Optimizing therapy in patients with atrial fibrillation and heart failure
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CHAPTER 5

Introduction
Atrial fibrillation (AF) and chronic heart failure have been described as the two epidemics of cardiovascular disease of the 21st century. The prevalence of AF increases with advancing age and is also associated with severity of heart failure reaching almost 50% in New York Heart Association (NYHA) class IV. The prognostic impact of AF on hospitalization for heart failure and mortality remains, however, uncertain. Beta-blockers are recommended as routine treatment in stable chronic heart failure in order to improve survival and reduce hospital admissions for heart failure. Although it is generally assumed that the effects of beta-blockade in AF are similar to those in sinus rhythm, no clear advantageous effects of beta-blockade in heart failure patients with AF have been demonstrated so far. This was also observed in post-hoc analyses of the Cardiac Insufficiency Bisoprolol Study (CIBIS) II trial bisoprolol had no effect in patients with heart failure and AF. These trials were, however, restricted to younger patients with low ejection fraction, whereas the additional prognostic influence of AF in heart failure appears to be most evident in heart failure with a preserved ejection fraction. Furthermore, the potential benefits of beta-blockers may differ between heart failure patients with a preserved as compared with an impaired ejection fraction.

In the present prespecified subanalysis of the Study of Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors With Heart Failure (SENIORS) trial, we investigated the effects of nebivolol in elderly patients with heart failure and co-existing AF, irrespective of LVEF. In brief, SENIORS was a prospective, multi-center, multinational, double blind, placebo controlled, randomized, clinical trial comparing nebivolol with placebo in elderly patients with heart failure on optimal standard therapy. The first patient was included in September 2000, the last patient in December 2003. The clinical follow-up lasted 21 months. The primary outcome was all-cause mortality or cardiovascular hospitalizations.

Abstract
Aims
Beneficial effects of beta-blockade remain unclear in heart failure patients who have atrial fibrillation (AF), especially in the elderly. We evaluated the effect of nebivolol on cardiovascular outcomes in elderly patients with heart failure and AF.

Methods and Results
The SENIORS trial showed an overall benefit of nebivolol compared with placebo in 2128 heart failure patients >70 years of age. At baseline AF was present in 738 (34.7%) patients. The primary outcome was all-cause mortality or cardiovascular hospitalizations. After 21 months the cumulative incidence of the primary outcome was significantly more common in patients with AF compared with those with sinus rhythm (38.5% vs. 30.4%, respectively, p<0.001). In patients with AF nebivolol had no beneficial effect on the primary outcome (nebivolol versus placebo, 37.1% vs. 39.8%, hazard ratio [HR] 0.92, 95% confidence Interval [CI], 0.73-1.17, p=0.46), in contrast to patients with sinus rhythm (28.1% vs. 32.9%, in the nebivolol versus placebo group, respectively, HR 0.82 [95% CI 0.67-0.99] p=0.049). In patients with AF, the primary outcome was similar in the impaired and preserved left ventricular ejection fraction (LVEF) groups (39.0% with LVEF ≤ 35% vs. 37.3% in patients with LVEF > 35%). There was also no evidence of benefit of nebivolol in AF patients stratified by LVEF.

Conclusion
Nebivolol failed to improve outcomes in elderly patients with stable heart failure and co-existing AF, irrespective of LVEF. Furthermore, in patients with AF outcome was comparable between patients with preserved and impaired LVEF.
in December 2002. Relevant national and local ethics review boards and regulatory authorities approved the study. Inclusion criteria were age > 70 years, written informed consent, and a history of chronic heart failure with at least 1 of the following features: documented hospital admission within the previous 12 months with a discharge diagnosis of congestive heart failure or within the previous six months a documented left ventricular ejection fraction < 35%. Main exclusion criteria were any recent change in cardiovascular drug therapy, contraindications to beta-blockers, and significant hepatic or renal dysfunction. A total of 2128 patients were included, of which 1067 were randomized to nebivolol. Nebivolol or placebo tablets were provided in identical packaging and tablet appearance. Study medication was titrated over a 16-week period from a starting dose of 1.25 mg daily to a target of 10 mg daily.

The primary outcome was a composite of all-cause mortality or cardiovascular hospitalizations and secondary outcomes were all-cause mortality, the composite of all-cause mortality or hospital admission for heart failure, and sudden cardiac death (all time to first event). All reported deaths and hospital admissions were referred to the independent Clinical Events Review Committee, blinded to treatment. Baseline ejection fraction was measured by echocardiography in 94%, nuclear imaging in 4%, and magnetic resonance imaging in 2% of patients. During the first four months of follow-up patients were closely monitored as medication was carefully titrated. Target dose of nebivolol was 10 mg or the maximum tolerated dose for the individual patient. For the duration of the maintenance phase it was advised to maintain the dose on the same individual dose of the study drug until the end of the follow-up period. During the titration phase patients were required to attend study visits at 1-2 weeks intervals. In this phase they were seen at least 5 times. Maximum period of drug titration was 16 weeks and the minimum 4 weeks. During the maintenance period, the first visit took place after 16 weeks after randomization, the second visit after 6 months and thereafter in intervals of 3 months until the 30 months visit which was also the end of study visit. A physical examination was performed, changes in concomitant medication were documented and an electrocardiogram was performed at each follow-up visit. After 6, 9, 12, 15, 24 and 30 months of follow-up blood samples were taken to assess liver and renal function and plasma glucose.

Definition of atrial fibrillation
Patients were classified as AF when there was AF on the baseline electrocardiogram or if AF was documented in their medical history. Further information on duration of AF nor on the type of AF (paroxysmal, persistent, or permanent) was known.

Statistical methods
Baseline descriptive statistics are presented as mean ± standard deviation or median (range) for continuous variables and counts with percentages for categorical variables. Differences between groups were evaluated by the Student t test and otherwise the Mann-Whitney U test, depending on normality of the data. Chi-square and Fisher’s exact test were used for comparison of categorical variables. The statistical tests were 2-sided, and p<0.05 was taken as the level of significance. The influence of AF on the effects of nebivolol in the SENIORS trial population was measured as a dependent variable. Hazard ratios were calculated using Cox proportional hazards models, with 95% confidence intervals and interaction tests for subgroups presented as appropriate. The primary outcome of interest was the composite of all-cause mortality or cardiovascular hospital admission (time to first event), and the secondary outcome was all-cause mortality. Other exploratory outcomes, including cardiovascular hospitalization as the other component of the primary outcome, and effects of nebivolol stratified by baseline ejection fraction (< 35% and > 35%) are also presented where considered appropriate. Testing for an interaction between the efficacy of nebivolol compared with placebo and AF was performed by constructing a Cox proportional-hazards model using terms for both the main effect and the interaction (i.e. to test whether nebivolol is superior in either of the groups [AF or sinus rhythm group]). An intention-to-treat analysis was used throughout.

Results
Patients
The present subanalysis of SENIORS consists of all (n=2128) patients who participated in the original SENIORS trial and followed up for a mean of 21 months, of whom 738 patients (34.7%) had AF documented on electrocardiogram at study entry. Baseline characteristics of patients with AF.
and sinus rhythm are shown in Table 1. Patients with AF were older, had a higher NYHA classification for heart failure, and less often coronary artery disease or diabetes. The heart rate at baseline in the AF group was 83±16 beats per minute. The nebivolol and placebo groups were well balanced in patients with AF (Table 2) as well in those with sinus rhythm (data not shown). Furthermore, dosages of nebivolol were equal between both groups.

Influence of atrial fibrillation on primary outcome
A total of 284 patients (38.5%) in the AF group and 423 patients (30.4%) in the sinus rhythm group reached the primary outcome of all-cause mortality or cardiovascular hospitalization (Figure 1, p<0.001). There was no significant difference in all-cause mortality between both groups, 139 (18.8%) patients with AF versus 222 patients (16.0%) with sinus rhythm at baseline (figure 1).

Heart rate difference by nebivolol
In patients with AF randomized to nebivolol, the heart rates at baseline and the end end of follow-up was 82.9±15.8 and 71.8±14.5 b.p.m., respectively (mean heart rate reduction of 10.9 b.p.m., p<0.001). In the placebo group heart rates were 83.4±16.2 and 80.6±16.4 b.p.m. at baseline and end of follow up, respectively (mean heart rate reduction of 2.4 beats per minute, p=0.02).
Influence of ejection fraction on outcome irrespective of whether they had AF at baseline or not (Table 4).

Nebivolol in preserved and impaired ejection fraction
In patients with AF and an ejection fraction of ≤ 35%, the primary outcome occurred in 84 (37.0%) versus 97 (40.9%) patients in the nebivolol versus placebo group, respectively (HR 0.8 [95% CI 0.65-1.17]) and in patients with an ejection fraction of > 35%, in 49 (36.8%) versus 52 (37.7%) patients in the nebivolol versus placebo group, respectively (HR 1.00 [95% CI 0.68-1.48]). In patients with sinus rhythm and an ejection fraction of ≤ 35%, the primary outcome occurred less frequently in patients treated with nebivolol and in sinus rhythm at baseline (28.1% versus 32.9%, respectively, HR 0.82 [95% CI 0.67-0.99], Table 3). Interaction tests for the primary outcome and all-cause mortality for the AF and sinus rhythm groups respectively were non-significant.

Influence of nebivolol on outcome in patients with atrial fibrillation
Kaplan-Meier curves for the primary outcome in patients with AF treated with nebivolol versus placebo are shown in Figure 2. The cumulative incidence of the primary outcome was 37.1% (n=134) in the nebivolol and 39.8% (n=150) in the placebo group (hazard ratio (HR) 0.92, 95% Confidence Interval [CI], 0.73 to 1.17, Table 3). There was also no difference in all-cause mortality between the nebivolol (n=67, 18.6%) and the placebo group (n=72, 19.1%, HR 0.98 [95% CI 0.70-1.36]). The primary outcome occurred less frequently in patients treated with nebivolol and in sinus rhythm at baseline (28.1% versus 32.9%, respectively, HR 0.82 [95% CI 0.67-0.99], Table 3). Interaction tests for the primary outcome and all-cause mortality for the AF and sinus rhythm groups respectively were non-significant.

Influence of ejection fraction on outcome
Ejection fraction did not influence primary outcome irrespective of whether they had AF at baseline or not (Table 4).

Table 2. Baseline characteristics of patients with atrial fibrillation split by treatment group.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Nebivolol (N=361)</th>
<th>Placebo (N=377)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age - yr</td>
<td>77±5</td>
<td>77±5</td>
<td>0.483</td>
</tr>
<tr>
<td>Female sex – no. (%)</td>
<td>129 (35.7)</td>
<td>133 (35.3)</td>
<td>0.897</td>
</tr>
<tr>
<td>Coronary artery disease – no. (%)</td>
<td>222 (61.5)</td>
<td>238 (63.1)</td>
<td>0.647</td>
</tr>
<tr>
<td>Hypertension – no. (%)</td>
<td>232 (64.3)</td>
<td>226 (60.0)</td>
<td>0.227</td>
</tr>
<tr>
<td>Diabetes – no. (%)</td>
<td>84 (23.3)</td>
<td>85 (22.6)</td>
<td>0.815</td>
</tr>
<tr>
<td>NYHA Class I – no. (%)</td>
<td>6 (1.7)</td>
<td>7 (1.9)</td>
<td>0.65</td>
</tr>
<tr>
<td>NYHA Class II – no. (%)</td>
<td>173 (47.9)</td>
<td>178 (47.2)</td>
<td></td>
</tr>
<tr>
<td>NYHA Class III – no. (%)</td>
<td>172 (47.7)</td>
<td>175 (46.4)</td>
<td></td>
</tr>
<tr>
<td>NYHA Class IV – no. (%)</td>
<td>10 (2.7)</td>
<td>17 (4.5)</td>
<td></td>
</tr>
<tr>
<td>Ejection Fraction</td>
<td>Mean - (%)</td>
<td>36±12</td>
<td>0.969</td>
</tr>
<tr>
<td>Median - (%)</td>
<td>34 (28-41)</td>
<td>33 (29-42)</td>
<td></td>
</tr>
<tr>
<td>≤ 35% – no. (%)</td>
<td>227 (63.1)</td>
<td>237 (63.2)</td>
<td></td>
</tr>
<tr>
<td>&gt; 35% – no. (%)</td>
<td>133 (36.9)</td>
<td>136 (36.8)</td>
<td></td>
</tr>
<tr>
<td>Heart rate - beats/min</td>
<td>83±16</td>
<td>83±16</td>
<td>0.668</td>
</tr>
</tbody>
</table>

* Plus–minus values are means±SD. NYHA = New York Heart Association functional class.
Table 4. Effect of ejection fraction in patients with atrial fibrillation and sinus rhythm on outcome.

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Atrial Fibrillation</th>
<th>Sinus Rhythm</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>EF≤35%</td>
<td>EF≥35%</td>
</tr>
<tr>
<td>Primary outcome (All-cause mortality or hospitalization)</td>
<td>181 (39.0)</td>
<td>101 (37.3)</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>89 (19.2)</td>
<td>49 (18.1)</td>
</tr>
<tr>
<td>Heart failure hospitalization</td>
<td>86 (18.5)</td>
<td>44 (16.2)</td>
</tr>
<tr>
<td>All-cause mortality or heart failure hospitalization</td>
<td>139 (30.0)</td>
<td>81 (29.9)</td>
</tr>
<tr>
<td>Cardiovascular mortality</td>
<td>62 (13.4)</td>
<td>36 (13.3)</td>
</tr>
</tbody>
</table>

| Hazard Ratio (95% CI)                 | 0.91 (0.71-1.16)   | 0.92 (0.66-1.32) |
| P-value for interaction                | 0.545              | 0.092           |

CI = Confidence interval; EF = Ejection Fraction.
predominantly in NYHA class II-III with mean ejection fraction of 28%. This study observed no relative risk reduction in patients with AF in contrast to patients in sinus rhythm.14 The present study included 738 AF patients mostly NYHA class II-III patients, 77 years of age with a mean ejection fraction of 36%. Comparatively, we also observed an attenuated effect of beta-blockade on all-cause mortality and cardiovascular hospitalizations in patients with AF. Furthermore, we demonstrated this effect not only in patients with an impaired left ventricular systolic function but as well in patients with a preserved ejection fraction.

How can this different effect of beta-blockers between HF patients with AF and sinus rhythm be explained? First, heart rate reduction by beta-blocker therapy may be less effective in patients with AF than in those with sinus rhythm since the mode of action of beta-blockers is different during AF and sinus rhythm. During sinus rhythm, beta-blockers exert their heart-rate lowering effect by targeting the sinus node, whereas during AF their main site of action is the atrioventricular node. In the present analysis, however, we found a similar mean reduction in heart rate for patients with both AF and sinus rhythm with comparable dosages of nebivolol. Second, it may well be that patients with AF and heart failure benefit from a slightly higher heart rate as compared to patients in sinus rhythm. AF patients in our study had a baseline (i.e. before start of beta-blocker therapy) heart rate of 83 beats per minute. After institution of nebivolol an average reduction in heart rate occurred of 11 beats per minute, leading to a mean heart rate of 72 beats per minute.20,21 In the above mentioned studies, comparable heart rate reductions in AF patients with bisoprolol, carvedilol and metoprolol, respectively, were achieved.14-16 In contrast, placebo did not reduce heart rates below 80 beats per minute. Thus, achieving low heart rates, i.e. strict rate control, may not be appropriate in patients with AF, which, is in agreement with the recently published Rate Control Efficacy in Permanent Atrial Fibrillation: a Comparison between Lenient versus Strict Rate Control II (RACE II) study.25-28 This may be explained by a loss of the atrial kick and the irregularity in ventricular response during AF, implying that patients with AF may need higher heart rates to maintain a similar cardiac output, possibly even more so during heart failure.29

Of interest and in line with our findings are recent observations of beta-blocker therapy in patients with heart failure and a preserved ejection fraction.30 Nevibolol as compared to placebo did not improve exercise capacity, possibly due to impaired chronotropic response during exercise. Data on the number of patients in AF, unfortunately, were not provided. Finally, patients with AF less often have underlying ischemic heart disease. Possibly, beta-blockers act differently in ischemic versus non-ischemic heart failure.

Notwithstanding the present findings, beta-blockade remains indicated in AF patients.31,32 In contrast to the recommendations in the heart failure guidelines which state that beta-blockers are recommended in all heart failure patients in order to reduce morbidity and mortality, in AF beta-blockers are recommended for rate control in order to reduce AF-related symptoms, but not to improve prognosis.31,32 As such, beta-blockers are frontline therapy in patients with AF and heart failure.

Heart failure with preserved or impaired ejection fraction

We were not able to demonstrate a difference in outcome between patients with a preserved and an impaired ejection fraction in SENIORS, regardless of underlying rhythm. In the main CHARM trial patients with an impaired ejection fraction were at a higher risk of mortality and heart failure hospitalizations. However, a subanalysis of CHARM showed that the presence of AF as an adverse prognostic indicator was of a greater magnitude in those with preserved ejection fraction.31,34 Consistent with this subanalysis, a recently published study showed that AF was independently related to death or heart failure hospitalization in heart failure patients with preserved ejection fraction.17

Study limitations

Several limitations of the present study should be addressed. First, this was a post hoc analysis of the SENIORS trial and therefore not specifically designed nor powered to investigate the effect of nebivolol in elderly patients with heart failure and AF. Although the results are consistent with previous subanalyses, they should be seen in that perspective. Secondly, AF specific information was limited as they were classified based on baseline electrocardiogram. Further information on duration of AF nor on the type of AF (paroxysmal, persistent, or permanent) was known. This may have led to an underestimation of the AF group as some could have had sinus rhythm during the baseline electrocardiogram but having (episodes of) AF during follow up.
Conclusions
In elderly patients with stable heart failure those who had AF were at a higher risk of all-cause mortality and cardiovascular hospitalizations. Furthermore, in patients with AF nebivolol had less effect on all-cause mortality and cardiovascular hospitalizations relative to patients in sinus rhythm at entry, and this effect was irrespective of ejection fraction. The effects of beta blockers in patients with heart failure and AF need to be further elucidated.

Conflict of interest
Dr. van Veldhuisen has received lecture fees from Menarini and was a member of the steering committee of the SENIORS trial. Dr. Böhm has received speaker fees from Menarini. Dr. Cohen-Solal has received lecture and consultancy fees from Menarini, and was a member of the steering committee for the SENIORS trial and received lecture fees. Dr. Babalis’s department has received a grant from Menarini. Dr. Flather has received research grant funding to his institution from Menarini and speaker fees from Menarini for lectures at scientific meetings and symposia. Dr. Coats has received honoraria from Menarini. The original SENIORS trial was supported by Menarini Ricerche SpA, Italy. Funding for additional statistical analyses for the present study to the Clinical Trials and Evaluation Unit in London were obtained. All members of the Steering Committee of the SENIORS trial have received honoraria for speaking on aspects of heart failure and beta-blockers at meetings funded by companies in the pharmaceutical industry.

References


