

## REVIEW

# Angiotensin receptor blockers in hypertension. New insights from Japan

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Angiotensin II receptor blockers (ARBs) are widely used in the treatment of patients with hypertension, heart failure, diabetic nephropathy and other clinical conditions. Several intervention trials and systematic overviews showed that both angiotensin-converting enzyme inhibitors and ARBs effectively reduce the risk of stroke, myocardial infarction and congestive heart failure in hypertensive patients. Two recent intervention trials conducted in Japan (JIKEI and Kyoto studies) suggested that the protective effect of ARBs on major cardiovascular events might be partly independent from the degree of blood pressure (BP) reduction. Both studies used a prospective randomized open blinded end point (PROBE) design. No significant differences emerged in both studies between the ARB group (valsartan) and the control group in the achieved BP. We made a pooled analysis of the JIKEI and Kyoto studies. Overall, valsartan significantly reduced the risk of the primary composite outcome (by 42%;  $P < 0.0001$ ), angina pectoris (by 38%;  $P < 0.0001$ ), heart failure requiring hospitalization (by 43%;  $P = 0.013$ ) and cerebrovascular events (by 42%;  $P = 0.002$ ). The protective effect on the dissecting aneurysm of aorta bordered statistical significance. These data reinforce the notion that the protective effect of angiotensin II inhibition is partly independent of BP reduction.

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## INTRODUCTION

Angiotensin II receptor blockers (ARBs) are increasingly used in the treatment of patients with hypertension, heart failure, diabetic nephropathy and other clinical conditions. The European Society of Hypertension/European Society of Cardiology (ESH/ESH) guidelines for the management of patients with hypertension include these drugs among first-line therapeutic options.<sup>1</sup> Interestingly, the use of ARBs is not limited to subjects with cough or other contraindications to angiotensin-converting enzyme inhibitors (ACEIs). For example, in a large US sample of elderly patients with left ventricular systolic dysfunction, a recent hospitalization for heart failure and no contraindications to use of ACEIs, only 68% of subjects were actually taking ACEIs, whereas an additional 8% of subjects were receiving ARBs.<sup>2</sup>

A large number of intervention trials and systematic overviews provided convincing evidence that both ACEIs and ARBs are effective in reducing the risk of stroke, myocardial infarction (MI) and congestive heart failure, in hypertensive patients.<sup>3–5</sup> Interestingly, some analyses suggested that at least part of the protective effect of these drugs on specific cardiovascular events such as MI and congestive heart failure might be independent of, or disproportionately greater than blood pressure (BP) reduction,<sup>6,7</sup> hence suggesting that other mechanisms of cardiovascular prevention may also be operative in patients treated with these drugs.

## BP REDUCTION AND CARDIOVASCULAR PROTECTION OFFERED BY ARBS

The argument that the protective effect of ARBs on major cardiovascular events is partly independent from the degree of BP reduction has been recently highlighted by two recent intervention studies conducted in Japan.

In the first of these studies, the Jikei study,<sup>8</sup> 3081 Japanese people with a mean age of 65 years who were being treated for hypertension, coronary heart disease or heart failure were assigned to either valsartan or other drugs not including angiotensin receptor blockers, in addition to the preexisting treatment. The median duration of follow-up was 3.1 years. At entry, BP was 139/81 mm Hg in both groups. It fell to 131/77 mm Hg in the valsartan group and 132/78 mm Hg in the control group, without any statistical differences between the two groups. The primary end point, a composite of cardiovascular morbidity and mortality, occurred in 92 patients in the valsartan group and 149 patients in the control group (2.13 vs. 3.45 per 100 patient years; hazard ratio (HR) 0.61, 95% confidence interval (CI) 0.47–0.79,  $P = 0.0002$ ). The advantage of valsartan over control was mainly attributable to a lower incidence of stroke and transient ischemic attack (HR 0.60, 95% CI 0.38–0.95,  $P = 0.028$ ), angina pectoris (HR 0.35, 95% CI 0.20–0.58,  $P < 0.0001$ ) and heart failure (HR 0.53; 95% CI 0.31–0.94,  $P = 0.029$ ) in the valsartan group.

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The second of these studies was the Kyoto Heart Study,<sup>9</sup> an intervention study conducted in 3031 Japanese patients with a mean age of 66 years and uncontrolled hypertension. These patients were randomized to either valsartan add-on or non-ARB treatment. Median follow-up was 3.27 years. At entry, BP was 157/88 mm Hg in both groups. It fell to 133/76 mm Hg in both groups at the end of study. The primary end point, a composite of cardiovascular morbidity and mortality, occurred in fewer patients (HR 0.55, 95% CI 0.42–0.72,  $P < 0.0001$ ) in the valsartan group than in the control group. The outcome difference between the two groups was accounted for by lesser incidence of stroke and transient ischemic attack (TIA) (HR 0.55, 95% CI 0.34–0.89,  $P = 0.015$ ), and angina pectoris (HR 0.51, 95% CI 0.31–0.86,  $P = 0.011$ ) in the valsartan group.

The Jikei study<sup>8</sup> and the Kyoto Heart Study<sup>9</sup> provide important new data that deserve to be discussed separately.

### EFFECTS OF ARBS ON THE RISK OF STROKE

The higher frequency of stroke, relative to coronary artery disease, typical of the Japanese population<sup>10</sup> could have facilitated the detection of a significant protective effect of valsartan over a traditional drug treatment devoid of ARBs. However, a preferential protective effect of ARBs on stroke emerged also in different studies conducted mostly in Caucasian individuals. For example, losartan induced a 25% reduction in the risk of stroke in the Losartan Intervention for End point Reduction (LIFE) Study, and such an effect accounted for most of the significant difference with respect to atenolol in the incidence of the primary outcome.<sup>11</sup>

We have recently completed a meta-analysis of available randomized head-to-head comparative trials conducted between ARBs and ACEIs. Six trials fulfilled the inclusion criteria, for a total of 49 924 patients.<sup>12</sup> In the pooled estimate, there were no significant differences between ARBs and ACEIs on the risk of MI (odds ratio (OR) 1.01, 95% CI 0.95–1.07,  $P = 0.75$ ), cardiovascular mortality (OR 1.03, 95% CI 0.98–1.08,  $P = 0.23$ ) and total mortality (OR 1.03, 95% CI 0.97–1.10,  $P = 0.20$ ). However, the risk of stroke was slightly lower with ARBs than with ACEIs (OR 0.92, 95% CI 0.85–0.99,  $P = 0.037$ ).<sup>12</sup> These data support the hypothesis that ARBs may exert a specific, albeit modest, protective effect against stroke, which may further enhance the overall degree of cerebrovascular protection beyond the overwhelming benefit due to BP reduction. This may favor the use of ARBs in subjects at high risk of stroke, such as those with a previous history of stroke or TIA, or the Asian people. In this setting, it should be remarked that both the JIKEI and Kyoto studies were conducted against a non-ARB group, not an ACEI group. A large study that did not support an ARB benefit in stroke survivors was the Prevention Regimen for Effectively Avoiding Second Strokes (PROFESS) Study.<sup>13</sup> In this study, the rate of recurrent stroke did not differ between telmisartan and placebo.<sup>13</sup> However, treatment was initiated quite early (within 90 days) after stroke and a trend toward a benefit in the ARB group seemed to emerged by the third year of follow-up.<sup>13</sup>

From a mechanistic point of view, experimental data suggest that ARBs might exert specific cerebrovascular protective effects, involving overstimulation of AT<sub>2</sub> receptors by the overflow of angiotensin II, which is expected to occur after the administration of ARBs, but not with ACEIs that actually reduce AT<sub>2</sub> receptor stimulation. In rats, the neurological outcome following induction of cerebral ischemia was improved by intracerebral administration of low doses of irbesartan, and such an effect was prevented by the coadministration of drugs blocking the AT<sub>2</sub> receptors.<sup>14</sup> In animal models of cerebral injury induced by cerebral artery occlusion, pretreatment with candesartan, but not with ramipril, effectively reduced the extent of infarct size.<sup>15</sup>

Direct support to the hypothesis of a protective effect of AT<sub>2</sub> receptor stimulation is provided by a study in genetically modified animals, in which the neurological damage induced by cerebral ischemia was more severe in AT<sub>2</sub> receptor-deleted mice than in control, wild-type mice.<sup>16</sup>

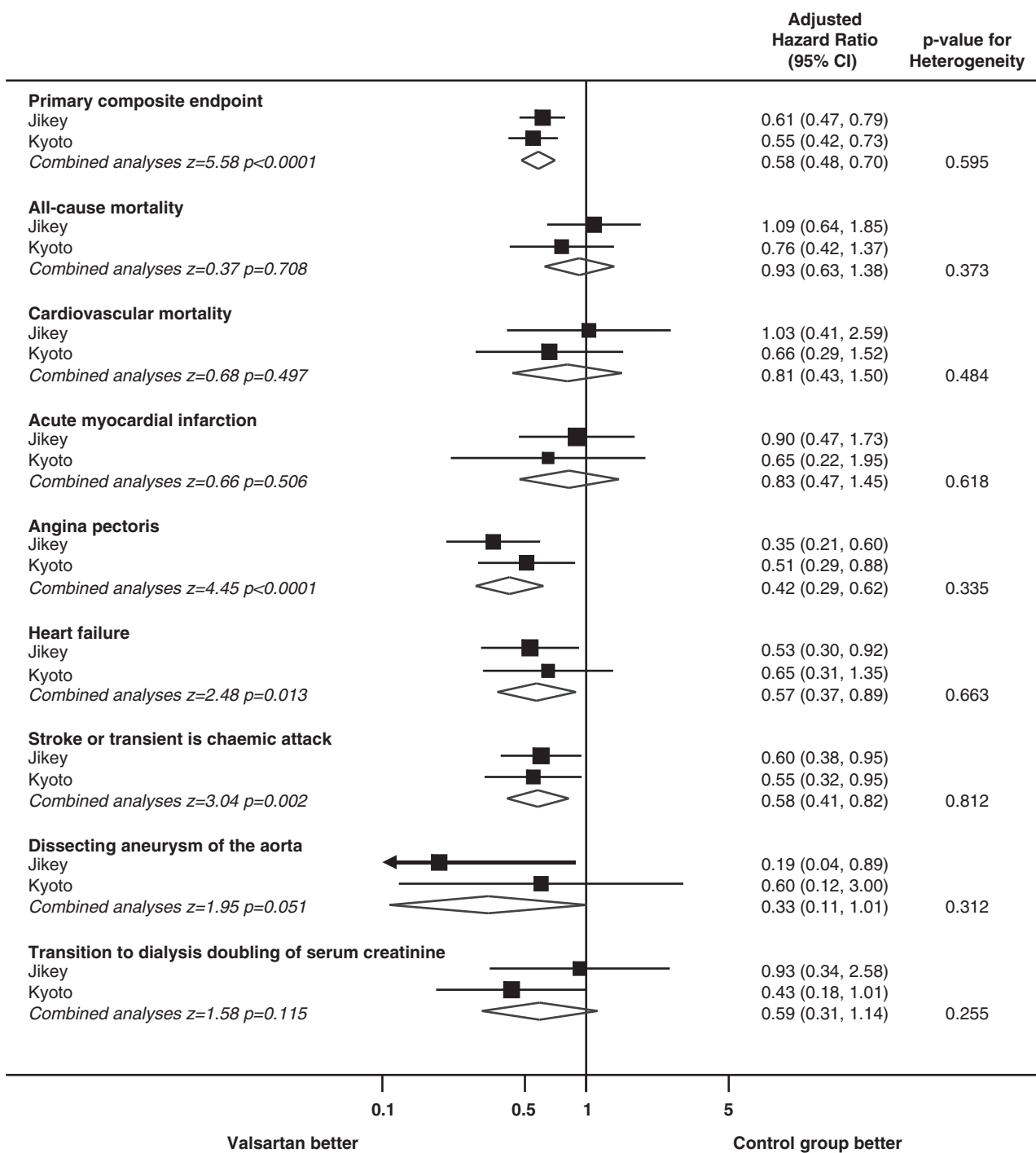
### EFFECTS ON ARBS ON THE RISK OF MI

Some years ago, Verma and Strauss<sup>17</sup> examined the results of randomized trials, which compared an ARB with a drug belonging to a different class in a variety of clinical conditions, including hypertension, heart failure and renal failure. These authors concluded that ARBs may increase the risk of MI, and that consequently patients had to be informed about the risk.<sup>17</sup> These conclusions triggered a hot scientific debate and anxious reactions by many patients treated with ARBs. However, the statistical methodology of that study was seriously questioned, and several subsequent meta-analyses conducted using more rigorous techniques were unable to demonstrate any excess risk of MI in patients treated with ARBs, thereby contradicting such claim.<sup>18,19</sup> In a meta-analysis from our group, cardiovascular mortality was significantly less with ARBs than with placebo (OR 0.91, 95% CI 0.83–0.99,  $P = 0.042$ ).<sup>19</sup> In a recent placebo-controlled study conducted in patients with high vascular risk, telmisartan reduced the risk of MI by 21%, and such a reduction bordered statistical significance (HR 0.79, 95% CI 0.62–1.01,  $P = 0.07$ ).<sup>20</sup> Conversely, in a recent meta-analysis by Messerli *et al.*,<sup>21</sup> ARBs were associated with a not significant 8% higher risk of MI (HR 1.08, 95% CI 1.00–1.18,  $P =$  not significant). However, these authors did not report a sensitivity analysis of their study. This is an important limitation, because their pooled estimate was largely driven by one single study, the Valsartan Antihypertensive Long-Term Use Evaluation (VALUE) trial,<sup>22</sup> in which the significant gradient between the two groups in the achieved BP levels could have conditioned the slightly higher risk of MI in the ARB group.<sup>22</sup>

### COMPARATIVE ASSESSMENT

Although the age of patients was comparable in the JIKEI and Kyoto studies, BP at entry was substantially higher in the latter study (157/88 vs. 139/81 mm Hg). Notwithstanding, achieved BP was almost identical in the two studies, thereby suggesting a more marked antihypertensive response in the setting of the Kyoto Study. The lack of differences in the achieved BP between the valsartan group and the control group was a constant of the two studies. It suggests that valsartan might exert protective effects on the cardiovascular system beyond those expected on the basis of BP reduction. We made a pooled analysis of Jikei and Kyoto studies (Figure 1). Overall, valsartan significantly reduced the risk of the primary composite outcome (by 42%;  $P < 0.0001$ ), angina pectoris (by 38%;  $P < 0.0001$ ), heart failure requiring hospitalization (by 43%;  $P = 0.013$ ) and cerebrovascular events (by 42%;  $P = 0.002$ ). The protective effect on the dissecting aneurysm of aorta bordered statistical significance. It is noteworthy that a remarkable consistency of effects on each of the various end points was observed in both studies (Figure 1).

At variance with the Jikei and Kyoto studies, two other studies conducted with another ARB, candesartan, in Asian people, failed to show outcome benefits in the ARB group.<sup>23,24</sup> The first of these studies, the Candesartan Antihypertensive Survival Evaluation in Japan (CASE-J), was a comparison between candesartan and amlodipine in hypertensive patients.<sup>23</sup> The second study, the Heart Institute of Japan Candesartan Randomized Trial for Evaluation in Coronary Artery Disease (HIJ-CREATE), was a comparison between candesartan and a non-ARB-based regimen in patients with coronary artery



**Figure 1** Pooled analysis of the Jikey and Kyoto studies. Valsartan significantly reduced the risk of the primary composite outcome (by 42%;  $P<0.0001$ ), angina pectoris (by 38%;  $P<0.0001$ ), heart failure requiring hospitalization (by 43%;  $P=0.013$ ) and cerebrovascular events (by 42%;  $P=0.002$ ).

disease and hypertension.<sup>24</sup> In both studies, the primary composite end point and its components did not show any statistical differences between the groups.<sup>23,24</sup> As commented by Messerli, it is difficult to ascertain whether the differences with respect to the two valsartan studies may be attributable to the specific ARB molecule, the trial design, the clinical characteristics of the patient population or the concomitant medications.<sup>21</sup> Similar to the CASE-J and HIJ-CREATE studies, the JIKEI and Kyoto studies used a prospective randomized open blinded end point (PROBE) design and a wide composite end

point, which included relatively soft outcome events such as angina pectoris and TIA. A common criticism shared by studies conducted with PROBE design is the observation that soft end points are likely to be affected by the judge of the doctor-in-charge, which could be conditioned by the awareness of randomization arm. It could be argued that harder component of the composite end point such as stroke alone<sup>9</sup> and combined with TIA,<sup>8</sup> as well as heart failure,<sup>8</sup> were significantly less frequent in the valsartan group than in the control group.

A randomized double-blind design remains the standard for drug evaluation. In the VALUE trial, a double-blind comparison between valsartan and amlodipine in hypertensive patients at high cardiovascular risk, a wide composite end point of cardiovascular morbidity and mortality did not differ between the two groups, with MI occurring less frequently with amlodipine ( $P=0.02$ ).<sup>22</sup> However, the differences between the two groups in the risk of MI were largely confined to the first 3 months of the study, in which achieved systolic BP was about 4.0 mmHg lower in the amlodipine group. The BP gradient between the two groups tended to vanish over the subsequent follow-up period and also the risk of MI did no longer differ significantly between the groups.<sup>22</sup>

## CONCLUSION

ARBs are effective and very well tolerated drugs, which should be considered as first-line antihypertensive agents.<sup>1</sup> Therapeutic interventions with ARBs are effective to slow down or block the progression of cardiovascular disease at different steps of the 'cardiovascular disease continuum',<sup>25</sup> with measurable clinical benefits. As each ARB is characterized by specific properties that may influence its clinical efficacy and differences among available ARBs emerged from clinical studies, generalization of results obtained with a specific ARB to all available ARBs may not be justified. The Jikei<sup>8</sup> and Kyoto<sup>9</sup> studies provided independent and concordant evidence indicating that valsartan, on top of optimized pharmacological therapy, reduces the risk of CV events and, in particular, the risk of stroke in Asian patients with hypertension and high cardiovascular risk. In patients with heart failure and left ventricular dysfunction, valsartan on top of optimized therapy including an ACE inhibitor, significantly reduced the morbidity/mortality combined end point and reduced the rate of rehospitalization due to worsening of heart failure.<sup>26</sup> In patients with MI complicated by heart failure or left ventricular dysfunction, alone or combined, valsartan reduced morbidity and mortality, with a protective effect similar to the ACE-inhibitor comparator captopril.<sup>27</sup> These findings support valsartan as an ARB with strong scientific documentation along the different steps of the cardiovascular disease continuum.

## CONFLICT OF INTEREST

The authors declare no conflict of interest.

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