The patient with left ventricular systolic dysfunction now and in the future

This review provides a concise overview of the current understanding of chronic heart failure, focusing on the landmark clinical trials that form the basis of clinical management of patients with left ventricular systolic dysfunction.

Heart failure is a common clinical syndrome, especially in the elderly. Since the first epidemiological studies our understanding of the pathophysiology of heart failure has improved dramatically, facilitating substantial improvements in the management of chronic heart failure with medical and device therapies. Despite these measures heart failure still carries a high morbidity and mortality and is associated with considerable health-care expenditure, the bulk of which is the result of frequent hospitalizations. As increasingly widespread access to modern health care prolongs life expectancy worldwide the socioeconomic burden that heart failure poses will only continue to grow, making it one of the major public health issues faced today. This review provides a concise overview of current understanding of heart failure, including the landmark clinical trials that formulate the basis of clinical management, and considers future directions.

Table 1. Diagnosis of heart failure

Diagnosis of heart failure with 'reduced' ejection fraction requires three conditions to be satisfied	1. Symptoms typical of heart failure
	2. Signs typical of heart failure
	3. Reduced left ventricular ejection fraction
Diagnosis of heart failure with 'preserved' ejection fraction requires four conditions to be satisfied	1. Symptoms typical of heart failure
	2. Signs typical of heart failure
	3. Normal or only mildly reduced left ventricular ejection fraction and left ventricle not dilated
	4. Relevant structural heart disease (left ventricular hypertrophy or left atrial enlargement) and/or diastolic dysfunction

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Mr William Kenworthy is Medical Student, University College London Medical School, London WC1E 6BT

Dr Kaushik Guha is Consultant in the Department of Cardiology, Portsmouth Hospitals NHS Trust, Portsmouth

Dr Rakesh Sharma is Consultant in the Department of Cardiology, Royal Brompton Hospital, London and the National Heart & Lung Institute, Imperial College, London

Correspondence to: Mr W Kenworthy (william.kenworthy.11@ucl.ac.uk)

Definitions

In the current European Society of Cardiology guidelines, heart failure is defined as 'a clinical syndrome in which patients have typical symptoms and signs resulting from an abnormality of cardiac structure or function' (McMurray et al, 2012). Any cardiac condition that compromises ventricular systolic or diastolic function (or both) may cause heart failure. *Table 1* outlines the criteria required for the diagnosis of heart failure with a reduced ejection fraction and heart failure with a preserved ejection fraction as listed in the current European Society of Cardiology guidelines (McMurray et al, 2012).

The New York Heart Association (NYHA) functional classification for heart failure (*Table 2*) stages patients according to the severity of their symptoms and is used to

Table 2. New York Heart Association (NYHA) functional classification of heart failure

NYHA class	Symptoms
Class I	No limitation of physical activity. Ordinary physical activity does not cause undue breathlessness, fatigue or palpitations
Class II	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in undue breathlessness, fatigue or palpitations
Class III	Marked limitation of physical activity. Comfortable at rest, but less than ordinary physical activity results in undue breathlessness, fatigue or palpitations
Class IV	Unable to carry on any physical activity without discomfort. Symptoms at rest can be present. If any physical activity is undertaken, discomfort is increased

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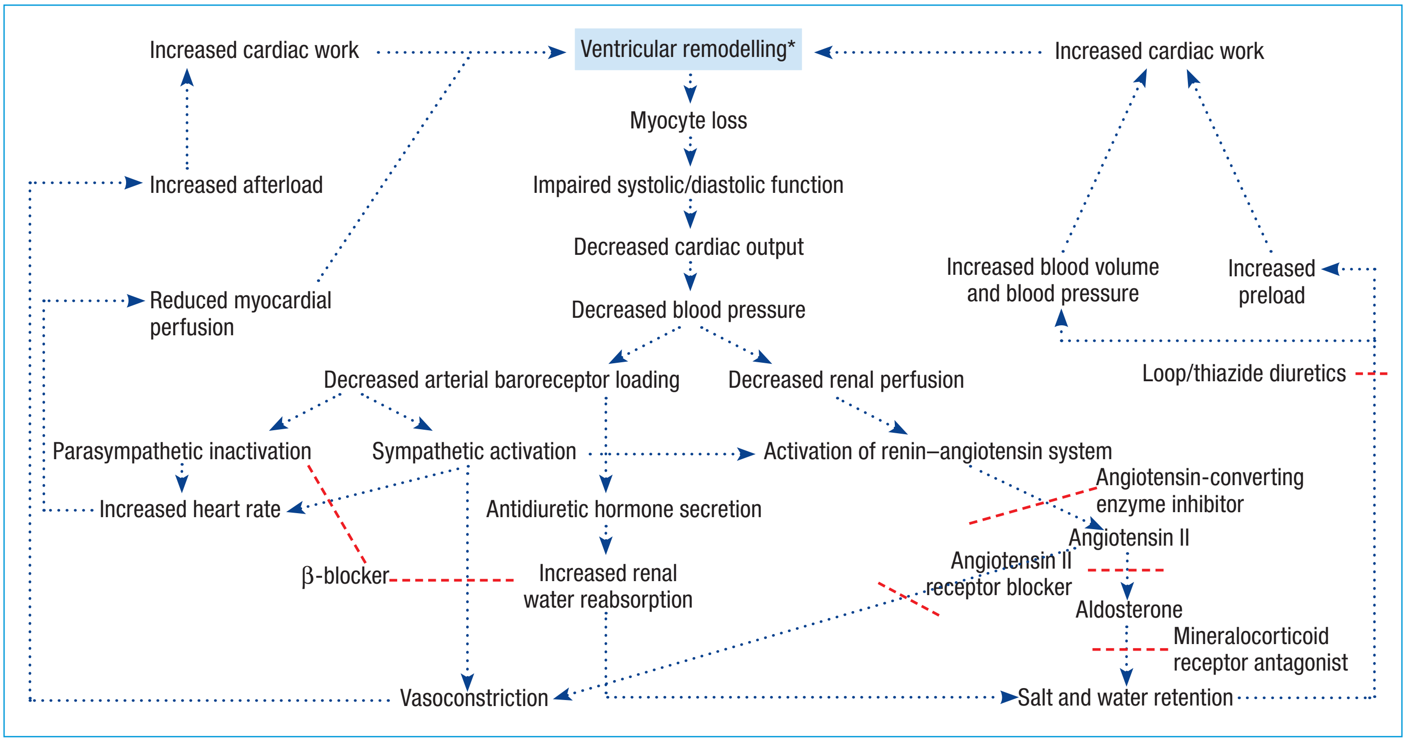
Figure 1. Pathophysiology and medical management of chronic heart failure. *Owing to neurohormonal activation (persistently high levels of angiotensin II, aldosterone and catecholamines bring about a process of left ventricular remodelling causing changes in cardiac metabolism, myocardial thinning and fibrosis).



monitor the response to treatment. Both acute and chronic forms of heart failure exist, but this review will concentrate on chronic heart failure.

Epidemiology

Heart failure may be difficult to diagnose accurately, which may in turn lead to inconsistent estimates of the prevalence and incidence as a byproduct of the different criteria used to define heart failure in epidemiological studies. However, it is clear that heart failure represents a major public health problem with the current prevalence estimated at over 5.8 million in the USA alone and over 23 million worldwide, although without robust data from countries such as India and China the latter figure is derived solely from western data and is likely to be a gross underestimate (McMurray et al, 1998; Lloyd-Jones et al, 2010). The prevalence and incidence of heart failure greatly increases with age (Cowie et al, 1999). Hence, as life expectancy increases in the developing world, along with exposure to risk factors for heart failure such as hypertension, coronary artery disease and obesity, the global prevalence of heart failure is expected to rise dramatically, marking a shift within this population from an acute illness to a chronic disease.

Prognosis and hospitalization

The prognosis of heart failure has improved over the past 10 years as a result of effective therapies and enhanced access to diagnostic facilities. Despite improvements in prognosis it still carries an adverse prognosis compared to many commonly occurring solid organ malignancies (Stewart et al, 2001; Levy et al, 2002). Hospitalization confers further risk and is associated with further adverse prognosis. Furthermore, inhospital mortality in the UK varies significantly depending on whether patients receive specialist input, with an inhospital mortality of ~5% in patients treated on cardiology wards compared to ~15% in those treated on general medical wards (Cleland et al, 2011).

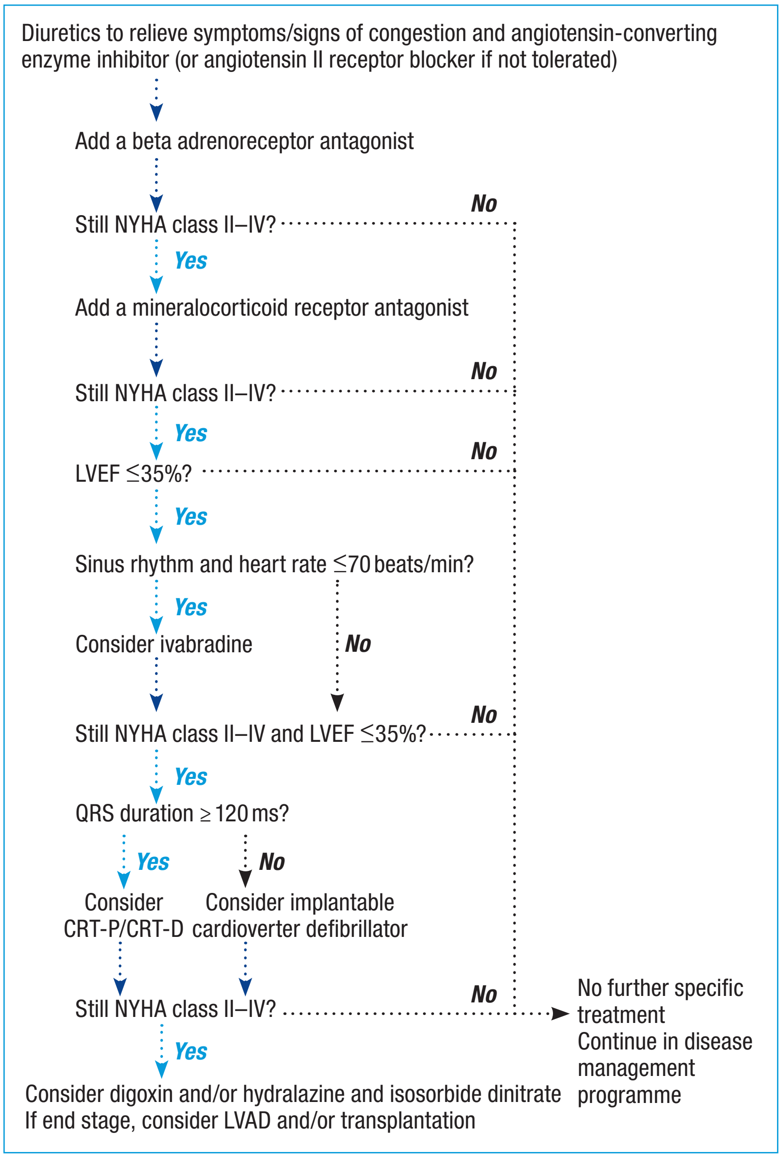
Heart failure remains a large economic burden for westernized countries and health-care systems. Within the NHS it is estimated to be responsible for approximately 2% of the total NHS expenditure (Stewart et al, 2002). Approximately 70% of the total costs are directly attributable to frequent, prolonged and repeated hospitalization.

Treatment: drugs

Heart failure is characterized by neurohormonal and sympathetic over-activation. The inappropriate stimulation of these critical autonomic systems disrupts homeostasis by interrupting the negative feedback loop, leading to fluid retention, sodium conservation and a rise in arterial blood pressure. If left unchecked, this ultimately results in a poorly functioning, dilated ventricle with limited contractility.

In the past 30 years there have been significant discoveries with regards to neurohormonal modulators and adrenoreceptor antagonists. The targets of the various heart failure treatments borne out of these advances in our understanding are shown in *Figure 1*, along with the stepwise treatment regimen as per European Society of Cardiology guidelines in *Figure 2* and the landmark studies for each

Figure 2. Algorithm for the management of chronic heart failure. CRT-P = cardiac resynchronization therapy pacemaker; CRT-D = cardiac resynchronization therapy defibrillator; LVAD = left ventricular assist device; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association. From McMurray et al (2012). With permission of Oxford University Press (UK) © European Society of Cardiology, www.escardio.org/



therapy in *Table 3*. However, it is notable that this large and robust evidence base is only applicable to those patients with left ventricular systolic dysfunction or heart failure with a reduced ejection fraction. The results of the respective agents in those with heart failure with a preserved ejection fraction are disappointing, so currently there are few therapeutic options directly targeted towards such patients. Therefore, the remainder of this review will focus on patients with heart failure with a reduced ejection fraction.

Angiotensin-converting enzyme inhibitors

Angiotensin-converting enzyme inhibitors are a cornerstone of the treatment of patients with heart failure with a reduced ejection fraction. The landmark CONSENSUS study randomized 253 hospitalized patients with heart failure with a reduced ejection fraction and NYHA class IV symptoms to enalapril or placebo in addition to conventional medical therapy and demonstrated a 40% reduction in mortality at 6 months in the intervention group as well as a significant improvement in NYHA classification (Anon, 1987). The overwhelming finding of rapid clinical improvement led to the termination of the study, but it was only after the completion of the SOLVD trial a few years later that the role of angiotensin-converting enzyme inhibitors in patients with NYHA class I–III became clear. In this study 2569 patients were randomized to either enalapril or placebo in addition to standard medical therapy and there was a 16% reduction in mortality associated with enalapril (Anon, 1991). Subsequently a number of other agents have been trialled and demonstrated to have similar efficacy to enalapril.

Angiotensin II receptor blockers

Up to 10% of the population may experience an angiotensin-converting enzyme inhibitor-induced cough (caused by the accumulation of bradykinin byproducts), which may become problematic for the individual patient. An alternative is the angiotensin II receptor blocker class. In the VALIANT study 14 703 patients post-myocardial infarction complicated by heart failure and/or left ventricular dysfunction were randomized into groups receiving valsartan or captopril monotherapy or a combination of the two. There were no significant findings between the arms with regard to the primary end point of all-cause mortality but the valsartan arm did meet non-inferiority criteria as compared to captopril for all-cause mortality, heart failure hospitalization, cardiovascular death and reinfarction (Pfeffer et al, 2003). However, the decision to switch to an angiotensin II receptor blocker must only be considered following rigorous clinical assessment and documentation to ensure that the angiotensin-converting enzyme inhibitor class for that individual is not erroneously discarded.

The fundamental action of both classes of drugs is to target the renin–angiotensin–aldosterone system that contributes to sodium and fluid retention, hypertension, myocardial fibrosis and potent vasoconstriction via aldosterone and angiotensin II.

Mineralocorticoid receptor antagonists

The final class of drugs targeting the renin–angiotensin–aldosterone system as part of the conventional 'triple therapy' are known as mineralocorticoid receptor antagonists. These drugs directly counteract the effect of aldosterone, which is a potent vasoconstrictor and potentiates myocardial fibrosis. Spironolactone was evaluated in RALES, a large randomized controlled trial, and it improved symptoms and reduced total mortality by 30% in severely symptomatic (NYHA class III) patients (Pitt et al, 1999). However, it is important to monitor for the development of hyperkalaemia, particularly when used in conjunction with angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers.

It was previously shown that up to 10% of patients taking spironolactone developed gynaecomastia (Pitt et al, 1999). The drug molecule was therefore redesigned in an attempt to limit the oestrogen mimetic side effects and this led to the establishment of eplerenone. This drug has been tested in EPHESUS, involving patients post-myocardial infarct, and EMPHASIS-HF, a study that recruited patients with mildly symptomatic chronic heart failure. In both studies eplerenone demonstrated its clinical effectiveness and justified its place in the current treatment algorithm (Pitt et al, 2003; Zannad et al, 2011).

Beta adrenoreceptor antagonists

The original clinical concern with these agents was their negative inotropic actions. However, through careful pilot studies and ultimately large randomized controlled studies, several of the more cardio-selective agents including bisoprolol, carvedilol, metoprolol succinate CR/XL and nebivolol have been shown to be clinically significant and prognostically beneficial in patients with left ventricular systolic dysfunction (Packer et al, 1996; Anon, 1999; Hjalmarson et al, 2000; Krum et al, 2003; Flather et al, 2005). Notably, however, this effect is not a class-based effect, hence such findings cannot be extrapolated generically to other agents including atenolol and bucindolol.

The patient should be initiated on such treatments when euvolaemic and careful monitoring is required to review pulse, blood pressure and generalized symptoms before proceeding to the next dose. The clinical benefit of these agents outweighs potential side effects such as malaise and lethargy but the ability to transiently cause side effects is well recognized and patients should be counselled so that this may be addressed pre-emptively.

Ivabradine

Ivabradine acts directly on ion channels located within the sinoatrial node that are responsible for a mixed inward sodium-potassium current known as the cardiac pacemaker 'funny' current (I_f). These channels contribute to the generation of spontaneous activity in the heart and mediate autonomic-dependent modulation of heart rate. The ability to therefore reduce heart rate with limited negative inotropic effects has been evaluated in SHIFT where it was shown that the careful initiation of ivabradine in association with standard medical therapy led to a significant reduction in events (Swedberg et al, 2010).

Digoxin

Digoxin is a cardiac glycoside extract that has some degree of positive inotropic effect and has previously been studied in the large DIG randomized study. This concluded that digoxin led to a reduction in heart failure hospitalization but had little effect on mortality (Digitalis Investigation Group, 1997). However, a comprehensive post-hoc analysis of the DIG trial found that although digoxin reduced heart failure hospitalizations compared with placebo irrespective of serum digoxin concentration, survival was only improved in patients randomized to digoxin at serum concentration 0.5–0.9 ng/ml (Ahmed et al, 2006). Within the current guidance digoxin remains an adjunctive therapy to be considered following the commencement of the other groups of medication, although it has been suggested that further trials should be undertaken in patients with worsening chronic heart failure who remain symptomatic and those with concurrent atrial fibrillation.

Table 3. Medical therapy in the treatment of chronic heart failure with reduced ejection fraction

Class	Examples	Key studies*
Angiotensin-converting enzyme inhibitors	Captopril, enalapril, ramipril	CONSENSUS, SOLVD
Angiotensin II receptor antagonists	Valsartan	VALIANT
Angiotensin receptor-neprilysin inhibitors	LCZ696	PARADIGM-HF
Beta-blockers	Bisoprolol, carvedilol, metoprolol succinate CR/XL, nebivolol	CIBIS II, COPERNICUS, MERIT-HF, SENIORS
Mineralocorticoid receptor antagonists	Spironolactone, eplerenone	RALES, EMPHASIS-HF, EPHESUS
Cardiac glycosides	Digoxin	DIG
	Ivabradine	SHIFT
Loop diuretics	Furosemide, bumetanide	
Thiazide diuretics	Bendroflumethiazide, metolazone	

** see glossary of studies for details*

Diuretics

Diuretics may be used to relieve symptoms of fluid congestion and a maintenance dose may be needed to create a homeostasis between preload and afterload. However, the dose should be subject to constant review with the knowledge that because of the fluctuation in the disease condition itself, doses may be subject to further change. There is no prognostic benefit conferred by the use of diuretics.

Angiotensin receptor-neprilysin inhibitors

The PARADIGM-HF trial compared an entirely new class of drug, the angiotensin receptor-neprilysin inhibitors, to enalapril and yielded impressive results. LCZ696 is a dual inhibitor that consists of the neprilysin inhibitor sacubitril and the angiotensin II receptor blocker valsartan. It works by antagonizing the angiotensin II receptor and neprilysin. The trial randomized 8442 patients with symptomatic left ventricular systolic dysfunction to either LCZ696 200 mg twice daily or enalapril at 10 mg twice daily. The primary outcome, which was a composite of death from

> “The prevalence of heart failure has fuelled the development of strategies to assess, monitor and treat subclinical heart failure in order to improve care and prevent hospitalization.”

cardiovascular causes and heart failure hospitalization, occurred in 914 patients (21.8%) in the LCZ696 group and 1117 patients (26.5%) in the enalapril group (McMurray et al, 2014). The significant findings from the study were associated with a suitable level of patient tolerability, low levels of reported symptomatic hypotension, renal dysfunction and angiooedema.

Treatment: devices

The cornerstone of treatment for patients with left ventricular systolic dysfunction is the rigorous and meticulous application of the classes of medications listed above. However, for selected populations an implantable cardiac device may be considered. Device therapy may be sub-categorized into implantable cardioverter defibrillators and cardiac resynchronization therapy, with the two therapies being non-exclusive. A full review of the literature is not possible within a generalized overview of heart failure.

Implantable cardioverter defibrillators

Patients with severe left ventricular systolic dysfunction are at risk of ventricular arrhythmia and sudden cardiac death. An implantable cardioverter defibrillator will ensure the treatment of both brady- and tachyarrhythmias, with the ultimate therapy being controlled DC current cardioversion to try and countermand dangerous arrhythmias. The landmark trial in this field was felt to be MADIT-II in which 1232 post-myocardial infarction patients with systolic dysfunction (left ventricular ejection fraction ≤30%) were randomized to either prophylactic implantable cardioverter defibrillator or conventional medical therapy. The trial was terminated early when it was found that prophylactic implantable cardioverter defibrillator reduced all-cause mortality compared to standard medical therapy through a reduction in sudden cardiac death (Moss et al, 1996). The trial is noteworthy as being the landmark trial within the area but demonstrated superior clinical efficacy using single chamber implantable cardioverter defibrillators (which are technologically inferior to currently available models).

The SCD-HeFT trial studied the effects of implantable cardioverter defibrillators upon the prevention of sudden cardiac death in a population with both ischaemic and non-ischaemic aetiologies and severe left ventricular systolic dysfunction. This demonstrated a significant reduction in mortality for the 2521 patient cohort (0.77, 97.5% confidence interval 0.62–0.96, *P*=0.007) (Bardy et al, 2005). Hence implantable cardioverter defibrillators have proved to be prognostically beneficial and therefore should be considered for selected patients.

Cardiac resynchronization therapy

Cardiac resynchronization therapy has offered another therapeutic option for patients who possess the conventional recommended criteria. The mechanistic basis of cardiac resynchronization therapy is to improve ventricular activation, reduce ventricular asynchrony (characterized by abnormal lateral and septal wall movement), reduce diastolic functional mitral regurgitation and improve filling times. It may be a pacing only option (CRT-P) or in combination with a defibrillator (CRT-D).

The role of cardiac resynchronization therapy has been evaluated in a number of large randomized trials. The landmark study was CARE-HF in which 813 patients were randomized to receive either medical therapy alone or with CRT-P. The addition of CRT-P to standard medical therapy was both prognostically and symptomatically beneficial and should be considered for selected populations (Cleland et al, 2005). Until recently cardiac resynchronization therapy was reserved for patients with symptomatic heart failure, on optimal tolerated medical therapy who had severe left ventricular systolic dysfunction (defined as left ventricular ejection fraction <35%) and a broad QRS duration (>120 ms) on the surface electrocardiogram. However, the EchoCRT group studied a series of 809 patients who had severe left ventricular systolic dysfunction with a narrow QRS duration of <130 ms and echocardiographic dyssychrony. The groups all had cardiac resynchronization therapy systems implanted but were randomized to being turned off or on. The trial was terminated prematurely by the data and safety monitoring committee because of the increased rate of deaths within the CRT-ON arm. There were 45 deaths in the CRT-ON arm and 26 in the CRT-OFF group (11.1% *vs* 6.4%, hazard ratio 1.81, 95% confidence interval 1.11–2.93, *P*=0.02) (Ruschitzka et al, 2013). Hence the findings demonstrated that cardiac resynchronization therapy should not be offered to patients with a narrow QRS duration (<130 ms) and may even result in increased mortality within such a cohort.

Left ventricular assist devices and cardiac transplantation

These treatment options are reserved for patients with advanced heart failure and under the jurisdiction of a cardiac transplant unit, so they are not covered within this review.

Monitoring

The prevalence of heart failure has fuelled the development of strategies to assess, monitor and treat subclinical heart failure in order to improve care and prevent hospitalization. Trials using permanent pacemakers, implantable cardioverter defibrillators or cardiac resynchronization devices to detect tachyarrhythmias and intrathoracic impedance (a measure of pulmonary congestion) have demonstrated a sensitivity of 76% in predicting clinical decompensation compared to 23% using patient-reported weight change (Abraham et al, 2011a). Trials of implantable haemodynamic sensors placed within the heart have also yielded promising results, with one study showing a 30% reduction in heart failure hospitalization among NYHA class III patients with a recent heart failure hospitalization using pulmonary artery sensors (Abraham et al, 2011b). The potential for home monitoring to improve the management of heart failure is substantial and may facilitate a shift from episodic and reactive treatment to proactive, preemptive therapeutic intervention.

Biomarkers

The symptoms and signs of heart failure are neither specific nor sensitive and thus the diagnosis of heart failure remains challenging even for experienced clinicians. A landmark study demonstrated that in 122 patients referred from primary care with a new diagnosis of heart failure only 35 (29%) patients met the case definition for new heart failure when reviewed by a panel of three cardiologists (Cowie et al, 1997). Crucially it was shown that levels of natriuretic peptides released in response to myocyte stress were much higher in patients with heart failure than in those with other diagnoses (29·2 *vs* 12·4 pmol/litre for atrial natriuretic peptide, 63·9 *vs* 13·9 pmol/litre for B-type natriuretic peptide, 1187 *vs* 410·6 pmol/litre for N-terminal-atrial natriuretic peptide, all $P<0·001$) (Cowie et al, 1997). At a cut-off value chosen to give a negative predictive value for heart failure of 98% (B-type natriuretic peptide ≥22·2 pmol/litre), the sensitivity, specificity and positive predictive value for B-type natriuretic peptide were 97%, 84% and 70% (Cowie et al, 1997). Therefore the authors concluded that plasma B-type natriuretic peptide concentration could prove to be a useful, cheap way to assess which patients with symptoms of heart failure were likely to require further clinical assessment in the primary care setting.

Over the last 10 years natriuretic peptides, particularly B-type natriuretic peptide and N-terminal-proB-type natriuretic peptide (NT-proBNP), have become an essential part of the diagnostic process. Natriuretic peptides can also be used for risk stratification and determining prognosis in patients with heart failure.

Conclusions

Heart failure continues to represent a major problem for global health economies. The treatment of patients with heart failure with a reduced ejection fraction has now evolved into an algorithm of neurohormonal antagonists and implantable cardiac devices. Current models of care fundamentally based on multidisciplinary team principles may not be able to cope with the increasingly elderly comorbid populations that are growing in size, globally. Despite the academic and clinical success of the previous 30 years, there is an increasing need for further investigative work focusing on technologies and pharmacology. It is imperative that the profession continues to improve upon current management strategies and optimize the use of effective therapies to reduce heart failure mortality further and interrupt the procession of recurrent hospitalizations. Additional work is urgently required in patients with severe advanced heart failure and those with heart failure with a preserved ejection fraction as both currently have limited therapeutic options. **BJHM**

KEY POINTS

- As life expectancy increases worldwide the socioeconomic burden of chronic heart failure, attributed primarily to frequent hospitalizations, will only continue to grow, making heart failure one of the major public health problems of today.
- There is now robust evidence supporting the use of a variety of medical and device therapies in the management of patients with left ventricular systolic dysfunction.
- Strategies to assess, monitor and treat subclinical heart failure in order to improve care and prevent hospitalization are needed to help cope with the increasingly elderly comorbid populations.
- Patients with severe advanced heart failure and those with a preserved ejection fraction remain a cause for concern as there are few therapeutic options available to them.

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GLOSSARY OF TRIALS

- CARE-HF — Cardiac Resynchronization in Heart Failure Study
- CONSENSUS — Cooperative North Scandinavian Enalapril Survival Study
- CIBIS II — Cardiac Insufficiency Bisoprolol Study II
- COPERNICUS — Carvedilol Prospective Randomized Cumulative Survival
- DIG — Digitalis Investigation Group
- EchoCRT — Echocardiography Guided Cardiac Resynchronization Therapy
- EMPHASIS-HF — Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure
- EPHESUS — Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study
- MADIT-II — Multicenter Automatic Defibrillator Implantation Trial II
- MERIT-HF — Metoprolol Succinate CR/XL Randomised Intervention Trial in Congestive Heart Failure
- PARADIGM-HF — Prospective Comparison of ARNI with ACE-I to Determine Impact on Global Mortality and Morbidity in Heart Failure
- RALES — Randomised Aldactone Evaluation Study
- SCD-HeFT — Sudden Cardiac Death in Heart Failure Trial
- SENIORS — Study of Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors With Heart Failure
- SHIFT — Systolic Heart failure treatment with If inhibitor ivabradine Trial
- SOLVD — Studies of Left Ventricular Dysfunction
- VALIANT — Valsartan in Acute Myocardial Infarction Trial

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