Use of carvedilol in the treatment of heart failure

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Carvedilol is a multiple action, non-specific, adrenergic beta-blocker, licensed for the treatment of mild, moderate and severe chronic heart failure. This article considers the evidence for using beta-blockers in general, and carvedilol in particular, in the treatment of heart failure. Evidence suggests that carvedilol should be considered as an alternative first-line initiation therapy.

Heart failure is a major cause of both morbidity and mortality in the UK. Every year between one and five patients per 1000 will be newly diagnosed with the condition and it will affect between three and 20 people per 1000 at some time in their lives (Department of Health, 2000). In people over the age of 75 years this figure rises to at least 80 per 1000.

The condition poses a significant burden on hospital services, accounting for around 5% of admissions to hospital medical wards. Over 100 000 admissions for heart failure occur each year, with an average stay of 8 days and an in-hospital mortality rate of 20% (Hobbs et al, 2000). Around 1–2% of UK health-care expenditure is spent on the management of heart failure (Petersen and Rayner, 2002).

Although there is some evidence that the admission rate for heart failure is falling, the prevalence of the condition is rising. This is a result, in part, of the ageing population and in part of the knock-on effect of increasingly successful treatment for myocardial infarction (MI). Having more MI survivors is likely to mean more patients with chronic heart failure (CHF), with one estimate predicting an increase in the prevalence of heart failure by 70% by the year 2010 (Hobbs et al, 2000).

TREATMENT

The onset of CHF tends to be slow, and the condition usually occurs secondary to other cardiovascular problems such as coronary heart disease, MI or hypertension.

Heart failure can be defined as an inability of the heart to pump blood at a rate sufficient to meet the requirements of the metabolizing tissues. Typical symptoms include dyspnoea, fatigue and fluid retention. The condition is also characterized by an activation of the angiotensin neurohormonal system. This initially helps to maintain the circulation but, over time, causes damage to the heart.

The aim of treatment is therefore to improve the patient's quality of life by reducing symptoms and controlling fluid retention, and to prolong life by blocking the neurohormonal activation.

Patients who have been diagnosed with heart failure will require treatment for the rest of their lives. This is likely to include a combination of non-pharmacological measures – dietary advice and lifestyle management – plus drug therapy. Patients whose symptoms fail to respond to these measures may require surgical intervention such as coronary artery bypass grafting or cardiac transplantation.

Until recently, drug therapy tended to rely on a combination of diuretics and angiotensin-converting enzyme (ACE) inhibitors. Diuretics are very effective at reducing fluid retention and other symptoms but, used on their own, can exacerbate the neurohormonal activation. Thus an ACE inhibitor is usually added at a low dose and titrated upward over 2–3 weeks with the goal of reaching the doses used in large-scale clinical trials, e.g. enalapril 10 mg twice daily or captopril 50 mg three times daily.

More recently, the important role that beta-blockers can play in the management of heart failure has been recognized – although this was not always the case.

BETA-BLOCKERS AND HEART FAILURE

For many years, beta-blockers were avoided in heart failure because of fears over their negative inotropic effects. However, recent trials

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have not only confirmed the safety of beta-blockers in heart failure but also shown that they can markedly improve survival of patients with CHF and left ventricular systolic dysfunction (Goldstein and Gottlieb, 2002). Indeed, when Cleland et al (1999) combined the data from 25 randomized controlled trials, involving 6511 patients with CHF, they found that beta-blockers reduced the risk of death by 36%.

As a result of such findings most cardiology guidelines (including those of the UK's National Service Framework for Coronary Heart Disease, the European Society of Cardiology, the American College of Cardiology and the American Heart Association) now recommend beta-blockers in combination with ACE inhibitors in all patients with mild, moderate and severe CHF resulting from left ventricular systolic dysfunction (Department of Health, 2000; Hunt et al, 2001; McMurray et al, 2001).

However, despite these recommendations, there is evidence that beta-blockers continue to be grossly underused in the treatment of CHF. In the UK it has been estimated that beta blockers are prescribed to only around 10% of patients treated for CHF (Petersen et al, 2002).

As a class of drugs, beta-blockers should not be considered entirely homogeneous. They can, in fact, be crudely divided into two different categories. There are those, such as metoprolol and bisoprolol, that are selective for the β1-receptor and there are non-selective beta-blockers such as carvedilol which blocks not only β1-, but also β2-receptors. Carvedilol also blocks α1-receptors, an action that confers vasodilating properties.

Evidence has emerged that the distinction between selective and non-selective beta-blockers may have clinical significance. A meta-analysis of 18 double-blind, placebo controlled trials involving 3023 patients showed that non-selective beta-blockers achieved a statistically significantly greater reduction in the risk of death than β1-selective agents (Lechat et al, 1998). Similarly, a meta-analysis of 21 trials with 5849 patients showed a statistically significant greater reduction in mortality with vasodilating agents compared to non-vasodilating agents (Bonet et al, 2000). Further clarification of the advantages or otherwise of non-selective beta blockers should emerge from a comparison of carvedilol with the β1-selective metoprolol, currently being carried out in the COMET (Carvedilol or Metoprolol European Trial) study (Poole-Wilson et al, 2002).

CARVEDILOL

Carvedilol (Eucardic®, Roche, Welwyn Garden City, UK) is a multiple-action, non-specific, adrenergic beta-blocker. It is one of only two beta-blockers to be licensed in the UK for the treatment of heart failure and is approved for use in the treatment of mild, moderate and severe disease. It should be used as an adjunct to standard therapies such as diuretics, digoxin and ACE inhibitors and in patients with euvolaemia.

Before treatment with carvedilol is initiated, the patient should be stabilized with ACE inhibitors, diuretics and, possibly, digoxin. The starting dose is 3.125 mg twice a day for 2 weeks. If this is well tolerated, the dose should be increased to 6.25 mg twice daily, followed by 12.5 mg twice daily and thereafter, 25 mg twice daily with intervals of at least 2 weeks between increased doses. The tablets should be taken with food to slow the rate of absorption and reduce the incidence of side effects.

To date, over 6000 patients on carvedilol have been studied in randomized placebo-controlled clinical trials. These have consistently shown the drug to improve left ventricular ejection fraction (LVEF), hospitalization and survival in patients with mild, moderate and severe heart failure (Packer et al, 1996).

Carvedilol was the first beta-blocker to be shown to benefit patients with severe heart failure in a large-scale, randomized placebo-controlled trial (Packer et al, 2001). The CarvedilOl ProspEctive RaNdomIzed CUmulative Survival (COPERNICUS) trial included 2289 predominantly male patients with symptoms of heart failure at rest or on minimal exertion and a LVEF of less than 25%, despite treatment with diuretics and ACE inhibitors or angiotensin II receptor antagonists.

The investigators, from 334 medical centres in 21 countries, showed a 35% relative risk reduction in all-cause mortality in patients treated with carvedilol for a mean period of 10.4 months. Hospitalization for heart failure was reduced by 33% and the combined risk of all-cause mortality and all-cause hospitalization was reduced by 24% in the carvedilol treatment arm.

These results led to the trial being stopped early on ethical grounds because of carvedilol's significant benefit to survival (P=0.00013).

Interestingly, a subsequent economic analysis (McMurray et al, 2001) of the above results suggested that adding carvedilol to the therapy of all patients in the UK who fitted the COPERNI-

CUS entry criteria would result in an 11% reduction in the total health-care costs per patient, per week.

Carvedilol has also shown impressive results when used in patients suffering left ventricular dysfunction following acute MI. In the CAPRICORN (CArvedilol Post infaRction survIval COntRol in Left Ventricular DysfunctioN) trial around 2000 patients from 160 sites in 17 countries were randomized to receive either long-term treatment with carvedilol or placebo following a proven MI and with a LVEF of 40% or less (Dargie, 2001). Around one third of the patients were also taking diuretics and 98% were on ACE inhibitors. The results showed a 23% reduction in all-cause mortality in the patients treated with carvedilol (*Table 1*). Compared with patients in the placebo arm, those treated with carvedilol were 41% less likely to suffer a subsequent heart attack during the 15-month follow-up period and 14% less likely to be hospitalized with heart failure.

The most recently presented results of carvedilol therapy indicate that its early combination with an ACE inhibitor could prevent the progression of heart failure in patients who currently have only mild symptoms of the disease (Remme, 2002).

The CARMEN (Carvedilol ACE Inhibitor Remodelling Mild CHF EvaluatioN) trial is the first large-scale direct comparison of a beta-blocking agent with an ACE inhibitor on the effects of left ventricular remodelling in CHF. Involving 572 patients aged an average of 62.3 years and enrolled from 65 sites in 13 countries, the trial featured a three-way randomization – carvedilol in combination with enalapril, enalapril alone or carvedilol alone.

On entry to the study, the patients had all been showing signs of mild, stable heart failure for at least 2 months. They had been on unmodified heart failure medication such as digoxin, diuretics, long-acting nitrates and/or vasodilators for at least 2 weeks before their baseline visit. Their LVEF was 39% or below.

The results showed that the patients who received early carvedilol with the ACE inhibitor demonstrated highly significant improvement in left ventricular remodelling compared with patients receiving either carvedilol or enalapril (P=0.002) alone. This reversal of remodelling was seen as early as the sixth month of therapy and was maintained over the whole 18-month trial period. Compared to the start of the study the patients receiving carvedilol alone showed a significant improvement of left ventricular remodelling. In contrast, the patients on the ACE inhibitor alone showed no such improvement.

Although it cannot be considered a hard clinical endpoint, improvement of left ventricular modelling has been associated with reduced mortality and morbidity in CHF. The CARMEN trial raises carvedilol from a second line, add-on agent to an alternative first-line initiation therapy. It also challenges the common perception that beta-blockers are less well tolerated than ACE inhibitors, as there was virtually no difference in safety or tolerability between any of the three treatment arms (*Table 2*).

The most common adverse effects seen with carvedilol therapy are dizziness, bradycardia, hypotension and fluid retention.

CONCLUSION

Effective, life-saving and life-enhancing treatment of CHF is now possible for most patients with mild, moderate and even severe forms of the disease. There is now clear, clinical evidence that initial concerns over the negative inotropic effects of beta-blockers are unfounded. Indeed, the addition of these agents to current accepted therapy could result in substantial improvements in the mortality rate.

TABLE 1.
Primary and secondary results of CAPRICORN

		Placebo (n=984)	Carvedilol (n=975)	Hazard ratio (95% CI)	Relative risk reduction*	P value
Primary endpoints	All-cause mortality	151 (15%)	116 (12%)	0.77 (0.6–0.98)	23%	0.031
	All-cause mortality or cardiovascular caused hospitalization	367 (37%)	340 (35%)	0.92 (0.8–1.07)	8%	0.297
Secondary endpoints	Sudden death	69 (7%)	51 (5%)	0.74 (0.51–1.06)	26%	0.098
	Hospitalization for heart failure	138 (14%)	118 (12%)	0.86 (0.67–1.09)	14%	0.215

From Dargie (2001). * 95% confidence interval (CI) figures not published

The choice of beta-blocker, however, should not be an arbitrary one. The distinction between those beta-blockers that are selective for the β1-receptor and those that also block the β2- and α1-receptors appears to have clinical relevance. The results of the ongoing COMET study are therefore eagerly awaited as this comparison of the non-selective carvedilol and the β1-selective metoprolol should help resolve this issue. There is a growing body of evidence that beta-blockers with a vasodilating action may offer additional protection over those that do not.

Carvedilol is the only non-specific beta-blocker available in the UK that has a vasodilating action and is licensed for the treatment of patients with mild, moderate and severe CHF. Recent research indicates that, given early in mild disease, carvedilol can prevent the progression of heart failure. Given post MI, it results in significantly improved mortality and given to patients with severe CHF, it can not only reduce all-cause mortality and hospitalization rates but it will also reduce medical costs. With evidence to suggest that the use of beta-blockers in CHF patients is still low, there is a strong case for considering the early addition of carvedilol to the existing therapy of most patients with this distressing and life-threatening disease. HM

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TABLE 2.
Adverse effects recorded in the CARMEN study

	Carvedilol and enalapril (*n*=191)	Carvedilol (*n*=191)	Enalapril (*n*=190)
% patients with any adverse effects	79	77	74
Total number of adverse effects	497	426	461
% patients with serious adverse effects	28	29	34
Total number of serious adverse effects	81	101	94
% patient withdrawals because of adverse effects	18	18	21
Total number of adverse effects leading to withdrawal	45	43	48

From Remme (2002)

KEY POINTS

- Heart failure poses a significant and growing health-care burden in terms of morbidity, mortality and cost.
- The addition of beta-blockers to established heart failure treatments, such as angiotensin-converting enzyme inhibitors and diuretics, results in highly significant improvements in mortality rates.
- Beta-blockers are currently under-used in heart failure.
- Beta-blockers can be divided into those that are specific for the β1-receptor and those that also block the α1- and β2-receptors.
- There is some evidence that non-specific beta blockers offer more protection than β1-specific agents.
- Carvedilol is a non-specific beta-blocker that has been shown to benefit patients with mild, moderate and severe heart failure.
- Used early in patients with mild heart failure, carvedilol helps delay the progression of the disease.
- Used post-myocardial infarction, carvedilol improves mortality and reduces the risk of a second infarction.
- Used in patients with severe heart failure, carvedilol improves mortality, reduces hospitalization and offers significant economic benefits to the health service.