**Comparison between nebivolol and ramipril in patients with hypertension and left ventricular hypertrophy: a randomized open blinded end-point (PROBE) trial**

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**Abstract. – Aims:** To compare the effects of nebivolol and ramipril on left ventricular hypertrophy in hypertensive patients.

**Materials and Methods:** The study was conducted with a pre-randomised blinded endpoint (PROBE) design in which 106 patients with mild-to-moderate hypertension and left ventricular hypertrophy were randomised to ramipril (n=52) or to nebivolol (n=54) and treated for 39 weeks. The doses of ramipril and nebivolol were 2.5 and 5 mg/day, respectively. After 4-8 weeks, in patients with not normalised diastolic blood pressure, a thiazide diuretic was added (indapamide 2.5 mg or hydrochlorothiazide 12.5 mg/day). In the ramipril group, thiazide diuretic was added in 97% of subjects and in nebivolol group in 92%. The effect of treatment on left ventricular mass was assessed by two-dimensional guided M-mode transthoracic echocardiography, at baseline and at the end of the treatment. Left ventricular mass index (LVMI) was calculated and indexed to body surface area (g/m²) and height².7 (g/height².7). Blood pressure (BP) was measured at baseline, after 4, 8, 12, 24 and 39 weeks with a standard mercury sphygmomanometer.

**Results:** Both left ventricular mass (LVM) and mass index (LVMI) decreased significantly after treatment with ramipril (LVMI −14.8 g/m², −7.3 g/height².7; p < 0.001), and after treatment with nebivolol (LVMI −31.9 g/m², −15.6 g/height².7; p < 0.001). The difference between ramipril and nebivolol (−17.1 g/m², −8.3 g/height².7) with regards to reduction of LVMI was statistically significant (p < 0.001). No differences were observed between the two groups in terms of normalization of LVMI. Both drugs decreased BP similarly after 39 weeks of treatment.

**Conclusions:** The present study shows that both nebivolol and ramipril decrease LVMI. Nebivolol 5 mg/daily treatment reduced LVM significantly more than ramipril 2.5 mg/daily. Both drugs similarly decreased BP during the treatment.

**Key Words:**
Left ventricular hypertrophy, Left ventricular mass index, Hypertension, Nebivolol, Ramipril.

**Introduction**

Left ventricular hypertrophy (LVH) is commonly present in patients with hypertension. LVH strongly predicts cardiovascular mortality and morbidity, independently of other cardiovascular risk factors and blood pressure values.1-3 Particularly, LVH is associated with increased incidence of new-onset atrial fibrillation, left ventricular dysfunction and heart failure.4-6

Antihypertensive treatments reduce LVH and decrease cardiovascular events.7-9 Evidence is accumulating that LVH development depends on the interaction of myocardial stretch and renin-angiotensin system activation, which induces myocyte hypertrophy and myocardial fibrosis.10,11 Drugs able to modulate myocardial fibrosis, as Angiotensin Converting Enzyme (ACE) inhibitors or angiotensin II receptor antagonists might, therefore, promote LVH regression, whereas beta-blockers are considered to have no significant effects.8,12-15

Nebivolol is a highly selective beta₁-receptor antagonist, with endothelial nitric oxide (NO) mediated vasodilatory properties, indicated to treat hypertension. Several studies showed that nebivolol, differently from other beta-blockers, has an antiproliferative activity that involves the nitric oxide pathway.17,18,21 The antihypertensive efficacy of nebivolol was established in several double blind controlled studies, in comparison with other beta-blockers, calcium antagonists, ACE-inhibitors, and angiotensin II receptor antagonists.16,22

However, the efficacy of nebivolol in reducing LVH has not been widely assessed yet, because only one study compared nebivolol with telmisartan in patients with LVH.23, showing that the two treatments have similar efficacy.
To clarify the possible effects of nebivolol for LVH reduction, our study aimed to compare the effect of ramipril and nebivolol in patients with hypertension and LVH.

**Patients and Methods**

**Study Design**

NERVE (Effects of NEbivolol and Ramipril on left VEntricular hypertrophy (LVH), quality of life and blood pressure in patients with mild to moderate hypertension associated with left ventricular hypertropy) was a multicenter, two parallel groups, Prospective Randomized Open Blinded End-point (PROBE) trial. The study was conducted in accordance to the Declaration of Helsinki, and under central and local Ethics Committee approval. Patients' written informed consent was obtained.

**Patients**

One hundred and thirty-four hypertensive patients with LVH were recruited among those attending Out-patient Clinic of 17 Cardiology centres. Including criteria were: LVH defined as left ventricular mass index (LVMI) ≥ 125 g/m² in men and 110 g/m² in women, mild-moderate (grade 1-2) hypertension (systolic blood pressure/diastolic blood pressure (SBP/DBP) > 140/90 mmHg), or to be on antihypertensive therapy.

Eligible patients underwent standard clinical examination, electrocardiogram, transthoracic echocardiography and routine laboratory analysis.

Patients were excluded from the study if they had severe hypertension (SBP ≥ 200 mmHg and/or DBP ≥ 115 mmHg; this target was chosen in order to include more patients in the analysis), age over 65 years, heart failure, coronary artery disease, valvular heart disease, arrhythmias, bradycardia, atrio-ventricular (A-V) block, secondary hypertension, obstructive pulmonary disease, diabetes (fasting glucose ≥ 126 mg/dL and HbA1c > 7%), renal disease (serum creatinine > 160 μmol/L), hepatic disease (liver enzymes higher than the double of the upper limit of reference range), or any other clinically relevant laboratory abnormality, breastfeeding, inadequate echocardiographic window, contraindications to ACE inhibitors or nebivolol. Pregnant or fertile female, unless adequately protected against pregnancy, were also excluded.

Selected patients entered in a 2 weeks run-in period during which they received indapamide 2.5 mg/day, after having discontinued any previous antihypertensive treatment (wash-out).

At the end of run-in period, 132 patients meeting the inclusion and exclusion criteria were randomized to ramipril 2.5 mg/daily or nebivolol 5 mg/daily for 39 weeks and indapamide was stopped.

**Measurements**

**Echocardiography**

Two-dimensional guided M-mode transthoracic echocardiography was performed in all patients by a trained cardiologist, using a commercial available imaging ultrasound instrument (Aloka, Zug, Switzerland). Recordings were obtained with the patient placed in the left lateral decubitus position. M-mode tracing of the left ventricle was obtained in the parasternal long axis views, following the American Society of Echocardiography recommendations.

Five consecutive cardiac cycles were averaged for every echocardiographic measurement. All images were recorded on a super-VHS tape and evaluated, at end of the trial, by a cardiologist blinded to the patient treatment.

The following parameters were measured: left ventricular internal end-diastolic (LVIDd) and end-systolic (LVIDs) diameters, intraventricular septal wall thickness (IVSWT) and left ventricular posterior wall thickness (LVPWT) at end-diastole and end-systole.

Left ventricular mass (LVM) was calculated according to Penn convention and was indexed to body surface area (BSA) and to height² to calculate the LVMI, expressed as g/m² and g/m², respectively. Patients were considered to have LVH when LVMI was ≥ 125 g/m² in men and ≥ 110 g/m² in women or ≥ 49 g/m² in men and ≥ 45 g/m² in women. Relative wall thickness (RWT) was calculated as 2 × LVPWT/LVIDd. Subjects with LVH were classified as having concentric hypertrophy if RWT was ≥ 0.42 or eccentric hypertrophy if RWT was ≤ 0.41. Echocardiographic evaluation was performed at the end of the run-in period and after 39 weeks of treatment.

To account for the lack of centralized interpretation of echocardiographic tracings, criteria to acquire the registrations have been well pre-specified, and the variability between investigators’ reported data and the centralized interpretation was measured in a randomly selected sample of 20 tracings.
Blood pressure was measured three times on the right arm in sitting position, with 10 minutes of rest between two consecutive measurements, using a standard mercury sphygmomanometer. Phase I and V Korotkoff sounds were used to determine systolic and diastolic blood pressure. Measurements were performed by the same investigator. The average of the three measurements was used for the analyses. Blood pressure was assessed at the end of the run-in period (baseline) and after 4, 8, 12, 24 and 39 weeks. If target blood pressure (DBP < 90 or DBP decrease ≥ 10 mmHg) was not achieved after 4-8 weeks, thiazide diuretics (preferably hydrochlorothiazide 12.5 mg/daily or indapamide 2.5 mg/daily) was added.

**Results**

At the end of the run-in period 132 patients were randomized to either ramipril (n=64) or nebivolol (n=68). Of these, 12 assigned to ramipril and 14 to nebivolol withdrew from the study. A total of 106 patients completed the 39-weeks treatment according to the protocol (52 on ramipril and 54 on nebivolol). Patients already treated for hypertension at the time of eligibility assessment were 56: 28 of them (44% of the ramipril group) were randomized to ramipril and 28 (41% of the nebivolol group) to nebivolol. Patients needing thiazide diuretic (indapamide or hydrochlorothiazide) as add-on therapy were 79.4% (on the initial 68 patients) in the nebivolol group and 76.6% (on the initial 64 patients) in the ramipril group (p = 0.536).

Demographics and hemodynamic parameters of patients treated with ramipril and nebivolol and having completed the study are reported in Table I. At randomisation, the two study groups were homogeneous, regarding age, gender, weight, height, body mass index, body surface area, SBP, DBP, heart rate (HR), LVM and LVMI.

Results related to left ventricular mass are summarized in Table II. LVMI (indexed to body surface area and to height²) was 145.2 g/m² (CI 95% 140-151) and 70.1 (CI 95% 67-73) g/height² in the ramipril group and 149.6 g/m² (CI 95% 144-155) and 74.0 (CI 95% 71-77) g/height² in the nebivolol group. In both groups LVH was concentric and severely abnormal²³. At the end of the treatment, both LVM (Figure 1A) and LVMI (Figure 1B) decreased with ramipril (−14.8 g/m² vs. baseline, p < 0.001) and were analysed in multi-variate analysis including age and gender as co-variables. All tests were performed at p < 0.05 (two-tailed).

**Adverse Events**

Adverse events (AEs) were spontaneously reported by the patient or recognised by the clinician at each visit.

**Statistical Analysis**

Data are presented as mean ± standard error (SE) and as 95% confidence interval (CI). All analyses were performed in SAS (version 8.2). Quantitative data were analyzed using analysis of variance (ANOVA) and Students’ t-test. Single parameters were considered as independent variables. Each of them was analyzed through a two-way ANOVA with factors “study group” (two levels, “ramipril” and “nebivolol”, between factor), and “time” (two levels, “pre-treatment” and “39-week”, within factor). Corrected Student’s t-tests were used for post-hoc analysis. Semi-quantitative data were tested using Wilcoxon Signed Rank test. Qualitative data and dichotomies were tested using the χ² test or Fisher’s exact probability test. Corrections were made for differences in baseline values. Furthermore, LVM and LVMI were analysed in multi-variate analysis including age and gender as co-variables. All tests were performed at p < 0.05 (two-tailed).
Table 1. Demographic data of the per protocol (PP) study population at randomisation and baseline measurements.

<table>
<thead>
<tr>
<th>Randomised to parameter:</th>
<th>Ramipril n = 52</th>
<th>Nebivolol n = 54</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at enrolment (years); mean ± SE (95% CI)</td>
<td>51.1 ± 0.87 (49.3-52.9)</td>
<td>50.4 ± 0.89 (48.7-52.2)</td>
<td>0.598§</td>
</tr>
<tr>
<td>Body height (cm); mean ± SE (95% CI)</td>
<td>166.8 ± 1.10 (164.6-169.1)</td>
<td>167.0 ± 1.15 (164.8-169.2)</td>
<td>0.886¶</td>
</tr>
<tr>
<td>Body weight (kg); mean ± SE (95% CI)</td>
<td>79.8 ± 1.43 (77.0-82.6)</td>
<td>83.5 ± 1.36 (80.8-86.3)</td>
<td>0.060†</td>
</tr>
<tr>
<td>BMI; mean ± SE (95% CI)</td>
<td>28.8 ± 0.58 (27.7-30.0)</td>
<td>30.1 ± 0.54 (29.9-31.1)</td>
<td>0.112‡</td>
</tr>
<tr>
<td>BSA (m²); mean ± SE (95% CI)</td>
<td>1.92 ± 0.02 (1.87-1.96)</td>
<td>1.97 ± 0.02 (1.93-2.00)</td>
<td>0.097γ</td>
</tr>
<tr>
<td>Gender (male/female)</td>
<td>25/27</td>
<td>26/28</td>
<td>1.000§§</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg) mean ± SE (95% CI)</td>
<td>158 ± 1.5 (155-162)</td>
<td>161 ± 1.6 (158-164)</td>
<td>0.208§</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg) mean ± SE (95% CI)</td>
<td>99.0 ± 0.7 (97.1-100.8)</td>
<td>99.8 ± 1.1 (98.0-101.6)</td>
<td>0.540§</td>
</tr>
<tr>
<td>Heart rate (b/min) mean ± SE (95% CI)</td>
<td>75.8 ± 1.1 (74.0-77.7)</td>
<td>75.3 ± 0.6 (73.5-77.1)</td>
<td>0.694§</td>
</tr>
<tr>
<td>Left ventricular mass mean ± SE (95% CI)</td>
<td>279 ± 6 (267-290)</td>
<td>293 ± 5 (283-304)</td>
<td>0.060§</td>
</tr>
<tr>
<td>Left ventricular mass-index (Devereux) Mean ± SE (95% CI)</td>
<td>145.2 ± 2.7 (140-151)</td>
<td>149.6 ± 2.6 (144-155)</td>
<td>0.251</td>
</tr>
<tr>
<td>Left ventricular mass-index (height².7) Mean ± SE (95% CI)</td>
<td>70.1 ± 1.4 (67-73)</td>
<td>74.0 ± 1.7 (71-77)</td>
<td>0.078</td>
</tr>
<tr>
<td>Relative wall thickness Mean ± SE (95% CI)</td>
<td>0.489 ± 0.012 (0.47-0.51)</td>
<td>0.492 ± 0.007 (0.47-0.51)</td>
<td>0.829</td>
</tr>
<tr>
<td>Race caucasian/Asian</td>
<td>52/0</td>
<td>54/0</td>
<td>1.000§§</td>
</tr>
</tbody>
</table>

§Student t-test; §§Fisher's exact probability.
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Ramipril [mean ± SE, 95% CI] [n = 52]</th>
<th>Nebivolol [mean ± SE, 95% CI] [n = 54]</th>
<th>( p ) Ramipril vs. Nebivolol</th>
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<tr>
<td></td>
<td>Baseline</td>
<td>At 39 weeks</td>
<td>( \Delta )</td>
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<tr>
<td>LVDd (mm); mean ± SE (95% CI)</td>
<td>49.35±0.68 (48.2, 50.5)</td>
<td>49.16±0.65 (48.0, 50.3)</td>
<td>-0.19 ± 0.34</td>
</tr>
<tr>
<td>IVWTd (mm); mean ± SE (95% CI)</td>
<td>12.50±0.24 (12.07, 12.93)</td>
<td>11.55±0.22 (11.09, 12.02)</td>
<td>-0.95 ± 0.16</td>
</tr>
<tr>
<td>LVPWTd (mm); mean ± SE (95% CI)</td>
<td>11.90±0.18 (11.60, 12.20)</td>
<td>11.07±0.17 (10.67, 11.47)</td>
<td>-0.83 ± 0.16</td>
</tr>
<tr>
<td>IV mass (g); mean ± SE (95% CI)</td>
<td>278.5±5.8 (267.5, 289.6)</td>
<td>249.2±6.9 (234.0, 263.5)</td>
<td>-29.3 ± 5.5</td>
</tr>
<tr>
<td>LV mass index g/m² mean ± SE (95% CI)</td>
<td>145.2±2.7 (139.9, 150.6)</td>
<td>130.4±3.6 (122.6, 138.2)</td>
<td>-14.8 ± 2.9</td>
</tr>
<tr>
<td>LV mass index g/height² mean ± SE (95% CI)</td>
<td>70.1±1.4 (67.0, 73.2)</td>
<td>62.8±1.7 (58.6, 67.1)</td>
<td>-7.3 ± 1.4</td>
</tr>
<tr>
<td>RWT; mean ± SE (95% CI)</td>
<td>0.48±0.012 (0.469, 0.510)</td>
<td>0.45±0.011 (0.434, 0.478)</td>
<td>-0.034 ± 0.006</td>
</tr>
<tr>
<td>Concentric ≥ 0.42</td>
<td>39 (75%)</td>
<td>32 (62%)</td>
<td>7 (17%)</td>
</tr>
<tr>
<td>Normalization of LVMI (g/m²)</td>
<td>21 (40%)</td>
<td>21 (39%)</td>
<td>28 (52%)</td>
</tr>
</tbody>
</table>

*Student t-test; §§Fisher’s exact probability.
33.4/19.7 in the nebivolol group. The difference between ramipril and nebivolol with regards to reduction of SBP and DBP was not statistically significant (SBP, \( p = 0.595 \); DBP, \( p = 0.612 \)). Response was defined as the reduction of DBP of \( \geq 10 \) mm and the reduction of SBP \( \geq 20 \) mmHg. Responders were 52 in the nebivolol group and 42 in the ramipril group (Figure 4A). The difference between nebivolol (96.3%) and ramipril (80.8%) with respect to response was statistically significant (\( p = 0.014 \), Figure 4B) in the per protocol population.

HR did not change with ramipril, but was significantly decreased by nebivolol (\(-5.8\) b/min, after 4 weeks \( p < 0.001 \) and \(-7.2\) b/min after 39 weeks, \( p < 0.001 \), with a significant difference between the two drugs (\( p < 0.001 \)).

Ramipril and nebivolol were well tolerated: cough occurred in 3 patients treated with ramipril. Drug adherence, evaluated by pills counting, was 96±4%.

**Discussion**

The results of our study show that the treatment with ramipril and nebivolol, combined with diuretics, provides statistically significant reduc-
tion of LVH, indexed to body surface area or to height. The rate of achieved target was significantly greater with nebivolol 5 mg/daily than with ramipril 2.5 mg/daily, being the difference between the two drugs, administered at the tested doses statistically significant (p < 0.001). Our findings are in agreement with those reported in previous studies with ramipril and with other inhibitors of renin-angiotensin system, which are considered, together with calcium channel blockers, the most efficacious agents in reducing LVH. Conversely, our results are not in line with studies that have shown a lower efficacy of beta-blockers in regression of left ventricular hypertrophy. Even though the number of responders in terms of blood pressure was higher with nebivolol 5 mg/daily than with ramipril 2.5 mg/daily, both drugs significantly decreased blood pressure in a similar way, so that the absolute values of DBP and SBP at the end of the treatment were similar in the two groups. Hence, the more pronounced effect of nebivolol may not be ascribed only to the reduction of blood pressure, but other factors might have concurred.

Nebivolol combines a selective beta1-adrenergic receptor blockade with a vasodilator property, mediated by the L-arginine/NO pathway. Moreover, differently from classical beta-blockers, nebivolol has been demonstrated to have antiproliferative activity, attributable to the increase of NO bioavailability also at coronary and cardiac level. NO is involved on LV fibrotic component regression. This property might have played an important role in the regression of LV fibrotic component, that characterize LVH. In addition, nebivolol reduces large arterial stiffness and central blood pressure which have a pathogenetic role in promoting LVH. All these pharmacological properties of nebivolol may contribute to decrease LVH.

This study have some limitations. First, this is a “one-dose comparison”, where Nebivolol 5 mg/daily was compared to Ramipril 2.5 mg/daily. Hence, the effects we have observed cannot be generalized to all the drug doses, but are specifically related to the dose administered. Second, another important limitation is the relatively small number of patients, because a high number withdrew from the study. This could have produced the unsignificant trend to higher blood pressure, LVM and LVMI at baseline in the nebivolol than in the ramipril group. However, in this work we evaluated changes from baseline, and not absolute values reached by patients at the end of the treatment, thus, limiting the possible effects of unbalanced starting points. Last, the study is limited by the lack of centralized interpretation of echocardiography tracings. However, the criteria to acquire the registrations have been well pre-specified and the variability between investigators’ reported data and the centralized interpretation in a randomly selected sample of 20 tracings was low (±15%). This held to the relatively small standard errors and narrow 95% confidence interval that strengthen the results obtained.

Conclusions

In hypertensive patients with LVH, nebivolol, combined with thiazide diuretics, significantly decreased LVMI. Moreover, Nebivolol was able to modify LV geometry from concentric to eccentric. Such effects were significantly higher in patients treated with nebivolol 5 mg/daily than in patients treated with ramipril 2.5 mg/daily. The clinical implication of these results is that the treatment with nebivolol/thiazides in hypertensive patients reduces the cardiovascular risk associated with LVH.

Summary Points

Left ventricular hypertrophy (LVH) is commonly present in patients with hypertension and it can be reduced by antihypertensive treatments, thus decreasing cardiovascular events.
Nebivolol is a highly selective β₁-receptor antagonist, with endothelial nitric oxide mediated vasodilatory properties, indicated to treat hypertension, but its efficacy in reducing LVH has not been yet assessed. The study was conducted with a pre-randomised blinded endpoint (PROBE) design in which 106 patients with mild-to-moderate hypertension and left ventricular hypertrophy were randomised to ramipril (n=52) or to nebivolol (n=54) and treated for 39 weeks.

Both nebivolol and ramipril reduced left ventricular mass and left ventricular mass index, but the effect of nebivolol was significantly higher than ramipril.

Nebivolol was also able to induce a statistically significant change in the left ventricular geometry evaluated by the relative wall thickness, a marker of cardiovascular risk. The more pronounced effect of nebivolol may not be ascribed only to the reduction of blood pressure, because reduction in SBP and DBP were similar over the course of the trial in both groups, but it may be related to its nitric oxide mediated anti-proliferative activity.

Nebivolol reduces arterial stiffness and central blood pressure which have a pathogenetic role in promoting left ventricular hypertrophy.

Treatment with nebivolol in hypertensive patients reduces the cardiovascular risk associated with left ventricular hypertrophy.

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