CHAPTER 5

Chapter 6

Beta-blockers and Outcome in Heart Failure and Atrial Fibrillation: A Meta-Analysis

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Summary

Background
Beta-blockers are widely used in patients with heart failure (HF) and atrial fibrillation (AF). Recommendation for these drugs in current HF guidelines, however, is based on populations in which the majority had sinus rhythm. Whether beta-blockers are as useful in atrial fibrillation (AF) is uncertain. We assessed the effect of beta-blockade on outcome in patients with HF and AF.

Methods
For this meta-analysis we used Medline to identify randomised controlled studies. Information about study design, sample characteristics, and outcome (HF hospitalization and mortality) was extracted.

Findings
We identified 4 studies which enrolled 8680 patients with HF and reduced systolic left ventricular function, and 1677 of them had AF (19%; mean age 69 years, 30% women); there were 842 patients treated with beta-blockers, and 835 with placebo. In patients with AF, beta-blockade did not reduce mortality (odds ratio (OR) = 0.86 (0.66-1.13), P = 0.28), while in patients with sinus rhythm there was a significant reduction (OR 0.63 (0.54-0.73), P<0.0001). There was a significant difference in the effect of beta-blocker therapy in AF versus sinus rhythm (P = 0.046). By meta-regression analysis we did not find confounding by all relevant covariates. When looking at HF hospitalizations in these studies, beta-blocker therapy was not associated with a reduction in patients with AF (OR 1.11 (0.85-1.47), P = 0.44), in contrast to those with sinus rhythm (OR 0.58 (0.49-0.68) P<0.0001) (P = 0.01 for difference in beta-blocker therapy effect between AF and sinus rhythm).

Interpretation
The effect of beta-blockers on outcome in HF patients who have AF is different than in those who have sinus rhythm. This finding may have implications for the place of these drugs in patients with AF and HF.

Funding
None.

Introductions
Beta-blockers are a cornerstone in the treatment of patients with heart failure (HF).1 Large scale trials with carvedilol (US Carvedilol Study2 and COPERNICUS3-4), metoprolol (MERIT-HF5), bisoprolol (CIBIS-II6), and nebivolol (SENIORS7) have shown that these drugs reduce morbidity and mortality in HF. As a result, they are now widely used and have received a class IA recommendation in current HF guidelines.1 Atrial fibrillation is common in HF, and depending on the severity of HF, occurs in up to 30-40% of all patients.8 The large HF trials that led to the recommendations also included a significant proportion of patients with AF. In current guidelines for HF the recommendation for beta-blockers is not restricted to patients with sinus rhythm, and indeed includes all HF patients, i.e. also those with AF, but it is unknown whether beta-blockers are equally effective and safe in these patients, as they are in those with sinus rhythm.

In patients with sinus rhythm with and without HF, lower heart rate is associated with a better outcome,9-11 and reduction of heart rate (by beta-blockers) probably plays an important role in the beneficial effect of these drugs. In patients with AF, with or without HF, lower heart rate, however, is not associated with a better outcome as was shown recently.12 Although patients with AF were included in the large HF trials, the absolute number of patients with AF in each individual study was rather limited.13-16 The aim of the present meta-analysis was therefore to assess the effect of beta-blockade on outcome (i.e. mortality and hospitalization for HF) in patients with both HF and AF.

Methods

Literature Search
We searched MEDLINE using search tools provided by Pubmed (http://www.ncbi.nlm.nih.gov/pubmed/clinical; used April 1st 2012) and via OVID. These search tools have been validated by Haynes et al. to optimize retrieval.17 We also used keywords including atrial fibrillation, heart failure, beta-blocker therapy, beta-blockade, medical therapy and a combination of these, and included papers published in English language. Furthermore, we reviewed reference lists from eligible studies, used the “see related articles” feature for key publications in PubMed, consulted the Cochrane Library, and searched
the ISI Web of Knowledge http://scientific.thomson.com/webofknowledge) for publications that cited key publications.

**Study Selection**

Studies were included which investigated the effect of placebo-controlled, randomized beta-blocker therapy in patients with AF at baseline, and HF with reduced systolic left ventricular ejection fraction (LVEF < 40%). We restricted our final search to beta-blockers that are registered for HF treatment, i.e. metoprolol, carvedilol, bisoprolol, nebivolol. For this reason one large outcome trial which examined bucindolol (BEST) was not included. One study (SENIORS) included both patients with reduced and preserved left ventricular ejection fraction. For the present analysis we only included patients with LVEF < 35%, since this was the cut-off used in that study, both in the methodology in the main study, and in the separate publication of the 2 groups. The subgroup of patients with AF and HF with a preserved ejection fraction are not presented here since beta-blockers are not recommended in these patients. The primary and secondary analysis consisted of secondary analyses of randomized controlled trials. Articles were excluded if: a) no data was available for outcome, b) data was only published in abstract form and c) no definition for HF was given: either by combination of symptoms and signs (using New York Heart Association functional class or physical examination), imaging (impaired left ventricular ejection fraction) or a combination of both. The primary outcome measure was defined as all cause mortality. Secondary outcome variable included heart failure hospitalization as reported in the individual reports. Furthermore, we evaluated the beta-blocker effect in both patients with AF and in those with sinus rhythm included in the same studies.

**Assessment of quality of studies for inclusion in analysis**

The quality of the individual studies was assessed by eleven factors: 1) sufficiently specified inclusion and exclusion criteria, 2) sufficient explanation of sample selection, 3) Specification of clinical and demographic variables, 4) representation of the study sample for the mentioned patient population, 5) specification of outcome measures, 6) definition of AF, 7) assessment of a dose-response relationship between beta-blocker therapy and outcome, 8) adjustment for possible confounders in the analysis, 9) reporting of lost to follow-up rates, 10) study design and 11) duration of follow up. Grading was as follows; good quality: eight-11 criteria, fair quality: five-seven criteria and poor quality: < five criteria.

**Statistical Analysis**

Meta-analysis was performed using a fixed-effects model to determine risk associated with beta-blocker therapy and all-cause mortality, as measured by combined crude mortality rates. In the secondary analysis, heart failure hospitalizations were studied in a similar matter. For comparison with patients in sinus rhythm, subgroup analysis was carried out by testing of heterogeneity across subgroups. Among studies heterogeneity of risk estimates was examined using a standard chi-square test and I² statistic for heterogeneity. I² is the percentage of variance that is due to between-study variance. Reasons for diversity in study results were explored using meta-regression analysis. Variables explored included age, sex, hypertension, diabetes, ischemic heart disease, left ventricular ejection fraction, heart rate, blood pressure and medical treatment. Results are presented as odds ratios (ORs) with their 95% confidence intervals (CIs) and p values. Evidence of publication bias was assessed by visual inspection of the Funnel plot. A P value of < 0.05 was considered statistically significant. Statistical analyses were performed using Stata 10.0, College Station, Texas and Revman 5.1.

**Role of the funding source**

No sponsor of any of the individual trials had any role in the study design, data collection, data interpretation, drafting, or review of the report.

**Results**

**Study search and general characteristics**

The search retrieved 248 citations, of whom four fulfilled all criteria as they investigated the randomized treatment allocation of beta-blocker therapy in patients with HF and AF (Figure 1). All of these studies were specific AF substudies from large HF outcome trials (US-Carvedilol, CIBIS II, MERIT-HF, and SENIORS) that studied the effect of beta-blockers. We were not able to retrieve data from one other large HF beta-blocker study (COPERNICUS), since presence of AF on electrocardiograms at baseline...
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Table 1. Study characteristics.

<table>
<thead>
<tr>
<th>First Author</th>
<th>Study</th>
<th>Published</th>
<th>F/U</th>
<th>N (% of total sample)</th>
<th>Type Patients</th>
<th>Endpoints</th>
<th>Major Exclusion Criteria</th>
<th>HR Reduction by beta-blocker (bpm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Joglar**</td>
<td>US-Carvedilol</td>
<td>2001</td>
<td>Max 400 days</td>
<td>136 (12%)</td>
<td>HF LVEF ≤ 35%</td>
<td>All-cause mortality</td>
<td>Stable HF Heart rate &lt; 68 bpm Class I or III anti-arrhythmic drugs</td>
<td>-13 in AF</td>
</tr>
<tr>
<td>Lechat††</td>
<td>CIBIS-II</td>
<td>2001</td>
<td>Max 800 days</td>
<td>521 (21%)</td>
<td>HF LVEF ≤ 35% NYHA III-IV</td>
<td>All-cause mortality HF Hospitalizations</td>
<td>Stable HF Heart rate &lt; 60 bpm Anti-arrhythmic drugs other than amiodarone</td>
<td>-8.8 in AF -10.8 in SR</td>
</tr>
<tr>
<td>Van Velthuisen†‡</td>
<td>MERIT-HF</td>
<td>2006</td>
<td>Mean F/U 1 year</td>
<td>556 (14%)</td>
<td>HF LVEF ≤ 40% NYHA II-IV</td>
<td>All-cause mortality HF Hospitalizations</td>
<td>Stable HF Heart rate &lt; 68 bpm CCB or Amiodarone</td>
<td>-14.8 in AF -13.7 in SR</td>
</tr>
<tr>
<td>Mulder**</td>
<td>SENIORS</td>
<td>2011</td>
<td>Mean F/U 21 months</td>
<td>464 (22%)</td>
<td>≥ 70 years HF admission &lt; 1 year or LVEF ≤ 35%</td>
<td>All-cause mortality</td>
<td>Stable HF BBL</td>
<td>-11 in AF -10.9 in SR</td>
</tr>
</tbody>
</table>

Only patients from SENIORS with LVEF ≤ 35% were included.

was similar for AF and sinus rhythm, although the baseline and end-of-titration heart rate were higher in AF patients. Dosages of beta-blockers were comparable in CIBIS-II, MERIT-HF, and SENIORS (no data of US-Carvedilol).

All-cause mortality. Follow up duration of the included studies ranged between a maximum of 13 months in the US-carvedilol study to a mean of 21 months in SENIORS. The crude mortality rates of AF patients with beta-blocker therapy versus those without were 13.5% and 15.7%, respectively, and for sinus rhythm with and without beta-blocker therapy 8.3% and 13.1%, respectively. This resulted in a combined mortality risk for AF patients of OR = 0.86 (0.66 – 1.13), P = 0.28 for beta-blocker therapy, versus a combined mortality risk for sinus rhythm patients of OR = 0.69 (0.54 – 0.87), P < 0.001 for beta-blocker therapy (Figure 3). There was a difference in the effect of beta-blocker therapy in AF versus sinus rhythm (P = 0.046). There was no heterogeneity observed among the studies with AF included (I² = 0%, P = 0.46). We performed meta-regression analysis to determine factors explaining possible confounding. We found no confounding by any of the explored variables. Figure 4 shows the Funnel plot for the main outcome analysis, which shows no evidence of publication bias.

Heart failure hospitalisations
Three of the four studies investigated the effect of beta-blocker therapy on HF hospitalisations, including 7586 HF patients with reduced systolic left ventricular function (1541 (20%) AF patients).

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Mean [IQR]</th>
<th>SD [IQR]</th>
<th>Total Mean</th>
<th>Total SD</th>
<th>Total [IQR]</th>
<th>Weight</th>
<th>N, Fixed/95% CI [IQR]</th>
<th>Mean Difference N, Fixed/95% CI [IQR]</th>
</tr>
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<tbody>
<tr>
<td>AF</td>
<td></td>
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<td></td>
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<td></td>
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<tr>
<td>CIBIS-II</td>
<td>-0.6</td>
<td>21.5</td>
<td>257</td>
<td>-0.2</td>
<td>137</td>
<td>204</td>
<td>4.9%</td>
<td>-9.90 (-11.15, -8.65)</td>
</tr>
<tr>
<td>MERIT-HF</td>
<td>-4.0</td>
<td>21.5</td>
<td>274</td>
<td>-4</td>
<td>23</td>
<td>202</td>
<td>3.4%</td>
<td>-19.30 (-24.10, -14.51)</td>
</tr>
<tr>
<td>SENIORS</td>
<td>-11</td>
<td>21.5</td>
<td>277</td>
<td>-28</td>
<td>22</td>
<td>286</td>
<td>4.1%</td>
<td>-8.39 (-11.08, -4.70)</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>All-cause mortality</td>
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<tr>
<td>Heart failure hospitalisations</td>
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<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>1.8</td>
<td>2.0</td>
<td>1.4</td>
<td>1.6</td>
<td>32</td>
<td>100</td>
<td>0.0%</td>
<td>10.13 (10.06, 10.19)</td>
</tr>
</tbody>
</table>

Beta-blocker therapy in AF patients was not associated with a reduction of HF hospitalisations (14.8% versus 16.2% events), resulting in an OR of 1.11 (0.85 – 1.47), P = 0.44 (Figure 2). In sinus rhythm patients (8.5% versus 14.3% events), beta-blocker therapy was associated with a reduction of HF hospitalisations (OR 0.58 (0.49 – 0.68), P < 0.00001). There was a difference in the effect of beta-blocker therapy in AF versus sinus rhythm (P < 0.001).

Discussion
The main finding of the present meta-analysis indicates that the effect of beta-blockers in patients with HF and AF is significantly different from the effect of these drugs in patients with HF and sinus rhythm. Indeed, beta-blockers were not found to have a favourable effect of HF hospitalisations or mortality in 1677 AF patients who had been enrolled in placebo-controlled, randomized studies.

This finding is important since HF patients with AF receive beta-blocker treatment. Beta-blockade is recommended in the current guidelines for HF and AF, albeit for different indications.1,22 In the HF guidelines, beta-blockers are recommended for all patients in order to reduce morbidity and mortality, without differentiation regarding rhythm (i.e. sinus rhythm or AF). As such, these drugs are part of the standard medical therapy for all patients with HF with reduced systolic left ventricular ejection fraction. In addition, beta-blocker therapy has been shown to prevent new-onset or recurrent AF in
In patients with sinus rhythm, it has been proven that a pronounced reduction in heart rate is associated with improved morbidity and mortality independent of the dose of the used beta-blocker, or by additive therapy with selective If-channel blockade. For patients with permanent AF, it was recently demonstrated, that a more strict rate control was not superior to a lenient rate control. Third, due to loss of the atrial kick and the irregularity in ventricular response during AF, patients with AF may need a higher heart rate to maintain a similar cardiac output, possibly even more so during heart failure.

Fourth, a low heart rate in patients with AF may be an expression of an underlying conduction disorder, which may be associated with impaired outcome itself. Finally, AF in patients with HF may be a marker of a poorer hemodynamic situation leading to a worse outcome. In addition to these potential explanations, we also cannot exclude the fact that the present findings could apply to some but not all beta-blockers, as differences in the pharmacological profiles of beta-blockers may have played a role. Metoprolol and bisoprolol are selective beta-1 receptor antagonists, and carvedilol and nebivolol are beta-blockers with additional vasodilating properties. A subanalysis of the COMET trial (in which there were 600 patients with AF) demonstrated that carvedilol had a

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Limitations

Although the number of AF patients in the included randomized studies was 1677, this is still rather low for survival analysis, and we cannot exclude the possibility that lack of power may have played a role. Nevertheless, although this number may have been small to detect an effect in the group of AF patients alone, there was a significant difference with regard to this (beta-blocker) treatment effect between AF and sinus rhythm patients, which further supports our findings. Also, in present analysis we pooled the effects of different beta-blocker therapies and thereby assumed a class-effect. However, specific differences in pharmacologic profiles may have added to the heterogeneity of our cohort and thereby results. Inherent limitations of pooled analysis of studies include the limited availability of confounding variables, including history of AF, duration of AF, pattern of AF (paroxysmal vs. persistent/permanent AF), new onset AF, dose response and tolerability of the drugs.

Conclusion

The present analysis shows that the effect of beta-blockade in HF patients with AF with regard to outcome is different than in HF patients with sinus rhythm. This may affect the place of these drugs in patients with AF and HF. Clearly, prospective randomized controlled trials in HF specifically aiming at AF patients are warranted to study the prognostic effects of beta-blockers in this population.
Conflicts of interest
Drs. Rienstra, Damman, and Mulder report no disclosures. Dr. Van Gelder received lecture fees from Bayer, Biotronik, Boehringer Ingelheim, BMS, Medtronic and Pfizer, and grant support from Medtronic and Biotronik.

References


