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Research Article

Differential effects of nebivolol and metoprolol on arterial stiffness, circulating progenitor cells, and oxidative stress

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Abstract

Unlike traditional beta receptor antagonists, nebivolol activates nitric oxide. We hypothesized that therapy with nebivolol compared with metoprolol would improve arterial stiffness, increase levels of circulating progenitor cells (PC), and decrease oxidative stress (OS). In a randomized, double–blind, cross–over study, 30 hypertensive subjects received either once daily nebivolol or metoprolol succinate for 3 months each. Pulse wave velocity and augmentation index were measured using tonometry. Flow cytometry was used to measure circulating PC. OS was measured as plasma aminothiols. Measurements were performed at baseline, and repeated at 3 and 6 months. No significant differences were present between the levels of OS, arterial stiffness, and PC numbers during treatment with metoprolol compared with nebivolol. In subgroup analyses of beta–blocker naïve subjects (n = 19), nebivolol reduced pulse wave velocity significantly compared with metoprolol (-1.4 ± 1.9 vs. -0.1 ± 2.2; $P = .005$). Both nebivolol and metoprolol increased circulating levels of CD34+/CD133 + PC similarly ($P = .05$), suggesting improved regenerative capacity. J Am Soc Hypertens 2015;9(3):206–213.

Keywords: Pulse wave velocity; beta blocker; aminothiols; CD34; CD133.

Introduction

Cardiovascular disease (CVD) is precipitated by the deleterious effects of known risk factors that include hypertension. The initiation and progression of sub–clinical and overt CVD is primarily a result of risk factor–mediated activation of oxidative stress (OS) and subsequent endothelial dysfunction that is characterized by reduced nitric oxide (NO) bioavailability.[1–3] The ultimate severity of underlying CVD is a manifestation of the balance between the injury inflicted by the risk factors and the mitigation of this damage by repair and regeneration from innate reparative processes that are mediated by stem and progenitor cells (PC).[4–7] Regenerative capacity nevertheless decreases with age and with risk factor exposure, and may thus represent a modifiable cardiovascular risk factor.

Beta–blocker therapy remains a pillar in the treatment of CVD. The wide array of available agents have heterogeneous pharmacokinetics, which often translate into significant differences in clinical effects.[8,9] Nebivolol is a selective beta–1 adrenergic blocker with a unique hemodynamic profile compared with traditional beta–receptor antagonists.[10] The anti–hypertensive effect of nebivolol is due in part to a direct vasodilatory effect mediated by enhanced

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Conflict of interest: None.

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NO release from endothelial cells by partial beta–2 and beta–3 receptors agonist activity.[11–16] Furthermore, nebivolol, but not metoprolol, limited transcription of pro–inflammatory genes in the endothelium and inhibited neo–intima formation in animal models.[17–20] Nebivolol therapy was also shown to reduce markers of OS in preclinical models and clinical studies.[21–24] Finally, in a murine myocardial infarction model, nebivolol increased early endothelial PC compared with metoprolol or placebo.[25]

Whether these observed vasculo–protective effects of nebivolol in experimental settings translate to subjects with hypertension has not been investigated. To study whether reduction in OS and stimulation of PC with nebivolol occurs independent of its antihypertensive effects, we compared the effects of nebivolol and metoprolol in subjects with hypertension. We hypothesized that nebivolol will selectively improve OS, stimulate circulating PC levels, and improve vascular dysfunction in subjects with hypertension.

Methods

Study Design

In a randomized, double–blind cross–over study, we administered either oral nebivolol or metoprolol for 3 months each to subjects with essential hypertension (Figure 1). The initial 5 mg daily dose of nebivolol was titrated to 10 mg daily after 2 weeks if their blood pressure (BP) remained >125/80 mm Hg, and subsequently titrated to 20 mg daily after another 2 weeks if the BP remained >125/80 mm Hg. Similarly, the initial 50 mg daily dose of metoprolol succinate was titrated to 100 mg daily after 2 weeks if BP remained >125/80 mm Hg, and further increased to 200 mg after 2 weeks if BP remained >125/80 mm Hg. Background antihypertensive therapy was maintained constant throughout the study except in the event of uncontrolled BP defined as >150/90 mm Hg. Following the first 3–month drug treatment period and after a washout period of 2 weeks, participants were crossed over in a double–blind manner to either metoprolol succinate 50 mg daily or Nebivolol 5 mg daily and titrated as described above. Primary (markers of OS and circulating PC) and secondary endpoints (arterial stiffness and compliance) were measured at baseline, 3 months, and 6 months.

Study Participants

A total of 96 subjects with a diagnosis of essential hypertension were screened, and 38 completed the baseline visit (Figure 1). Hypertensive patients with BP >135/85 mm Hg were eligible to participate, and those with BP <135/85 mm Hg had their anti–hypertensive medication doses decreased or discontinued. Pre–menopausal women and subjects with acute illnesses, arrhythmias, heart failure, acute coronary syndromes, or with a BP >165/95 mm Hg at baseline were excluded. Concomitant use of aspirin, statins, thiazide diuretics, calcium channel blockers, clonidine, vasodilators, or angiotensin antagonists was permitted, and subjects had to be on stable medical therapy for at least 2 months before enrollment. Patients with controlled BP (BP <140/90 mm Hg) and treated with beta–adrenergic antagonists at the time of enrollment had this withheld for 2 weeks and switched to the study medication at the time of randomization. Similarly those with controlled BP underwent a second washout period prior to crossing over to the alternate therapy. Studies were performed at the Emory University Hospital Clinical Research Network

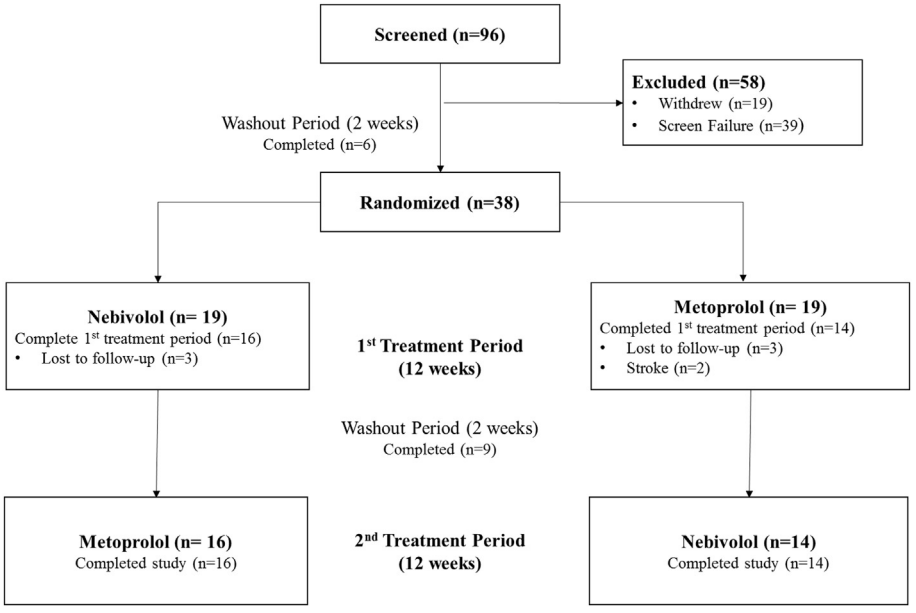

Figure 1. Study flow diagram.