The Valsartan Antihypertensive Long-Term Use Evaluation (VALUE) Trial
Outcomes in Patients Receiving Monotherapy


Abstract—In the main Valsartan Antihypertensive Long-Term Use Evaluation (VALUE) report, we investigated outcomes in 15 245 high-risk hypertensive subjects treated with valsartan- or amlodipine-based regimens. In this report, we analyzed outcomes in 7080 patients (46.4%) who, at the end of the initial drug adjustment period (6 months), remained on monotherapy. Baseline characteristics were similar in the valsartan (N=3263) and amlodipine (N=3817) groups. Time on monotherapy was 3.2 years (78% of treatment exposure time). The average in-trial blood pressure was similar in both groups. Event rates in the monotherapy group were 16% to 39% lower than in the main VALUE trial. In the first analysis, we censored patients when they discontinued monotherapy (“censored”); in the second, we counted events regardless of subsequent therapy (intention-to-treat principle). We also assessed the impact of duration of monotherapy on outcomes. No difference was found in primary composite cardiac end points, strokes, myocardial infarctions, and all-cause deaths with both analyses. Heart failure in the valsartan group was lower both in the censored and intention-to-treat analyses (hazard ratios: 0.63, P=0.004 and 0.78, P=0.045, respectively). Longer duration of monotherapy amplified between-group differences in heart failure. New-onset diabetes was lower in the valsartan group with both analyses (odds ratios: 0.78, P=0.012 and 0.82, P=0.034). Thus, despite lower absolute event rates in monotherapy patients, the relative risks of heart failure and new-onset diabetes favored valsartan. Moreover, these findings support the feasibility of comparative prospective trials in lower-risk hypertensive patients. (Hypertension. 2006;48:385-391.)

Key Words: clinical trials ■ heart failure ■ diabetes mellitus

Rationale
There were 3 major reasons to undertake the analysis of VALUE patients treated with monotherapy. First, modern outcome trials are designed to directly compare ≥2 antihypertensive drugs, but in practice, the addition of other drugs is frequently required to achieve a good BP control. The question of “pure” comparison of 2 drugs is of scientific interest. This is the second report to analyze monotherapy outcomes in trials of an ARB in hypertension.3

Second, the VALUE protocol mandated 2 monotherapy steps before other drugs could be added to the regimen. At the end of the drug adjustment period, 46% of patients remained assigned to monotherapy. This permitted investigation of possible pharmacological differences between the comparator...
drugs in a larger group of patients in VALUE than in other trials of ARBs.\textsuperscript{3,4}

Third in the main study,\textsuperscript{1,2} a between-group BP difference confounded the interpretation of results. In the monotherapy group, VALUE study physicians chose not to use other BP-lowering drugs at the end of the drug adjustment period. This suggested that good BP control had been achieved in both monotherapy groups and allowed us to address the main study question \textit{"for the same level of BP control"} valsartan would be superior to amlodipine in reducing cardiac morbidity and mortality.

\section*{Methods}

\subsection*{Study Design}

VALUE was a double-blind, active-controlled parallel-group trial. Details about exclusion and inclusion criteria and criteria for assessment of high cardiovascular risk are described in the main study article.\textsuperscript{1} The trial was monitored by an independent safety monitoring board. The end points were adjudicated by an expert end point committee. The trial protocol was approved by all of the involved ethics committees, and the trial was undertaken in accordance with the Declaration of Helsinki. All of the patients gave written informed consent.

\subsection*{Outcome Measures}

In this analysis, as in the main trial,\textsuperscript{1} the primary end point was time to first cardiac event. Prespecified secondary end points were fatal and nonfatal myocardial infarction (MI), fatal and nonfatal heart failure (HF), fatal and nonfatal stroke, and all-cause mortality. An analysis of new-onset diabetes was also prespecified.

\subsection*{Population and Treatment}

VALUE patients were randomly assigned to valsartan- or amlodipine-based regimens without a placebo run-in period\textsuperscript{1} Most patients (89.9\%) were treated previously for hypertension. To achieve a treatment goal of $<140/90$ mm Hg, a 5-step monthly upward titration of medication was implemented within the first 6 months of the study. The first dose of valsartan or amlodipine was 80 mg or 5 mg, respectively, and this could be increased to 160 mg or 10 mg, respectively. Next, hydrochlorothiazide in 2 additional steps (12.5 and 25 mg) could be given and, finally, other antihypertensive drugs excluding ARBs, CCBs, and angiotensin-converting enzyme inhibitors could be added.

To qualify for this subanalysis, a patient had to receive monotherapy with one of the study drugs at the end of the medication up-titration period of 6 months. Of the total 7080 patients available for this analysis, 3263 were randomly assigned to valsartan and 3817 to the amlodipine group.

\section*{Statistical Methods}

Cox regression models were used to assess differences in times to clinical events between treatment arms. Age, the presence of coronary heart disease, and the presence of left ventricular (LV) hypertrophy at baseline were used as a priori covariates. Treatment effects were measured by hazard ratios and 95\% CIs based on Cox regression models. Event rates over time are presented as Kaplan–Meier curves.

Only the time to the first cardiac event was considered in the composite primary end point. For other prespecified end points, only the first event in one category was counted, but a single patient could have one event in each category. Differences between groups in frequency were analyzed with $\chi^2$ tests. Differences between groups for continuous variables were analyzed by Student’s $t$ tests. All of the tests were 2-sided, and significance level was set at 5\%.

The first analysis investigated whether the 2 study drugs had differential effects on clinical outcomes. Patients were censored if and when they started additional antihypertensive drugs. Only events occurring while on monotherapy were counted (censored population). The second analysis examined whether differences observed in the first analysis were clinically important. All of the events, regardless of the drug regimen at the time of the event, were entered in the Cox model (intention-to-treat with monotherapy population [ITT]). In the third analysis, we investigated the effect of duration of monotherapy on outcomes. Patients who persisted on monotherapy were monitored at each of the subsequent return visits, until the 48-month visit. At each

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{trial_profile.png}
\caption{Trial profile.}
\end{figure}
time point, the outcomes throughout the entire duration of the trial were counted according the ITT principle.

To detect new-onset diabetes, we first excluded all of the patients who, at entry, were diagnosed with diabetes, received antidiabetic agents, or had fasting blood glucose levels ≥7.0 mmol/L. New-onset diabetes was diagnosed if: (1) diabetes was reported as an adverse event, (2) patient started receiving antidiabetic drugs or insulin, and (3) at the end of the study fasting blood glucose was ≥7.0 mmol/L. The prevalence of new diabetes in the 2 groups was evaluated by odds ratios and their 95% CIs both in the censored and in the ITT population.

Results

Population

The trial profile is given in Figure 1. A total of 0.9% of patients in the valsartan group and 1.1% in the amlodipine group did not have complete data. These patients are included in the ITT analysis.

Comparisons of baseline characteristics of the 2 monotherapy groups, as well as a comparison of the pooled monotherapy group to the rest of VALUE participants, are given in Table 1. The baseline BP in the amlodipine group was 1.0/0.5 mm Hg higher than in the valsartan group. Risk and disease factors were well balanced in the 2 monotherapy groups with exception of the LV strain pattern, which was more prevalent in the amlodipine group. Both groups received a similar number of antihypertensive drugs before random assignment. Compared with 8165 VALUE patients who were up-titrated to other drugs, the 7080 monotherapy patients had lower baseline BP and more frequently treated with 1 drug and less frequently with multiple drugs before random assignment (Table 1). Furthermore, monotherapy patients had significantly lower values in 11 of 15 demographic, risk, and disease categories. Prevalence of smoking and coronary heart disease was higher, and there were fewer women in the monotherapy group.

Data

The average time on medication for the 7080 patients in this report was 4.1 years (interquartile range [IQR]: 4.0 to 4.9 years). The average time on monotherapy was 3.2 years (78% of exposure time; IQR: 1.7 to 4.5 years). The average daily dose of valsartan was 117.0 mg (IQR: 80 to 155 mg), and amlodipine was 7.1 mg (IQR: 5.0 to 9.7 mg). The incidence of various end points during the study was substantially lower in the monotherapy compared with the nonmonotherapy group (Table 2).

BP levels throughout the study in the censored and ITT population are shown in Figure 2. In the censored population, the outcomes throughout the entire duration of the trial were counted according the ITT principle.

TABLE 1. Baseline Characteristics

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Monotherapy Population Comparison</th>
<th>P*</th>
<th>P†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Valasartan (N=3263)</td>
<td>Amlodipine (N=3817)</td>
<td></td>
</tr>
<tr>
<td>Age±SD</td>
<td>66.9±8.3</td>
<td>66.8±8.2</td>
<td>0.656</td>
</tr>
<tr>
<td>% women</td>
<td>1358 (41.6)</td>
<td>1521 (39.9)</td>
<td>0.151</td>
</tr>
<tr>
<td>White race</td>
<td>2927 (89.7)</td>
<td>3385 (88.7)</td>
<td>0.554</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>28.0±4.7</td>
<td>28.0±4.8</td>
<td>0.830</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>150.0±17.9</td>
<td>151.0±18.0</td>
<td>0.013</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>86.5±10.4</td>
<td>87.0±10.1</td>
<td>0.020</td>
</tr>
<tr>
<td>Qualifying disease factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>1513 (46.4)</td>
<td>1855 (48.6)</td>
<td>0.199</td>
</tr>
<tr>
<td>Peripheral arterial disease</td>
<td>450 (13.8)</td>
<td>525 (13.8)</td>
<td>0.729</td>
</tr>
<tr>
<td>Stroke or transient ischemic attack</td>
<td>567 (17.4)</td>
<td>725 (19.0)</td>
<td>0.122</td>
</tr>
<tr>
<td>LV strain pattern</td>
<td>123 (3.8)</td>
<td>192 (5.0)</td>
<td>0.018</td>
</tr>
<tr>
<td>Qualifying risk factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td>857 (26.3)</td>
<td>995 (26.1)</td>
<td>0.877</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>976 (29.9)</td>
<td>1171 (30.7)</td>
<td>0.291</td>
</tr>
<tr>
<td>Total cholesterol (&gt;240 mg/dl or &gt;6.2 mmol/L)</td>
<td>1089 (33.4)</td>
<td>1211 (31.7)</td>
<td>0.234</td>
</tr>
<tr>
<td>LV hypertrophy</td>
<td>343 (10.5)</td>
<td>409 (10.7)</td>
<td>0.941</td>
</tr>
<tr>
<td>Proteinuria (≥1 on dipstick)</td>
<td>668 (20.5)</td>
<td>766 (20.1)</td>
<td>0.995</td>
</tr>
<tr>
<td>Serum creatinine (&gt;1.7 mg/dl or &gt;150 μmol/L)</td>
<td>93 (2.9)</td>
<td>92 (2.4)</td>
<td>0.274</td>
</tr>
<tr>
<td>No. of pills taken at baseline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>3435 (48.5)</td>
<td>1800 (47.2)</td>
<td>0.291</td>
</tr>
<tr>
<td>2</td>
<td>2260 (31.9)</td>
<td>1247 (32.7)</td>
<td>0.291</td>
</tr>
<tr>
<td>3</td>
<td>670 (9.5)</td>
<td>403 (10.6)</td>
<td>0.291</td>
</tr>
</tbody>
</table>
| % Untreated at baseline           | 348 (10.7)                            | 367 (9.6) | <0.001   | 715 (10.1) | 461 (5.6) | <0.001

Baseline characteristics. Data are shown as No. of patients and (%). ± = SD. P values by χ² for categorical variables and by t test for continuous variables.

* Amlodipine vs valsartan monotherapy.
† Nonmonotherapy vs pooled monotherapy.
‡ By χ² for 3 categories.
the BP fell promptly and similarly in both monotherapy groups. By the sixth study month, the average BP was 137.7/ 89.0 mm Hg in the valsartan and amlodipine groups, respectively. The average BP from month 6 to month 54 was 0.1/0.7 mm Hg lower in the amlodipine group. The BP control rate (complete control was seen in the amlodipine group after adjusting for history of coronary heart disease and presence of LV hypertrophy at baseline. This difference remained statistically significant also in the ITT population (P<0.045; Figure 5). The excess of HF in the amlodipine group was particularly pronounced in long-term monotherapy users (Figure 6).

In the censored population, there was a higher incidence of new-onset diabetes in the amlodipine group (N=252; 9.9%) than in the valsartan group (N=171; 7.8%; relative risk ratio: 0.772; P=0.012). A higher incidence of new diabetes in the amlodipine group was confirmed also in the ITT analysis (P=0.034; Figure 5).

Contrary to the finding of an excess of MI in the valsartan group in the main VALUE study (P=0.02), no significant excess of MI was found in the censored (P=0.779; Figure 4) or in the ITT (P=0.243, Figure 5) monotherapy populations. The odds ratio of MIs in the monotherapy population was close to unity at all of the time points in the trial (Figure 6).

The incidence of edema was 9.9% in the valsartan and 23.7% in the amlodipine group (P=0.001). Hypokalemia was reported in 1.5% of the valsartan group and 2.9% of the amlodipine group (P=0.001). Angina was seen in 12.2% of the valsartan group compared with 8.1% of the amlodipine group (P=0.001). More headaches (P=0.03; 11.6% versus 9.9%), diarrhea (P=0.002; 7.4% versus 5.6%), and syncope (P=0.008; 1.4% versus 0.8%) were seen in the valsartan group. At the last visit or study, end data on proteinuria were available in 83.3% of the valsartan group and 82.6% of the amlodipine group. Proteinuria was seen in 14% of the valsartan group and 17.2% of the amlodipine group (P<0.001). Serum creatinine was 102.7 nmol/L in the valsartan group and 98.7 in the amlodipine group (P<0.0001). Compared with the baseline, creatinine increased (+3.91 nmol/L) in the valsartan group and decreased (−0.26) in the amlodipine group (P=0.001).

**Discussion**

This subanalysis of the VALUE study had several justifications. The patient subgroup that received monotherapy at 6 months in VALUE was larger than in any other trial of ARBs.

### TABLE 2. Events in Monotherapy and Nonmonotherapy Populations

<table>
<thead>
<tr>
<th>Event</th>
<th>Monotherapy (N=7080)</th>
<th>Nonmonotherapy (N=8165)</th>
<th>Ratio of Monotherapy/Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary composite end point</td>
<td>20.4</td>
<td>31.5</td>
<td>0.65</td>
</tr>
<tr>
<td>Cardiac mortality</td>
<td>6.9</td>
<td>11.3</td>
<td>0.61</td>
</tr>
<tr>
<td>Cardiac morbidity</td>
<td>15.2</td>
<td>21.0</td>
<td>0.72</td>
</tr>
<tr>
<td>MI</td>
<td>9.0</td>
<td>11.8</td>
<td>0.76</td>
</tr>
<tr>
<td>HF</td>
<td>8.8</td>
<td>14.3</td>
<td>0.62</td>
</tr>
<tr>
<td>Stroke</td>
<td>7.6</td>
<td>10.8</td>
<td>0.70</td>
</tr>
<tr>
<td>All-cause death</td>
<td>20.6</td>
<td>29.4</td>
<td>0.70</td>
</tr>
<tr>
<td>New-onset diabetes</td>
<td>10.8</td>
<td>12.8</td>
<td>0.84</td>
</tr>
</tbody>
</table>

Events per 1000 patient years. New-onset diabetes is in % of patients at risk.

### Figures

**Figure 2. BP in the censored and ITT population.**
in hypertension and so lent itself to a robust statistical analysis. The question of whether different pharmacological properties of drugs can elicit different outcomes should preferably be investigated in patients who receive the drugs of interest without the confounding influence of other agents. Unlike the total VALUE cohort, patients remaining on monotherapy with the 2 comparison drugs had similar BP control throughout the trial so that BP difference did not confound the interpretation of results. Compared with the rest of the VALUE participants, the monotherapy patients had a milder baseline cardiovascular risk profile and a lesser incidence of in-trial events. Recent hypertension trials have focused on comparing outcomes in patients at high risk of cardiovascular events. Data in less severe forms of hypertension are of clinical and research interest and are lacking.

The focus on potential differences between treatments dictated the hierarchy of analytical approaches in this article. To determine whether there were differences in outcomes between

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**Figure 3.** Primary composite cardiac end points in the censored population. Kaplan–Meier curves of time to first event. Number of event and (%): V (valsartan)=174 (5.3%) and A (amlodipine)=256 (6.7%).

**Figure 4.** Kaplan–Meier curves for secondary end points and all-cause death in the censored population. MI: V (valsartan)=83 (2.5%), A (amlodipine)=103 (2.7%). HF: V=58 (1.8%), A=122 (3.2%). Stroke: V=74 (2.3%), A=88 (2.3%). All-cause deaths: V=204 (6.4%), A=252 (6.6%).
the 2 drugs, events were counted only while patients actually took monotherapy. Next, the question of clinical relevance had to be addressed with the usual ITT approach. Finally, the effect of duration of monotherapy on the incidence of MI and HF were examined in detail, because these end points trended differently in the monotherapy analysis than for the overall study. Results of these analyses were internally consistent. Findings in the censored group were confirmed in the ITT approach and the duration of monotherapy supported the validity of the HF and MI findings.

Our finding of significantly more HF in the amlodipine group extends the existing evidence that CCBs offer less protection against HF. In a meta-analysis of trials comparing CCBs with placebo, a substantial BP decrease in the CCB group did not translate into a reduction of HF. Ours is the first direct comparison of ARB and CCB monotherapy in hypertension. It has been suggested that in some trials the excess HF with CCB might have reflected the inability to differentiate CCB-induced edema from HF. In VALUE, a group of experts used prespecified criteria to adjudicate reported cases of HF. In no case was the diagnosis made solely on the basis of ankle edema. We have no data to address the mechanism of this difference in events but speculate that excessive sympathetic activation by CCB or cardioprotective properties of drugs that interfere with the renin–angiotensin system may contribute.

In the present analysis, a significant reduction of new diabetes in the valsartan group was found both in the censored and the ITT analyses. Reduced rates of new-onset diabetes were reported in hypertension trials comparing ARBs, angiotensin-converting enzyme inhibitors, and CCBs with diuretics and /-blockers. Because /-blockers and diuretics impair glucose metabolism, it was not clear whether these differences reflected positive effects of the newer drugs or negative effects of the older ones. Our finding that new-onset diabetes occurred less often in the valsartan than in the amlodipine group suggests that blockade of the renin–angiotensin system may contribute.

The lower rate of MI reported in the amlodipine group in the main trial was not seen in the monotherapy population. The BP levels in the 2 monotherapy groups were similar throughout the entire study. This supports the argument that the reported MI difference in the main trial reflected BP differences in the early phase of the trial.

More than two thirds of patients in both monotherapy groups had good BP control at the last visit or study end. Whereas the control rate was 2.8% higher in the amlodipine group, our results suggest that a stepwise increase of an ARB or a CCB monotherapy could be a good strategy for BP control in selected patients with high-risk hypertension. Patients who had a near-to-target systolic BP with previous monotherapy (average baseline BP was 150.5 ± 17.9 mm Hg) are more likely to respond to a stepwise monotherapy regimen.

Limitations
Subanaylses violate the initial random assignment of patients. In this report, the size of the 2 treatment arms was unequal. However, baseline demographic characteristics, concomitant disease factors, and the number of drugs used previously for treatment of hypertension were similar in both groups.

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**Figure 5.** Between-group differences in the ITT population. *odds ratio. Primary composite end point: V (valsartan)=281 (8.6%), A (amlodipine)=342 (8.96%). MI: V=137 (4.2%), A=142 (3.7%). HF: V=107 (3.3%), A=164 (4.3%). Stroke: V=108 (3.3%), A=127 (3.3%). All-cause death: V=297 (9.1%), A=349 (9.1%).

<table>
<thead>
<tr>
<th>Event</th>
<th>HR</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
<td>0.978</td>
<td>(0.835-1.145)</td>
<td>0.779</td>
</tr>
<tr>
<td>Heart failure</td>
<td>0.779</td>
<td>(0.611-0.994)</td>
<td>0.045</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>1.150</td>
<td>(0.909-1.455)</td>
<td>0.243</td>
</tr>
<tr>
<td>Stroke</td>
<td>0.994</td>
<td>(0.769-1.285)</td>
<td>0.965</td>
</tr>
<tr>
<td>All-cause death *</td>
<td>1.003</td>
<td>(0.860-1.172)</td>
<td>0.965</td>
</tr>
<tr>
<td>New-onset diabetes *</td>
<td>0.825</td>
<td>(0.691-0.986)</td>
<td>0.034</td>
</tr>
</tbody>
</table>

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**Figure 6.** Between-group differences in HF and MI at various time points in the study. At each point, number of events was calculated for the entire duration of the study.
Because this analysis was limited to responders to monotherapy, a selection bias was inevitable. These potential weaknesses must be weighed against the advantage of analyzing outcomes with 2 primary drugs without the confounding influence of other therapies.

**Perspectives**

A post hoc analysis confined to those patients who could be managed on monotherapy (a subgroup at lower cardiovascular risk than the full study cohort) has enabled us to explore 2 key issues in the VALUE outcomes trial. First, it became possible to directly compare 2 treatments of interest without the confounding effects of adding other drugs; and, second, potential differences in BP between the treatment arms were largely eliminated, thus avoiding a further impediment to interpretation. This strategy facilitated comparison of an ARB and a CCB, suggesting in this monotherapy patient subgroup that the former agent seemed to have advantages in preventing HF and diabetes.

Of perhaps greater importance, when considering the design of future clinical trials, these data indicate that observations in hypertensive patients whose risk profiles and responses to antihypertensive therapy are typical of clinical practice can provide valuable outcomes information. Indeed, it should be noted that two thirds of fatal outcomes in hypertension occur in patients with stage 1 disease.

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**References**


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