

## Update on the Efficacy of Angiotensin Receptor Blockers in Treatment of Hypertension

### **Abstract**

Angiotensin II, the principal effector peptide of the renin-angiotensin-aldosterone system (RAAS), has potent vasoconstrictive and other effects that can lead to cardiac and renal complications. Angiotensin receptor blockers (ARBs), which block the effects of angiotensin II at the receptor level, antagonize angiotensin II's vasoconstrictive and prooxidant effects, decrease aldosterone secretion, and mitigate sympathetic activity. The antihypertensive efficacy of the ARBs has been demonstrated in large clinical trials. In addition to their blood pressure-lowering effect, these agents also provide cardiovascular (CV) protection and reduce CV mortality as effectively as other classes of antihypertensive agents. By inhibiting the RAAS, the ARBs also have renoprotective effects and are indicated for the treatment of hypertension in patients with diabetes. They have also been shown to lower the incidence of new-onset diabetes in high-risk hypertensive patients. Combining ARBs with other antihypertensive drugs increases their antihypertensive efficacy.

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Angiotensin II is the principal effector peptide of the renin-angiotensin-aldosterone system (RAAS).<sup>1</sup> In addition to being a potent vasoconstrictor, angiotensin II also mediates many additional processes, such as aldosterone production, vasopressin release, oxidative stress, sodium and water retention, and sympathetic activation—all of which can lead to hypertension.<sup>2</sup> Angiotensin receptor blockers (ARBs) act to block the effects of angiotensin II at the receptor level without changing the levels of bradykinins and prostaglandins.<sup>3-5</sup> By reducing circulating levels of angiotensin II, ARB inhibitors antagonize angiotensin II's vasoconstrictive and prooxidant effects, decrease aldosterone secretion, and mitigate sympathetic activity.<sup>6</sup>

The antihypertensive efficacy of the ARB

class of drugs, sometimes referred to as “sartans,” has been demonstrated in numerous clinical trials. Conlin and colleagues conducted a meta-analysis of 43 published randomized, controlled clinical trials comparing ARBs with placebo, other antihypertensive classes, and each other.<sup>7</sup> Pooled data from these studies involving 11 281 patients treated with ARBs showed that the weighted average of diastolic and systolic blood pressure (BP) reductions and responder rates among agents were comparable, irrespective of starting doses, monotherapy dose titration, and combination therapy with hydrochlorothiazide (HCTZ). Even when assessing head-to-head studies, the meta-analysis found no differences in efficacy or responder rates between agents (Table). Titration to a combination of ARB + HCTZ produced the greatest antihypertensive effect.

### **Cardiovascular Protection**

The Optimal Trial in Myocardial Infarction with the Angiotensin Receptor Blocker Losartan (OPTIMAAL) study reported no significant difference in overall mortality for losartan or captopril.<sup>8</sup> However, other parameters showed trends for less benefit for losartan than captopril. The cause of this disparity remains uncertain, but could relate to the specific ARB used or the chosen dosage.

One of the largest, long-term studies of postmyocardial infarction (MI) patients, the Valsartan in Acute Myocardial Infarction (VALIANT) trial, compared valsartan with captopril and also with combination therapy (valsartan + captopril) in 14 703 patients at high risk for death after a heart attack because of left ventricular (LV) dysfunction.<sup>9</sup> Patients were randomized to 1 of the

**Table.** Summary of Weighted Average Antihypertensive Efficacy From 43 Published Randomized, Controlled Trials of ARBs Published Before 2004

	N	Total (%)	DBP (mm Hg)	95% CI	SBP (mm Hg)	95% CI	Responders (%)
<b>ARB monotherapy starting dose</b>							
Losartan 50 mg	2359	50	-8.2	(-8.5, -7.9)	-10.4	(-10.9, -9.8)	48
Valsartan 80 mg	1455	31	-8.8	(-9.4, -8.2)	-10.9	(-11.8, -10.0)	49
Irbesartan 150 mg	582	12	-8.7	(-9.3, -8.1)	-11.2	(-12.2, -10.2)	53
Candesartan 8 mg	336	7	-8.9	(-10.1, -7.7)	-11.8	(-14.0, -9.7)	55
Across products	4732	100	-8.5		-10.8		49.5
<b>ARB monotherapy titration</b>							
Losartan 50 mg-100 mg	2217	52	-10.0	(-10.3, -9.6)	-13.1	(-13.7, -12.5)	56
Valsartan 80 mg-160 mg	855	20	-9.6	(-10.5, -8.7)	-12.4	(-14.0, -10.8)	56
Irbesartan 150 mg-300 mg	610	14	-10.4	(-11.0, -9.8)	-13.8	(-14.9, -12.8)	63
Candesartan 8 mg-16 mg	593	14	-9.5	(-10.3, -8.7)	-14.7	(-16.2, -13.1)	53
Across products	4275	100	-9.9		-13.3		56.6
<b>Starting dose ARB/HCTZ combination</b>							
Losartan 50 mg/HCTZ 12.5 mg	1605	71	-12.0	(-12.3, -11.6)	-16.5	(-17.2, -15.8)	70
Valsartan 80 mg/HCTZ 12.5 mg	190	8	-13.6	(-14.6, -12.5)	-19.7	(-21.4, -18.0)	66
Irbesartan 150 mg/HCTZ 12.5 mg	181	8	-12.4	(-13.5, -11.3)	-16.1	(-18.2, -14.0)	66
Candesartan 8 mg/HCTZ 12.5 mg	298	13	-9.9	(-11.0, -8.8)	-20.6	(-22.9, -18.3)	56
Across products	2274	100	-11.9		-17.3		68

The 95% confidence intervals (95% CIs) were calculated from the mean and standard deviation. Responder rates were typically the percent of treated patients who achieved a DBP <90 mm Hg or had a decline in DBP of >10 mm Hg.

ARB indicates angiotensin receptor blocker; DBP, diastolic blood pressure; SBP, systolic blood pressure; CI, confidence interval; HCTZ, hydrochlorothiazide.

Source: Reference 7.

3 treatment groups and titrated to the maximum tolerated dose of the study medication valsartan 160 mg twice daily, captopril 50 mg 3 times daily, or valsartan 80 mg twice daily plus captopril 50 mg 3 times daily.

Valsartan was as effective as captopril in increasing survival and reducing cardiovascular (CV) events, including recurrent heart attack and hospitalizations for heart failure in study subjects (Figures 1 and 2). All-cause mortality, the primary end point, was similar in the 3 treatment groups: 19.9% in the valsartan group, 19.3% in the combination group, and 19.5% in the captopril group.

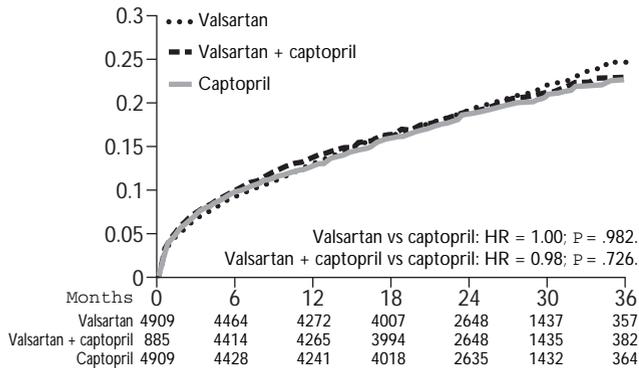
Adverse events occurred most frequently in patients receiving combination therapy. The rate of angioedema was similar in all 3 groups. With monotherapy, cough, rash, and taste disturbance occurred more frequently

in the captopril group, whereas hypotension and renal dysfunction occurred more frequently in the valsartan group.

Based on findings from the VALIANT trial, the US Food and Drug Administration recently approved valsartan for reduction of CV death in high-risk heart attack survivors.

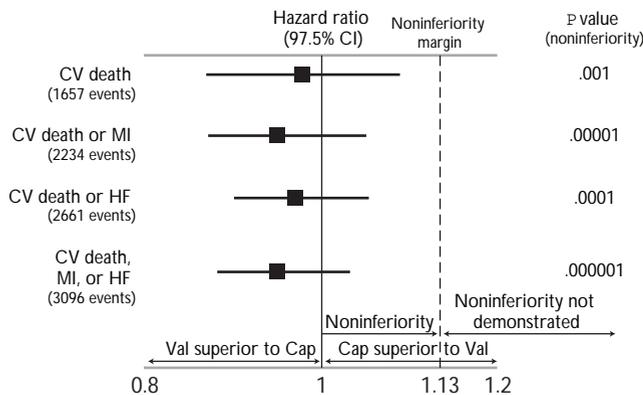
The Valsartan Antihypertensive Long-term Use Evaluation (VALUE) study sought to demonstrate that for the same level of BP control, a valsartan-based regimen would be superior to an amlodipine-based regimen in reducing cardiac morbidity and mortality.<sup>10</sup> This prospective double-blind, randomized, active-controlled, 2-arm, parallel-group comparison trial had a response-dependent dose-titration scheme and enrolled 15 245 patients 50 years of age who had hypertension and were at high risk for developing

**Figure 1.** Mortality by Treatment in VALIANT



VALIANT indicates Valsartan in Acute Myocardial Infarction; HR, hazard ratio.

**Figure 2.** Cardiovascular Mortality and Morbidity in VALIANT



VALIANT indicates Valsartan in Acute Myocardial Infarction; CV, cardiovascular; MI, myocardial infarction; HF, heart failure; Val, valsartan; Cap, captopril; CI, confidence interval.

cardiovascular disease (CVD). Subjects were randomized to either valsartan 80 mg/day or amlodipine 5 mg/day and followed for a mean of 4.2 years. If the BP goal of <140/90 mm Hg was not achieved at 4 weeks, doses could be titrated to valsartan 160 mg/day or amlodipine 10 mg/day and HCTZ 12.5 mg/day could be added. Other antihypertensive drugs could also be used, with the exception of angiotensin-converting enzyme inhibitors (ACEIs), calcium channel blockers (CCBs), ARBs, or diuretics other than HCTZ. (Loop diuretics were permitted in patients with impaired renal func-

tion or heart failure.)

Although BP reductions were greater in the amlodipine group, the majority of patients in both groups reached the BP goal, showing that both treatments effectively reduced BP in hypertensive patients at high CV risk. Cardiac and all-cause mortality rates did not differ between the 2 treatment groups. The rate of hospitalization for heart failure was 4.6% (n = 354) with valsartan versus 5.3% (n = 400) with amlodipine (P = .12). The rate of stroke was 4.2% (n = 322) versus 3.7% (n = 281) with valsartan and amlodipine, respectively. The rate of MI was 4.8% (n = 369) versus 4.1% with valsartan and amlodipine, respectively. The most frequently reported adverse event, edema, was twice as common in the amlodipine group. Dizziness, headache, angina pectoris, and diarrhea were more frequently reported in the valsartan group, although the frequency of these events was low.

Although the Losartan Intervention For Endpoint Reduction of Hypertension (LIFE) and Study on Cognition and Prognosis in the Elderly (SCOPE) trials both indicated that ARBs prevent CV and cerebrovascular end points more effectively than other antihypertensives,<sup>11,12</sup> these findings were not confirmed in the VALUE trial.<sup>10</sup> However, there were significant differences in baseline patient characteristics in these 3 trials. Whereas patients with a recent history of stroke were excluded from the LIFE and SCOPE trials, the VALUE study did not exclude this population. Moreover, inclusion criteria for VALUE required all participants to have both CV risk factors and CVD, making them more likely candidates for heart failure. Within this high-risk population, the protective effects of ARB therapy may have been less pronounced.

A meta-analysis of findings from these 3 studies was presented at the 2005 American Society of Hypertension (ASH) scientific meeting confirmed that mortality outcomes with ARBs were comparable to those with other antihypertensive drugs.<sup>13</sup> In LIFE and SCOPE, however, an ARB reduced the occurrence of the primary end point of LV hypertrophy (LIFE) and major cardiac events (SCOPE) and stroke compared with controls. Despite the favorable all-cause mortality

results for ARB-treated patients, they were nonetheless reported to be at increased risk for MI (relative risk ratio, 1.12; 95% confidence interval [CI] 1.01-1.26;  $P = .041$ ).

To further evaluate the effect of valsartan on prevention of CV events in patients with hypertension, a retrospective observational study was undertaken and reported at the 2005 ASH scientific meeting.<sup>14</sup> This large health insurance claims database analysis of members of more than 70 health plans compared both CV and renal outcomes for patients taking valsartan ( $N = 6664$ ), lisinopril ( $N = 17\,422$ ), or metoprolol ( $N = 5437$ ). Patients were free of MI, stroke, renal failure, heart failure, ventricular arrhythmias, and cardiac arrest during the pretreatment period.

After adjustment for baseline characteristics, patients receiving valsartan had a significant 30% lower risk of major CV or renal events compared with those receiving metoprolol (hazard ratio [HR], 0.70; 95% CI 0.57-0.88;  $P = .0016$ ). Compared with lisinopril-treated patients, valsartan-treated patients had a significantly lower risk of developing heart failure (HR, 0.69; 95% CI 0.51-0.93;  $P = .0159$ ) and diabetes (HR, 0.81; 95% CI 0.68-0.96;  $P = .0167$ ). The incidence of major CV or renal events was 1.6%, 2.3%, and 2.1% in the valsartan, lisinopril, and metoprolol groups, respectively (HR, 1.01 for valsartan vs lisinopril;  $P = .9608$ ; HR, 0.78,  $P = .0787$  for valsartan vs metoprolol).<sup>14</sup>

The Losartan Heart Failure Survival Study (Elite II), a double-blind, randomized, controlled trial of 3152 patients 60 years of age with New York Heart Association class II to IV heart failure was conducted to determine whether losartan was superior to captopril in reducing mortality. No significant differences in all-cause mortality, sudden death, or resuscitated arrests were found between the 2 treatment groups.<sup>15</sup> The Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity (CHARM) study analyzed the efficacy of candesartan as monotherapy or as an added therapy with other antihypertensives in reducing mortality and morbidity in patients with heart failure. Reduced CV mortality and morbidity (15%) was reported in patients with an LV ejection fraction of

40%.<sup>16</sup> In patients with LV ejection fractions 40% who were ACEI intolerant, the study found significantly reduced CV death and hospitalization for heart failure.<sup>17</sup>

Collectively, these results indicate that ARBs offer protection against CV risks in addition to a BP-lowering effect that is comparable (and possibly superior) to that of other antihypertensives.

### ARBs and Diabetes

Hypertension affects approximately 20% to 60% of patients with diabetes, depending on obesity, ethnicity, and age.<sup>18</sup> Like ACEIs, ARBs favorably affect the progression of diabetic nephropathy, reducing albuminuria, and slowing progression to macroalbuminuria.<sup>19-22</sup> Because both BP reduction and blockade of the RAAS have renoprotective effects,<sup>23</sup> ARBs are indicated for treatment of hypertension in patients with diabetes and chronic kidney disease.<sup>24</sup>

CV risk factors tend to cluster in diabetes and metabolic syndrome, leading to an increase in CV oxidative stress and impaired endothelial function. Drugs that suppress the activation of the RAAS are of particular value in the treatment of hypertension associated with the metabolic syndrome or diabetes. In these patients, there is increased sensitivity to RAAS-mediated oxidative stress and subsequent endothelial dysfunction. ARBs have been shown to abrogate the inhibition of arterial relaxation induced by angiotensin II, reduce oxidative stress, and suppress the formation of inflammatory cytokines and adhesion molecules that promote atherosclerosis.<sup>23</sup>

ARBs have been associated with reduction in the incidence of new-onset diabetes in high-risk hypertensive patients. In the VALUE trial, a valsartan-based regimen was associated with a greater reduction in new-onset diabetes compared with amlodipine, the comparator drug (13.1% vs 16.4%;  $P < .001$ ).<sup>10</sup> This would suggest a greater benefit from an ARB versus a dihydropyridine CCB, above and beyond BP control in patients with diabetes.

Several studies presented at the 2005 ASH scientific meeting contributed new data regarding the efficacy of ARBs in diabetic patients. In a randomized, double-

blind study, the ARBs olmesartan medoxomil, valsartan, losartan, or placebo were administered in a forced-titration regimen to patients with hypertension and type 2 diabetes, gestational, borderline, or diet-controlled diabetes, glucose intolerance, elevated fasting glucose or hyperglycemia.<sup>25</sup> Starting doses were olmesartan 20 mg/day, valsartan 80 mg/day, and losartan 50 mg/day, and doses were titrated to maximums of olmesartan 40 mg/day, valsartan 320 mg/day, and losartan 50 mg twice daily.

Of the 3 treatments, olmesartan achieved the greatest mean reduction from baseline to week 8 in seated diastolic BP (-15.4 mm Hg vs -8.3 mm Hg valsartan and -7.2 mm Hg losartan). In addition, 19% of olmesartan-treated patients achieved *The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure* (JNC 7) recommended BP goal for patients with diabetes, <130/80 mm Hg, at week 8. Patients in the other study arms did not achieve this goal. Similar results were achieved at week 12.

Another study focused on microalbuminuria to assess the efficacy of irbesartan in reducing this widely accepted CV risk in patients with hypertension and diabetes.<sup>26</sup> This prospective, open-label, observational study of 1657 patients with and without diabetes assessed outcomes for patients treated with irbesartan alone or combined with HCTZ. At 1 year, both patients with and without diabetes realized significant reductions in mean systolic BP and diastolic BP ( $P < .01$ ). Notably, fasting plasma glucose and total and low-density lipoprotein cholesterol also diminished significantly in both groups. Additionally, patients with diabetes showed a significant reduction in triglycerides. BP goals were achieved in 46% of patients with diabetes (<130/80 mm Hg) and 90.7% of nondiabetics (<140/90 mm Hg). The proportion of patients with microalbuminuria decreased by 21.2% in patients with diabetes and 27.3% in nondiabetics at 1-year follow-up ( $P < .001$ ).

Combining other classes of antihypertensive agents with an ARB markedly increases antihypertensive efficacy in patients with diabetes. Bakris and colleagues examined

the number of antihypertensive drugs needed to reach target (across several studies) in patients with renal disease or diabetes.<sup>27</sup> This analysis indicated that >65% of people with diabetes and hypertension required 2 or more antihypertensive medications to achieve the suggested target BP goal of 130/80 mm Hg to optimally reduce CV risks and preserve renal function. However, a recent review of published medical literature on the renal effects of ARBs indicated that maximizing the ARB dose before adding additional therapies or another renal-protecting agent (ACEI or nondihydropyridine CCB) may be superior to adding another class of antihypertensive, even if similar BP can be achieved.<sup>23</sup>

### Conclusion

The medical literature has confirmed that the ARBs provide CV protection, and are highly effective in reducing CV mortality. By inhibiting the RAAS they also offer renoprotective qualities. For this reason, ARBs are indicated for treatment of hypertension in patients with diabetes and kidney disease. Notably, therapy with ARBs has been associated with reductions in the incidence of new-onset diabetes in high-risk hypertensive patients. There also appears to be substantial benefit when ARBs are combined with other drugs in an aggressive approach to BP control.

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