Editorial

Beta-blocking in heart failure patients
Balancing the evidence

Maria Gabriella Marinoneb, Faisal Al-Nasserb, Darrel Francisb, Massimo F. Piepolia,b,*

a Clinical Cardiology Department, Imperial College School of Medicine, London SW3 6LY, UK.
b Emergency Department, Polichirurgico Hospital, Cantone del Cristo, Piacenza 29100, Italy

Received 5 July 2000; received in revised form 30 January 2001; accepted 14 February 2001

Abstract

Evidence for the effectiveness of beta-blockers in the management of patients with heart failure is now compelling with a database of over 13,000 patients enrolled in randomised prospective placebo-controlled clinical trials. However, this therapy remains vastly underused in clinical practice. The different points challenging the widespread use beta-blockade agents in the routine treatment in heart failure are presented and discussed. After a review of the potential mechanism hypothesised behind the benefits of beta-blockers in heart failure, the controversial effects on the haemodynamics, exercise tolerance, hospitalisation and mortality are underlined.

Keywords: Beta-blockers; Heart failure

1. Introduction

Traditionally beta-blockade agents (BB) have been considered contraindicated in chronic heart failure (CHF) because of their acute negative inotropic effects. However, the last decade has seen growing interest in, and acceptance of, their potential beneficial effect in this condition, because despite extensive use of angiotensin converting enzyme (ACE) inhibition and the availability of surgical therapy the prognosis for CHF patients remains poor. Recent studies have underlined the key role played by the neuro-hormonal alterations and their prognostic importance in CHF. Activation of neuro-hormonal systems causes excessive vasoconstriction and volume expansion and worsening symptoms and signs of CHF: the benefit of blockade of renin–angiotensin–aldosterone system with ACE inhibition is well established. There may also be additional benefits from blockade of the sympathetic nervous system with BB, complementary to those provided by ACE inhibitors. Clinical trials have shown beneficial effects of BB on left ventricular function in CHF patients, and larger trials have demonstrated the effects of BB on survival in patients after myocardial infarction with evidence of heart failure.

Potential benefit of BB in CHF has been investigated in a number of studies: although enthusiasm has surrounded the presentation of more recent data (CIBIS-II, MERIT-HF, COPERNICUS), this therapy remains vastly under-utilised in clinical practice. Although it is estimated that 85% of CHF patients would benefit from BB, a recent French study...
revealed that only 5% of patients actually received this treatment in practice [1]. A perception exists that the clinical benefit of BB demonstrated in large trials is difficult to be replicated in everyday practice.

A literature review using MEDLINE identified 29 randomised-controlled studies involving a total of 13295 patients (Table 1). At the beginning, several uncontrolled trials suggested potential benefits in CHF of BB therapy: most were small with short follow-up periods. They have been followed by a number of randomised, placebo-controlled trials of carvedilol (11 studies), metoprolol (9), bucindolol (4), bisoprolol (2), nebivolol (2), labetalol (1), and acebutolol (1).

2. Mechanisms behind BB therapy in CHF

The most obvious clinical effect of BB is heart rate reduction. Decreased heart rate brings prolongation of diastole, which would be beneficial to the failing heart. BB increases deceleration time and late diastolic filling [2]. In a state of increased wall stress, owing to dilatation and elevated filling pressure, a longer diastoling filling time may improve myocardial perfusion [3]. The myocardial metabolic pattern is also altered favourably, with a shift from lipolytic- to carbohydrate-based energy generation, which is more energy-efficient with less oxygen consumption per ATP molecule produced [4].

**Table 1**

Randomised controlled trials of beta-blockers in congestive heart failure

<table>
<thead>
<tr>
<th>Study, years</th>
<th>Patients total</th>
<th>Drug</th>
<th>Follow-up (months)</th>
<th>LVEF (% Δ)</th>
<th>Exercise tolerance</th>
<th>Mortality</th>
<th>Hospitalization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Currie, 1984 [41]</td>
<td>10</td>
<td>M</td>
<td>1</td>
<td>+3</td>
<td>↔</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anderson, 1985 [42]</td>
<td>50</td>
<td>M</td>
<td>19</td>
<td>+2</td>
<td>↔ ↔ ↔</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Engelmeier, 1985 [27]</td>
<td>25</td>
<td>M</td>
<td>10</td>
<td>+8</td>
<td>↔ ↔ ↔</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leung, 1985 [43]</td>
<td>12</td>
<td>L</td>
<td>2</td>
<td>↑</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pollock, 1990 [44]</td>
<td>20</td>
<td>Bc</td>
<td>3</td>
<td>0</td>
<td>↑ ↔ ↔</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gilbert, 1990 [45]</td>
<td>24</td>
<td>Bc</td>
<td>3</td>
<td>+8</td>
<td>↔ ↔</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lechat, 1991 [46]</td>
<td>12</td>
<td>N</td>
<td>1.5</td>
<td>↓</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paolisso, 1992 [47]</td>
<td>10</td>
<td>M</td>
<td>3</td>
<td>↑</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Krum, 1993 [48]</td>
<td>49</td>
<td>C</td>
<td>3</td>
<td>+5</td>
<td>↑ ↔ ↓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Olsen, 1993 [49]</td>
<td>60</td>
<td>C</td>
<td>4</td>
<td>+10</td>
<td>↔ ↔ ↑</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wisenbaugh, 1993 [50]</td>
<td>29</td>
<td>N</td>
<td>3</td>
<td>+8</td>
<td>↔ ↔ ↔</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fisher, 1994 [51]</td>
<td>50</td>
<td>M</td>
<td>6</td>
<td>+5</td>
<td>↔ ↔ ↓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metra, 1994 [52]</td>
<td>40</td>
<td>C</td>
<td>4</td>
<td>+10</td>
<td>↑ ↔ ↔</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bristow, 1994 [53]</td>
<td>139</td>
<td>Bc</td>
<td>3</td>
<td>+4</td>
<td>↓ ↔ ↔</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eichhorn, 1994 [54]</td>
<td>25</td>
<td>M</td>
<td>3</td>
<td>+8</td>
<td>↔ ↔ ↓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colucci, 1996 [55]</td>
<td>366</td>
<td>C</td>
<td>7</td>
<td>+10</td>
<td>↔ ↓ ↔</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PRECISE, 1996 [38]</td>
<td>278</td>
<td>C</td>
<td>6</td>
<td>+8</td>
<td>↔ ↔ ↓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carvedilol efficacy, 1996 [56]</td>
<td>105</td>
<td>C</td>
<td>↓</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MOCHA, 1996 [16]</td>
<td>345</td>
<td>C</td>
<td>5.5</td>
<td>+4</td>
<td>↔ ↓ ↓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ANZ, 1997 [12]</td>
<td>415</td>
<td>C</td>
<td>12–19</td>
<td>+5.3</td>
<td>↔ ↓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kukin, 1999 [35]</td>
<td>67</td>
<td>C vs. M</td>
<td>6</td>
<td>+5</td>
<td>↑</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CIBIS II, 1999 [18]</td>
<td>2697</td>
<td>B</td>
<td>16</td>
<td>↓ ↓</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MERIT-HF, 1999 [19]</td>
<td>3991</td>
<td>M</td>
<td>12</td>
<td>↓ ↓</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>COPERNICUS, 2000</td>
<td>2289</td>
<td>C</td>
<td>11</td>
<td>↓ ↓</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Summary**

<table>
<thead>
<tr>
<th>Total:</th>
<th>Mean:</th>
<th>Mean:</th>
</tr>
</thead>
<tbody>
<tr>
<td>13295</td>
<td>7.2</td>
<td>+5</td>
</tr>
</tbody>
</table>

* (A, acebutolol; Bc, bucindolol; Bs, bisoprolol; C, carvedilol; L, labetalol; LVEF, left ventricular ejection fraction; M, metoprolol; N, nebivolol; ↔ no effect; ↑, increase; ↓ reduction).
Chronic BB therapy reduces the effects of sympathetic stimulation and circulating catecholamines decreases peripheral norepinephrine [5] and myocardial norepinephrine stores [6]. These effects may be mitigated, however, by compensatory up-regulation of beta1-receptors, although such effect may be specific to some agents (such as metoprolol) [7] but not others (i.e. carvedilol or bucindolol) [4].

Finally BB may help reverse the immune dysfunction commonly seen in CHF, by increasing the number of T-suppressor and natural killer cells [8]. This effect was suggested to be due to a blockade of sympathetic-induced changes in immunologic function; the cause of idiopathic dilated cardimypathy is still under investigation but a role has been proposed for auto-immunity. There is evidence that at least some of these patients express beta-1 receptor antibodies, which may be physiologically active with beta-agonistic function [9].

3. Haemodynamic effects of BB therapy in CHF

Based on these patho-physiological mechanisms, it would have not been surprising to observe benefit in haemodynamics after BB therapy. In fact almost all studies showed improvement in left ventricular ejection fraction (with the exception of the oldest trial from Ikram et al. [10]). However it appeared that the principal beneficiaries in haemodynamic terms were CHF patients with non-ischaemic aetiology who gained increased left ventricular ejection fraction and decreased pulmonary capillary wedge pressure. In contrast CHF patients with coronary artery disease have shown rather more conflicting results [11]. Changes in haemodynamic status do not necessarily translate into improvement in clinical status. For example in the Australia–New Zealand Heart Failure trial [12] the improvements in cardiac output and left ventricular ejection fraction were unrelated not only to changes in exercise tolerance but even to the progression of symptoms in ischaemic cardiomyopathy.

4. Exercise tolerance

The data on exercise capacity have been conflicting. Although some studies have shown statistically significant improvements in total exercise duration with BB, the majority did not or even demonstrated a reduction (Table 1). This is a crucial point because the major limiting factors in CHF patients are early occurrence of fatigue and shortness of breath on effort and therefore treatments for these symptoms would have great impact on quality of life.

It has been hypothesised that the improvement in exercise capacity may be related to either beta1-selectivity or to the ability to increase beta1-receptor sensitivity by metoprolol, because the effect was not seen in the less selective agents (i.e. bucindolol or carvedilol).

Finally, in the measurement of exercise tolerance, cardiopulmonary test is a well established, objective and reproducible procedure. However this may not be the case with BB as long term BB can cause an artefactual decrease in peak O2 consumption due to a delayed chronotropic response induced by the drug [13].

5. Hospitalisation and mortality

The most recent and largest trials have investigated the effect of BB on hospitalisation and mortality in CHF (Table 1). Although it seems there is a general agreement concerning the benefit of BB on morbidity in CHF, such clear data concerning mortality have only recently surfaced.

In the Metoprolol in Dilated Cardiomyopathy (MDC) trial [14], significant improvements in haemodynamics and symptoms as well as fewer hospital admission were seen in the group treated with BB, yet there was no statistically significant effect on mortality. In Cardiac Insufficiency Bisoprolol Study (CIBIS) [15] trial, significantly fewer patients under BB therapy required hospitalisation, but again there were no significant changes in mortality. More favourable data on survival benefit have been shown by the recent and larger trials, such as MOCHA [16], US-Carvedilol [17], CIBIS-II [18], MERIT-HF, [19], and COPERNICUS.

The mechanisms of improved survival with BB treatment remain unclear. In the meta-analysis by Heidenreich et al. [20] (but published before the presentation of the most recent trials), the reduction
in non-sudden cardiac death was more marked than the reduction in sudden death (42% vs. 16% reduction). This difference was most notable in the non-carvedilol trials, which showed a difference in sudden death (4% increase in the odds of death) compared with non sudden cardiac death (34% decrease). This suggests that BB may be preventing or delaying the progression of CHF rather than exerting an antiarrhythmic effect. Nevertheless, the two largest non-carvedilol trials had different results. The CIBIS-II trial showed a lower frequency of sudden death among patients on bisoprolol, and these authors hypothesised an important anti-arrhythmic effect. The MERIT-HF trial found a reduction in both sudden death and death from worsening heart failure.

In the evaluation of the effects of mortality data of the trials of BB in CHF, three more observations should be considered. Deaths occurred during the initial open label phases of three trials of carvedilol [11,16,21], and the final reports did not include these deaths in the mortality statistics. It is possible that BB treatment contributed to the deaths and that therefore the reported mortality benefits are overestimated. More importantly, when in 1997 an overview of 17 published controlled trials of BB in CHF was performed, the mean mortality rate was only 11% per year [20]: a similar low mortality rate (13%) has been reported in the control population of CIBIS-II trial [18]. This suggests that the patients studied in these trials were highly selected, with respect to the general population of CHF patients whose annual mortality is around 20% despite therapy with ACE inhibitors [22,23].

Finally among patients coming from the “Randomized Evaluation of Strategies for Left Ventricular Dysfunction” (RESOLVD) trial, after four months of optimal therapy and maximal tolerated doses of ACE inhibitors, the metoprolol arm showed a 2.5 increase in risk of heart failure hospitalizations in comparison with the placebo arm, but no explanation for this finding was provided [24].

6. Responders to BB treatment

Subgroups of the heterogeneous population of CHF patients may respond differently to BB therapy or have not been specifically investigated in published trials. Of particular interest are those with more advanced CHF class (NYHA functional class IV). In one review of published data, patients with CHF in NYHA class IV were found to be more likely to develop adverse events during initiation and dose titration, when compared to less symptomatic patients [25]. Further data are necessary before applying this treatment to the generality of patients with advanced CHF: this is disappointing because the potential to save lives may be greater in this group.

The COPERNICUS (Carvedilol Prospective Randomized Cumulative Survival Trial) study recently and prematurely terminated enrolled patients in severe heart failure (2000 patients in class IV NYHA) because of evidence of significant benefit: full presentation of its results are therefore eagerly awaited.

Evidence is also lacking for symptoms-free patients with left ventricular dysfunction. Furthermore, little is known of their effects in children with cardiomyopathy. Only one multicentre study [26] has investigated the effect of adding metoprolol to standard therapy in children. Although there was a wide age-range (2 to 15 years) and only a small number of patients, 11 out of 15 showed significant improvement in left ventricular ejection fraction. Further data are warranted to better define children who may benefit most and which BB is most efficacious.

Most troublesome is the lack of data on the value of BB in the presence of co-morbidities (such as diabetes, chronic obstructive airway disease, renal failure, peripheral vasculopathy), or in CHF due to valvular disease, or diastolic dysfunction.

Finally more information is needed about the value of this therapy in older patients (>75 years) and female patients, groups that make up a large population of the CHF patients. BB can be tolerated well by older patients, but few studies have included these groups of patients [20], whose sizes will grow in the near future.

In order to identify the subgroups of patients who may potentially get more benefit from BB, it would be intellectually attractive to use elevated heart rate and high levels of catecholamines as predictor of good response [27], but this must be tempered by the finding of Woodley et al. [28] who found that patients with more advanced clinical condition or higher venous norepinephrine levels did not show greater improvement with BB.
7. BB therapy and CHF aetiology

As mentioned before, the aetiology of the CHF seems to play a key role in the response to BB therapy. Most of the less recent studies have been performed in non-ischaemic cardiomyopathy. Although well recognised by every cardiologist, they account for only 10 percent of all heart failure cases [29].

In fact in CHF mainly due to non-ischaemic origin, long term BB showed to result in significant haemodynamic improvement with increased left ventricular ejection fraction and stroke volume and to a decrease in pulmonary capillary wedge pressure. CIBIS trial [15] showed that only CHF without history of myocardial infarction improvement in prognosis was observed.

The only prospectively designed study to stratify the response to BB by aetiology in CHF was published by Woodley and co-workers in 1991 [28]. Beneficial effects in ejection fraction, pulmonary capillary wedge pressure, stroke work index were seen in idiopathic cardiomyopathy while in ischaemic the effects were smaller and not significant. However in this study, the population with ischaemic cardiomyopathy presented poorer clinical and haemodynamic conditions with respect to the idiopathic cardiomyopathy population: lower ejection fraction, poorer exercise capacity, and increased daily doses of diuretics. The higher benefit in the non-ischaemic population has been confirmed in a small recent study [30].

Yamada et al. have hypothesised that the reason for the poorer response in ischaemic cardiomyopathy, is that certain types of myocardial fibrosis may cause unresponsiveness to BB [31]. In an open study on patients with ischaemic cardiomyopathy, regional wall motion improved in severely akinetic segments but deteriorated in normally contracting segments. The therapeutic response was attenuated in patients in whom more than 50% of the left ventricle was akinetic [32].

Beta-receptor pathways have been found to differ between the two different aetiologies [33]. Thus it may be necessary to have a sufficient amount of viable myocardium to respond to BB. Patients with ischaemic CHF have a higher degree of beta-adrenergic receptor desensitisation and uncoupling with adenyl-cyclase: roles for ischaemia and scar development after myocardial infarction have been suggested.

More data are warranted to clarify the role played by the aetiology in the response to BB, as coronary artery disease is the leading cause of CHF. Interestingly, the recent CIBIS II study found benefit in ischaemic as well as non-ischaemic (in contrast to the predecessor CIBIS) and this was attributed to the different inclusion criteria adopted [34], while the meta-analysis of Heidenrech et al. [20] implied that both aetiological groups may benefit from BB.

The CHRISTMAS study (Carvedilol Hibernating Reversible Ischaemia Trial; Marker of Success) has been recently designed to investigate the effect of substrate in CHF patients and ischaemic heart disease, and in particular whether hibernating or stunned myocardium, in contrast to myocardium scar, may respond particularly to BB.

8. Final open questions on BB therapy in CHF

8.1. Which BB drug?

Different BB agents, with different pharmaco-dynamic properties, have been investigated (Table 1). One of the earliest and most frequently studied in CHF is metoprolol, a second-generation BB without specific vasodilating properties. Bucindolol is a vasodilative, non-cardioselective BB. Carvedilol is a third-generation BB that combines non-selective BB, alpha blockade, and antioxidant effects. It is the only BB approved by the US Food and Drug Administration for heart failure. A recent comparative study of these two agents showed parallel beneficial effects over 6 months on left ventricular ejection fraction (+5%), symptoms, and exercise tolerance (peak O₂ consumption +1 ml/kg/min) [35]. It was concluded that effect on cardiac function may be class effect, and selectivity or non-selectivity does not seem to be of importance. It is worth noting that this study, was plagued by a high dropout rate (20%) amongst those treated with either BB: such high rates are typical of BB studies on CHF, as outlined above. The on-going trial COMET, designed to compare the efficacy of metoprolol versus carvedilol in 3000 CHF patients, may provide further insight in this aspect.
However the results of a recent, prematurely ended trial (Beta Blocker Evaluation of Survival Trial, BEST) have shown that not all BB therapy are equal. In the BEST trial (n=2708) [36], bucindolol a non-selective BB with intrinsic sympathomimetic activity, failed to reduce mortality among patients with moderate-to-severe CHF. Experts are divided concerning the reason for this failure. It was hypothesised that the severity of the patient population may have played a role, but this explanation was ruled out when the COPERNICUS study was prematurely stopped due to evidence of benefit in severe CHF. Others have suggested that BB may not be indicated for African-American patients (who comprised 23% of the population): but this does not seem the case as subanalysis of other studies involving African-American patients failed to show any gender effect [37].

8.2. Where should we start the BB therapy in CHF patients?

The initiation of BB can be associated with transient deterioration of symptoms and therefore it should involve careful up-titration over several weeks. Although an ability to predict who is at highest risk of adverse event would be valuable in utilising scarce resources, the PRECISE trial indicates that this is not yet possible [38]. Current clinical guidelines therefore emphasise the importance of a long, step-by-step titration of the drug under strict surveillance. Thus in some units it is current policy to start the BB therapy only on in-patients, following the protocol of the CIBIS trial [15]. Furthermore, withdrawal from BB also presents potentially serious problems and physicians must be willing to follow their patients carefully during BB withdrawal.

Therefore whether BB become standard therapy for heart failure will be greatly influenced by the clinicians overseeing patient care. Cardiologists manage less than a fifth of heart failure patients. The rest are treated by general practitioners. Among their patients with heart failure, general practitioners are treating about half with ACE inhibitors. It seems unlikely that these physicians will take the extensive steps necessary to add BB if their patients are clinically stable.

8.3. Increased stroke with BB in CHF?

One worrying finding of the CIBIS-II study was an increased admission rate for stroke in patients on bisoprolol [18]. The results were not discussed in details nor was it stated whether this occurred predominantly among patients with very low ejection fraction. The study included patients in NYHA class IV, with higher risk of thrombus formation in the heart. One possible explanation is that improvements in ventricular performance by BB may result in thrombus release and embolic stroke (a situation analogous to the increased stroke risk around the time of conversion of atrial fibrillation, resulting from restoration of atrial contraction). The recommendation of anticoagulation therapy in CHF [39] may need to be strengthened for patients on BB therapy.

9. Conclusion

In our opinion, currently available data indicating improvements in haemodynamics, clinical symptoms and prognosis are still raising some concerns regarding the widespread use of BB in all patients with CHF.

To the patient, CHF is principally a disorder of exercise intolerance, and we ought to establish that exercise capacity is improved across a broad spectrum of patients before recommending widespread use.

The experience with other agents in CHF, such as positive inotropes (that produce favourable acute haemodynamic and clinical effects) and moxonidine (that significantly reduces sympathetic tone) which later were found to increase medium- and long-term mortality indicates the importance of getting more data before routinely using BB in CHF. Our current fascination with the ‘hard’ endpoint of mortality may blind us to the fact that many patients may be more interested in adding quality rather than quantity to their lives. There is no reason to assume that all patients would balance the trade-off between quality and quantity in the same way. Just as some might prefer to receive few days of median survival in return for yielding the symptomatic benefit of milrinone, there may be many more who are unwilling to face a deterioration in symptoms and quality of life in return for the possibility of an increase in life expectancy on BB treatment.

Further investigation of the effects of BB in CHF of ischaemic aetiology is warranted, as there is some
evidence that this may respond differently from idiopathic. For this reason, new and update guidelines, such as those proposed by the Italian Association of Hospital Cardiologists (ANMCO), may be valuable in helping physicians to select CHF patients before starting BB therapy [40].

References


[27] Engelmeier RS, O’Connell JB, Walsh R, Rad N, Scanlon PJ, Gunnar RM. Improvement in symptoms and exercise tolerance by meto-
[36] Eichhorn EJ. Personal Communication. 72nd Scientific Session of the AHA, Atlanta, USA, 7–10 November 1999