Do Valsartan and Losartan Have the Same Effects in the Treatment of Coronary Artery Disease?

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Background Many angiotensin II type 1 receptor blockers (ARBs) are available for clinical use, but because they do not all have the same effects, the present study investigated whether all benefits conferred by ARBs are class effects.

Methods and Results Study 1 was a case–control study of patients with coronary artery disease, which showed that a non-depressor dose of valsartan significantly decreased the rate of target lesion revascularization at 6 months after stenting compared with the control group without ARB treatment. In Study 2, 44 patients with acute myocardial infarction who randomly received an initial lower dose of either valsartan or losartan after stenting were evaluated. The late loss and decrease in %diameter stenosis in the valsartan group were significantly lower than those in the losartan group as assessed by quantitative coronary angiography after 6 months. In addition, the valsartan group showed a significantly lower expression of intracellular adhesion molecule-1 and L-selectin.

Conclusion A non-depressor dose of ARB may have beneficial effects on coronary restenosis that are associated with the regulation of adhesion molecules, and these effects might not be a class effect of ARBs. (*Circ J* 2007; 71: 32–38)

Key Words: Adhesion molecules; Angiotensin II type 1 receptor blockers; Class effects; Coronary artery disease

The type 1 (AT₁) receptor for the octapeptide hormone angiotensin II (AngII) is a member of the G-protein coupled receptor superfamily (GPCR)! AngII is a major regulator of blood pressure (BP), electrolyte balance and endocrine function related to cardiovascular homeostasis as well as disease.^{2,3}

Many AT₁ receptor blockers (ARBs) are available for clinical use, but when their efficacy has been compared, differences have been observed as pleiotropic effects, such as regression of left ventricular mass;⁴ a reduction in renal nitric oxide (NO) production;^{5,6} lowering of plasma levels of plasminogen activator inhibitor type-1 antigen and monocyte chemoattractant protein-1;⁷ and prevention of human coronary artery contraction;⁸ except with regard to their ability to lower BP. Therefore, these abilities of ARBs may not be class effects.

There is another important issue to address. Although several clinical trials have evaluated the effects of ARBs, such as losartan (Losartan in the Elderly II trial)⁹ valsartan (Valsartan in Heart Failure Trial)¹⁰ and candesartan (Candesartan in Heart Failure-Assessment of Reduction in Mortality and Morbidity trial)¹¹ on morbidity and mortality in patients with heart failure, they did not show the same results. Although there are important differences in the design and hypothesis of these 3 trials that must be taken

into account when comparing their results and interpreting their clinical impact, we should also consider whether all ARBs have the same effects.

The most important effect of ARBs is their antagonism, which can block AngII-induced signaling. Because the differential effects of ARBs are independent of BP lowering in most studies,^{5–13} each ARB may have a particular characteristic mechanism for achieving AngII antagonism, such as the mode in which it binds AT₁ receptor (surmountable or insurmountable type), selectivity for AT₁ receptor, half-life in blood and inverse agonism!^{4,15} These differences in ARBs may be important for the ability of each ARB and might induce differential effects.

Although valsartan has been shown to be effective at preventing coronary restenosis in an open-label clinical study (Val-PREST),¹⁶ there have been no reports on whether all ARBs have the same effect in the treatment of coronary artery disease (CAD). Therefore, in the present study we first confirmed whether valsartan decreased the rate of restenosis after stenting compared with controls (Study 1) and then we compared the differential effects of valsartan and losartan after stent implantation in patients with ST-elevation myocardial infarction (STEMI) (Study 2). In Study 2, to determine the mechanisms at the molecular level, we analyzed the expression of cell adhesion molecules and chemokines, which play a role in the progression of atherosclerosis, induced by ARBs. Based on the results, we show here that ARBs might lead to new therapeutic strategies for targeting cardiovascular disease.

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Table 1 Patient, Angiographic and Stent Implantation Procedure Characteristics in Study 1

	Control (n=38)	Valsartan (n=45)	Losartan (n=55)	p value
Age, years	63±2	63±2	67±1	NS
Female, %	25	22	20	NS
BMI, kg/m ²	24±1	24±1	23±1	NS
HT, %	68	76	59	NS
HL, %	72	69	53	NS
DM, %	35	35	38	NS
ACS, %	72	78	67	NS
Smoking, %	55	55	59	NS
Medication, %				
Statin	46	44	33	NS
CCB	42	22	27	NS
-blockers	6	3	8	NS
Long-acting nitrates	15	0	10	NS
No. of coronary arteries				
Narrowed >50% 1/2/3, %	36/27/36	25/53/23	35/48/17	NS
ACC/AHA lesion classification, %				
A/B1/B2/C	0/45/48/6	0/30/58/13	6/27/54/13	NS
Coronary artery, %				
LAD/LCX/R	47/22/31	45/18/38	43/15/33	NS
Percent stenosis				
Pre-stent, %	93±1	95±1	96±1	NS
Post-stent, %	4±2	4±2	4±2	NS
Stent				
Type				
Radius, %	85	81	87	NS
Velocity, %	15	19	13	NS
Size				
Length, mm	18±1	19±1	19±1	NS
Diameter, mm	3.6±0.1	3.8±0.1	3.7±0.1	NS
Maximal inflation pressure, atm	8.3±0.4	8.3±0.4	8.5±0.3	NS

Values are mean±SD.

NS, not significant; BMI, body mass index; HT, hypertension; HL, hyperlipidemia; DM, diabetes mellitus; ACS, acute coronary syndrome; CCB, calcium-channel blocker; ACC, American College of Cardiology; AHA, American Heart Association; LAD, left anterior descending; LCX, left circumflex; R, right.

Methods

Subjects and Study Design

In Study 1, the subjects were 303 consecutive patients who underwent implantation with a Radius or Velocity stent at Fukuoka University Hospital and Fukuoka Tokusukai Hospital between 1998 and 2002. Patients who initially received valsartan or losartan were selected as cases: valsartan-treatment group (n=45, average dose, 52±4 mg/day from the day after stenting) or losartan-treatment group (n=55, 31±1 mg/day from the day after stenting). Age-, sex- and body mass index-matched patients who underwent implantation with a Radius or Velocity stent but did not receive ARBs (n=38) were assigned as controls. Follow-up coronary angiography was performed at 6 months after stenting and we assessed the rates of target lesion revascularization (%TLR) and restenosis (%RS). Patients with acute myocardial infarction (AMI; within 3 weeks of onset), heart failure, vascular disease or hepatic dysfunction (viral or nonviral, transaminases more than 3-fold greater than the normal value) were excluded from Study 1.

Study 2 included 44 consecutive initial STEMI patients who underwent coronary angiography and were found to have significant coronary stenosis (>50% luminal narrowing), and who had undergone coronary revascularization with a stent for the culprit lesion at Fukuoka University Hospital between 2002 and 2004. Four subjects were excluded because 2 had undergone coronary artery bypass grafting, 1 had lung cancer, and 1 was diagnosed with dissecting aneurysm of the aorta. After stent implantation, pa-

tients were randomly assigned to treatment with valsartan (n=20, average dose=38±5 mg/day) or losartan (n=20, 28±2 mg/day) beginning the day after stenting. The physicians determined the doses of ARBs based on the results of BP monitoring because BP was relatively low after AMI. In addition, low doses of ARBs were used so that we could analyze the potential ability of ARBs to prevent coronary restenosis independent of their ability to lower BP. Follow-up coronary angiography was performed at 6 months. We assessed the absolute changes in lipid profile, C-reactive protein (CRP), adhesion molecules and chemokines, as well as stenosis measured by quantitative coronary angiograms (QCA) between the post-stent and follow-up angiograms.

None of the patients suffered a cardiac event during the studies. All patients received 100 mg of aspirin and 200 mg of ticlopidine daily in both studies. Stents were implanted according to standard protocols. The Ethics Committee of Fukuoka University Hospital approved the study and informed consent was given by each patient.

Patients with total cholesterol ≥220 mg/dl or triglycerides ≥150 mg/dl were considered to have hyperlipidemia (HL), and statins were administered to these patients. Patients with systolic or diastolic BP ≥140 mmHg or 90 mmHg or who were under antihypertensive treatment were considered to have hypertension (HT). Patients who were being treated for diabetes mellitus (DM) or who had a fasting glucose concentration more than 126 mg/dl were considered to have the disease. The other patients underwent a 75-g oral glucose tolerance test for the diagnosis of DM.

Fig 1. (a) Rates of target lesion revascularization (%TLR) and restenosis (%RS) in the valsartan, losartan and control groups. * $p < 0.05$ vs comparative groups. (b) Changes in blood pressure in the valsartan, losartan and comparative groups. Closed, open and gray bars indicate the control, valsartan, and losartan groups, respectively. NS, not significant; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR heart rate; M, months.

Table 2 Patient, Angiographic and Stent Implantation Procedure Characteristics in Study 2

	Valsartan (n=20)	Losartan (n=20)	p value
Age, years	62±4	67±2	NS
Female, %	15	35	NS
BMI, kg/m ²	23±1	23±1	NS
HT, %	47	53	NS
DM, %	33	25	NS
HL, %	67	65	NS
Smoking, %	73	60	NS
Medication, %			
CCB	13	15	NS
-blockers	25	10	NS
Diuretics	33	26	NS
NG	26	20	NS
Statin	80	65	NS
Nicorandil	53	55	NS
CRP, mg/dl	2.3±0.5	2.5±0.6	NS
No. of coronary arteries			
Narrowed >50% 1/2/3, n	10/5/5	11/7/2	NS
Coronary artery, n			
LAD/LCX/R	10/1/9	8/1/11	NS
Stent implantation			
Type			
Be stent, n	0	1	NS
Bx velocity, n	5	5	NS
Driver, n	2	0	NS
Duraflex, n	1	0	NS
Multi-link, n	6	9	NS
Radius, n	5	4	NS
S660, n	0	1	NS
Tsunami, n	1	0	NS
Size			
Length, mm	21±1	19±1	NS
Diameter, mm	3.3±0.1	3.2±0.1	NS
Maximal inflation pressure, atm	14±1	14±1	NS

NG, nitroglycerin; CRP, C-reactive protein. Other abbreviations see in Table 1.

Blood Sampling

In Study 2, blood sampling was performed at 1 week and 6 months after starting ARB treatment. Because the expression of monocyte CD11a/CD18 and intracellular adhesion molecule-I (ICAM-I) is significantly increased up to 72 h throughout the acute phase of myocardial infarction (MI),¹⁷ we did not analyze the expression levels before ARB treatment. In addition, the increased monocyte CD11a was accompanied by an increased number of monocytes and a greater expression of CD11a per cell in the MI group. We determined the plasma lipid profile, CRP, adhesion molecules, chemokines, plasma soluble ICAM-I (sICAM-I), monocyte chemoattractant protein-1 (MCP-1) and regulated upon activation, normal T cell-expressed and secreted (RANTES). When CRP was less than 0.3 mg/dl, a test for highly sensitive CRP was also performed.

Expression of the adhesion molecules, CCR and CXCR, on neutrophils, monocytes and lymphocytes was measured using flow cytometric analysis (Beckman Coulter) as described previously.^{17,18} Briefly, whole blood staining was performed with fluorescein-isothiocyanate (FITC)-conjugated anti-CD11a, anti-CD18, anti-ICAM-1, anti-L-selectin, anti-VLA-4, anti-CCR2, anti-CCR5, anti-CXCR2, and anti-CXCR3 monoclonal antibodies (mAbs). Whole blood (100 µl) was incubated with saturating concentrations of FITC-conjugated mAbs. Erythrocytes were lysed and leukocytes were fixed (Immunoprep™, Beckman Coulter) by a TQ prep Workstation (Beckman Coulter). The cells were then washed and flow cytometric analysis was performed immediately. mAb binding was assessed by flow cytometry with a FACScan (Beckman Coulter). To analyze monocytes, lymphocytes and neutrophils, a gate was set in the forward angle vs right angle scatter.

The concentrations of sICAM-1 and MCP-1 in plasma were determined in duplicate by specific enzyme immunoassays (R&D Systems) according to the manufacturer's

Fig 2. (a) Changes in systolic blood pressure (SBP), diastolic blood pressure (DBP) and heart rate (HR) in the valsartan and losartan groups. Minimum lumen diameter (MLD) (b), % diameter stenosis (%DS) (c), late loss (d) and reference (e) as assessed by quantitative coronary angiography. $\Delta\%$ DS (%DS at 6 months (M) – %DS at pre) in the losartan and valsartan groups according to medication with or without statins (f). Open and gray bars indicate the valsartan and losartan groups, respectively. * $p < 0.05$ vs pre; # $p < 0.05$ vs valsartan group. NS, not significant.

instructions. At our laboratory, the intra- and inter-assay coefficients of variation were each 5%.

Coronary Angiography

Coronary angiograms were divided into 15 segments according to the classification of the American Heart Association Grading Committee. All angiograms were analyzed qualitatively and quantitatively at the angiographic core laboratory of Fukuoka University Hospital. QCA was performed on all qualifying angiograms using CME, MEDIS (The Netherlands), immediately after the procedure (pre) and at the 6-month follow-up.¹⁹ Binary restenosis was defined as >50% diameter stenosis (DS). QCA analysis included stent measurement (minimum lumen diameter (MLD) confirmed within proximal and distal stent borders) and a systematic analysis of the proximal and distal stent edges.

Statistical Analysis

Statistical analysis was performed using the SAS software package (version 6.12, Statistical Analysis System, SAS Institute Inc, Cary, NC, USA) at Fukuoka University. Data are shown as the mean $\pm$ standard error. Categorical variables such as gender were compared between cases and controls by chi-square analysis. Differences in continuous variables between groups were examined by both an analysis of variance and Wilcoxon's rank-sum test. A value of $p < 0.05$ was considered significant.

Results

Study 1

The baseline clinical characteristics are shown in Table 1. There were no differences between the 3 groups with respect to age, sex, body mass index (BMI), medication, prevalence of HT, HL, acute coronary syndrome or DM. In addition, no significant difference was found in angiographic variables, type of stent, maximal balloon inflation pressure or percent stenosis post-stent implantation.

With regard to angiographic findings, the restenosis rate in the control group (30%) tended to be nonsignificantly higher than that in the losartan (20%) and valsartan (20%) groups. The %TLR was 27% in the control group, 19% in the losartan group ($p > 0.05$ vs control group), and 10% in the valsartan group ($p < 0.05$ vs control group) (Fig 1a). Because statin treatment was associated with the difference in %TLR, we compared the %TLR in the with- or without-statin-treatment groups. Although the with-statin-treatment losartan group did not show a difference in %TLR compared with the valsartan groups, the without-statin-treatment %TLR in the valsartan group (12%) was approximately half that in the losartan group (25%), but this difference was not significant. Because the patients without statin treatment might show a differential effect in %TLR between the losartan and valsartan groups, we further analyzed this point in Study 2. In addition, neither systolic nor diastolic BP in the control, valsartan and losartan groups changed

Fig 3. Expression levels of ICAM-1 in leukocytes (a), CD11a/CD18 in monocytes (b), plasma soluble ICAM-1 (c), CCR2 in monocytes (d), plasma MCP-1 (e) and L-selectin in monocytes (f) in the valsartan and losartan groups at 1 week (W) and 6 months (M) after stent implantation. Open and gray bars indicate the valsartan and losartan groups, respectively. * $p < 0.05$ vs at week 1 (See text for abbreviations).

during the study (Fig 1b).

Study 2

There were no differences in age, sex, BMI, the incidences of HT and DM, medication (calcium-channel blocker, β -blocker, nitroglycerin, diuretics, nicorandil and statins), or the type, length, diameter or maximal inflation pressure of the stent between the groups (Table 2). In addition, there were no differences in the angiographic characteristics or stent implantation procedures between the groups.

Based on the QCA results, the %RS (valsartan group vs losartan group: 15% vs 40%) and %TLR (valsartan group vs losartan group: 10% vs 35%) in the valsartan group were lower than those in the losartan group, but these differences were not significant. Although there was no difference in MLD or the reference among the groups (Figs 2b,e), %DS at 6 months in the valsartan group was significantly lower than that in the losartan group (Fig 2c). In addition, the late loss in the valsartan group was significantly lower (Fig 2d). Because statin treatment is associated with %DS, we analyzed the %DS between the with- and without-statin-treatment groups. Although there was no significant difference in the percentage of statin treatment between the groups, previous reports suggest that statin treatment is associated with the rate of coronary restenosis. Although the statin-treated losartan group did not show a difference in $\Delta\%$ DS

(%DS at 6 months – %DS at pre) compared with the statin-treated valsartan groups, $\Delta\%$ DS in the valsartan group without statin treatment was significantly lower than that in the losartan group without statin treatment (Fig 2f). Because the patients without statin treatment in the valsartan group showed a significant suppression of DS, valsartan and losartan may not have the same effect on %DS.

At 6 months, the expression levels of almost all of the adhesion molecules and chemokines in leukocytes were decreased in both groups (Fig 3). Although the CRP levels were similar in the groups at pre (Table 2) and 6 months (valsartan group: 0.09 ± 0.02 mg/dl; losartan group: 0.12 ± 0.03), expression levels of ICAM-1 in the neutrophils and L-selectin in the monocytes in the valsartan group were significantly lower than those in the losartan group at 6 months (Figs 3a,f). In addition, the expression level of CCR2 in the monocytes in the valsartan group tended to be lower (Fig 3d).

Discussion

Many basic and clinical studies have shown that ARBs are useful for preventing the development of various cardiovascular diseases;^{3–11} however, it appears that ARBs may not all have the same effects in the treatment of CAD. In the present study, valsartan may have been more effective than losartan at preventing coronary restenosis. When

patients were not treated with a statin, the differential effect was remarkable. Because statin therapy is associated with preventing coronary restenosis,^{20,21} statin treatment may negate the difference between valsartan and losartan.

We should consider the differences between losartan and valsartan, such as inverse agonism, their mode of binding to AT₁ receptor (valsartan is an insurmountable type, whereas losartan is a surmountable type), area under the drug concentration time curve, AT₁ receptor selectivity, half-life in blood etc. The ability to detect agonist-independent signal transduction by GPCRs has been developed over the past decade and ligands described as inverse agonists, which can block these activities, have been identified. Valsartan exhibited strong inverse agonism in an in vitro study (Miura S. unpublished data), whereas losartan was a weak inverse agonist.¹⁴ Inverse agonism was also shown to be important for inhibiting pathological disadvantage in an in vivo study. We should also consider the results of 2 very important studies. In the first study, losartan prevented AngII-induced, but not mechanical stretch-induced, vascular endothelial growth factor (VEGF) secretion in human mesangial cells.²² AngII and stretching can each induce VEGF production, suggesting that both AngII- and stretch-induced AT₁ receptor signals exist. If losartan is a strong inverse agonist, the stretch-induced signal should be blocked. To clarify this point, in the second study by Zou et al, they reported that mechanical stress activated the AT₁ receptor independent of AngII stimulation, and this activation was blocked by the inverse agonist candesartan.²³ Candesartan significantly suppressed the development of cardiac hypertrophy independent of BP lowering in a model of pressure overload by constricting the transverse aorta of angiotensinogen knock-out mice. In addition, because coronary stenting chronically stretches the vessel and thus may activate AT₁ receptor, the inverse agonism of valsartan may have blocked activation in Studies 1 and 2 of our investigation.

Losartan is gradually metabolized into Exp3174, which exhibits inverse agonism.¹⁴ Although losartan has effects for 3–4 h from the time of administration, and Exp3174 works afterwards, we can not analyze the differences between the effects of losartan and Exp3174 in a clinical study. The difference in the effects of losartan and valsartan might be due to differences in biochemical characteristics, including binding mode or inverse agonism. In the present Studies 1 and 2, we were able to determine which oral medication (losartan or valsartan) was useful for preventing coronary restenosis. In addition, we used low doses of ARBs (≈60% of the average dose used in Japan: losartan 50 mg/day or valsartan 80 mg/day) because we considered that with these low doses we would be able to identify the fundamental effects of ARBs independent of any BP-lowering effect.

The increased expression of cellular adhesion molecules and chemokines on leukocytes and endothelial cells is an essential step in atherosclerotic CAD^{24–26} because these molecules regulate the different steps in leukocyte migration from the blood stream into the vessel wall. Although previous reports have compared ARBs, treatment with ARBs leads to a decrease in adhesion molecules, such as ICAM-1,^{27,28} vascular adhesion molecule-1 and chemokines,²⁸ E-selectin²⁹ and MCP-1.³⁰ In addition, monocyte and endothelial cell activation markers were found to be significantly decreased in patients with type 2 DM after treatment with valsartan.³¹ Thus, ARBs have novel effects that contribute to anti-inflammatory activity through the downregulation of

adhesion molecules and chemokines, which are pleiotropic effects independent of BP lowering, and in the present study these were found to be critical factors in the abilities of ARBs to prevent coronary restenosis. The different abilities of valsartan and losartan may lead to different results in preventing coronary restenosis.

Study Limitations

First, Study 1 was retrospective and Study 2 comprised a relatively small number of patients. However, because there were no significant differences in the baseline characteristics between the valsartan and losartan groups, we believe that our study contributes to understanding the effects of valsartan and losartan in the prevention of restenosis after stenting. A carefully designed large-scale study is needed to confirm the effects of valsartan and losartan. Second, we did not use intravascular ultrasound, which provides more useful information regarding neointimal formation.

In conclusion, a non-depressor dose of ARB may have beneficial effects on coronary restenosis that are associated with the regulation of adhesion molecules, and these effects might not be a class effect of ARBs. ARB-based therapy holds the promise of greatly reducing the incidence of coronary events.

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