COMMENTARY

Therapeutic implications of high-dose angiotensin receptor blocker monotherapy in mild-to-moderate hypertensive patients

Yuichiro Yano and Kazuomi Kario

Hypertension Research (2010) **33**, 981–983; doi:10.1038/hr.2010.149; published online 19 August 2010

The objectives of antihypertensive treatment are to prevent the occurrence of cardiovascular diseases, and consequent functional impairment and death.^{1,2} According to the results from several clinical trials, the relative risk of stroke decreases by 30–40% and that of ischemic heart diseases by 15–20%, with a reduction of 10–20 mm Hg in the systolic blood pressure (BP) and 5–10 mm Hg diastolic BP.^{1,2} Several classes of antihypertensive drugs are available today; among them, the drugs to be used as a first line of treatment should be selected from Ca channel blockers, angiotensin receptor blockers (ARBs), angiotensin-converting enzyme inhibitors, diuretics, and β -blockers. Although all these drugs provide a sufficient hypotensive effect and can prevent the occurrence of cardiovascular diseases, the real-world results have been the unsatisfactory, that is, only 20–30% of the overall hypertensive population can achieve a satisfactory BP reduction (to the target values of <140/90 mm Hg) by the use of any one agent alone, with the exception of subjects with grade 1 hypertension.^{3,4} Furthermore, our previous studies conducted in treated hypertensive patients (the Jichi Morning Hypertension Research (J-MORE) study, $n=969$) showed that only about 20% of our outpatients were adequately controlled based

on both office BP and out-of-office BP (home systolic BP <135 mm Hg) measurement.⁵

Recent large clinical trials have demonstrated that the majority of patients require two or more antihypertensive drugs from different classes to achieve the target BP levels.^{6–8} As a result, several combination therapies using two drugs in fixed doses have been introduced, and a three-drug preparation that combines a Ca channel blocker, an ARB, and a thiazide diuretic has also recently been made available. There is evidence to suggest that a combination of antihypertensive drugs can have potential benefits attributable to possible synergistic pharmacological and physiological actions.^{9,10} In fact, a recent meta-analysis of combination therapy has suggested that low doses of two or three drugs may be preferable to standard doses of one or two drugs, that is, the average reduction in systolic/diastolic BP was 9/6 mm Hg by one drug at the standard dose, and 11/7 mm Hg by one drug at twice the standard dose, whereas the average reduction in BP by two drugs even at a half dose was 13/7 mm Hg.¹⁰ Furthermore, the adverse effects associated with the use of combinations of two drugs were reported to be less severe than the additive adverse effects from the administration of the two drugs independently. In that analysis, a clear dose-dependent adverse reaction could be seen for thiazide, Ca channel blockers, and β -blockers, but not for ARBs. In particular, therapy with twice the standard dose of thiazide, Ca channel blockers, or β -blockers had pronounced adverse effects (9–18%), whereas adverse effects were observed in only 2% of patients receiving twice the standard dose of ARBs. This

means that the BP-lowering effects of ARBs were dose-dependent, but the adverse effects of ARBs were not dose dependent. This notion is strengthened by the results of the ValTop study published in the present issue of *Hypertension Research*.¹¹

The ValTop study was a controlled, randomized, double-blind trial. A total of 4004 patients with uncomplicated mild-to-moderate hypertension (mean diastolic BP: 95–109 mm Hg) were started on a 4-week open-label treatment with valsartan 160 mg. Among them, 3776 patients (mean age: 55 years) were assigned to receive valsartan 160 mg ($n=1900$) or 320 mg ($n=1876$) for an additional 4 weeks. The objective of the study was to assess the BP-lowering effect of 4-week treatment with a once-daily monotherapy of valsartan 320 mg, compared with valsartan 160 mg, in patients who were or were not controlled by an initial open-label treatment with valsartan 160 mg. After 4 weeks of open-label treatment with valsartan 160 mg, the mean reduction of systolic/diastolic BP was $-12/-10$ mm Hg. In the next phase of the trial, the patients assigned to receive an up-titration to 320 mg valsartan showed more significant BP reduction in both systolic and diastolic BP ($-2.6/-1.2$ mm Hg, $P<0.001$), compared with the patients remaining on 160 mg valsartan. The BP reduction achieved by up-titration of valsartan in this study was similar to those achieved in other studies using ARBs.^{9,12} Intriguingly, the additional BP reduction by up-titration to 320 mg valsartan was observed not only in patients who had an initial good response to the 160 mg dose, but also in those who had a poorer response to the initial

Dr Y Yano is at the Divisions of Community and Family Medicine, University of Miyazaki, Miyazaki, Japan and at the Department of Medicine, Division of Cardiovascular Medicine, Jichi Medical University School of Medicine, 3311-1 Yakushiji, Shimotsuke, Tochigi, 329-0498, Japan. Dr K Kario is at the Department of Medicine, Division of Cardiovascular Medicine, Jichi Medical University School of Medicine, 3311-1 Yakushiji, Shimotsuke, Tochigi, 329-0498, Japan.
E-mail: kkario@jichi.ac.jp

160 mg dose. This is in line with a recent study, in which a poor BP reduction was achieved by a conventional dose of valsartan (160 mg) in African-American patients, who exhibit salt sensitivity and expanded plasma volume and thus are resistant to ARBs; however, at a higher dose of valsartan (320–640 mg), both a greater BP reduction and a greater proteinuria reduction were observed in African-American patients.¹³ The mechanisms remain unclear, but higher dose renin-angiotensin-aldosterone system blockade could have more favorable effects on vascular, or aldosterone production, or intrarenal renin-angiotensin-aldosterone system which causes renal vasoconstriction and in turn affect intrarenal sodium and water handling, than those with conventional dose of renin-angiotensin-aldosterone system blockade.¹⁴ Accordingly, in the clinical setting, patients who had less response to a smaller dose of ARBs may still attain a significant BP-lowering effect with early, aggressive up-titration of ARBs. This strategy may be of critical importance in specific high-risk populations (that is, patients with congestive heart failure, myocardial infarction, or renal failure), as the Valsartan Antihypertensive Long-term Use Evaluation trial conducted in hypertensive patients at high cardiovascular risk suggested that the greater BP reduction (−3.8/−2.2 mmHg) seen in amlodipine- than in valsartan-treated patients in the first 6 months of treatment was accompanied by a difference in the rate of cardiovascular events in favor of the more effectively treated group.⁸ In addition, high-dose administration of ARBs has been proposed for such high-risk populations because of prognostic benefits independent of BP-lowering.^{15–18}

In the ValTop study, adverse effects occurred in 15% of the patients during the open-label phase; headache was the most frequent event (1.4%), followed by nasopharyngitis, dizziness, and back pain. Actually, few patients had adverse effects suspected to be study drug related (4.3%, open label, 2.5% double blind, 1.9% extension phase) and none of those was classified as serious issues. This finding is similar to the results of previous studies,^{9,12,16,17} in which there was no evidence of dose-dependent adverse effects by ARBs. Hypotension, renal impairment, and hyperkalaemia can result from an overamplification of the effect of ARBs on inhibition of the renin-angiotensin-aldosterone system.¹² However, in the ValTop study, the incidence of these adverse events was very low. After the double-blind phase, an extension study of an additional 28 weeks was carried out, and

showed that the reduction of BP persisted to 32 weeks with no further increment drug adverse effects. This finding confirms that improving the tolerability profile of any antihypertensive drug has the potential to improve patient compliance, which in turn favors better BP control.

In the current state of hypertensive treatment, monotherapy still remain the standard initial approach for reducing BP in most hypertensive patients, although combination therapy has been proposed as a first choice particularly when there is a high cardiovascular risk, that is, in individuals in whom BP is markedly above the hypertension threshold ($\geq 160/100$ mmHg), or in patients with subclinical organ damage, diabetes or renal failure.² If the BP target cannot be reached by the initial approach with monotherapy, combination therapy rather than a stepwise increase in dose of one drug should be considered because combination therapy has substantial advantages in terms of BP lowering as well as sparing adverse effects compared with high-dose monotherapy. However, from the results of the ValTop study, a stepwise increase with early, aggressive up-titration in ARBs would seem to be appropriate, because high-dose ARBs achieve a substantial reduction of BP, have fewer adverse effects, and may have prognostic benefits independent of BP lowering. The cost disadvantage of ARBs has become much less of an issue, as generic preparations for each of these drug classes will soon become available. Further prospective studies will be needed to assess whether high-dose ARBs are effective in reducing cardiovascular events not only in certain specific high-risk populations, such as patients with congestive heart failure, myocardial infarction, or renal failure, but also in uncomplicated mild-to-moderate risk hypertensive patients.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

- 1 Oghihara T, Kikuchi K, Matsuoka H, Fujita T, Higaki J, Horiuchi M, Imai Y, Imaizumi T, Ito S, Iwao H, Kario K, Kawano Y, Kim-Mitsuyama S, Kimura G, Matsubara H, Matsuura H, Naruse M, Saito I, Shimada K, Shimamoto K, Suzuki H, Takishita S, Tanahashi N, Tsuchihashi T, Uchiyama M, Ueda S, Ueshima H, Umemura S, Ishimitsu T, Rakugi H, Japanese Society of Hypertension Committee. The Japanese Society of Hypertension Guidelines for the Management of Hypertension (JSH 2009). *Hypertens Res* 2009; **32**: 3–107.
- 2 Mancia G, De Backer G, Dominiczak A, Cifkova R, Fagard R, Germano G, Grassi G, Heagerty AM, Kjeldsen SE, Laurent S, Narkiewicz K, Ruilope L, Rynkiewicz A, Schmieder RE, Boudier HA, Zanchetti A, Vahanian A, Camm J, De Caterina R, Dean V,

- Dickstein K, Filippatos G, Funck-Brentano C, Hellemans I, Kristensen SD, McGregor K, Sechtem U, Silber S, Tendera M, Widimsky P, Zamorano JL, Erdine S, Kiowski W, Agabiti-Rosei E, Ambrosioni E, Lindholm LH, Viigimaa M, Adamopoulos S, Agabiti-Rosei E, Ambrosioni E, Bertomeu V, Clement D, Erdine S, Farsang C, Gaita D, Lip G, Mallion JM, Manolis AJ, Nilsson PM, O'Brien E, Ponikowski P, Redon J, Ruschitzka F, Tamargo J, van Zwieten P, Waeber B, Williams B. 2007 Guidelines for the Management of Arterial Hypertension: The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens* 2007; **25**: 1105–1187.
- 3 Morgan TO, Anderson AI, MacInnis RJ. ACE inhibitors, beta-blockers, calcium blockers, and diuretics for the control of systolic hypertension. *Am J Hypertens* 2001; **14**: 241–247.
- 4 Dickerson JE, Hingorani AD, Ashby MJ, Palmer CR, Brown MJ. Optimisation of antihypertensive treatment by crossover rotation of four major classes. *Lancet* 1999; **353**: 2008–2013.
- 5 Ishikawa J, Kario K, Hoshida S, Eguchi K, Morinari M, Kaneda R, Umeda Y, Ishikawa S, Kuroda T, Hojo Y, Shimada K, J-MORE Study Group. Determinants of exaggerated difference in morning and evening blood pressure measured by self-measured blood pressure monitoring in medicated hypertensive patients: Jichi Morning Hypertension Research (J-MORE) Study. *Am J Hypertens* 2005; **18**: 958–965.
- 6 Jamerson K, Weber MA, Bakris GL, Dahlof B, Pitt B, Shi V, Hester A, Gupta J, Gatlin M, Velazquez EJ. Benazepril plus amlodipine or hydrochlorothiazide for hypertension in high-risk patients. *N Engl J Med* 2008; **359**: 2417–2428.
- 7 Dahlof B, Sever PS, Poulter NR, Wedel H, Beevers DG, Caulfield M, Collins R, Kjeldsen SE, Kristinsson A, McInnes GT, Mehlsen J, Nieminen M, O'Brien E, Ostergren J. Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): a multicentre randomised controlled trial. *Lancet* 2005; **366**: 895–906.
- 8 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. *Lancet* 2004; **363**: 2022–2031.
- 9 Law MR, Wald NJ, Morris JK, Jordan RE. Value of low dose combination treatment with blood pressure lowering drugs: analysis of 354 randomised trials. *BMJ* 2003; **326**: 1427–1434.
- 10 Gupta AK, Arshad S, Poulter NR. Compliance, safety, and effectiveness of fixed-dose combinations of antihypertensive agents: a meta-analysis. *Hypertension* 2010; **55**: 399–407.
- 11 Parati G, Asmar R, Bilo G, Kandra A, Giovanni RD, Mengden T. Effectiveness and safety of high-dose valsartan monotherapy in hypertension treatment: the ValTop study. *Hypertens Res* 2010; **33**: 986–994.
- 12 Püchler K, Laeis P, Stumpe KO. Blood pressure response, but not adverse event incidence, correlates with dose of angiotensin II antagonist. *J Hypertens Suppl* 2001; **19**: S41–S48.
- 13 Weir MR, Hollenberg NK, Zappe DH, Meng X, Parving HH, Viberti G, Remuzzi G. Antihypertensive effects of double the maximum dose of valsartan in African-American patients with type 2 diabetes mellitus and albuminuria. *J Hypertens* 2010; **28**: 186–193.
- 14 Willemsen JM, Rabelink TJ, Boer P, Gaillard CA. Disparate systemic and renal blocking properties of angiotensin II antagonists during exogenous angiotensin II administration: implications for treatment. *J Hum Hypertens* 2004; **18**: 857–863.
- 15 Pfeffer MA, McMurray JJ, Velazquez EJ, Rouleau JL, Køber L, Maggioni AP, Solomon SD, Swedberg K, Van de Werf F, White H, Leimberger JD, Henis M,

- Edwards S, Zelenkofske S, Sellers MA, Califf RM, Valsartan in Acute Myocardial Infarction Trial Investigators. Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. *N Engl J Med* 2003; **349**: 1893–1906.
- 16 Weinberg AJ, Zappe DH, Ashton M, Weinberg MS. Safety and tolerability of high-dose angiotensin receptor blocker therapy in patients with chronic kidney disease: a pilot study. *Am J Nephrol* 2004; **24**: 340–435.
- 17 Hollenberg NK, Parving HH, Viberti G, Remuzzi G, Ritter S, Zelenkofske S, Kandra A, Daley WL, Rocha R. Albuminuria response to very high-dose valsartan in type 2 diabetes mellitus. *J Hypertens* 2007; **25**: 1921–1926.
- 18 Konstam MA, Neaton JD, Dickstein K, Drexler H, Komajda M, Martinez FA, Riegger GA, Malbecq W, Smith RD, Guptha S, Poole-Wilson PA, HEAAL Investigators. Effects of high-dose versus low-dose losartan on clinical outcomes in patients with heart failure (HEAAL study): a randomised, double-blind trial. *Lancet* 2009; **374**: 1840–1848.