The Effect of Valsartan, Captopril, or Both on Atherosclerotic Events After Acute Myocardial Infarction

An Analysis of the Valsartan in Acute Myocardial Infarction Trial (VALIANT)

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OBJECTIVES

We attempted to compare the effect of an angiotensin-converting enzyme (ACE) inhibitor and angiotensin receptor blocker (ARB) on atherosclerotic events.

BACKGROUND

Angiotensin-converting enzyme inhibitors and ARBs interrupt the renin-angiotensin system by distinct mechanisms. It is not clear whether ARBs reduce atherosclerotic events such as myocardial infarction (MI) like ACE inhibitors. This evidence gap may reflect the nature of the studies conducted, to date. Placebo-controlled studies enrolled cohorts at low risk of atherosclerotic events (e.g., patients with chronic heart failure, most treated with an ACE inhibitor). One of the main active controlled trials was confounded by a blood pressure difference between treatments.

METHODS

We compared the effects of captopril, valsartan, and their combination on atherosclerotic events in 14,703 patients randomized in the Valsartan in Acute Myocardial Infarction Trial (VALIANT).

RESULTS

The number of individuals adjudicated as having a fatal or non-fatal MI in the captopril group was 559 (total investigator reported events 798), 587 (796) in the valsartan group, and 554 (756) in the combination group; valsartan versus captopril, p = 0.651 (0.965); combination versus captopril, p = 0.187 (0.350). Overall, all atherosclerotic events examined occurred at a similar frequency in the captopril and valsartan groups.

CONCLUSIONS

Angiotensin receptor blockers appear to be as effective as ACE inhibitors in reducing atherosclerotic events, even when used in addition to other secondary preventive treatments. These data, although not conclusive, also support the hypothesis that adding an ARB to an ACE inhibitor may have a small additional anti-infarction effect, a possibility that needs to be prospectively tested. (J Am Coll Cardiol 2006;47:726–33) © 2006 by the American College of Cardiology Foundation

Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) are two distinct pharmacologic classes that both reduce the actions of angiotensin II at the type 1 receptor (1). Each has other unique pharmacologic effects that may be of therapeutic importance. Angiotensin-converting enzyme inhibitors, by blocking kininase II, also inhibit the breakdown of bradykinin (2). On the other hand, the reflex increase in angiotensin II, resulting from blockade of the AT1 receptor, is believed to lead to enhanced stimulation of the unblocked AT2 receptor (3). Augmentation of bradykinin and stimulation of the AT2 receptor may have additional vascular (e.g., vasodilator) and non-vascular (e.g., fibrinolytic and growth) effects relevant to cardiovascular protection (2,3).

It is still not clear, however, whether ARBs possess the broad spectrum of cardiovascular benefits, such as reduction in risk of myocardial infarction (MI), already demonstrated by ACE inhibitors. Angiotensin receptor blockers reduce the risk of hospital admission for worsening heart failure (and death) in patients with chronic heart failure (CHF) (4–6). In patients with hypertension, the ARB losartan reduced stroke more than the beta-blocker atenolol (but did not preferentially affect the risk of other adverse cardiovascular events, including MI), despite equal reduction in blood pressure (7). More recently, hypertensive patients treated with the calcium-channel blocker amlodipine had a lower...
risk of MI compared to those treated with valsartan (8). Angiotensin-converting enzyme inhibitors, on the other hand, clearly reduce the risk of atherosclerotic events including MI, stroke, and, possibly, unstable angina and the need for coronary revascularization (9–13). Recently, however, one ARB has been shown to reduce the development of atherosclerosis in an experimental animal model, and treatment with others has been shown to decrease blood markers of inflammation in patients with hypertension (14–16).

An even more uncertain issue is whether adding an ARB to an ACE inhibitor might further reduce atherosclerotic events. This combination does reduce the risk of hospital admission for worsening heart failure (and cardiovascular death) in CHF, but its effect on MI, stroke, and other atherosclerotic events, especially MI, is not well defined (4,5,17).

The aim of this report, therefore, is to describe, in detail, the comparative effects of an ACE inhibitor (captopril), an ARB (valsartan), and their combination on atherosclerotic events in the Valsartan in Acute Myocardial Infarction Trial (VALIANT) (18–20).

**METHODS**

**Trial design.** The design of VALIANT has been reported in detail (18,20). Essentially, patients eligible for any one of the three reference studies—Survival And Ventricular Enlargement (SAVE) (21), Acute Infarction Ramipril Efficacy (AIRE) (22), or TRAndolapril Cardiac Evaluation (TRACE) (23)—were recruited. Therefore, patients had to be enrolled between 12 h and 10 days after the onset of acute MI and to have either: 1) left ventricular systolic dysfunction; or 2) clinical evidence of heart failure; or 3) both. Hypotension or shock, renal impairment, ongoing clinical instability (such as angina or arrhythmia), and

<table>
<thead>
<tr>
<th>Table 1. Baseline Characteristics of the Patients in VALIANT</th>
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<tbody>
<tr>
<td><strong>Characteristics</strong></td>
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<tr>
<td>Age, yrs</td>
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<tr>
<td>Female gender</td>
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<tr>
<td>Blood pressure, mm Hg</td>
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<tr>
<td>Systolic</td>
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<tr>
<td>Diastolic</td>
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<tr>
<td>Medical history</td>
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<tr>
<td>Myocardial infarction</td>
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<td>Hypertension</td>
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<td>Diabetes mellitus</td>
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<td>Heart failure</td>
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<td>Stroke</td>
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<td>Smoking</td>
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<td>CABG</td>
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<tr>
<td>PCI</td>
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<td>Thrombolytic therapy</td>
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<tr>
<td>Primary PCI</td>
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<tr>
<td>Other PCI after MI but before randomization</td>
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<tr>
<td>Medication*</td>
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<tr>
<td>ACE inhibitors</td>
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<tr>
<td>ARBs</td>
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<tr>
<td>Beta-blockers</td>
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<tr>
<td>Aspirin</td>
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<tr>
<td>Other antiplatelet agents</td>
</tr>
<tr>
<td>Potassium-sparing diuretics</td>
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<tr>
<td>Other diuretics</td>
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<tr>
<td>HMG-CoA reductase inhibitors</td>
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</tbody>
</table>

Values are means ± SD or n (%). *Treatment with angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) was stopped before randomization.

CABG = coronary artery bypass grafting; HMG-CoA = 3-hydroxy-3-methylglutaryl coenzyme A; MI = myocardial infarction; PCI = percutaneous coronary intervention; VALIANT = Valsartan in Acute Myocardial Infarction Trial.
Intolerance or contraindication to ACE inhibitor use were the major exclusion criteria. Patients were randomized, equally, to receive captopril (up to 50 mg thrice daily), valsartan (up to 160 mg twice daily), or the combination of these two drugs (up to captopril 50 mg thrice daily and valsartan 80 mg twice daily) and followed up for a mean of 24.7 months.

**Trial end-points.** The primary end point of VALIANT was all-cause mortality. The secondary end points included cardiovascular mortality and a number of composites of cardiovascular mortality and non-fatal cardiovascular events including MI, hospitalization for heart failure, stroke, and resuscitation after cardiac arrest.

The Clinical End Points Committee (CEC) in VALIANT adjudicated all deaths and the first non-fatal event in the composite described above. As in the report of the primary results of VALIANT, the analyses of time to first events in the present report were carried out using CEC adjudicated end points, with the exception of hospitalized angina and revascularization (i.e., coronary artery bypass grafting [CABG] or percutaneous coronary intervention), which were not adjudicated. Conversely, we used investigator-reported diagnoses to calculate the total number of events that occurred.

**Statistical analysis.** Rates of baseline clinical characteristics are reported as means with standard deviations or frequencies and percents. The number of patients experiencing an event (and rates) was estimated using the Kaplan-Meier method, and a log-rank test was used for statistical comparisons. Cox proportional hazards models were used to
calculate p values and hazard ratios with 95% confidence intervals. To compare the total number of atherosclerotic events reported per patient rather than the number of patients with events, we employed a negative binomial regression model with an offset adjustment to account for differential periods of follow-up between patients (24). Because beta-blockers and statins also reduce the risk of atherosclerotic events, we also examined whether treatment with either of these drugs at baseline modified the effect of randomized therapy. The interaction of each concomitant medication with the two treatment arms was included into the previously developed multivariable models. The SAS statistical software (SAS Institute Inc., Cary, North Carolina) was used for all statistical analyses. The p values of 0.025 were used as critical values for statistical significance for each of the two valsartan treatments with captopril alone.

RESULTS

The baseline characteristics of the 14,703 patients included in the intention-to-treat analysis of VALIANT are summarized in Table 1.

**Individual atherosclerotic events.** Figure 1 shows the proportion of patients experiencing individual atherosclerotic events, estimated using time to first adjudicated event. Table 2 shows the total number of each type of atherosclerotic end point (accounting for multiple events), using investigator-reported diagnoses.

The number of patients experiencing an event and the number of events for MI were no different in the valsartan and the captopril groups. The Kaplan-Meier analysis of time to first event showed a trend to fewer patients experiencing infarction in the combination treatment group although this was not statistically significant. There was no
difference between the three treatment groups with respect to the number of individuals experiencing an episode of angina (or the total number of episodes). Similarly, there was no statistically significant difference between the treatment groups with respect to coronary revascularization procedures that were performed after randomization in about 25% of patients. The Kaplan-Meier analysis of time to first event showed a trend to fewer patients experiencing stroke in the combination treatment group although this was not statistically significant, and the number of strokes overall was small (occurring in only about 4% of patients).

**Composite atherosclerotic end points.** Table 3 shows a hierarchy of composite atherosclerotic end points, including cardiovascular death. There was no statistically significant difference between treatments for any composite end point.

**Blood pressure.** At one year, the mean systolic/diastolic blood pressure was 127/76 mm Hg in the captopril group, 127.75 mm Hg in the valsartan group, and 125/75 mm Hg in the captopril plus valsartan group (valsartan vs. captopril, \( p = 0.70 \) systolic, 0.32 diastolic; combination versus captopril, \( p < 0.001 \) for both systolic and diastolic). The mean systolic blood pressure overall during the trial was slightly lower in the valsartan compared to captopril group (0.9 mm Hg, \( p < 0.001 \)) and in the combination compared to captopril group (2.2 mm Hg, \( p < 0.001 \)).

**Interactions between randomized therapy and background treatment given at baseline.** Background beta-blocker treatment did not modify the effect of study treatment. There was, however, an interaction between statin treatment taken at baseline and randomized therapy (Fig. 2).

**DISCUSSION**

With the demonstrated effectiveness of ACE inhibitors in reducing the risk of death, heart failure, and recurrent infarction in patients with acute MI, the reference treatment in VALIANT was an ACE inhibitor, captopril, and not placebo (25). The dosing regimen for captopril was that previously shown to reduce the risk of death and MI (and other cardiovascular events) in the SAVE study and supported by other studies (10,13). The anti-atherosclerotic effects of other ACE inhibitors have also been documented in the Studies Of Left Ventricular Dysfunction (SOLVD) (enalapril) (9), the Heart Outcomes Protection Evaluation (HOPE) (ramipril) (11), and EUROpean trial of Reduction Of cardiac events with Perindopril in patients with stable coronary Artery disease (EUROPA) (perindopril) (12), as well as in meta-analyses (13). It is now known that ACE inhibitors not only reduce the risk of infarction but also decrease the risk of stroke and the need for coronary revascularization (9–13). Their effect on unstable angina is less clear, possibly because of the difficulties in adjudicating the exact cause of admission in patients hospitalized with chest pain.

By contrast, it has not been clear whether ARBs also reduce coronary events. This lack of evidence may be related to the nature of the studies conducted, to date, with these agents. The presently completed placebo-controlled studies

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**Table 3. Composite Cardiovascular Mortality and Morbidity Outcomes**

<table>
<thead>
<tr>
<th>End Point</th>
<th>Captopril Group (n = 4,909)</th>
<th>Valsartan Group (n = 4,909)</th>
<th>Valsartan and Captopril (n = 4,885)</th>
<th>Valsartan vs. Captopril p Value</th>
<th>Combination vs. Captopril p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV death or MI*</td>
<td>1,132 (25.2)</td>
<td>1,102 (26.1)</td>
<td>1,096 (25.9)</td>
<td>0.97 (0.89–1.05)</td>
<td>0.399</td>
</tr>
<tr>
<td>CV death or MI or angina*</td>
<td>1,496 (33.3)</td>
<td>1,462 (33.4)</td>
<td>1,462 (34.0)</td>
<td>0.97 (0.90–1.04)</td>
<td>0.433</td>
</tr>
<tr>
<td>CV death or MI or angina or revascularization*</td>
<td>2,178 (47.6)</td>
<td>2,122 (47.0)</td>
<td>2,144 (47.8)</td>
<td>0.97 (0.91–1.03)</td>
<td>0.264</td>
</tr>
<tr>
<td>CV death or MI or angina or revascularization or stroke*</td>
<td>2,228 (48.8)</td>
<td>2,175 (48.1)</td>
<td>2,197 (48.8)</td>
<td>0.97 (0.91–1.03)</td>
<td>0.286</td>
</tr>
</tbody>
</table>

*Analyzed as time to first event. The p values are based on log-rank rank tests.

CI = confidence interval; CV = cardiovascular; HR = hazard ratio; MI = myocardial infarction.
have been conducted in patient cohorts with a low risk of atherosclerotic events (i.e., patients with CHF, many already treated with an ACE inhibitor) with little resultant power to detect a treatment difference between the ARB and placebo (4,6). The remaining large studies have been active-controlled studies in hypertensive subjects (7,8). Here, for equal blood pressure reduction, treatment with losartan led to a lower risk of stroke (but not of MI) compared to atenolol (7). In the recent Valsartan Antihypertensive Long-term Use Evaluation trial (VALUE), the risk of both stroke and MI were higher in patients treated with valsartan compared to those treated with amlodipine although blood pressure was reduced more in the amlodipine group, particularly in the first year when the difference in MI was most pronounced (the systolic/diastolic difference was 4.0/2.1 mm Hg at 1 month and 2.0/1.6 mm Hg at 6 months) (8).

VALIANT, therefore, provides an excellent opportunity to evaluate the comparative effect of ARBs and ACE inhibitors on atherosclerotic events (and on the effect of combined ACE inhibitor-ARB treatment, compared to ACE inhibitor monotherapy) (18,19).

Not only was valsartan compared to an evidence-based dose of a proven ACE inhibitor, but these treatments were used on top of extensive background anti-platelet, beta-blocker, and statin treatment, as well as coronary revascularization (18,19). Furthermore, this large patient cohort, as anticipated, accrued a substantial number of atherosclerotic events (18,19).

We found that the risk of the individual atherosclerotic events studied was comparable in the valsartan and captopril groups as were the rates of the fatal and non-fatal cardiovascular composite end points. This assessment was based on a large number of individual events (e.g., approximately 800 MIs per treatment group compared to <400 per group in the VALUE study) and very large numbers of patients experiencing any atherosclerotic event (over 2,000 per treatment group for the composite of cardiovascular death, MI, hospitalization for angina, or stroke).

It is of interest that the risk of recurrent MI and stroke tended to be less in the valsartan added to captopril group compared to the captopril monotherapy group and that these apparent differences occurred early after randomization. It is important to note, however, that these effects were identified in a retrospective analysis, are modest in size, and are not statistically significant. There is, however, experimental evidence to support the hypothesis that there might be more clinical benefit from both agents used together than either alone. One or more greater blockade of the action of angiotensin II or the putative, protective, effects of augmentation of bradykinin with ACE inhibitors and enhanced stimulation of the AT2 receptor with ARBs may be relevant (1–3,14). Whatever the mechanism, blood pressure was slightly (2.2 mm Hg systolic) but significantly (p < 0.001) lower in the combination treatment group than in the captopril group after randomization. In the VALUE study, a comparably small difference was associated with a lower incidence of MI in the amlodipine-based treatment group, though the difference in that trial occurred in individuals with a much higher baseline blood pressure (compared to the relatively low blood pressure in VALIANT) (8). Arguably, however, a recent placebo-controlled trial with nifedipine in patients with ischemic heart disease suggests that blood pressure reduction is not the whole explanation for the differences observed in coronary events in these various studies (26).

The value of combining an ARB with an ACE inhibitor in patients with stable coronary heart disease (or at high risk of developing coronary disease) should, however, be clarified by the ONgoing Telmisartan Alone and in Combination with Ramipril Global Endpoint trial (ONTARGET). In

Figure 2. Cumulative Kaplan-Meier event-free survival rates in the combination of treatment by statin groups in Valsartan in Acute Myocardial Infarction Trial (VALIANT). The p values are for interactions of statin with valsartan versus captopril and of statin with combination therapy versus captopril (from an adjusted Cox proportional hazards model). MI = myocardial infarction.
In this study, “full-dose” ARB is being added to full-dose ACE inhibitor unlike in VALIANT (17). This approach was not possible in VALIANT, where treatment was initiated and quickly titrated in the acute phase of MI, because there is concern about excessive lowering of blood pressure in this relatively unstable situation (27). For that reason, a submaximal target dose of valsartan (80 mg twice daily as opposed to 160 mg twice daily) was employed in VALIANT. In this setting, even addition of this reduced dose of valsartan to full-dose captopril led to an excess of adverse events related to hypotension. Hypotension is likely to be less frequent and of less concern in the patients enrolled in the ONTARGET study.

In a post-hoc analysis, we found that there was an interaction between baseline statin therapy and valsartan. Such findings must be interpreted cautiously and may arise from the play of chance. However, mechanistic interactions between cholesterol and the renin-angiotensin system (RAAS) and between statins and inhibitors of the RAAS (and valsartan specifically) have been described (28–30).

Whether or not there is a therapeutic interaction that favorably influences clinical outcomes may be worthy of exploration in other datasets.

There are limitations to the current analysis. Though we had a very large number of events, not all of these were adjudicated. Adjudication practice varies between trials and for individual types of event. Of all events examined here, the greatest concern is probably that investigator designated hospitalized angina may not always have accurately identified a true acute coronary syndrome. Our analysis could also have been confounded by the proportion of patients discontinuing treatment differing between treatment groups. However, the difference was small, and, if anything, would have tended to reduce the effect of combination therapy. The proportion stopping treatment for reasons other than death was 21.6% in the valsartan group, 23.4% in the captopril group, 20.5% in the valsartan group, and 21.6% in the valsartan group; 23.4% in the captopril group.

In summary, this analysis of the very large and high-risk cohort of patients with acute MI in VALIANT suggests that ARBs are as effective as ACE inhibitors in reducing atherosclerotic events, even when given in addition to other secondary preventive treatments. These data also suggest, but do not prove, that adding an ARB to an ACE inhibitor may have a small additional anti-infarction effect.

**REFERENCES**


