Evidence-based Cardiology

Beta-blocking agents in heart failure

Should they be used and how?

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Introduction

Although early reports suggested that propranolol could cause worsening of chronic heart failure, this was not a consistent feature of /?-adrenoceptor blockade. In recent decades, the view has emerged that sympathetic activation in chronic heart failure, although initially serving to maintain cardiac output, is deleterious to cardiac function and survival in the long term. This has led clinicians to attempt to reduce sympathetic activity or its consequences.

In 1974 Waagstein et al. reported that the /?-selective blocker practolol was well tolerated in patients with acute myocardial infarction despite signs of heart failure. Relief of ischaemia rather than a beneficial effect on the failing circulation could have been responsible for any benefit observed. In an attempt to exclude improvement in ischaemia as the cause of benefit, further studies were conducted, and showed improvement in dilated cardiomyopathy, suggesting that relief of ischaemia may not be the only mechanism of benefit.

Subsequently, observational reports, small controlled trials and withdrawal studies showed benefits of /?-blockers on symptoms, exercise capacity, ventricular function, neurohormonal activity and mortality in chronic heart failure. Recently, several large placebo-controlled, randomized trials have reinforced the evidence for the clinical benefits of /?-blockade in chronic heart failure and suggested that they may also reduce mortality. This article reviews these results and discusses whether /?-blocking agents should be used in chronic heart failure and if so, how.

Mechanisms of the effect of /?-blockers

/?-blockers could improve the prognosis of chronic heart failure by preserving or improving cardiac function through several mechanisms.

In-vitro studies show that propranolol protects cardiac myocytes from the cardiotoxic effects of catecholamines. /?-adrenoceptors are downregulated in chronic heart failure, /?-adrenoceptors are uncoupled from adenyl cyclase, Gi proteins are up-regulated and /?-adrenoceptor phosphorylation is increased.

Selective and non-selective /?-blockers reduce renin secretion. This may mimic some of the actions of angiotensin-converting enzyme (ACE) inhibitors or prevent 'escape' of angiotensin II suppression from long-term ACE inhibition, providing a theoretical rationale for believing that ACE inhibitors and /?-blockers may act in synergy in chronic heart failure. The effect of /?-blockers on plasma noradrenaline is inconsistent and may depend on the baseline level of neurohormonal activation. The lack of increase in plasma noradrenaline is of interest as blockade of receptor systems commonly leads to an increase of the relevant agonist. Myocardial dysfunction and necrosis in chronic heart failure may be related to the concentration of catecholamines in the myocardial interstitium rather than the plasma concentration. In this respect, it is interesting that carvedilol, but not metoprolol, may selectively reduce cardiac adrenergic drive. Enhanced baroreflex function may improve ventriculo-arterial coupling, reducing aortic impedance and improving circulatory efficiency.

/?-blockers may improve cardiac function by reducing heart rate, resulting in lower myocardial energy expenditure, prolonged diastolic filling and increased effective myocardial blood flow due to the prolonged coronary vascular diastolic perfusion time.
Table I Studies (n ≥ 40) of the effects of β-blockers on symptoms, exercise capacity and ventricular function in patients with heart failure

<table>
<thead>
<tr>
<th>First author, year</th>
<th>Drug</th>
<th>Duration [Ref no]</th>
<th>Aetiology</th>
<th>NYHA</th>
<th>LVEF</th>
<th>Initial, Max+ (Average dose)</th>
<th>Symptoms and morbidity</th>
<th>Exercise capacity</th>
<th>Ventricular function</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Selective β-blocking agents</strong></td>
<td></td>
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<tr>
<td>MDC trial, 1992</td>
<td>Metoprolol</td>
<td>12–18 months[59]</td>
<td>DCM 100%</td>
<td>II/III</td>
<td>5 mg day⁻¹–50 mg t.d.s. (108 mg . day⁻¹)</td>
<td>QoL P&lt;0.01</td>
<td>NYHA P&lt;0.01</td>
<td>Bicycle max.</td>
<td>LVEF+6% P&lt;0.001 PCWP reduced, CO increased, SVR no change</td>
</tr>
<tr>
<td>Fisher, 1994</td>
<td>Metoprolol</td>
<td>6 months[26]</td>
<td>IHD 100%</td>
<td>II/III</td>
<td>6-25 mg b.d.–50 mg b.d. (87 mg . day⁻¹)</td>
<td>NYHA P&lt;0.02</td>
<td>Bicycle max</td>
<td>Better P&lt;0.05</td>
<td>LVEF+4% P&lt;0.05</td>
</tr>
<tr>
<td>CIBIS, 1994</td>
<td>Bisoprolol</td>
<td>23 months[50]</td>
<td>DCM 36%, IHD 55%, hypertension 6%, valve 4%</td>
<td>III</td>
<td>1-25 mg . day⁻¹–5 mg . day⁻¹ (3-8 mg . day⁻¹)</td>
<td>NYHA P&lt;0.03</td>
<td>Not done</td>
<td>Not done</td>
<td></td>
</tr>
<tr>
<td><strong>Non-selective vasodilating β-blocking agents</strong></td>
<td></td>
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<tr>
<td>Woodley, 1991</td>
<td>Bucindolol</td>
<td>3 months[62]</td>
<td>DCM 56%, IHD 44%</td>
<td>II/III</td>
<td>12-5 mg b.d. 100 mg b.d. (85 mg . b.d.)</td>
<td>QoL ns</td>
<td>NYHA ns</td>
<td>Treadmill max: ns</td>
<td>LVEF+4% (rest and ex.) P&lt;0.05</td>
</tr>
<tr>
<td>Bristow, 1994</td>
<td>Bucindolol</td>
<td>3 months[8]</td>
<td>DCM 71%, IHD 29%</td>
<td>II/III</td>
<td>12-5, 50 or 200 mg day⁻¹</td>
<td>QoL ns</td>
<td>NYHA ns</td>
<td>Treadmill max:</td>
<td>LVEF+5% P&lt;0.02</td>
</tr>
<tr>
<td><strong>Vasodilating β-blocking agents with α, adrenergic blocking activity</strong></td>
<td></td>
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<tr>
<td>Krum, 1995</td>
<td>Carvedilol</td>
<td>3-5 month[70]</td>
<td>IHD 27%, DCM 63%, valve 10%</td>
<td>II/III/IV</td>
<td>3-125 mg b.d.–25 mg b.d.</td>
<td>NYHA P=0.008</td>
<td>Symptoms P&lt;0.001</td>
<td>6-min walk:</td>
<td>LVEF+7.0% P&lt;0.005 PAP reduced P&lt;0.001</td>
</tr>
<tr>
<td>Metra, 1994</td>
<td>Carvedilol</td>
<td>6 months[8]</td>
<td>DC 100%</td>
<td>III</td>
<td>6-25 mg b.d.–25 mg b.d. (40 mg . day⁻¹)</td>
<td>QoL P&lt;0.001</td>
<td>NYHA P&lt;0.001</td>
<td>Bicycle max.</td>
<td>LVEF+11% P&lt;0.001</td>
</tr>
</tbody>
</table>

**Note:** NYHA = New York Heart Association; LVEF = Left Ventricular Ejection Fraction; QoL = Quality of Life; PCWP = Pulmonary Capillary wedge pressure; CO = Cardiac Output; SVR = Systemic Vascular Resistance; PAP = Pulmonary Arterial Pressure.
<table>
<thead>
<tr>
<th>First author, year</th>
<th>Drug</th>
<th>Duration [Ref no]</th>
<th>n</th>
<th>Mean age (years)</th>
<th>Aetiology</th>
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<th>Initial, Max+ (Average dose)</th>
<th>Symptoms and morbidity</th>
<th>Exercise capacity</th>
<th>Ventricular function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olsen, 1995</td>
<td>Carvedilol</td>
<td>4 months[680]</td>
<td>n=60</td>
<td>52</td>
<td>DCM 72%, IHD 28%</td>
<td>II/III</td>
<td>20%</td>
<td>3-125 mg b.d.–50 mg b.d. (80 mg, day−1)</td>
<td>QoL, P&lt;0.05</td>
<td>Bicycle max and submax; LVEF+10% (rest and ex.)</td>
<td>P&lt;0.0001</td>
</tr>
<tr>
<td>MOCHA 1995</td>
<td>Carvedilol</td>
<td>6 months[738]*</td>
<td>n=345</td>
<td>59</td>
<td>DCM 60%, IHD 40%</td>
<td>II/III</td>
<td>≤35%</td>
<td>Dose-ranging study 6-25, 12-5 and 25 mg b.d.</td>
<td>NYHA not reported</td>
<td>Fewer pts required hospitalizations (P&lt;0.005)</td>
<td>6 and 9-min walk: No effect</td>
</tr>
<tr>
<td>PRECISE 1995</td>
<td>Carvedilol</td>
<td>6 months[739]*</td>
<td>n=276</td>
<td>59</td>
<td>DCM 60%, IHD 40%</td>
<td>II/III</td>
<td>≤35%</td>
<td>6 25 mg b.d.–50 mg b.d.</td>
<td>QoL, P&lt;0.05</td>
<td>6-min walk: Better P=0.07 LVEF+5%</td>
<td>P=0.0011</td>
</tr>
<tr>
<td>Colucci 1995</td>
<td>Carvedilol</td>
<td>12 months[740]*</td>
<td>n=264</td>
<td>59</td>
<td>DCM 60%, IHD 40%</td>
<td>II/III</td>
<td>≤35%</td>
<td>6 25 mg b.d.–50 mg b.d.</td>
<td>NYHA: ns</td>
<td>Not reported</td>
<td>LVEF+9.2%</td>
</tr>
<tr>
<td>Cohn 1995</td>
<td>Carvedilol</td>
<td>6 months[741]*</td>
<td>n=100</td>
<td>59</td>
<td>DCM 60%, IHD 40%</td>
<td>II/IV</td>
<td>≤35%</td>
<td>6 25 mg b.d.–50 mg b.d.</td>
<td>Pt ass: P=0.001</td>
<td>No change</td>
<td>LVEF+9%</td>
</tr>
<tr>
<td>ANZ 1995</td>
<td>Carvedilol</td>
<td>18 months[742]*</td>
<td>n=415</td>
<td>67</td>
<td>IHD 100% Mostly II</td>
<td>29%</td>
<td>3-125 mg b.d.–25 mg b.d.</td>
<td>QoL, ns</td>
<td>Trend to worse symptoms at 6 months</td>
<td>Treadmill max and Walk Test: No change</td>
<td></td>
</tr>
</tbody>
</table>

LVEF = change in absolute %. CO = cardiac output; PCWP = pulmonary capillary wedge pressure; SVR = systemic vascular resistance; QoL = quality of life score; NYHA = New York Heart Association Class. Under exercise capacity: Max = maximal; Submax = submaximal; VO2 = peak oxygen consumption. DCM = dilated cardiomyopathy; IHD = ischaemic heart disease; PAP = pulmonary artery pressure; Pt ass = patient global assessment; Physician ass = physician assessment; ns = not significant; *abstract.
Improvements in myocardial force-frequency relationships have also been reported\textsuperscript{27-29}. At heart rates in the physiological range, the normal myocardium increases its force of contraction as heart rate increases, whereas the force of contraction of the failing myocardium may decline. The failing heart may be most efficient at a reduced heart rate. Global subendocardial ischaemia may contribute to ventricular dysfunction in patients with chronic heart failure even when epicardial coronary artery disease is absent\textsuperscript{30,31}. A reduction in recurrent infarction, as demonstrated in the post-myocardial infarction studies\textsuperscript{32,33}, could also contribute to the benefits of \(\beta\)-blockade on ventricular dysfunction and prognosis.

It is important to note that, at least with non-vasodilating \(\beta\)-blockers, there may be an acute fall in ejection fraction and that even after 1 month of treatment no improvement may be observed\textsuperscript{30}. Improvements in ejection fraction and reduction in cardiac volumes are apparent by 3 months and further improvement may be expected up to 18 months after initiation\textsuperscript{34}.

The immediate effect of \(\beta\) adrenoceptor blockade in chronic heart failure is a rise in systemic vascular resistance. This increase is reversed with longer term therapy\textsuperscript{35}, possibly a response to improving cardiac function\textsuperscript{36} or reduced sympathetic drive\textsuperscript{37}. After acute administration to patients with chronic heart failure, carvedilol appears to reduce systemic vascular resistance, whereas propranolol increases it and metoprolol has a variable effect\textsuperscript{38,39,40}. The vasodilating activity of carvedilol, and possibly other vasodilating \(\beta\)-blockers, may prevent the acute rise in systemic vascular resistance.

\(\beta\)-blockers could reduce the progression of, and mortality in, chronic heart failure by reducing the frequency of supraventricular and ventricular arrhythmias. In addition to the direct electrophysiological effects of \(\beta\)-blockade, reductions in sympathetic drive, heart rate and myocardial ischaemia, improved baroreflex function and the prevention of episodic hypokalaemia resulting from surges in sympathetic activity with stress or exercise\textsuperscript{40-43} could all contribute to the anti-arrhythmic effects of \(\beta\)-blockers. Improved cardiac function could also reduce the propensity to arrhythmias.

Several \(\beta\)-blockers have vasodilating activity, mediated by \(\alpha_1\)-adrenoceptor antagonism in the case of carvedilol\textsuperscript{44} and labetalol\textsuperscript{45} but independent of adrenoceptor blockade with bucindolol\textsuperscript{46,47} and nebivolol\textsuperscript{48}. Vasodilating activity could bring benefits in patients with chronic heart failure by reducing pre- and afterload (though hypotension may be more likely after acute administration). Blockade of \(\beta_1\)- and \(\beta_2\)- and \(\alpha_1\)-adrenoceptors may protect the myocardium from elevated catecholamines to a greater extent than \(\beta_1\)-blockade alone.

Carvedilol has antioxidant properties in vitro\textsuperscript{49,50} and inhibits vascular smooth muscle cell proliferation\textsuperscript{51,52}. These actions seem to be independent of \(\beta\)-receptor blockade. Inhibition of vascular smooth muscle cell proliferation could retard the progression of coronary atheroma and alter the vascular remodelling that occurs in chronic heart failure. A beneficial effect of other \(\beta\)-blockers on the atherosclerotic process has been reported, although this effect remains controversial\textsuperscript{53}.

Carvedilol has also been reported to downregulate cellular adhesion molecules, thereby inhibiting inflammatory infiltration and reducing tissue damage in response to infarction\textsuperscript{54,55}.

**Objectives of treatment of heart failure**

The objectives of treatment of chronic heart failure can be defined as to prolong and improve active life. Treatment should aim to improve or maintain the quality of life, to prevent major morbid events such as hospitalization or recurrent myocardial infarction, and to delay death. Preventing progression of cardiac dysfunction is an integral part of achieving these aims. Measuring quality of life is difficult and must not be solely equated with improving symptoms. Treatment could improve the symptoms of the disease but be associated with severe side-effects thereby reducing overall quality of life.

**Do \(\beta\)-blockers improve quality of life in heart failure?**

The principal placebo-controlled, double-blind, randomized studies of \(\beta\)-blockers reported in chronic heart failure are summarized in Table 1. Trials of less than 3 months’ duration or on fewer than 40 patients are excluded. Studies that enrolled over 200 patients are further described in Table 2.

A patient’s quality of life can be assessed in terms of NYHA class, symptom scores or global assessment by the physician or patient. Most studies with \(\beta_1\)-selective agents have shown an improvement in symptoms. Larger studies with metoprolol\textsuperscript{55,56} as well as some\textsuperscript{57,58} but not all\textsuperscript{16,22} smaller studies, have shown an improvement in NYHA class and this has also been reported with bisoprolol\textsuperscript{59}. A trial of acebutolol\textsuperscript{60}, a \(\beta\)-blocker with high intrinsic sympathomimetic activity, suggested that patients deteriorated on active therapy, but the adverse outcome in this study may have been related to the absence of a dose-titration phase. Xamoterol could also be considered a \(\beta\)-blocker with high intrinsic sympathomimetic activity and it increased mortality in patients with advanced chronic heart failure\textsuperscript{61}. However, this study also omitted a dose-titration phase. The adverse outcome in trials of \(\beta\)-blockers with intrinsic sympathomimetic activity may have been related to the smaller reduction in heart rate compared with drugs without intrinsic sympathomimetic activity, or to the absence of a titration phase in these studies. In contrast, the outcome of studies with non-selective \(\beta\)-blockers has not been consistent. Bucindolol and nebivolol have generally not improved quality of life\textsuperscript{21,62-65}.

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The one published trial on labetalol, on only 12 patients, reported an improvement in NYHA class\(^6\) and mortality of 13\%. More recently, carvedilol, which is also an \(\alpha_1\)- and a non-selective \(\beta\)-blocker, has also been shown to improve quality of life\(^{67-69}\). NYHA class\(^6\) or patient and physician global assessment\(^{69,70}\). As these trials cumulatively included over 1000 patients, this is powerful evidence of symptomatic benefit. In contrast, the Australia–New Zealand (ANZ) trial reported a trend towards worse symptoms and worsening NYHA class at 6 months\(^7\), although by 18 months such differences had disappeared\(^7\). The lack of symptomatic benefit in this population may reflect the fact that they had mild chronic heart failure (30\% NYHA class I, 60\% class II).

The positive effects described above were obtained in studies of longer than 3 months. In interpreting these observations, it is important to consider the duration of treatment as well as the properties of the drug.

### Do \(\beta\)-blockers retard the progression of heart failure?

During long-term therapy, \(\beta\)-blockers increase the left ventricular ejection fraction by about 5–9\% compared with placebo\(^{21,31,56,60-62,67-74}\). In contrast, ACE inhibitors increase left ventricular ejection fraction by only 2\%\(^7\).

In the Metoprolol in Dilated Cardiomyopathy (MDC) trial, patients receiving metoprolol experienced a reduction in hospitalization, a reduced need for cardiac transplantation and a trend towards a reduction in a combined endpoint of death and the need for cardiac transplantation\(^5\). The Cardiac Insufficiency Bisoprolol Study (CIBIS) trial, in patients with dilated cardiomyopathy or ischaemic heart disease, reported a significant reduction in hospitalization for worsening chronic heart failure\(^5\). No striking difference in other cardiovascular events (myocardial infarction, stroke or heart transplantation) was seen between the placebo and bisoprolol groups.

The U.S. trial programme on carvedilol enrolled patients into one of four protocols according to their degree of functional impairment (mild, moderate or severe impairment, and a dose-ranging study in patients with moderate impairment). A reduction in a combined endpoint of chronic heart failure progression was noted in patients with mild functional impairment\(^7\). A reduction in cardiovascular hospitalization was noted in patients with moderate functional impairment\(^8\) and hospitalization for all causes was reduced in the dose-ranging protocol\(^7\). In the ANZ trial\(^7\), all the patients had chronic heart failure due to ischaemic heart disease. Despite improvements in left ventricular ejection fraction, patients receiving carvedilol did not show a reduction in worsening chronic heart failure, though the combined end-point of myocardial infarction, unstable angina or need for revascularization fell and, at 18 months, there was a reduction in the combined end-point of total hospitalization or death\(^7\).

The increase in left ventricular ejection fraction with \(\beta\)-blockers could partly be the result of a reduction in heart rate. However, if a reduction in heart rate was the sole cause of the increase in left ventricular ejection fraction, an increase in cardiac volumes might have been expected. Studies of \(\beta\)-blockers in chronic heart failure have shown either no change in cardiac volume\(^21,63\) or a decrease\(^7\). Early evidence suggests that \(\beta\)-blockers can also, long-term, prevent progressive left ventricular hypertrophy in chronic heart failure\(^5\), similar to the effect observed with ACE inhibitors\(^7\).

### Effects of \(\beta\)-blockers on exercise performance

Most studies with metoprolol, a \(\beta_1\)-selective blocker, show an improvement in exercise capacity in the long term\(^{15-38}\). The effects of bisoprolol on exercise performance have not been reported. A short-term study of acebutolol suggested an adverse effect\(^6\). In contrast, studies with non-selective \(\beta\)-blockers including bucindolol\(^21,62-64\) and nebivolol\(^6\) and most of the studies on carvedilol have shown no improvement in maximal or submaximal exercise capacity\(^69-73\). Some of the small studies with carvedilol\(^67,70\) and labetalol\(^6\) have suggested that \(\beta\)-blockers with \(\alpha_1\)-blocking activity improve exercise capacity but improvement in exercise capacity has not been a consistent feature in the larger trials of carvedilol. No comparative trial of exercise performance between \(\beta\)-blockers has been carried out.

The relevance of exercise testing to the quality of daily life is complex; exercise capacity may not be a useful measurement of the efficacy of \(\beta\)-blockers\(^7\). Reduction of the increase in heart rate during exercise may limit increases in cardiac output that could, in turn, prevent improvements in ventricular function being translated into improved exercise performance. Metoprolol appears to induce upregulation of \(\beta_1\)-adrenoceptors, in contrast to carvedilol and, to some extent, bucindolol\(^79,80\). \(\beta_2\)-receptors contribute to the increase in heart rate during exercise. \(\beta_1\)-receptor up-regulation and lack of \(\beta_2\)-receptor inhibition with metoprolol may allow improvement in exercise capacity not observed consistently with other \(\beta\)-blockers. Inhibition of \(\beta_2\)-adrenoceptor-mediated peripheral vasodilatation during exercise may also be important in limiting the effects of non-selective drugs.

Caution in interpreting the results of exercise tests on carvedilol is required. If an agent reduces mortality then more patients with severe chronic heart failure will be eliminated in the placebo arm leading to an apparent improvement in performance on placebo. A lack of difference in exercise performance between placebo and carvedilol could conceal a true benefit with the \(\beta\)-blocker.

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<table>
<thead>
<tr>
<th>Study (Ref no)</th>
<th>n</th>
<th>Mean age (years)</th>
<th>Aetiology</th>
<th>NYHA</th>
<th>LVEF</th>
<th>Doses: Initial Maximum Mean</th>
<th>Worsening HF</th>
<th>Hospitalization</th>
<th>Myocardial infarction</th>
<th>Other endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDC Trial 1993&lt;sup&gt;1&lt;/sup&gt; Metoprolol (M)</td>
<td>383</td>
<td>49</td>
<td>DCM 100%</td>
<td>II/III</td>
<td>5 mg. day&lt;sup&gt;-1&lt;/sup&gt;</td>
<td>Not stated</td>
<td>51 readmissions on M, 83 on P (&lt;P&lt;0.05)</td>
<td>Not stated (patients with IHD excluded)</td>
<td>Death or need for transplantation: reduced from 20-1% to 12.9% (&lt;P=0.058) Transplantation: reduced from 10.1% to 1% (&lt;P=0.0001)</td>
<td></td>
</tr>
<tr>
<td>CIBIS 1994&lt;sup&gt;2&lt;/sup&gt; Bisoprolol (B)</td>
<td>641</td>
<td>60</td>
<td>DCM 36%; IHD 35%; HBP 6%; Valve 4%</td>
<td>III</td>
<td>1-25 mg. day&lt;sup&gt;-1&lt;/sup&gt;</td>
<td>Reduced from 48% to 33% (&lt;P&lt;0.001)</td>
<td>For HF: reduced 28-0% to 19% (&lt;P&lt;0.01)</td>
<td>Only 5 MIs reported (3 on B, 2 on P)</td>
<td>Not done</td>
<td></td>
</tr>
<tr>
<td>ANZ Trial, 1995&lt;sup&gt;3&lt;/sup&gt; Carvedilol (C)</td>
<td>415</td>
<td>67</td>
<td>IHD 100%</td>
<td>Mostly II</td>
<td>3-125 mg b.d.; 25 mg b.d.</td>
<td>ns</td>
<td>All cause: reduced by 33% (&lt;P=0.052)</td>
<td>Trend to reduction in MI, unstable angina or need for revascularization</td>
<td>Death or hospitalization for all causes reduced by 41% on C (&lt;P=0.02)</td>
<td></td>
</tr>
<tr>
<td>U S trials 1996&lt;sup&gt;4&lt;/sup&gt; Carvedilol (C)</td>
<td>1094</td>
<td>59</td>
<td>DCM 53; IHD 47%</td>
<td>II-IV</td>
<td>6-25 mg b.d.; 50 mg b.d.</td>
<td>Reduced by C</td>
<td>Cardiovascular: reduced from 19.6% to 14.1% (&lt;P=0.036)</td>
<td>Reduced from 2% to &lt;1% (&lt;P=0.06)</td>
<td>89% completed C versus 83% completing P (&lt;P=0.002) Risk of death or hospitalization reduced from 24.6% to 15.8% (&lt;P&lt;0.001)</td>
<td></td>
</tr>
</tbody>
</table>

MI=myocardial infarction; HF=heart failure; DCM=dilated cardiomyopathy; IHD=ischaemic heart disease; ns=not significant; P=placebo.
Do \(\beta\)-blockers reduce mortality in heart failure?

The MDC trial reported a reduction in the combined endpoint of death and the need for heart transplantation, but a non-significant 19% relative excess of deaths was seen in the metoprolol group\(^5\). In CIBIS, the effect on overall mortality (relative risk reduction 20%) was not significant, though mortality was significantly reduced in patients without a history of myocardial infarction (relative risk reduction 47%) and those with dilated cardiomyopathy (relative risk reduction 52%)\(^5\). Two of the individual protocols in the U.S. trial programme showed a significant reduction in mortality\(^2\). The combined analysis of the entire programme indicated a 65% relative reduction in mortality with carvedilol \((P=0.001)\), which was similar in patients with mild or more severe chronic heart failure, and with ischaemic or non-ischaemic aetiology\(^7\). Sudden deaths and deaths from pump failure were reduced to a similar extent by carvedilol. The ANZ trial, conducted exclusively in patients with mild chronic heart failure, showed a non-significant (23%) reduction in mortality with carvedilol at 18 months\(^1\), the result possibly reflecting the fairly good overall prognosis in this population. It is not clear if the greater effect of carvedilol on mortality in the U.S. trials reflects differences between \(\beta\)-blockers, different study populations or just the greater size of the U.S. trial. The clinical significance of the pharmacological differences between \(\beta\)-blockers can be elucidated only by controlled comparative trials.

As almost all patients in these trials were receiving ACE inhibitors, the effects of \(\beta\)-blockade on mortality were in addition to those resulting from ACE inhibition. There is very little experience of the effects of \(\beta\)-blockade on patients with chronic heart failure who are not receiving ACE inhibitors.

Altogether, the MDC trial, the CIBIS, the U.S. carvedilol trial programme and the ANZ trial enrolled over 2500 patients with chronic heart failure of varying degrees of severity and of ischaemic and non-ischaemic origin (Table 3). The mortality on placebo was 12.8% falling to 8.3% on a \(\beta\)-blocker \((P<0.001)\) over a follow-up of about 13 months, a relative risk reduction of about 37% and an absolute benefit of 45 lives saved per 1000 treated. The absolute benefit is similar to that of ACE inhibition in the SOLVD treatment trial\(^8\), in which about 35 lives had been saved per 1000 treated with enalapril at 15 months.

In the SOLVD treatment trial, 1-year mortality was 16% in the placebo group; this fell to 12% with enalapril\(^9\). In the U.S. carvedilol trials, mortality at a median follow-up of 6-5 months in the placebo group was 7.8%. By extrapolation, the mortality of this population, almost all of whom were receiving ACE inhibitors, was similar to that observed in the active treatment group of the SOLVD treatment trial. Thus, despite differences in the study populations, mainly a higher proportion of dilated cardiomyopathy in the carvedilol trials, their prognosis was very similar.

### Which patients should (and should not) be treated?

Decompensated patients and those dependent on inotropic agents should not be given a \(\beta\)-blocker until they have reverted to a compensated state on oral therapy. Patients with bronchial asthma should not receive a \(\beta\)-blocker, while great caution should be exercised before using them in chronic obstructive airways disease.

It is difficult to extrapolate from the \(\beta\)-blocker trial populations to the wider community with chronic heart failure. In the mortality studies of \(\beta\)-blockade, the mean age of patients has ranged from 49 years to 67 years, whereas the mean age of chronic heart failure patients in the community is 74 years\(^3\). Dilated cardiomyopathy constituted 100% of patients in the MDC trial, about 55% in the U.S. trials and about 35% in the CIBIS. The results of these trials, supported by smaller studies, indicate that patients with proven symptomatic dilated cardiomyopathy should be treated with a
What are the optimal doses of \(\beta\)-blockers?

### Starting dose

In patients with chronic heart failure, \(\beta\)-blockers should, as a rule, be started at a low dose and titrated up slowly. It is advisable to introduce \(\beta\)-blockade at the starting doses used in the large clinical trials: carvedilol, 3-125-6.25 mg b.d. \[^{169,71-74}\] metoprolol, 5 mg b.d. \[^{159}\] or 6-25 mg b.d. \[^{131}\] and bisoprolol, 1-25 mg/day \[^{59}\]. The dose should be doubled at weekly or 2-weekly intervals, according to clinical response, towards the target dose. Sicker patients should generally be titrated more slowly than patients with less severe disease. The benefits of \(\beta\)-blockers on the clinical progression of chronic heart failure suggest that they might be most effective if introduced early in the course of the condition. Patients with less severe chronic heart failure might have less hypotension and early worsening of chronic heart failure during introduction of \(\beta\)-blocker therapy than patients with advanced chronic heart failure, adding to the safety of treatment. However, \(\beta\)-blockade will probably be less well tolerated in a less carefully selected population in whom the inclusion and exclusion criteria of a clinical trial are not imposed \[^{87}\], or if dose titration is not employed.

### Target dose

Dose-response studies of carvedilol and bucindolol have suggested that higher doses are associated with greater increases in left ventricular ejection fraction. The doseranging study of carvedilol also suggested a greater reduction in mortality with higher doses \[^{73}\]. Further studies are required to determine the optimum dose of each \(\beta\)-blocker. Until then, it is appropriate to use the target doses in the clinical trials (carvedilol 25-50 mg b.d., metoprolol 50 mg b.d.-t.d.s, or bisoprolol 5 mg/day. The results of clinical trials suggest that up to 3 months' treatment may be required before symptoms improve.

### When should \(\beta\)-blockers be stopped?

Clinical trials indicate that \(\beta\)-blockers are much safer to use than has been previously suggested, provided careful dose titration is employed. However, about 5% of patients who, on the basis of criteria used for clinical trials, are thought to be suitable for \(\beta\)-blockade will not tolerate its introduction because they develop hypotension or worsening chronic heart failure; this percentage is higher in severe chronic heart failure. In patients who experience worsening symptoms of chronic heart failure, the doses of ACE inhibitor or diuretic, or both, should be increased, whereas the doses of these agents should be reduced in the event of symptomatic hypotension. Patients who require an increase in diuretic therapy to control worsening chronic heart failure during the introduction of carvedilol nonetheless appear to benefit from long-term \(\beta\)-blockade \[^{69}\]. If adjustment of other medications does not relieve side-effects, reduction or withdrawal of \(\beta\)-blockade should be considered.

Another scenario is the patient who has tolerated the introduction of a \(\beta\)-blocker and shows clear signs of benefit, but who later deteriorates. Should \(\beta\)-blockers be withdrawn if such patients fail to respond to other simple measures? We do not know.

### Summary

Experience accumulated from several large trials strongly suggests that \(\beta\)-blockers should be used for the management of chronic heart failure \[^{87}\]. It is appropriate to add \(\beta\)-blockade to conventional therapy such as diuretics, ACE inhibitors and digoxin, as this was the approach used in the major trials. It is appropriate to treat patients with mild, moderate and, when stable, severe chronic heart failure. The benefits obtained include improvements in left ventricular function, reductions in symptoms and morbidity, improvement of quality of life, and delay of clinical progression, reflected in a reduced need for cardiac transplantation and, probably, a reduction in mortality. \(\beta\)-blockers are much better tolerated, when used appropriately in selected patients, than was previously supposed.
To confirm the improvement in survival recently reported with carvedilol, further prospective trials using different β-blockers are warranted. No major comparative trials have been carried out between β-blockers in chronic heart failure, therefore it is not known whether the differences between them are clinically significant. The optimal dose of β-blocker and the effect in patient groups excluded from or poorly represented in the clinical trials (e.g. elderly patients) have yet to be determined. Placebo-controlled mortality trials with bucindolol (BEST) and bisoprolol (CIBIS-II) are under way[18,90]. A large study of carvedilol versus metoprolol (COMET), added to conventional treatment, is planned.

References


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