Treatment of heart failure and patient outcomes in real life
Dobre, Daniela

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Tolerability and dose-related effects of nebivolol in elderly patients with heart failure: data from the SENIORS trial

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ABSTRACT

Aims To assess tolerability and dose-related effects of the β-blocker nebivolol in elderly patients with heart failure (HF).

Methods and Results The SENIORS trial assessed the effects of nebivolol in elderly patients with HF. The present post-hoc analysis included patients who reached a maintenance dose or never tolerated any dose by the end of titration phase. Patients assigned to nebivolol (N=1031) were classified into four groups, according to the last tolerated dose: 0 mg (n=74), low dose (1.25 or 2.5 mg, n=142), medium dose (5 mg, n=172), and target dose (10 mg, n=688). Patients tolerating low doses were remarkable similar to those tolerating high doses, although they had lower systolic and diastolic blood pressure, and were slightly older. Further, they had a higher prevalence of comorbidities. After adjustment, all cause mortality or cardiovascular (CV) hospitalisation was significantly reduced in the target dose group compared to placebo (HR 0.75; 95% CI 0.63-0.90). The medium dose group had rather a similar benefit compared to the target dose group, although not statistically significant (HR 0.73; 95% CI 0.52-1.02), while the low dose group achieved no significant benefit (HR 0.88; 95% CI 0.64-1.20). Patients unable to tolerate any dose of nebivolol had a markedly increased risk of death or CV hospitalisation (HR 1.95; 95% CI 1.38-2.75).

Conclusions The β-blocker nebivolol is well tolerated in elderly HF population. High doses (i.e medium to target) appear superior to low doses. Patients unable to tolerate any dose of nebivolol have the worst outcome.
INTRODUCTION

Heart failure (HF) has emerged as a major public health problem among the elderly population. In Europe, 6-10% of people aged over 65 years have the disorder, and the average age of the patient in the community is 76 years.1-3 The syndrome of HF may arise in presence of either a depressed or a normal left ventricular ejection fraction (LVEF).4 In older patients, HF with preserved LVEF is common.5,6

In elderly patients with HF prescription of a β-blocker raises two major concerns, tolerability and efficacy. Recent data suggest that β-blockers are well tolerated in the elderly7, yet target doses may be difficult to achieve in certain subgroups, such as patients with low blood pressure, and those with advanced disease.8-10 In turn, prescription of low doses may raise concerns over efficacy since older patients may respond differently to medication.11

In patients with HF, one randomised trial has shown that β-blockade produce a dose-dependent improvement in survival.12 In contrast, subgroup analyses in major β-blocker trials have not shown a clear dose-response effect.13,14 The average age of the patients in these trials has been 63 years, and patients with a LVEF > 40% were excluded.

The SENIORS trial assessed the effects of the β-blocker nebivolol in elderly patients (age ≥ 70 years) with HF. About one third of the patients had a preserved LVEF.15 Nebivolol was initiated with a low dose, and, if tolerated, was carefully up-titrated to a target dose of 10 mg daily, or the highest tolerated dose. Overall, nebivolol reduced the combined end point of death or cardiovascular admission. This outcome represented an average-dose effect of nebivolol, as the trial was not designed as a dose-response study.

In this study, we aimed to assess tolerability and dose-related effects of nebivolol in elderly patients from the SENIORS trial.

METHODS

Patients
The present study is a post-hoc analysis of the SENIORS trial. The study design and results of SENIORS have been published previously.15 Briefly, 2128 patients aged ≥ 70 years and with a history of HF were randomly assigned to nebivolol (1067 patients) or placebo (1061 patients). The initial dose of nebivolol was 1.25 mg once daily, and, if tolerated,
it was increased to 2.5 and 5 mg, respectively, every 1-2 weeks, reaching a target of 10 mg once daily over a maximum of 16 weeks. Up-titration could be stopped or delayed depending on symptoms, side effects, or the judgment of the local investigator.

This study examine patients reaching a maintenance dose or not tolerating any dose by the end of titration phase. We analysed the data by classifying the patients assigned to nebivolol into four groups, according to the dose achieved at the end of the titration phase: 0 mg (patients who could not tolerate any dose), low dose (1.25 or 2.5 mg), medium dose (5 mg), and target dose (10 mg). A total of 67 patients (36 in the nebivolol group and 31 in the placebo group) were excluded from this analysis. These were patients who discontinued the study before the end of titration phase despite initial tolerance of study drug. In the nebivolol group, discontinuation took place due to following reasons: patient request (16), death (11), lost to follow-up (4), adverse event, ie. stroke (1), hospitalisation (2), and worsening HF (2). In the placebo group, discontinuation took place as follows: patient request (17), death (9), lost to follow-up (1), adverse event, ie. myocardial infarction (1), patient not taking medication correctly (2), and mandatory indication to β-blocker (1). By excluding these patients, we identified the group truly intolerant to any dose during up-titration. The population of the present study consisted therefore of 1031 patients in the nebivolol group and 1030 patients in the placebo group.

Clinical outcomes
The primary outcome was the composite of death or cardiovascular (CV) hospitalisation. Secondary outcomes included the composite of CV mortality or CV hospitalisation, and the composite of all-cause mortality or all-cause hospitalisation. We analysed only composite outcomes because the number of events in medium and low-dose nebivolol groups was too small for appropriate analysis of individual outcomes.

Statistical analysis
Logistic regression analysis was used to assess the relationship between each baseline characteristic and dose groups. The association between dose of nebivolol and clinical outcomes was assessed using multivariate Cox proportional hazard models. We controlled for baseline characteristics that had an independent association with the dose achieved up to p < 0.10. Adjustment was performed with the following variables: age, gender, heart rate, systolic blood pressure, diastolic blood pressure, creatinine, hypertension, myocardial infarction, prior CABG, prior PTCA, and prescription of aldosterone antagonists, antiarrhythmics, and calcium antagonists. In the Cox proportional analysis
we compared each dose group with all placebo patients that reached the maintenance
dose or never tolerated any titrated dose (N=1030). Results are expressed as hazard ratio
(HR) with 95% confidence interval (CI).
Survival curves were estimated by the Kaplan-Meier method. Statistical analysis was
performed by using SAS software (version 9.1, SAS Institute, NC, USA).

RESULTS

Baseline patient characteristics
Patient characteristics at baseline are shown in Table 1. In the nebivolol group (N=1031)
a total of 668 (67%) patients reached the target dose, while 127 (12%), and 142 (14%)
reached medium and target doses, respectively. A total of 74 (7%) patients were unable
to tolerate any dose of nebivolol during up-titration. Patients who reached lower doses
were remarkable similar with those who reached target doses, although they were
significantly older, and had a lower systolic and diastolic blood pressure. Also, they were
more likely to have a lower heart rate, and higher creatinine levels. Patients tolerating low
doses of nebivolol were also those who had a higher prevalence of myocardial infarction
as the underlying cause of HF, whereas history of hypertension was more frequent
among those tolerating target doses. No significant difference was observed across the
four groups with regard to well-defined measures of HF severity, such as NYHA class,
and LVEF. Also, there was no significant difference in associated comorbidities, such as
atrial fibrillation or diabetes. However, there was a pattern of more severe disease among
patients not tolerating any dose or low doses of medication. The use of antiarrhythmics
and calcium antagonists was higher among patients tolerating low doses, whereas a
similar proportion received ACE Inhibitors or digitalis.

Clinical outcomes
The proportion of patients who suffered death or CV admission decreased with an
increasing dose of nebivolol. Similarly, a higher proportion of patients on low doses
experienced a secondary outcome.
Table 1: Baseline characteristics in relation to dose of study medication at the end of titration phase

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>Placebo (N=1030)</th>
<th>Intolerant to any dose (N=74)</th>
<th>Low dose (1.25+2.5 mg) (N=142)</th>
<th>Medium dose (5 mg) (N=127)</th>
<th>High dose (10 mg) (N=688)</th>
<th>Pvalue*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics and major baseline characteristics</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>76±4.5</td>
<td>76.7 ±5.1</td>
<td>76.6 ±4.9</td>
<td>76.9 ±4.9</td>
<td>75.7 ±4.5</td>
<td>0.002</td>
</tr>
<tr>
<td>Sex (women) (%)</td>
<td>35.6</td>
<td>40.5</td>
<td>35.2</td>
<td>29.1</td>
<td>40.7</td>
<td>0.09</td>
</tr>
<tr>
<td>NYHA (III + IV)(%)</td>
<td>41.1</td>
<td>45.9</td>
<td>40.1</td>
<td>40.9</td>
<td>39.7</td>
<td>0.47</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>36.2 ±12.1</td>
<td>34.9 ±14.5</td>
<td>35.7 ±13.0</td>
<td>37.4 ±12.8</td>
<td>35.9 ±12.1</td>
<td>0.98</td>
</tr>
<tr>
<td>LVEF &lt;= 35% (%)</td>
<td>64.6</td>
<td>67.6</td>
<td>65.2</td>
<td>63.5</td>
<td>64.1</td>
<td>0.68</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>78.8 ±13.6</td>
<td>76.7 ±12.4</td>
<td>72.8 ±10.1</td>
<td>76.7 ±13.2</td>
<td>81.0 ±13.9</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>139.8 ±21.1</td>
<td>137.4 ±23.1</td>
<td>134.2 ±20.6</td>
<td>135.3 ±18.6</td>
<td>140.7±19.5</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>80.8 ±11.3</td>
<td>77.7 ±11.2</td>
<td>78.4 ±10.6</td>
<td>78.7 ±11.4</td>
<td>81.8 ±10.5</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Creatinine (μmol/L)</td>
<td>102.7 ±34.2</td>
<td>110.3 ±40.5</td>
<td>107.0 ±39.1</td>
<td>105.3 ±33.6</td>
<td>98.7 ±33.3</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Medical History (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Atrial Fibrillation</td>
<td>35.6</td>
<td>29.7</td>
<td>33.8</td>
<td>32.3</td>
<td>33.7</td>
<td>0.63</td>
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<tr>
<td>Diabetes</td>
<td>25.0</td>
<td>35.1</td>
<td>31.7</td>
<td>22.9</td>
<td>25.9</td>
<td>0.12</td>
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<td>Hypertension</td>
<td>62.3</td>
<td>52.7</td>
<td>55.6</td>
<td>57.5</td>
<td>64.7</td>
<td>0.004</td>
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<td>Myocardial Infarct</td>
<td>43.6</td>
<td>56.8</td>
<td>55.6</td>
<td>46.5</td>
<td>40.0</td>
<td>&lt;.001</td>
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<tr>
<td>Prior CABG</td>
<td>8.8</td>
<td>21.6</td>
<td>12.0</td>
<td>10.2</td>
<td>7.8</td>
<td>&lt;.001</td>
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<tr>
<td>Prior PTCA</td>
<td>3.3</td>
<td>9.5</td>
<td>6.3</td>
<td>6.3</td>
<td>2.9</td>
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<td>Smoking</td>
<td>5.3</td>
<td>6.8</td>
<td>4.2</td>
<td>6.3</td>
<td>4.5</td>
<td>0.49</td>
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<td>Medications (%)</td>
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<tr>
<td>ACE Inhibitors</td>
<td>83.3</td>
<td>78.4</td>
<td>85.2</td>
<td>81.9</td>
<td>82.8</td>
<td>0.83</td>
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<tr>
<td>Aldosterone Antagon</td>
<td>26.0</td>
<td>29.7</td>
<td>35.2</td>
<td>46.5</td>
<td>23.5</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Angiotensin II Antagonists</td>
<td>8.4</td>
<td>10.8</td>
<td>9.9</td>
<td>7.1</td>
<td>7.6</td>
<td>0.29</td>
</tr>
<tr>
<td>Antiarrhythmics</td>
<td>18.4</td>
<td>29.7</td>
<td>26.8</td>
<td>17.3</td>
<td>10.9</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Aspirin</td>
<td>51.1</td>
<td>56.8</td>
<td>50.7</td>
<td>54.3</td>
<td>53.5</td>
<td>0.99</td>
</tr>
<tr>
<td>CA Antagonists</td>
<td>14.5</td>
<td>21.6</td>
<td>12.7</td>
<td>11.0</td>
<td>11.0</td>
<td>0.07</td>
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<tr>
<td>Cardiac Glycoside</td>
<td>43.0</td>
<td>31.1</td>
<td>38.7</td>
<td>42.5</td>
<td>41.3</td>
<td>0.25</td>
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<td>Diuretics</td>
<td>85.5</td>
<td>89.2</td>
<td>89.4</td>
<td>88.2</td>
<td>85.3</td>
<td>0.11</td>
</tr>
<tr>
<td>Lipid Lowering drugs</td>
<td>22.3</td>
<td>29.7</td>
<td>22.5</td>
<td>20.5</td>
<td>20.5</td>
<td>0.18</td>
</tr>
<tr>
<td>Vitamin K Antagonists</td>
<td>24.3</td>
<td>20.3</td>
<td>26.1</td>
<td>16.5</td>
<td>21.7</td>
<td>0.93</td>
</tr>
</tbody>
</table>

*Resulting from the logistic regression model having nebivolol dose as response and each baseline characteristic as a covariate

Data are shown as mean ±SD for continuous variables and as percentages for discrete variables

SBP = systolic blood pressure; DBP = diastolic blood pressure; CABG = coronary artery bypass grafting

PTCA = percutaneous coronary intervention; SD = standard deviation
In univariate survival analysis, nebivolol in high dose was associated with a significant reduction of all cause mortality or CV hospitalisation compared to placebo (HR 0.74; 95% CI 0.62-0.88). Nebivolol in medium and low dose was associated with a non significant effect (HR 0.81; 95% CI 0.58-1.13, and HR 0.94, 95% CI 0.69-1.29, respectively). Patients unable to tolerate any dose of nebivolol had a markedly risk of death or CV admission (HR 2.15, 95% CI 1.55-3.00).

After adjustment, nebivolol in target dose remained associated with a significant reduction of all cause mortality or CV hospitalisation (HR 0.75; 95% CI 0.63-0.90) (Table 2). Nebivolol in medium dose had a similar benefit to the target dose (~25% relative risk reduction), although of borderline statistical significance (HR 0.73; 95% CI 0.52-1.02). In contrast, nebivolol in the low dose group achieved no significant benefit (HR 0.88; 95% CI 0.64-1.20). Patients unable to tolerate any dose of nebivolol remained with the worst outcome, with two-fold higher risk of death or CV hospitalisation (HR 1.95; 95% CI 1.38-2.75).

Figure 1 shows the Kaplan Meier survival curves in patients receiving nebivolol at different doses or placebo. The beneficial effects of target- and medium doses of nebivolol on primary outcome appeared early after the end of titration phase and were constant during follow-up. Patients intolerant to any dose of nebivolol had a clear higher risk of death or CV hospitalisation compared to the placebo. Similar results were obtained on secondary outcomes (Table 2 and Figure 2).
Table 2: Relative risk of outcome events with Nebivolol compared to Placebo

<table>
<thead>
<tr>
<th>OUTCOMES</th>
<th>PLACEBO (N=1030)</th>
<th>NEBIVOLOL (N=688)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intolerant to any dose (N=74)</td>
<td>Low dose (1.25 +2.5 mg) (N= 142)</td>
</tr>
<tr>
<td>All cause mortality or CV hospitalisation †</td>
<td>34.7</td>
<td>52.7</td>
</tr>
<tr>
<td>CV mortality or CV hospitalisation</td>
<td>41.1</td>
<td>62.2</td>
</tr>
<tr>
<td>All cause mortality or all cause hospitalisation</td>
<td>32.4</td>
<td>48.6</td>
</tr>
</tbody>
</table>

*Hazard ratio (95% Confidence Intervals) adjusted for age, heart rate, systolic BP, diastolic BP, creatinine, hypertension, myocardial infarction, prior CABG, prior PTCA, aldosterone antagonists, antiarrhythmics and calcium antagonists.

† CV: Cardiovascular
**Figure 1:** Time to all-cause mortality or CV hospitalisation in patients receiving placebo and nebivolol at target dose, medium dose, low dose, or not tolerating any dose of nebivolol.

- **Target-dose Nebivolol Group:**
  - Nebivolol: HR = 0.75 (0.63 | 0.90)
  - Placebo: HR = 0.73 (0.52 | 1.02)

- **Medium-dose Nebivolol Group:**
  - Nebivolol: HR = 0.88 (0.64 | 1.20)
  - Placebo: HR = 1.95 (1.38 | 2.75)

- **Low-dose Nebivolol Group:**
  - Nebivolol: HR = 0.88 (0.64 | 1.20)
  - Placebo: HR = 1.95 (1.38 | 2.75)

- **Patients not tolerating any dose of Nebivolol:**
  - Nebivolol: HR = 0.88 (0.64 | 1.20)
  - Placebo: HR = 1.95 (1.38 | 2.75)
**Figure 2:** Hazard ratio and 95% confidence interval for primary and secondary outcomes by Nebivolol dose

**All cause mortality or CV hospitalisation**
- Pts. not tolerating any Neb dose
- Low Dose (1.25 mg + 2.5 mg)
- Medium Dose (5 mg)
- High Dose (10 mg)

**CV mortality or CV hospitalisation**
- Pts. not tolerating any Neb dose
- Low Dose (1.25 mg + 2.5 mg)
- Medium Dose (5 mg)
- High Dose (10 mg)

**All cause mortality or all cause hospitalisation**
- Pts. not tolerating any Neb dose
- Low Dose (1.25 mg + 2.5 mg)
- Medium Dose (5 mg)
- High Dose (10 mg)

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**DISCUSSION**

The present study shows that nebivolol is well tolerated in elderly patients with HF. The majority of patients reached the target dose of 10 mg, and less than one third achieved medium or low doses. Only 7% of patients were unable to tolerate any dose of nebivolol. Although some differences among the four dose groups were observed, patients were remarkably similar. The data show a significant reduction in the risk of death or CV hospitalisation with the target dose of nebivolol compared to placebo. The beneficial effects appeared early after the beginning of treatment and were constant during follow-up. Medium doses appeared to have a similar benefit compared to the high doses, while low doses achieved no benefit. However, the number of patients in both groups was too small to allow firm conclusions. Patients unable to tolerate any dose of nebivolol had the worst outcome, with two times higher risk of death or CV hospitalisation. Similar results were obtained on secondary outcomes.
An important novel finding of the present study is that patients unable to tolerate any dose of nebivolol have the worst prognosis, on all clinical outcomes. The tolerability of nebivolol was dependent on the clinical status, as patients unable to tolerate any dose had lower systolic and diastolic blood pressure, and lower heart rate. Further, they were slightly older, and had a higher prevalence of renal dysfunction and diabetes. However, it is of notice that patients unable to tolerate any dose did not differ significantly on well accepted markers of severity, such as LVEF. This is in consent with a previous study which shows that severity of HF, per se, does not appear to be a predictor of successful β-blocker titration in patients with idiopathic dilated cardiomyopathy. Instead, rather preserved blood pressure may be a predictor of normal titration. However, another study has found LVEF, along with low diastolic blood pressure, advanced age and chronic obstructive airway disease (COPD) as a predictor of tolerability in elderly patients with HF. While tolerability of nebivolol was clearly dependent on the clinical profile, it is also possible that physicians were more likely to withhold the treatment if side effects occurred in patients with such profile, i.e. were older, and had lower blood pressure. Given the markedly increased risk on all outcomes in these patients, efforts should be made to initiate β-blocker therapy.

Most RCTs with β-blockers in HF have not been designed as dose-response studies. To date, only the MOCHA trial, a small, 6-month study was designed to evaluate the dose-related effects of carvedilol in patients with mild to moderate HF. The study found a dose-related improvement in mortality and LVEF. In contrast to these findings, posthoc subgroup analyses in both MERIT-HF and CIBIS II trials did not show a clear dose-response effect of metoprolol and bisoprolol on survival when compared to placebo. Subgroup analysis in the COMET trial has shown a higher benefit of target versus subtarget doses of β-blockers, but subtarget doses included patients on both medium and low doses. However, posthoc findings are generally limited by the fact that sicker patients are usually prescribed lower doses of β-blockers, when they may be the ones that need β-blockers the most.

Data from observational studies are contradictory. A large observational study has found a similar benefit on survival with prescription of high and low dose β-blocker therapy. In contrast, in the Euro Heart Failure Survey patients who were treated with high doses of β-blockers achieved a higher benefit than patients treated with low doses. In a cohort of patients with advanced HF and preserved LVEF also a higher benefit of high-dose therapy was observed. However, in observational studies high dose was defined as ≥ 50% of target dose achieved in RCTs, and therefore no clear distinction between the effect of target, medium and low dose therapy was made. The results of
these studies rather suggest that patients who achieve at least medium doses do better than those on lower doses. In contrast to these studies, our trial data show the differential effects of various nebivolol doses. While target and medium doses appear to achieve a similar benefit, lower doses seem the least beneficial.

The titration of β-blockers in clinical trials is performed with a gradual increase in dosage guided by tolerance until the target dose is achieved. Compared to the randomised trial setting, in clinical practice a lower percentage of patients may receive target doses, and more patients may receive medium or low doses. The important finding of our study is that even medium doses of nebivolol may be effective in elderly HF population.

The proportion of patients who reached the target dose in SENIORS is higher than that reported in previous β-blocker trials. Nebivolol is a beta-1-selective blocker whose haemodynamic profile is different from that of classical β-blockers. Its mechanism of action combines beta-adrenergic blocking activity with vasodilating properties mediated by nitric oxide modulation on endothelial cells. This good tolerability of nebivolol may be related to its peculiar vasodilating properties.

Our study has a number of limitations. First, since it is a post-hoc analysis, it is not possible to ascertain whether a particular dose is optimal. Patients were not randomised to receive different doses of nebivolol, and the dose prescribed was influenced by patients’ characteristics and physicians’ decisions. Second, medium and low dose groups included a small number of patients, and the analysis may have lacked the power to demonstrate a statistically significant effect. Third, we assessed only composite outcomes as primary and secondary end-points, as the number of events in medium and low-dose nebivolol groups was too small for appropriate analysis of individual outcomes.

In conclusion, nebivolol is well tolerated in elderly heart failure patients. High doses (i.e medium to target) appear superior to low doses. Patients unable to tolerate any dose of nebivolol have the worst outcome.

REFERENCES


Tolerability and dose-related effects of nebivolol in elderly patients with HF: data from the SENIORS trial


