Review

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Rationale for nebivolol/valsartan combination for hypertension: review of preclinical and clinical data

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To treat hypertension, combining two or more antihypertensive drugs from different classes is often necessary. β-Blockers and renin–angiotensin–aldosterone system inhibitors, when combined, have been deemed 'less effective' based on partially overlapping mechanisms of action and limited evidence. Recently, the single-pill combination (SPC) of nebivolol (Neb) 5 mg – a vasodilatory β1-selective antagonist/β3 agonist – and valsartan 80 mg, an angiotensin II receptor blocker, was US Food and Drug Administration-approved for hypertension. Pharmacological profiles of Neb and valsartan, alone and combined, are well characterized. In addition, a large 8-week randomized trial in stages I–II hypertensive patients ($N = 4161$) demonstrated greater blood pressure-reducing efficacy for Neb/valsartan SPCs than component monotherapies with comparable tolerability. In a biomarkers substudy ($N = 805$), Neb/valsartan SPCs prevented valsartan-induced increases in plasma renin, and a greater reduction in plasma aldosterone was observed with the highest SPC dose vs. valsartan 320 mg/day. This review summarizes preclinical and clinical evidence supporting Neb/valsartan as an efficacious and well tolerated combination treatment for hypertension.

Keywords: aldosterone, angiotensin II receptor blockers, beta-blockers, hypertension, mechanism of action, nebivolol, renin–angiotensin system inhibitors, valsartan, vasodilation

Abbreviations: β1-AR, β1-adrenoreceptor; β2-AR, beta-2 adrenoreceptor; β3-AR, beta-3 adrenoreceptor; ABPM, ambulatory blood pressure monitoring; ACE, acetylcholinesterase; ADMA, asymmetrical dimethylarginine; AIx, augmentation index; Angio I, angiotensin I; Angio II, angiotensin II; ARB, angiotensin receptor blocker; ATP, adenosine triphosphate; AT$_1$-R, angiotensin I receptor; AT$_2$-R, angiotensin II receptor; AUC, area under the curve; AUC$_{0-\tau}$,ss, steady-state AUC from time 0 to the dosing interval; BP, blood pressure; cAMP, cyclic adenosine monophosphate; cGMP, cyclic guanosine monophosphate; C_{max}, peak plasma concentration; $C_{max,ss}$, peak plasma concentration at steady state; CV, cardiovascular; eNOS, endothelial nitric oxide synthase; HR, heart rate; IgA, immunoglobulin A; JNC, Joint National Committee; LSM, least squares mean; LV, left ventricular; Neb, nebivolol; NO, nitric oxide; O$_2^-$, superoxide; PAH, pulmonary arterial hypertension; PP, pulse pressure; PRA, plasma renin activity; RAAS, renin–angiotensin– aldosterone system; ROS, reactive oxygen species; SPC, single-pill combination; SS, steady state; T_{max}, time to maximum plasma concentration; Val, valsartan

INTRODUCTION

Treatment guidelines [1] and position papers [2] have attempted to summarize available knowledge regarding the effectiveness of certain antihypertensive drug class combinations. Such efforts, although commendable, have failed to take into account heterogeneity within each drug class or the quality of available evidence. For example, combinations between β-blockers and renin–angiotensin–aldosterone system (RAAS) inhibitors have been deemed 'less effective' [2] based on the results of two trials [3,4] and a concern that an overlapping mechanism of action (renin suppression) would not yield a blood pressure (BP)-reducing effect that would justify treatment with two agents instead of one. A recent randomized, Phase 3 trial (NAC-MD-01; $N = 4161$) has provided convincing evidence that at least one β-blocker/RAAS inhibitor combination consisting of the β$_1$-selective adrenergic blocker with β$_3$ agonistic vasodilatory properties, Neb [5], and the angiotensin II (Angio II) receptor blocker (ARB), valsartan, is more effective in reducing BP than its component monotherapies [6]. This study, which examined a range of Neb/valsartan single-pill combination (SPC) doses (5/80, 5/160, 10/160, 10/320, or 20/320 mg/day), provided the basis for the recent US Food and Drug Administration approval of the 5/80-mg/day SPC for the treatment of hypertension.

This review will examine the pharmacologic rationale for the Neb/valsartan combination and summarize the pharmacokinetic, pharmacodynamic, and clinical findings related to its use.

MECHANISMS OF ACTION AND CLINICAL PHARMACOLOGY

Nebivolol

Neb is a highly selective β_1-adrenoreceptor (β_1-AR) antagonist with vasodilator properties [7]. It is a racemic mixture in which the β_1-selective antagonism is mediated by the d-isomer (for doses up to 20 mg/day) [8,9]. The l-isomer activates the β_3-receptor, which may be the basis for the vasodilatory and endotheliotropic effects observed with Neb treatment [9–11]. The high selectivity of the d-isomer for β_1-AR over beta-2 adrenoreceptor allows for limited effects of Neb on airway reactivity and insulin sensitivity, and provides a low negative inotropic effect in patients with heart failure; however, this selectivity is lessened at doses more than 10 mg and in poor metabolizers [8]. Neb has no sympathomimetic activity and inhibits peripheral α_1-receptor activity only at supratherapeutic doses [9,11]. Possible mechanisms behind the antihypertensive actions of Neb include nitric oxide (NO) release [12], decreased heart rate (HR), decreased myocardial contraction, reduction in tonic sympathetic outflow from cerebral vasomotor centers to the periphery, suppression of renin activity, and vasodilation/attenuation of peripheral vascular resistance [7].

Neb is rapidly absorbed following oral administration, with plasma concentrations peaking between 1.5 and 4 h after dosing; absolute bioavailability in extensive metabolizers (most patients) is 96% [13,14]. The d-isomer has a half-life of approximately 12 h in most patients, and its levels in plasma increase in a dose-dependent manner up to 20 mg/day. Exposure to the l-isomer is higher than that of its active metabolite, with a two-fold higher area under the curve (AUC) compared with that of the d-isomer [13,14]. Less than 1% of the drug is excreted unchanged in the urine, and the primary route of metabolism is hepatic oxidation.

In the United States, Neb is available as 2.5, 5, 10, and 20 mg tablets and is approved at dosages up to 40 mg/day [7]; the range of approved doses reflects those used in the majority of Neb hypertension clinical trials in the United States (2.5–40 mg). In the European Union, Neb is available as 5-mg tablets and is approved at 5 mg/day [15]. In both the United States and the European Union, Neb is approved for use as a monotherapy or in combination with other BP-lowering drugs.

Valsartan

Angio II, an oligopeptide hormone, causes arteriolar vasoconstriction and remodeling, endothelial cell apoptosis, superoxide (O_2^-) anion production, aldosterone secretion, and other processes that lead to increased peripheral vascular resistance and endothelial dysfunction; two primary angiotensin receptor types mediate these changes: type 1 (AT_1) and type 2 (AT_2) [16–19].

The ARB valsartan is a highly selective, 'insurmountable' antagonist of AT_1 receptors (AT_1-Rs) with a 20 000-fold greater affinity for AT_1 over AT_2 receptors [20]. Valsartan

has one primary metabolite that has a very low affinity for the AT_1-R and is essentially inactive. The main antihypertensive effect of valsartan is mediated by a reduction in Angio II activation of the AT_1-R in vascular smooth muscle, resulting in decreased peripheral vascular resistance via numerous mechanisms. BP reduction is substantially present within 2 weeks, and maximal reduction is attained at approximately 4 weeks [21].

The peak plasma concentration (C_{max}) of valsartan occurs within 2–4 h after dosing, and absolute bioavailability is roughly 25%. The AUC and C_{max} values of valsartan increase approximately linearly with increasing doses. Orally administered valsartan is primarily excreted unchanged within feces ($\approx$80% of dose) and urine ($\approx$13% of dose). Approximately 20% of dose is recovered as metabolites [21].

Nebivolol/valsartan combination

A single-center, randomized, open-label, three-way crossover trial in healthy volunteers ($N = 30$) found that the steady-state AUC from time 0 to the dosing interval ($AUC_{0-\tau,ss}$), C_{max} at steady state ($C_{max,ss}$), and time to maximum plasma concentration (T_{max}) for Neb and its metabolites (d-nebivolol, l-nebivolol, d/l-Neb, and the Neb glucuronides) were significantly lower following treatment with a combination of Neb (20 mg) and valsartan (320 mg) vs. Neb alone [22]. For valsartan, a significantly lower $AUC_{0-\tau}$ at steady state ($AUC_{0-\tau,ss}$) was observed with the Neb/valsartan combination compared with valsartan alone, but $C_{max,ss}$ and T_{max} were similar. Steady-state interactions between valsartan and all Neb entities examined were observed; however, the extent of these interactions suggests that they are not clinically meaningful. A sharp increase in mean plasma renin activity (PRA) and plasma Angio II levels that occurred in participants who were receiving valsartan for 7 days was significantly attenuated with concomitant Neb administration. Compared with either monotherapy, mean 24-h urine aldosterone at Day 7 was substantially decreased after combined treatment [22].

ENDOTHELIAL EFFECTS

The endothelium plays a critical role in vascular homeostasis through fluid filtration, hormonal trafficking, modulation of tone, structure and function of blood vessels [23], and large arterial stiffness [24]. Endothelial dysfunction, an early feature in the progression of vascular damage, can lead to cardiovascular disease and chronic kidney disease [25]. NO, a metastable free radical, is a key mediator of endothelial vasodilation, renal fluid retention, and platelet aggregation/adhesion [26]. NO production is a calcium-dependent process catalyzed by the dimerized (coupled) enzyme, endothelial NO synthase (eNOS) (Fig. 1) [27]. Conditions that cause uncoupling of eNOS lead to a reduction in endothelial NO levels and production of O_2^-, a free radical and proatherogenic mediator that can react with any available NO to form peroxynitrite, a proapoptotic, proinflammatory oxidant that has been associated with pathological conditions such as neurodegeneration and vascular disease [28]. Conversely, upregulation of eNOS coupling increases NO production and inhibits free-radical reactions, resulting in reduced endothelial dysfunction and hypertension.
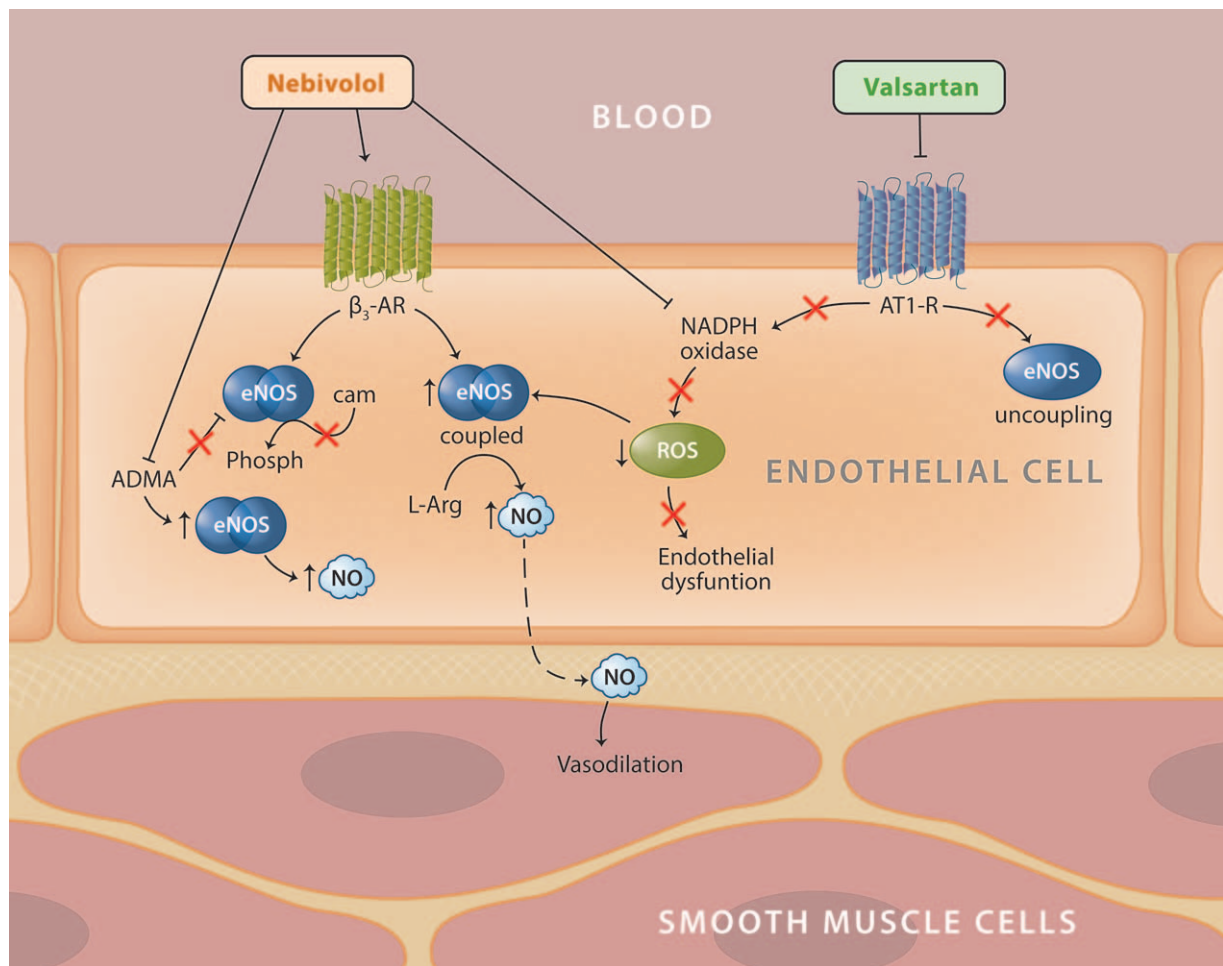
FIGURE 1 Endothelial effects of nebivolol and valsartan. β2-AR, beta-2 adrenoreceptor; β3-AR, beta-3 adrenoreceptor; ADMA, asymmetric dimethylarginine; AT1-R, angiotensin I receptor; cAMP, cyclic adenosine monophosphate; eNOS, endothelial nitric oxide synthase; NADPH, nicotinamide adenine dinucleotide phosphate; NO, nitric oxide; ROS, reactive oxygen species.

Nebivolol

The stimulation of β3-adrenoreceptors via Neb has been shown to activate eNOS and stimulate NO production (Fig. 1) [29], which in turn activates an endothelial-derived NO/cyclic GMP (cGMP) signaling pathway [30]. Neb can stimulate NO production indirectly by lowering the levels of asymmetrical dimethylarginine (ADMA), an endogenous eNOS inhibitor and a product of methylation of arginine residues in proteins by arginine methyltransferase [5]. High ADMA levels in the plasma are associated with cardiovascular morbidity and mortality related to endothelial dysfunction [31]. In individuals with hypertension, Neb treatment results in a decrease in ADMA levels, which is closely related to a decrease in systolic blood pressure (SBP) [32,33]. Moreover, Neb can reduce endothelial dysfunction through direct interaction with free radicals in which reactive oxygen species (ROS) are scavenged in a receptor-independent manner [34]. An additional hypothesis of the vasodilatory effects of Neb posits that Neb reduces O_2^- production through inhibition of eNOS uncoupling and/or stimulation of a calcium-dependent increase in eNOS within renal glomeruli [35–37].

A study in dogs found that Neb-induced vasodilation was dose-dependent and abolished upon removal of the endothelium or through eNOS inhibition, indicating a pathway that includes stimulation of eNOS [38]. These results were also supported by another study of Neb using a rat model of Angio II-induced hypertension with severe endothelial dysfunction and a marked impairment of NO/cGMP signaling [39]. In this study, Neb (10 mg/kg per day), but not metoprolol (10 mg/kg per day), normalized endothelial function and increased plasma NO bioavailability, as demonstrated by the increases in plasma nitrite and whole blood hemoglobin–NO levels. In addition, Neb, but not metoprolol, inhibited upregulation of the activity and expression of the vascular NADPH oxidase and prevented eNOS uncoupling, demonstrated by reduced vascular O_2^- formation [39]. Collectively, these studies demonstrate that the effects of Neb on endothelial function are independent of β1-adrenergic receptor blockade.

A recent study demonstrated that Neb induces endothelium-dependent and NO-dependent relaxation of the pulmonary arteries in rats with pulmonary arterial hypertension (PAH) [40]. This effect was abolished when the endothelium was removed or when NOS was inhibited.

In addition, Neb corrected PAH-related endothelial dysfunction and the proinflammatory phenotype of the PAH-related phenotype of endothelial cells taken from PAH patients and decreased vascular remodeling in experimental pulmonary hypertension. Although clinical studies are necessary to confirm the effects of Neb on PAH [41], the various mechanisms by which Neb can potentially decrease and reverse cardiovascular dysfunction are of great interest.

Valsartan

Activation of the AT_1-R limits bioavailability of NO by reducing NO release and increasing NO inactivation, whereas blocking the AT_1-R using ARBs has been shown to significantly increase endothelium-dependent vasodilation in individuals with hypertension [42–44]. Valsartan significantly improves endothelial function and reduces oxidative stress in patients with essential hypertension [45]. This reduction in oxidative stress has been associated with an increase in NO production [43,45,46], but valsartan also increases NO levels through inhibition of eNOS uncoupling and activation of coupled eNOS [47,48]. In addition, valsartan reduces endothelial dysfunction via a cyclooxygenase-mediated mechanism, which is thought to increase the levels of NO precursors, eNOS, cofactors (e.g. arginine and tetrahydrobiopterin), and reduce the levels of endogenous eNOS inhibitors [45,49–51].

EFFECTS ON THE RENIN–ANGIOTENSIN–ALDOSTERONE SYSTEM AND THE KIDNEY

Stimulation of the RAAS through low BP causes the kidneys to release the enzyme renin, which triggers a signal transduction cascade resulting in production of Angio II. Angio II can stimulate secretion of vasopressin and aldosterone (thus increasing fluid retention), trigger release of adrenaline and noradrenaline (thereby increasing vasoconstriction), and induce changes in cardiac contractility and HR [52]. Of note, Angio II also affects vascular structure through autocrine/paracrine secretion of inflammatory cytokines and growth factors [52]. It should also be mentioned that aldosterone can be produced in extra-adrenal tissues (notably, the blood vessels, the heart, and the brain) [53] and that its receptor is expressed in numerous tissues as well [54], allowing for multiple pathways in which this hormone can affect BP regulation and cardiovascular risk.

Nebivolol

Reduced PRA has been observed following treatment with Neb [51,55] and other β-blockers [56,57] through a mechanism that is thought to act via $β_1$-dependent inhibition of the sympathetic innervation of the juxtaglomerular apparatus (i.e., through $β_1$-mediated inhibition of renin release) (Fig. 2). Neb also has been shown to reduce the concentration of plasma aldosterone (resulting in less fluid retention and decreased blood volume) [58] as well as to reduce proteinuria (through an increase in bioavailable NO) and to lower the activity of NADPH oxidase, thereby lowering the concentration of ROS, which are implicated in the pathogenesis of hypertension [39,59,60]. Neb has also been shown to induce relaxation of glomerular microvasculature through adenosine triphosphate (ATP) efflux, which stimulates NO release from glomerular endothelial cells via stimulation of P2Y purinergic receptors [37].
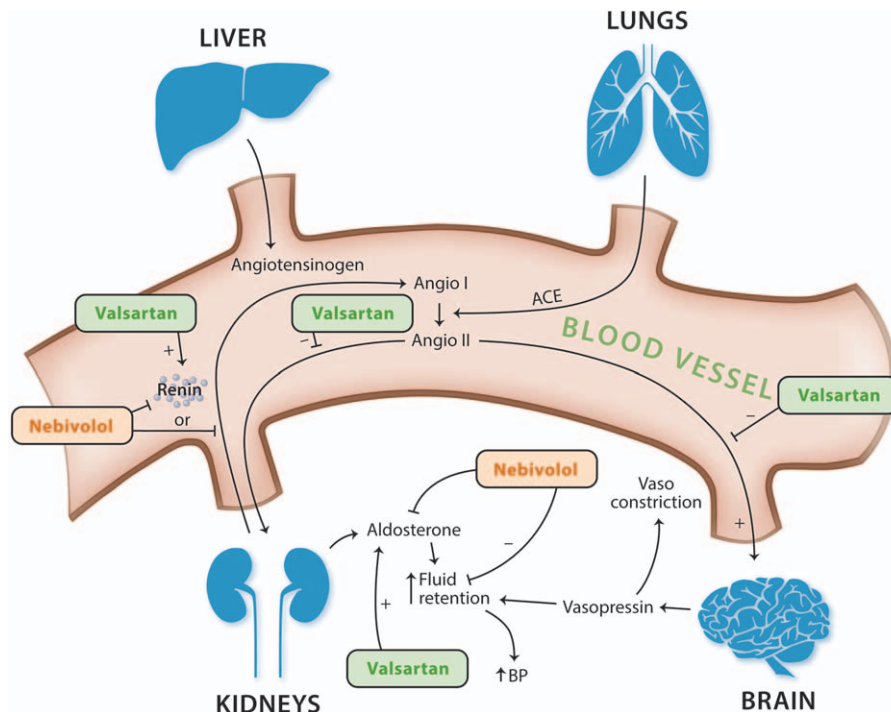

FIGURE 2 Effects of nebivolol and valsartan on the renin–angiotensin–aldosterone system. ACE, acetylcholinesterase; Angio I, angiotensin I; Angio II, angiotensin II; BP, blood pressure; RAAS, renin–angiotensin–aldosterone system.

Valsartan

Valsartan achieves its antihypertensive effects through inhibition of Angio II to the AT$_1$-R [61], which also results in a reactive increase in PRA [52] and, in some patients, an increase in aldosterone concentration back to baseline levels (so-called aldosterone escape) [62]. In addition, valsartan has been shown to reduce microalbuminuria in patients with type 2 diabetes in a BP-independent manner [63], a phenomenon observed with other ARBs as well [64,65]. Finally, valsartan reduces the levels of urinary angiotensinogen (a marker of intrarenal RAAS activity), renal tissue gene expression of angiotensinogen, and Angio II immunoreactivity in the kidneys of patients with immunoglobulin A (IgA) nephropathy [66].

EFFECTS ON CENTRAL BLOOD PRESSURE

Central BP may be a better predictor of certain aspects of cardiovascular morbidity and mortality than peripheral (brachial) BP [67–69], and 24-h central BP has been shown to be better than 24-h peripheral BP in predicting left ventricular (LV) structure and function [70,71]. Compared with other treatments, both valsartan and Neb have been shown to be efficacious in decreasing central BP. For example, the combination of valsartan–amlodipine was shown to reduce central systolic pressure, pulse pressure (PP), and the augmentation index (AIx) more than the atenolol–amlodipine combination, despite a similar effect of the two combinations on brachial BP [72]. Similarly, Neb was found to reduce the parameters of central hemodynamics to a greater extent than other β-blockers (metoprolol, carvedilol, and atenolol), despite similar reductions in brachial BP [73–76]. Furthermore, the reductions in brachial PP and central BP observed with Neb, but not metoprolol, were shown to correlate with a reduction in LV wall thickness [74].

EFFECTS ON BLOOD PRESSURE AND BIOMARKERS IN PATIENTS WITH HYPERTENSION

An 8-week, randomized, double-blind, placebo-controlled trial (NAC-MD-01; $N = 4161$) was conducted to assess the efficacy and safety of the Neb/valsartan SPCs in adults with Stage 1 or 2 hypertension [Joint National Committee 7 (JNC7) criteria [77]] [6]. In that trial, participants were randomized to receive Neb (5 or 20 mg/day) monotherapy, valsartan (80 and 160 mg/day) monotherapy, Neb/valsartan SPC (5/80, 5/160, or 10/160 mg/day), or placebo for 4 weeks; the dosages were doubled during Weeks 5–8 (Neb 10 or 40; valsartan 160 or 320; and SPC 10/160, 10/320, or 20/320 mg/day).

At the end of the study, the DBP reduction from baseline (the primary efficacy parameter) with the Neb/valsartan SPCs was significantly lower than with the corresponding monotherapies (Fig. 3a). In addition, significantly greater reductions in favor of the Neb/valsartan SPCs vs. monotherapy components were observed for all SBP (Fig. 3b) comparisons by study end. The results at Week 4, which include the approved SPC 5/80 mg/day dose, mirrored

those of the results at study end, with significantly greater BP-lowering effects (DBP and SBP) of the majority of the Neb/valsartan SPCs compared with monotherapy components; the only exception was the 5/160 SPC vs. valsartan 160 for SBP (Fig. 3a and b). No dose response was observed for the SPCs, which likely reflects the relatively flat dose responses of the component monotherapies [78,79].

The percentage of patients who reached BP control (JNC7 criteria [77]) at endpoint was greater in the SPC groups than in the monotherapy groups. Specifically, the percentage achieving control in the SPC 10/160 group (49%) was significantly greater than in patients who were treated with Neb 10 (39%; $P < 0.001$) or valsartan 160 (36%; $P < 0.001$); similarly, a significantly greater percentage of patients achieved control in the SPC 20/320 group (52%) than in the valsartan 320 (36%; $P < 0.0001$) or Neb 40 groups (45%; $P = 0.023$). This effect was also evident at Week 4 with the SPC 5/80 (42%) vs. monotherapy components (31% Neb 5, 33% valsartan 80; $P < 0.01$, both) and SPC 5/160 (41%) vs. monotherapies (31% Neb 5, 32% valsartan 160; $P < 0.001$, both). Additional analyses revealed that the SPCs were efficacious across a wide range of phenotypes and that a reduction in PP with SPC 10/160 was significantly greater than the one observed with Neb 10 ($P = 0.021$), suggesting an added benefit on central hemodynamics. Finally, the adverse events and clinical laboratory parameters were similar between the SPCs and their component monotherapies.

A substudy conducted within the NAC-MD-01 trial ($N = 805$) examined patients' BP using ambulatory BP monitoring (ABPM) and their levels of PRA and plasma aldosterone [80]. Those examinations revealed that at Week 8, the SPC 10/160 was significantly more effective in lowering ABPM than the component monotherapies valsartan 160 (SBP/DBP; $P < 0.001$, both) and Neb 10 (DBP; $P < 0.01$); in addition, the SPC 20/320 reduced 24-h DBP and SBP significantly more than valsartan 320 ($P < 0.01$, both) but not Neb 40. From baseline to endpoint, PRA increased in valsartan-treated groups (53.8–72.8%) and decreased in Neb-treated (51.3–65.4%) and SPC-treated groups (3.2–39.0%) (Fig. 4a). At Week 8, all SPC doses were effective in reducing PRA compared with their corresponding valsartan monotherapy doses ($P < 0.001$, all), but not when compared with the corresponding Neb doses (Fig. 4a). Plasma aldosterone increased with placebo (17.1%) and decreased with all active treatments at endpoint [range: 11.1 (valsartan 160)–35.1% (SPC 20/320)] (Fig. 4b). The SPC 20/320 produced significantly greater decreases than valsartan 320 but not Neb 40 ($P < 0.05$); numerical decreases were observed in the other active treatment groups (Fig. 4b). A post-hoc analysis with pooled active treatment groups demonstrated a significant correlation between 24-h, daytime, and nighttime ABPM reduction and baseline PRA in participants treated with Neb and SPCs, but not with valsartan; baseline aldosterone levels were correlated with 24-h, daytime, and night-time ABPM reduction in those treated with the SPCs, but not with the monotherapies [80].

Neb has previously been shown to decrease PRA in a dose-dependent manner [58,81], and the substudy data indicate that it can attenuate the reactive rise in PRA
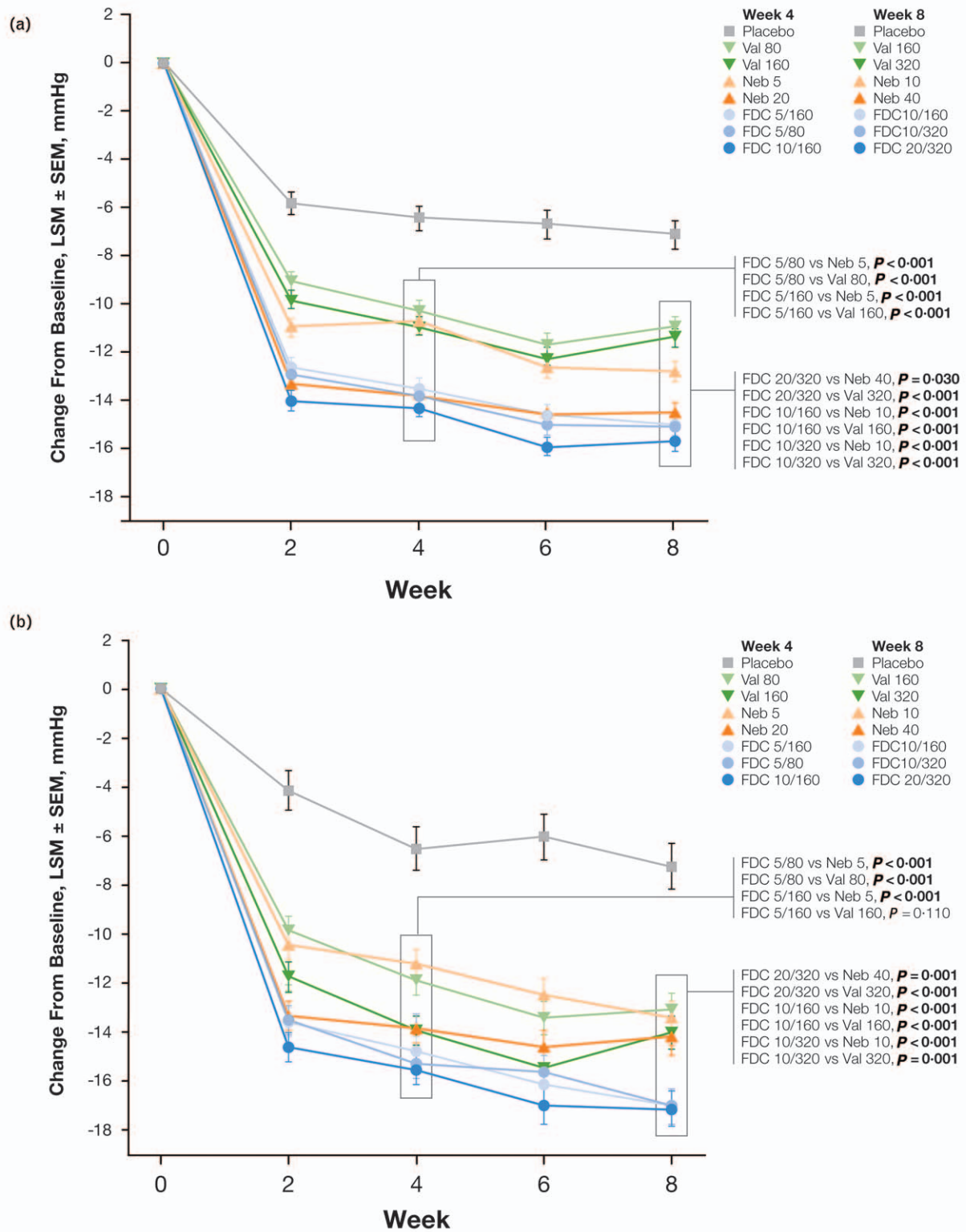
FIGURE 3 . Trial NAC-MD-01: changes from baseline in trough seated DBP (a) and SBP (b) by visit. Bold *P* values indicate significance. LSM, least squares mean; Neb, nebivolol; SEM, standard error of the mean; SPC, single-pill combination; Val, valsartan. Reproduced with permission from [6].
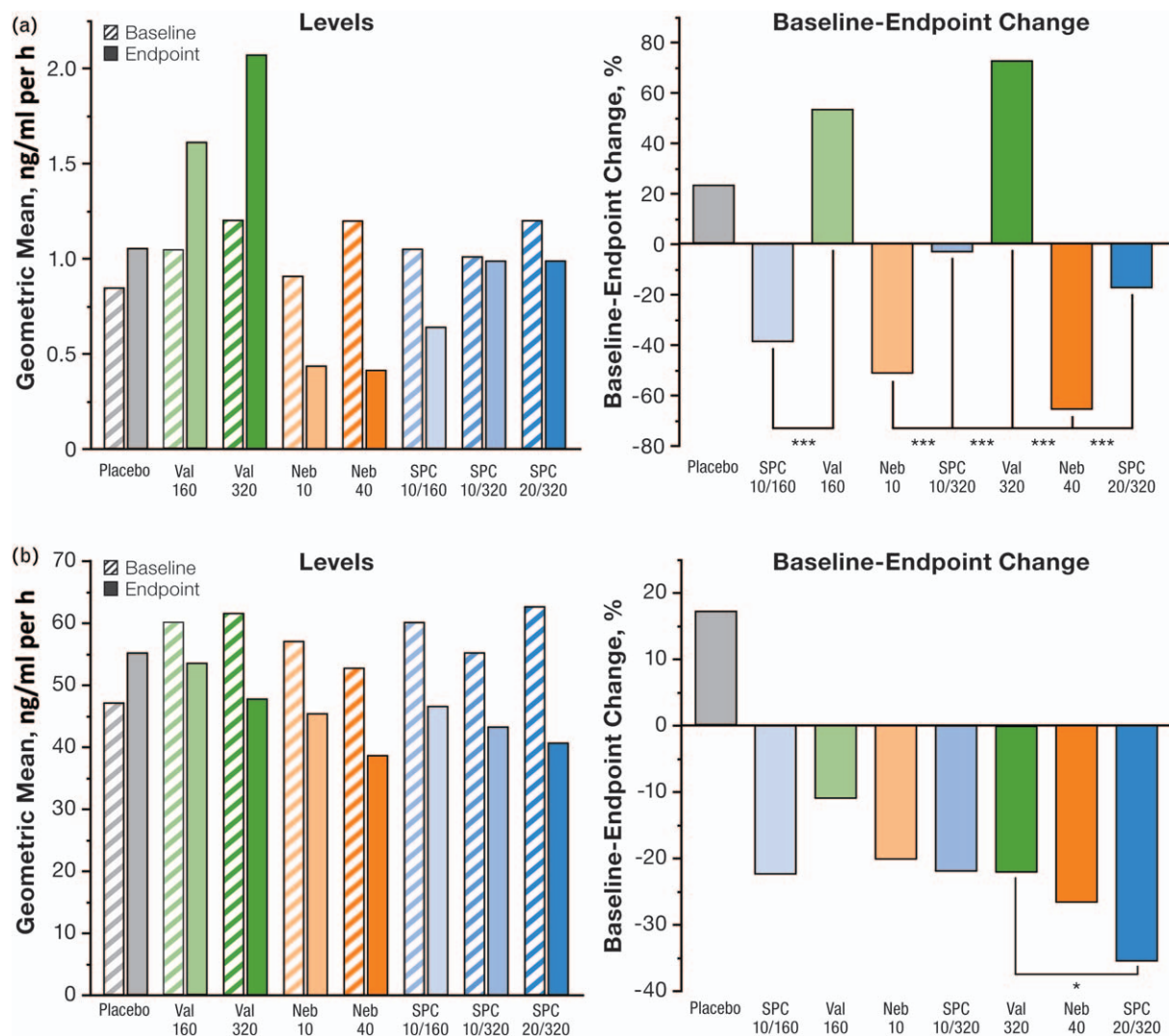
FIGURE 4 . Plasma renin activity (a) and plasma aldosterone (b) levels (b1) and baseline–endpoint change (b2) following 8 weeks of treatment with placebo, valsartan, nebivolol, or the single-pill combination. Neb, nebivolol; PRA, plasma renin activity; SPC, single-pill combination; Val, valsartan. Modified with permission from [80]. $^*P < 0.05$; $^{***}P < 0.001$.

observed with valsartan treatment, suggesting that the Neb/valsartan combination can be used to attain dual RAAS blockade. Furthermore, a significantly greater reduction in aldosterone levels observed with SPC 20/320 mg/day than with valsartan 320 mg/day suggests a potential of the combination to counter the valsartan-associated 'aldosterone escape'. The results from this substudy were in contrast to those seen when aliskiren (a direct renin inhibitor) was added to valsartan to produce a dual RAAS blockade. Following treatment with this combination, a synergistic increase in PRA occurred [82]. Moreover, no favorable clinical response was produced from the aliskiren/valsartan combination, possibly due to the excessive increase in renin and prorenin activity [83,84]. It should also be noted that increases in PRA such as these may give rise to unfavorable cardiovascular outcomes that are independent of BP reduction [85].

β-Blocker/RAAS inhibitor combinations have been considered less effective for BP reduction compared with other antihypertensive drug combinations based on a lack of additive drug effects observed in a study examining the combination of atenolol and enalapril [3] and from the primary analysis of the COSMOS study examining carvedilol and lisinopril [4]. β-Blockers, however, can vary in vasodilatory, β_1-selectivity, and other properties. The mechanisms that contribute to the effectiveness of Neb (i.e. endothelium-dependent vasodilation via NO, high β_1 selectivity, and/or β_3 receptor agonism) [86,87] may differentiate the Neb/valsartan combination from previously studied β-blocker/RAAS inhibitors.

CONCLUSION

Neb and valsartan reduce BP via complementary mechanisms. In combination, their efficacy surpasses that of component monotherapies. Additive effects have not been observed with other β-blocker/RAAS combinations [3,4]. Hence, a Neb/valsartan combination is an efficacious and well tolerated treatment option for patients with hypertension.

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Conflicts of interest

In the past 2 years, T.D.G. has received personal fees from Forest Laboratories, an Allergan affiliate. J.R.C. received honoraria for advisory board meetings and research funding from Forest. B.P. has no potential conflicts to disclose. A.J. and H.M.W. are employees, present (A.J.) or former (H.M.W.) of the article's sponsor.

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Reviewers' Summary Evaluations

Reviewer 1

The manuscript addresses a very interesting subject. For many years it was accepted that the combination of a β-blocker with a renin–angiotensin–aldosterone system (RAAS) inhibitor was 'less effective' than other combinations, due to a partially overlapping mechanism of action of these two drugs and, more important, the limited evidence. This paper shows preclinical and clinical studies on the single pill combination of nebivolol 5 mg and valsartan 80 mg, a combination recently approved by the FDA to treat hypertension, supporting that nebivolol/valsartan is an efficacious and well tolerated combination treatment for hypertension. The issue is interesting and new information is provided.

Reviewer 2

The ESH/ESC guidelines proposed the use of β-blockers as first line treatment in hypertension since they are as effective as the other major classes of antihypertensive agents in preventing cardiovascular events. Although β-blockers appear to have more side-effects (tend to increase body weight and, particularly when used in combination with diuretics, to facilitate new-onset diabetes in predisposed patients), these limitations are not shared by some of the vasodilating beta-blockers such as nebivolol. The administration of vasodilating β-blockers, and especially nebivolol, improves insulin resistance, and at the same time reduces central blood pressure. Although the combination of a renin–angiotensin system blocker with a β-blocker was not suggested by current guidelines, several studies mentioned in this manuscript suggest that nebivolol/valsartan combination is an efficacious and well tolerated treatment option for patients with arterial hypertension.