Time to Achieve Blood-Pressure Goal: Influence of Dose of Valsartan Monotherapy and Valsartan and Hydrochlorothiazide Combination Therapy

Matthew R. Weir, Drew Levy, Nora Crikelair, Ricardo Rocha, Xiangyi Meng, and Robert Glazer

Background: Our objective was to assess time to achieve blood-pressure (BP) goal with incremental doses of valsartan alone, and together with hydrochlorothiazide (HCTZ), in patients with uncomplicated hypertension.

Methods: This analysis pooled patient-level data from nine randomized, double-blind, fixed-dose, placebo-controlled trials (N = 4278) of once-daily valsartan 80 mg, 160 mg, and 320 mg, and valsartan/hydrochlorothiazide (HCTZ) 80/12.5 mg, 160/12.5 mg, 160/25 mg, 320/12.5 mg, and 320/25 mg. Kaplan-Meier methods estimated the cumulative proportion of patients achieving BP <140/90 mm Hg over 8 weeks and the median time to BP goal. The HCTZ 12.5-mg and 25-mg doses were pooled for the time-to-goal analysis in patients receiving combinations with valsartan 160 mg or 320 mg.

Results: Overall, the median time-to-goal was 8.1 weeks with valsartan 160 mg, 6.1 weeks with valsartan 320 mg, 2.6 weeks with valsartan 160 mg/HCTZ, and 2.1 weeks with valsartan 320 mg/HCTZ. In patients with stage 2 hypertension, the median time-to-goal was 4.3 weeks with valsartan 160 mg/HCTZ and 2.4 weeks with valsartan 320 mg/HCTZ. Goal rates by Week 4 for valsartan/HCTZ exceeded rates by Week 8 with the same doses of valsartan alone. Overall, the proportion that achieved BP goal by Week 8 was 32.6% with valsartan 80 mg, 48.4% with valsartan 160 mg, 54.2% with valsartan 320 mg, 74.6% with valsartan 160 mg/HCTZ, and 84.8% with valsartan 320 mg/HCTZ, versus 24.2% with placebo. With valsartan 320 mg/HCTZ, 75.8% of stage 2 patients and 94% of stage 1 patients reached BP goal by Week 8. Discontinuation rates due to adverse events were generally low across doses.

Conclusions: In both stage 1 and stage 2 hypertension, BP control is achieved more frequently and promptly when patients receive higher doses of valsartan monotherapy or valsartan combination therapy, with a favorable benefit-risk profile.

The Seventh Report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) recommends considering the initiation of antihypertensive therapy with more than one agent among patients requiring BP reductions 20/10 mm Hg. Most patients at high risk will require ≥2 antihypertensive agents to achieve their BP goal, and the use of combination therapy may allow goal achievement in a shorter time than monotherapy. In addition, earlier treatment efficacy may contribute to improving patient adherence, which is essential for the reduction of cardiovascular risk.

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Angiotensin II Type 1 receptor blockers (ARBs) effectively lower BP with a low incidence of adverse events. The accumulated evidence from large clinical-outcome trials suggests that higher doses of ARBs are associated with greater reductions in cardiovascular risk, and that selecting the appropriate dose may be as important as the choice of antihypertensive agent. Studies demonstrated that the addition of hydrochlorothiazide (HCTZ) augments the BP-lowering efficacy of ARBs, without a substantial increase in adverse events. Few analyses, however, provide sufficient observations over the duration of the treatment period to use survival analysis methods to estimate time to BP goal.

### Methods

#### Design of Analysis

The selection of studies for inclusion in this analysis was based on the following criteria: randomized, parallel-group, placebo-controlled design; placebo run-in phase; administration of daily doses of valsartan or valsartan/HCTZ; a duration of at least 4 weeks and a maximum of 8 weeks with no dose titration; and no administration of supplemental antihypertensive medication. A total of nine of 17 available trials met the inclusion criteria, and all had similar eligibility criteria (Table 1). 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 one trial, 6 weeks in one trial, and 8 weeks in the remaining seven trials. In all nine trials, the primary end point for the original analyses was mean diastolic BP (DBP) at the end of the study (measured with patients seated in eight trials, and supine in one trial). The results of seven of these trials were published.

The current analysis included patients who received daily doses of 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. Patients received a fixed dose of valsartan or valsartan/HCTZ, with the exception of the valsartan/HCTZ 320/12.5-mg and 320/25-mg arms, in which patients received valsartan/HCTZ 160/12.5 mg for the first week after randomization and were then force-titrated to higher doses. Although four studies evaluated other antihypertensive agents, only patients receiving valsartan in combination with HCTZ were included in this analysis.

### Table 1. Multicenter, randomized, double-blind, placebo-controlled, parallel-group trials included in the meta-analysis

<table>
<thead>
<tr>
<th>Duration of treatment (wk)</th>
<th>Doses (mg)*</th>
<th>Eligibility</th>
<th>No. randomized</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Val: 80, 160</td>
<td>DBP ≥95 and ≤115 mm Hg, 18 to 70 y</td>
<td>46 25</td>
</tr>
<tr>
<td>4</td>
<td>Val: 80</td>
<td>DBP ≥95 and ≤115 mm Hg, 18 to 80 y</td>
<td>112 111</td>
</tr>
<tr>
<td>6</td>
<td>Val: 80</td>
<td>DBP &gt;95 and ≤115 mm Hg, ≥65 y</td>
<td>283 144</td>
</tr>
<tr>
<td>8</td>
<td>Val: 80, 160, 320</td>
<td>DBP ≥95 and ≤115 mm Hg, 21 to 80 y</td>
<td>445 145</td>
</tr>
<tr>
<td>8</td>
<td>Val: 80</td>
<td>DBP ≥95 and ≤115 mm Hg, 20 to 79 y</td>
<td>136 142</td>
</tr>
<tr>
<td>8</td>
<td>Val: 80, 160, 320</td>
<td>DBP ≥95 and ≤115 mm Hg, 18 to 80 y</td>
<td>482 93</td>
</tr>
<tr>
<td></td>
<td>Val/HCTZ: 80/12.5, 160/12.5, 160/25</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Val: 80, 160, 320</td>
<td>DBP ≥95 and &lt;110 mm Hg, ≥18 y</td>
<td>378 127</td>
</tr>
<tr>
<td>8</td>
<td>Val: 160, 320</td>
<td>DBP ≥95 and &lt;110 mm Hg, ≥18 y</td>
<td>833 165</td>
</tr>
<tr>
<td></td>
<td>Val/HCTZ: 160/12.5, 320/12.5, 320/25</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Val: 160, 320</td>
<td>DBP ≥95 and &lt;110 mm Hg, ≥18 y</td>
<td>406 205</td>
</tr>
<tr>
<td>Total</td>
<td>Val: 160, 320</td>
<td></td>
<td>3121 1157</td>
</tr>
</tbody>
</table>

DBP = diastolic blood pressure; HCTZ = hydrochlorothiazide; SBP = systolic blood pressure; Val = valsartan.

* Indicates only those doses evaluated in the original studies that are included in the analysis.
doses of ≥80 mg alone or in combination with HCTZ were included in this analysis.

This secondary analysis of data pooled from multiple trials was intended to evaluate time-to-goal for various approaches to treatment involving valsartan, but was not designed, as in a single, sufficiently powered, randomized trial, to make definitive dose-versus-dose comparisons. Imbalances in the contribution of various trials to the combination-therapy arms confounded the comparison of the valsartan/HCTZ 320/12.5-mg versus 320/25-mg doses and the valsartan/HCTZ 160/12.5-mg versus 160/25-mg doses. Whereas the higher dose of the diuretic produced a greater response than the lower dose in the primary efficacy analyses in the two original trials that evaluated the valsartan 160-mg and 320-mg combination doses,

22,25 a dose response was not observed in the current analysis. Therefore, to simplify the presentation of the results of the time-to-goal analysis, the valsartan/HCTZ 160/12.5-mg and 160/25-mg doses were combined, as were the valsartan/HCTZ 320/12.5-mg and 320/25-mg doses.

In all studies, systolic BP (SBP) and DBP were measured at trough (24 h postdose) at 2-week or 4-week intervals using a sphygmomanometer. Three of the nine studies did not have measurements available at 2 weeks after randomization. The efficacy variable for this analysis was the first time to achieve the JNC 7 goal for patients with uncomplicated hypertension,1 defined as BP <140/90 mm Hg. The efficacy variable was analyzed for the overall population and by hypertension stage according to JNC 7 classification. Stage 1 hypertension was defined as SBP 140 to <160 and DBP 90 to <100 mm Hg. Stage 2 hypertension was defined as SBP ≥160 or DBP ≥100 mm Hg.1

Statistical Methods

The analysis comprised descriptive summaries of patient-level data pooled from the nine eligible trials. The efficacy analysis was based on the intent-to-treat (ITT) population (N = 4278), which included patients who received at least one dose of the randomized trial drug (valsartan, valsartan/HCTZ, or placebo) and had baseline and at least one postbaseline BP measurements. The Kaplan-Meier product-limit estimator26–28 method was used to estimate the cumulative proportion of patients achieving their BP goal at each week (from weeks 2 to 8), with 95% confidence intervals (CIs), for the ITT population overall and for the hypertension stage subgroups. Kaplan-Meier curves were constructed to illustrate the cumulative proportion of patients achieving their BP goal as a function of time over 8 weeks of treatment. The time point at which 50% of patients reach end point (median time-to-goal) is the estimate conventionally used to compare groups with Kaplan-Meier methodology. The median time-to-goal and 95% CIs were calculated as the time at which 50% of patients achieved their BP goal. Because Kaplan-Meier analysis was based on the actual number of days from time of randomization, two patients without a recorded visit date were not included in the efficacy calculations.

Adverse events were summarized, regardless of relationship to treatment, for all patients randomized to the doses of interest who received at least one dose of study drug in the nine trials included in this analysis. If a patient experienced more than one episode of an adverse event, that patient was counted only once for each type of event.

Results

Patients

Baseline characteristics for the ITT population are shown in Table 2. The mean age ranged from 51.7 years in the valsartan/HCTZ 80/12.5-mg group to 57.1 years in the valsartan 80-mg group. Percentages of men and women were comparable across dose groups. For other baseline characteristics, there was some variation across doses. Because patients were selected for baseline DBP levels in all trials, there appeared to be somewhat greater variation in baseline SBP than in DBP values across dose groups.

Time to JNC 7 Goal

The cumulative proportion of patients achieving their JNC 7 goal of <140/90 mm Hg by specific time points (2, 4, and 8 weeks) for the overall ITT population is shown in Fig. 1. Within each dose group, including placebo, goal rates increased over time for the three time points analyzed. Rates of achieving BP goal generally increased across dose groups with incremental valsartan monotherapy and valsartan/HCTZ doses at each of the three time points analyzed. By Week 8, the proportion of patients achieving their JNC 7 goal was 48.4% with valsartan 160 mg and 54.2% with valsartan 320 mg, versus 32.6% with valsartan 80 mg and 24.2% with placebo. With combination therapy, 74.6% achieved their JNC 7 goal with valsartan 160 mg/HCTZ, and 84.8% with valsartan 320 mg/HCTZ, by Week 8.

Increasing doses of valsartan and valsartan/HCTZ consistently facilitated achieving JNC 7 goals at earlier time points. In the overall population, the JNC 7 goal rate with valsartan 160 mg by 4 weeks was comparable to that with 80 mg by 8 weeks (approximately 33%). At every dose level and for each time point, combination therapy facilitated earlier goal achievement compared with monotherapy. Goal rates by Week 4 for the 80-mg, 160-mg, and 320-mg combination doses exceeded rates by Week 8 with the same monotherapy doses. For example, 56.4% of patients achieved their JNC 7 goal with valsartan 160 mg/HCTZ by 4 weeks versus 48.4% with valsartan 160 mg by 8 weeks.

Kaplan-Meier estimates of the proportion of patients achieving their JNC 7 goal over the study period in the ITT population overall and by hypertension stage are shown in Figs. 2, 3, and 4. The general pattern of earlier achievement of JNC 7 goal with incrementally higher
Tolerability

Adverse events occurring in ≥3% of any dose group are shown in Table 4, presented in descending order of frequency according to incidence in the highest combination dose group. Overall, the most common adverse event was dizziness, which occurred in 2.4% to 5.2% of patients in the valsartan monotherapy groups, 7.3% to 16.0% in the valsartan/HCTZ groups, and 2.8% in the placebo group. The incidence of headache was similar across all dose groups, including placebo. Fatigue occurred at similar rates among patients receiving placebo or monotherapy and was somewhat increased among patients receiving combination therapy. The incidence of peripheral edema was low and similar across dose groups, ranging from

doses of valsartan and valsartan/HCTZ, and of increasing BP control within dose groups over time, was observed overall and in patients with stage 1 or stage 2 hypertension. Across the 8-week study period, the 320-mg combination doses resulted in a greater proportion of patients reaching their goal at earlier time points than all other doses. In the stage 1 subgroup, similar goal rates were observed at end of the study with the 160- and 320-mg combination doses.

In terms of time-specific prevalence of goal achievement, the magnitude of effect was greater in the stage 1 than in the stage 2 subgroup, which, by definition, had higher mean BP at baseline. Among stage 1 patients, 72.0% and 74.7% achieved their JNC 7 goal by Week 8 with valsartan 160 mg and 320 mg, respectively, versus 56.8% with valsartan 80 mg and 45.7% with placebo. With valsartan/HCTZ, 92% to 94% of stage 1 patients reached their goal with the 160-mg and 320-mg combination doses, respectively. In the stage 2 subgroup, 60.6% of patients achieved their goal with valsartan 160 mg/HCTZ and 75.8% with valsartan 320 mg/HCTZ by Week 8, compared with 12.2% of patients receiving placebo. A substantially higher percentage of patients in this subgroup achieved their BP goal by 4 weeks with the 320-mg combination doses (52.7%) than by 8 weeks with 320-mg monotherapy (39.4%).

The median time to achieve JNC 7 goal (ie, the time point at which 50% of patients reached their goal) is shown in Table 3. Overall, the median time-to-goal was approximately 8 weeks with valsartan 160 mg and valsartan/HCTZ 80/12.5 mg, 6 weeks with valsartan 320 mg, 3 weeks with the 160-mg combinations, and 2 weeks with the 320-mg combination doses. In patients with stage 1 hypertension, the median time-to-goal was approximately 6 weeks for valsartan 80 mg, 3 weeks for valsartan 160 mg, and 2 weeks for the combinations doses. In patients with stage 2 hypertension, the median time-to-goal was >8 weeks with monotherapy; with combination therapy, the median time-to-goal was approximately 4 weeks with valsartan 160 mg/HCTZ and 2 weeks with the 320-mg combination doses.

### Table 2. Patient baseline characteristics: ITT population

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Placebo (n = 1,157)</th>
<th>Val 80/12.5 mg (n = 96)</th>
<th>Val 160/25.5 mg (n = 96)</th>
<th>Val 320/12.5 mg (n = 96)</th>
<th>Val 160/25 mg (n = 97)</th>
<th>Val 320/12.5 mg (n = 96)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (y)</td>
<td>56.3 (29.6)</td>
<td>57.1 (27.4)</td>
<td>57.1 (26.0)</td>
<td>56.3 (26.0)</td>
<td>57.1 (26.0)</td>
<td>56.3 (26.0)</td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>125 (16.2)</td>
<td>125 (16.2)</td>
<td>125 (16.2)</td>
<td>125 (16.2)</td>
<td>125 (16.2)</td>
<td>125 (16.2)</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>78 (11.4)</td>
<td>78 (11.4)</td>
<td>78 (11.4)</td>
<td>78 (11.4)</td>
<td>78 (11.4)</td>
<td>78 (11.4)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>28.9 (5.3)</td>
<td>28.9 (5.3)</td>
<td>28.9 (5.3)</td>
<td>28.9 (5.3)</td>
<td>28.9 (5.3)</td>
<td>28.9 (5.3)</td>
</tr>
</tbody>
</table>

**BMI** = body mass index (kg/m²); DBP = diastolic blood pressure; HCTZ = hydrochlorothiazide; ITT = intent-to-treat; SBP = systolic blood pressure; SD = standard deviation; Val = valsartan.
0.4% with valsartan/HCTZ 160/12.5 mg to 2.4% with valsartan/HCTZ 320/12.5 mg and 320/25 mg, compared with 2.0% with placebo. The rate of discontinuation because of adverse events was generally low at all doses analyzed.

Discussion

The Kaplan-Meier approach applied to data pooled from nine randomized, placebo-controlled trials and involving >4000 patients improves our ability to describe the relationship between dose and time to achieving BP goal. The results suggest that more prompt effects were attained with increasing doses of valsartan monotherapy and combination valsartan/HCTZ. The 160-mg and 320-mg doses of valsartan facilitated an earlier achievement of BP goal compared with valsartan 80 mg, with and without the addition of the diuretic, overall and in patients with stage 1 and stage 2 hypertension. Rates of achieving BP goal by Week 4 with valsartan 160-mg monotherapy and valsartan 160-mg combination doses approximated those by Week 8 for the valsartan 80-mg monotherapy and valsartan/HCTZ 80/12.5-mg doses, respectively, for the ITT population overall and for both subgroups. In this analysis, dizziness was reported less frequently with valsartan 160 mg than with valsartan/HCTZ 80/12.5 mg. The incremental antihypertensive response observed with the addition of HCTZ 12.5 mg to valsartan 80 mg may come at the cost of more frequent adverse events (eg, dizziness), which are common with thiazide diuretics. Thus, when patients who are started on valsartan 80 mg do not have an adequate BP response, clinical judgment should be used to determine
whether to add HCTZ 12.5 mg to the regimen or to titrate the valsartan dose up to 160 mg.

Consistently higher percentages of patients receiving combination therapy achieved their BP goal at earlier time points compared with valsartan monotherapy. However, at all dose levels, the effect of therapy increased over time, with the largest effect observed at the end of the study (8 weeks). By that time, 74.6% of patients overall had reached their goal with valsartan 160 mg/HCTZ and 84.8% with 320 mg/HCTZ.

This analysis enables the estimation of the median time-to-goal that can be expected across the range of doses. In the overall population, the median time-to-goal was approximately 8 weeks with valsartan 160 mg, 6 weeks with valsartan 320 mg, 3 weeks with valsartan 160 mg/HCTZ, and 2 weeks with 320 mg/HCTZ. Among patients with stage 2 hypertension, who are typically more difficult to treat and require greater BP reductions to reach goal, the median time-to-goal was approximately 4 weeks with valsartan 160 mg/HCTZ and 2 weeks with 320 mg/HCTZ. Although the clinical benefit derived from achieving BP goal in 2 weeks versus 8 weeks is unknown, delays in the first months of treatment were shown in clinical trials to increase cardiovascular risk. Prompt treatment effect was also shown to improve patient adherence to antihypertensive therapy.

Regardless of the patient population, BP control was achieved more frequently and promptly when patients received combination therapy. In stage 2 patients, only those receiving higher doses of valsartan combination therapy were able to achieve control in excess of 50%. In stage 1, BP control rates >50% were achieved with both monotherapy and combination therapy, with the greatest effect being observed with combination therapy and the higher doses of valsartan monotherapy.

These results may have implications for both reaching BP goals in the short term and potentially improving...
Table 3. Median time in weeks (<95% confidence interval) to achieve blood pressure goal (<140/90 mm Hg): ITT population

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Val 80 mg</th>
<th>Val/HCTZ 80/12.5 mg</th>
<th>Val 160 mg</th>
<th>Val 160 mg/HCTZ</th>
<th>Val 320 mg</th>
<th>Val 320 mg/HCTZ</th>
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</thead>
<tbody>
<tr>
<td>Overall NE (n = 1156*)</td>
<td>9.7 (9.1–9.8)</td>
<td>7.9 (4.1–4.8)</td>
<td>8.1 (7.1–4.3)</td>
<td>7.9 (4.1–4.3)</td>
<td>8.0 (4.1–4.3)</td>
<td>8.7 (8.1–8.0)</td>
<td>6.1 (4.1–4.3)</td>
</tr>
<tr>
<td>Stage 1</td>
<td>6.3 (8.0–8.4)</td>
<td>6.0 (4.1–8.0)</td>
<td>6.1 (4.1–4.3)</td>
<td>3.1 (2.3–4.1)</td>
<td>3.1 (2.3–4.1)</td>
<td>3.4 (2.1–4.1)</td>
<td>1.6 (1.3–1.9)</td>
</tr>
<tr>
<td>Stage 2</td>
<td>9.7 (9.7–9.7)</td>
<td>9.0 (8.6–10.1)</td>
<td>4.3 (4.1–6.1)</td>
<td>9.0 (8.6–10.1)</td>
<td>4.3 (4.1–6.1)</td>
<td>8.7 (8.1–8.0)</td>
<td>2.4 (2.1–4.1)</td>
</tr>
</tbody>
</table>

HCTZ = hydrochlorothiazide; ITT = intent-to-treat; NE = not estimable; Val = valsartan.
* Two patients were not assigned to either the stage 1 or stage 2 subgroup.

Table 4. Occurrence of most common* adverse events, n (%)

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n = 1169)</th>
<th>Val 80 mg (n = 786)</th>
<th>Val/HCTZ 80/12.5 mg (n = 96)</th>
<th>Val 160 mg (n = 915)</th>
<th>Val 160 mg/HCTZ 160/12.5 mg (n = 264)</th>
<th>Val/HCTZ 160/25 mg (n = 94)</th>
<th>Val 320 mg (n = 656)</th>
<th>Val/HCTZ 320/12.5 mg (n = 168)</th>
<th>Val/HCTZ 320/25 mg (n = 169)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dizziness</td>
<td>33 (2.8)</td>
<td>19 (2.4)</td>
<td>7 (7.3)</td>
<td>23 (2.5)</td>
<td>21 (8.0)</td>
<td>15 (16.0)</td>
<td>34 (5.2)</td>
<td>12 (7.1)</td>
<td>16 (9.5)</td>
</tr>
<tr>
<td>URTI</td>
<td>25 (2.1)</td>
<td>14 (1.8)</td>
<td>4 (4.2)</td>
<td>21 (2.3)</td>
<td>10 (3.8)</td>
<td>1 (1.1)</td>
<td>22 (3.4)</td>
<td>9 (5.4)</td>
<td>9 (5.3)</td>
</tr>
<tr>
<td>Headache</td>
<td>112 (9.6)</td>
<td>48 (6.1)</td>
<td>11 (11.5)</td>
<td>47 (5.1)</td>
<td>22 (8.3)</td>
<td>9 (9.6)</td>
<td>37 (5.6)</td>
<td>10 (6.0)</td>
<td>7 (4.1)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>16 (1.4)</td>
<td>11 (1.4)</td>
<td>6 (6.3)</td>
<td>10 (1.1)</td>
<td>8 (3.0)</td>
<td>9 (9.6)</td>
<td>13 (2.0)</td>
<td>4 (2.4)</td>
<td>7 (4.1)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>17 (1.5)</td>
<td>19 (2.4)</td>
<td>1 (1.0)</td>
<td>37 (4.0)</td>
<td>11 (4.2)</td>
<td>1 (1.1)</td>
<td>17 (2.6)</td>
<td>15 (8.9)</td>
<td>7 (4.1)</td>
</tr>
<tr>
<td>Nausea</td>
<td>14 (1.2)</td>
<td>12 (1.5)</td>
<td>0 (0.0)</td>
<td>13 (1.4)</td>
<td>2 (0.8)</td>
<td>3 (3.2)</td>
<td>10 (1.5)</td>
<td>3 (1.8)</td>
<td>5 (3.0)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>12 (1.0)</td>
<td>12 (1.5)</td>
<td>2 (2.1)</td>
<td>14 (1.5)</td>
<td>9 (3.4)</td>
<td>2 (2.1)</td>
<td>12 (1.8)</td>
<td>5 (3.0)</td>
<td>4 (2.4)</td>
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<tr>
<td>Back pain</td>
<td>13 (1.1)</td>
<td>15 (1.9)</td>
<td>2 (2.1)</td>
<td>14 (1.5)</td>
<td>9 (3.4)</td>
<td>3 (3.2)</td>
<td>8 (1.2)</td>
<td>3 (1.8)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Discontinued because of</td>
<td>32 (2.7)</td>
<td>14 (1.8)</td>
<td>1 (1.0)</td>
<td>15 (1.6)</td>
<td>10 (3.8)</td>
<td>7 (7.4)</td>
<td>21 (3.2)</td>
<td>5 (3.0)</td>
<td>5 (3.0)</td>
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HCTZ = hydrochlorothiazide; URTI = upper respiratory tract infection; Val = valsartan.
* Incidence >3% for any dose, listed in descending order of frequency for the highest combination dose.
clinical outcomes in the long term. According to recent estimates from the National Health and Nutrition Examination Survey, approximately one-third of all hypertensive adults in the US and two-thirds of those treated reach JNC 7 goals. Recent clinical trials suggest that it is important to achieve prompt BP control, as this may translate into a reduction of cardiovascular risk. The current analysis to achieve prompt BP control, as this may translate into a reduction of cardiovascular risk.4–6 The current analysis demonstrates that prompt and substantial BP reductions are possible in a high percentage of patients, even those with stage 2 hypertension, and provides an estimate of the time and magnitude of effect that may be expected with valsartan monotherapy and combination therapy.

Higher doses of valsartan alone and in combination with HCTZ were generally not associated with an increase in adverse events over 8 weeks of treatment. The incidence of adverse events remained low across doses, with the possible exception of an increased rate of dizziness at higher doses that appeared to be related to the diuretic dose. Furthermore, adverse events commonly associated with other classes of antihypertensive agents, such as cough with angiotensin-converting enzyme inhibitors30–32 and peripheral edema with calcium channel blockers, occurred infrequently in this patient population.

This analysis is subject to several limitations. This was a secondary analysis of existing clinical-trial data that was not designed to make definitive conclusions about differences in efficacy between doses. There was heterogeneity among studies, and there may be unknown influences on trial-specific effect rates. The valsartan/HCTZ 80/12.5-mg and 160/25-mg dose groups were small and were evaluated in single studies. Another inconsistency across trials and treatment arms was the availability of Week 2 measurements. However, the bias introduced by these missing data would be expected to have a minimal impact on results. The strengths of the dataset are its size, placebo-controlled design, and lack of bias by not allowing any dose titration.

Despite its limitations, this analysis contributes to our understanding of the effect of dose on time to BP goal in the absence of data from clinical trials designed to address this question. Aggregating data from multiple studies may provide better representation of the responses expected to be observed in clinical practice. The large number of observations at multiple time points also permits the analysis of time as a continuous variable, rather than categorization in a limited set of time points with an attendant loss of information. These results indicate a relationship between increasing valsartan dose, with and without HCTZ, and time to achievement of BP goal among hypertensive populations and patient subgroups of interest.

Conclusions

In this pooled analysis of data from nine randomized, double-blind, placebo-controlled trials of valsartan and valsartan/HCTZ in uncomplicated hypertension, higher doses of valsartan alone and combined with a thiazide diuretic were more likely to allow patients to achieve their BP goal and resulted in more rapid achievement of BP goal than lower doses, with a favorable benefit-risk profile. The greatest efficacy and the most rapid time-to-goal were observed in patients receiving the two-drug combination compared with monotherapy and placebo at all dose levels. An adequate dosing of valsartan, alone and with HCTZ, has the potential to help a substantial proportion of patients achieve clinically meaningful BP reductions within the first few weeks of initiating antihypertensive therapy.

References


