REVIEW ARTICLE

Beta-blockers in heart failure—a cardioprotective therapy?

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SUMMARY

Heart failure remains a major cause of morbidity and mortality despite optimum treatment with angiotensin-converting enzyme inhibitors and diuretics. Meta-analysis of recent placebo-controlled, randomized trials suggest that treatment with beta-blockers may significantly reduce mortality by 35%.

INTRODUCTION

Heart failure is a major cause of morbidity and mortality. The prognosis for those who are breathless on minimal exertion (NYHA grade III or IV) is poor, with 12.4% mortality at 1 year and 34.5% at 4 years (1). This is despite current ‘optimal’ treatment with diuretics and angiotensin-converting enzyme (ACE) inhibitors. This figure is comparable to the 40% overall 5-year survival for patients with carcinoma of the colon (2).

Heart failure is associated with high levels of circulating catecholamines (3, 4). Plasma levels of noradrenaline are related to the severity of heart failure (5) and to the prognosis (6). Increased sympathetic tone is associated with tachycardia, activation of the renin–angiotensin–aldosterone system (RAAS) and vasoconstriction, leading to reduced left ventricular filling, increased left ventricular afterload and increased myocardial oxygen consumption in the presence of reduced myocardial perfusion (7). High sympathetic tone may contribute to the increased incidence of cardiac arrhythmias seen in patients with heart failure (8). In this state of continuous sympathetic drive, β-receptors are down-regulated (9). Beta-blocker therapy may reverse some of these changes.

MECHANISM OF ACTION

Beta-blockers reduce heart rate and contractility and prolong diastole, resulting in increased myocardial efficiency and improved balance of oxygen requirement and delivery (10, 11). An increase in myocardial β-receptor density has been reported in response to long-term β-blocker treatment in heart failure (12–14). Sympatholytic effects reduce vasoconstriction in the long term, both by direct action on vascular smooth muscle and via reduced RAAS activity (15). This also reduces sodium and water retention by the kidney. Beta-blockers reduce the probability of cardiac arrhythmogenesis (16, 17). Lipophilic β-blockers, such as carvedilol and metoprolol, may cross the blood–brain barrier and increase vagal activity via central β-receptor antagonism (18, 19). This reduces heart rate variability, a recognized risk factor for arrhythmia and sudden death (20). Non-selective β-blockers may protect against hypokalaemia.

Some β-blockers have actions in addition to those of β-receptor antagonism. For instance, carvedilol is an...
α-antagonist and may cause acute vasodilatation with reduced systemic vascular resistance and left ventricular filling pressure (21). It is the only β-blocker with significant antioxidant activity (22, 23) and it also has a negative effect on the proliferation of vascular smooth muscle (24). It is unclear whether these additional actions are of relevance to the mechanism of action in heart failure.

HAEMODYNAMIC EFFECTS

Treatment of heart failure with β-blockers causes an acute fall in systolic blood pressure and heart rate with no improvement in left ventricular ejection fraction or filling pressure (25). Improved diastolic function (left ventricular filling) may be an early change as a consequence of the reduction in heart rate and prolongation of diastole (26). Long-term treatment (3–12 months) results in improved left ventricular ejection fraction (LVEF) (25, 27) and reduces left ventricular end-systolic and end-diastolic diameters (12, 27).

IMPACT ON MORBIDITY

Subjective improvement in symptoms of heart failure is reported in some (25, 28) but not all trials (27, 29). Likewise, improvement in objective measures of exercise capacity (25) is a variable finding. Beta-blockers appear to significantly reduce hospital admission rates in patients with heart failure (25, 27, 29). In addition, a significant 90% reduction in the pre-specified endpoint of need for cardiac transplantation was demonstrated in the MDC trial of metoprolol in patients with idiopathic dilated cardiomyopathy (25).

IMPACT ON MORTALITY

The ‘ideal’ treatment for heart failure not only improves symptoms but also extends patient survival. However, the assessment of new treatment strategies for heart failure is not straightforward and it is now widely understood that improvements in symptoms and/or haemodynamic function do not necessarily correlate with improved long-term survival. For instance, diuretics improve symptoms of heart failure but there is no evidence of mortality benefit. Positive inotropes and partial β-agonists, such as milrinone (30) and xamoterol (31), improve symptoms in the short term but have an adverse effect on survival. A recent trial of digoxin for the treatment of heart failure with preserved sinus rhythm showed no effect on mortality, although there was a reduction in hospital admissions (32). Thus, assessment of new, effective, cardioprotective treatments for heart failure can only be made by the use of randomized, controlled trials with hard clinical end-points. Such trials need to examine the additional benefit of a new treatment when added to current ‘optimal’ treatment, i.e. diuretics and ACE inhibitors.

There have been four placebo-controlled, randomized trials of β-blockers for the treatment of heart failure that have recruited more than 200 patients and reported in full (25, 27–29). Each of these differ slightly in design: aetiology of heart failure; age of participants; severity of symptoms; drug used; number of patients; length of follow-up. Taken together these trials give an indication of the likely role of β-blocker therapy in heart failure. Details of these trials are given in Table 1 and the results are discussed below.

Only the U.S. Carvedilol Heart Failure Study programme was designed to have sufficient power to detect a change in mortality as an end-point (29). The other trials were designed to examine the effects on combined end-points. The U.S. Carvedilol programme demonstrated a significant 65% reduction in all-cause mortality in the treatment group (29). Meta-analysis of all four trials, accepting the fact that they each use different drugs for varying severity and aetiology of heart failure, and are followed-up for differing lengths of time, suggests a significant 35% overall reduction in mortality in response to β-blockers (95% confidence intervals (95% CI)=18–49%). A recent meta-analysis of these trials and 17 other smaller trials suggested that there was a 31% reduction in mortality in those treated with a β-blocker (95% CI=11–46%) (33).

When the results are assessed according to the aetiology of heart failure, there appears to be a greater mortality benefit in patients with a non-ischaemic (50% relative reduction in mortality, 95% CI=31–64%) rather than an ischaemic (36%, 95% CI=14–53%) cause of heart failure. There appears to be no difference in mortality benefit in relationship to severity of heart failure as judged by LVEF.

Further support for the mortality benefits of β-blockers in heart failure may be gained from the trials of oral β-blockers following myocardial

inclusion (34, 35). In these trials, propranolol and timolol reduced mortality by 27% and 43%, respectively. In each study, in a pre-specified group of patients with evidence of left ventricular dysfunction, the reduction in mortality was even greater (31% and 48%, respectively). Hence, in these patients with ischaemic left ventricular dysfunction, β-blockers were shown to have a significant impact on mortality. It should be noted that these trials pre-date the use of aspirin, thrombolysis and ACE inhibitors in the management of acute myocardial infarction.

### THE OPEN-LABEL RUN-IN PHASE AND DOSE TITRATION

Three of the trials included an open-label run-in phase designed to identify patients intolerant of β-blockers (25, 27, 29). Considerable care was taken to start at very low doses (metoprolol 10 mg/day (25), bisoprolol 1-25 mg/day (28), carvedilol 3-125–6-25 mg b.d. (27, 29)). Dose titration was achieved over 2–10 weeks.

During the run-in period 107 (5·5%) of the 2056 patients withdrew due to adverse effects, and there were seven deaths (all in the U.S. Carvedilol programme). Randomization following successful completion of an open-label phase makes interpretation of the long-term effects of β-blockers in heart failure more straightforward. However, a clinician needs to take any adverse effects in the initial run-in period into account when deciding whether to start therapy in an individual patient. In the U.S. Carvedilol programme the total number of deaths whilst taking carvedilol was 29 (seven in run-in and 22 after randomization) compared to 31 in the placebo group. Thus, if deaths in the open-label, run-in phase are included, treatment with carvedilol is no longer demonstrated to have a significant impact on mortality.

### COMPARISON WITH THE ACE INHIBITOR EXPERIENCE

The SOLVD treatment trial demonstrated a 16% reduction in mortality in 2569 patients randomized to enalapril or placebo (35·2% and 39·7%, respectively) and followed-up for a mean of 41-4 months (1). The 12-month mortality was reduced from 15·6 to 12·4% (a relative reduction of 23%). The mean placebo group mortality for the trials of β-blockers in heart failure was 12·8%, with a mean treatment group mortality of 8·3% (a further relative risk reduction of 35%). Thus, it may be concluded that the benefit from β-blockers is truly in addition to that of ACE inhibitors.

The trial experience with β-blockers in heart failure is considerably less than that with ACE inhibitors. There have been 2004 deaths (941 in treatment groups) in 24 180 people-years follow-up in trials of ACE inhibitors for heart failure (1, 36–38). This compares to 261 deaths (118 in treatment groups) in

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**Table 1. Details of trials of β-blockers in patients with heart failure**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Drug</th>
<th>No. of subjects</th>
<th>Aetiology of heart failure</th>
<th>Mean age (years)</th>
<th>% of men</th>
<th>NYHA class at entry</th>
<th>Use of ACE inhibitors (%)</th>
<th>Mean ejection fraction at entry (%)</th>
<th>Mean follow-up (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDC (25)</td>
<td>Metoprolol</td>
<td>383</td>
<td>Idiopathic 100%</td>
<td>49</td>
<td>72</td>
<td>II–III</td>
<td>93%</td>
<td>79</td>
<td>22</td>
</tr>
<tr>
<td>CIBIS (28)</td>
<td>Bisoprolol</td>
<td>641</td>
<td>Idiopathic 35% Ischaemic 55%</td>
<td>60</td>
<td>83</td>
<td>III</td>
<td>95%</td>
<td>90</td>
<td>25·4</td>
</tr>
<tr>
<td>U.S. (29)</td>
<td>Carvedilol</td>
<td>1094</td>
<td>Idiopathic 48% Ischaemic 52%</td>
<td>58</td>
<td>77</td>
<td>II–III</td>
<td>97%</td>
<td>95</td>
<td>22·5</td>
</tr>
<tr>
<td>ANZ (27)</td>
<td>Carvedilol</td>
<td>415</td>
<td>Ischaemic 100%</td>
<td>67</td>
<td>80</td>
<td>I</td>
<td>30%</td>
<td>86</td>
<td>28·4</td>
</tr>
</tbody>
</table>

2868 person-years follow-up in trials of β-blockers in heart failure (25–29). The trial experience with β-blockers is thus approximately a tenth of that with ACE inhibitors.

CONCLUSIONS

Beta-blockers offer the exciting prospect of an additional cardioprotective treatment in patients with heart failure. At present their use should be confined to patients with stable heart failure who are already receiving ACE inhibitors. Current experience suggests that they should be started by a specialist at low (‘sub-therapeutic’) doses and that the dose should be increased slowly.

It is not clear whether the particular drug, the aetiology of the heart failure or the left ventricular ejection fraction are important determinants of successful treatment. Further large, long-term, randomized, controlled trials are required to answer these questions.

REFERENCES
