

## ***Management of chronic heart failure***

In essence chronic heart failure (CHF) is the inability of the heart to maintain an adequate cardiac output to suit the needs of the individual with a normal filling pressure. In its untreated form, the primary manifestations are frequently of increased pulmonary and peripheral venous pressure ("backward failure"), yet once treated, the residual abnormalities are usually those of inadequate organ perfusion and/or blood pressure ("forward failure").

### ***Aetiology***

In Europe, the majority of patients with heart failure have coronary artery disease and have lost functionality of segments of myocardium after myocardial infarction. Of the remaining patients with normal coronary arteries, a specific cause can rarely be identified with certainty, and so the second largest aetiological category is "idiopathic dilated cardiomyopathy". In some patients, clues about the origin of the cardiac dysfunction may be identified: a history of prolonged heavy alcohol intake (alcoholic cardiomyopathy), an immediately preceding viral illness (postviral dilated cardiomyopathy) or prior severe valvular disease (particularly regurgitation). Other important causes (because of the opportunity for specific treatment) include haemochromatosis and hypothyroidism. Causes can be categorised into groups as shown in Table 1.

A different group of conditions cause increased tissue demand for blood flow, resulting in features of heart failure even though absolute cardiac output may be supranormal. These include severe anaemia, hyperthyroidism, Paget's disease and arteriovenous malformations. Recognising these causes is important for the condition to be successfully treated.

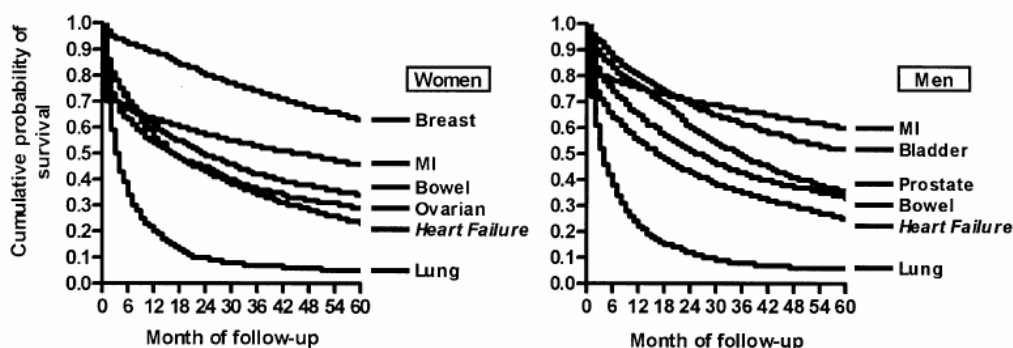
Table 1  
Causes of low output heart failure

Myocardial disease
ischaemic
non-ischaemic dilated cardiomyopathy
toxic
alcohol,
doxorubicin, adriamycin
postviral
infiltrative
haemochromatosis, sarcoid, amyloid,
glycogen storage disease, Fabry's disease
myocarditis (i.e. evidence of inflammation)
autoimmune
idiopathic
Chagas'
nutritional (e.g. wet beri-beri)
endocrine (e.g. hypothyroidism)
Chronic increased cardiac work
Chronic hypertension
Aortic stenosis
Mitral regurgitation
Aortic regurgitation
Limitations to filling
Pericardial tamponade
Constrictive pericarditis
Restrictive cardiomyopathy
Other
Sustained tachycardia
Bradycardia, complete heart block
Atrial fibrillation
Negatively inotropic drugs

## ***Pathophysiology***

Dilatation of the heart is inherently an unstable process. By Laplace's law (wall tension  $\propto$  luminal pressure  $\times$  radius of curvature), dilatation leads to an increase in wall tension which favours further dilatation. Unless the initial dilatation is due to a short-term and reversible insult, the natural history of this disease is generally of a long-term deterioration. However, the syndrome of CHF is far more complex than simple chamber dilatation. There is widespread disruption of the neurohormonal milieu, including activation of the renin-angiotensin system, elevation of circulating catecholamines, and increases in neuropeptides such as brain and atrial natriuretic peptides (BNP and ANP). There is excess sympathetic activation and reduction in parasympathetic tone. Physiological reflexes are also deranged: the stabilising force of the arterial baroreflex is attenuated, while the excitatory chemoreflex and ergoreflex are enhanced. Recent work suggests that there is also overactivation of the inflammatory-immune systems, and that these may be important in the development of the state of cardiac cachexia, characterised by weight loss and severe neurohormonal and reflex derangement and a very poor prognostic outlook.

## Prognosis



The poor outlook for heart failure has caused the disease to be likened to cancer. It is, however, important to recognise that there is a broad spectrum of prognosis. Important aspects of the prognostic assessment are listed in Table 2. Of these, the most widely accepted powerful predictor of early mortality is peak oxygen uptake (peak  $\text{VO}_2$ ) during exercise. Assessment of prognosis is important not only to answer patients' questions but also in selecting treatments.

Table 2. Adverse prognostic markers in CHF

### Severe symptoms

NYHA class III or IV

Cachexia (substantial unintended weight loss not resulting from diuresis)

### Cardiopulmonary physiology

Decreased peak oxygen uptake (peak  $\text{VO}_2$ )

Enhanced exercise hyperpnea ( $\text{VE}/\text{VCO}_2$  slope)

Periodic breathing

Enhanced chemoreflexes and metaboreflexes

### Cardiac physiology

Dilated and/or poorly contractile ventricle

Raised pulmonary capillary wedge pressure

Reduced cardiac output response to exercise

Reduced heart rate variability

### Ischaemic aetiology

### Blood

Decreased serum sodium

Increased creatinine

Increased uric acid

Anaemia

Immune activation

Neurohormonal activation (adrenergic, renin-angiotensin system, natriuretic peptides)

## Treatment

Once the diagnosis has been made, an attempt should be made to treat the underlying cause. However, this article will concentrate on management of established left ventricular dysfunction. Useful general advice to patients with CHF includes cessation of smoking, moderation of alcohol intake (even if not thought to be the aetiology of heart failure in that patient), avoidance of dietary salt supplementation and regular programme of physical exercise. In some countries in Europe, exercise can be prescribed as a therapy and takes place in specialised rehabilitation units under supervision.

### Angiotensin-converting enzyme inhibitors

Angiotensin-converting enzyme inhibitors (ACE inhibitors) have the most well-proven role in the treatment of patients with chronic heart failure. Trials including SOLVD, CONSENSUS and SAVE have shown that they substantially reduce mortality across all classes of heart failure. Their use as a first-line therapy for any severity of chronic heart failure is now standard. They are contraindicated in severe aortic stenosis (because by inducing peripheral vasodilatation they may reduce tissue perfusion dangerously) and in bilateral renal artery stenosis (because they remove the ability of the kidney to preserve its own perfusion pressure). Other than these rare conditions, the use of these drugs is primarily limited by side-effects, of which the commonest is cough (resulting from prolongation of action of irritant peptides in the lung), also there are rare cases of angio-oedema. When administering ACE inhibitors, care must be taken that their hyperkalaemic effects are not potentiated by concurrent potassium-sparing diuretics. The serum potassium and creatinine should be monitored to exclude hyperkalaemia or exacerbation of renal dysfunction.

ACE inhibitors

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<i>Licensed ACEI</i>	<i>Starting dose (mg)</i>	<i>Target dose (mg)</i>
Captopril	6.25 three times daily	50–100 three times daily
Cilazapril*	0.5 once daily	1–2.5 once daily
Enalapril	2.5 twice daily	10–20 twice daily
Fosinopril*	10 once daily	40 once daily
Lisinopril	2.5–5.0 once daily	30–35 once daily
Perindopril*	2.0 once daily	4 once daily
Quinapril*	2.5–5.0 once daily	10–20 once daily
Ramipril	2.5 once daily	5 twice daily or 10 once daily

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### Handling common problems

Low blood pressure, if asymptomatic, need not be cause for dose reduction or termination. If there are symptoms, the first step should be to reduce diuretic dosage, and then if necessary, the dose of any hypotensive agent other than ACEi or beta blocker, and then finally the dose of ACEi or beta blocker

If cough arises, it is worthwhile to look for pulmonary oedema before assuming the cause is the ACEi. If the ACEi causes cough on two occasions, it is now reasonable to change the patient to an angiotensin II receptor antagonist.

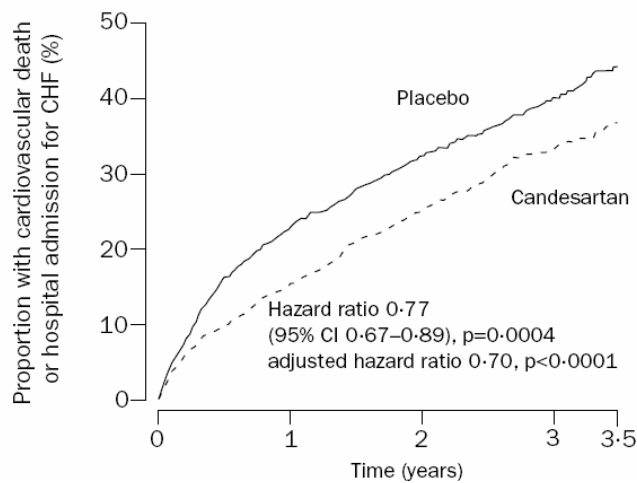
A creatinine rise of up to 30% is *not* cause for withholding or reducing ACEi. Larger rises in creatinine may trigger investigation for renal artery stenosis.

Potassium rises with ACEi. Below 6.0 mmol/l, this is not cause for discontinuation of ACEi. Amiloride (such as in co-amilofruse) should be discontinued in most patients once ACEi are established (especially if angiotensin II receptor antagonists and/or spironolactone are added).

## Angiotensin II antagonists

Angiotensin receptor II antagonists such as losartan and valsartan are promising as alternatives to ACE inhibitors. They certainly have the advantage of a reduced occurrence of side-effect cough. In one major trial (ELITE I), they appeared to give a better mortality than ACE inhibitors, but when this question was restudied formally (ELITE II), no difference was seen between the two. A recent study (Val-HeFT) has shown that in patients not suitable for ACE inhibitors, valsartan showed a clear benefit over placebo. Moreover, valsartan given in addition to ACE inhibitors provided further, albeit smaller, benefits. However, when background treatment was ACE inhibitor and beta blocker, addition of valsartan caused significant harm. A third large study (CHARM-Alternative) again showed benefit of Angiotensin receptor antagonists, in patients not on ACEi.

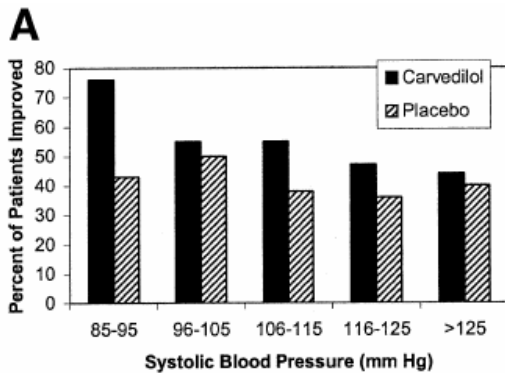
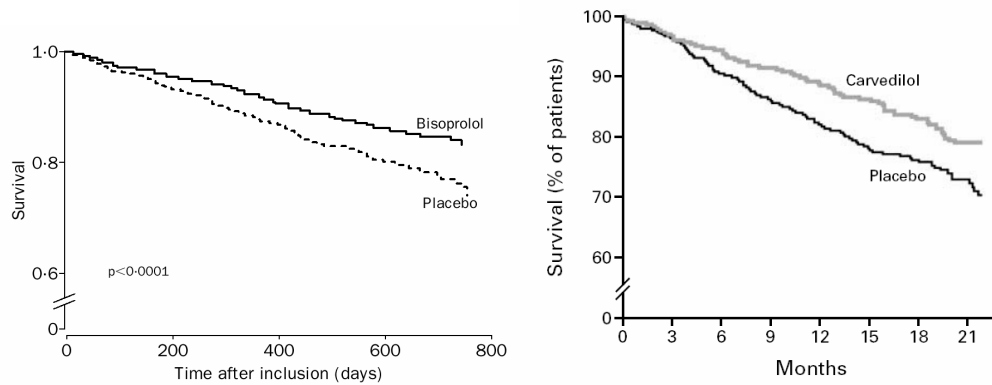
### Prognostic benefit of angiotensin II receptor antagonist: CHARM Alternative



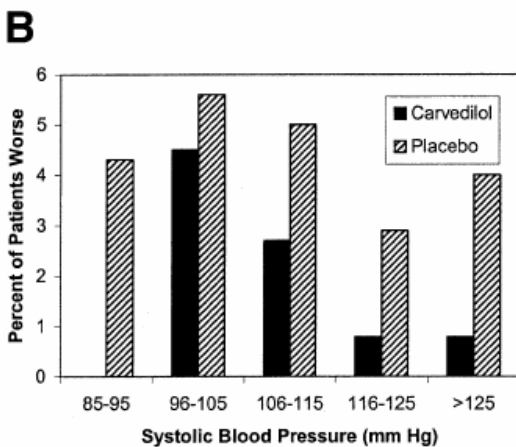
## Beta-blockers

Beta-adrenoceptor blockers, historically considered contraindicated in CHF, are now recognised as beneficial for symptoms and survival across all classes of heart failure, including NYHA class IV. Large studies have confirmed efficacy and safety for carvedilol, bisoprolol and a long-acting preparation of metoprolol. It is important that the patients begin on small doses, which are increased slowly (over a period of several weeks) under supervision with observation of symptoms and blood pressure. It is not uncommon for there to be a transient deterioration during the uptitration process, which is best managed by a short-term increase in diuretic therapy.

Survival benefits of beta blockers (CIBIS II and carvedilol trials shown)



Low blood pressure does not contraindicate beta blocker administration.

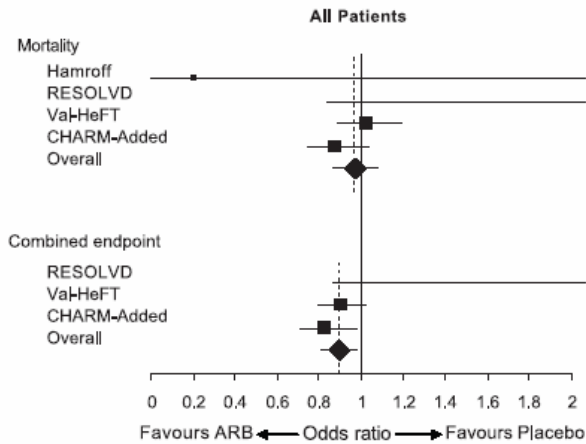


This panel shows data from the COPERNICUS study of carvedilol in severe heart failure.

Even though the patients with lower blood pressures were sicker, they were more likely to have an improvement in symptoms if they were given beta blocker than if they were given placebo.

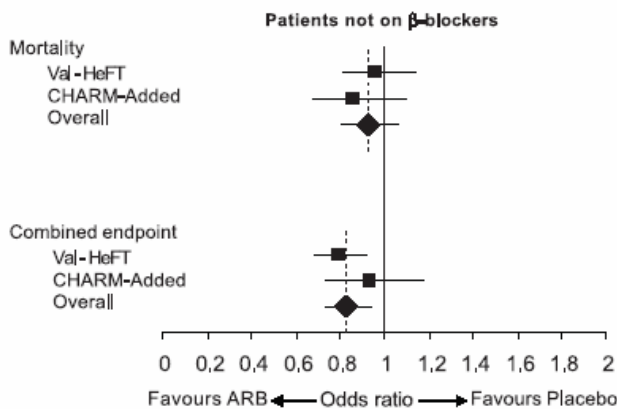
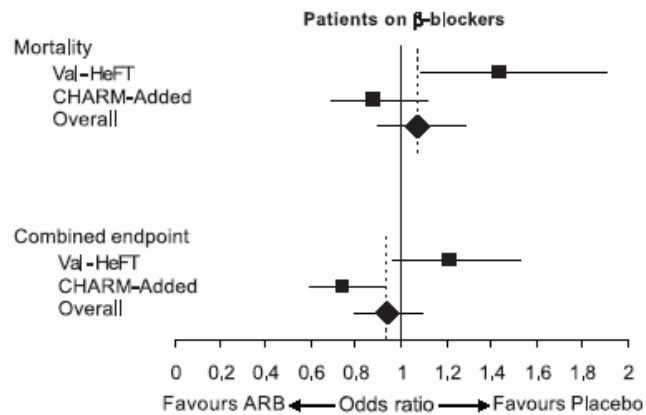
## Combining ACEi, beta blocker and AII receptor antagonist?

While treatment with either angiotensin-converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARBs) is superior to placebo in the treatment of heart failure patients, controversy still surrounds the effects of ARBs in patients already receiving an ACEi. Even more controversial is the wisdom of administering ARBs in patients already on an ACEi and beta-blocker.



Meta-analysis of the randomised controlled trials (the largest of which are CHARM Added and Val-HeFT) found a significant reduction in the combined endpoint (odds ratio [OR] = 0.89; 95% confidence interval [CI] 0.81–0.98), but no significant reduction in mortality itself (OR = 0.97; CI: 0.87–1.08).

For patients concomitantly on beta-blockers, there was no significant effect on mortality (OR = 1.08; CI: 0.90–1.29) or on the combined endpoint (OR = 0.94; CI: 0.82–1.10).



For patients not on concomitant beta-blockers, there is clear evidence of a reduction in the combined endpoint (OR = 0.83; CI: 0.73–0.94), but not on mortality (OR = 0.93; CI: 0.81–1.06).

In summary, there is now good evidence for the use of ARBs to prevent events in patients with heart failure on ACEi who are not suitable for beta-blockers.

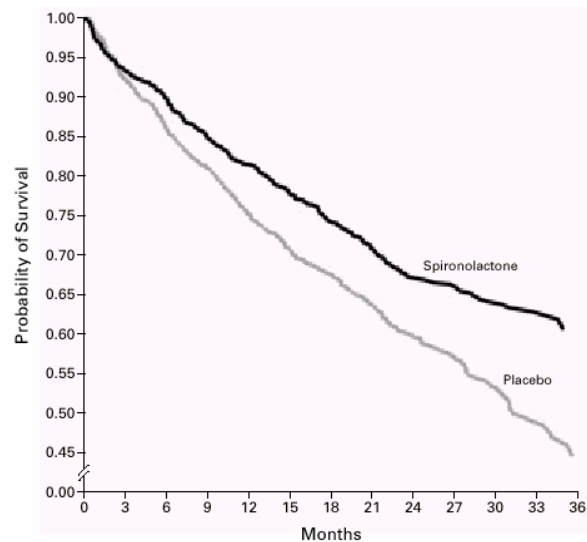
## Aldosterone antagonism

Low dose spironolactone (average daily dose only 26mg) has been found to improved symptoms and survival in patients with severe heart failure (RALES trial) on a background of digoxin, loop diuretic and ACE inhibitors and (in a few) beta blockers.

At this dose, no significant diuretic effect can be expected, and the current belief is that the benefit arises from extrarenal antagonism of aldosterone, protecting against myocardial and vascular fibrosis, direct vascular damage, baroreceptor dysfunction and the diminished uptake of norepinephrine by the myocardium.

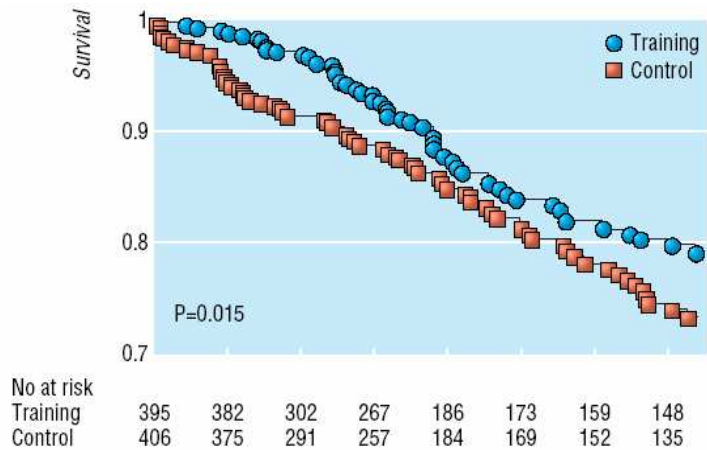
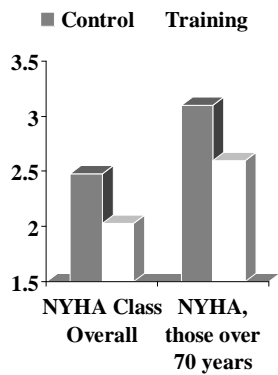
Recent data from the EPHEBUS trial suggests that an alternative agent, epleronone, may be able to work by a similar mechanism, but with more specific antimineralocorticoid effects, avoiding much of the sex-hormone consequences of spironolactone such as gynaecomastia and breast pain. Epleronone data are currently only available for initiation early after myocardial infarction.

Results of RALES trial of spironolactone



## Supervised exercise training

It is many years since physicians have stopped telling patients with heart failure to “take it easy” and “not strain the heart”. Recent data now indicates that the exact converse is good advice. Specifically, supervised exercise training (in a hospital or rehabilitation centre) rather than simply routine advice to take regular exercise has been shown to substantially improve symptoms and, in meta-analysis, to improve survival.

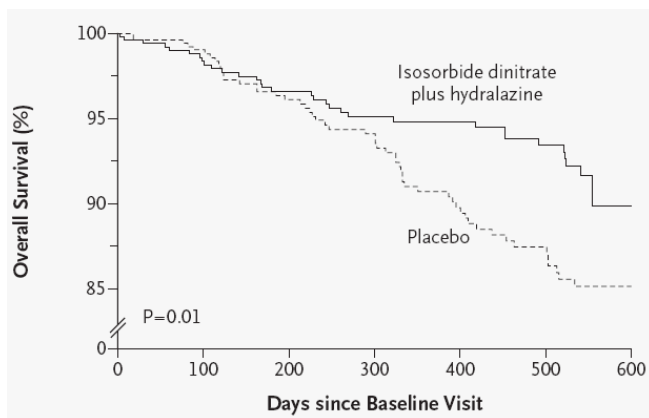


## Diuretics

Although enthusiasts for evidence-based medicine may observe that there is no randomised controlled trial evidence supporting the use of diuretics in heart failure, there seems little clinical doubt that these drugs are useful in counteracting fluid overload and thus alleviating symptoms. Their role is so well-established that no future placebo-controlled clinical trial is likely to ever be approved. Loop diuretics, such as furosemide or bumetanide, are most commonly used. Thiazides (such as bendroflumethiazide or metolazone) when applied in combination with loop agents, have a powerful potentiating effect. Monitoring of renal function is useful, since there is frequently an increase in creatinine and (especially) urea when diuretics are administered. Amiloride can be added if there is a tendency to hypokalaemia.

## Vasodilators

Before ACE inhibition became routine in CHF, the combination vasodilatory regime of isosorbide dinitrate and hydralazine was established by the V-HeFT II trial. Despite being replaced by ACE inhibitors, it remains theoretically a rational alternative for patients who are intolerant of ACE inhibition and angiotensin II receptor antagonists.



Recent data in African-American patients, who have been found to have a less-hyperactive renin-angiotensin system than white counterparts, suggests that they may gain additional benefits from adding combination nitrate and hydralazine to full conventional heart failure therapy. It is noteworthy that this population (the AAHeFT) did not suffer from the chronic low blood pressure typically seen in most fully-treated heart failure patients in the UK.

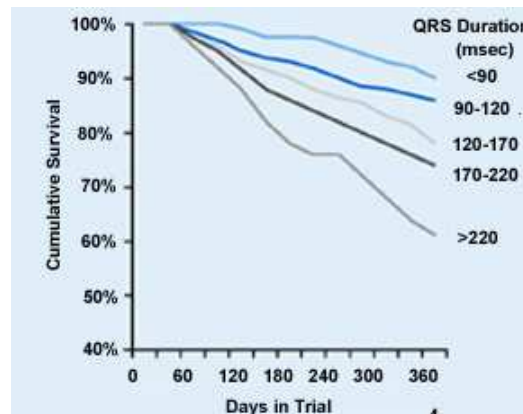
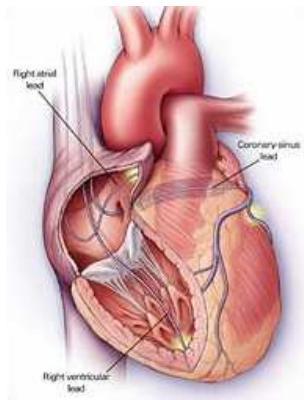
## Digoxin

Digoxin has a long history of use in patients with heart disease — indeed for some decades, it was the only pharmacologically active cardiovascular medication available to physicians. It is widely used to control ventricular rate in atrial fibrillation. The DIG-1 trial has demonstrated a symptomatic, but not survival, benefit in heart failure; this finding has led to its adoption as a routine therapy in some regions (e.g. USA) but not in others (e.g. most of Europe).

## Device therapy

Standard dual-chamber pacemakers may be helpful shortening atrioventricular delay, thus lengthening diastole and lowering filling pressures, which can relieve symptoms. Moreover they can allow higher doses of beta blocker to be used.

Biventricular pacemakers, which pace the right ventricular apex and the left ventricle (via the coronary sinus) can relieve incoordination which is another important cause of raised filling pressures, especially (but not exclusively) in patients with widened QRS complex. These have been shown to improve symptom status and six-minute walk distance, hospitalisation and recently, in the CARE-HF study, all-cause mortality.



Ventricular tachyarrhythmias are a common mode of death in patients with heart failure. Recent studies have shown that implantable cardioverter-defibrillators can significantly reduce mortality in patients at high risk of ventricular arrhythmia. The indications for their implantation are widening, but high cost remains a problem.

## Surgical treatment

The ultimate treatment for intractable heart failure is *transplantation*. Donor hearts are in short supply, and so rationing systems are in place do direct the available organs to those who are most likely to benefit. The patients given the highest priority are therefore those with the poorest prognosis (such as those with peak exercise oxygen uptakes below 14 ml/kg/min) while remaining free of other major organ failure that might impair short- or long-term survival after transplantation (e.g. renal failure; pulmonary arterial hypertension). Mechanical ventricular assist devices, once considered only a short-term

bridge to transplantation , are now being developed for use as long-term maintenance therapy for severe heart failure.

### ***Conclusion***

Chronic heart failure is increasing in prevalence in the Western world, as survival after myocardial infarction improves and the population ages. It has a high morbidity and mortality. Successful medical treatment strategies involving carefully antagonising the body's maladaptive hormonal responses, offer important opportunities to improve not only symptoms but also the poor prognosis. It has now been recognised that even technically simple intervention such as supervised exercise training can improve symptoms and survival. Newer therapies such as cardiac resynchronisation and prophylactic implantable defibrillators may soon develop a formal role, if survival benefit is confirmed at sustainable financial cost.