β-BLOCKERS IN CONGESTIVE HEART FAILURE

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ABSTRACT: Activation of the sympathetic nervous system (SNS) and renin-angiotensin system (RAS) plays a pivotal role in the pathophysiology and progression of the disease in chronic heart failure (CHF). Blocking the activation of the RAS with angiotensin converting enzyme inhibitors not only improves symptoms but also prolongs life in symptomatic CHF. Does a similar analogy hold true for the use of β-blockers in CHF? Evidence from a number of small trials and several recent large prospective trials show that β-blockers may improve ventricular function and symptoms in CHF. In a combination of trials investigating the use of carvedilol (an α1- and β-blocker) in congestive heart failure a mortality benefit appears to be evident. There are still a number of key questions that remain unanswered regarding the tolerability, patient type and stage of CHF in which β-blockers should be advocated. Several large-scale trials are in progress to answer some of these questions and also to add further information regarding its efficacy and impact on survival. (JUMMEC 1999: 1:26-33)

KEYWORDS: Beta-adrenoreceptor antagonist, congestive heart failure.

Introduction

In clinical practice, the idea of giving a negative inotropic agent to patients with congestive heart failure (CHF) would be considered counter intuitive. Therefore, it may seem paradoxical to learn that β-blockers, long recognised as “negative inotropes”, are seriously being considered as a new approach in the treatment of CHF. However, any new approach or treatment of CHF must address two fundamental issues, namely the ability to improve the patient’s quality of life and the ability to prolong survival. Previous experience tells us that these two closely related but distinct parameters may be influenced in different ways by different agents. By the same token, CHF is not a single entity, and therapy that is effective for CHF with one cause may not be effective for CHF with other causes. Moreover, treatment that is useful at one stage in the natural history of CHF may not be beneficial at another stage. Finally, some CHF therapies may have beneficial short-term effects but over a period of time may lose these effects and may even adversely affect mortality. All these issues are relevant to the use of β-blockers in CHF. This review will discuss in turn the following questions: Do β-blockers improve symptoms and functional capacity? Do β-blockers prolong survival? What are the likely mechanism(s) for these beneficial effects? Are β-blockers useful in all types of CHF? How safe are β-blockers and should they be used routinely?

Do β-blockers improve symptoms and functional capacity?

β-blocker as a treatment for CHF was first described in 1975 by Waagstein and colleagues (1). Their report was based on clinical experience in 7 patients with idiopathic dilated cardiomyopathy and with resting tachycardia who were treated with alprenolol or propranolol for approximately 5 months. All the patients showed haemodynamic improvement, and no adverse effects were reported. The rationale for this novel therapy was based on the investigators’ experience with β-blockade in patients with acute myocardial infarction (2). The same Swedish investigators published additional data on long term benefits with β-blockade (3) and reported deterioration after withdrawal of β-blockers in patients who had “improved conspicuously” (4). It is important to note that none of these studies were randomized. Since β-blockers could aggravate CHF (5), the use of β-blockers was initially greeted with skepticism, which was reinforced by 2 small short-term controlled trials which failed to show any benefit (6,7). It has since been argued that both these 2 trials might have been too small and too brief (<4 weeks) to define the potential benefits of these drugs. Furthermore, both these studies were crossover studies which may have
permitted any favourable effects of the β-blocker to have crossed over into the placebo treatment period and thus limited the ability to detect any difference between active and placebo therapy.

In the 1990s, experimental findings led to a resurgence of interest in the clinical use of β-blockers as treatment for CHF. Experiments in ventricles from explanted failing human hearts exposed to prolonged adrenergic activity show progressive desensitization of cardiac β-adrenergic receptors which desensitize the heart to sympathetic stimulation (8,9). This desensitization is due to β-receptor downregulation and also changes in the regulating G proteins that couple the receptors to adenylate cyclase (10). At the same time, studies in animal models using intact hearts and cell cultures as well as clinical observations in patients with cardiomyopathy due to pheochromocytoma suggest that prolonged activation of the sympathetic nervous system may exert a direct sustained deleterious effect on myocardial function and contribute to progressive myocardial damage (11-13). Such deleterious long term effects of excessive sympathetic stimulation on cardiac mechanical performance may outweigh any immediate benefits of inotropic support to the failing myocardium, thus providing a rationale for the use of β-blockers in CHF.

In the last decade, there have been at least 17 trials of β-blockers in CHF (4 open and 11 randomized controlled) involving a total of 2905 patients (14-30). Table 1 summarizes the results of these studies. The possibility of publication bias leading to selective reporting of favourable results needs to be considered as does the widespread use of pragmatic (rather than intention to treat) analysis. Even allowing for these confounding influences and that the studies differed in design, duration of treatment, choice of β-blocker and patient characteristics, the findings were fairly consistent with improvements in symptoms, exercise capacity, left ventricular function and haemodynamic and neurohormonal indices. Of the few large-scale placebo controlled trials, the Metoprolol in Dilated Cardiomyopathy trial was the first and was published in 1993 (25). Three hundred and eighty-three patients with mild to moderate CHF (NYHA functional class 1-3) caused by idiopathic dilated cardiomyopathy and not associated with significant ischaemic heart disease were randomized to receive either metoprolol or placebo in addition to other standard therapy for CHF including diuretics, digoxin and angiotensin converting enzyme inhibitors. Over the 12 to 18 months assessment period, metoprolol significantly improved haemodynamic status (ejection fraction and pulmonary capillary wedge pressure) and treadmill exercise times. In addition, the rate of deterioration of the patients who received metoprolol was slowed as judged by the clinical end point of “being assessed as requiring cardiac transplantation” during the study period (2 vs 19 patients; metoprolol vs placebo respectively). There was also a reduction in the hospitalization/emergency room visits for decompensation in the metoprolol-treated group. Quality of life, assessed

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<th>Table 1. Summary of 14 major trials of β-blockers in congestive heart failure.</th>
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**Keynotes:** DB = double blind; O = Open; DCM = idiopathic dilated cardiomyopathy; IHD = ischemic heart disease; + = improvement; = no change; na = not available
at the end of follow-up or the latest assessment before an endpoint was reached, improved significantly more in the metoprolol group than the placebo group. These results are supported by the recently published Cardiac Insufficiency Bisoprolol Study (CIBIS) which randomized 641 patients with CHF of various etiologies to receive either bisoprolol or placebo and were followed for almost 2 years (28). There was significant improvement in functional status in the bisoprolol treated group; fewer patients in the bisoprolol group required hospitalization for cardiac decompensation and more patients improved by at least one New York Heart Association functional class by the end of the treatment.

An assessment of the data from these trials show that the improvement in left ventricular function associated with the use of β-blockers have been impressive, with improvements in left ventricular ejection fractions greater than any form of CHF therapy (31). For example, vasodilators, angiotensin converting enzyme inhibitors or inotropic treatment does not typically increase left ventricular ejection fraction by more than 5% relative to change in a placebo group, whereas it is common for β blockers to increase left ventricular ejection fraction by 6-15% in idiopathic dilated cardiomyopathy (22,24) and 4-8% in ischaemic cardiomyopathy (27). These findings have justifiably been questioned because none of the other agents slow the heart rate to the same extent as β blockers and it could be argued that the decrease in heart rate could have contributed to an improvement in ejection fraction by allowing more ventricular filling. Both left ventricular ejection fraction and the plot of stroke volume versus pulmonary capillary wedge pressure are a load-dependent measure of cardiac function and it is possible that some of these effects of β-blockers might be load mediated. To address these issues, Eichhorn and colleagues recently conducted a study of the haemodynamic effects of bucindolol, a new generation β blocker with some vasodilatory properties, in CHF patients (32). Confounding influences of changes in heart rate and loading conditions were avoided by performing all measurements at matched atrial pacing rates and measurements of interest were indices of cardiac performance that were relatively load independent. Bucindolol augmented contractility as assessed by the end systolic pressure volume relation and the peak positive dP/dt and diastolic volume relation and also improved myocardial relaxation as shown by a reduction in the time constant of left ventricular isovolumic relaxation. These changes in systolic and diastolic function were achieved without any rise in myocardial oxygen consumption, indicating an improvement in the efficiency of myocardial energetic.

The findings related to exercise capacity in the trials conducted to date have been somewhat conflicting. Although most studies have reported statistically significant improvement in total exercise duration with β-blockade (14,16,18-21,23,25-27), others have not (15,22,24). Long term β-blockade can attenuate maximal oxygen consumption; consequently, maximal exercise testing may not be the most appropriate method for assessing improvement in functional capacity. In a recent randomized trial of the effects of carvedilol, a combined α- and β-blocker, submaximal exercise time (determined by stressing patients at a workload fixed at 85% of their baseline maximal oxygen consumption) was significantly increased in the carvedilol group compared with the placebo group whereas maximal exercise time was not changed (33). This method of assessing submaximal performance is often preferred by patients and may better reflect the likelihood of their regular daily physical activity than does maximal exercise testing.

Do β-blockers prolong survival?

In addition to quality of life, patient survival is another consideration in the treatment of CHF. Trials of β-blockers have not been shown to decrease mortality in any appropriately designed study. Although, Swedberg et al. reported in 1979 that patients with CHF treated with β-blockers had a significantly better survival experience, this data was compared with retrospectively selected controls (34). Sacks et al. (35) have highlighted the problems related to historical, rather than concurrent randomised controls, stating that studies using historical controls are prone to producing false positive conclusions.

Until recently, most of the studies have been small and lack the statistical power to define an effect on mortality. The Metoprolol in Dilated Cardiomyopathy Trial was the first large scale placebo controlled trial that tested the effects of β-blockade on mortality although it should be noted that it had a predefined combined endpoint with fatal (all-cause mortality) and non-fatal components (clinical deterioration to a point at which cardiac transplantation would normally be offered as a treatment option). The study showed no difference in all-cause mortality between the groups (23 vs 19, metoprolol vs placebo treated groups respectively). The authors argued that because the patients were on optimum therapy (including angiotensin converting enzyme inhibitors) on entry into the trial, there had been too few deaths for the trial to detect an effect. They also argued that because the trial design was such that patients with the highest risk of death were placed on a waiting list for heart transplantation and therefore patients who were transplanted would otherwise have died. This latter possibility is supported by the finding of a significant difference in favour of metoprolol in the combined overall endpoint of death or transplantation (25 vs 38, metoprolol vs placebo respectively, p=0.06, Fig 1). In the recently published CIBIS trial (28), the main endpoint was mortality and the results showed a 20% risk reduction with bisoprolol (67 patients died on placebo, 53 on bisoprolol; relative risk, 0.80) but this observed reduction did not reach statistical significance (p=0.22) (Fig 2). No
significant difference was also observed in sudden death rate (17 on placebo, 15 on bisoprolol) or death related to documented ventricular tachycardia or fibrillation (7 on placebo, 4 on bisoprolol).

Despite the absence of significant benefit in mortality for the entire population in the CIBIS trial, subgroup analysis according to the etiology of CHF was of interest. Among 303 patients with a history of myocardial infarction, 19% died on placebo compared with 21% on bisoprolol (p=0.55). However, among 338 patients without a history of myocardial infarction, 22.5% died on placebo and 12% died on bisoprolol (p=0.01). There is no clear explanation for this differential effect since it might be anticipated that β-blockade would confer cardiac protection in ischaemic patients. After myocardial infarction, β-blockade therapy has largely proven to be beneficial with a 20% to 25% reduction in 1-year mortality and in nonfatal myocardial infarction rate (36,37). In addition, benefit appears to be greater in high risk patients with a history of compensated or mild congestive heart failure before randomization (38,39). However, it must be emphasized that this subgroup analysis of the CIBIS trial should be interpreted with some caution as no stratification based on etiology of CHF was performed at randomization which would exclude valid separate analysis according to these subgroupings. Therefore these results of subgroup analysis can be considered only suggestive, and differential results of bisoprolol efficacy according to etiology must await formal studies.

Four moderately large randomized, placebo-controlled, US trials (29) with carvedilol, designed to look at symptomatic and other non-fatal endpoints, also prospectively reported mortality, for safety reasons, to a common Data and Safety Monitoring Board (DSMB). The DSMB recommended early termination of this programme of carvedilol trials (after a median follow-up of only 6.5 months) based on the finding of a significant 65% relative reduction in death in the active therapy group compared to the placebo group - placebo group mortality 7.8% and carvedilol group mortality 3.2% after a median follow-up of 6.5 months (P=0.001) (30). Four meta-analyses, (40,43) published before these results became available supported a benefit of beta blockers on left ventricular function, symptoms and hospitalization but not total mortality (unless cardiac transplant was equated with death). An updated metaanalysis (44), following the publication of the US trials and a less favourable Australian-New Zealand study, supports a reduction in total mortality, although this new overview is necessarily biased by the relatively large size of the carvedilol trials compared to previous beta-blocker trials. Three further large, placebo-controlled mortality trials with beta-blockers ( bucindilol, bisoprolol and metaprolol) are still underway, as is a trial comparing candesilol to metoprolol.

**Figure 1.** Metoprolol in Dilated Cardiomyopathy Trial: Likelihood of reaching the primary endpoint of death or need for heart transplantation. 211 patients were followed for 12 months and 178 for 18 months. 31 patients in the placebo group reached a primary endpoint compared with 25 in the metoprolol, representing a risk reduction of 34% (p=0.058).

*With permission from Waagstein et al. (25)*

**Figure 2.** CIBIS Trial. Survival curves (Kaplan-Meier) in 641 CIBIS patients: 67 patients died receiving placebo, and 53 died receiving bisoprolol. Risk reduction on bisoprolol: 0.80 (95% confidence interval + 0.65 - 1.15).

*With permission from the CIBIS Investigators (28)*

**What are the likely mechanisms for the beneficial effects of β-blockers in CHF?**

The mechanisms for the positive impact of β-blockers in CHF are not clear and a number of hypotheses have been proposed. Some investigators have proposed that protection from catecholamine toxicity may be one mechanism for the improvement in left ventricular function. As alluded to earlier, studies in animal models using intact hearts and cell cultures, as well as clinical observations in patients with cardiomyopathy due to pheochromocytoma have confirmed the adverse impact of high levels of catecholamines on the heart (11-13). Several mechanisms could be involved in catecholamine mediated cardiotoxicity including intracellular calcium accumulation (45) and generation of free radicals by catecholamine metabolites such as adrenochrome (46). In CHF, catecholamines may also mediate their adverse effects by increasing metabolic demand on an already energy
starved myocardium. Catecholamines may also compromise coronary blood flow by shortening diastole and by causing vasoconstriction. With respect to the latter, it is now recognised that successful revascularisation is capable of causing marked improvement in some patients with depressed ventricular function due to stunned or hibernating myocardium. It is possible that β-blocker induced alteration of supply/demand imbalance can mediate similar recovery in patients with CHF. β-blockers might also improve contractility in patients with abnormally prolonged mechanical restitution by slowing heart rate and thereby allowing systole to occur in the more advantageous plateau portion of the restitution curve (47).

The observation that only prolonged therapy (>4 weeks) with β-blockers can produce haemodynamic and clinical improvement suggests that the deleterious effect of catecholamines is reversible and that long periods of protection from the actions of endogenous catecholamines are required for the recovery of cardiac function.

Because the defect in contractile function seen in CHF may be caused, in part, by a deficiency of intracellular cyclic AMP which is related to a loss of myocardial β-receptors, some workers have suggested that β-blockers might be effective in CHF because they increase the density (upregulate) of β-receptors and thus sensitize the heart to the positive inotropic and lusitropic (relaxant) actions of endogenous catecholamines (48). This hypothesis, however, fails to explain a number of observations. Firstly, although β-blockers increase the density of β-receptors, they would not at the same time block these receptors from the effects of endogenous catecholamines, and thus prevent any favourable haemodynamic effect of endogenous sympathetic stimuli might exert on the upregulated receptors. Second, B-receptor upregulation occurs rapidly (within hours or days) after the institution of treatment with β-blockers, but the beneficial haemodynamic effect of β-blockers are delayed (for several months). Thirdly, in patients with idiopathic dilated cardiomyopathy, there is no correlation between the degree of improvement in ejection fraction and the changes in receptors (49). Finally, an anti-ischaeic and anti-arrhythmic effect of β-blocker might be important in the prevention of sudden death in CHF. However, no effect on sudden death has so far been observed in all the trials of β-blockers in CHF except in subgroup analysis of the post-infarction trials of the BHAT trial and the Norwegian Timolol study when the greatest reduction in cardiac mortality was among patients with evidence of CHF. In particular, in the BHAT study, there was a striking 47% reduction in the incidence of sudden death in this high-risk cohort compared with only a 13% reduction in patients without a history of CHF.

Are β-blockers useful in all types of CHF?

Most of the early trials were confined to the relatively uncommon condition of idiopathic dilated cardiomyopathy but more recently β-blockers have been evaluated in patients with CHF secondary to other causes including coronary artery disease. It has been suggested that β-blockers may be less beneficial in CHF associated with coronary artery disease than in patients with idiopathic cardiomyopathy (18,22,28). Several reasons have been proposed. Firstly, it has been argued that the chronicity of coronary artery disease and the relatively large areas of fibrosis that may be associated with previous myocardial infarction may prevent any marked increases in ejection fraction. Biopsy data from studies of idiopathic cardiomyopathy suggest that the extent and type of fibrosis predicts the "likelihood of increased ejection fraction with β-blocker therapy" (50).

Some data (51) suggest that alteration of the inhibitory G proteins may differ in failing hearts with ischaemia versus idiopathic dilated cardiomyopathy. This difference has some functional relevance to inotropic responsiveness to endogenous catecholamines. Conceivably, it may influence the response to β-adrenergic blockade as well.

There is some support for this from the subgroup analysis in the CIBIS trial which suggested an enhanced action on bisoprolol in patients without ischaemia, in the absence of a history of myocardial infarction or in patients with an idiopathic dilated cardiomyopathy (28).

However, as discussed earlier, caution should be exercised when interpreting this data from the CIBIS trial since no stratification based on etiology was performed at randomization. Besides, Fisher et al. (27) recently reported a definite symptomatic and functional improvement in patients with CHF secondary to coronary artery disease with a mean increase in ejection fraction of 4% and 10 (20%) of 38 patients had improvement in ejection fraction of greater than 8%.

It is also not clear what stage of CHF β-blockers should be used in. Since CHF show different pathophysiologic changes at various stages in its evolution, it could be unrealistic to accept a single agent or class of agents as effective throughout the natural history of the disorder. It could be argued that β-blockade may be unnecessary in early CHF where there is no or minimal activation of the sympathetic nervous system. There have been no trials of β-blockers in early CHF. Most of the trials have been in symptomatic patients. In the Metoprolol in Dilated Cardiomyopathy Trial, eligible patients had symptomatic CHF with ejection fractions less than 40%. Another requirement was that patients had achieved a state of compensated CHF by means of conventional CHF treatment which included digitalis, diuretics, angiotensin converting enzyme inhibitors and nitrates. Eighty two percent of the placebo and 78% of the metoprolol treated pa-
sients were on an angiotensin converting enzyme inhibitor and improvement in myocardial function was not affected by concomitant treatment with an angiotensin converting enzyme inhibitor and the authors suggested that the 2 types of drugs produced improvement by different mechanisms.

**How safe are β-blockers and should β-blockers be recommended for routine use?**

There is no doubt that some patients remain very intolerant to these drugs. Even with cautious dosing, some patients who had participated in these trials have to be withdrawn because of worsening CHF, bradycardia or hypotension. It is difficult to glean from the published results the incidence of acute intolerance, it may range from 0%-30%. Intolerance may occur even with small initial doses in approximately 10% to 15% of patients (29). Das Gupta et al. (18) reported a 29% incidence of intolerance to a single 12.5 mg dose of carvedilol. In the Metoprolol in Dilated Cardiomyopathy Trial, about 5% of the original eligible patient group were intolerant of the smallest dose and had to be excluded. It is also unclear whether patients with decompensated or severe CHF are liable to be intolerant since some of these seem to tolerate β-blockade without problems and one group has even reported the successful use of low-dose metoprolol on patients with end stage CHF requiring inotropic support (52). In the US carvedilol trial, 7.8% of the placebo group and 5.7% of the carvedilol group discontinued the study medication because of adverse reactions. Since there is some difficulty in identifying patients that may become intolerant to β-blockers and the evidence to date have yet to show an impact on mortality, it could be argued that the available data does not justify the widespread use of β-blockers in all patients with CHF. The experience with other agents in CHF, such as xamoterol (53) and milrinone (54) which produce favorable short-term haemodynamic and clinical effects but actually increase mortality in the long term, indicates the importance of mortality data in the consideration of general treatment recommendations. But are there any CHF patients which might be considered suitable for a therapeutic trial of β-blockade. It could be argued that a carefully selected group of patients who remain symptomatic despite being on maximal therapy may benefit from this novel approach. Clearly, treatment must be started at an extremely low dose. A useful description of how to use beta-blockers in heart failure is given in the recent European Society Guidelines on the treatment of heart failure (55) as shown in Table 2.

**Conclusion**

Thus, the role for modulation of β-adrenergic nervous system in CHF has been encouraging with reports of improvements in symptoms, left ventricular function and functional capacity. To date, trials of β-blockers in CHF have yet to show an effect on mortality, although an analyses of a combination of trials of carvedilol suggest that it may have a benefit. The exact mechanisms by which benefit may be mediated are still to be determined. Besides this, there are still a number of unanswered questions. Exactly which patient population may derive the most benefit remains unclear. What stage of CHF may benefit from β-blockers? How long should we treat these patients with a β-blocker? Which β-blocker should we use? Most of the early studies have used metoprolol. More recently, attention has switched to the newer generation of β-blockers with vasodilating properties such as bucindolol. These agents have been developed in the hope that they might be less likely to precipitate acute haemodynamic deterioration than conventional β-blockers. It has also been argued that since β₂ selective blockers, such as metoprolol, do not block the β₂ receptor there is still the potential for catecholamine stimulated myocardial β₂ receptors to result in arrhythmias and sudden death. Furthermore, metoprolol does not block presynaptic β₁ receptors and therefore does not reduce plasma norepinephrine (56) which is an important prognostic marker in CHF. The β₁ β₂ receptor antagonist bucindolol has been shown to reduce plasma norepinephrine (26) and it has mild vasodilator properties which may be the reason why this drug appears to be better tolerated than propanolol in CHF (17, 22). This is the rationale for

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<th>Target total daily dose (mg)</th>
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<tr>
<td>Metoprolol (MCD trial) (25)</td>
<td>5 Wk1</td>
<td>10 Wk2 30 Wk3 50 Wk4 75 Wk5 100 Wk6 150 Wk7</td>
<td>100-150</td>
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<tr>
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<td>1.25 Wk2 2.5 Wk3 3.75 Wk4-7 5 Wk8-1 7.5 Wk9-1 10 Wk12-5</td>
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<tr>
<td>Carvedilol (US trial) (30)</td>
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selection of bucindolol in the NHLB/VA Cooperative study, Beta Blocker Evaluation of Survival Trial (BEST). This trial along with several large scale controlled trials are already in progress to assess the long term safety and efficacy of β-blockers in CHF and, most important of all, their impact on survival. Until these large trials are completed, the use of β-blockers remains a promising but as yet unestablished form of treatment for CHF.

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