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Additivity of nebivolol/valsartan single-pill combinations versus other single-pill combinations for hypertension

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The single-pill combination (SPC) comprising nebivolol (5 mg), a vasodilatory β_1-selective antagonist/β_3-agonist, and valsartan (80 mg), a renin-angiotensin-aldosterone system inhibitor, is the only Food and Drug Administration–approved β-blocker/renin-angiotensin-aldosterone system inhibitor SPC for hypertension. Additive effects of four nebivolol/valsartan SPC doses (5 mg/80 mg, 5/160 mg, 10/160 mg, 10/320 mg nebivolol/valsartan) were compared with five Food and Drug Administration–approved non–β-blocker/renin-angiotensin-aldosterone system inhibitor SPCs (aliskiren/hydrochlorothiazide, aliskiren/amlodipine, valsartan/amlodipine, aliskiren/valsartan, and telmisartan/amlodipine). Additivity is the ratio of placebo-adjusted SPC blood pressure (BP) reduction to the placebo-adjusted monotherapy component BP reduction sums. A weighted average of comparator scores was calculated and compared vs nebivolol/valsartan. Additivity ratio scores for nebivolol/valsartan SPCs (diastolic BP range: 0.735–0.866; systolic BP range: 0.717–0.822) were similar to the comparator weighted average (diastolic BP: 0.837; systolic BP: 0.825). Among the nebivolol/valsartan SPCs, 5/80 mg had the greatest additivity (diastolic BP: 0.866; systolic BP: 0.822). BP reduction contributions with monotherapy were similar for nebivolol/valsartan 5/80 mg SPC. Additivity scores for nebivolol/valsartan and select non–β-blocker/renin-angiotensin-aldosterone system inhibitor SPCs were comparable.

1 | INTRODUCTION

In the United States, hypertension continues to be one of the most widespread, modifiable conditions and remains a leading risk factor for cardiovascular disease.[1] Of the approximately 58 million Americans receiving treatment for hypertension, nearly 44 million (75%) will require more than one drug to achieve blood pressure (BP) control (systolic BP [SBP]/diastolic BP [DBP] <140/90 mm Hg).[2,3] By combining two antihypertensive drugs with complementary mechanisms of action rather than simply doubling the dose of a single drug, better efficacy and/or tolerability can be achieved through additive drug effects.[4,5] Treatment combinations are additive when they confer greater BP reductions than either monotherapy alone.[5] Additivity is complete when the BP-lowering effect of the combination is equal to the sum of the effects of the monotherapies.[4]

In previous trials, combinations consisting of a β-blocker and a renin-angiotensin-aldosterone system (RAAS) inhibitor, such as an angiotensin receptor blocker (ARB) or an angiotensin-converting enzyme inhibitor (ACEI), have demonstrated a lack of additivity compared with other antihypertensive combinations.[5,6] For example, results from a study in which the β_1-selective, nonvasodilatory β-blocker atenolol was combined with enalapril[7] and, more recently, the primary

analysis of the COSMOS (Coreg and Lisinopril Combination Therapy in Hypertensive Subjects) study examining the non–β_1-selective, vasodilatory β-blocker carvedilol plus lisinopril,[8] failed to show additive drug effects. These combinations may have lacked additive BP-lowering effects as a result of similar mechanisms of action of the component monotherapies (ie, RAAS inhibition).[9-11]

Nebivolol is an effective and well-tolerated β_1-selective adrenergic blocker with β_3-agonistic vasodilatory effects, which differentiates it from other β-blockers such as metoprolol and atenolol (nonvasodilatory, β_1-selective) and carvedilol (vasodilatory, non–β_1-selective).[12,13] Nebivolol also has a better tolerability profile than other β-blockers (2.8% adverse event–related discontinuations for nebivolol vs 2.2% placebo[14]) and minimal metabolic effects.[15,16] Valsartan, an ARB that selectively blocks the angiotensin II type 1 receptor and reduces oxidative stress, is also effective in reducing BP with a good safety and tolerability profile.[17–19] Evidence that a β-blocker/RAAS inhibitor combination–specifically combinations with nebivolol–may be an effective treatment option for patients with hypertension arose from two recently reported double-blind, placebo-controlled studies in which greater BP-lowering effects were observed when nebivolol was combined with either an ACEI or an ARB versus monotherapy. First, in a study of participants with stage II diastolic hypertension, treatment with the free-pill combination of nebivolol and the ACEI lisinopril significantly reduced BP to a greater extent than either monotherapy.[20] Second, a trial of nebivolol and the ARB valsartan delivered as a single-pill combination (SPC) to participants with stage I or II hypertension resulted in greater BP-lowering effects than those observed with either monotherapy component.[21]

While additive effects have been observed with various doses of the nebivolol/valsartan SPCs,[21] it is unknown whether these effects are comparable to those seen with other, non–β-blocker/RAAS inhibitor antihypertensive SPCs. This article reports findings from analyses that compared the additive BP-lowering effects of several dose combinations of nebivolol/valsartan SPCs with non–β-blocker/RAAS inhibitor SPCs recently approved by the US Food and Drug Administration for the treatment of hypertension.

2 | METHODS

2.1 | Data

BP data for four nebivolol/valsartan SPCs (nebivolol 5 mg/valsartan 80 mg, 5/160 mg, 10/160 mg, and 10/320 mg) were obtained from a previously reported phase 3, randomized, double-blind, placebo-controlled trial (NAC-MD-01; NCT01508026).[21] Five Food and Drug Administration–approved, non–β-blocker/RAAS inhibitor SPCs were identified as comparators: aliskiren/hydrochlorothiazide (150/12.5 mg, 150/25 mg, 300/12.5 mg, 300/25 mg)[22]; aliskiren/amlodipine (150/5 mg, 150/10 mg, 300/5 mg, 300/10 mg)[23,24]; aliskiren/valsartan (150/160 mg, 300/320 mg)[25]; valsartan/amlodipine (160/5 mg, 160/10 mg, 320/5 mg, 320/10 mg)[26]; and telmisartan/amlodipine (40/5 mg, 40/10 mg, 80/5 mg, 80/10 mg).[27] BP data for the comparators were collected from pivotal, randomized, double-blind, placebo-controlled efficacy and safety trials available on the Drugs@FDA website.[28]

All trials occurred over 8 weeks and included a single-blind run-in period ranging from 2 to 6 weeks. At least one active treatment was uptitrated in all trials: amlodipine doses were doubled after 1 to 2 weeks,[23,24,26] hydrochlorothiazide doses were doubled after 1 week,[22] and doses of all active treatments were doubled in the aliskiren/valsartan and nebivolol/valsartan trials after 4 weeks.[21,25]

2.2 | Trial populations

The trial populations for these analyses were generally similar and included men and women 18 years and older with stage I or II hypertension (DBP 90–110 mm Hg, with the exception of telmisartan/amlodipine [DBP ≥95–119 mm Hg]). Key exclusion criteria included secondary or severe hypertension (SBP/DBP ≥180/110 mm Hg), heart failure, and uncontrolled diabetes mellitus. The majority of trials also excluded participants with hypertensive encephalopathy/stroke, valvular heart disease, myocardial infarction, and history of transient ischemic attack.[28] Details of the inclusion and exclusion criteria for all trials have been previously published.[21–27]

2.3 | Additivity analysis

Additivity was defined as the ratio of placebo-adjusted (ie, incremental) BP reduction with SPC over the sum of placebo-adjusted BP reductions with corresponding monotherapy components in each study. An additivity ratio score of 1.0 represents complete additivity, <1.0 represents partially additive, and >1.0 represents a synergistic effect. Additivity scores were calculated for the various dose combinations of nebivolol/valsartan and each of the identified comparator SPCs, along with standard errors and corresponding 95% confidence intervals (CIs). A weighted average of the additivity ratio scores for all comparator SPCs was calculated for comparison with the nebivolol/valsartan SPC. The inverse variance of the score for each SPC was used as weight in the average to account for differences in study population sizes. In addition, placebo-adjusted additivity difference scores were calculated. Difference scores were defined as the placebo-adjusted BP reduction with SPC minus the sum of placebo-adjusted BP reductions with corresponding monotherapy components in each study.

To determine whether each component of the SPC contributes to the overall effect, contribution scores were calculated as the placebo-adjusted ratio of the monotherapy BP reduction to the SPC BP reduction for each component drug. Ratio scores with a 95% CI upper bounds <1.0 for both monotherapies indicate that each component contributes to the SPC effect, and a ratio score with a 95% CI that covers the value of 1.0 for at least one of the monotherapies indicates that the single component may account for the full effect of the SPC.

To assess the sensitivity of additivity scores to patient characteristics, additivity ratio scores were also computed for patient subgroups (ie, diabetes mellitus status, baseline DBP, BMI, age, and race) for the nebivolol/valsartan 10/160-mg and 10/320-mg SPCs combined. Subpopulation data were not available for the 5/80-mg and 5/160-mg

doses. Consistency in scores across subgroups would indicate similar additivity across different patients and support the comparison of results across studies where patient populations may differ. Details of the equations used in calculations of additivity and contribution scores are provided in the Data S1.

3 | RESULTS

The additivity ratio scores were similar for the nebivolol/valsartan SPCs and for the majority of the non–β-blocker/RAAS inhibitor SPCs, with most scores below 1, indicating partial additivity (Figure 1A,B). SBP and DBP additivity ratio scores for nebivolol/valsartan SPCs (score range SBP: 0.717–0.822; DBP: 0.735–0.866) were similar to comparator non–β-blocker/RAAS inhibitor SPCs for hypertension (SBP: 0.718–1.073; DBP: 0.715–1.285) and numerically greater than several doses of the comparators, such as telmisartan/amlodipine (SBP: 0.772–0.797; DBP: 0.715–0.800 [Figure 1A,B]). The nebivolol/valsartan 5/80 mg/d SPC had the highest additivity ratio score of the nebivolol/valsartan SPC doses (additivity ratio score SBP: 0.822; 95% CI, 0.636–1.062; DBP: 0.866; 95% CI, 0.708–1.059 [Figure 1A,B]). The additivity ratio score of nebivolol/valsartan SPCs was similar to the weighted average of the comparator SPCs for both SBP (additivity ratio score, 0.825; 95% CI, 0.786–0.867) and DBP (ratio score, 0.837; 95% CI, 0.794–0.883 [Figure 1A,B]). SBP and DBP additivity ratio scores that exceeded 1 were obtained only for aliskiren/hydrochlorothiazide (150/25 mg) and aliskiren/amlodipine (150/5 mg). DBP additivity ratio scores that exceeded 1 also were observed with two higher doses of aliskiren/hydrochlorothiazide (300/12.5 mg and 300/25 mg).

Additivity difference scores were also comparable between the nebivolol/valsartan SPCs and the majority of the non–β-blocker/RAAS inhibitor SPCs. All scores were <1, indicating partial additivity (Figure 1C,D).

In terms of the individual monotherapy contributions, the individual contribution scores for the monotherapy components of each SPC for both SBP and DBP were comparable, with most SPC doses demonstrating a 95% upper bound CI <1, indicating that both components contributed to the BP-lowering effect (Figure 2). A small number of doses had upper bounds of the SBP contribution scores exceeding 1: valsartan in the nebivolol/valsartan 5/160-mg dose (ratio score + 95% CI upper bound: 0.841 + 0.192 = 1.03) and amlodipine in both the 150/10-mg (0.834 + 0.172 = 1.01) and 300/10-mg aliskiren/amlodipine (0.869 + 0.181 = 1.05) doses; therefore, the BP-lowering effect of these SPCs may be primarily driven by a single component (Figure 2A).

Additivity scores were relatively stable across subpopulations, indicating that the additivity of nebivolol/valsartan SPCs can be compared with the additivity in populations with different patient characteristics

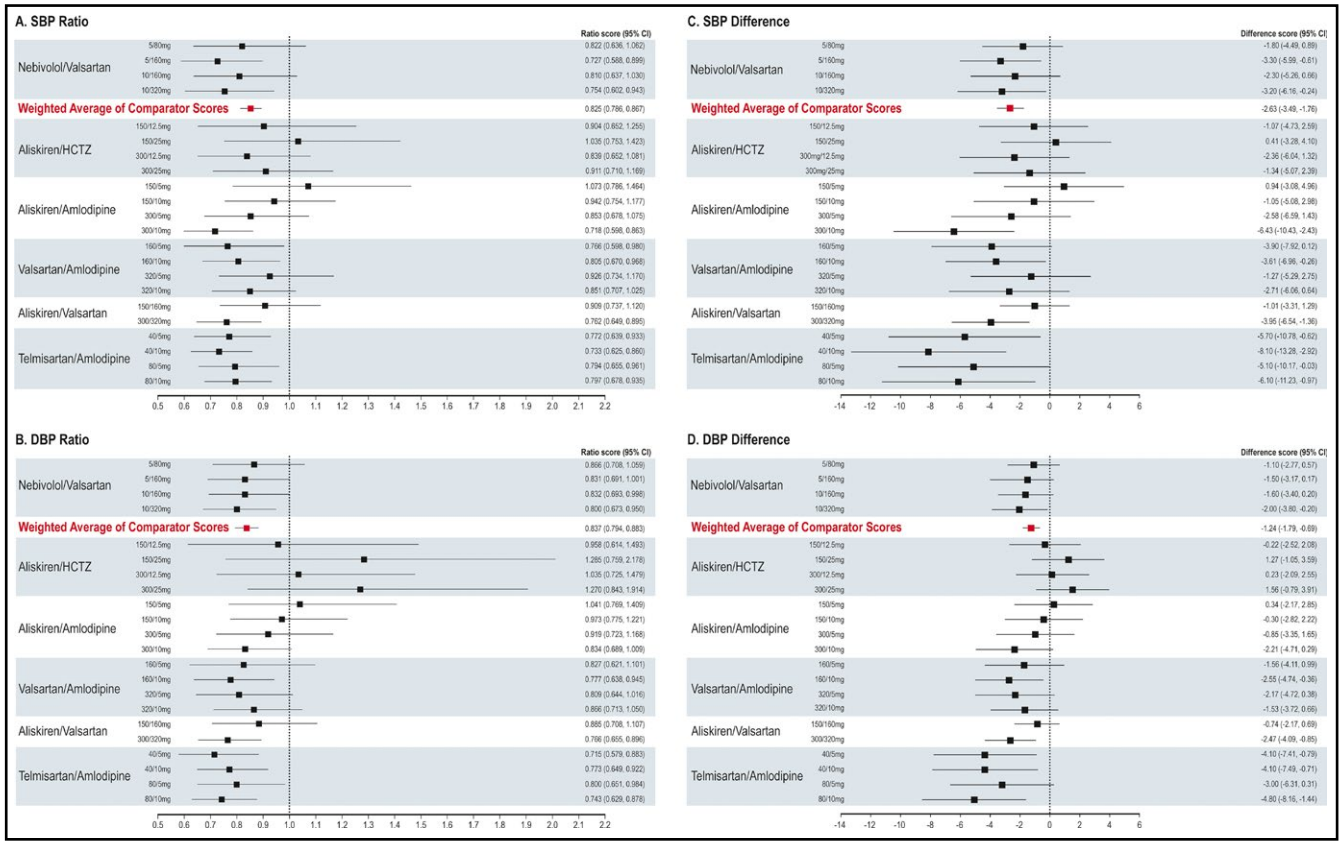

FIGURE 1 Placebo-adjusted additivity ratio and difference scores. Difference scores are presented as mm Hg and error bars represent the 95% confidence intervals (CIs). DBP indicates diastolic blood pressure; HCTZ, hydrochlorothiazide; SBP, systolic blood pressure

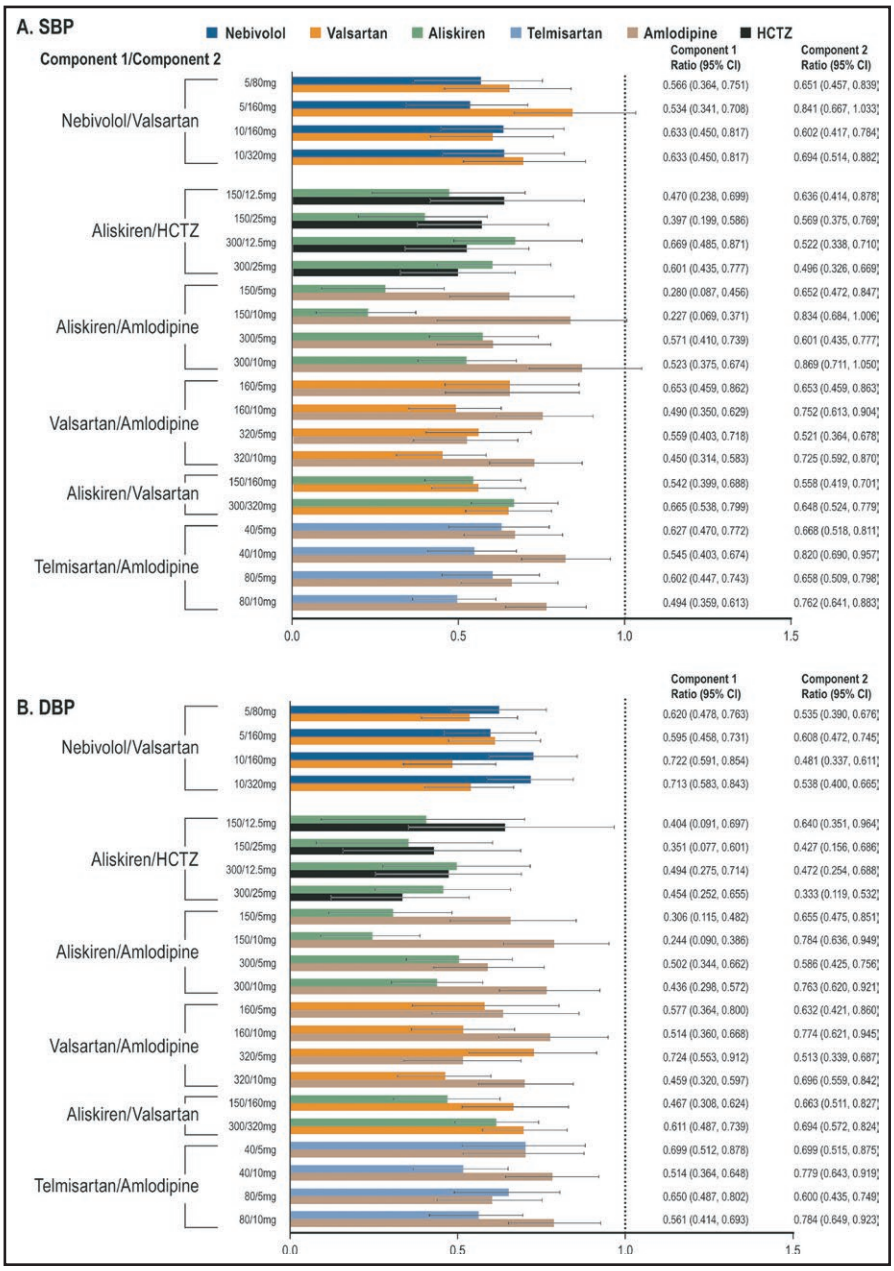

FIGURE 2 Contributions of monotherapy components to single-pill combination (SPC) effect: mean ratio scores. Error bars represent the 95% confidence intervals (CIs). DBP indicates diastolic blood pressure; HCTZ, hydrochlorothiazide; SBP, systolic blood pressure

(Figure 3). The wide CIs noted for the black, diabetes mellitus, and 65 years and older subgroups are attributable to small sample sizes.

4 | DISCUSSION

The results of this analysis indicate that the BP-lowering effects of the nebivolol/valsartan SPCs are partially additive, with the lowest dose (5/80 mg) demonstrating the greatest additivity scores. The additivity of the nebivolol/valsartan SPCs are comparable to the additivity of other recently approved non–β-blocker/RAAS inhibitor SPCs for the treatment of hypertension. In terms of individual monotherapy contribution, both components contributed to the overall effect for the majority of the SPC doses. These results are in contrast to the long-standing opinion that combining a β-blocker with a RAAS inhibitor is a less effective drug combination (than, for instance, a diuretic or calcium channel blocker combined with an ACEI, ARB, or direct renin inhibitor) as a result of potential overlapping mechanisms of action.[29]

Recommendations against combining a β-blocker and a RAAS inhibitor were largely based on negative results from an early study of the nonvasodilatory β-blocker atenolol combined with enalapril[7] and results from a more recent study in which the vasodilatory, non–β_1-selective β-blocker carvedilol was combined with lisinopril (COSMOS).[8]

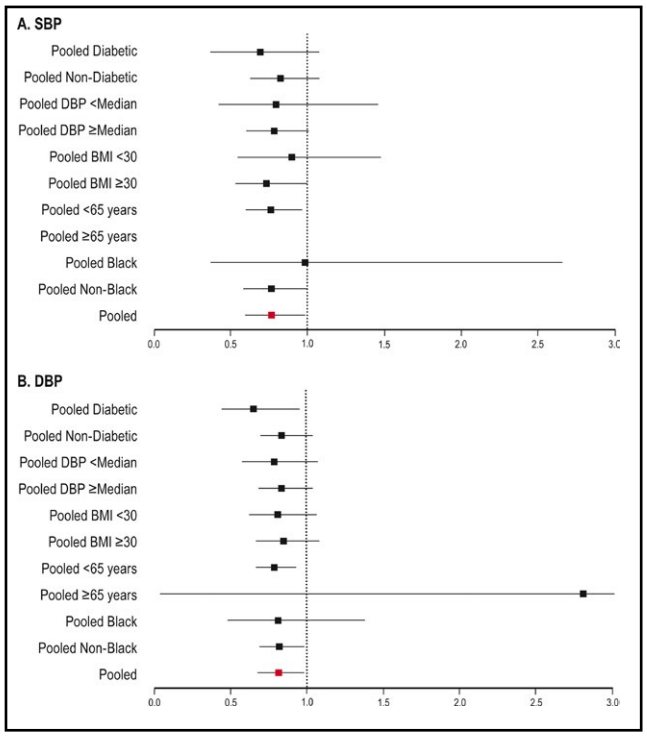

FIGURE 3 Placebo-adjusted subpopulation additivity scores and 95% confidence intervals (CIs) for nebivolol/valsartan single-pill combinations 10/160- and 10/320-mg doses combined. Error bars represent the 95% CIs. Due to the width of the 95% CIs for the pooled age group 65 years and older in Figure B, the *x* axis was curtailed for readability. Systolic blood pressure (SBP) reduction for the age group 65 years and older was greater in the placebo group. As such, the placebo-adjusted point estimate is negative and not shown on the current scale. BMI indicates body mass index; DBP, diastolic blood pressure

No additive reductions were observed in the COSMOS study, which enrolled 654 individuals with stage I or II hypertension randomized to carvedilol or lisinopril monotherapy or several dose combinations of the two (model-adjusted mean change seated SBP and DBP range: −10.4 to −10.9 mm Hg and −6.2 to −7.4 mm Hg for carvedilol/lisinopril combinations vs −6.3 and −4.4 mm Hg for carvedilol monotherapy and −8.0 and −7.0 mm Hg for lisinopril monotherapy; not significant).[8] In contrast to the primary outcomes of COSMOS, a greater BP-lowering effect was attained when nebivolol (5, 10, or 20 mg/d) was added to background ACEI or ARB therapy in patients with uncontrolled hypertension (least squares mean change SBP and DBP range: −3.7 to −6.2 mm Hg and −3.3 to −4.6 mm Hg for combinations vs −0.1 and −3.3 mm Hg for background treatment [$P < .02$ all][30]; least squares mean change SBP and DBP: −7.3 and −7.3 mm Hg for combinations [all nebivolol doses combined] vs −3.5 and −4.0 mm Hg for ACEI or ARB monotherapy [$P \leq .05$ both][31]). A greater number of participants achieved BP control with nebivolol combination treatment than with ACEI or ARB alone (53% to 65.1% combinations vs 41.3% background treatment; $P < .05$ all[30]). Lastly, in a phase 3, pivotal trial, the nebivolol/valsartan combinations were more effective in reducing BP than the component monotherapies in a population of adults with stage I and II hypertension (mean change SBP and DBP range: −17.7 to −17.8 mm Hg and −14.8 to −15.7 mm Hg for nebivolol/valsartan SPCs vs −14.2 to −15.1 mm Hg and −10.8 to −14.4 mm Hg for nebivolol or valsartan monotherapy; $P \leq .03$ all).[21]

Additive BP-lowering effects are best achieved by combining drugs with different, yet complementary, mechanisms of action[5]; however, not every combination of drugs from complementary drug classes produces strong additive effects. In this analysis, for example, the additivity scores of the telmisartan/amlodipine SPCs were typically lower than those of the other CCB/RAAS inhibitor SPCs, particularly aliskiren/amlodipine. Conversely, combinations with some overlapping mechanisms of action, such as a β-blocker combined with a RAAS inhibitor, can provide additive effects on BP as shown in this analysis with the nebivolol/valsartan SPCs. Although generally counterintuitive, the additive effects observed with the combination of this particular β-blocker (nebivolol) and RAAS inhibitor (valsartan) may be attributable to the multi-modal effects of nebivolol, which makes nebivolol distinct from other β-blockers. The class of β-blockers is heterogeneous in terms of their pharmacology and hemodynamic effects, and heterogeneity in their overall clinically relevant effects has been observed.[12,32] Thus, the positive results of the current analysis may be explained by the multiple mechanisms of action for nebivolol such as vasodilation, decreased peripheral resistance, decreased myocardial contractility, and suppression of renin activity.[13,33] In addition, nebivolol is highly selective for the β_1-receptors (ie, cardioselective), produces endothelium-dependent vasodilation via nitric oxide, and is also a β_3-receptor agonist.[12,32] Differences in receptor affinity and vasodilatory pathways may explain the better tolerability profile of nebivolol over other β-blockers[16] and may also explain why the nebivolol/valsartan combination has shown greater additivity[21] than other nonvasodilatory or non–β_1-selective β-blocker and RAAS inhibitor combinations in previous hypertension trials.[7,8]

Based on the analyses presented, the nebivolol/valsartan SPC was additive in terms of reducing BP from baseline and both monotherapy components contributed to the overall effect of the SPC. These results support the notion that effective BP reduction with a combination of a β-blocker and a RAAS inhibitor may depend on the particular drugs combined. In multiple studies, both nebivolol and valsartan monotherapies have been shown to be safe and effective in patients with hypertension,[21] including in populations susceptible to treatment-resistant hypertension (eg, elderly, black).[34-36] This analysis of the additivity of the nebivolol/valsartan SPCs compared with other approved SPCs for the treatment of hypertension further supports its clinical utility.

5 | STUDY LIMITATIONS

Limitations of this study include the retrospective nature of this post hoc analysis. The studies included in this analysis were of slightly different design and, thus, may be subject to selection bias and confounding. All results reported herein (for nebivolol/valsartan and all comparators) are placebo adjusted, and, in that way, are adjusted for any confounding. The subgroup results were reported to demonstrate that additivity scores for the nebivolol/valsartan SPCs are relatively

stable across different types of patients. These were not meant to be compared with other SPCs. As such, corresponding data were not extracted or reported for these. The analyses as a whole were designed to show that the additivity for nebivolol/valsartan is comparable to other SPCs and that it is similarly additive in different types of patients.

6 | CONCLUSIONS

The additivity scores of nebivolol/valsartan SPCs and selected non–β-blocker/RAAS inhibitor SPCs are comparable, with both components contributing to the BP-lowering effect.

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CONFLICTS OF INTEREST

J. Ishak is employed by Evidera, a consulting firm that received funding from Allergan to plan and conduct the analyses reported in the article. M. Rael is employed by Evidera, a consulting firm that received funding from Allergan to plan and conduct the analyses reported in the article. H. Punzi has received speaker and consultant fees from AstraZeneca and Allergan and research grants from Ferrer Internacional S.A., Boehringer Ingelheim, Actelion, AstraZeneca, Allergan, and the National Institutes of Health. A. Gradman is a consultant and investigator for Allergan and is a consultant, investigator, and speaker for Novartis. He is also a consultant and speaker for Servier (France) and Takeda and is a speaker for Glenmark (India), Pfizer (India), and for the American College of Cardiology. L. Anderson is a paid medical writer employed by Prescott Medical Communications Group, Chicago, IL. M. Patel, S. Ali, and W. Ferguson are employees of Allergan plc. J. Neutel functioned as a principal investigator in this study.

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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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