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Effects of Add-On Nebivolol on Blood Pressure and Glucose Parameters in Hypertensive Patients With Prediabetes

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In this multicenter trial, the effects of nebivolol added to an angiotensin-converting enzyme (ACE) inhibitor or angiotensin II receptor blocker (ARB) were assessed in patients with hypertension (diastolic blood pressure [DBP] 80–110 mm Hg) and prediabetes (fasting blood glucose 100–125 mg/dL and/or 2-hour oral glucose tolerance test [OGTT] 140–199 mg/dL). After a 4-week run-in period (in which lisinopril [10 mg/d] or losartan [50 mg/d] treatment was initiated), patients with DBP 90–110 mm Hg were randomized (2:2:1) to 12-week, double-blind treatment with nebivolol (n=223; 5–40 mg/d), hydrochlorothiazide (HCTZ; n=212; 12.5–25 mg/d), or placebo (n=102), titrated to achievement of 130/80 mm Hg. The primary outcome measure was DBP (last observation carried forward, intent to treat population); secondary measures included systolic blood pressure (SBP) and glucose levels. At baseline, overall mean values for body mass index, triglycerides, and high-density lipoprotein cholesterol were 32.3 kg/m^2, 1.7 mmol/L, and 1.3 mmol/L, respectively. At week 12, nebivolol and placebo groups demonstrated a decrease of −9.4 and −5.0 mm Hg, respectively (P<.001) for DBP and −10.4 and −7.8 mm Hg for SBP (P=.147). The mean changes in area under the curve OGTT were 0.0 mg/dL (nebivolol), 6.9 mg/dL (HCTZ; P=.024 vs nebivolol), and −1.0 mg/dL (placebo). Adverse event–related discontinuation rates were 10.3%, 6.6%, and 2.0%, respectively. Nebivolol, added to an ACE inhibitor or ARB, provides additional blood pressure reduction with little or no effect on glucose metabolism in hypertensive patients with prediabetes. *J Clin Hypertens (Greenwich).* 2013;15:270–278. ©2013 Wiley Periodicals, Inc.

It has been estimated that diabetes affects 13% of US adults,[1] which currently amounts to approximately 23 million people.[2] Age-adjusted mortality among individuals with diabetes is about twice the mortality observed in individuals without diabetes, and this increased risk of mortality is not fully explained by the higher number of risk factors associated with diabetes.[3,4]

An additional 30% to 35% (53–62 million) of US adults have been estimated to have prediabetes, defined as impaired fasting glucose (IFG) levels (100–125 mg/dL; 19% to 26% of the total population), impaired glucose tolerance (IGT; 2-hour levels after oral intake of 75 g glucose in the range of 140–199 mg/dL; 5% to 14%), or both (10%).[1,5] Such individuals are at a greater risk of developing diabetes[6] and, similar to those with diabetes, have a higher risk of cardiovascular (CV) mortality[7,8] compared with individuals with normal glucose levels.

The situation is further complicated in individuals with hypertension, of whom approximately two thirds have been estimated to have prediabetes or diabetes.[9] In that population, both prediabetes and diabetes have been associated with an increased risk of all-cause and CV-related mortality in a manner independent of coexisting hypertension.[10,11] Because of this additional CV risk, the current guidelines for patients with hypertension and diabetes recommend more stringent goals for blood pressure (BP) control (<130/80 mm Hg) than for patients with uncomplicated hypertension (<140/90 mm Hg).[12,13] The attainment of these goals typically requires therapy with $\geq$2 drugs.[13–15] Recent meta-analyses suggest that a target systolic BP (SBP) in the range of 130 to 135 mm Hg is acceptable for patients with prediabetes or diabetes, except for those with a high risk of stroke,[16,17] in part because of a higher occurrence of serious adverse effects associated with drug-induced achievement of very low BP targets.[16] The 2010 American Diabetes Association's (ADA's) guidelines recommended angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs) as first-line treatment for hypertension in individuals with diabetes[18]; however, those guidelines, the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7), and the 2007 guidelines of the European Society of Hypertension point out that all major classes of antihypertensives should be considered.[13,18,19]

Nevertheless, certain classes of antihypertensives, such as thiazide diuretics and β-blockers, have been associated with an increased risk of dysglycemia, including new-onset prediabetes and diabetes,[20–23] which prompted the ADA to list these drug classes as agents that can result in "drug- or chemical-induced diabetes."[24] Available data suggest that the risk of drug-induced prediabetes and diabetes is predominantly associated with traditional, nonvasodilatory

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β-blockers (atenolol, propranolol, metoprolol), but not with more recent vasodilatory agents (carvedilol, nebivolol).[21,25,26] However, the effects of vasodilatory β-blockers on glycemic control in patients with hypertension and prediabetes have not been thoroughly studied.

The objective of this phase IV study was to evaluate the effects of add-on nebivolol, a β_1-selective blocker with nitric oxide (NO)–dependent vasodilatory properties,[27] in individuals with prediabetes who were receiving background therapy of an ACE inhibitor or ARB. Specifically, the study evaluated the effects of nebivolol on BP (vs placebo) and on glycemic parameters (vs hydrochlorothiazide [HCTZ]).

METHODS

Study Ethics

This trial (NCT00673790) was conducted in compliance with the International Conference on Harmonisation (ICH) Guidances on General Considerations for Clinical Trials, Good Clinical Practice, and the Code of Federal Regulations (21 CFR § 312.120). The study protocol, amendments, and forms were approved by the institutional review boards at the study centers in the United States, in agreement with 21 CFR, Part 56. All patients provided written informed consent prior to participating in any study procedure.

Participants

Participants were men and women aged 18 to 80 years with a diagnosis of primary hypertension and with diastolic BP (DBP) at screening in the range of 90 mm Hg to 110 mm Hg if currently untreated, 85 mm Hg to 105 mm Hg if taking 1 antihypertensive medication, or 80 mm Hg to 95 mm Hg if taking 2 antihypertensive medications. Individuals were included in the trial if fasting blood (plasma or serum) glucose (FBG) levels were 100 mg/dL to 125 mg/dL or if plasma glucose levels were 140 mg/dL to 199 mg/dL 2 hours after an oral glucose tolerance test (2-hour OGTT).

Individuals with secondary hypertension, fasting triglycerides >400 mg/dL, a pulse rate <55 beats per minute, or body mass index (BMI) >45 kg/m^2 were not eligible to participate in the study. Additional exclusion criteria were the presence of clinically significant respiratory disease (eg, bronchial asthma, reactive airways disease, and chronic obstructive pulmonary disease), coronary artery disease, clinically significant cardiac conduction defects, liver disease, renal impairment, untreated thyroid disease, and any disease or condition that might interfere with study conduct or confound interpretation of study results. Women who were pregnant or breastfeeding and individuals with a history of myocardial infarction, cerebrovascular accident, angina, transient arrhythmia, or transient ischemic attacks within 6 months prior to screening, who had used antidiabetic drugs or niacin within 6 months prior to screening, or who had used any unapproved medication within 3 months prior to screening were not allowed to participate. Abnormal or clinically significant results of physical examination, laboratory tests, and electrocardiography (ECG) at screening also resulted in disqualification from the study.

Study Design

This was a phase IV randomized, double-blind, placebo- and active-controlled, parallel-group, multicenter trial. Following a 1-week screening, patients entered a 4-week run-in phase, during which they were treated with either an ACE inhibitor (lisinopril, 10 mg/d) or an ARB (losartan, 50 mg/d). Patients taking an ACE inhibitor at screening were assigned to open-label lisinopril treatment; those taking an ARB were assigned to losartan. Patients who were receiving neither drug class at screening were randomly assigned to receive either lisinopril or losartan (1:1). All other antihypertensive therapies were discontinued.

Following the run-in phase, patients were randomized (2:2:1) to 12 weeks of double-blind add-on treatment with nebivolol (5 mg/d), HCTZ (12.5 mg/d), or placebo, titrated to 10 mg/d, 20 mg/d, or 40 mg/d (nebivolol), or 25 mg/d (HCTZ), as needed to achieve optimal BP control (SBP <130 mm Hg; DBP <80 mm Hg). Patients were evaluated at screening (for inclusion), at weeks –4 and –2 of the run-in phase, at randomization (week 0; baseline), and at weeks 3, 6, 9, and 12 of the double-blind treatment phase.

Randomization and Blinding Procedures

A list of patient randomization codes was generated and implemented by Perceptive Informatics (Northbrook, IL), and an electronic version was stored on a secured server. This list identified each patient by randomization number and included the corresponding treatment assignment. The unblinding of the randomization codes was permissible only in cases of emergency. The investigational products (placebo, nebivolol, HCTZ) were identical in appearance (size, shape, and color), taste, and packaging.

Assessments

BP was measured at each study visit as trough seated cuff SBP and DBP using an automatic BP monitor (Omron). Three separate seated trough cuff measurements were taken at each clinic visit following a 5-minute rest period, with 1 to 5 minutes between measurements. The mean of these 3 measurements was recorded as the BP value for each visit. To monitor changes in glucose parameters, fasting plasma glucose and 2-hour OGTT were assessed at week 2 (visit 3; beginning of run-in phase) and at the end of the study (week 12). In addition, FBG was calculated as the average of fasting serum glucose assessed at randomization (visit 4, week 0) and fasting plasma glucose, determined at week 2 and week 12. When either fasting serum glucose or fasting plasma glucose measurement was not available, the other represented FBG.

Homeostasis model assessment of insulin resistance (HOMA-IR)[28]—calculated as (fasting plasma glucose [FPG, mmol/L] × fasting plasma insulin [FPI, mU/L])/22.5—was determined at baseline and week 12.[28]

Safety was assessed at each clinic visit by means of vital signs and adverse events (AEs), and additionally at screening, randomization, and end of study by means of physical examination and clinical laboratory evaluations.

Protocol-Based Efficacy and Safety Parameters

The primary efficacy parameter was change from baseline to week 12 in trough seated DBP (nebivolol vs placebo). The secondary parameters comprised the change from baseline to week 12 in plasma glucose levels after 2-hour OGTT with 75 g of glucose (key secondary parameter; nebivolol vs HCTZ), trough seated SBP (nebivolol vs placebo), FBG (nebivolol vs HCTZ), and HOMA-IR (nebivolol vs HCTZ). Additional efficacy parameters (all nebivolol vs HCTZ) included the incidence of new-onset diabetes (FPG $\geq$126 mg/dL or plasma glucose 2 hours after OGTT $\geq$200 mg/dL) at week 12, and changes from baseline to week 12 in the levels of hemoglobin A_{1c} (HbA_{1c}), fasting triglycerides, cholesterol (total, high-density lipoprotein [HDL], and low-density lipoprotein [LDL]), and adiponectin. Safety parameters included the incidence of treatment-emergent AEs (TEAEs) and changes from baseline in vital signs and clinical laboratory parameters, including changes that were potentially clinically significant (PCS).

Post Hoc Efficacy Parameters

Post hoc analyses were performed to evaluate baseline to week 12 changes in DBP and SBP for the HCTZ treatment group (no statistical between-group comparisons were performed) and the area under the curve (AUC) changes during the first 2 hours of OGTT (nebivolol vs HCTZ comparisons were performed).

Sample Size Determination and Data Analysis

For the primary efficacy parameter (baseline to endpoint change in DBP), assuming a common standard deviation (SD) of 8.5 mm Hg, 200 patients in the nebivolol group and 100 patients in the placebo group were required to detect a difference of 3.5 mm Hg with 90% power at a significance level of .05 (2-sided). For the key secondary parameter (baseline to endpoint changes in glucose levels using OGTT), assuming a common SD of 37 mg/dL, 170 patients in the nebivolol group and HCTZ group each were required to detect a between-group difference of 11.5 mg/dL with an approximate power of 80% at a significance level of .05 (2-sided).

The primary efficacy analysis was based on the intent-to-treat (ITT) population, defined as all patients who received at least one dose of double-blind medication and had at least 1 postbaseline assessment of trough seated DBP; the last-observation-carried-forward (LOCF) approach was used to impute missing data. Sensitivity analyses were performed using the observed cases (OC) approach. For all efficacy parameters, baseline was defined as week 0 (randomization), except for OGTT and FBG, for which baseline was defined as the last assessment before the first dose of double-blind treatment. All statistical tests were 2-sided (α=.05), with 2-sided 95% confidence intervals. Between-group comparisons were performed by means of an analysis of covariance model, with treatment group and study center as factors and baseline value as a covariate. The Hochberg procedure was used to adjust for multiplicity among the secondary outcome measures.

Safety analyses were based on the safety population, defined as all patients who received at least one dose of double-blind study drug, and are presented using descriptive statistics. For safety analyses, the last assessment made prior to the first dose of double-blind study medication was considered baseline.

RESULTS

Study Flow, Baseline Characteristics, and Drug Exposure

The study flow is presented in Figure 1. The treatment groups were similar in their baseline demographic and clinical characteristics (Table I). The majority of patients were men (56.1%), white (68.9%), younger than 65 years (82.5%), and had a mean BMI of 32.3 kg/m^2. At the end of the double-blind treatment phase, 133 (59.6%) nebivolol-treated patients were receiving the 40-mg dose and 190 (89.6%) HCTZ-treated patients were receiving the 25-mg dose.

BP Outcomes

At the end of week 12, nebivolol—added to lisinopril or losartan—was significantly more effective than placebo in reducing trough seated DBP (Figure 2, Table II); this difference was also significant using the OC approach (−10.1 mm Hg vs −5.2 mm Hg, P<.001). The mean baseline to endpoint reduction in trough seated SBP (secondary efficacy parameter) was not significantly different using the LOCF approach between the nebivolol- and placebo-treated patients (Figure 2, Table II), but it was significant among the patients who completed the trial (OC: −11.4 mm Hg vs −7.9 mm Hg, P=.039). BP reductions observed in the HCTZ arm are presented in Table II.

Glycemic and Lipid Outcomes

The protocol-specified analysis of 2-hour OGTT (key secondary parameter) showed a numerically greater but statistically nonsignificant increase in plasma glucose levels in the HCTZ group, compared with the nebivolol group; however, a post hoc analysis of the AUC OGTT data suggested a significant increase in plasma glucose levels in the HCTZ group compared with the nebivolol group (Figure 3, Table II). The mean baseline to endpoint increase in FBG among HCTZ-treated patients was significantly greater than the increase observed

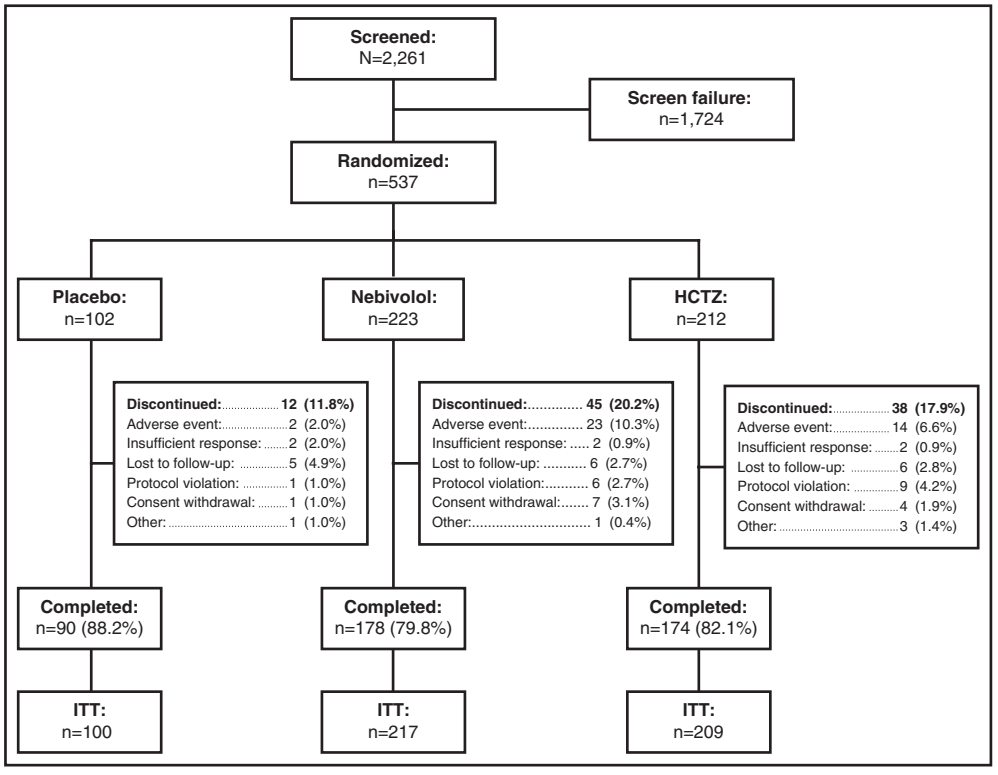

FIGURE 1. Study flow. HCTZ indicates hydrochlorothiazide; ITT, intent-to-treat population.

among nebivolol-treated individuals (Figure 3, Table II). No significant differences were found between the nebivolol and HCTZ groups in change from baseline for the HOMA-IR (Figure 3, Table II) or for HbA_{1c}, triglycerides, total cholesterol, or LDL cholesterol (data not shown). Baseline to endpoint changes were significantly different between nebivolol and HCTZ groups for levels of HDL cholesterol (least-squares mean±standard error: −2.3±0.6 mg/dL vs −0.4±0.6 mg/dL, respectively; P=.003) and adiponectin (−0.80±0.15 μg/mL vs −0.13±0.15 μg/mL; P<.001), both in favor of HCTZ. In the placebo group, 6 of 100 (6.0%) participants were diagnosed with diabetes during the study, compared with 24 of 217 (11.1%) in the nebivolol group and 33 of 209 (15.8%) in the HCTZ group. The rates of new-onset diabetes in the nebivolol and HCTZ groups were not significantly different.

Safety and Tolerability

During the double-blind treatment phase, 2.0% (2 of 102), 10.3% (23 of 223), and 6.6% (14 of 212) of the placebo-, nebivolol-, and HCTZ-treated patients, respectively, discontinued the trial because of an AE (Figure 1). During that period, a total of 537 patients experienced 546 TEAEs (placebo: 54 [52.9%] patients, 114 TEAEs; nebivolol: 118 [52.9%] patients, 250 TEAEs; HCTZ: 90 [42.5%] patients, 182 TEAEs). The rates of common TEAEs (those occurring in ≥2% of patients in any group) are presented in Table III.

Bradycardia was the only common TEAE that was experienced by a higher percentage of nebivolol-treated patients (5.4% [12 of 223]) than patients treated with both HCTZ (0) and placebo (0) (Table III); in all cases, it was of mild or moderate severity. Most TEAEs were mild or moderate in severity (placebo: 93.9% [107 of 114]; nebivolol: 95.2% [238 of 250]; HCTZ: 95.1% [173 of 182]). No severe TEAEs occurred in ≥2% of patients in any group. In the placebo group, 23.7% (27 of 114) and 0.9% (1 of 114) TEAEs were judged to be possibly related or related to double-blind treatment, respectively, compared with 23.6% (59 of 250) and 5.6% (14 of 250) in the nebivolol group and 26.9% (49 of 182) and 5.5% (10 of 182) in the HCTZ group.

In the period between the first dose of double-blind medication and 30 days following the last dose of double-blind medication, 2.0% (2 of 102) of placebo-treated patients experienced a serious AE (SAE), compared with 2.7% (6 of 223) of patients treated with nebivolol and 3.8% (8 of 212) treated with HCTZ. In the nebivolol group, two instances of an SAE (one stroke and one case of noncardiac chest pain) were considered possibly related to double-blind treatment. In the HCTZ group, one instance of cardiac arrest was considered possibly related to treatment, and one instance of angioedema was considered related to treatment. There were 4 deaths: in the nebivolol group, one patient died from stroke and one died from cancer. In the HCTZ group, one patient died from cardiac

TABLE I. Demographic and Clinical Characteristics at Baseline (Safety Population)

Characteristic	Placebo (n=102)	Nebivolol (n=223)	HCTZ (n=212)
Age, y[a]	55.2±11.3	54.4±9.6	55.7±10.4
Men, No. (%)	64 (62.7)	122 (54.7)	115 (54.2)
Race, No. (%)			
White	76 (74.5)	151 (67.7)	143 (67.5)
Black	14 (13.7)	55 (24.7)	43 (20.3)
Other	12 (11.8)	17 (7.6)	26 (12.2)
Ethnicity, No. (%)			
Hispanic	20 (19.6)	50 (22.4)	44 (20.8)
Non-Hispanic	82 (80.4)	173 (77.6)	168 (79.2)
Weight, kg[a]	93.6±20.3	93.2±17.7	93.9±19.1
BMI, kg/m^{2a}	31.8±5.2	32.5±4.9	32.4±5.2
Trough seated SBP, mm Hg[a]	151.8±11.4	151.5±11.4	151.9±13.3
Trough seated DBP, mm Hg[a]	93.3±8.5	94.1±7.8	93.8±8.5
Trough seated HR, bpm[a]	74.6±11.1	73.1±10.4	73.7±11.6
FBG, mg/dL[a]	104.4±10.8	104.4±12.6	104.4±10.8
2-h OGTT, mg/dL[a]	131.5±36.0	135.1±45.0	138.7±43.2

Abbreviations: BMI, body mass index; bpm, beats per minute; DBP, diastolic blood pressure; FBG, fasting blood glucose; HCTZ, hydrochlorothiazide; HR, heart rate; OGTT, oral glucose tolerance test; SBP, systolic blood pressure. [a]Mean±standard deviation.

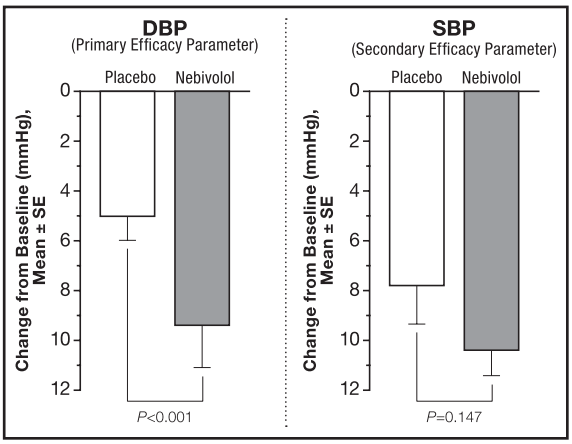

FIGURE 2. Change from baseline to week 12 in trough seated diastolic blood pressure (DBP) (intent-to-treat population [ITT], last observation carried forward [LOCF]). SE indicates standard error of the mean.

arrest and one from myocardial infarction. The cases of cancer and myocardial infarction were considered not related to treatment; stroke and cardiac arrest were considered possibly related to treatment.

Mean baseline to endpoint changes in vital signs and clinical laboratory parameters were generally small and similar between groups. From baseline to endpoint, patients in the placebo group experienced a mean±SD weight change of −0.5±3.4 kg, compared with 0.0±2.9 kg in the nebivolol group and −0.1±2.9 kg in the HCTZ group. The percentages of patients who experienced body weight loss ≥7% were as follows: placebo, 2.0% (2 of 100); nebivolol, 2.3% (5 of 217); HCTZ, 1.9% (4 of 209). However, the assessment of available data yielded a rate of 71.9% (23 of 32) for placebo-treated patients who experienced a shift from normal to high levels of glucose, compared with 42.6% (26 of 61) and 40.4% (23 of 57) in the nebivolol and HCTZ groups, respectively. Postbaseline shifts in HbA_{1c} values from normal to high occurred in 8.2% (6 of 73) of placebo-treated patients, 14.8% (20 of 135) of patients treated with nebivolol, and 17.5% (22 of 126) of patients treated with HCTZ, which was also reflected in the rates of new-onset diabetes (placebo, 6% [6 of 100]; nebivolol, 11.1% [24 of 217]; HCTZ, 15.8% [33 of 209]). In addition, a shift from normal to low levels of HDL cholesterol occurred in 8.2% (5 of 61), 10.3% (15 of 145), and 6.5% (8 of 124) of patients in the placebo, nebivolol, and HCTZ groups, respectively; the shift rates from normal to high LDL cholesterol were 16.9% (10 of 59), 16.2% (17 of 105), and 19.0% (24 of 126). The shift rates from normal to high creatinine were 1.1% (1 of 89; placebo), 6.6% (12 of 181; nebivolol), and 3.4% (6 of 176; HCTZ). The PCS increases in plasma glucose values (ie, >1.2-fold higher than the upper limit of normal) were measured in 7.8% (6 of 77), 15.5% (25 of 161), and 22.4% (37 of 165) of placebo-, nebivolol-, and HCTZ-treated patients, respectively. The proportions of patients with baseline to endpoint potassium changes from normal to low were similar between groups (placebo, 1.1% [1 of 93]; nebivolol, 0 [0 of 177]; HCTZ, 1.6% [3 of 185]).

DISCUSSION

In this study, nebivolol treatment (5–40 mg/d), administered as add-on to an ongoing therapy with an ACE inhibitor or ARB, resulted in a significant additional reduction in DBP in patients with hypertension and prediabetes, compared with placebo, and had little or no effect on glucose metabolism and lipid parameters when compared with HCTZ treatment. In this patient population, 12-week adjunctive therapy with nebivolol was well tolerated.

The results of this study are in agreement with data obtained from previous trials. Treatment with nebivolol as add-on or combination therapy has been shown to provide a significant BP reduction in several randomized trials,[29–32] including those in which ACE inhibitors or ARBs were used as background therapy[31] or in initial combination.[33] In addition, a neutral or favorable metabolic profile of nebivolol has been demonstrated in several studies of patients with dysglycemia. A small (N=25), randomized, crossover trial of 16-week treatment with nebivolol (2.5–5 mg/d) or atenolol (50–100 mg/d) found that atenolol—but not nebivolol—was associated with reduced insulin sensitivity (measured using a euglycemic-hyperinsulinemic clamp test) in

TABLE II. Primary, Secondary, and Post Hoc Outcome Measures (ITT, LOCF)

Outcome Measure	Placebo (n=100)	Nebivolol (n=217)	HCTZ (n=209)
Primary efficacy parameter			
DBP, mm Hg			
No.	100	215	208
Baseline[a,b]	93.3±8.4	94.1±7.9	93.8±8.5
Change from baseline[a,b]	−5.0±9.5	−9.4±8.9	−8.4±9.5
LSMD (95% CI)	−4.3 (−6.4 to −2.3)		NA[c]
P value	<.001		NA[c]
Secondary efficacy parameters			
2-h OGTT, mg/dL (key secondary parameter)			
No.	90	179	177
Baseline[a,b]	130.0±36.0	134.7±43.9	136.3±41.6
Change from baseline[a,b]	1.4±37.6	4.9±39.1	8.1±42.5
LSMD (95% CI)	NA[c]	−2.0 (−10.1 to 6.1)	
P value	NA[c]	.627	
SBP (mm Hg)			
No.	100	215	208
Baseline[a,b]	151.7±11.5	151.3±11.3	151.9±11.3
Change from baseline[a,b]	−7.8±15.7	−10.4±14.8	−13.8±15.1
LSMD (95% CI)	−2.7 (−6.3 to 0.9)		NA[c]
P value	.147		NA[c]
FBG, mg/dL			
No.	93	201	192
Baseline[a,b]	103.7±10.4	104.3±11.9	104.6±10.4
Change from baseline[a,b]	0.0±11.0	1.3±13.5	5.4±18.4
LSMD [95% CI]	NA[c]	−4.7 (−7.6 to −1.6)	
P value	NA[c]	.002	
HOMA-IR			
No.	90	184	184
Baseline[a,b]	4.4±4.6	4.6±3.3	5.0±4.3
Change from baseline[a,b]	0.0±4.1	0.6±5.0	1.5±7.8
LSMD (95% CI)	NA[c]	−1.0 (−2.2 to 0.2)	
P value	NA[c]	.097	
Post hoc efficacy parameter[d]			
AUC OGTT, mg/dL			
No.	86	156	156
Baseline[a,b]	151.6±28.1	157.3±33.7	155.8±27.5
Change from baseline[a,b]	−1.0±23.5	−1.0±26.8	7.6±24.9
LSMD (95% CI)	NA[c]	6.5 (−12.2 to −0.9)	
P value	NA[c]	.024	

Abbreviations: AUC, area under the curve; CI, confidence interval; DBP, diastolic blood pressure; FBG, fasting blood glucose; HbA_{1c}, glycosylated hemoglobin; HCTZ, hydrochlorothiazide; HDL, high-density lipoprotein; HOMA-IR, homeostatic model assessment of insulin resistance; ITT, intent to treat; LDL, low-density lipoprotein; LOCF, last observation carried forward; LSMD, least-squares mean difference; NA, not applicable; OGTT, oral glucose tolerance test; SBP, systolic blood pressure. [a]Mean±standard deviation. [b]For DBP, SBP, and HOMA-IR, baseline was defined as week 0 (randomization); for FBG, OGTT, and AUC OGTT, it was defined as week 2. [c]Statistical comparisons with other groups were not performed, per protocol specifications. [d]Observed cases.

patients with IGT.[34] Additional studies in patients with hypertension and type 2 diabetes have shown similar results: in a randomized, parallel-group, 24-week trial of 30 patients with hypertension and type 2 diabetes, neither nebivolol (5 mg/d) nor atenolol (50 mg/d) was shown to adversely affect carbohydrate metabolism (in terms of glucose infusion rate and whole body glucose utilization assessed using a euglycemic-hyperinsulinemic clamp test, HbA_{1c}, and urinary C-peptide excretion) or lipid levels (triglycerides and cholesterol [HDL, LDL, total]).[35] A randomized, double-blind, 12-week crossover pilot study of 12 patients with hypertension and type 2 diabetes did not find significant between-group or within-group changes in insulin sensitivity (assessed using the euglycemic-hyperinsulinemic clamp test) in the total body or in the blood vessels for nebivolol (5 mg/d) or the ACE inhibitor enalapril (10 mg/d).[36] In an open-label study of patients with hypertension and type 2 diabetes (N=26), 6 months of treatment with nebivolol (5 mg/d) did not worsen HbA_{1c}, total cholesterol, or

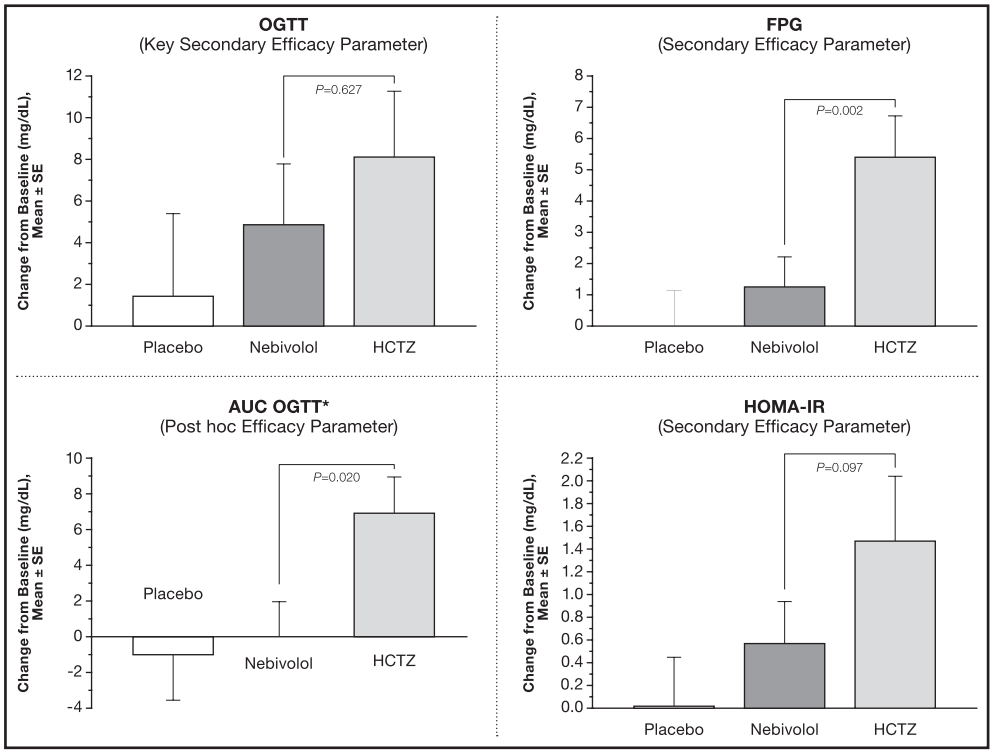

FIGURE 3. Change from baseline to week 12 in oral glucose tolerance test (OGTT), area under the curve (AUC) OGTT, fasting blood glucose (FBG), and homeostatic model assessment of insulin resistance (HOMA-IR) (intent to treat [ITT], last observation carried forward [LOCF]). *Observed cases (OC). HCTZ indicates hydrochlorothiazide; SE, standard error of the mean.

triglycerides or cause weight gain, although significant increases in HDL cholesterol (5 mg/dL [0.13 mmol/L]) and LDL subfractions (27 mg/dL [0.7 mmol/L]) were observed.[37] Most recently, a 12-week open-label study of patients with hypertension and type 2 diabetes (N=5031) demonstrated reductions in mean glucose levels and HbA_{1c} across several age groups in patients treated with nebivolol as monotherapy (21.4%), add-on therapy (53.7%; 48.4% treated with an ACE inhibitor or ARB), or replacement therapy (24.2%).[38] Taken

TABLE III. Common TEAEs[a] During the 12-Week Double-Blind Treatment Phase (Safety Population)

TEAE	Placebo (n=102)	Nebivolol (n=223)	HCTZ (n=212)
Any common TEAE	34 (33.3)	63 (28.3)	42 (19.8)
Bradycardia	0	12 (5.4)	0
Headache	7 (6.9)	12 (5.4)	12 (5.7)
Upper respiratory tract infection	7 (6.9)	12 (5.4)	10 (4.7)
Diarrhea	5 (4.9)	11 (4.9)	1 (0.5)
Back pain	1 (1.0)	7 (3.1)	8 (3.8)
Dizziness	4 (3.9)	5 (2.2)	6 (2.8)
Nasopharyngitis	3 (2.9)	4 (1.8)	0
Cough	3 (2.9)	3 (1.3)	1 (0.5)
Fatigue	2 (2.0)	3 (1.3)	7 (3.3)
Nausea	3 (2.9)	3 (1.3)	4 (1.9)
Sinusitis	3 (2.9)	2 (0.9)	5 (2.4)
Vomiting	3 (2.9)	1 (0.4)	0
Insomnia	4 (3.9)	0	2 (0.9)
Myalgia	3 (2.9)	0	1 (0.5)

Values are expressed as number (percentage). Abbreviations: HCTZ, hydrochlorothiazide; TEAE, treatment-emergent adverse event. [a]Common TEAEs were defined as those whose rate was at least 2.0% in any treatment group.

together, these data suggest that the neutral glycemic effect of nebivolol added to an ACE inhibitor or ARB treatment regimen is not caused by a beneficial glycemic effect of the RAAS inhibitors but by pharmacologic effects of nebivolol itself, such as NO-mediated vasodilation.[25]

Similar results have been obtained in patients with hypertension and normal glucose levels. For example, in a randomized pilot study (N=30) involving patients with hypertension and dyslipidemia, 12-week treatment with nebivolol (5 mg/d) or atenolol (50 mg/d), followed by 12 weeks of add-on pravastatin treatment (40 mg/d), resulted in a significant reduction in HOMA-IR in the nebivolol group but not in the atenolol group.[39] In addition, a pooled post hoc analysis of 3 pivotal 12-week monotherapy trials of nebivolol (N=1811) showed no statistically significant between-group differences in change from baseline for glucose, total cholesterol, or LDL cholesterol levels (Mori, A and Giles, TD; data presented at the 2010 Southern Medical Association Conference, Kissimmee, FL). In a recent randomized, placebo-controlled crossover trial of amiloride, HCTZ, nebivolol, and HCTZ-nebivolol combination (N=37), 4 weeks of treatment with HCTZ and HCTZ-nebivolol was associated with significant and similar increases in blood glucose (assessed using 2-hour OGTT) vs placebo, whereas the effect of nebivolol monotherapy was found to be metabolically neutral.[40] Finally, a randomized combination trial (N=656) in patients with stage II hypertension treated for 6 weeks with nebivolol 20 mg/d plus lisinopril 40 mg/d reported no clinically significant changes from baseline in metabolic parameters (FBG or lipids).[32]

STUDY STRENGTHS AND LIMITATIONS

To date, this is the largest prospective randomized trial designed and powered to evaluate the glycemic effects of nebivolol treatment as an efficacy parameter, as opposed to capturing the effects on glucose levels as a safety signal. The fact that the study was conducted in individuals with prediabetes addresses the needs of a substantial subset of US adults with an elevated cardiovascular risk[5,8] who have been largely overlooked in β-blocker trials; in addition, the use of ACE inhibitors and ARBs as background treatment facilitates generalization of our findings into real-life context. Our trial lends further support to the view that nebivolol treatment is generally metabolically neutral.[21,25]

The limitations of this study include a relatively large placebo effect for both DBP and SBP, which complicates our understanding of the magnitude of the effect that nebivolol would have in a real-life setting on patients with prediabetes who receive ACE inhibitor/ARB treatment. Although automatic oscillometric devices, in theory, should eliminate the observer bias and treatment expectations from physicians and nurses, they cannot eliminate the expectation bias of patients themselves. Probably the best approach to eliminate or significantly reduce placebo response in a hypertension trial would be to use ambulatory BP monitoring.[41] Additionally, the AUC analysis of the OGTT data, although clinically relevant and justified, was conducted post hoc; therefore, its results need to be verified in a prospective trial.

CONCLUSIONS

Our data indicate that nebivolol was well tolerated and significantly reduced DBP in patients with hypertension and prediabetes already receiving an ACE inhibitor or ARB. Results of the protocol-specified and post hoc analyses suggest that nebivolol has an overall neutral effect on well-established clinical measures of glucose metabolism.

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