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 dialted cardiomyopathy*

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RÉSUMÉ:

L'insuffisance cardiaque congestive (ICC) pose un problème de santé publique de taille pour le Canada. Bien que l'utilisation des inhibiteurs de l'enzyme de conversion de l'angiotensine (IECA) ait freiné la morbidité et la mortalité chez les patients atteints de cette affection, les taux de mortalité à un an et à cinq ans associés à l'ICC demeurent inquiétants. Cependant, de nouvelles données indiquent que les bêta-bloquants, traditionnellement contre-indiqués dans l'ICC, pourraient être bénéfiques pour un sous-groupe de patients.

En effet, les bêta-bloquants pourraient exercer un effet bénéfique dans le traitement de l'ICC en inhibant la stimulation du système nerveux sympathique et du système rénine-angiotensine-aldostérone, en conférant une protection contre les effets cardiotoxiques de la norépinéphrine et en rétablissant la réponse du myocarde aux β-agonistes par l'élévation du seuil de régulation des β-récepteurs. À ce jour, de petites études bien contrôlées ont démontré des améliorations de la fonction systolique. Ces études avaient en commun l'ajout d'un β-bloquant au traitement classique, l'accroissement par palier graduel de la dose et l'administration du traitement pendant des périodes prolongées. La réussite thérapeutique a été observée principalement chez les patients souffrant de myocardiopathie congestive dilatée.

De nombreuses questions devront trouver réponses quant à l'utilisation des β-bloquants dans le traitement de l'ICC, notamment en ce qui concerne le moment idéal pour amorcer le traitement, l'effet sur la mortalité et quels sont les patients les plus susceptibles de tirer le maximum d'avantages d'un tel traitement. Malgré que les données actuelles semblent être prometteuses, des recherches plus poussées sont nécessaires.

Mots clés : *β-bloquants, ICC, myocardiopathie congestive dilatée*

INTRODUCTION

Congestive heart failure (CHF) is an important public health problem afflicting approximately 250,000 Canadians.[1] 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.[2] More recently, trials studying the effects of ACE inhibitors in conjunction with traditional therapies have demonstrated reductions in mortality and morbidity.[3-8] However, prognosis for CHF patients remains guarded. The overall five-year, post-diagnosis mortality rate for all patients with CHF is 50%.[1] Patients with severe CHF (New York Heart Association [NYHA] functional

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class IV), have a one year mortality rate of approximately 50%.[9] Clearly, novel treatment strategies are needed.

Traditionally, ß-blockers have been containdicated 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.[10] Prolonged SNS activation is now considered to be detrimental to heart function, contributing to the progression of CHF.[11,12] Consequently, the role of ß-blockers in heart failure is generating much interest. This article will review the pathogenesis of CHF, the rationale behind ß-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.[12] 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.[13,14]

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.[13,14]

As renal perfusion decreases with failing cardiac ouput, 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 ß-receptors with a subsequent diminution of sensitivity to stimulation.[15] The excess catecholamines may also be directly cardiotoxic and produce further impairment of contactile function.[16] 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.[16] 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.[17,18]

Rationale for ß-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.[9,10,19,20] Clinical trials have demonstrated an improved quality of life, and reduced morbidity and mortality in CHF patients treated with ACE inhibitors.[3-8] Research is now directed towards determining whether ß-blockers will produce similar results.

ß-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 resensitize the myocardium to ß-agonists by increasing the number of functional β_1 receptors via up-regulation.[10] Metoprolol therapy in CHF patients has been shown to increase myocardial β_1 receptor density, presumably by blocking the down-regulating effects of norepinephrine.[21] As well, beta-blockers may enhance mechanical performance of the heart by correction of regional wall abnormalities. Recently developed ß-blockers such as bucindolol and carvedilol produce vasodilation in addition to beta blockade. The resulting decrease in afterload may also help improve cardiac function.[21,22]

CLINICAL TRIALS

Small, randomized, double-blind, placebo-controlled studies have demonstrated improvements in systolic function in CHF patients receiving chronic administration of ß-blockers primarily metoprolol, bucindolol, and carvedilol (Table I).[23-32] Common characteristics of these studies include: addition of ß-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 ß-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

Ref. #	Drug & Dose (mg)[1]	# Pts.	Duration of Therapy (mos)	Type of CHF	NYHA FC	RESULTS*
23	Bucindolol 12.5, 50, 200	139	3	IDC, ISHD	I-IV	Dose-related improvement in LVEF in bucindolol-tx subjects. All 3 bucindolol doses prevented myocardial function deterioration. (i.e., ↓LVEF > = 5 units)
24	Metoprolol 100	25	12	IDC	Not specified	Metoprolol treatment resulted in: ↑EC, ↑NYHA FC, ↑LVEF compared to baseline; ↑EC, ↑NYHA FC compared to placebo.
25	Bucindolol 200	24	3	IDC	II, III	Bucindolol tx. pts. had improvements in symptoms, LVSWI, PCWP, NYHA FC, ↓NE. No beneficial changes in placebo group.
26	Carvedilol 50	32	3.5	Not specified	III, IV	Compared with placebo, carvedilol tx. pts. had improvements in: LVEF, SVI, NYHA FC, EC & ↓PCWP, ↓SVR.
27	Labetalol 100-400	12	2	IDC	II-IV	Compared to placebo, labetalol tx. pts. had improvements in NYHA FC, EC, and CO during exercise.
28	Carvedilol 50	20	6	IDC	Not specified	Carvedilol tx. pts. - ↑CI, ↑SVI, ↓PCWP at rest & during peak exercise from baseline. No beneficial changes in placebo group.
29	Bucindolol 200	19	3	IDC, ISHD	II-IV	Bucindolol tx. pts. - ↑LVEF, ↑EC, ↑CO, ↓PCWP compared to baseline. No beneficial changes in placebo.
30	Bucindolol Dose not specified	20	3	Not specified	Not specified	Bucindolol tx. pts. - ↑CO, ↑EC, compared to baseline.
31	Nebivolol	24	3	IDC, ISHD	II, III	Nebivolol tx. pts. - ↑SV, ↑LVEF, ↓LVEDP compared to placebo.
32	Bucindolol 200	49	3	IDC, ISHD	Not specified	Compared to placebo, bucindolol tx. pts. - ↑LVEF, ↓LV size, ↑SWI, ↓symptoms. Sub-group analysis of ISHD pts. showed improvement only in LV size.

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 50mg tid. Patients in NYHA functional classes II and III were initiated with a dose of 25mg bid and increased to 50mg tid or 100mg 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 ß-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 5mg bid and increased in 5mg to 25mg 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 ß-blockers currently undergoing phase III trials for use in CHF.[9] Third generation ß-blockers produce vasodilation as well as ß-blockade.[34] Bucindolol exhibits a direct vasodilatory action on vascular smooth muscle while carvedilol's vasodilation is due to α_1 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 ß-blockers.[9] Initial bucindolol doses of 6.25 or 12.5 mg bid have been well-tolerated in 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 100mg bid demonstrated improvement from baseline values in exercise tolerance as judged by treadmill time (mean increase from 445 to 530 secs, 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.[23] 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 ß-blockers in heart failure due to ischemic heart disease (ISHD), as well as due to IDC. Forty nine patients with either IDC (n=22) of ISDC (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 weeks 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 ß-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 ß-blocker therapy in CHF

Despite the positive results obtained in the reviewed studies, a number of controversies exist regarding ß-blocker use in CHF. A number of studies have demonstrated unfavourable results with ß-blocker use in CHF.[37-41] Also, the effect of

ß-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 ß-blocker use in CHF (Table II). However, general differences in the study design of positive result and negative result trials may explain the disparate findings. The duration of ß-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 ß-blockers' negative inotropic effect. Positive studies typically initiated small ß-blocker doses and titrated slowly. For example, Engelmeier et al[24] 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 ß-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, to date, ten randomized, double-blind, placebo-controlled trials have produced positive results with ß-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 ß-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 ß-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 ß-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 β_1 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 ß-blockers' effect on CHF mortality,

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

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

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 ß-blocker use in post-myocardial infarction patients which included patients with left ventricular dysfunction (LVD), were retrospectively analyzed.[43] Six of the 16 trials contained sufficient information to assess mortality. While two of the studies demonstrated an increase in mortality with ß-blocker use compared to placebo, four studies demonstrated a decrease in mortality with ß-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 ß-blockers in CHF. It is unknown which CHF patients, etiologies, or stages would most benefit from ß-blocker therapy. A number of trials studying whether patient baseline hemodynamic parameters predict response to ß-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 ($\geq 8\%$) 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 ß-blocker use in heart failure due to ISHD,[22,23,32] the majority of beneficial results has 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 ß-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 ß-blocker therapy be limited to CHF due to IDC until more research demonstrates a positive response to ß-blocker therapy in CHF due to diverse etiologies.[10]

Guidelines do not exist regarding the stage(s) of CHF at which ß-blockers should be initiated. Since heart failure exhibits different pathophysiologic changes at various stages, it may be unrealistic to expect ß-blockers to be effective in all stages.[34] Acutely decompensated patients would likely experience further cardiac deterioration with ß-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 ß-blockers. Consequently, the practitioner has little guidance regarding the stage of CHF that is most appropriate for the initiation of ß-blockers.

Dosing Issues

As CHF is not a Health Protection Branch (HPB)-approved indication for ß-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, ß-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 ß-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, ß-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 posess beta$_1$ 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. ☒

REFERENCES

1. Teo KK, Ignaszewski AP, Gutierrez R, et al. Contemporary medical management of left ventricular dysfunction and congestive heart failure. *Can J Cardiol* 1992;8:611-9.
2. Ho KL, Anderson KM, Kannel WB, et al. Survival after the onset of congestive heart failure in Framington heart study subjects. *Circulation* 1993;88:107-15.
3. The Acute Infarction Ramipril Efficacy (AIRE) Study Investigators. Effect of ramipril on mortality and morbidity of survivors of acute myocardial infarction with clinical evidence of heart failure. *Lancet* 1993;342:821-8.
4. Captopril-Digoxin Group. Comparative effects of therapy with captopril and digoxin in patients with mild to moderate heart failure. *JAMA* 1988;259:539-44.
5. Cohn JN, Johnson G, Ziesche S, et al. A comparison of enalapril with hydralazine-isosorbide dinitrate in the treatment of chronic congestive heart failure. *N Engl J Med* 1991;325:303-10.
6. The CONSENSUS Trial Study Goup. Effects of enalapril on mortality in severe congestive heart failure. *N Engl J Med* 1987;316:1429-35.
7. Pfeffer MA, Braunwald E, Moye LA, et al. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med* 1992;327:669-77.
8. The SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fraction and congestive heart failure. *N Engl J Med* 1991;325:293-302.
9. Bristow MR. Pathophysiologic and pharmacologic rationales for clinical management of chronic heart failure with beta-blocking agents. *Am J Cardiol* 1993;71:12C-22C.
10. Krukemeyer JJ. Use of ß-adrenergic blocking agents in congestive heart failure. *Clin Pharm* 1990;9:853-63.
11. Francis GS, Goldsmith SR, Levine B, et al. The neurohumoral axis in congestive heart failure. *Ann Intern Med* 1984;101:370-7.
12. Johnson JA, Lalonde RL. Congestive heart disease. In: DiPiro JT, Talbert RL, Hayes PE, Yee GC, Matzke GR, Posey LM, eds. Pharmacotherapy. Norwalk: Appleton and Lange 1993:160-93.
13. Gohn JN, Vevine TB, Olivari MT, et al. Plasma norepinephrine as a guide to prognosis in patients with chronic heart failure. *N Engl J Med* 1984;311:819-23.
14. Levine TB, Francis GS, Godsmith R, et al. Activity of the sympathetic nervous system and renin-angiotensin system assessed by plasma hormone levels and their relationship to hemodynamic abnormalities in congestive heart failure. *Am J Cardiol* 1982;49:1659-66.
15. Bristow MR, Ginsburg R, Minobe W, et al. Decreased catecholamine sensitivity and beta-adrenergic-receptor density in failing human heart. *N Engl J Med* 1982;307:205-11.
16. Greenberg BH. Mechanical characteristics of the failing left ventricle. *J Cardiovasc Pharmacol* 1989;14 (suppl 5):S62-8.
17. Geltman EM. Mild heart failure: diagnosis and treatment. *Am Heart J* 1989;118:1277-91.
18. Parmley WW. Pathophysiology and current therapy of congestive heart failure. *J Am Coll Cardiol* 1989;13:771-85.
19. Packer M. How should physicians view heart failure? The philosophical and physiological evolution of three conceptual models of the disease. *Am J Cardiol* 1993;71:3C-11C.
20. Domanski MJ, Eichorn EJ. Beta blockade in congestive heart failure – the need for a definitive study. *Am J Cardiol* 1994;73:597-9.
21. Waagstein F, Caidahl K, Wallentin I, et al. Long-term b-blockade in dilated cardiomyopathy. *Circulation* 1989;80:551-63.
22. Das Gupta P, Broadhurst P, Raftery EB, et al. Value of carvedilol in congestive heart failure secondary to coronary artery disease. *Am J Cardiol* 1990;66:1118-23.
23. Bristow MR, O'Connell JB, Gilbert EM, et al. Dose-response of chronic b-blocker treatment in heart failure from either idiopathic dilated or ischemic cardiomyopathy. *Circulation* 1994;89:1632-42.
24. Engelmeier RS, O'Connell JB, Walsh R, et al. Improvement in symptoms and exercise tolerance by metoprolol in patients with dilated cardiomyopathy: a double-blind, randomized placebo-controlled trial. *Circulation* 1985;72:536-46.
25. Gilbert EM, Anderson JL, Deitchman D, et al. Long-term b-blocker vasodilator therapy improves cardiac function in idiopathic dilated cardiomyopathy: a double-blind, randomized study of bucindolol versus placebo. *Am J Med* 1990;88:223-9.
26. Krum H, Schwartz B, Sacknee-Bernstein J, et al. Double-blind, placebo-controlled study of the long-term efficacy of carvedilol in patients with severe heart failure treated with converting-enzyme inhibitors. *J Am Coll Cardiol* 1993;21:114A (abstract)
27. Leung WH, Lau CP, Wong CK, et al. Improvement in exercise performance and hemodynamics by labetalol in patients with idiopathic dilated cardiomyopathy. *Am Heart J* 1990;119:884-90.
28. Metra M, D'Aloia A, Panina G, et al. Effects of acute and chronic carvedilol on resting and exercise hemodynamics of patients with idiopathic cardiomyopathy. *J Am Coll Cardiol* 1993;21:114A (abstract)
29. Pollock SG, Lystash J, Tedesco CL, et al. Usefulness of bucindolol in congestive heart failure. *Am J Cardiol* 1990;66:603-7.
30. Pollock SG, Lystash JC, Tedesco CL, et al. Bucindolol - beta blockade with vasodilation improves congestive heart failure. *Circulation* 1989;80:II-118. (abstract)
31. Wisenbaugh T, Katz I, Davis J, et al. Long-term (3 month) effects of a new beta-blocker (Nebivolol) on cardiac performance in dilated cardiomyopathy. *J Am Coll Cardiol* 1993;21:1094-1100.
32. Woodley SL, Gilbert EM, Anderson JL, et al. B-blockade with bucindolol in heart failure caused by ischemic versus idiopathic dilated cardiomyopathy. *Circulation* 1991;84:2426-41.
33. Waagstein F, Bristow MR, Swedberg K, et al. Beneficial effects of metoprolol in idiopathic dilated cardiomyopathy. *Lancet* 1993;342:1441-6.
34. Fowler MB. Controlled trials with beta blockers in heart failure: metoprolol as the prototype *Am J Cardiol* 1993;71:45C-53C.
35. Anderson JL, Lutz JR, Gilbert EM, et al. A randomized trial of low-dose

beta-blockade therapy for idiopathic dilated cardiomyopathy. *Am J Cardiol* 1985;55:471-5.

36. Anderson JL, Gilbert EM, O'Connell JB, et al. Long-term (2 Year) beneficial effects of acute b-adrenergic receptor blockade in congestive cardiomyopathy. *J Am Coll Cardiol* 1991;17:1373-81.

37. Ikram H, Chan W, Bennett Sl, et al. Hemodynamic-inotropic response to b-blocker with intrinsic sympathomimetic activity in patients with congestive cardiomyopathy. *Br Heart J* 1979;42:311-5.

38. Binkley PF, Lewe RF, Lima JJ, et al. Hemodynamic-inotropic response to b-blocker with intrinsic sympathomimetic activity in patients with congestive cardiomyopathy.

Circulation 1986;74:1390-8.

39. Currie PJ, Kelly MJ. Oral B-adrenergic blockade with metoprolol in chronic severe dilated cardiomyopathy. *J Am Coll Cardiol* 1984;3:203-9.

40. Ikram H, Fitzpatrick D. Double-blind trial of chronic oral B-blockade in congestive cardiomyopathy. *Lancet* 1981;2:490-3.

41. Taylor SH, Silke B. Hemodynamic effects of B-blockade in ischemic heart failure. *Lancet* 1981;2:835-7.

42. CIBIS Investigators and Committees. A randomized trial of b-blockade in heart failure. *Circulation* 1994;90:1765-73.

43. Held P. Effects of beta blockers on ventricular dysfunction after myocardial infarction: tolerability

and survival effects. *Am J Cardiol* 1993;71:39C-44C.

44. Gilbert EM, Mestroni L, Anderson JL, et al. Can response to B-blocker therapy in idiopathic dilated cardiomyopathy be predicted by baseline parameters? *Circulation* 1989;80:428 (abstract)

45. Bennett Sk, Fisher ML, Krichten C, et al. Ischemic cardiomyopathy treated with metoprolol: baseline heart rate predicts likelihood of increased ejection fraction. *Circulation* 1993;88:1-105 (abstract)

46. Yamada T, Fukunami M, Ohmori M, et al. Which subgroup of patients with dilated cardiomyopathy would benefit from long-term beta-blocker therapy? A histologic viewpoint. *J Am Coll Cardiol* 1993;21:628-33.