Original Paper

Evaluation of the Dose Response With Valsartan and Valsartan/Hydrochlorothiazide in Patients With Essential Hypertension

Matthew R. Weir, MD;[1] Nora Crikelair, BS;[2] Drew Levy, PhD;[2] Ricardo Rocha, MD;[2] Venkatram Kuturu, MS;[2] Robert Glazer, MD[2]

This patient data meta-analysis included 9 randomized, double-blind, placebo-controlled trials (N=4278) of once-daily valsartan 80, 160, or 320 mg or valsartan/hydrochlorothiazide 80/12.5, 160/12.5, 160/25, 320/12.5, or 320/25 mg given for 4 to 8 weeks. Efficacy variables included: (1) mean change in systolic blood pressure (BP) and diastolic BP; and (2) proportion of patients reaching BP goal (<140/90 mm Hg) at the end of the study. Results showed that incremental systolic and diastolic BP reductions were achieved with increasing doses. Starting doses of valsartan 160 mg provided greater BP reductions and a higher proportion of patients reaching goal than 80 mg; combination therapy was more effective than monotherapy. BP goal rates increased incrementally with higher doses. With valsartan/hydrochlorothiazide 320/25 mg, 74.9% overall, 88.8% of stage 1, and 62.1% of stage 2 patients reached BP goal. The rate of discontinuation due to adverse events was low with both monotherapy and combination treatment. Higher starting doses may enable patients to achieve greater initial BP reductions and reach BP goal more rapidly.
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From the Department of Medicine, Division of Nephrology, University of Maryland School of Medicine, Baltimore, MD;[1] and Novartis Pharmaceuticals Corporation, East Hanover, NJ[2]
Address for correspondence:
Matthew R. Weir, MD, Division of Nephrology, University of Maryland School of Medicine, 22 South Greene Street, Room N3W143, Baltimore, MD 21201
E-mail: mweir@medicine.umaryland.edu
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It is well established that lowering blood pressure (BP) reduces the risk of death from stroke, myocardial infarction, and heart failure,[1] yet the most recent national estimates of BP control rates indicate that only 33% of the approximately 65 million persons in the United States with hypertension, and 64% of those treated, reach recommended goal BPs.[2,3] Results of large clinical outcomes trials demonstrate a correlation between the degree of BP lowering and target organ protection and the incremental benefit of small differences in achieved BP.[4] Accumulated evidence suggests that differences in achieved systolic BP (SBP) account for most of the difference in clinical outcomes.[5,6]

The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) recommends that therapy with more than one antihypertensive agent be considered in patients with SBP more than 20 mm Hg or diastolic BP (DBP) more than 10 mm Hg above goal (ie, BP >160/100 mm Hg).[1] Similarly, the European Society of Hypertension guidelines recommend consideration of low-dose combination therapy among patients at high cardiovascular risk, as determined by elevated BP level and the presence of other risk factors.[7] The JNC 7 designates the target BP as <140/90 mm Hg, or <130/80 mm Hg for persons with diabetes mellitus and/or chronic kidney disease. Since there is a 2-fold increase in cardiovascular risk for each

Table I. Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Trials Included in the Meta-Analysis

Study	Treatment Duration, wk	Drug and Dose, mg*	Eligibility Criteria DBP, mm Hg (Age, y)	No. of Patients Val ± HCTZ (n=3121)	No. of Patients Placebo (n=1157)
1	4	Val: 80, 160	95–115 (18–70)	46	25
2	6	Val: 80	95–115 (18–80)	112	111
3	8	Val: 80, 160	>95 and <115 (≥65)	283	144
4	8	Val: 80, 160, 320	95–115 (21–80)	445	145
5	8	Val: 80	95–115 (20–79)	136	142
6	8	Val: 80, 160 Val/HCTZ: 80/12.5, 160/12.5, 160/25	95–115 (18–80)	482	93
7	8	Val: 80, 160, 320	≥95 and <110 (≥18)	378	127
8	8	Val: 160, 320 Val/HCTZ: 160/12.5, 320/12.5, 320/25	≥95 and <110 (≥18)	833	165
9	8	Val: 160, 320	≥95 and <110 (≥18)	406	205

*Indicates only those doses evaluated in the original studies that are included in the meta-analysis. DBP indicates diastolic blood pressure; Val, valsartan; and HCTZ, hydrochlorothiazide.

20/10-mm Hg increase in BP,[8] BP reductions of this magnitude should substantially decrease risk.

Clinical trial experience with angiotensin II type 1 receptor blockers (ARBs) over the past 10 years demonstrates that this class of antihypertensive agents effectively lowers BP with a low incidence of adverse events.[9] The addition of hydrochlorothiazide (HCTZ) to an ARB, an angiotensin-converting enzyme inhibitor (ACEI), or a calcium channel blocker regimen augments BP-lowering efficacy without a substantial increase in adverse events.[10–12] Few studies have analyzed multiple randomized, double-blind, placebo-controlled trials to evaluate the specific dose-response efficacy of ARBs alone and with the addition of HCTZ for the treatment of hypertension.[13,14]

Meta-analyses using patient-level data are increasing in many therapeutic areas, including hypertension, to more accurately estimate treatment effects and identify predictors of response.[15–18] Individual patient data meta-analyses rather than single studies provide for a more precise estimate and evaluation of treatment effects in a range of patient subgroups and an estimation of the dose-response relationship.[19] Patient data meta-analyses offer advantages over those using summary data from published studies. These include integration of the totality of relevant data from a collection of studies, accuracy and reliability of data, a standardized approach to extracting data, and the ability to explore the relationship between patient characteristics and response.[19,20] It has been suggested that patient data meta-analyses be considered the gold standard when individual data are available.[20]

Therefore, we performed a meta-analysis of individual patient data from 9 randomized, double-blind, placebo-controlled trials to evaluate the effect of initial therapy with an ARB, valsartan, as monotherapy and combined with HCTZ. The objective of this analysis was to assess the relative BP-lowering efficacy and tolerability of fixed incremental doses across the dose range using all data from relevant phase 3 clinical trials. To achieve this, studies selected were those that did not titrate dose based on response.

METHODS

Meta-Analysis Design

Selection of studies for inclusion in the meta-analysis was based on the following criteria: randomized, parallel-group, placebo-controlled design; placebo run-in phase; administration of daily doses of valsartan and/or valsartan/HCTZ; duration of at least 4 weeks and a maximum of 8 weeks with no dose titration based on response; and no administration of supplemental antihypertensive medication. A total of 9 out of 17 available trials met the inclusion criteria, all with similar eligibility criteria and primary end points (Table I). All trials had a 2- to 4-week placebo run-in period before randomization, followed by a double-blind treatment period of 4 weeks in 1 trial, 6 weeks in 1 trial, and 8 weeks in the remaining 7 trials. In all 9 trials, the primary end point was mean DBP at the end of the study (measured seated in 8 trials, supine in 1 trial). Results of 6 of these trials have been published previously.[21–26]

The current analysis focused on patients who received daily doses of an ARB, valsartan (80, 160, or 320 mg) or valsartan/HCTZ (80/12.5, 160/12.5, 160/25, 320/12.5, or 320/25 mg), that are currently marketed for the treatment of hypertension.

Table II. Patient Baseline Characteristics (Intent-to-Treat Population)

Parameter	Placebo (n=1157)	Val 80 mg (n=782)	Val/HCTZ 80/12.5 mg (n=96)	Val 160 mg (n=907)	Val/HCTZ 160/12.5 mg (n=261)	Val/HCTZ 160/25 mg (n=94)	Val 320 mg (n=646)	Val/HCTZ 320/12.5 mg (n=168)	Val/HCTZ 320/25 mg (n=167)
Mean age, y	56.3±12.6	57.1±12.4	51.7±11.9	56.5±12.9	53.0±10.6	52.6±11.1	55.0±11.3	52.1±11.4	53.6±11.1
Stage 1	409 (35.4)	246 (31.5)	40 (41.7)	359 (39.3)	123 (47.1)	35 (37.2)	271 (42.0)	87 (51.8)	80 (47.9)
Stage 2	746 (64.5)	536 (68.5)	56 (58.3)	551 (60.7)	138 (52.9)	59 (62.8)	375 (58.0)	81 (48.2)	87 (52.1)
Sex									
Male	607 (52.5)	422 (54.0)	58 (60.4)	467 (51.5)	153 (58.6)	51 (54.3)	360 (55.7)	87 (51.8)	78 (46.7)
Female	550 (47.5)	360 (46.0)	38 (39.6)	440 (48.5)	108 (41.4)	43 (45.7)	286 (44.3)	81 (48.2)	89 (53.3)
Age ≥65 y	343 (29.6)	252 (32.2)	14 (14.6)	284 (31.3)	41 (15.7)	17 (18.1)	129 (20.0)	21 (12.5)	20 (12.0)
Ethnicity									
White	971 (83.9)	689 (88.1)	69 (71.9)	721 (79.5)	192 (73.6)	68 (72.3)	497 (76.9)	115 (68.5)	115 (68.9)
African American	87 (7.5)	55 (7.0)	12 (12.5)	83 (9.2)	46 (17.6)	15 (16.0)	69 (10.7)	35 (20.8)	33 (19.8)
Other	99 (8.6)	38 (4.9)	15 (15.6)	103 (11.4)	23 (8.8)	11 (11.7)	80 (12.4)	18 (10.7)	19 (11.4)
BMI ≥30 kg/m^2	444 (38.4)	309 (39.5)	49 (51.0)	388 (42.8)	146 (55.9)	47 (50.0)	290 (44.9)	92 (54.8)	92 (55.1)
Overall SBP	156.3±15.5	158.3±15.8	153.0±14.4	155.5±15.6	151.6±13.5	155.9±14.8	153.4±12.8	150.7±12.7	152.5±11.7
Overall DBP	100.2±4.3	100.7±4.4	101.0±4.9	100.1±4.3	99.8±4.0	101.4±4.8	99.6±4.1	99.2±3.7	99.2±3.6
Stage 1 SBP	144.8±9.7	145.9±9.0	142.3±9.5	144.0±9.5	143.5±9.4	142.9±8.4	144.5±8.7	143.2±9.1	145.6±8.6
Stage 1 DBP	96.9±1.4	96.9±1.6	97.4±1.4	97.0±1.4	97.2±1.5	97.5±1.3	96.6±1.8	96.8±1.6	97.0±1.4
Stage 2 SBP	162.7±14.2	164.0±14.9	160.7±12.3	162.9±14.2	158.9±12.5	163.6±12.1	159.8±11.3	158.7±11.0	158.8±10.5
Stage 2 DBP	102.1±4.3	102.4±4.2	103.5±4.9	102.1±4.3	102.1±4.1	103.7±4.7	101.8±3.9	101.7±3.6	101.3±3.8

Data are presented as mean ± SD or number (percentage). Val indicates valsartan; HCTZ, hydrochlorothiazide; BMI, body mass index; SBP, systolic blood pressure; and DBP, diastolic blood pressure.

Table III. Blood Pressure (BP) Reductions From Baseline to End of Study: Intent-to-Treat Population (N=4278)*

Drug and Dose, mg	No.	Mean Reduction, mm Hg (95% CI) SBP	Mean Reduction, mm Hg (95% CI) DBP	Mean Placebo-Adjusted Reduction, mm Hg (95% CI) SBP	Mean Placebo-Adjusted Reduction, mm Hg (95% CI) DBP
Placebo	1157	5.9 (5.1–6.7)	6.0 (5.5–6.4)	–	–
Val 80	782	11.2 (10.2–12.2)	9.0 (8.4–9.5)	6.7 (5.8–7.7)	3.9 (3.3–4.4)
Val/HCTZ 80/12.5	96	16.8 (14.1–19.5)	12.1 (10.5–13.7)	15.1 (12.4–17.8)	8.1 (6.5–9.7)
Val 160	907	14.3 (13.4–15.3)	11.1 (10.5–11.6)	7.8 (6.9–8.7)	4.8 (4.2–5.3)
Val/HCTZ 160/12.5	261	19.5 (17.9–21.2)	14.5 (13.5–15.6)	15.3 (13.6–16.9)	8.7 (7.7–9.8)
Val/HCTZ 160/25	94	23.2 (20.3–26.2)	16.1 (14.2–18.0)	21.6 (18.6–24.5)	12.2 (10.3–14.1)
Val 320	646	14.9 (13.8–16.1)	11.5 (10.8–12.2)	8.3 (7.2–9.4)	5.3 (4.7–6.0)
Val/HCTZ 320/12.5	168	21.7 (19.7–23.7)	15.0 (13.7–16.2)	15.9 (13.9–17.9)	8.1 (6.8– 9.3)
Val/HCTZ 320/25	167	25.5 (23.4–27.6)	16.6 (15.3–17.9)	19.8 (17.7–21.9)	9.7 (8.4–10.9)

*In regression analyses, the slopes of change from baseline in systolic BP (SBP) and diastolic BP (DBP) on treatment (ordinal) were 1.8998 ($P<.0001$ for trend) and 1.1136 ($P<.0001$ for trend), respectively. CI indicates confidence interval; Val, valsartan; and HCTZ, hydrochlorothiazide.

Table IV. Occurrence of Most Common* Adverse Events

Event, No. (%)	Placebo (n=1169)	Val 80 mg (n=786)	Val/HCTZ 80/12.5 mg (n=96)	Val 160 mg (n=915)	Val/HCTZ 160/12.5 mg (n=264)	Val/HCTZ 160/25 mg (n=94)	Val 320 mg (n=656)	Val/HCTZ 320/12.5 mg (n=168)	Val/HCTZ 320/25 mg (n=169)
Dizziness	33 (2.8)	19 (2.4)	7 (7.3)	23 (2.5)	21 (8.0)	15 (16.0)	34 (5.2)	12 (7.1)	16 (9.5)
URTI	25 (2.1)	14 (1.8)	4 (4.2)	21 (2.3)	10 (3.8)	1 (1.1)	22 (3.4)	9 (5.4)	9 (5.3)
Headache	112 (9.6)	48 (6.1)	11 (11.5)	47 (5.1)	22 (8.3)	9 (9.6)	37 (5.6)	10 (6.0)	7 (4.1)
Fatigue	16 (1.4)	11 (1.4)	6 (6.3)	10 (1.1)	8 (3.0)	9 (9.6)	13 (2.0)	4 (2.4)	7 (4.1)
Nasopharyngitis	17 (1.5)	19 (2.4)	1 (1.0)	37 (4.0)	11 (4.2)	1 (1.1)	17 (2.6)	15 (8.9)	7 (4.1)
Discontinued due to adverse events	32 (2.7)	14 (1.8)	1 (1.0)	15 (1.6)	10 (3.8)	7 (7.4)	21 (3.2)	5 (3.0)	5 (3.0)

*Incidence of >4% for any dose, listed in descending order of frequency for the highest combination dose. Val indicates valsartan; HCTZ, hydrochlorothiazide; and URTI, upper respiratory tract infection.

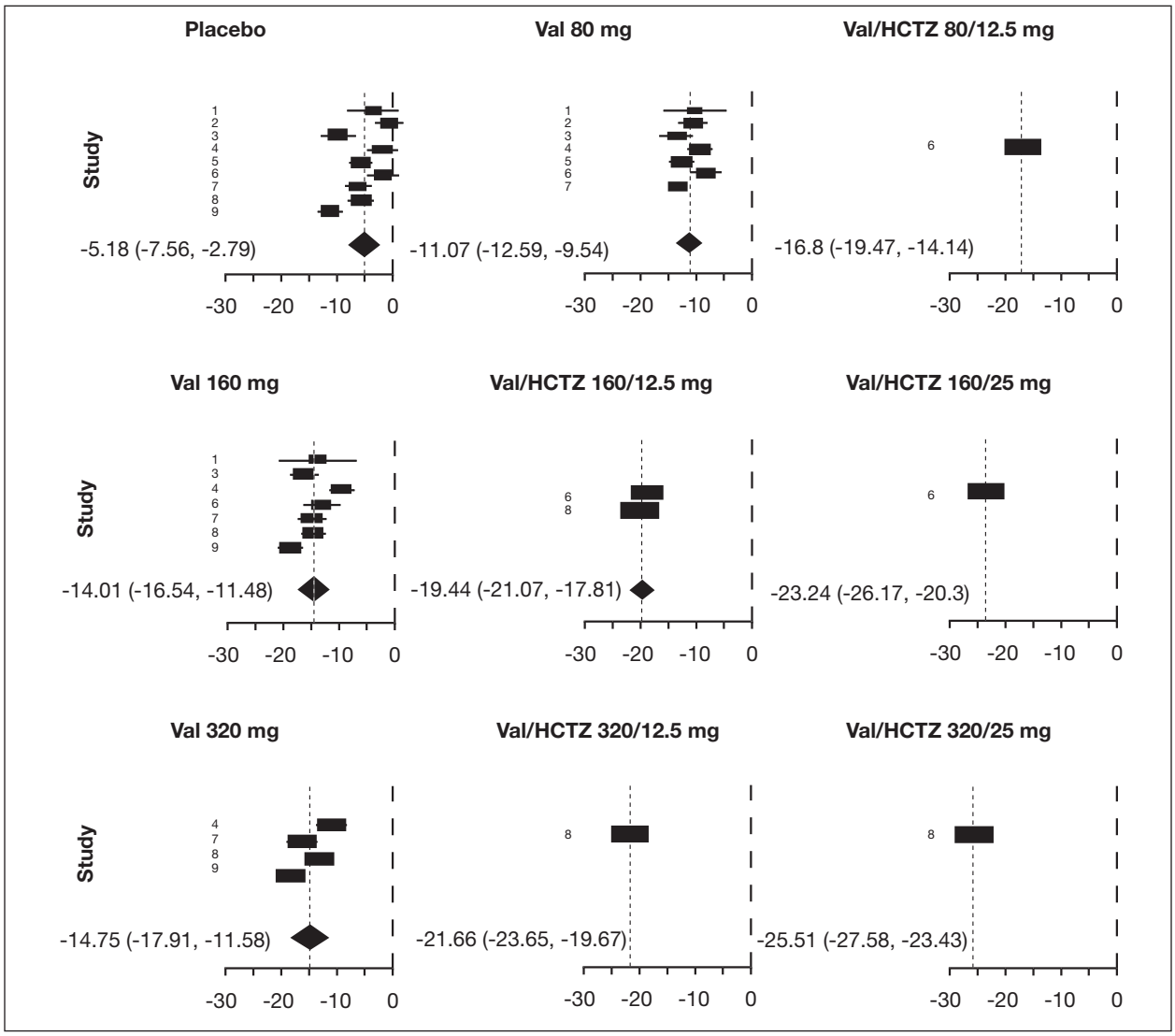

Figure 1. Individual study estimates and summary effects by dose for mean systolic blood pressure reductions (mm Hg) from baseline to end of study. Numbers on the left side of graphs correspond to studies shown in Table I. Summary effects are presented as mean (95% confidence interval). Val indicates valsartan; HCTZ, hydrochlorothiazide.

Patients received a fixed dose of the ARB or the ARB/HCTZ combination, with the exception of the 320/12.5-mg and 320/25-mg arms, in which patients received 160/12.5 mg of valsartan/HCTZ for the first week postrandomization and were then force-titrated to the higher doses. Although 4 of the studies evaluated other antihypertensive agents, only patients receiving valsartan in doses of at least 80 mg alone or in combination with HCTZ were included in this analysis.

In all studies, SBP and DBP were measured at trough (24 hours after last dose) using a sphygmomanometer at 2- or 4-week intervals for the duration of the trial; 3 of the 9 studies did not have measurements available at 2 weeks postrandomization. Efficacy variables for the meta-analysis included: (1) mean change in SBP and DBP from baseline to the end of the study; and (2) achievement of JNC 7 goal,[1] defined as the proportion of patients reaching BP of <140/90 mm Hg at the end of the study.

Statistical Methods

The meta-analysis comprised descriptive summaries of individual patient-level data from 9 placebo-controlled, double-blind, parallel-group trials of valsartan and valsartan/HCTZ. The efficacy analysis was based on the intent-to-treat (ITT) population (N=4278), which included all patients who received at least 1 dose of the randomized trial drug (valsartan, valsartan/HCTZ, or placebo) and had a baseline and at least 1 postbaseline BP measurement. Mean change in SBP and DBP from baseline to the end of the study

was determined using the last observation carried forward. Summary statistics (means, SDs) were calculated by dose for change in SBP and DBP from baseline to end of study; 95% confidence intervals (CIs) for change from baseline were also calculated. Placebo-adjusted BP reductions were calculated by subtracting study-specific mean BP reductions in the placebo group from BP reductions for each patient.

The number and proportion of patients attaining JNC 7 goal were calculated by dose based on BP measurement at the final visit; 95% CIs were calculated for all proportions. Analyses were performed for the following subgroups: hypertension stage based on the JNC 7 classification (stage 1 defined as SBP 140 mm Hg to <160 mm Hg and/or DBP 90 mm Hg to <100 mm Hg; stage 2 defined as SBP ≥160 mm Hg and/or DBP ≥100 mm Hg); sex; age 65 years and older; ethnicity; and body mass index (BMI) ≥30 kg/m^2.

For achieving goal across doses, *P* values were generated using the Cochran-Armitage trend test. For change from baseline in SBP and DBP, the estimates of slopes of their regression on treatment (coded as ordinal levels) were calculated. In addition, *P* values of testing the hypotheses of 0 slope were calculated.

Adverse events were summarized, regardless of relationship to treatment, for all patients who received at least 1 dose of the study drug(s) (n=4317); if a patient experienced more than 1 episode of a particular adverse event, that patient was counted only once for each type of event.

RESULTS

Study-Level Data

To explore heterogeneity among studies, individual study estimates for SBP reductions from baseline to the end of the study were plotted by dose. Figure 1 shows individual study estimates and summary effects for SBP reductions for each dose of active drug and placebo. There was substantial heterogeneity among trials, even in the absence of treatment. Of note, 4 dose levels were evaluated in single trials (80/12.5, 160/25, 320/12.5, and 320/25 mg) and 1 dose level (160/12.5 mg) was evaluated in 2 of the 9 trials.

Patient-Level Data

Baseline characteristics of patients in the ITT population and subgroups are presented by valsartan and valsartan/HCTZ dose in Table II. Mean age ranged from 51.7 to 57.1 years. Percentages of men and women were comparable across dose groups; in the other subgroups (hypertension stage, age, ethnicity, and BMI), there was some variation across doses. Mean baseline SBP and DBP values overall and for subgroups by hypertension stage are also shown in Table II. As patients were selected for baseline DBP levels in all trials, there appeared to be somewhat greater variation in baseline SBP than DBP values across doses. As would be expected, the subgroup of patients 65 years and older had higher mean baseline SBP values (157.8±14.1 years to 169.3±15.0 years) than the overall population, but similar mean baseline DBP values (97.6±3.2 years to 101.3±4.8 mm Hg years).

BP Reduction

BP reductions, both absolute and placebo-adjusted, are provided in Table III. In the ITT population overall and in all subgroups, the mean reductions from baseline in both SBP and DBP at the end of the study were greater with all doses of valsartan and valsartan/HCTZ than with placebo. Incremental reductions in SBP and DBP were evident with increasing doses, with the greatest BP reduction observed with the 320/25-mg dose. SBP reductions of 25.5 mm Hg (95% CI, 23.4–27.6 mm Hg) and DBP reductions of 16.6 mm Hg (95% CI, 15.3–17.9 mm Hg) were noted with this dosage, compared with reductions for the aggregate placebo measure of 5.9 mm Hg (95% CI, 5.1–6.7) and 6.0 mm Hg (95% CI, 5.5–6.4), respectively.

Similar patterns of BP response were seen in subgroups of patients with stage 1 and stage 2 hypertension (data not shown). Patients with stage 2 hypertension, however, had greater SBP reductions across doses than those with stage 1 hypertension or the study population overall. At the 320/25-mg dose, SBP reductions in patients with stage 1 hypertension were 21.9 mm Hg (95% CI, 19.0–24.8 mm Hg) compared with 3.7 mm Hg (95% CI, 2.4–4.9 mm Hg) with placebo. In patients with stage 2 hypertension, SBP reductions with 320/25 mg were 28.8 mm Hg (95% CI, 25.9–31.7 mm Hg) compared with 7.2 mm Hg (95% CI, 6.1–8.3 mm Hg) with placebo.

In the overall population, mean SBP reductions were 14.3 mm Hg (95% CI, 13.4–15.3 mm Hg) with valsartan 160 mg and 11.2 mm Hg (95% CI, 10.2–12.2 mm Hg) with valsartan 80 mg (mean difference of 3.1 mm Hg), compared with 5.9 mm Hg (95% CI, 5.1–6.7 mm Hg) with placebo. Mean DBP reductions were 11.1 mm Hg (95% CI, 10.5–11.6), 9.0 mm Hg (95% CI, 8.4–9.5), and 6.0 mm Hg (95% CI, 5.5–6.4), respectively (mean

difference of 2.1 mm Hg between higher and lower valsartan doses and 5.1 and 3.0 mm Hg, respectively, compared with placebo). The addition of HCTZ 12.5 and 25 mg provided greater BP reductions, with SBP reductions of 19.5 mm Hg (95% CI, 17.9–21.1 mm Hg) and 23.2 mm Hg (95% CI, 20.3–26.2 mm Hg) with valsartan/HCTZ 160/12.5 and 160/25 mg, respectively (added effect of the diuretic, 5.2 and 8.9 mm Hg, respectively).

A similar pattern of improved BP response with increasing doses was seen in all patient subgroups analyzed by sex, age, ethnicity, and BMI. Mean SBP reductions in patients 65 years and older, African-American patients, and those with BMI 30 kg/m^2 or more are shown in Figure 2. In all subgroups, valsartan combined with HCTZ provided consistently greater BP reductions than the same doses of valsartan alone. The combination doses with HCTZ 25 mg appeared to have minimal benefit over the 12.5-mg combinations in elderly patients, whereas in obese patients the benefit of increasing the HCTZ dose was clearly evident. It should be noted that the smaller numbers in patient subgroups limits these observations, and that a more robust BP response results primarily from adding thiazide rather than by pushing the valsartan monotherapy dose.

JNC 7 Goal

The percentage of patients achieving JNC 7 goal BP (<140/90 mm Hg) at the end of the study in the ITT population increased with higher doses of valsartan monotherapy and valsartan/HCTZ combination therapy (*P*<.0001 for trend, Cochran-Armitage trend test). Similar patterns were observed overall (Figure 3) and in hypertension stage subgroups (Figure 4). In the overall population, approximately 60% of subjects achieved the JNC 7 goal of <140/90 mm Hg at the end of the study with valsartan/HCTZ 160/12.5–25 mg, 64.3% with 320/12.5 mg, and 74.9% with 320/25 mg, compared with 39.3% with valsartan 160 mg and 16.5% with placebo. In patients with stage 1 hypertension, a comparable pattern of higher goal attainment rates with the addition of HCTZ to each incremental dose of valsartan is evident. The proportion attaining JNC 7 goal was 88.8% with valsartan/HCTZ at the highest combination dose. As expected, the percentage reaching JNC 7 goal was lower among patients with stage 2 hypertension at baseline compared with the overall population and the stage 1 subgroup. Nevertheless, JNC 7 goal achievement reached 62.1% in the stage 2 subgroup at the highest combination dose.

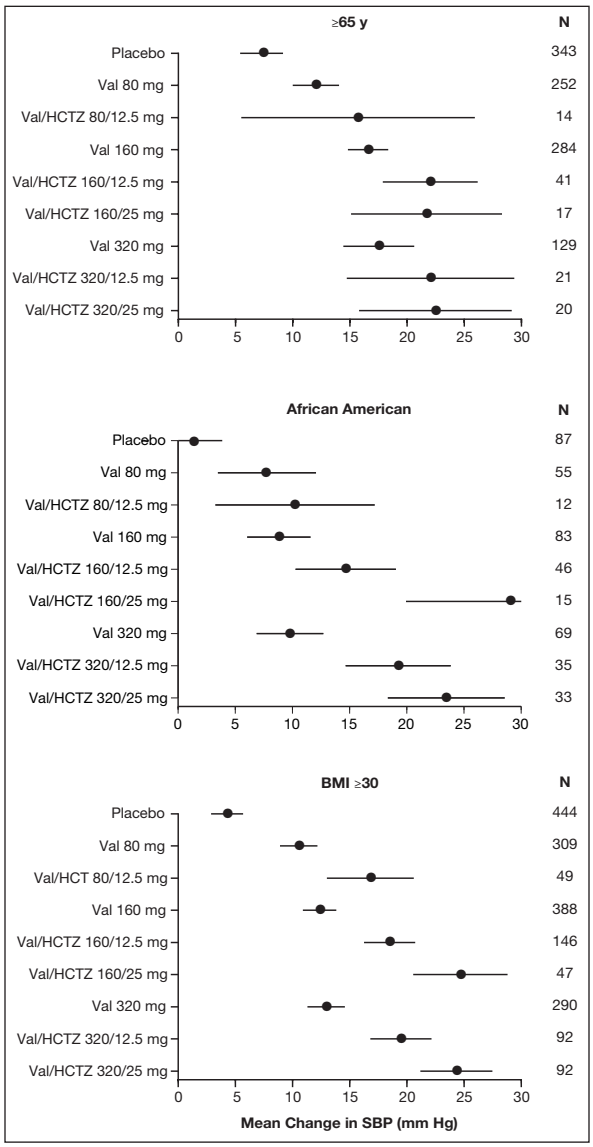

Figure 2. Mean change in systolic blood pressure from baseline to end of study in patient subgroups according to age (65 years and older), ethnicity (African American), and body mass index (BMI) ≥30 kg/m^2. N indicates the number of patients randomized to each dose group; Val, valsartan; HCTZ, hydrochlorothiazide; and SBP, systolic blood pressure.

Tolerability

The safety population comprised all patients randomized in the 9 trials included in this analysis (N=4317). The most common adverse events included dizziness, upper respiratory tract infection, headache, fatigue, and nasopharyngitis (Table IV). No pattern of increasing incidence of headache or fatigue was evident with increased doses of valsartan or valsartan/HCTZ; however, there was an increase in the occurrence of dizziness at higher doses of the combination, which is not unexpected. Rates of hypotension and syncope

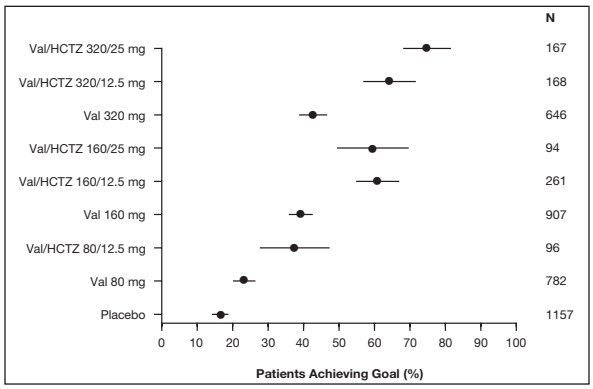

Figure 3. Proportion of patients achieving Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) goal (<140/90 mm Hg) at the final study visit in the intent-to-treat population (N=4278). P<.0001 for trend, Cochran-Armitage trend test. Abbreviations are expanded in the legend for Figure 2.

were low (fewer than 1.5%) across all dose groups, including elderly patients. The incidence of dizziness in elderly patients receiving valsartan monotherapy 80 mg (4.4%), 160 mg (2.4%), and 320 mg (5.3%) was only slightly greater compared with placebo (2.9%). The incidence of dizziness in the elderly receiving the combination was 2.7% overall; the number of patients was small. Rates of adverse events associated with other classes of antihypertensive agents were similar between valsartan monotherapy (pooled), combination therapy (pooled), and placebo (Table IV). A low rate of discontinuations due to adverse events was observed at all doses.

DISCUSSION

In the current analysis of more than 4000 patients, greater BP reductions were observed with increasing daily doses of valsartan and valsartan/HCTZ throughout the available dose range in the overall study population, as well as in subgroups representing a range of patients with hypertension commonly seen in clinical practice. Daily doses of valsartan 160 mg consistently provided greater BP-lowering efficacy than the 80-mg dose, and the addition of HCTZ at doses of 12.5 and 25 mg yielded further substantial BP reductions. Maximum BP reductions were observed with daily doses of valsartan/HCTZ 320/25 mg.

This analysis was intended to provide clinicians with estimates of BP response based on the aggregate of available patient-level data. Estimates of absolute BP reductions and rates of achieving BP goal across the full range of doses provide guidance as to the increments of response that can be expected in clinical practice. Although placebo-adjusted estimates are provided here for completeness, and are necessary for causal inference in establishing the efficacy of new treatments, absolute reductions and rates of achieving BP goal provide a basis for evaluating the efficacy of established treatments in clinical practice. Therefore, placebo-adjusted BP reductions should be interpreted cautiously.

The incremental BP reductions with higher doses of the ARB alone and in combination with HCTZ were generally not accompanied by an increase in adverse events. The incidence of adverse events remained low, with the possible exception of dizziness, for which the increased rate at higher doses of the combination may be related to lower BP levels. Adverse events such as cough,[27–29] peripheral edema,[30,31] and hypokalemia[1] occurred infrequently.

ARB/diuretic combination therapy, as well as combination therapy with an ACEI/diuretic or calcium channel blocker/diuretic, may be especially effective in patient populations with poor BP control on monotherapy. This includes the majority of patients with severe hypertension, and patients with comorbidities who have lower BP goals.[32] Combination therapy may facilitate achievement of BP goal in a shorter period of time than monotherapy, and a fixed-dose regimen may simplify treatment and lower cost.[1] Simpler dosing regimens, less need for regimen changes, and tolerability all contribute to patient adherence.[33,34]

In the current analysis, higher doses of valsartan and valsartan/HCTZ helped patients achieve JNC 7 goal BP levels. A greater proportion of patients achieved the JNC 7 goal at study end with combination therapy compared with monotherapy. Overall, approximately 60% of patients achieved goal BP with valsartan/HCTZ 160/12.5 to 25 mg and 75% with 320/25 mg, compared with approximately 40% on monotherapy. In subgroups of patients with stage 1 and stage 2 hypertension, approximately 89% and 62% of patients, respectively, achieved the JNC 7 goal BP at the highest combination dose. It should be noted that patients with stage 2 hypertension had greater BP reductions although fewer reached goal due to higher baseline BP.

Results of this study expand on findings of an earlier analysis of summary data from 9 studies of valsartan monotherapy showing dose-responsive efficacy.[13] In addition, in the current analysis valsartan and valsartan/HCTZ effectively lowered SBP and DBP in elderly patients, and BP reductions in this subgroup were comparable to those observed in the overall population. This analysis is also consistent with the results of the African American Diovan (Valsartan) Amlodipine (Norvasc) Clinical

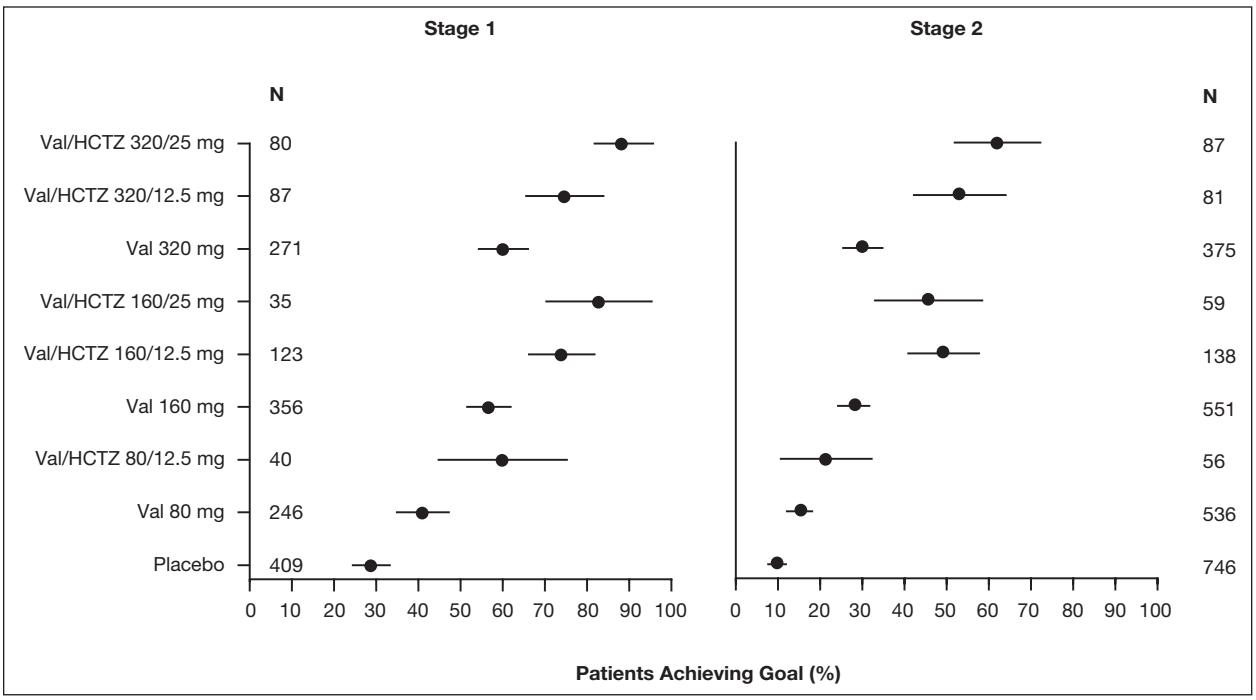

Figure 4. Proportion of patients achieving JNC 7 goal (<140/90 mm Hg) at the final study visit in patients with stage 1 and stage 2 hypertension. P*<.0001 for trend, Cochran-Armitage trend test. Abbreviations are expanded in the legends for Figure 2 and Figure 3.*

Efficacy (AADVANCE) trial,[35] in which combination therapy with valsartan/HCTZ 160/12.5 mg demonstrated efficacy for lowering BP in African American patients with mild-to-moderate hypertension.[35] Although it is believed that an ACEI or ARB monotherapy is not as effective in African American patients, combination therapy with a thiazide-type diuretic and a renin–angiotensin system blocker is effective. Results of this analysis also suggest BP-lowering efficacy among the subgroup of patients with BMI ≥30 kg/m^2, especially with the combination therapy.

This analysis has several limitations. The studies included were not designed to compare dose levels. In addition, the number of patients receiving valsartan/HCTZ 80/12.5 mg and 160/25 mg was smaller than the other dose groups, and 4 of the dose levels were evaluated in single studies. The small number of patients in some subgroups (eg, African American patients) and variation in numbers of patients across doses within subgroups precludes definitive conclusions. Nevertheless, the consistent pattern of results suggests a dose-responsive effect across doses and subgroups.

CONCLUSIONS

This individual patient data meta-analysis of results from 9 randomized, double-blind, placebo-controlled trials of once-daily valsartan and valsartan/HCTZ demonstrates dose-responsive efficacy, with a minimal increase in adverse events at higher doses. Aggregating patient-level data from multiple trials of similar design enables estimation of treatment effect across the dose range and in subgroups of patients. There were consistent results across subgroups analyzed according to hypertension stage, sex, age, ethnicity, and BMI, which further demonstrates the utility of ARB monotherapy and in combination with HCTZ in the range of patients typically seen in clinical practice. Combination therapy was substantially more effective than monotherapy in all analyses for all subgroups. Although both the 80-mg and 160-mg starting doses of valsartan were effective in lowering BP, better results were obtained with the 160-mg starting dose. The higher starting dose may enable patients to achieve greater initial BP reductions and reach BP goal more rapidly.

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