



NEW PRODUCT EVALUATION

Occasional review: beta-blockers in heart failure April 2002

Introduction

The prevalence of heart failure has been estimated at 1-2% of the population¹ and is increasing, fuelled by an aging population and a greater number of myocardial infarction survivors. This has significant implications for both individual patients and the wider issue of health economics. It is important to note that the prognosis for patients with moderate to severe heart failure is worse than most malignancies.²

Beta-blockers have traditionally been used for the treatment of hypertension and angina. More recently, their use in secondary prevention after acute myocardial infarction has been endorsed in the National Service Framework for Coronary Heart Disease. However, the use of specific beta-blockers in the treatment of heart failure is novel, particularly as this class of drug was previously contra-indicated. This review will summarise the role of beta-blocker therapy in heart failure, highlighting its advantages as an adjunct treatment to ACE inhibitors and diuretics.

The scientific basis of beta-blocker use

In heart failure, the renin-angiotensin-aldosterone system (RAAS) and the sympathetic nervous system (SNS) are activated as a physiological compensatory mechanism to falling output. This rapidly becomes deleterious rather than beneficial as RAAS activation contributes to worsening heart failure through its suppression of myocardial function and increasing fluid retention. The use of angiotensin converting enzyme (ACE) inhibitors are therefore appropriate in the treatment of patients with left ventricular failure. Numerous RCTs have now shown reduced morbidity and mortality following use of these agents. Further, the RALES study has recently published evidence to support add-on therapy with low dose spironolactone, an aldosterone antagonist.³ Spironolactone is probably best initiated after assessment by a specialist in those patients with moderate heart failure who remain symptomatic despite maximal therapy with diuretic, ACE inhibitor and beta-blocker.

Activation of the sympathetic nervous system in heart failure also leads to higher circulating levels of noradrenaline (NA) and those patients

with the greatest plasma concentration have the poorest prognosis. NA promotes vasoconstriction, increased cardiac work and increased risk of cardiac arrhythmias. Blockade of noradrenaline using beta-blockers provides both haemodynamic and neurohumoral benefits in heart failure.

The Evidence

Following the findings from smaller trials that revealed a trend towards improving LV function and symptoms, three large randomised controlled studies have been published highlighting that beta-blockers save lives.^{4,5,6}

Carvedilol is a non-selective beta-blocker with beta₂-antagonist and anti-oxidant activity. The US Carvedilol Heart Failure Study investigated 1094 patients with predominantly mild to moderate (NYHA class II-III) stable heart failure.⁴ This study was stopped early on the basis that the addition of carvedilol to conventional therapy (including ACE inhibitor, diuretics and digoxin) led to a reduction in mortality at 6 months, from 7.8% to 3.2%, a 65% reduction. Importantly 80% of patients tolerated the maximum 25mg twice-daily dose. In addition, carvedilol therapy led to a significant reduction in hospitalization. Few patients (3%) with severe (NYHA IV) heart failure were included in this study, but more recently the COPERNICUS trial concluded that benefit extended to this patient group.⁷

Bisoprolol is a highly selective beta₁-blocker. The CIBIS-II study involved 2647 patients with moderate to severe (NYHA III-IV) stable heart failure.⁵ This study compared outcome in patients given bisoprolol or placebo, in addition to conventional therapy (diuretic and ACE inhibitor). Nearly half (42%) of those given bisoprolol reached the target dose of 10 mg daily. Again, the study was terminated early at a mean of 16 months due to improved outcomes. A reduction in all-cause mortality from 17.3% to 11.8%, with a reduction in sudden death from 6.3% to 3.6% was found in those taking bisoprolol. In addition, fewer patients on bisoprolol were admitted to hospital for worsening heart failure (18% vs 12%). Seventeen per cent of patients had severe heart failure (only those with stable disease

were included in the trial), and subgroup analysis of this group's outcome was similar to that of patients with moderate heart failure, although it did not reach statistical significance. **Metoprolol** is a selective beta₁-blocker. The MERIT-HF study used metoprolol-XL, a formulation of metoprolol not currently available in the UK. This study involved 3991 patients with predominantly mild and moderate (NYHA II-III), stable heart failure.⁶ The study was conducted in a similar way to the above trials and again stopped early due to improved survival in those taking metoprolol. At a mean follow-up of 12 months, metoprolol add-on therapy led to a significant 34% relative risk reduction in all-cause mortality (11% to 7.2%). Subgroup analysis comparing severity of heart failure did not show any significant differences, however only 3.6% of patients had severe heart failure.

Metoprolol is not currently licensed in the UK for treatment of heart failure.

Clinical Practice

Initiation:

Only **carvedilol** and **bisoprolol** are currently licensed for the treatment of heart failure. Carvedilol is indicated for the treatment of mild, moderate and severe heart failure as adjunct therapy to ACE inhibitor, diuretics (and digoxin). For bisoprolol, the indication is similar, ejection fraction should be below 35%. Patients must be euvolaemic and usually have remained stable for at least two weeks prior to commencing therapy. For both products, it is recommended that an experienced specialist initiates treatment and supervises up-titration of dose.

Importantly, there is no evidence at this time for the use of atenolol or other beta-blockers, these are not licensed in heart failure and should not be used.

Titration of dose:

Careful up-titration of therapy should follow the protocols used in the published studies. This should minimise worsening of heart failure and ensure that the maximum tolerated dose is achieved. Stabilization of between one and four weeks at each dose increment is necessary before a dose increase, depending on the protocol. Patients should be maintained on the maximum tolerated dose; the target for carvedilol is 25 mg bd and bisoprolol is 10 mg od. The following table details specific titration protocols:

Increment	Bisoprolol dose
Initiation	1.25 mg od for one week
Step 1	2.5 mg od for one week
Step 2	3.75 mg od for one week
Step 3	5 mg od for 4 weeks
Step 4	7.5 mg od for 4 weeks
Step 5	10 mg od maintenance

Increment	Carvedilol dose
Initiation	3.125 mg bd for at least 2 weeks
Step 1	6.25 mg bd for at least 2 weeks
Step 2	12.5 mg bd for at least 2 weeks
Step 3	25 mg bd maintenance

Problems:

The commonest problem is worsening heart failure, often after an increase in dose. Unless this causes acute pulmonary oedema, it is appropriate to maintain the current beta-blocker dose and increase the diuretic temporarily. The patient should be stable before increasing the dose further. Only in the event of significant adverse events (e.g. severe hypotension, cardiogenic shock, symptomatic bradycardia), should the beta-blocker be discontinued; the patient may require hospital admission if this occurs. Serious adverse events such as these do not preclude beta-blocker therapy being introduced at later date using a lower dose, once the patient is stable.

SUMMARY

- **The prevalence of heart failure is increasing and often associated with a poor prognosis.**
- **There is substantial evidence that beta-blocker therapy, as an adjunct to ACE inhibitors and diuretics, saves additional lives and reduces hospitalisations.**
- **All patients with stable chronic heart failure should be considered.**
- **Only carvedilol and bisoprolol are licensed for the treatment of heart failure in the UK.**

References:

- 1 Cleland JG, Khand A, Clark A. The heart failure epidemic: exactly how big is it? *Eur Heart J* 2001; **22**: 623-26.
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- 3 Pitt B, Zannad F, Remme W et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. *New Engl J Med* 1999; **341**:709-17.
- 4 Packer M, Bristow M, Cohn J, et al. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. US carvedilol heart failure study group. *N Engl J Med* 1996; **334**:1349-55
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- 6 Merit-HF study group. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). *Lancet* 1999; **353**:2001-7
- 7 Packer M, Coats A, Fowler M, et al. Effect of carvedilol on survival in severe chronic heart failure. *New Engl J Med* 2001; **344**:1651-8.

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