 μg/kg per min, as long as systolic blood pressure is higher than 95–100 mm Hg. Typically, nitroprusside is started at a dose of 0·1–0·2 μg/kg per min and advanced as needed to augment clinical and haemodynamic status, with a systolic pressure of 85–90 mm Hg as a lower limit for dose titration, provided that adequate systemic perfusion is maintained. Nesiritide is generally used at an infusion rate of 0·01 μg/kg per min, following a standard loading bolus.

Few randomised controlled trials have been done to guide selection of an intravenous vasodilator. Findings of one study support use of nesiritide[119] but it is controversial,[120] as is use of positive inotropic agents. Although these drugs are necessary for patients with severely reduced cardiac output, they might be associated with increased risk for mortality.[121] Frequently used positive inotropic agents include dobutamine, dopamine, milrinone, and, in some countries, enoximone and levosimendan.

Heart failure with preserved ejection fraction

Heart failure with preserved ejection fraction is considered separately to systolic heart failure because of differences in underlying causes, epidemiology, and pathophysiology, and variations in the evidence base with respect to appropriate management. Prevalence and incidence of this subtype remain largely unclear, mainly because clearcut diagnosis is difficult. In particular, a definitive diagnosis of heart failure with preserved ejection fraction needs invasive assessment of pressure-volume relations within the heart and requires this measurement to be undertaken temporally proximate to heart failure presentation.[122] Although this method might be the gold standard, it is rarely achievable in everyday clinical practice.

Several echocardiographic variables could be indicative of heart failure with preserved ejection fraction, including transmitral and pulmonary venous doppler filling profiles.[123] Use of the E/A ratio can be confounded by so-called pseudonormalisation as disease advances.[124] Tissue doppler imaging provides load-independent information with respect to left-ventricular diastolic filling, with various measures suggestive of impairment of diastolic relaxation. BNP plasma amounts are raised in patients with heart failure with preserved ejection fraction but, in general, to a lesser extent than those in people with systolic heart failure.[125] Prognosis has been described variably as similar to or less severe than that of systolic heart failure, depending on the study undertaken.[126,127]

Pathophysiologically, heart failure with preserved ejection fraction is characterised by excessive fibrosis[128] and myocyte hypertrophy, leading to abnormal left-ventricular relaxation filling, and diastolic distensibility, diastolic stiffness, or a combination of these. Typical causal factors include hypertension, diabetes, and myocardial ischaemia. Pressure overload hypertrophy from valvular heart disease (typically, aortic valvular stenosis) is also a highly prevalent cause. This condition is seen most frequently in older patients and in women, and it is predominated by background systemic hypertension.[129] Importantly, the clinical presentation of heart failure with preserved ejection fraction could be identical to that of systolic heart failure.

Unlike for systolic heart failure, very few comprehensive assessments have been done of treatment modalities for heart failure with preserved ejection fraction. In particular, the contribution of neurohormonal activation has been less well explored and, thus, the role of blockade of key systems—well established therapeutically in systolic heart failure—is more uncertain.

Research on ACE inhibitors has generally been done on a small scale. However, in the PEP-CHF study, workers assessed perindopril in an elderly population with heart failure with preserved ejection fraction.[90] Fewer major clinical events were noted at 1 year with the drug, but overall, the primary clinical endpoint (all-cause mortality or admission for chronic heart failure) did not differ between perindopril and placebo at trial end.

Similarly, studies of ARBs have been limited and those that have been undertaken have not yielded overwhelmingly beneficial results. A non-significant reduction was recorded in the primary endpoint of cardiovascular death and heart failure admission in the CHARM-Preserved study of candesartan versus placebo.[89] However, no mortality benefit was noted. Further, in a small echo-based trial of valsartan in patients with hypertension and diastolic dysfunction, no significant echocardiographic reversal of diastolic variables was seen independent of blood pressure-lowering effects.[130] The hypothesis that angiotensin II has an active role in pathogenesis and progression of diastolic dysfunction will be tested in the I-PRESERVE trial of irbesartan.[131]

Despite the theoretical benefits of heart-rate slowing and catecholamine inhibitory effects (permitting more adequate filling of the left ventricle during diastole) in patients with heart failure with preserved ejection fraction, very few studies have been done that are specifically focused on β blockers. The SENIORS study[73] included a cohort (about a third of the overall population) who might have had relative preservation of systolic function on the basis of entry criteria. A similar beneficial effect on mortality and admission for cardiovascular events (the primary study endpoint) was seen in the impaired systolic versus the preserved systolic function group.

Unlike in systolic heart failure, digoxin would seem to have a very limited role, if any, in heart failure with preserved ejection fraction. Within the DIG study, 988 patients (15%) had a left-ventricular ejection fraction of greater than 45%. In this group, no survival benefit was noted compared with placebo and, overall, no reduction was recorded in admissions (all-cause).[132]

Perhaps the therapeutic approach most likely to be of benefit in heart failure with preserved ejection fraction is blockade of aldosterone. This hormone is profibrotic and prohypertrophic, key components of the disease process. Furthermore, aldosterone antagonists are effective blood pressure-lowering drugs. Workers on a trial of 4000 patients are currently studying spironolactone in this setting.[133]

Statins have anti-ischaemic, antifibrotic, and anti-inflammatory actions. Findings of a small study of patients with heart failure with preserved ejection fraction showed enhanced survival with statins, additional to background treatments.[134] Part of the GISSI-HF population,[87] on whom researchers are testing the role of statins in heart failure, has preserved systolic function.

Many additional approaches are currently under investigation. These include direct antifibrotic drugs, copper-chelation agents, and advanced glycation end-product inhibitors.[23,135] Advanced glycation end-product

inhibitors might have a role in the disease process of heart failure with preserved ejection fraction, even in the absence of overt diabetes mellitus.[135]

Palliation

Palliative care is sometimes overlooked as a component of management of the heart failure patient. Modern principles focus on individualisation of programmes for people who have a strong possibility of death within 12 months.[136] This group includes those with advanced symptoms and poor quality of life who have proven resistant to the best pharmacological regimens and other therapeutic strategies.

The main aim of palliative care is symptom control. Management of dyspnoea is an important part of heart failure management. The goal is to lessen a patient's subjective sensation of dyspnoea rather than correct underlying pathophysiological abnormalities. Palliative approaches could include use of oxygen, benzodiazepines, opioids (used very judiciously),[137] parenteral diuretics, and other measures such as advice on posture, relaxation modalities, and ensuring an adequate airflow.

Other end-of-life issues might include management of uraemia, severe lower-limb oedema, pain, cachexia, and anaemia. Parenteral inotropic support could be used for these conditions, not to prolong life but rather to relieve severe symptoms.[29] Another issue relevant to palliation of the heart failure patient is whether to deactivate implantable defibrillators.[138]

Future developments

The future of heart failure management lies in several key areas. These include enhanced approaches to prevention, greater precision in diagnosis, further individualisation of treatment (including novel pharmacological agents), development of new devices, and exploration of gene-based and cell-based strategies.

With respect to prevention, earlier elucidation of risk of disease will be on the basis of known risk factors and emerging diagnostic blood markers. For example, cardiotrophin I seems to be activated very early in the evolution of cardiac dysfunction.[139] This process could allow intervention with treatments directed at patients most likely to go on to develop left-ventricular dysfunction and heart failure to ameliorate this progressive process.

Other approaches that could assist in diagnosis include proteomics, whereby large differences might be seen in the proteome of the failing and non-failing heart.[140] This technique could yield not only novel diagnostics but also potential targets for future treatments.

Although existing drugs are of considerable therapeutic benefit, effectiveness is highly variable between individual patients. To boost benefits, individualisation of treatment is beginning for many disease states, and this process will undoubtedly come to heart failure. Pharmacogenomic profiling could increase effectiveness and reduce side-effects of specific drugs.[141]

Selection of agents in the future might also be based on neurohormonal profile. Tracking the response to treatment by assessment of changes in plasma concentrations of key hormones after start of treatment is also being investigated intensively. Sequential BNP measurement for therapeutic guidance has been studied.[142]

Various implanted devices already provide right-sided pressure-measurement information, detect impedance across the chest wall (a surrogate marker for fluid in the lungs),[143] and can transmit information directly via the placement of a transducer in the left atrium.[144] Such methods promise to detect changes in volume status earlier than that which might be apparent clinically to either patient or doctor. Thus, treatments can be begun earlier than otherwise considered, potentially preventing exacerbation of volume overload.

Notwithstanding the shortage of success with new drugs for both systolic heart failure and heart failure with preserved ejection fraction, many potential targets remain for therapeutic intervention on the basis of growing understanding of disease mechanisms. Novel pharmacological approaches include manipulation of neurohormonal systems—eg, inhibition of urotensin II and augmentation of natriuretic peptides such as urodilatin, urocortin, and adrenomedullin.[135] Knowledge has increased of intracellular signalling pathways via which many existing agents modulate their effects. Various protein kinases represent important targets; selective inhibitors of these systems have been developed and are currently being assessed for management of heart failure and other indications.[145]

Direct targeting of myocardial contractile function has generally been judged unsuccessful, because long-term use of inotropic agents (other than digoxin) has resulted in excess mortality—largely via proarrhythmic mechanisms. However, new agents seem to enhance actin-myosin contractility independent of changes in intracellular calcium and cyclic AMP, alterations that have bedevilled earlier direct inotropic drugs. One such molecule, CK-1827452 (Cytokinetics, San Francisco, CA, USA), is in clinical development.[146]

Many other agents targeted at comorbid disease states associated with heart failure are in development. Notwithstanding some failures in this setting,[91,92] several drugs remain under investigation for diabetic cardiomyopathy, anaemia, and cardiorenal syndrome.[135]

Cell-based treatments are undergoing considerable preclinical and clinical assessment for systolic left-ventricular dysfunction, with and without accompanying ischaemia. Approaches include both adult and embryonic stem cells. Of adult stem cells, both erythroid precursor cells and mesenchymal stem cells are being assessed. Mesenchymal stem cells hold much therapeutic promise because of their low immunogenic potential and, thus, the theoretical ability for them to be used in an autologous manner—ie, off the shelf.[147] However, as yet, supportive clinical data are scarce in

heart failure. Transplantation of skeletal muscle myoblasts to the myocardium has also been studied,[148] although generation of arrhythmias has somewhat limited enthusiasm for this approach.

Gene-based approaches have targeted fundamental cellular and molecular processes that underlie ongoing myocardial dysfunction. These include sarcoplasmic endoplasmic reticulum calcium ATPase (SERCA)[135] and phospholamban.[149] Issues about effectiveness and safety of delivery vectors has been a constraint on these strategies. Mode of delivery is also relevant. Various techniques are under investigation, including direct intracoronary injection, cardiac recirculation, and systemic administration.

Conflict of interest statement

HK has received grant and research support within the past 12 months from National Health and Medical Research Council, Medtronic, Scios, BUPA, Pfizer, and GlaxoSmithKline, and consultancy and speaker honoraria from Amgen, AstraZeneca, Medtronic, St Jude Medical, Roche, Novartis, Sanofi-Aventis, Pfizer, Mesoblast, and Gilead. HK is a member of the following advisory boards: Biotronik, Novartis, Sanofi-Aventis, Pfizer, Mesoblast, Apollo Life Sciences, and Gilead. WTA has received grant and research support within the past 12 months from National Institutes of Health, Medtronic, Paracor, and St Jude Medical, and consultancy and speaker honoraria from Amgen, AstraZeneca, Medtronic, Novartis, Pfizer, Respironics, St Jude Medical, and GlaxoSmithKline. WTA is a member of the following advisory boards: BioEnergy, Biotronik, CardioKine, CardioKinetix, CardioMEMS, Department of Veterans Affairs Cooperative Studies Program, Edwards Lifesciences, Inovise, Medtronic, National Institutes of Health, Paracor, St Jude Medical, and Sunshine Heart.

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