Prognostic benefit of beta-blockers in patients not receiving ACE-Inhibitors

Henry Krum¹*, Steven Joseph Haas¹, Eric Eichhorn², Jalal Ghali³, Edward Gilbert⁴, Philippe Lechat⁵, Milton Packer⁶, Ellen Roecker⁷, Patricia Verkenne⁸, Hans Wedel⁹, and John Wikstrand¹⁰,¹¹

¹NHMRC Centre of Clinical Research Excellence in Therapeutics. Departments of Epidemiology and Preventive Medicine and Medicine, Monash University Central and Eastern Clinical School, Alfred Hospital, Melbourne 3004, Australia;²Cardiology Division, Department of Internal Medicine, University of Texas Southwestern and Dallas VA Medical Centers, Dallas, TX, USA;³Cardiac Centers of Louisiana, Shreveport, LA, USA;⁴Division of Cardiology, School of Medicine, University of Utah, Salt Lake City, UT, USA;⁵Pharmacology Department, Pitie-Salpetriere Hospital, Paris, France;⁶Division of Circulatory Physiology, Columbia University College of Physicians and Surgeons, New York, NY, USA;⁷University of Wisconsin, Madison, WI, USA; and ¹Global Head Established Products—Clinical Research, Merck KGaA, Darmstadt, Germany;⁸Nordic School of Public Health, Göteborg, Sweden;¹⁰Wallenberg Laboratory for Cardiovascular Research, Sahlgrenska University Hospital, Göteborg, Sweden; and ¹¹AstraZeneca, Mölndal, Sweden

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Aims Beta-blockers (BBs) confer significant prognostic benefit in patients (pts) with systolic chronic heart failure (CHF). However, major trials have thus far studied BBs mainly in addition to ACE-Inhibitors or angiotensin receptor blockers (ARBs) as background therapy. The magnitude of the prognostic benefit of BBs in the absence of ACE-I or ARB has not as yet been determined.

Methods and results We performed a meta-analysis of all placebo-controlled BB studies in patients with CHF (n > 200). Trials were identified via Medline literature searches, meeting abstracts, and contact with study organizations. Results for all-cause mortality and death or heart failure hospitalization were pooled using the Mantel–Haenszel (fixed effects) method. The impact of BB therapy on all-cause mortality in CHF, in the absence (4.8%) and presence (95.2%) of ACE-I (or ARB), was determined from six trials of 13 370 patients. The risk ratio (RR) for BBs vs. placebo was 0.73 [95% confidence interval (CI) 0.53–1.02] in the absence of ACE-I or ARB at baseline, compared with a RR of 0.76 (95% CI 0.71–0.83) in the presence of these agents. When ACE-Inhibitors were analysed in the same way (pre-BB), a RR of 0.89 (0.80–0.99) vs. placebo was observed in studies of >90 days. The impact of BB therapy on death or HF hospitalization in systolic CHF, in the absence and presence of ACE-I, was determined from three trials of 8988 patients. The RR for BBs vs. placebo was 0.81 (95% CI 0.61–1.08) in the absence of ACE-I or ARB at baseline, compared with a RR of 0.78 (95% CI 0.74–0.83) in the presence of these agents. When ACE-Is were analysed in the same way (pre-BB), a RR of 0.85 (95% CI 0.78–0.93) vs. placebo was observed in studies of >90 days.

Conclusion The magnitude of the prognostic benefit conferred by BBs in the absence of ACE-I appears to be similar to those of ACE-Is in systolic CHF. These data therefore suggest that either ACE-Is or BBs could be used as first-line neurohormonal therapy in patients with systolic CHF. Prospective studies directly comparing these agents are required to definitively address this issue.

KEYWORDS Chronic heart failure; Beta-blocker; ACE-Inhibitor; Mortality; Hospitalization

Introduction

Beta-blocker (BB) therapy has been found to be clinically beneficial when studied in the treatment of established systolic chronic heart failure (CHF). However, these trials have generally been designed to evaluate the efficacy of BBs as add-on therapy to background ACE-Inhibitors (or angiotensin receptor blockers, ARBs). Therefore, it has been difficult to elucidate the magnitude of the benefit conferred by BB therapy in the absence of ACE-Inhibitors (or ARBs).

Thus, the aim of the present study was to perform a meta-analysis regarding the clinical effects of BB therapy (for all-cause mortality and death or heart failure hospitalization) in systolic CHF patients not receiving background ACE-Inhibitor (or ARB) at baseline, within the major placebo-controlled BB trials.
**Methods**

We identified via Medline and EMBASE search, as well as search of abstracts at key cardiology meetings, placebo-controlled mortality trials of BB therapy in patients with established systolic CHF ($n > 200$), in which details of baseline ACE-Inhibitor and ARB usage among study participants was published. We then communicated directly with the study organizers to obtain the required information regarding clinical outcomes in patients who were and were not receiving background ACE-Inhibitor or ARB at baseline. Study investigators provided numbers of patients and events according to use or non-use of baseline ACE-Inhibitor or ARB. Investigators from all six studies identified responded with these data.

Results of individual trials for all-cause mortality and death or heart failure hospitalization were pooled using the Mantel–Haenszel (fixed effects) method of meta-analysis using the STATA version 7.0 program. STATA calculates relative risks and 95% confidence intervals (CIs) for each study involved in the meta-analysis and assigns relative weights according to the contribution of each study to each analysis. Tests of heterogeneity were performed. Statistical significance was set at the 0.05 level on the basis of two-way z-tests and $\chi^2$ tests.

Historical comparison of ACE-Inhibitor efficacy in the pre-BB era of systolic CHF management was performed using the same methodology, on the basis of data derived from the systematic review of Garg and Yusuf. $^2$ Raw event data was re-analysed utilizing the logit, on the basis of data derived from the systematic review of systolic CHF management was performed using the same methodology.

Two of the six studies were able to provide baseline demographic and clinical data on patients who were and were not receiving background ACE-Inhibitor or ARB at baseline.

**Baseline characteristics of patients who were or were not receiving ACE-Inhibitor or ARB at baseline**

Two of the six studies were able to provide baseline demographic and clinical data on patients who were and were not receiving ACE-Inhibitor or ARB as background therapy at baseline.

In the COPERNICUS$^5$ study, patients were well matched within the two groups (i.e. ACE-Inhibitor/ARB yes or no) for age, gender, left-ventricular ejection fraction, etiology of heart failure, systolic blood pressure, heart rate, serum sodium, and per cent hospitalized for heart failure within the previous 12 months.

However, within COPERNICUS, patients not on ACE-Inhibitor (or ARB) at baseline had a higher serum creatinine (150 ± 47 $\mu$mol/l) compared with those who were receiving these agents (133 ± 36 $\mu$mol/l), $P = 0.021$ for difference. In addition, there was greater use of spironolactone in patients not receiving ACE-Inhibitor (or ARB) at baseline (31%) compared with those who were receiving these agents (19%), $P < 0.02$ for difference.

In the MERIT-HF$^2$ study, patients in the two groups were well matched at baseline for race, gender, systolic and diastolic blood pressure, heart rate, and NYHA class. However, patients not receiving ACE-Inhibitors or ARBs at baseline were significantly older ($P < 0.05$), had lower body mass index, higher serum creatinine, and lower use of calcium channel blockers and nitrates than the majority who were receiving background ACE-Inhibitors or ARBs.

**Results**

**BB systolic CHF trials meeting meta-analysis criteria**

**BB CHF trials that met the criteria for this meta-analysis are listed in Table 1.** Six trials met these criteria enrolling a total of over 13 000 patients.$^{3–8}$ 4.8% of these patients within these trial cohorts were not receiving background ACE-Inhibitor or ARB at baseline.

**Table 1. BB CHF mortality trials meeting criteria for meta-analysis**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Beta-blocker</th>
<th>$n$</th>
<th>% on ACE-I/ARB</th>
<th>Entry criteria</th>
<th>Duration (months)</th>
<th>Study primary endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>BEST</td>
<td>Bucindolol</td>
<td>2708</td>
<td>91.0</td>
<td>III–IV, EF &lt;35</td>
<td>24</td>
<td>Death from any cause</td>
</tr>
<tr>
<td>CIBIS-I</td>
<td>Bisoprolol</td>
<td>641</td>
<td>89.7</td>
<td>III–IV, EF &lt;40</td>
<td>21</td>
<td>Mortality</td>
</tr>
<tr>
<td>CIBIS-II</td>
<td>Bisoprolol</td>
<td>2647</td>
<td>96.2</td>
<td>III–IV, EF &lt;35</td>
<td>15.6</td>
<td>All-cause mortality</td>
</tr>
<tr>
<td>COPERNICUS</td>
<td>Carvedilol</td>
<td>2289</td>
<td>97.0</td>
<td>III–IV, EF &lt;25</td>
<td>10.4</td>
<td>Death from any cause</td>
</tr>
<tr>
<td>MERIT-HF</td>
<td>Metoprolol CR/XL</td>
<td>3991</td>
<td>89.5</td>
<td>II–IV, EF ≤40</td>
<td>12</td>
<td>All-cause mortality and all-cause mortality in combination with all-cause admission to hospital</td>
</tr>
<tr>
<td>US carvedilol</td>
<td>Carvedilol</td>
<td>1094</td>
<td>95.0</td>
<td>II–IV, EF &lt;35</td>
<td>6.5</td>
<td>Mortality</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>13370</td>
<td>95.2</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Only three BB blocking agents have been found to be of clinical benefit and are thus utilized in medical practice in the treatment of systolic CHF. These agents are bisoprolol, carvedilol, and extended-release metoprolol.5–8 Five of the six trials meta-analysed evaluated these treatments,5–8 the exception being BEST3 (which studied bucindolol).

When data for clinically utilized beta-blocking agents were analysed for mortality in a similar manner to the preceding meta-analysis, it was observed that a RR of 0.67 was obtained for both groups: 0.67 (95% CI 0.43–1.04, \( P = 0.073 \)) inpatients not receiving ACE-Inhibitor/ARB at baseline and 0.67 (95% CI 0.43–1.04, \( P = 0.073 \)) for those who were receiving these agents.

The effect of ACE-Inhibitor therapy on all-cause mortality in patients with systolic CHF in the pre-BB era of CHF management was assessed from re-analysis of the Garg dataset.2

In studies of >90 days duration, the RR was 0.89 (95% CI 0.80–0.99). Overall, the RR was 0.85 (95% CI 0.77–0.94).

### Table 2: Effect of BB vs. placebo in CHF patients who were or were not receiving ACE-Inhibitor or ARB at baseline

<table>
<thead>
<tr>
<th>Study</th>
<th>PBO n</th>
<th>BB n</th>
<th>RR (95% CI)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>BEST</td>
<td>25</td>
<td>93</td>
<td>0.84 (0.51–1.39)</td>
<td>38.1</td>
</tr>
<tr>
<td>CIBIS-I</td>
<td>4</td>
<td>29</td>
<td>0.43 (0.08–2.16)</td>
<td>6.6</td>
</tr>
<tr>
<td>CIBIS-II</td>
<td>8</td>
<td>46</td>
<td>1.28 (0.57–2.85)</td>
<td>13.2</td>
</tr>
<tr>
<td>COPERNICUS</td>
<td>11</td>
<td>32</td>
<td>0.53 (0.22–1.26)</td>
<td>17.0</td>
</tr>
<tr>
<td>MERIT-HF</td>
<td>12</td>
<td>76</td>
<td>0.62 (0.28–1.39)</td>
<td>20.0</td>
</tr>
<tr>
<td>US carvedilol</td>
<td>2</td>
<td>19</td>
<td>0.10 (0.00–1.89)</td>
<td>5.2</td>
</tr>
<tr>
<td>Total</td>
<td>62</td>
<td>295</td>
<td>0.73 (0.53–1.02)</td>
<td>37.6</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study</th>
<th>PBO n</th>
<th>BB n</th>
<th>RR (95% CI)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>BEST</td>
<td>424</td>
<td>1261</td>
<td>0.92 (0.82–1.03)</td>
<td>37.6</td>
</tr>
<tr>
<td>CIBIS-I</td>
<td>63</td>
<td>292</td>
<td>0.63 (0.59–1.15)</td>
<td>5.5</td>
</tr>
<tr>
<td>CIBIS-II</td>
<td>220</td>
<td>1274</td>
<td>0.66 (0.54–0.80)</td>
<td>19.5</td>
</tr>
<tr>
<td>COPERNICUS</td>
<td>179</td>
<td>1101</td>
<td>0.68 (0.55–0.84)</td>
<td>16.0</td>
</tr>
<tr>
<td>MERIT-HF</td>
<td>205</td>
<td>1925</td>
<td>0.67 (0.55–0.83)</td>
<td>18.1</td>
</tr>
<tr>
<td>US carvedilol</td>
<td>29</td>
<td>379</td>
<td>0.44 (0.26–0.75)</td>
<td>3.3</td>
</tr>
<tr>
<td>Total</td>
<td>1120</td>
<td>6232</td>
<td>0.76 (0.71–0.83)</td>
<td>37.6</td>
</tr>
</tbody>
</table>

**Figure 1** Effect of BB vs. placebo in CHF patients who were not (left panel) or were (right panel) receiving ACE-I or ARB at baseline.

**Endpoint of death or heart failure hospitalization**

Three studies contributed data to the endpoint of death or HF hospitalization. These studies were BEST,3 COPERNICUS,6 and MERIT-HF7.

Inpatients who were receiving ACE-Inhibitor or ARB at baseline, the overall RR was 0.78 (95% CI 0.74–0.83, \( P < 0.001 \)). Inpatients who were not receiving ACE-Inhibitor or ARB at baseline, the RR was 0.81 (95% CI 0.61–1.08, \( P = 0.148 \)). Direct head-to-head comparison of these CIs revealed no statistically significant difference (\( P = 0.8136 \) via z-test).
There was an increase in death or CHF hospitalization events in patients not receiving ACE-Inhibitor or ARB at baseline vs. those who were. There was a beneficial impact of BB therapy in both groups (Figure 3).

The effect of ACE-Inhibitor therapy in systolic CHF in the pre-BB era of CHF management was assessed from re-analysis of the Garg dataset, with reference to the endpoint of death or heart failure hospitalization.

The RR for ACE-Inhibitor therapy vs. placebo on the endpoint of death or heart failure hospitalization in studies of 90 days duration was 0.85 (95% CI 0.78–0.93). Overall, there was a RR of 0.66 (95% CI 0.61–0.71), favouring ACE-Inhibitor therapy.

Discussion

The present meta-analysis observed an approximately similar impact of BB therapy on the endpoints of all-cause mortality as well as death and heart failure hospitalization in both the presence and absence of ACE-Inhibitor or ARB at baseline. When compared with ACE-Inhibitors analysed the same way in the pre-BB era of systolic CHF management, the relative risk reduction achieved with beta-blockade appeared similar to or exceeded that of ACE-Inhibitor therapy in studies of >90 days.

Therefore, the findings of the present study would suggest that BBs could be considered as an alternative first-line neurohormonal agent in a manner analogous to the way ACE-Inhibitor therapy is currently prescribed. The widespread utilization of neurohormonal blocking therapy and guidelines recommendations supporting ACE inhibition prior to the introduction of beta-blockade therefore appears to be primarily based on the historical sequence of study of these agents, i.e. ACE-Inhibitor therapies were studied before beta-blockade. The BB studies were thus performed in the era of background ACE-Inhibitor therapy in the majority of patients.

There are a number of theoretical reasons why BB therapy may be advantageous early in the course of CHF disease management. Firstly, sympathetic activation occurs before renin–angiotensin system activation in CHF. Thus, the adverse consequences of activation of the sympathetic nervous system theoretically need to be intervened on as early as possible to maximize therapeutic benefit in this setting.

Next, BBs have been demonstrated to reduce sudden death, a beneficial effect not as readily observed with renin–angiotensin blocking therapies. Given that sudden death is a more frequent mode of death early in the course of HF disease progression than in the end-stages this may be of substantial clinical benefit.

Finally, the anti-remodelling effects of beta-blockade appear to be greater in magnitude than that observed for ACE-Inhibitors.

On the other hand, initiating therapy with an ACE-Inhibitor may provide a beneficial early unloading effect in the left ventricle.

The previous observations are supported by the findings of a recent randomized trial comparing initiation of BB (carvedilol) to ACE-Inhibitor in systolic HF patients. In that study, left-ventricular function, brain natriuretic peptide, and achieved carvedilol dose were all improved with a BB first strategy.

The previous observations are no substitute for a prospective randomized major clinical outcome trial comparing the two strategies head-to-head over the period of initiation of therapy. Such a study is currently under way (CIBIS III).

Caveats

There are a number of important caveats to consider in analyses such as that presented in the present manuscript. Firstly, patients able or unable to tolerate ACE-Inhibitor or ARB at baseline may differ. There is clear evidence from the baseline characteristics of the patients evaluated in the present study (at least from COPERNICUS and MERIT-HF) that this is indeed the case. In addition, differences between the two groups were observed in rates of clinically significant events, among placebo treated patients particularly combined death and heart failure hospitalization.

Crude RRs were evaluated in assessing the impact of these therapies. We were unable to use hazard ratios and Cox proportional hazards modelling to take into account time to these events occurring.

As with all meta-analyses, there is heterogeneity in study design, patient populations and outcomes within individual trials that may make these studies difficult to interpret. Indeed, heterogeneity was noted in a number of analyses performed when $\chi^2$ testing was performed.

There was a relatively small number of events noted in the group of patients not receiving ACE-Inhibitor or ARB in comparison with the overall group of patients within the
meta-analysis. These small numbers of events greatly increase the possibility of spurious results within individual trials and possibly in the overall analysis.

The 95% CIs for the benefit of beta-blockade in patients not on ACE-Inhibitors crosses the line of no effect, therefore it cannot be definitively concluded that BBs are beneficial in the absence of ACE-Inhibitors.

Finally, comparisons with the older ACE-Inhibitor trials were retrospective, historical and post hoc in nature.

Conclusions

Despite the caveats outlined previously, the magnitude of the prognostic and morbidity/mortality benefit of BBs in the absence of ACE-Inhibitor or ARB appeared in this analysis to be similar to those of ACE-Inhibitors.

These data therefore suggest that either ACE-Inhibitors or BBs could be used as first-line neurohormonal therapy in patients with systolic CHF. Prospective trials, directly comparing these two strategies, are required to definitively address this issue.

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