Nebivolol Monotherapy for Patients With Systolic Stage II Hypertension: Results of a Randomized, Placebo-Controlled Trial

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ABSTRACT

Background: Elevated systolic blood pressure (SBP) is an independent risk factor for cardiovascular events and mortality.

Objective: The goal of this study was to assess whether nebivolol (NEB), a vasodilatory β_1-selective blocker, is a safe and efficacious monotherapy for individuals with systolic stage II hypertension.

Methods: In this multicenter trial, 18- to 64-year-olds who had not used antihypertensive treatment for at least 4 weeks and had SBP/diastolic blood pressure (DBP) of 160 to 180/90 to 110 mm Hg were randomized to receive double-blind medication for 6 weeks (NEB, n = 290; placebo [PBO], n = 142). Depending on response, the starting dose (5 mg/d) could be increased directly to 20 mg/d. Primary parameters were baseline–end point changes in trough seated SBP and DBP (intent-to-treat [ITT] population); the Hochberg method was used to control the type I error ($\alpha = 0.05$). Responder analysis was also performed. Safety and tolerability assessment included monitoring of adverse events (AEs).

Results: Mean age at baseline (ITT) was 50.7 years, and the mean SBP/DBP values were 167/101 mm Hg; 202 (47.3%) participants were women, 276 (63.9%) had body mass index ≥30 kg/m^2, 152 (35.2%) were black, and 161 (37.3%) were Hispanic. Completion rates were 79.7% (PBO) and 90.3% (NEB). After 2 weeks of treatment, 92% and 95% participants in the NEB and PBO groups, respectively, had SBP in the range of 130 to 180 mm Hg and were titrated to the 20-mg/d NEB dose or its matching PBO tablet. After 6 weeks of treatment, the NEB group experienced significant mean reductions compared with the PBO group for both SBP (−18.2 vs −12.3 mm Hg; $P < 0.001$) and DBP (−12.3 vs −5.7 mm Hg; $P < 0.001$), down to mean SBP/DBP values of 149/89 mm Hg and 155/95 mm Hg, respectively, and had a significantly higher percentage of individuals who achieved BP control (SBP/DBP <140/90 mm Hg, 30.6% vs 17.3%; $P = 0.004$). Post hoc analyses suggest that NEB was not efficacious in reducing SBP in black participants. Mean changes in pulse rate were −12.8 beats/min for the NEB group and −1.6 beats/min for the PBO group ($P < 0.001$). Rates of discontinuations due to an AE (NEB vs PBO) were 1.4% in both groups, rates of any treatment-emergent AEs were 19.7% versus 19.0%, and rates of serious AEs were 0.3% versus 2.1%. The most common AEs (NEB vs PBO) were headache (2.1% vs 2.8%) and hypertension (0.7% vs 2.1%).

Conclusions: NEB monotherapy was an efficacious and well-tolerated treatment option for these study individuals with systolic stage II hypertension, but most of them would need combination therapy to achieve BP control. ClinicalTrials.gov identifier: NCT01057251. (*Clin Ther.* 2013;35:142–152) © 2013 Elsevier HS Journals, Inc. All rights reserved.

Key words: antihypertensive, β_1-selective blocker, clinical trial, nebivolol, stage II hypertension, tolerability.

INTRODUCTION

Approximately one third of US adults (66.4–76.8 million) have hypertension[1,2]; of those, 7.6 to 8.8

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Accepted for publication December 20, 2012.
http://dx.doi.org/10.1016/j.clinthera.2012.12.015
0149-2918/$ - see front matter

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million (11.5%)[2] are estimated to have stage II hypertension, which is defined as systolic blood pressure (SBP) ≥160 mm Hg or diastolic blood pressure (DBP) ≥100 mm Hg.[3] The risk of cardiovascular mortality is markedly higher in individuals with stage II hypertension compared with age-matched individuals with stage I hypertension (SBP 140–59 mm Hg or DBP 90–99 mm Hg).[4] That risk seems to be driven by SBP in a manner independent of age; SBP levels >160 mm Hg have been associated with an unadjusted mortality rate among men of 66.6 per 10,000 person-years, compared with rates of 37.4 and 15.4 per 10,000 person-years for SBP of 140 to 159 mm Hg and <140 mm Hg, respectively.[5] Although the prevalence of stage I hypertension in the entire adult population is 2.3 times higher than that of stage II hypertension,[5] that ratio changes with age: among individuals in their fifties, ~17% and ~5% can be expected to have stage I and stage II hypertension, respectively, whereas those rates increase to 28% and 32% in individuals who are aged ≥80 years.[5] Age is also associated with hypertension type: isolated systolic hypertension is significantly more prevalent in individuals who are aged ≥65 years compared with their younger counterparts (37.4% vs 19.2%).[6] Therefore, the status of SBP as an independent cardiovascular risk factor,[5] the observation that stage II SBP is associated with approximately twice the mortality rate compared with stage I SBP,[5] and the fact that resistant hypertension is mostly a consequence of uncontrolled SBP[7] (isolated systolic hypertension accounts for 57%−77% of such cases) all suggest a need for therapies that can effectively reduce stage II SBP to recommended levels.

Nebivolol is a β_1-selective blocker with nitric oxide–dependent vasodilatory properties,[8] approved in the United States for the treatment of stage I and II hypertension. Available post hoc analyses suggest that nebivolol may be an efficacious monotherapy for the treatment of stage II hypertension,[9] but prospective, randomized studies that have evaluated the effects of β-blockers on stage II hypertension seem to be scarce. Herein we summarize the results of a randomized trial that was conducted to assess the efficacy and safety of nebivolol in individuals with systolic stage II hypertension.

METHODS

Ethical Conduct

The study was conducted in full compliance with The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use guidelines for Good Clinical Practice, which have been adopted by the US Food and Drug Administration, and in accordance with the ethical principles that originate in the Declaration of Helsinki and the 21 Code of Federal Regulations (§312.120). In addition, the study was approved by all participating institutional review boards. All individuals enrolled had to have the mental capacity to understand the study and its procedures and to provide written informed consent for participation.

Study Design

This was a Phase IV, randomized, double-blind, placebo-controlled multicenter trial (NEB-MD-20; NCT01057251) in individuals with systolic stage II hypertension. After screening, individuals receiving antihypertensive treatment entered a 4-week, single-blind placebo washout phase; those who had not used antihypertensive medication for ≥4 weeks before screening were randomized to treatment without entering the washout phase. Qualifying participants were randomized (2:1) to 6-week double-blind treatment with 5 mg/d of nebivolol (titrated directly to 20 mg/d after 2 weeks if SBP was 130–180 mm Hg and the previous dose was well tolerated) or placebo, taken each morning. The decision to increase the nebivolol dosage from 5 to 20 mg/d directly (ie, to skip the intermediate dosage of 10 mg/d) was made because it was estimated that the study population would most likely need a higher dosage to achieve BP control. In addition, reducing the number of titration steps would result in a shorter study duration, thereby reducing the time that participants receiving placebo would be without active therapy. After 6 weeks of double-blind treatment, the study drug was tapered in a 1-week withdrawal phase. For safety reasons (ie, to timely discover potentially dangerous increases in BP), all participants were given an OMRON home BP measurement device (Omron Healthcare, Inc, Lake Forest, Illinois) for use at their own discretion.

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