Treatment for heart failure: good news and bad

Ravi Assomull, Perry M Elliott

Heart failure is a common disorder associated with significant morbidity, mortality and financial burden to health services. The pharmacotherapy of heart failure, including new treatments, will be discussed.

Heart failure is a complex syndrome resulting from any cardiac disorder that impairs the ability of the heart to support a physiological circulation (National Collaborating Centre for Chronic Conditions, 2003). It is estimated that approximately 900 000 people in the UK suffer from heart failure (Petresen et al, 2002), of whom 55% are male and 45% female. The mortality from the time of diagnosis is 40% at 1 year and 10% per annum thereafter (Cowie et al, 2000). The survival rates from heart failure are equivalent to those of colon cancer and worse than for other common cancers such as carcinoma of the breast, prostate, and bladder (MacIntyre et al, 2000).

Aside from the high level of morbidity and mortality, the treatment of heart failure accounts for a substantial proportion of the health-care budget. Currently, heart failure treatment results in a total of 1 million inpatient bed days and costs the NHS £625 million annually; 70% of this is spent on hospitalization (Petresen et al, 2002).

Pharmacotherapy remains the mainstay of treatment. The major classes of drugs used to treat heart failure are: angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), beta-adrenoceptor receptor blocking drugs (β-blockers), aldosterone antagonists (spironolactone, eplerenone), digoxin and diuretics. In addition, anticoagulants are used in patients who have co-existing atrial fibrillation; they are also used empirically in patients with severe systolic impairment.

ACEI AND ARB THERAPIES

Several large, multicentre, double-blinded, randomized controlled trials have shown a significant reduction in mortality and hospitalizations with the use of ACEI in patients with heart failure (Flather et al, 2000). Moreover, the benefit from these drugs is greatest in patients with the most severe left ventricular impairment. Patients who have evidence of left-ventricular systolic impairment but who do not have symptoms of heart failure also benefit from these drugs.

ACEI have relatively few adverse effects; renal function may deteriorate in patients with pre-existing renal impairment, but close monitoring of blood biochemistry following the addition or up-titration of ACEI usually avoids a clinically-significant change. The most common side effect is an irritating dry cough, which is reversed by cessation of the drug. The cough is thought to result from the accumulation of bradykinin, which is normally broken down by ACE.

ARBs are relatively new treatments for heart failure. Their use is based on the observation that non-ACE conversion of angiotensin I to angiotensin II occurs in some patients; angiotensin receptor blockade should therefore result in more complete inhibition of angiotensin II activity than ACE inhibition. Another potential advantage of ARBs is that they do not lead to accumulation of bradykinin, and can therefore be used in patients with an ACEI cough.

The Candesartan in Heart failure: Assessment of Reduction in Mortality and Morbidity (CHARM) studies determined the efficacy of candesartan as an add-on to standard heart failure therapy including ACEI (CHARM Investigators and Committees, 2003); this combination was well-tolerated and resulted in a small but statistically significant reduction in cardiovascular mortality. The National Institute for Clinical Excellence (NICE) guidelines, published before the release of the CHARM trials, recommend reserving ARBs for use in those who are intolerant of ACEI; they may also have a role as 'add-on' therapy in treatment of refractory heart failure.

Despite the evidence base, several studies have shown that prescriptions of ACEI are lower than would be expected in the UK. Data from the

Dr Ravi Assomull is Research Fellow, Cardiovascular Magnetic Resonance Unit, Royal Brompton Hospital, London and **Dr Perry M Elliott** is Senior Lecturer, The Heart Hospital, University College London, London W1G 8PH

Correspondence to: Dr PM Elliott

General Practice Research Database show that less than 50% of patients are prescribed ACEI (Petresen et al, 2002). Practices' prescribing patterns are marked by heterogeneity. Of the 211 practices surveyed, the proportion of heart-failure patients treated with ACEI varied from 0% to 100% (Petresen et al, 2002). The elderly and women were less likely to be prescribed ACEI.

The EuroHeart Failure Survey (Swedberg et al, 2003) studied 11 304 patients from 24 countries in Europe who were admitted to hospital for the treatment of heart failure. This study confirmed the relatively low prescription rates of ACEI with just over 60% of the total group being prescribed an ACEI. The survey also demonstrated the variation in prescription rates between countries. Prescription rates in Russia were over 80%, while those in Sweden were approximately 40%. The UK prescription rate was approximately 50%, corroborating the findings of the UK General Practice Research Database. Patients who were elderly or who had recently had a stroke were less likely to receive an ACEI, whereas those who had diabetes or ischaemic heart disease were more likely to receive one. The study also demonstrated that doses of ACEI were substantially lower than those prescribed in randomized trials.

ß-BLOCKERS

Several large randomized studies have demonstrated improved cardiac haemodynamics, symptoms, rates of hospitalization and prognosis in patients with heart failure treated with β-blockers (Shibata et al, 2001). A significant percentage of heart-failure patients die suddenly as a result of arrhythmia, and it is thought that β-blockers suppress these malignant rhythms; they also prevent or attenuate the adverse remodelling of the ventricles that leads to progressive heart failure.

The trial data suggest that carvedilol, metoprolol modified release and bisoprolol all reduce mortality and symptoms at all grades of heart failure, with the greatest relative benefit in the most severe cases. β-blockers are probably not equal in their effect in heart failure; however, only two β-blockers (carvedilol and bisoprolol) are licensed for the treatment of heart failure in the UK and there are no comparative data on their relative efficacy. A direct head-to-head trial of carvedilol and metoprolol, the Carvedilol Or Metoprolol European Trial (COMET), reported improved survival in the carvedilol group (Poole-Wilson et al, 2003).

Current guidelines suggest that β-blockers should be used in all patients with impaired systolic function, irrespective of symptoms. Therapy should be initiated at a low dose with gradual up-titration to the target dose for that drug or to the maximally-tolerated dose. Patients should be reviewed clinically to ensure that they are haemodynamically stable to allow a further escalation in dosage. Patients should also be examined to ensure they have not become fluid-overloaded as a result of increased β-blockade. Patients should be warned that their symptoms may initially deteriorate before improving; a temporary increase in diuretic dose may be needed during this titration phase.

The General Practice Research Database and the Euroheart surveys show that the problem of low prescribing is even greater for β-blockers than for ACEI. In UK general practice, only 10% of patients with heart failure are treated with β-blockers; the European average is 37%. These studies also reveal that the dose of β-blocker prescribed is far below the target doses prescribed in clinical trials. Patients admitted to a cardiology ward or those with ischaemic heart disease are more likely to be prescribed β-blockers; those with pulmonary or renal disease are less so.

THE ALDOSTERONE ANTAGONISTS

Aldosterone promotes the retention of sodium and increases renal excretion of potassium and magnesium. It also increases sympathetic activation and baroreceptor dysfunction, and causes myocardial and vascular fibrosis. ACEI reduce aldosterone levels in the plasma, but this effect is often transient. The Randomized Aldactone Evaluation Study (RALES) showed that, in patients with moderate-to-severe heart failure, the addition of spironolactone, a direct aldosterone antagonist, at a dose of 25 mg resulted in increased life expectancy and reduced rates of hospitalization when compared to placebo (Pitt et al, 1999). In this trial, spironolactone was added to treatment with ACEI and a loop diuretic. The main hazard associated with spironolactone is the risk of hyperkalaemia and renal impairment. In addition, hormonal effects of spironolactone result in painful gynaecomastia and erectile dysfunction. A new aldosterone antagonist, eplerenone, has shown to be of similar prognostic benefit in patients with systolic dysfunction following myocardial infarction (MI) without the endocrine side effects (Pitt et al, 2003).

A quadrupling in the prescriptions of spironolactone following the publication of RALES has been reported; this has been paralleled by a five-fold increase in levels of hospital admission as a result of hyperkalaemia and a seven-fold increase in mortality associated with hyperkalaemia (Juurlink et al, 2004). The initial RALES trial

reported no significant clinical problem with hyperkalaemia; however, in clinical practice judicious monitoring of blood biochemistry and careful selection of patients is mandatory.

DIGOXIN

Digoxin is the only orally-active inotrope currently recommended in the treatment of chronic congestive heart failure. It is extensively used to control heart rate in patients who have atrial fibrillation; it also reduces hospital admissions for worsening heart failure in patients who are in sinus rhythm. There is, however, no beneficial effect on life expectancy, and there is some evidence that high plasma levels (above 0.9 mmol/litre) are associated with an increased mortality (Digitalis Investigation Group, 1997). Nevertheless, digoxin remains a useful therapy in patients with symptoms refractory to diuretic, ACEI and β-blocker therapy; levels need to be monitored closely to maintain a plasma concentration of 0.5–0.8 mmol/litre (Gottlieb, 2000).

ANTICOAGULATION

Clear evidence that anticoagulation reduces the risk of thromboembolism in patients with heart failure and atrial fibrillation exists but no large study of anticoagulation in patients who are in sinus rhythm has been conducted (Snow et al, 2003). The Warfarin and Antiplatelet Therapy in Heart failure (WATCH) trial (Massie et al, 2004) failed to show significant differences between aspirin, warfarin and clopidogrel in the primary composite endpoint of all-cause mortality, non-fatal MI, and non-fatal stroke. This trial showed that patients on warfarin had a significantly lower rate of hospitalization than those treated with aspirin. However, this trial recruited only 40% of the 4500 patients that were required to achieve statistical power.

The Warfarin/Aspirin Study in Heart failure (WASH) trial (Cleland et al, 2004) also showed no significant differences in the effect of aspirin and warfarin on mortality, although aspirin 300 mg was associated with a greater rate of hospitalization for cardiovascular reasons. In reality, it is unlikely that there will ever be an adequately powered, double-blinded study to provide evidence for the use of warfarin in patients with heart failure who are in sinus rhythm.

OTHER THERAPIES

The sudden cardiac death (SCD) rate for patients with heart failure is 6–9 times the general age-adjusted population rate; in the majority of cases the cause of death is malignant ventricular arrhythmia, although other causes such as heart block and thromboembolism may also contribute. The Multicenter Automatic Defibrillator Implantation Trial and Multicenter unSustained Tachycardia trial established that implantable cardiac defibrillators (ICD) significantly reduce mortality in patients with heart failure who have a history of ventricular fibrillation (VF) or haemodynamically unstable ventricular tachycardia (VT) in electrophysiological studies (Gold and Nisam, 2000). The NICE guideline for ICD implantation recommends primary prevention in heart failure patients who have moderate to severely impaired systolic function with non-sustained VT on Holter monitoring and inducible VT in electrophysiological studies.

However, the recently presented SCD-HeFT trial suggests that electrophysiological testing may be unnecessary; implantation of an ICD in patients in New York Heart Association II–III heart failure (secondary-to-coronary artery disease and non-ischaemic causes) with an ejection fraction <35% and who were on appropriate medical therapy resulted in a 25% reduction in mortality when compared with amiodarone therapy or placebo (Bardy, 2004); this effect became significant after 18 months' follow-up.

SCD-HeFT is the first trial to show strong evidence that the decision to implant an ICD should be driven by the degree of systolic dysfunction as opposed to the presence of arrhythmia; however, the economic consequences are substantial. At a conservative estimate, if 200 000 people met the SCD-HeFT criteria for ICD implantation in the UK, the cost of implantation of the ICD would be £4 billion. A degree of rationing and careful patient selection will be necessary to ensure sensible distribution of the limited funding available.

Subgroup analysis from existing trials should clarify this. For example, in the Defibrillators in non-ischaemic Cardiomyopathy Treatment Evaluation (DEFINITE) trial (Kadish et al, 2004), patients with a non-ischaemic cardiomyopathy had significantly lower rates of arrhythmic deaths compared to a matched group treated with medication alone. Sub-group analysis in this study showed that patients of male gender with ejection fraction <20%, NYHA class III, and QRS >120 ms were most likely to derive the greatest benefit from ICD implantation.

Patients with heart failure and left bundle–branch block have dyscoordinate contraction of the septum and the left ventricular free wall. This dysynchrony results in increased end-diastolic volume, reduced contractility and exacerbates mitral regurgitation. Cardiac resynchronization therapy using biventricular pacemakers (BiVPPM) to pace the lateral wall and

the septum simultaneously significantly improves cardiac function. The lateral left ventricular wall is paced by means of an additional third lead that passes through the coronary sinus into a lateral cardiac vein.

The Comparison of Medical therapy, Pacing, And defibrillation in heart failure (COMPANION) trial evaluated the use of BiVPPM in patients with moderate-to-severe heart failure on optimal medical therapy with a prolonged QRS duration on electrocardiogram (Bristow et al, 2004). Patients implanted with a BiVPPM had a reduced risk of death from any cause or first hospitalization when compared to heart failure patients on medical therapy alone (control group). Moreover, when the BiVPPM was combined with an ICD, there was a significant reduction (36%) in death from all causes when compared with the control group.

SPECIALIST CLINICS

There is evidence that the specialist heart failure clinics are an effective and economically viable way of ensuring patients are started on appropriate treatment and their treatment titrated up to maximally-tolerated doses. The interventions of the nurse-led services have also been credited with significantly reducing the number of heart failure admissions (Stewart and Horowitz, 2003).

CONCLUSIONS

The bad news is that the prevalence of heart failure is increasing as the population ages, and in spite of an abundance of evidence for effective treatments such as ACEI and β-blockers, appropriate drug therapy is underused in everyday practice. In addition, newer treatments such as ICDs and cardiac resynchronization therapy are likely to pose major ethical dilemmas for those planning health-care provision. The good news is that the quality of basic care is improving, and is likely to improve further with the development of heart failure as a sub-speciality in cardiology. HM

Conflict of interest: none

Bardy GH, Lee KL, Mark DB et al (2005) The Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) Investigators. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. *N Engl J Med* **352**: 225–37

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

Candesartan in Heart failure: Assessment of Reduction in Mortality and Morbidity (CHARM) Investigators and Committees (2003) 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* **362**: 767–7

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

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

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

Flather MD, Yusuf S, Kober L et al (2000) Long-term ACE-inhibitor therapy in patients with heart failure or left ventricular dysfunction: a systematic overview of data from individual patients. ACE-Inhibitor Myocardial Infarction Collaborative Group. *Lancet* **355:** 1575–81

Gold MR, Nisam S (2000) Primary prevention of sudden cardiac death with implantable cardioverter defibrillators: lessons learned from MADIT and MUSTT. *Pacing Clin Electrophysiol* **23:** 1981–5

Gottlieb S (2000) Digoxin levels should be kept to a minimum in men with heart failure. *Br Med J* **326:** 468

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

Kadish A, Dyer A, Daubert JP et al (2004) Prophylactic defibrillator implantation in patients with nonischemic dilated cardiomyopathy. *N Engl J Med* **350:** 2151–8

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

Massie BM, Krol WF, Ammon SE et al (2004) The Warfarin and Antiplatelet Therapy in Heart Failure trial (WATCH): rationale, design, and baseline patient characteristics. *J Card Fail* **10:** 101–12

National Collaborating Centre for Chronic Conditions (2003) Chronic Heart Failure: National clinical guideline for diagnosis and management in primary and secondary care. http://www.rcplondon.ac.uk/pubs/books/CHF/index.asp (accessed 28 January 2005)

Petresen S, Rayner M, Wolstenhome J (2002) *Coronary Heart Disease Statisitics: heart failure supplement.* British Heart Foundation, London

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

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

Poole-Wilson PA, Swedberg K, Cleland JG et al (2003) Comparison of carvedilol and metoprolol on clinical outcomes in patients with chronic heart failure in the Carvedilol Or Metoprolol European Trial (COMET): randomised controlled trial. *Lancet* **362:** 7–13

Shibata MC, Flather MD, Wang D (2001) Systematic review of the impact of beta blockers on mortality and hospital admissions in heart failure. *Eur J Heart Fail* **3:** 351–7

Snow V, Weiss KB, LeFevre M et al (2003) Management of newly-detected atrial fibrilation: a clinical practice guideline from the American Academy of Family Physicians and the American College of Physicians. *Ann Intern Med* **139**: 1009–17

Stewart S, Horowitz JD (2003) Specialist nurse management programmes: economic benefits in the management of heart failure. *Pharmacoeconomics* **2:** 225–40

Swedberg K, Cleland J, Aguilar JC et al (2003) The EuroHeart Failure Survey programme- a survey on the quality of care among patients with heart failure in Europe. Part 2: treatment. *Eur Heart J* **24:** 464–74

KEY POINTS

- Heart failure is a leading cause of mortality and morbidity in the UK.
- The prevalence of heart failure continues to grow as the population ages.
- Well-established therapies such as angiotensin-converting enzyme inhibitors and β-blockers exist for treatment but are surprisingly underutilzed.
- Newer therapies such as implantable cardiac defibrillators and biventricular pacemakers have been shown to be of prognostic benefit but their high cost require careful patient selection and a degree of rationing.
- The quality of heart-failure treatment has shown signs of improvement and these will continue as the scale of the problem is recognized.