The Role of Beta-blockers In Congestive Heart Failure

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ABSTRACT

Congestive heart failure (CHF) is an important public health problem in Canada. While angiotensin converting enzyme (ACE) inhibitors have decreased morbidity and mortality in patients suffering from this syndrome, one- and five-year mortality rates remain grim. Although traditionally β-adrenergic blocking agents have been contraindicated in CHF, more recent data indicate these agents may be beneficial in a subset of patients.

β-blockers may produce beneficial effects in CHF by inhibiting stimulation of sympathetic nervous system and renin-angiotensin-aldosterone systems, protecting against norepinephrine’s cardiotoxic effects and restoring myocardial response to β-agonists via up-regulation of β-receptors. To date, small, well-controlled studies have demonstrated improvements in systolic function. Common to these trials was the addition of the β-blocker to traditional therapy, gradual incremental dosage increases, and extended durations of therapy. Success was seen predominately in patients suffering from idiopathic dilated cardiomyopathy.

Many questions remain regarding the use of β-blockers in CHF including optimal time of therapy initiation, effect on mortality, and prediction of which patients will benefit most. Although evidence appears promising, further work is needed.

Key Words: β-blockers, CHF, Idiopathic dilated cardiomyopathy

INTRODUCTION

Congestive heart failure (CHF) is an important public health problem afflicting approximately 250,000 Canadians. Despite the plethora of medical interventions available for the treatment of CHF, epidemiological data indicate there has been no improvement in length of survival following the onset of CHF from 1948 to 1988. More recently, trials studying the effects of ACE inhibitors in conjunction with traditional therapies have demonstrated reductions in mortality and morbidity. However, prognosis for CHF patients remains guarded. The overall five-year, post-diagnosis mortality rate for all patients with CHF is 50%.

Patients with severe CHF (New York Heart Association [NYHA] functional class III or IV) have a poorer prognosis. These patients have been shown to benefit from the use of β-blockers. β-blockers may inhibit the central sympathetic nervous system’s effects on the heart and peripheral sympathetic nervous system’s effects on peripheral vascular resistance. Even though these agents have been contraindicated in CHF, recent data indicate these agents may be beneficial in a subset of patients.

The beneficial effects of β-blockers in CHF may be due to their ability to inhibit stimulation of sympathetic nervous system and renin-angiotensin-aldosterone systems, protecting against norepinephrine’s cardiotoxic effects and restoring myocardial response to β-agonists via up-regulation of β-receptors. To date, small, well-controlled studies have demonstrated improvements in systolic function. Common to these trials was the addition of a β-blocker to traditional therapy, gradual incremental dosage increases, and extended durations of therapy. Success was seen predominately in patients suffering from idiopathic dilated cardiomyopathy.

Many questions remain regarding the use of β-blockers in CHF including optimal time of therapy initiation, effect on mortality, and prediction of which patients will benefit most. Although evidence appears promising, further work is needed.
class IV), have a one year mortality rate of approximately 50%. Clearly, novel treatment strategies are needed.

Traditionally, β-blockers have been contraindicated in CHF since sympathetic nervous system (SNS) stimulation was believed necessary for maintaining cardiac output and blood pressure in the failing heart by increasing heart rate, contractility, and peripheral vasoconstriction. Protracted SNS activation is now considered to be detrimental to heart function, contributing to the progression of CHF. Consequently, the role of β-blockers in heart failure is generating much interest. This article will review the pathogenesis of CHF, the rationale behind β-blocker use in CHF, the clinical experience with this therapy, and the controversies associated with it.

**Pathogenesis of CHF**

CHF may result from a number of disorders. Common causes include: dilated cardiomyopathy, hypertension, valvular stenosis, valvular regurgitation, and reduction in viable muscle mass due to ischemic heart disease. Although a vast array of etiologies may result in sufficient ventricular dysfunction to result in the clinical syndrome of CHF, the pathophysiologic mechanisms ultimately activated as ventricular performance decreases appear to be similar. The initial insult is usually an abnormal increase in load or loss of myocytes. As a result the remaining myocytes hypertrophy, and an alteration in the collagen matrix occurs with a resultant geometric change (remodelling) of the left ventricle. Pressure or volume overload causes ventricular hypertrophy, which helps return contractility to a near normal state. As the pressure or volume overload persists, the hypertrophied myocardial cells eventually become fibrotic and contractility decreases. Hypertrophy also increases the stiffness of the ventricle and slows ventricular relaxation, impairing diastolic function.

The sympathetic nervous system (SNS) is activated within seconds of a decrease in cardiac output providing an immediate support mechanism in patients with heart failure. Norepinephrine (NE) released from myocardial adrenergic nerve terminals serves an important compensatory role, maintaining cardiac output by increasing both contractility and heart rate. Plasma NE concentration is elevated in proportion to the degree of heart failure and patients with the highest norepinephrine concentrations have the poorest prognosis.

As renal perfusion decreases with failing cardiac output, preload is increased through stimulation of the renin-angiotensin-aldosterone (RAA) system. Angiotensin II is an important compensatory substance leading to increased systemic vascular resistance, increased blood pressure, and therefore, maintenance of organ perfusion. It also facilitates release of NE from adrenergic nerve terminals, adding to the level of sympathetic activation, and stimulates aldosterone release with resultant sodium and water retention (increased preload).

The compensatory mechanisms play an important role in maintaining cardiac function; however, a detrimental overshoot of these mechanisms frequently occurs. Constant exposure of the heart to catecholamines causes a down-regulation of β-receptors with a subsequent diminution of sensitivity to stimulation. The excess catecholamines may also be directly cardiotoxic and produce further impairment of contractile function. Cardiotoxic effects may be due to calcium overload, as well as decreased synthesis of contractile proteins in response to norepinephrine exposure. Subsensitivity of the myocardial adrenergic pathway is also demonstrated. The peripheral vasoconstriction mediated by increased sympathetic activity, angiotensin II, and other possible mechanisms such as arginine vasopressin (AVP), causes an increase in systemic vascular resistance or afterload. Increased afterload prevents optimal myocardial fiber shortening and causes a further decrease in cardiac output, leading to further increases in sodium and water retention and SNS activity. Thus, the compensatory mechanisms in CHF eventually initiate a vicious cycle which leads to continued worsening and downward spiralling of the failing heart.

**Rationale for β-blocker use in CHF**

Since continued stimulation of the SNS and RAA system probably contributes to progressive cardiac dysfunction and mortality, long-term CHF therapy should be directed at modulating these compensatory responses. Clinical trials have demonstrated an improved quality of life, and reduced morbidity and mortality in CHF patients treated with ACE inhibitors. Research is now directed towards determining whether β-blockers will produce similar results.

β-blockers may produce beneficial effects in CHF via several mechanisms. They may inhibit SNS activation of the RAA system, protect against NE's direct cardiotoxic effects, and desensitize the myocardium to β-agonists by increasing the number of functional β1 receptors via up-regulation. Metoprolol therapy in CHF patients has been shown to increase myocardial β1 receptor density, presumably by blocking the down-regulating effects of norepinephrine. As well, beta-blockers may enhance mechanical performance of the heart by correction of regional wall abnormalities. Recently developed β-blockers such as bucindolol and carvedilol produce vasodilation in addition to beta blockade. The resulting decrease in afterload may also help improve cardiac function.
CLINICAL TRIALS
Small, randomized, double-blind, placebo-controlled studies have demonstrated improvements in systolic function in CHF patients receiving chronic administration of B-blockers primarily metoprolol, bucindolol, and carvedilol (Table I). 23-32 Common characteristics of these studies include: addition of B-blocker therapy to pre-existing CHF therapy consisting of diuretics, ACE inhibitors, and/or digoxin; gradual dosage increments after demonstration of a positive response to a small test dose; continuation of therapy for an extended duration ranging from two to 12 months, and enrollment of subjects with heart failure primarily due to idiopathic dilated cardiomyopathy (IDC). Beneficial results were often determined via an improvement in symptoms, exercise capacity, and various hemodynamic measurements such as pulmonary capillary wedge pressure (PCWP), cardiac index, and left ventricular ejection fraction (LVEF).

Of the currently marketed B-blockers, metoprolol has been the most extensively studied in CHF, albeit primarily in uncontrolled trials. In one of the earliest controlled trials, 25 patients, with a mean NYHA functional class of 2.6, were randomized to either placebo or metoprolol in increasing doses at four- to six-week intervals to a maximum of 100mg/day for a one-year duration.24 After six months, metoprolol-treated patients showed improvements in exercise capacity, determined by maximal oxygen consumption scores, (p<0.0001), and NYHA functional class (p<0.001) compared to placebo. These improvements were sustained over the remaining six months of therapy. Similar results were found in an uncontrolled study in which 33 patients with IDC were administered metoprolol.21 Metoprolol was initiated in NYHA functional class IV patients at a dose of 5mg bid.

Table I. Randomized, placebo-controlled, double-blind positive result trials of B-Blockers in CHF

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Drug &amp; Dose (mg)</th>
<th># Pts.</th>
<th>Duration of Therapy (mos)</th>
<th>Type of CHF</th>
<th>NYHA FC</th>
<th>RESULTS*</th>
</tr>
</thead>
<tbody>
<tr>
<td>23</td>
<td>Bucindolol 12.5, 50, 200</td>
<td>139</td>
<td>3</td>
<td>IDC, ISHD</td>
<td>I-IV</td>
<td>Dose-related improvement in LVEF in bucindolol-tx subjects. All 3 bucindolol doses prevented myocardial function deterioration. (i.e., ( \downarrow \text{LVEF} &gt; 5 \text{ units} ))</td>
</tr>
<tr>
<td>24</td>
<td>Metoprolol 100</td>
<td>25</td>
<td>12</td>
<td>IDC</td>
<td>Not specified</td>
<td>Metoprolol treatment resulted in: ( \uparrow \text{EC} ), ( \text{NYHA FC} ), ( \downarrow \text{LVEF} ) compared to baseline; ( \uparrow \text{EC} ), ( \text{NYHA FC} ) compared to placebo.</td>
</tr>
<tr>
<td>25</td>
<td>Bucindolol 200</td>
<td>24</td>
<td>3</td>
<td>IDC</td>
<td>II, III</td>
<td>Bucindolol tx. pts. had improvements in symptoms, LVSWI, PCWP, NYHA FC, ( \downarrow \text{NE} ). No beneficial changes in placebo group.</td>
</tr>
<tr>
<td>26</td>
<td>Carvedilol 50</td>
<td>32</td>
<td>3.5</td>
<td>Not specified</td>
<td>III, IV</td>
<td>Compared with placebo, carvedilol tx. pts. had improvements in: LVEF, SVI, NYHA FC, EC &amp; PCWP at rest &amp; during peak exercise from baseline. No beneficial changes in placebo group.</td>
</tr>
<tr>
<td>27</td>
<td>Labetalol 100-400</td>
<td>12</td>
<td>2</td>
<td>IDC</td>
<td>II-IV</td>
<td>Compared to placebo, labetalol tx. pts. had improvements in NYHA FC, EC, and CO during exercise.</td>
</tr>
<tr>
<td>28</td>
<td>Carvedilol 50</td>
<td>20</td>
<td>6</td>
<td>IDC</td>
<td>Not specified</td>
<td>Carvedilol tx. pts. - ( \uparrow \text{EC} ), ( \text{TSI} ), ( \text{PCWP at rest} ) &amp; during peak exercise from baseline. No beneficial changes in placebo group.</td>
</tr>
<tr>
<td>29</td>
<td>Bucindolol 200</td>
<td>19</td>
<td>3</td>
<td>IDC, ISHD</td>
<td>II-IV</td>
<td>Bucindolol tx. pts. - ( \uparrow \text{LVEF} ), ( \text{EC} ), ( \text{TSI} ), ( \text{PCWP} ) compared to baseline. No beneficial changes in placebo group.</td>
</tr>
<tr>
<td>30</td>
<td>Bucindolol 200</td>
<td>20</td>
<td>3</td>
<td>Not specified</td>
<td>Not specified</td>
<td>Bucindolol tx. pts. - ( \uparrow \text{EC} ), ( \text{TSI} ), ( \text{PCWP} ) compared to baseline.</td>
</tr>
<tr>
<td>31</td>
<td>Nebivolol</td>
<td>24</td>
<td>3</td>
<td>IDC, ISHD</td>
<td>II, III</td>
<td>Nebivolol tx. pts. - ( \uparrow \text{SV} ), ( \text{LVEF} ), ( \text{LVEDP} ) compared to placebo.</td>
</tr>
<tr>
<td>32</td>
<td>Bucindolol 200</td>
<td>49</td>
<td>3</td>
<td>IDC, ISHD</td>
<td>Not specified</td>
<td>Compared to placebo, bucindolol tx. pts. - ( \uparrow \text{LVEF} ), ( \downarrow \text{LV size} ), ( \downarrow \text{SV} ), ( \downarrow \text{symptoms} ). Sub-group analysis of ISHD pts. showed improvement only in LV size.</td>
</tr>
</tbody>
</table>

Ref. = reference.
1 = Dosages were increased gradually, Pts. = patients, NYHA = New York Heart Association, FC = functional class, IDC = idiopathic dilated cardiomyopathy, ISHD = ischemic heart disease,

* \( p<0.05 \), LVEF = left ventricular ejection fraction, EC = exercise capacity, LVSWI = left ventricular stroke work index, PCWP = pulmonary capillary wedge pressure, NE = norepinephrine, SVI = stroke volume index, SVR = systemic vascular resistance, CO = cardiac output, CI = cardiac index, MOA = mechanism of action, SV = stroke volume, LVEDP = left ventricular end diastolic pressure, SWI = stroke work index.
Doses were increased approximately every seven days to a maximum of 50 mg tid. Patients in NYHA functional classes II and III were initiated with a dose of 25 mg bid and increased to 50 mg tid or 100 mg bid. Patients were treated for six to twenty months.\(^{21}\) Beneficial results again developed slowly, starting within three months of therapy and requiring 12 months of therapy for some patients. Patients demonstrated a mean increase in ejection fraction from 24% to 42% (p<0.0001), a mean decrease in left ventricular end-diastolic dimension (7.3 to 6.4 cm, p<0.0001), and a mean decrease in PCWP from baseline values (23.8 to 10.7 mm Hg, p<0.0001). After patients demonstrated a beneficial effect with metoprolol therapy, the effect of withdrawal and re-institution of β-blocker therapy was evaluated. Following metoprolol withdrawal in the 24 patients participating, four died and 12 clinically deteriorated within 12 months of withdrawal. Eight patients exhibited no change in their condition. Reinstitution of metoprolol in patients who had deteriorated resulted in improved ejection fraction in all such patients (23%-33%, p<0.002).

In the largest placebo-controlled trial of metoprolol use in CHF patients, 383 patients in NYHA functional classes II and III were followed for 12 to 18 months.\(^{33}\) Metoprolol was initiated with a test dose of 5 mg bid and increased in 5 mg to 25 mg increments over seven weeks to a target dose of 100-150 mg daily. At 12 months, metoprolol-treated patients demonstrated improved ejection fraction (13% vs 6%, p<0.0001), exercise time (76 vs 15 sec, p=0.046), and a greater decrease in PCWP (5 vs 2 mm Hg) from baseline. Also, only two metoprolol-treated patients met criteria for heart transplantation at the end of the follow-up period as compared to 19 placebo-treated patients (p=0.0001).

Bucindolol and carvedilol are third generation β-blockers currently undergoing phase III trials for use in CHF.\(^{9}\) Third generation β-blockers produce vasodilation as well as β-blockade.\(^{34}\) Bucindolol exhibits a direct vasodilatory action on vascular smooth muscle while carvedilol's vasodilation is due to α₁ receptor blockade.\(^{9}\) The vasodilation may offset the negative inotropic effect of bucindolol and carvedilol making them better acutely tolerated in CHF patients than traditional β-blockers.\(^{9}\) Initial bucindolol doses of 6.25 or 12.5 mg bid have been well-tolerated compared to over 95% of CHF subjects.\(^{9,25,32}\)

Like metoprolol, bucindolol has been shown effective in CHF due to IDC\(^{23,24,29,32,35,36}\) After three months of therapy, 12 patients given bucindolol 100 mg bid demonstrated improvement from baseline values in exercise tolerance as judged by treadmill time (mean increase from 445 to 530 seconds, p=0.04), mean improvement in quality of life scores (61 to 40 in the Minnesota Living with Heart Failure Questionnaire, p=0.0001), and improvement in hemodynamic parameters such as cardiac output (mean increase from 4.0 to 4.7 L/min, p=0.02) and PCWP (mean decrease of 42 to 28 mm Hg, p=0.04).\(^{29}\) Patients given placebo (n=7) did not significantly improve on any of the above parameters.

Some of bucindolol's beneficial outcomes in CHF may be dose-dependent. The effect of low (12.5 mg/day), medium (50 mg/day), and high doses (200 mg/day) of bucindolol were compared to placebo in 139 patients.\(^{27}\) The majority of the patients in this trial concurrently received digoxin, a diuretic and an ACE inhibitor. Improvement in LVEF and left ventricular size correlated with dose as higher bucindolol doses produced greater beneficial effects. Interestingly, only the low and high bucindolol doses prevented left ventricular deterioration defined by a LVEF decline of ≥ 5 units (p=0.02).

The medium bucindolol dose produced a nonsignificant trend towards preventing left ventricular deterioration (p=0.075).

Woodley et al\(^{32}\) were one of the first investigators to determine the efficacy of β-blockers in heart failure due to ischemic heart disease (ISHD), as well as due to IDC. Forty nine patients with either IDC (n=22) or ISHD (n=29) and treated with an ACE inhibitor, digoxin and furosemide were randomized to either bucindolol (initiated at 12.5 mg bid and titrated to a maximum of 100 mg bid) or placebo therapy using a double-blind randomized design. After twelve months of bucindolol therapy, the IDC group exhibited improved ejection fraction, left ventricular size, symptoms score, venous NE levels, and stroke work index as compared to placebo. The only parameter showing improvement in the ISHD group was left ventricular size. These results suggest that heart failure etiology may determine responsiveness to β-blocker therapy.\(^{32}\) In contrast Bristow et al\(^{23}\) found no difference in the effect of bucindolol in heart failure due to IDC or ISHD. Both patient groups demonstrated improved LVEF after 12 weeks of therapy compared to placebo. Carvedilol was also found effective in CHF secondary to ISHD.\(^{22}\) Symptomatic and hemodynamic improvement such as increases in exercise time (4.3 to 7.1 mins, p<0.0001), stroke volume index (31 to 40 mL, p<0.0005), and ejection fraction (27% to 31%, p<0.02) were demonstrated in 11 of 12 patients after eight weeks of carvedilol therapy.

**Controversies with β-blocker therapy in CHF**

Despite the positive results obtained in the reviewed studies, a number of controversies exist regarding β-blocker use in CHF. A number of studies have demonstrated unfavourable results with β-blocker use in CHF.\(^{37-41}\) Also, the effect of
β-blockers on CHF mortality is unclear and criteria for their use in CHF have yet to be established.

Studies with negative results
In contrast to the positive studies reviewed, a number of trials have demonstrated negative results with β-blocker use in CHF (Table II). However, general differences in the study design of positive result and negative result trials may explain the disparity findings. The duration of β-blocker therapy in negative result trials was short ranging from one dose to one-month of therapy.37-41 Positive trials indicate an immediate beneficial response is rare. In these trials, significant clinical improvement occurred only after a minimum of two months of therapy. Consequently, the duration of therapy in the studies with negative results may have been insufficient to determine efficacy.

The dosage regimen employed in studies with negative results may have been inappropriate. A small initial dose is important to prevent acute cardiovascular decompensation due to β-blockers’ negative inotropic effect. Positive studies typically initiated small β-blocker doses and titrated slowly. For example, Engelmeier et al24 initiated patients on 6.25mg of metoprolol and increased the dose once or twice weekly in 6.25 to 12.5mg increments over four to six weeks. In contrast, most studies with negative results used high initial doses of β-blockers, for example, 200mg bid of acebutalol, which may explain their poor patient tolerance, lack of significant improvement, and adverse effect.38-40

Finally, disparity in the sample size and study design between positive result and negative result studies exist (see Tables I and II). The mean sample size of the negative trials (n = 11 patients) is smaller than that of positive trials (n = 36 patients). Three of the five negative trials were uncontrolled while, todate, ten randomized, double-blind, placebo-controlled trials have produced positive results with β-blockers in CHF.

Effect on mortality
As a 50% one-year mortality rate remains associated with CHF patients in NYHA functional class IV, an important consideration for drugs used in CHF is their effect on survival.2 While β-blockers have produced symptomatic and hemodynamic improvement in heart failure, they have not been shown to improve mortality associated with CHF.20 Three placebo-controlled studies have looked at the effect of β-blocker therapy on CHF mortality. Fifty patients with CHF due to IDC and with a mean NYHA functional class of 2.8, were randomized to standard CHF drug therapy or standard CHF drug therapy plus metoprolol or placebo and followed for thirteen months.33 Ninety-four percent of patients were in NYHA functional classes II and III and 80% were receiving additional CHF medication. Again, no differences in mortality between the groups were found.

The largest prospective heart failure mortality study of β-blockade involved 641 patients with CHF of varying etiologies. Ninety-five percent of patients were in NYHA functional class III. Three hundred and twenty patients received bisoprolol, a β1 selective blocker, while 321 patients received placebo in addition to their current heart failure treatment regimens.42 The mean follow-up period of 1.9 years failed to demonstrate improved survival in patients on bisoprolol compared to patients on placebo. It should be noted that the follow-up periods of these three studies may have been too short and sample sizes too small to result in significant differences.

In an attempt to determine β-blockers’ effect on CHF mortality,

Table II. Negative result trials of β-Blockers in CHF

<table>
<thead>
<tr>
<th>Ref. #</th>
<th>Study Design</th>
<th>Drug &amp; Dose</th>
<th># Pts</th>
<th>Duration of Therapy</th>
<th>Type of CHF</th>
<th>NYHA FC</th>
<th>RESULTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>37</td>
<td>UC</td>
<td>Acebutalol 25mg IV</td>
<td>10</td>
<td>1 dose</td>
<td>IDC</td>
<td>Not specified</td>
<td>15 min post dose - non-sign ↓ in CI, LVEF, + SVI</td>
</tr>
<tr>
<td>38</td>
<td>UC</td>
<td>Pindolol 10mg</td>
<td>10</td>
<td>4 doses over 2 days</td>
<td>IDC</td>
<td>Not specified</td>
<td>3 pts. withdrew due to pindolol intolerance. In remaining pts., ↓CI, ↓SVI, ↑TSV</td>
</tr>
<tr>
<td>39</td>
<td>R, DB, PC, CO</td>
<td>Metoprolol 100-200mg</td>
<td>10</td>
<td>1 month</td>
<td>IDC</td>
<td>Not specified</td>
<td>Compared with placebo, no sign. differences in LVEF, CI, or EC. ↑ in SVI</td>
</tr>
<tr>
<td>40</td>
<td>R, DB, PC, CO</td>
<td>Acebutalol 400mg</td>
<td>15</td>
<td>1 month</td>
<td>IDC</td>
<td>II, III</td>
<td>↓EC, ↑CT ratio. Non-sign trend in ↓LVEDV, ↑LVEF</td>
</tr>
<tr>
<td>41</td>
<td>UC</td>
<td>Oxprenolol 20mg</td>
<td>8</td>
<td>1 dose</td>
<td>ISHD</td>
<td>III, IV</td>
<td>1 hr post-dose, ↓CO.</td>
</tr>
</tbody>
</table>

Ref. = reference.
1=Dosages were not adjusted gradually, Pts.=patients, NYHA=New York Heart Association, FC=functional class, UC=uncontrolled, R=randomized, PC=placebo-controlled, DB=double-blind, CO=crossover, IDC=idiopathic dilated cardiomyopathy, ISHD=ischemic heart disease.
* CI=cardiac index, LVEF=left ventricular ejection fraction, SVI=stroke volume index, SVR=systemic vascular resistance, EC=exercise capacity.
CT=cardiothoracic, LVEDV=left ventricular end diastolic volume, CO=cardiac output.
sixteen studies on β-blocker use in post-myocardial infarction patients which included patients with left ventricular dysfunction (LVD), were retrospectively analyzed. Six of the 16 trials contained sufficient information to assess mortality. While two of the studies demonstrated an increase in mortality with β-blocker use compared to placebo, four studies demonstrated a decrease in mortality with β-blocker use. The significance of this positive finding is questionable since only a small portion of the 16 studies could be included in the analysis, patients with moderate to severe CHF were excluded from the studies, and the definition of LVD was vague and differed among the studies. Also, extrapolation to patients with CHF but without a history of myocardial infarction is tenuous at best.

**Patient selection**

Available data do not provide general recommendations for instituting β-blockers in CHF. It is unknown which CHF patients, etiologies, or stages would most benefit from β-blocker therapy. A number of trials studying whether patient baseline hemodynamic parameters predict response to β-blocker therapy have produced conflicting results. Gilbert et al.44 studied LVEF, heart rate, cardiac index, PCWP, blood pressure, and exercise time in patients given three to six months of metoprolol or bucindolol. Responders (LVEF increase of ≥0.05) and non-responders (LVEF increase of <0.05 or a decrease in LVEF) did not differ on these variables. In a similar study, Bennett et al.45 found patients with a marked increase in LVEF (≥8%) after six to twelve months on metoprolol therapy had higher resting and peak exercise heart rates than patients with a smaller LVEF increase. Yamada et al.46 found no difference between good responders (improvement of at least one NYHA functional class or an increase in LVEF ≥0.10) and poor responders in baseline hemodynamic variables. However, left ventricular endomyocardial biopsies performed prior to metoprolol administration revealed less myocardial fibrosis in good responders than in poor responders.

Heart failure has a number of diverse causes. Ischemic heart disease (ISHD) is the etiology in the majority of CHF patients and IDC is responsible for a large portion of the remainder.1 While a limited number of studies have demonstrated positive results with β-blocker use in heart failure due to ISHD,22,23,32 the majority of beneficial results have involved patients with heart failure due to IDC.23,25,27,29,31,32 One well-designed study demonstrated patients with heart failure due to IDC had a significantly greater clinical improvement with β-blocker therapy than patients with heart failure due to ISHD.32 These results indicate the degree of positive response may depend upon heart failure etiology. It has been suggested β-blocker therapy be limited to CHF due to IDC until more research demonstrates a positive response to β-blocker therapy in CHF due to diverse etiologies.10

Guidelines do not exist regarding the stage(s) of CHF at which β-blockers should be initiated. Since heart failure exhibits different pathophysiologic changes at various stages, it may be unrealistic to expect β-blockers to be effective in all stages.34 Acutely decompensated patients would likely experience further cardiac deterioration with β-blocker administration due to their negative inotropic effect.10,24 While positive results have been obtained with clinically stable NYHA functional class II, III, and IV CHF patients, it has not been determined if patients at varying CHF stages respond differently to β-blockers. Consequently, the practitioner has little guidance regarding the stage of CHF that is most appropriate for the initiation of β-blockers.

**Dosing Issues**

As CHF is not a Health Protection Branch (HPB)-approved indication for β-blockers, manufacturer recommended dosages are unavailable. The reviewed studies may be used as a rudimentary dosing guideline. In nearly all the trials with favourable results, β-blocker dosages were adjusted gradually after a small initial dose.20,22,24,26,28,29 For example, Engelmeier et al.24 began subjects on 6.25mg daily of metoprolol and increased the dose slowly over four to six weeks to a maximum of 100mg daily. Another important aspect of treatment is the expected time to onset of beneficial results. In the reviewed studies, the shortest treatment duration to show clinical improvement was two months. In one study, response to bucindolol continuously improved over 24 months of therapy.36 Consequently, efficacy of β-blocker therapy should be evaluated only after three months of therapy and for a prolonged period thereafter.

In conclusion, based on an increasing number of clinical trials, β-blockers appear to be promising therapeutic agents in clinically stable patients with CHF due to IDC when added to standard CHF medication therapy. Their role in CHF needs to be further defined to determine the specific clinical settings in which they would be most effective. Large, long-term trials including patients with diverse CHF etiologies and with mortality as an endpoint are needed.1 The increasing prevalence and continuing poor prognosis associated with CHF suggest the positive results demonstrated thus far should not be overlooked and merit further investigation. At the present time, these agents should be used with caution in CHF and only under the close supervision of a cardiologist. Patients most likely to benefit are those in NYHA class III or IV with increased heart rates. The agent selected should possess beta1 selective properties (e.g., metoprolol) or vaso-
dilative properties (e.g., bucindolol). Dosage should include a small test dose with a slow upward titration over a one-month period. Patients who have recently suffered myocardial decompensation or have signs of poor perfusion should not be considered as candidates.

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