Beta-blockers in heart failure

Future directions

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The rationale for beta-blockade in heart failure is now well established. Heart failure mortality, which is predicted by neurohormonal activation, remains high despite modern treatment including ACE inhibition, and additional neurohormonal blockade has further therapeutic potential. Previous clinical trial experience in heart failure, most of which has been in patients with idiopathic cardiomyopathy, indicates consistent improvement in ventricular function although variable changes in symptoms and exercise performance. However, the major burden of heart failure occurs in patients with ischaemic heart disease and in this respect it is notable that beta-blockade following myocardial infarction confers significant mortality benefit in subgroups with heart failure. The Australia and New Zealand carvedilol heart failure study is the largest completed study of beta-blocker treatment in patients with heart failure of ischaemic aetiology, including 415 patients randomized to carvedilol or placebo and indicating excellent tolerability of a titrated dose regimen and improved ventricular function after 6 months of treatment. An overview of all currently available randomized clinical trials of beta-blockade in heart failure, which includes more than 1600 patients, indicates a mortality risk reduction of approximately 20% but with wide confidence intervals. A large scale trial with several thousand patients is required to detect reliably a plausible 15-20% mortality reduction with beta-blockade in heart failure. The dissociation of clinical and mortality effects demonstrated with other heart failure treatments indicates the necessity for an appropriately powered mortality study which could define a major improvement in heart failure therapy for the future.

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Introduction

Congestive heart failure is an important cause of morbidity and mortality in many countries. It is a common reason for hospital admission and accounts for 1-2% of total health care expenditure in developed countries. The rationale for the use of beta-blockers in heart failure is related to several considerations. First, the persisting poor prognosis for patients with congestive heart failure despite the application of modern treatment including angiotensin converting-enzyme (ACE) inhibitors. Second, the prognostic importance of neurohormonal activation in heart failure and the benefit from neurohormonal blockade in this context. Third, the substantial mortality benefit demonstrated with beta-blockade following myocardial infarction also evident in subgroups with heart failure. Fourth, previous randomized clinical trials with different beta-blockers in heart failure which have included assessment of tolerability, exercise performance and ventricular function. Finally, meta-analysis of all available randomized clinical trial data which indicates probable mortality benefit and mandates a definitive large scale mortality study. The value of clinical studies in heart failure with surrogate end-points only has recently been questioned. The effects of treatment on clinical status may be dissociated from survival effects and thus long term assessment of morbidity and mortality end-points is essential for complete evaluation.

Heart failure mortality

Mortality ranges widely according to heart failure severity from 15% annually in the community in unselected patients to 50% annually among those with severe heart failure (New York Heart Association functional class IV) treated conventionally. With the application of ACE inhibition, in the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS I), enalapril treatment reduced mortality in patients with severe heart failure, NYHA functional class IV, from approximately one-half to one-third during one year. In the Studies of Left Ventricular Dysfunction (SOLVD), patients with moderate heart failure, NYHA functional class II-III, were treated with enalapril or placebo in addition to conventional treatment for an average period of 3-4 years. Mortality was reduced...
with ACE inhibitor treatment from 39.7% to 35.2% (risk ratio 0.84, 95% confidence intervals 0.74–0.95). Thus modern treatment with ACE inhibition has been proven beneficial but the mortality reduction achieved is modest and the prognosis remains very poor despite such treatment.

**Neurohormonal alterations in heart failure**

Compensatory changes in the sympathetic and parasympathetic nervous systems, in the renin-angiotensinaldosterone system and in plasma arginine vasopressin occur in heart failure, partially offset by increases in vasodilator prostaglandins and natriuretic peptides. Atrial natriuretic peptide, renin, angiotensin II and norepinephrine are each independently predictive of mortality. Agents that block these activated neurohormonal systems have therapeutic potential in heart failure. The benefits of ACE inhibitors are well established. There may also be complementary benefits provided through blockade of the sympathetic nervous system with the use of adrenergic blockers. Alterations in the adrenergic pathway, including beta-adrenergic receptors and effector mechanisms in heart failure, are the subject of ongoing research and have been recently reviewed.

**Beta-blockade following myocardial infarction**

Long term therapy with beta-blockade following myocardial infarction confers considerable mortality benefit. This benefit is also applicable to the subgroups of myocardial infarction patients with a history of previous heart failure or digitalis treatment and those with low blood pressure or signs of heart failure at the time of acute infarction. However these trials were generally in highly selected groups of patients and traditional concern remains about the use of beta-blockers in patients with significant left ventricular impairment following myocardial infarction. Considering combination treatment, it is relevant that the mortality benefit demonstrated with ACE inhibition in patients with asymptomatic left ventricular dysfunction following myocardial infarction, was also evident in those receiving beta-blocker treatment.

**Clinical trials of beta-blockers in heart failure**

Following initial favourable clinical reports of the use of beta-blockers in patients with congestive cardiomyopathy, a large number of randomized clinical trials have been conducted and these have recently been summarized. Sixteen randomized controlled trials including a total of more than 900 patients with predominantly idiopathic dilated cardiomyopathy have employed different beta-blockers and a range of treatment durations. Changes in exercise tolerance have been variable but improvement in ventricular function, when assessed, has been more consistent, with a weighted mean absolute increase in ejection fraction in the beta-blocker group compared with the control group of 5.4%. Some data suggest that possibility of a different response in patients with heart failure due to ischaemic heart disease compared with idiopathic dilated cardiomyopathy. Data on mechanisms of improvement are few and conflicting, although improved myocardial contractility with long term treatment has been demonstrated.

**Beta-blockade and survival in heart failure**

In the recently reported Metoprolol in Dilated Cardiomyopathy Study 383 patients were randomized to metoprolol or placebo and followed for 12–18 months. There were significant improvements in haemodynamic variables and symptoms and fewer hospital admissions in the beta-blocker-treated group. Fewer metoprolol-treated patients were placed on the cardiac transplant list but there was no statistically significant effect on total mortality. Preliminary reports from a study with bisoprolol which included a total of 641 patients with NYHA functional class III–IV heart failure of different aetiologies, indicate a reduction in mortality from 20% to 16% with mean follow-up 1.9 years (risk ratio 0.80, 95% confidence intervals 0.51–1.15).

An overview of all available randomized clinical trials involving 1616 patients, 74% with idiopathic dilated cardiomyopathy, median NYHA functional class 2.7 and ejection fraction 23%, with average duration of follow-up 15 months, indicates mortality reduction from 13.0% in controls to 10.5% with beta-blockade (risk ratio 0.82, 95% confidence intervals 0.6–1.1, \(P=0.19\)). An overview with this number of patients has reasonable power to detect a one-third reduction in mortality but only a 50% chance of detecting a one-quarter reduction.

**Carvedilol in heart failure**

Carvedilol is a non-selective beta-adrenergic antagonist without intrinsic sympathomimetic activity and with vasodilator properties due to alpha 1-receptor antagonism. Vasodilator action of carvedilol may reduce the potential cardio-depressant effect and the risk of early decompensation with initial treatment. Carvedilol is widely approved for the treatment of hypertension and will be filed for angina. A number of clinical studies with carvedilol in heart failure are currently in progress which involve a total of approximately 1450 patients in the United States, Australia and New Zealand.
The Australia and New Zealand Heart Failure Research Group randomized trial of carvedilol is the largest completed study of beta-blocker treatment in patients with heart failure of ischaemic aetiology, including 415 patients randomized to carvedilol or placebo. A preliminary report from this study[23] indicates excellent tolerability of a titrated dose regimen and improved ventricular function after 6 months treatment. The clinical profile of carvedilol makes this agent most suitable for application in a definitive mortality study of beta-blockade in heart failure.

A beta-blocker heart failure mortality study

It is now well understood that different treatment aims in heart failure can be met through different mechanisms. Congestive symptoms may be relieved through haemodynamic improvement, particularly through reduction of elevated ventricular filling pressures. Improved exercise tolerance may result from peripheral circulatory improvement and muscular conditioning. Prolonged survival may be achieved most effectively through blockade of overactivated neurohormonal systems. Furthermore, short-term clinical effects may be dissociated from the mortality effect of heart failure treatments. Thus, definitive mortality data are mandatory if a new treatment is to gain wide clinical acceptance, aside from purely regulatory considerations.

Table 1  A beta-blocker heart failure mortality study

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<th>2 year event rate in control group (%)</th>
<th>Risk reduction (%)</th>
<th>Power (%)</th>
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Sample size estimates with 80% power (P=0.05, two-sided) to detect 15% or 20% risk reductions with 2 year event rate in controls of 10–30%.

Table 2  A beta-blocker heart failure mortality study

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Event rates in control group required, assuming about 3000 patients recruited, average follow-up 2 years and 80% or 90% power (P=0.05, two-sided) for detection of 15 or 20% risk reductions.

Summation of all available clinical data with beta-blockers in heart failure, indicate equivocal symptomatic change and exercise improvement although ventricular function is clearly improved. In patients with chronic stable heart failure, it appears unlikely that beta-blockers will necessarily confer appreciable immediate clinical improvement, the most likely benefit long term being improved survival which may be substantial. A large scale clinical trial with several thousand patients is required to reliably detect a plausible 15–20% mortality reduction. Crucial to the design of such a trial is the inclusion of a sufficiently high risk population, with an annual control group mortality of 10% or greater to allow assessment of mortality benefit with a practical sample size (Table 1). Conversely, recruitment of about 3000 patients should allow detection of 15–20% risk reductions with annual event rates greater than 10% with reasonable power (Table 2). Such mortality studies are presently being initiated and could define a major improvement in heart failure therapy for the future.

References