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Efficacy of nebivolol-valsartan single-pill combination in obese and nonobese patients with hypertension

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Antihypertensive efficacy of single-pill combinations (SPCs) consisting of a β_1-selective adrenergic blocker with vasodilatory properties via β_3-agonism (nebivolol) and an angiotensin II receptor blocker (valsartan) was demonstrated in an 8-week phase 3 trial (NCT01508026). In this post hoc analysis, seated blood pressure, heart rate, 24-hour ambulatory blood pressure monitoring, plasma aldosterone, estimated glomerular filtration rate, and safety measures were assessed in obese (body mass index >32 kg/m^2; n=1823) and nonobese (body mass index <27 kg/m^2; n=847) adults with hypertension (stage I or II) treated with nebivolol-valsartan SPCs, nebivolol or valsartan monotherapy, or placebo. At week 8, reductions from baseline in blood pressure and ambulatory blood pressure monitoring were greater with SPCs and most nebivolol and valsartan monotherapy doses vs placebo regardless of obesity status. Aldosterone declined with all active treatments and estimated glomerular filtration rate remained steady. The nebivolol-valsartan 5/80 mg/d SPC was efficacious regardless of degree of obesity.

1 | INTRODUCTION

Controlling blood pressure (BP) is an important health priority to reduce the serious health consequences associated with hypertension, such as heart failure, stroke, and end-stage renal failure.[1,2] Hypertension is uncontrolled in approximately 50% of the more than one third of Americans older than 20 years who have hypertension,[3] and nearly 400 000 deaths annually have been attributed to complications associated with this condition.[1]

A key risk factor for developing hypertension is being overweight or obese.[2,4,5] Hypertension has been associated with lifestyle factors that lead to obesity, including physical inactivity, high caloric intake, and poor diet.[6] Approximately 41% of obese Americans have hypertension.[7] While lifestyle changes are recommended for patients with hypertension (especially those with obesity-related hypertension), many are unable to control their BP through lifestyle or diet modifications alone.

The pathogenesis of obesity-related hypertension is multifactorial and involves neural, hormonal, renovascular, and immune systems. Obesity directly[8] or indirectly[9] activates the sympathetic nervous system,[10] resulting in increased activity of the renin-angiotensin-aldosterone system (RAAS). Along with elevated BP, obese individuals—particularly those with excess abdominal fat—are more likely to have increased cardiac output and higher aldosterone plasma levels, leptin, and fasting insulin levels.[11,12] These obesity-related effects can complicate the effective management of hypertension with antihypertensive drugs.

Based on the underlying pathophysiology of the obese population with hypertension, we reviewed the efficacy of the nebivolol and valsartan single-pill combination (SPC) in a large (N=4118), phase 3 randomized trial of adults with hypertension by obesity status.[13] Nebivolol is a highly selective β_1-adrenergic blocker with vasodilatory properties via β_3-agonism, and valsartan is an angiotensin II receptor blocker (ARB). The nebivolol 5 mg/valsartan 80 mg/d SPC is the only β-blocker/RAAS inhibitor combination approved by the US Food and Drug Administration (FDA) for the treatment of hypertension. In a post hoc analysis of this trial, the antihypertensive efficacy of nebivolol-valsartan SPCs and the effects on biomarker levels in a subgroup of obese (body mass index [BMI] >32 kg/m^2) and nonobese (BMI <27 kg/m^2) participants were examined and are reported here.

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2 | METHODS

2.1 | Study design

The details of the phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose-titration trial (NAC-MD-01; NCT01508026) were previously reported.[13] Briefly, after a 1-week screening period, participants entered a 6-week single-blind placebo run-in phase, followed by an 8-week double-blind treatment period. Participants were randomized 2:2:2:2:2:2:2:1 to 4 weeks of double-blind treatment with nebivolol-valsartan SPC 5/80, 5/160, or 10/160 mg/d; nebivolol monotherapy 5 or 20 mg/d; valsartan monotherapy 80 or 160 mg/d; or placebo. At the beginning of week 5, dosages were doubled to nebivolol-valsartan SPC 10/160, 10/320, or 20/320 mg/d; nebivolol 10 or 40 mg/d; or valsartan 160 or 320 mg/d. After 8 weeks of double-blind treatment, the dosages were tapered over a 1-week double-blind down-titration phase. In a subgroup of trial participants, 24-hour ambulatory BP monitoring (ABPM) and neurohormonal biomarker data were examined.

2.2 | Participants

Eligible participants were men or women 18 years and older with stage 1 or 2 hypertension (the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure 7 criteria[4]), with diastolic BP (DBP) measurements of ≥95 mm Hg and <110 mm Hg (untreated) or ≥90 mm Hg and <110 mm Hg (treated; only participants with ≥95 mm Hg at randomization were enrolled) and a seated heart rate (HR) of ≥55 beats per minute. Participants were also required to have normal or clinically nonsignificant results on physical examination, laboratory tests, and electrocardiogram at screening. Key exclusion criteria were secondary hypertension, severe hypertension (systolic BP [SBP] ≥180 mm Hg or DBP ≥110 mm Hg), current treatment with four or more antihypertensive medications (including components of the nebivolol-valsartan SPC), contraindication to discontinuing antihypertensive treatment, upper arm circumference >42 cm, the presence of symptomatic coronary artery disease, reactive airways disease, chronic obstructive pulmonary disease, second- or third-degree heart block or sick sinus syndrome, type 1 diabetes or poorly controlled type 2 diabetes (glycated hemoglobin ≥8%), any surgery (such as lap-band or gastric bypass) that may interfere with absorption of medication, or uncontrolled thyroid disease within 3 months of screening.

2.3 | Study procedures

Seated BP was measured using an automatic monitoring device (Omron HEM-705CP, Lake Forest, IL, USA). After a 5-minute rest, four seated BP measurements were taken 2 to 5 minutes apart; the mean of the last three values constituted the BP for the visit. HR was measured via electrocardiography at screening, baseline, and week 8.

For the ABPM/biomarkers substudy, ABPM measurements were recorded at baseline and at week 8 using a Spacelabs 90207 (Snoqualmie, WA, USA) oscillometric device that was set to automatically measure and record BP; data were processed by BioClinica (Princeton, NJ, USA). Sitting HR and peak BP were measured between 2 and 4 hours post-dose, prior to blood sample collection. Blood samples for the assessment of plasma aldosterone and estimated glomerular filtration rate (eGFR) were collected at baseline and at weeks 4 and 8. All samples were immediately frozen in a mixture of ethanol and ice and shipped on dry ice to the central laboratory (Keystone Bioanalytical Inc., North Wales, PA, USA). Aldosterone levels were determined using high-performance liquid chromatography coupled with tandem mass spectrometry; eGFR was calculated using serum creatinine values and the Modification of Diet in Renal Disease Study equation.[14]

2.4 | Current analyses

The key outcomes of the analyses reported here were change from baseline in clinic seated BP, HR, ABPM, and eGFR at week 8, and change from baseline in plasma aldosterone concentration and potassium levels at weeks 4 and 8. Week 8 data included placebo and pooled doses for each of the three active groups: SPCs, nebivolol, and valsartan as described further below. Data at week 4 included the 5/80 mg SPC as this was the final assessment timepoint for the singular FDA-approved dose.

Data for clinic BP, HR, ABPM, aldosterone, and eGFR at week 8 were pooled into one of four groups based on double-blind treatment randomization: (1) the SPC group, which included all participants treated with nebivolol-valsartan SPCs (10/160, 10/320, or 20/320 mg/d); (2) the nebivolol group, which included all patients treated with nebivolol 10 or 40 mg/d; (3) the valsartan group, which included all participants treated with valsartan 160 or 320 mg/d; and (4) the placebo group. To further evaluate the FDA-approved nebivolol-valsartan 5/80 SPC, change from baseline in BP and potassium levels were evaluated at week 4 prior to the per-protocol doubling of doses.

Changes in clinic BP were determined for obese (baseline BMI >32 kg/m^2) and nonobese participants (baseline BMI <27 kg/m^2) within the intention-to-treat (ITT) population (obese: n=1823 [44.3%]; nonobese: n=847 [20.6%]). Changes in ABPM and plasma aldosterone were examined for participants in the ABPM-biomarkers substudy (obese: n=375 [47.1%]; nonobese: n=148 [18.6%]; ITT). HR, eGFR, and potassium level changes were analyzed for participants in the safety population (obese: n=1841 [44.3%]; nonobese: n=851 [20.5%]). The ITT population included all randomized participants who took at least one dose of double-blind drug and had at least one DBP measurement after baseline. The safety population comprised all randomized participants who took at least one dose of double-blind study drug. Because of small sample sizes, ABPM and aldosterone data should be interpreted with caution. The BMI categories of >32 kg/m^2 and <27 kg/m^2 were chosen to clearly delineate obese and nonobese participants, as BMI can vary due to normal weight fluctuations.

Pooled week 8 clinic BP (ITT) and HR (safety population) were analyzed using an analysis of covariance model with the pooled treatment group, obesity subgroup (obese: >32 kg/m^2 and nonobese:

<27 kg/m^2), and pooled treatment-by-subgroup interaction as factors and the baseline value as a covariate. Missing BP, ABPM, and aldosterone data were imputed using the last-observation-carried-forward (LOCF) approach. eGFR and HR values are presented as observed data. ABPM at week 8, as well as aldosterone levels (ITT) and eGFR at weeks 4 and 8 (safety population) are presented as descriptive.

For the comparison of change from baseline in clinic BP at week 4 between nebivolol-valsartan 5/80 mg/d and monotherapies or placebo, analysis of covariance models similar to those utilized at week 8 were used for pairwise comparisons (treatment included SPC 5/80 mg/d; nebivolol 5 and 20 mg/d; valsartan 80 and 160 mg/d; and placebo treatment groups in the model). These analyses were based on the ITT population using an LOCF approach for missing data.

3 | RESULTS

3.1 | Baseline characteristics

Overall, demographic and clinical characteristics between the pooled treatment groups were similar within each BMI subgroup with the exception of Hispanic ethnicity. In the obese subgroup, a higher percentage of Hispanics was observed in the SPC treatment group (39.2%) vs the valsartan group (33.8%). In the nonobese subgroup, the percentage of Hispanics was highest in the placebo group (54.9%) compared with the SPC (44.5%), nebivolol (37.8%), and valsartan (39.6%) treatment groups (Table 1). Regardless of treatment group, obese participants were slightly younger than nonobese participants (mean range: 49.2–49.7 vs 52.2–53.8 years), and a greater percentage were black (11.9% obese vs 6.3% nonobese) or had type 2 diabetes (18.7% vs 9.8%).

3.2 | BP measurements

3.2.1 | Clinic BP (pooled doses)

At week 8, all pooled active treatments significantly reduced DBP and SBP from baseline vs placebo regardless of obesity status (Figure 1A,B). In both BMI groups, the SPCs significantly lowered DBP and SBP vs nebivolol and valsartan monotherapies (Figure 1C,D).

In the obese participants, nebivolol treatment resulted in significantly greater reductions in DBP vs valsartan (least squares mean difference [LSMD]=−3.34, P<.001). In the nonobese participants,

TABLE 1 Baseline demographic and clinical characteristics of BMI subgroups (ITT population)

Obese (BMI >32 kg/m^2)	PBO (n=138)	SPC (n=712)	NEB (n=512)	VAL (n=461)
Age, mean±SD, y	49.2±9.3	49.7±9.8	49.7±10.3	49.5±9.8
Women, No. (%)	67 (48.6)	340 (47.8)	243 (47.5)	201 (43.6)
White, No. (%)	119 (86.2)	598 (84.0)	426 (83.2)	397 (86.1)
Black, No. (%)	16 (11.6)	85 (11.9)	68 (13.3)	49 (10.6)
Hispanic, No. (%)	50 (36.2)	279 (39.2)	186 (36.3)	156 (33.8)
Weight, mean±SD, kg	108.0±16.3	107.1±18.2	106.9±18.7	108.4±19.0
BMI, mean±SD, kg/m^2	37.4±4.3	37.5±5.0	37.4±4.8	37.6±4.7
Type 2 diabetes, No. (%)	21 (15.2)	139 (19.5)	93 (18.2)	87 (18.9)
HR, mean±SD, bpm	71.3±10.2	71.8±10.7	71.5±10.6	70.9±10.2
DBP, mean±SD, mm Hg	99.9±3.5	99.9±3.6	99.9±3.6	100.1±3.9
SBP, mean±SD, mm Hg	155.0±11.5	154.5±11.7	155.2±11.7	156.0±12.1
Nonobese (BMI <27 kg/m^2)	**PBO (n=51)**	**SPC (n=330)**	**NEB (n=241)**	**VAL (n=225)**
Age, mean±SD, y	52.2±10.7	52.3±9.7	53.8±10.8	53.3±10.4
Women, No. (%)	24 (47.1)	159 (48.2)	119 (49.4)	107 (47.6)
White, No. (%)	43 (84.3)	277 (83.9)	193 (80.1)	191 (84.9)
Black, No. (%)	3 (5.9)	23 (7.0)	19 (7.9)	8 (3.6)
Hispanic, No. (%)	28 (54.9)	147 (44.5)	91 (37.8)	89 (39.6)
Weight, mean±SD, kg	69.4±10.1	70.7±10.8	70.0±10.3	71.2±10.0
BMI, mean±SD, kg/m^2	24.6±1.6	24.7±2.0	24.6±1.9	24.8±1.8
Type 2 diabetes, No. (%)	5 (9.8)	33 (10.0)	23 (9.5)	22 (9.8)
HR, mean±SD, bpm	70.3±9.1	69.5±9.8	70.0±9.2	69.3±10.8
DBP, mean±SD, mm Hg	99.5±3.3	99.3±3.3	99.9±3.5	99.4±3.5
SBP, mean±SD, mm Hg	155.2±12.2	155.0±11.5	154.6±11.5	155.2±12.3

Pooled doses: single-pill combination (SPC; nebivolol-valsartan) (10/160, 10/320, and 20/320 mg/d); nebivolol (NEB; 10 and 40 mg/d); valsartan (VAL; 160 and 320 mg/d).

Abbreviations: BMI, body mass index; bpm, beats per minute; DBP, diastolic blood pressure; HR, heart rate; ITT, intention-to-treat; PBO, placebo; SBP, systolic blood pressure; SD, standard deviation.

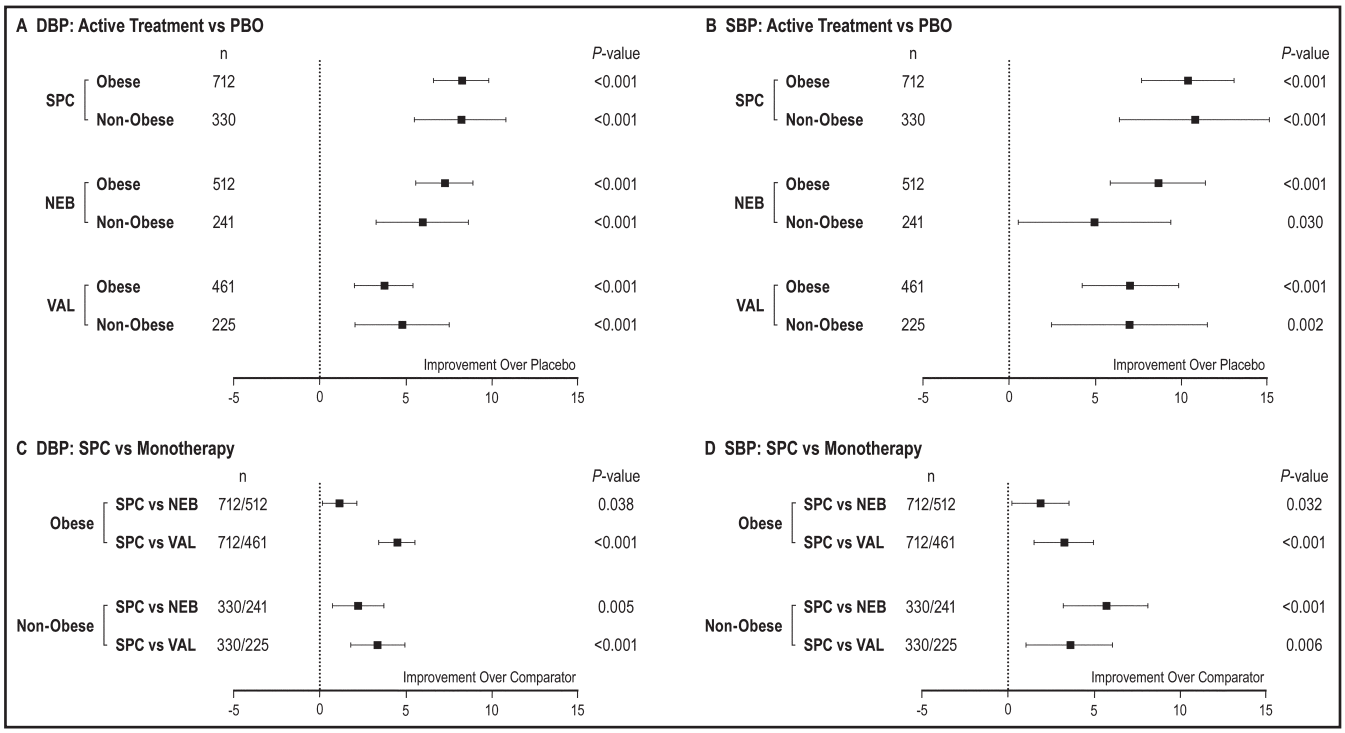

FIGURE 1 Change from baseline in blood pressure at week 8 by obesity status (pooled doses; intention-to-treat population; last observation carried forward). Obese=body mass index (BMI) >32 kg/m^2; non-obese=BMI <27 kg/m^2. Pooled doses: single-pill combination (SPC; nebivolol [NEB]-valsartan [VAL]) (10/160, 10/320, and 20/320 mg/d); NEB (10 and 40 mg/d); and VAL (160 and 320 mg/d). Least squares mean differences between active treatment and placebo presented; error bars represent 95% confidence intervals. Placebo (PBO) group (A and B): obese n=138; non-obese n=51. DBP indicates diastolic blood pressure; SBP, systolic blood pressure

nebivolol reduced DBP to a similar extent as valsartan (LSMD=−1.09, *P*=.201). Pooled nebivolol and valsartan monotherapies lowered SBP to a similar extent (no between-group differences: LSMD=−1.38, *P*=.150 obese; LSMD=2.12, *P*=.125 nonobese).

3.2.2 | Clinic BP (5/80 dose)

At week 4, significantly greater BP-lowering effects were observed with the 5/80 SPC vs nebivolol 5 mg and valsartan 80 mg monotherapies regardless of obesity status (Figure 2A,B). Compared with the higher dose of valsartan (160 mg/d), SPC 5/80 treatment resulted in significantly greater reductions in DBP and similar reductions in SBP in both BMI subgroups (Figure 2). Compared with the higher dose of nebivolol (20 mg/d), SPC 5/80 significantly reduced SBP in the nonobese group (*P*=.002) and was similarly effective in lowering SBP in the obese group; SPC 5/80 lowered DBP to a similar extent as nebivolol 20 mg/d in both BMI groups (Figure 2).

3.2.3 | ABPM 24-hour substudy (pooled doses)

At week 8, all active pooled doses numerically reduced 24-hour ambulatory DBP and SBP from baseline vs placebo regardless of obesity status (Figure 3). The SPCs had numerically greater DBP- and SBP-lowering effects than nebivolol or valsartan alone in obese and nonobese individuals. Nebivolol had a numerically greater BP-lowering effect vs valsartan in both BMI groups (Figure 3).

3.3 | Heart rate

In both BMI groups, the pooled SPC and nebivolol doses significantly lowered HR vs placebo and pooled valsartan at week 8 (Figure 4). HRs were similar between pooled SPC-treated participants and those treated with pooled nebivolol monotherapy.

3.4 | Biomarkers substudy (pooled doses)

In participants who had both baseline and postbaseline values at week 4 (ITT population of the ABPM-biomarkers substudy), baseline geometric mean aldosterone concentration per treatment group ranged from 51.4 to 61.3 pg/mL for obese participants and from 51.5 to 61.6 pg/mL for nonobese individuals. At week 4, the SPCs and nebivolol monotherapies reduced plasma aldosterone from baseline in both BMI groups (Figure S1A). At week 8, the SPCs numerically decreased plasma aldosterone concentrations from baseline vs placebo in both BMI groups and compared with valsartan in the obese group (Figure S1B). Nebivolol numerically reduced aldosterone vs placebo regardless of BMI, and numerically reduced aldosterone over valsartan in the obese participants. The nonobese placebo group had a 63.9% increase in plasma aldosterone at week 8.

3.5 | eGFR (pooled doses)

In participants who had both baseline and postbaseline values at week 8, mean baseline eGFR per treatment group ranged from

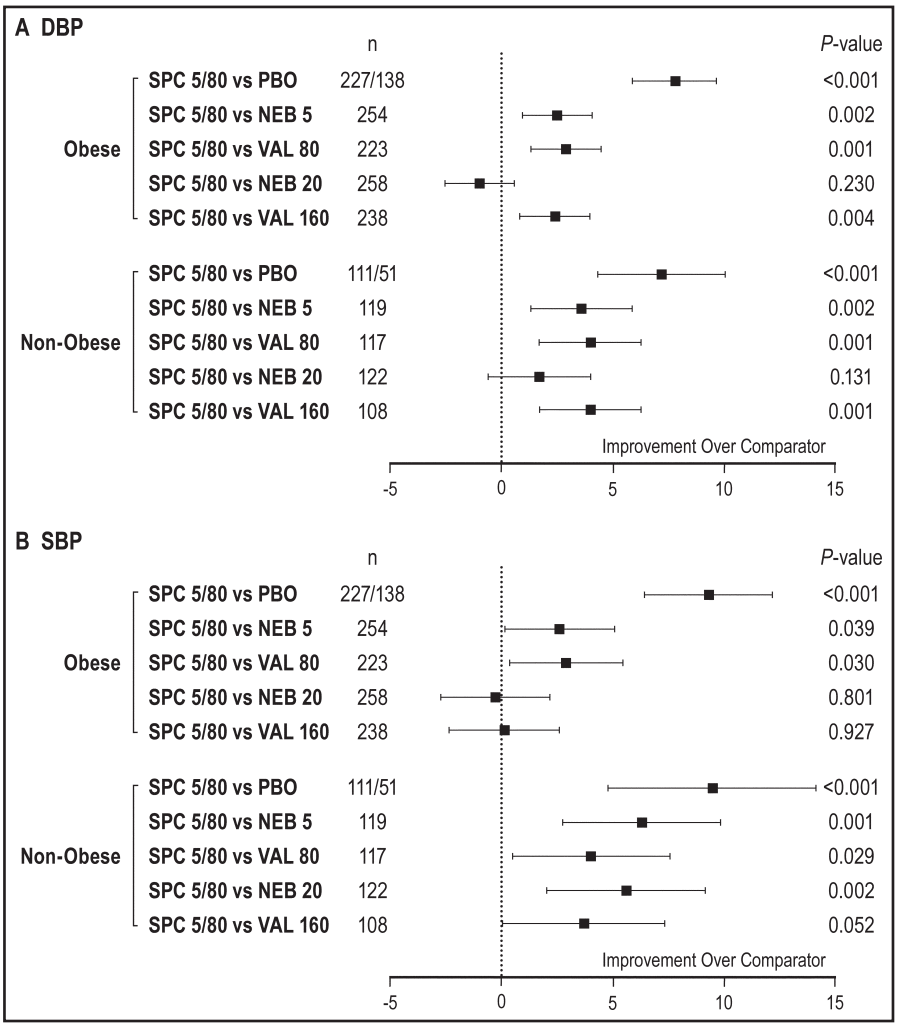

FIGURE 2 Change from baseline in blood pressure for nebivolol (NEB)-valsartan (VAL) 5/80 mg/d at week 4 by obesity status (intention-to-treat population; last observation carried forward). Obese=body mass index (BMI) >32 kg/m^2; non-obese=BMI <27 kg/m^2. Least squares mean differences between single-pill combination (SPC; NEB-VAL) and comparator presented; error bars represent 95% confidence intervals. DBP indicates diastolic blood pressure; PBO, placebo; SBP, systolic blood pressure

84.3 to 85.1 mL/min/1.73 m^2 for obese participants and from 80.6 to 82.1 mL/min/1.73 m^2 for nonobese participants (safety population). Numeric but clinically negligible changes from baseline in eGFR were observed at week 8 regardless of obesity status (Figure S2).

3.6 | Potassium (nonpooled doses)

Increases in potassium levels with active treatment were generally similar to those observed in the placebo group at week 4 regardless of obesity status (see Table S1). At week 8, the nonobese SPC group had a numerically greater increase in potassium than placebo-treated participants (3.2% SPC vs 0% placebo).

4 | DISCUSSION

In this analysis from a large phase 3, placebo-controlled trial, the BP-lowering effects of the recently FDA-approved nebivolol-valsartan SPC were demonstrated in participants with stage I or II hypertension regardless of obesity status. Overall, the nebivolol-valsartan SPCs were more effective than the component monotherapies. To our knowledge, this is the first analysis of the effects of a β-blocker and a RAAS inhibitor combination by baseline obesity status.

The findings with nebivolol monotherapy reported here support those of a pooled analysis of three pivotal nebivolol trials (N=2016)[15] in which comparable antihypertensive efficacy of nebivolol was demonstrated between obese and nonobese trial participants. Other β-blockers such as atenolol[16] and metoprolol[17] have been shown to be less effective in nonobese patients than obese patients as a result of adrenergic antagonism. The apparent differences between nebivolol—a highly selective β_1-adrenergic receptor blocker—and atenolol or metoprolol (both β_1-selective, nonvasodilatory agents) may be attributed to the additional vasodilatory properties of nebivolol that occur via endothelium-derived nitric oxide release by β_3-adrenergic activation.[18–20]

When examining long-term cardiovascular outcomes in hypertensive patients, there may be a differential response to antihypertensive treatment based on BMI. A post hoc analysis of the 3-year Avoiding Cardiovascular Events in Combination Therapy in Patients Living With Systolic Hypertension (ACCOMPLISH) trial[21] revealed that rates of composite cardiovascular outcomes (cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke) in hypertensive nonobese patients (BMI <25 kg/m^2) treated with angiotensin-converting enzyme

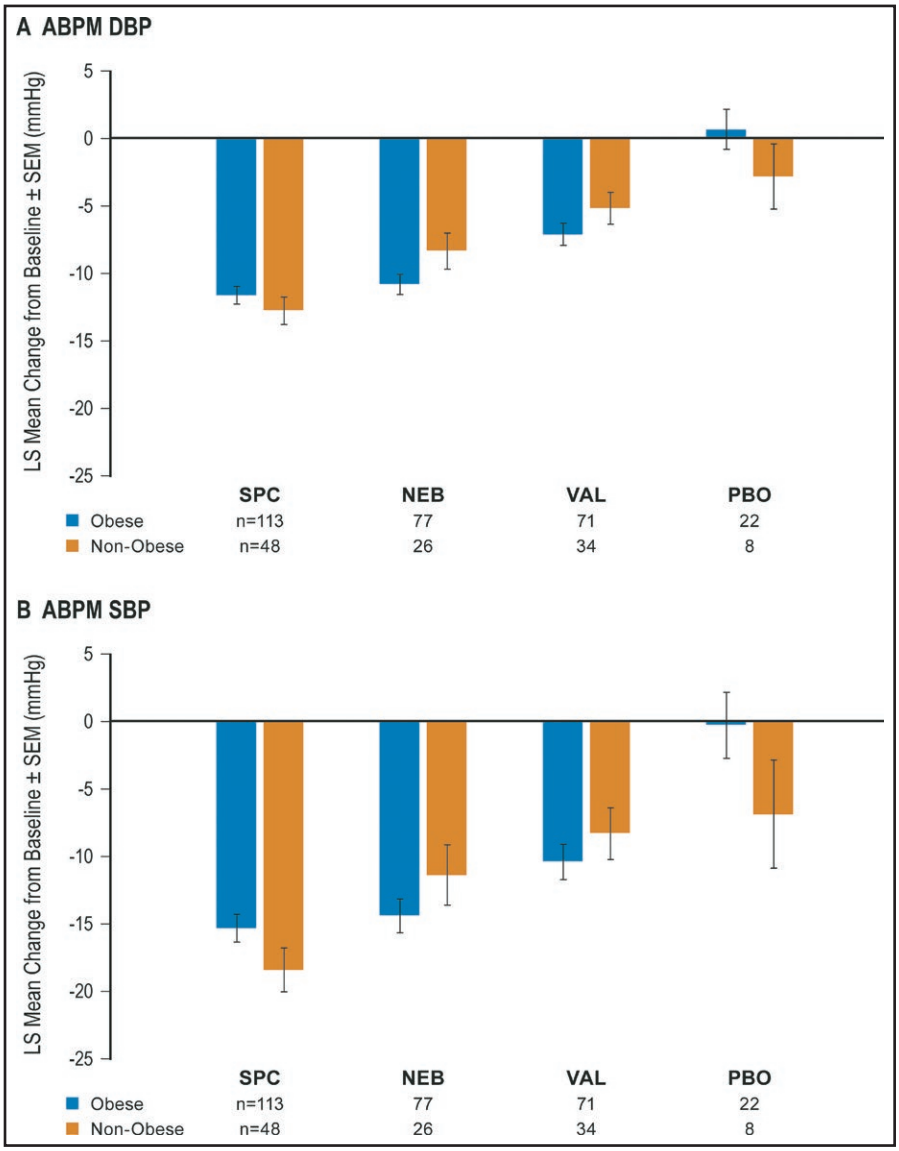

FIGURE 3 24-Hour ambulatory blood pressure monitoring (ABPM) change from baseline in blood pressure at week 8 (pooled doses; intention-to treat population; last observation carried forward). Obese=body mass index (BMI) >32 kg/m^2; non-obese=BMI <27 kg/m^2. Pooled doses: single-pill combination (SPC; nebivolol [NEB]-valsartan [VAL]) (10/160, 10/320, and 20/320 mg/d); NEB (10 and 40 mg/d); and VAL (160 and 320 mg/d). DBP indicates diastolic blood pressure; LS, least squares; PBO, placebo; SBP, systolic blood pressure; SEM; standard error of the mean

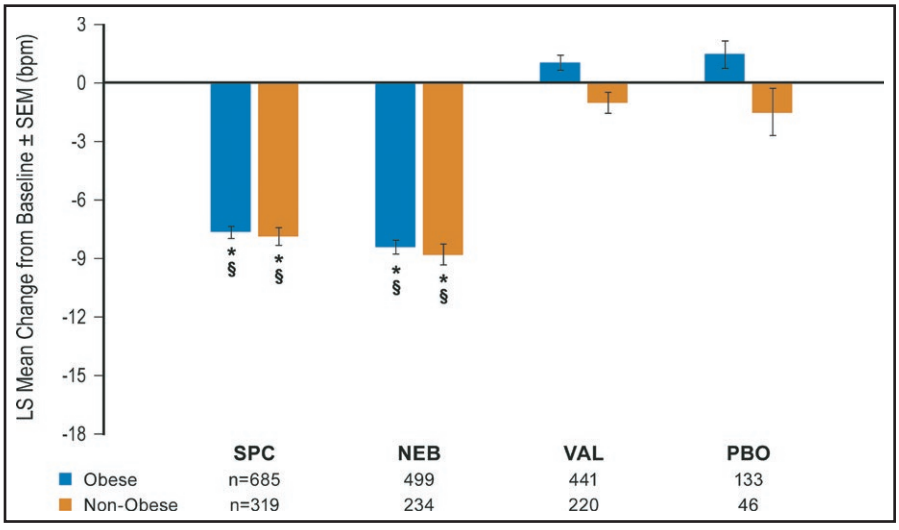

FIGURE 4 Change from baseline in heart rate at week 8 (safety population). Obese=body mass index (BMI) >32 kg/m^2; non-obese=BMI <27 kg/m^2. Pooled doses: single-pill combination (SPC; nebivolol [NEB]-valsartan [VAL]) (10/160, 10/320, and 20/320 mg/d); NEB (10 and 40 mg/d); and VAL (160 and 320 mg/d). *$P \leq .05$ vs placebo (PBO). §$P \leq .05$ vs VAL. bpm indicates beats per minute; LS, least squares; SEM, standard error of the mean

inhibitors (ACEIs) and hydrochlorothiazide (HCTZ) was 68% higher compared with the ACEI/HCTZ–treated obese group (BMI ≥30). In the obese group, cardiovascular outcomes were similar regardless of whether they received an ACEI/HCTZ or an ACEI/CCB combination whereas the nonobese group taking an ACEI/CCB combination had a 43% lower composite event risk than the nonobese ACEI/HCTZ–treated participants.[21] In a shorter-term large, randomized trial of the nebivolol/valsartan SPCs, the overall efficacy of SPCs were clinically significant regardless of obesity status. A potentially variable response by BMI was observed with nebivolol/valsartan 20/30 mg as the nonobese participants experienced a smaller reduction in SBP (−7.8 mm Hg) than obese patients (−10.5 mm Hg), but between-group differences were not analyzed.[13]

While it is unclear whether the pharmacological class of drug treatment affects the BP-reducing efficacy in obese patients, certain drugs may not be appropriate choices for this population because of other effects. For example, the commonly used nonvasodilating β-blockers atenolol and metoprolol, as well as the diuretic HCTZ, are known to negatively impact the metabolic profiles of patients.[22,23] Nebivolol, a third-generation vasodilating β-blocker, has demonstrated a neutral effect on metabolic parameters,[19,24] which may be due in part to the activation of β_3-adrenoreceptors.[25] Valsartan does not affect triglyceride or cholesterol levels or circulating glucose or insulin.[26] Valsartan also has been associated with a decrease in the risk for developing diabetes.[27] Thus, the largely neutral or even beneficial metabolic effects of nebivolol[23] and valsartan[26] monotherapies lend further support for their use in obese patients with hypertension.

In the biomarkers substudy, aldosterone levels generally declined with treatment regardless of obesity status. As expected, the reductions with the pooled combination therapy were generally greater than with either pooled dose monotherapy component alone. Interestingly, the nebivolol component of the SPC appears to be driving the aldosterone reductions observed in obese participants, as valsartan did not reduce aldosterone compared with nebivolol monotherapy. An unusually high increase in plasma aldosterone was observed in nonobese placebo-treated patients, which could indicate an abrupt change in diet upon entering the clinical study. The decrease in plasma aldosterone concentration in obese participants treated with the nebivolol-valsartan SPC may be of particular importance as obesity is associated with pathological vascular changes mediated by an increase in aldosterone levels. Elevated aldosterone may also contribute to impaired glucose homeostasis and left ventricular remodeling and is associated with resistant hypertension.[28] Thus, reducing its concentration may provide therapeutic benefits independent of weight loss, although this requires further investigation.

STUDY LIMITATIONS

Key limitations of this analysis are its post hoc status and the small sample size of the ABPM substudy. Additionally, the nonobese placebo group had a higher percentage of Hispanics than the other nonobese pooled treatment groups. A greater placebo response has been observed in Hispanic participants in phase 3 nebivolol and nebivolol/valsartan clinical trials,[13,29] thus the placebo response in this study may be overestimated. Despite this aberration, the nebivolol/valsartan SPC was still more effective than placebo in this group.[30] In spite of nominal reductions in aldosterone levels, especially with the SPCs,[31] aldosterone breakthrough—a phenomenon that affects approximately 30% of individuals receiving RAAS inhibitors[32,33]—could occur with longer nebivolol-valsartan treatment. The duration of this study did not allow for this assessment. Further research is needed to determine whether such an effect would occur with longer treatment.

CONCLUSIONS

This post hoc analysis of the only FDA-approved SPC for hypertension comprising a β-blocker and a RAAS inhibitor suggests that nebivolol-valsartan SPCs are efficacious in reducing BP in individuals regardless of obesity status. In addition, significant reductions in aldosterone levels were evident in both obese and nonobese participants compared with placebo.

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FINANCIAL DISCLOSURE

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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