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COMMENTARY

Magic ARB, or magic trial?

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Nearly a decade has passed since angiotensin II receptor blockers (ARBs) have appeared with great anticipation as a type of cardioprotective drug that was an effective alternative to ACE inhibitors with their adverse effects, most prominently cough.

The expectation was high because animal data showed a remarkable cardioprotective effect beyond the blood pressure-lowering effect, supporting the theory that blocking the renin–angiotensin system at the receptor level would achieve perfect cardioprotection. However, theory and clinical practice are not always consistent. Although many clinical trials of ARBs have been published over the past several years, the results of most of these trials have fallen short of the expectations of the investigators and the medical community.

For example, in the VALUE trial,[1] valsartan was inferior to a calcium channel blocker in the prevention of myocardial infarction. The TRANSCEND trial[2] failed to prove the superiority of telmisartan to placebo in the prevention of cardiovascular events. PRoFESS[3] failed to find that telmisartan prevented stroke recurrence. I-PRESERVE[4] failed to show a beneficial effect of irbesartan on left ventricular diastolic function. GISSI-AF[5] failed to find that valsartan prevented the recurrence of atrial fibrillation.

Exceptionally, however, two clinical trials, JIKEI-HEART[6] and KYOTO-HEART,[7] showed remarkable cardiovascular protection by valsartan in high-risk Japanese patients.

An editorial by Dr Paolo Verdecchia posted on the *Hypertension Research* stated that the protective effect of valsartan is independent of blood pressure (BP) reduction, based on the results of these two Japanese clinical trials. Although the favorable editorial by Dr Verdecchia is appreciated, it does not take into account several important contradictions with other reliable clinical trials of ARBs conducted in Japan and Europe.

In the JIKEI-HEART and KYOTO-HEART studies, there are two common findings. One is that both showed significant and remarkable cardioprotection by valsartan, but the most marked reductions were attributed to angina pectoris, congestive heart failure and stroke, including transient ischemic attack, all three of which are subjective in their assessment. In terms of objective, hard end points, such as myocardial infarction and cardiovascular death, there was no significant difference between the valsartan treatment group and the non-ARB treatment group.

A second commonality is that, very importantly, the prospective randomized open-blinded end-point trial design was used for both JIKEI-HEART and KYOTO-HEART. For the conduct of a clinical trial using the prospective randomized open-blinded end-point design, soft end points, such as hospitalization due to angina pectoris or congestive heart failure, should not be included in the primary composite end point because of the subjectivity of their assessment. The inclusion of soft end points in the primary composite end point could also contribute to earlier termination of the trial based on reaching the specified number of end points, but this could comprise more soft end points *vs.* hard end points and thus magnify the effect of the test drug.

Although JIKEI-HEART and KYOTO-HEART showed a significant reduction in angina pectoris with valsartan treatment compared with non-ARB treatment, which consisted mainly of calcium channel blocker, the VALUE trial, in which a double-blind design was adopted, actually showed that valsartan had a significantly lower preventive effect on angina pectoris and myocardial infarction compared with the calcium channel blocker amlodipine. In the VALUE trial,[1] the incidence of angina pectoris was significantly more frequent in the valsartan-treated group than in the amlodipine-treated group (13.7 *vs.* 9.5%). Notably, the incidence of angina pectoris reported as a serious adverse event was significantly higher in the valsartan-treated group than in the amlodipine-treated group (4.4 *vs.* 3.1%, $P<0.0001$).

Is the ARB valsartan especially effective against angina pectoris only in Japanese patients? Although all patients with angina pectoris reportedly underwent coronary angiography after hospitalization in both JIKEI-HEART and KYOTO-HEART, it is plausible that the physician who had the right to decide on hospitalization was influenced by knowledge of the drugs that were prescribed for the patient, including the study drug, thus introducing a confounding factor in interpreting the trial results.

In contrast to the results in JIKEI-HEART and KYOTO-HEART, two other trials in Japanese patients, CASE-J[8] and HIJ-CREATE,[9] in which the cardioprotective effect of the ARB candesartan was evaluated, did not show a greater benefit of ARB treatment in comparison with calcium channel blocker or non-ARB treatment. Although there were positive results with candesartan in animal studies, as stated by Dr Verdecchia in his editorial, candesartan was not significantly more cardioprotective than a calcium channel blocker in high-risk Japanese patients in the CASE-J trial. Moreover, in CASE-J, a significantly greater dose of anti-hypertensive drugs was required for the candesartan group compared with the CCB group to achieve a similar blood pressure level.

It is incredibly good that a nearly twofold difference in incidence of cardiovascular events was observed in the KYOTO-HEART study, despite strict BP control until systolic BP was 133/76 mm Hg in both treatment groups.

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The interpretation of results from clinical trials must be done with caution, particularly results with the same class of drug that are inconsistent between trials and apart from our clinical experience. Only hard end points should be used as primary end points to ensure objective assessment in trials conducted with open design. Further, these hard end points, such as myocardial infarction and cardiovascular death, not angina pectoris, are what matters most to high-risk patients.

1 Julius S, Kjeldsen SE, Weber M, Brunner HR, Ekman S, Hansson L, Hua T, Laragh J, McInnes GT, Mitchell L, Plat F, Schork A, Smith B, Zanchetti A. Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine; the VALUE randomised trial. *Lancet* 2004; **363**: 2022–2031.

2 The Telmisartan Randomised AssessmeNt Study in ACE iNtolerant subjects with cardiovascular Disease (TRANSCEND) Investigators. Effects of the angiotensin-receptor blocker telmisartan on cardiovascular events in high-risk patients intolerant to angiotensin-converting enzyme inhibitors: a randomised controlled trial. *Lancet* 2008; **372**: 1174–1183.

3 Yusuf S, Diener HC, Sacco RL, Cotton D, Ounpuu S, Lawton WA, Palesch Y, Martin RH, Albers GW, Bath P, Bornstein N, Chan BP, Chen ST, Cunha L, Dahlöf B, De Keyser J, Donnan GA, Estol C, Gorelick P, Gu V, Hermansson K, Hilbrich L, Kaste M, Lu C, Machnig T, Pais P, Roberts R, Skvortsova V, Teal P, Toni D, VanderMaelen C, Voigt T, Weber M, Yoon BW. Telmisartan to prevent recurrent stroke and cardiovascular events. *N Engl J Med* 2008; **359**: 1225–1237.

4 Massie BM, Carson PE, McMurray JJ, Komajda M, McKelvie R, Zile MR, Anderson S, Donovan M, Iverson E, Staiger C, Ptaszynska A. Irbesartan in patients with heart failure and preserved ejection fraction. *N Engl J Med* 2008; **359**: 2456–2467.

5 Disertori M, Latini R, Barlera S, Franzosi MG, Staszewsky L, Maggioni AP, Lucci D, Di Pasquale G, Tognoni G. Valsartan for prevention of recurrent atrial fibrillation. *N Engl J Med* 2009; **360**: 1606–1617.

6 Mochizuki S, Dahlöf B, Shimizu M, Ikewaki K, Yoshikawa M, Taniguchi I, Ohta M, Yamada T, Ogawa K, Kanae K, Kawai M, Seki S, Okazaki F, Taniguchi M, Yoshida S, Tajima N. Valsartan in a Japanese population with hypertension and other cardiovascular disease (Jikei Heart Study): a randomised, open-label, blinded endpoint morbidity-mortality study. *Lancet* 2007; **369**: 1431–1439.

7 Sawada T, Yamada H, Dahlöf B, Matsubara H. Effects of valsartan on morbidity and mortality in uncontrolled hypertensive patients with high cardiovascular risks: KYOTO HEART Study. *Eur Heart J* 2009; **30**: 2461–2469.

8 Ogihara T, Nakao K, Fukui T, Fukiyama K, Ueshima K, Oba K, Sato T, Saruta T. Effects of candesartan compared with amlodipine in hypertensive patients with high cardiovascular risks. Candesartan antihypertensive survival evaluation in Japan trial. *Hypertension* 2008; **51**: 393–398.

9 Kasanuki H, Hagiwara N, Hosoda S, Sumiyoshi T, Honda T, Haze K, Nagashima M, Yamaguchi J, Origasa H, Urashima M. Angiotensin II receptor blocker-based vs non-angiotensin II receptor blocker-based therapy in patients with angiographically documented coronary artery disease and hypertension: the Heart Institute of Japan Candesartan Randomized Trial for Evaluation in Coronary Artery Disease (HIJ-CREATE). *Eur Heart J* 2009; **30**: 1203–1212.