



SUMMARY SHEET FOR

Carvedilol

(Eucardic⁰)

For the treatment of chronic heart failure

The previous MTRAC guidance on carvedilol was updated to reflect changes in prescribing practice.

Licensed indication

MTRAC has reviewed carvedilol for the following indication:

'the treatment of stable, mild, moderate, or severe chronic heart failure as adjunct to standard therapies e.g. diuretics, digoxin, and ACE inhibitors in patients with euvolaemia'.¹

Background information

Heart failure can be defined as 'a state in which an abnormality of cardiac function is responsible for failure of the heart to pump blood at a rate commensurate with the requirements of the metabolising tissues or, to do so only from an elevated filling pressure'.² Symptoms are generally non-specific and include fatigue, dyspnoea, swollen ankles and exercise intolerance.

The overall prevalence of chronic heart failure (CHF) is estimated at 10-20 per 1000 population, with an annual incidence of 1-5 per 1000. Both prevalence and incidence rise with advancing age.²

Heart failure is a major cause of morbidity and mortality.² CHF is considered to impair the quality of life more than any other chronic medical disorder.²

Prognosis in patients with CHF depends on severity (as indicated by symptoms and exercise capacity, commonly using the New York Heart Association [NYHA] classification), age and sex, with a poorer prognosis in male patients.²

Current treatment options

Patients with heart failure require life-long treatment. Pharmacological treatment aims to improve both patients' quality of life and survival. Diuretics and angiotensin converting enzyme (ACE) inhibitors, combined with non-pharmacological measures, form the basis of initial treatment.³ Digoxin may be added in selected patients.

There are now considerable clinical trial data to support the use of beta-blockers in patients with CHF resulting from left ventricular systolic dysfunction.^{4,5} NICE guidelines on chronic heart failure state that 'beta-blockers licensed for heart failure should be initiated in patients with heart failure due to left ventricular systolic dysfunction after diuretic and ACE inhibitor therapy (regardless of whether or not symptoms persist).⁶

Carvedilol and bisoprolol are the only beta-blockers licensed for use for heart failure in the UK.

Dosage and administration

The Summary of Product Characteristics (SPC) states that:

'initiation of therapy should only be under the supervision of a hospital physician, following a thorough assessment of the patient's condition'.

Before treatment is initiated, patients should be stabilised on optimal therapy with ACE inhibitors and diuretics (and optionally digoxin).

The recommended starting dose of carvedilol is 3.125mg twice a day (bd) for 2 weeks. Provided this dose is tolerated, the dose should then be increased to 6.25mg bd, followed by 12.5mg bd and thereafter 25mg bd with intervals of at least 2 weeks between dose increases. The recommended maximum daily dose is 25mg bd for all patients with severe CHF and for patients with mild to moderate CHF weighing < 85kg, and 50mg bd in patients with mild to moderate CHF weighing > 85kg. The tablets should be taken with food to slow the rate of absorption and reduce the incidence of side effects.¹

Patients require careful monitoring during dose titration.⁶ In those with systolic blood pressure <100mmHg, transient worsening of cardiac failure or fluid retention may occur. Carvedilol should be used with caution in patients taking digoxin, since both carvedilol and digoxin may slow A-V conduction.¹

Clinical efficacy

Carvedilol for the treatment of **mild** to **moderate** heart failure has been evaluated in over 1500 patients enrolled in 5 double-blind, placebo-controlled, phase III trials (4 US, 1 Australia-New Zealand).⁷⁻¹¹ Patients enrolled in these trials were around 60 years old, predominantly male, with NYHA class II or III heart failure currently treated with diuretics and ACE inhibitors (and digoxin in some cases).

These phase III trials all had an open-label, 2-3 week challenge (run-in) phase. Approximately 8% of patients were withdrawn from the trials during this phase (at least half because of adverse events including 10 deaths). The remaining patients were randomised to carvedilol or placebo, with double-blind dose titration and maintenance treatment. The

duration of the studies ranged from 6 to >19 months. The US carvedilol heart failure program (4 trials) was terminated early when a significant effect of carvedilol on survival became evident.

Treatment with carvedilol was consistently associated with a significant improvement in left ventricular ejection fraction (LVEF, $p < 0.01$). Variable effects were seen on NYHA class and global assessment of symptoms. Generally treatment had no significant effect on exercise tolerance or quality of life.⁷⁻¹¹

In a combined analysis of the 4 US trials ($n=1094$) the risk of death was reduced by 65% (ARR 4.6%, $p < 0.001$) and the risk of cardiovascular hospitalisation by 27% (ARR 5.5%, $p < 0.005$).¹² However, the number of deaths and cardiovascular hospitalisations on which these data are based is small, $n=53$ and $n=176$ respectively. No significant treatment effect on mortality or cardiovascular hospitalisations was apparent in the Australia-New Zealand trial ($n=415$).¹¹ The combined risk of cardiovascular hospitalisation or death was significantly reduced by 36% (ARR 8.8%, $p < 0.001$) in the US combined analysis⁹ and the combined risk of hospitalisation or death was significantly reduced by 26% in the Australia-New Zealand trial ($p=0.02$).¹¹

The efficacy of carvedilol in the management of **severe** heart failure has been evaluated in a large, randomised, double-blind, placebo-controlled trial (COPERNICUS, $n=2289$).¹³ Patients enrolled in this trial were aged about 60 years, predominantly male with symptoms of heart failure at rest or on minimal exertion and LVEF $< 25\%$ despite treatment with diuretics and ACE/angiotensin II inhibitors.¹³

The trial was stopped early due to a significant positive treatment effect on survival. Carvedilol treatment for a mean of 10.4 months was associated with a 35% reduction in the risk of death (ARR 5.6% $p=0.002$) and 24% reduction in the combined risk of death or hospitalisation (ARR 8% $p < 0.001$). Further trials with carvedilol in different populations of heart failure patients are underway.

Adverse effects

Frequently reported adverse events with carvedilol therapy in the clinical trials include dizziness, bradycardia, hypotension and oedema.

Costs

At current prices one year's treatment with carvedilol 25mg bd costs £327 with carvedilol and £125 with bisoprolol 10mg daily.

Summary

Carvedilol is one of only two beta-blockers licensed in the UK for the treatment of CHF. In clinical trials involving over 1500 patients it has been shown to significantly improve LVEF and to reduce the risk of hospitalisation and death in patients with mild, moderate and severe heart failure already treated with ACE inhibitors and diuretics, compared with placebo. Treatment needs to be initiated slowly under careful medical supervision.

References

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