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A Prospective Randomized Study of the Use of an Oral Angiotensin II Receptor Blocker to Prevent Restenosis after Percutaneous Coronary Intervention

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ABSTRACT

The drug-eluting stent (DES) has greatly decreased rates of restenosis after percutaneous coronary intervention (PCI). However, there is insufficient evidence for their use in certain conditions. Oral angiotensin II receptor blockers(ARBs) were recently reported to prevent restenosis after PCI. In the present study, we examined whether the addition of an angiotensin II receptor blocker to the standard treatment after PCI can prevent restenosis. Immediately after undergoing successful PCI, 145 consecutive subject patients with 164 lesions were randomly assigned to either a control group (75 patients with 86 lesions) or a valsartan group (70 patients with 78 lesions). Six months after administration, we performed follow-up coronary angiography of 65 lesions in the valsartan group and of 73 lesions in the control group. Restenosis was defined as restenosis of at least 50% stenosis on quantitative coronary angiography (QCA). Target lesion revascularization (TLR) was evaluated concurrently. The restenosis rate was significantly lower in the valsartan group (29.2%) than in the control group (46.6%, $p<0.05$). Among patients with acute myocardial infarction (AMI), restenosis was significantly inhibited in those receiving valsartan. The TLR rate in patients with AMI was slightly but not significantly lower in the valsartan group (0%) than in the control group (20.7% ; $p=0.082$), but in the valsartan group the TLR rate was significantly lower in patients with AMI (0%) than in patients with stable angina pectoris (28.6%, $p<0.05$). The present study clearly shows that valsartan inhibits restenosis after PCI, especially in patients with AMI, and can be used for patients who cannot tolerate drug-eluting stents.

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Key words : valsartan, percutaneous coronary intervention, restenosis, acute myocardial infarction, angiotensin II type 2 receptor

INTRODUCTION

The advent of the drug eluting stent (DES) has greatly improved the problem of restenosis after percutaneous coronary intervention (PCI). However, evidence for the effectiveness of DESs for some lesions is lacking. A small numbers of studies have examined the prevention of restenosis with oral agents, e.g., angiotensin-converting enzyme (ACE) inhibitors and statins. However, the restenosis-preventing effect of these agents has not been demonstrated. In recent years, oral angiotensin II receptor

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blockers (ARBs) have shown a significant preventative effect on restenosis after PCI[1]. However, no large-scale studies in Japan have been reported. Therefore, in the present study, we examined whether valsartan, an ARB, can prevent restenosis after PCI.

SUBJECTS AND METHODS

At the Saitama Prefectural Cardiovascular and Respiratory Disease Center, 145 consecutive patients with 164 coronary artery lesions who had undergone PCI were randomly assigned immediately after successful PCI to one of two groups using the envelop method. Seventy patients with 78 lesions were assigned to a valsartan group and received valsartan (40 to 80 mg per day) along with standard treatments, and 75 patients with 86 lesions were assigned to a control group and did not receive valsartan. The findings obtained with quantitative coronary angiography (QCA) were assessed in 138 lesions for which follow-up coronary angiography (CAG) had been previously conducted immediately after PCI and again approximately 6 months later. Twenty-five patients with 26 lesions were excluded for one or more of the following reasons: discontinued medication; no restudy; death; discontinued visit to the hospital; and attending physician determined that the patient was ineligible for other reasons (e.g., hypotension, hyperkalemia, advanced age, and chronic renal failure).

There was no significant difference between the valsartan group and the control group with respect to coronary risk factors. However, the percentage of patients with acute myocardial infarction (AMI) was significantly greater in the control group (Table 1).

All patients received aspirin (100 mg per day) for approximately 6 months and ticlopidine (200 mg per day) for approximately 1 month. The patients' attending physicians were requested to provide routine medical care at their discretion, and the use of other oral medications was not limited. This method was used because: 1) the Saitama Prefectural Cardiovascular and Respiratory Disease Center emphasizes coordination among medical specialties and 2) a local physician was usually in charge of treating the chronic phase of the disease. Unfortunately, drugs were discontinued or changed frequently, and new drugs were administered at frequent intervals. Because we envisaged that the details of drug control would be insufficiently comprehended, we used this method in expectation of obtaining better drug control in routine medical care. Patients for whom use of drugs for 6 consecutive months could be verified are shown in Table 2. ACE inhibitors were not administered to the valsartan group but were administered to the control group.

Table 1. Patient background

	Valsartan group (n=65)	Control group (n=73)	p value
Age	64.9±8.9	62.4±16.6	NS
M/F	43/22	54/19	NS
ACS	35 (53.8%)	41 (56.2%)	NS
AMI	12 (18.5%)	28 (38.4%)	<0.05
Stable AP	30 (46.2%)	32 (43.8%)	NS
HT	39 (60.0%)	33 (45.2%)	NS
HLP	35 (53.8%)	30 (41.1%)	NS
DM	21 (32.3%)	19 (26.0%)	NS
Smoking	17 (26.2%)	19 (26.0%)	NS

M/F=Male/Female; HT=hypertention; HLP=hyperlipidemia; DM=diabetes mellitus
Mean±SD: Age

There was no significant difference between the groups in lesion background or findings obtained with QCA (Tables 3 and 4).

Stents were used for 56 lesions (86.2%) in the valsartan group and for 53 lesions (72.6%) in the control group. The surgeon determined both the procedure and the type of stent (NIR, Bx velocity, Multi Linc, Trister, S670, Radius). The types of procedure did not differ between the groups (Table 5). Stents tended to be used more frequently in the valsartan group, although no significant difference was

Table 2. Combined oral drugs

	Valsartan group (n=65)	Control group (n=73)	p value
Statin	7 (10.8%)	12 (16.4%)	NS
Ca antagonist	5 (7.7%)	8 (11.0%)	NS
β blocker	10 (15.4%)	20 (27.4%)	NS
ACE inhibitor	0 (0%)	13 (17.8%)	<0.0005

Table 3. Lesion background

	Valsartan group (n=65)	Control group (n=73)	p value
LAD	32 (49.2%)	34 (46.6%)	NS
LCx	17 (26.2%)	16 (21.9%)	NS
RCA	16 (24.6%)	19 (26.0%)	NS
LIMA	0 (0%)	2 (2.7%)	NS
RIMA	0 (0%)	3 (4.1%)	NS

LAD=left anterior descending coronary artery; LCx=left circumflex coronary artery; RCA=right coronary artery; LIMA=left internal mammary artery; RIMA=right internal mammary artery

Table 4. Lesion background (QCA)

	Valsartan group (n=65)	Control group (n=73)	p value
A/B1	17 (26.2%)	16 (21.9%)	NS
B2/C	48 (73.8%)	57 (78.1%)	NS
Pre RD	2.89± 0.51	2.75± 0.56	NS
Pre MLD	0.84± 0.34	0.76± 0.41	NS
Pre %DS	77.67±15.4	82.12±17.4	NS
Pre LL	15.54± 7.7	13.57± 8.4	NS

RD=reference diameter; MLD=minimum lumen diameter; DS=diameter stenosis; LL=lesion length

Table 5. Therapeutic procedures

	Valsartan group (n=65)	Control group (n=73)	P value
POBA	9 (13.8%)	20 (27.4%)	NS
Stent	56 (86.2%)	53 (72.6%)	NS
NIR	26 (40.0%)	23 (31.5%)	NS
Bx velocity	14 (21.5%)	15 (20.5%)	NS
Multi Link	13 (20.0%)	9 (12.3%)	NS
Trister	1 (1.5%)	5 (6.8%)	NS
S670	3 (4.6%)	2 (2.7%)	NS
Radius	0 (0%)	3 (4.1%)	NS
ROTA	7 (10.8%)	4 (5.5%)	NS

POBA=plain old balloon angioplasty; ROTA=Rotablator

found between the two groups. All patients with AMI received stents.

Following the American Heart Association guidelines, restenosis was defined as (50% stenosis determined with QCA during follow-up CAG approximately 6 months after PCI. Furthermore, target lesion revascularization (TLR) was conducted for the following reasons: typical angina pectoris, positive findings during exercise stress testing, and evident ischemia from exercise- or drug-loaded technitium myocardial scintigraphy.

This study was conducted with the approval of the Ethics Committee of the Department of Cardiology of the Saitama Cardiovascular and Respiratory Center. The Chi-square test was used for statistical analysis. A p value less than 0.05 was considered to indicate statistical significance.

Results

The restenosis rate was significantly lower in the valsartan group (29.2%; 19 of 65 lesions) than in the control group (46.6%, 34 of 73 lesions; $p<0.05$; Fig. 1). However, the rates of instent stenosis did not differ significantly between the valsartan group (26.8%, 15 of 56 lesions) and the control group (43.4%, 23 of 53 lesions). The overall restenosis and instent restenosis rates did not differ significantly between the groups ($p=0.068$).

The TLR rate did not differ significantly between the valsartan group (21.5%, 14 of 65 lesions) and the control group (20.5%, 15 of 73 lesions; Fig. 2).

Among patients with AMI, however, the restenosis rate was 8.3%(1 of 12 lesions) in the valsartan group and 46.4% (13 of 28 lesions) in the control group. Therefore, restenosis was inhibited significantly ($p<0.05$) in the valsartan group in case. The TLR rate was 0% (0 of 12 lesions) in the valsartan group and was 20.7% (6 of 28 lesions) in the control group. Therefore, valsartan tended to decrease the rate of TLR ($p=0.082$), although no significant difference was

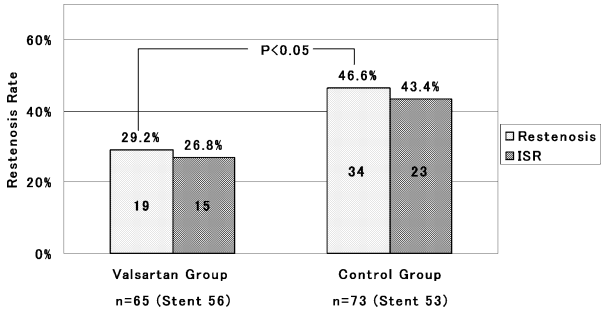

Fig. 1 Comparisons of restenosis rate between the valsartan group and the control group. The instent restenosis (ISR) rates tended to be nearly identical to the overall ISR rate.

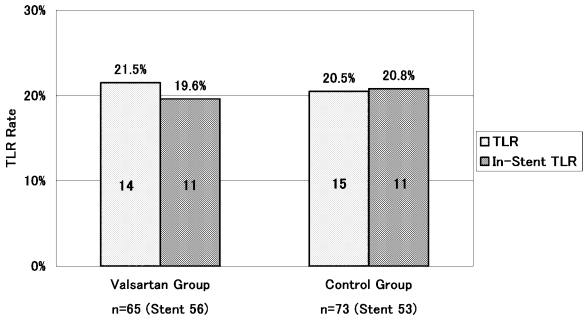

Fig. 2 Comparisons of the TLR rates between the valsartan group and the control group. The instent TLR rates tended to be nearly identical to the overall TLR rate.

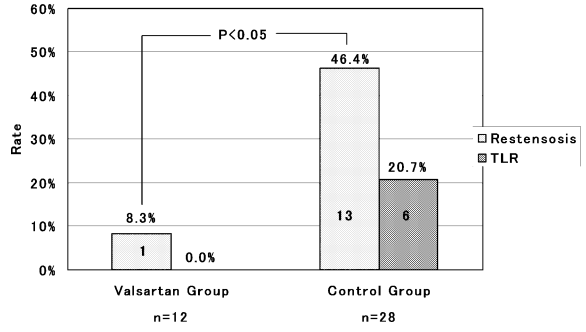

Fig. 3 Comparisons of AMI patients in the valsartan group and the control group with respect to restenosis rate and TLR rate.

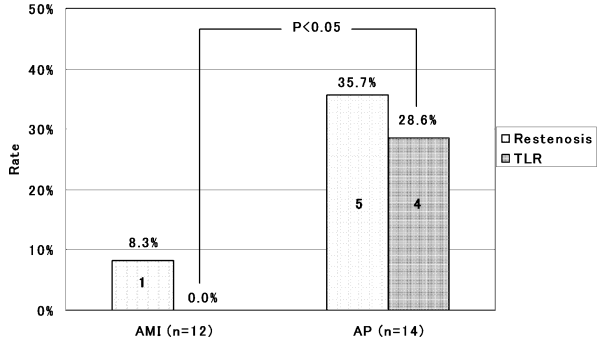

Fig. 4 Comparisons of AMI patients and stable AP patients in the valsartan group with respect to restenosis rate and TLR rate.

found between the two groups. The control group yielded outcomes that were similar to the overall outcome, while the valsartan group tended to show a lower TLR rate (Fig. 3). This result leads us to consider that the restenosis-inhibitory effect of valsartan can be attributed to outcomes in patients with AMI. Among patients treated with valsartan, those with AMI had a significantly lower TLR rate (0%, 0 of 12 lesions) than did patients with stable angina pectoris (28.6%, 4 of 14 lesions). Therefore, valsartan significantly reduced the rate of TLR ($p<0.05$) in patients with AMI (Fig. 4).

DISCUSSION

In cultured rat vascular smooth-muscle cells, angiotensin II (AII) acts on vascular smooth muscle cells mainly through the AII type 1 (AT_1) receptor to accelerate vascular wall remodeling by stimulating the hypertrophy and proliferation of vascular smooth muscle cells of arterial walls[2,3]. Furthermore, AII promotes the proliferation of vascular smooth muscle cells in the arterial walls after balloon-induced damage *in vivo*[4]. This finding suggests that ACE inhibitors inhibit the conversion from angiotensin I (AI) to AII and might prevent restenosis after PCI by also producing prostacyclin and nitric oxide through another mechanism, i.e., hyperproduction of bradykinins. However, no decrease in restenosis rates has been noted in clinical studies, including MERCATOR[5] and MARCATOR[6]. One possible interpretation is that ACE inhibitors cannot prevent restenosis after PCI because humans have pathways for converting AI to AII through enzymes other than ACE, e.g., chymase[7]. For this reason, ARBs, which selectively inhibit the AT1 receptor and block at the receptor level ACE, chymase, and AII produced via other pathways, might be effective. In the canine model, in which the activity of chymase-like enzymes is increased where vascular damage is observed in humans, ARB effectively inhibited neointima formation[8]. In fact, one report has noted that valsartan significantly reduces stent restenosis[1].

Our study in Japanese patients has also found that valsartan significantly reduces restenosis and would be effective for the Japanese population. The results of our study are supported by the significant efficacy of valsartan for patients with AMI.

Possible reasons for valsartan's effectiveness, especially for patients with AMI, include differences in the structure of vascular walls that are injured by PCI and differences in neurohumoral factors and

enzyme activity in the body. The major pathologic findings of unstable plaque, which provokes AMI, are thin fibrous capsules, large lipid pools, infiltration of inflammatory cells, such as macrophages and T cells, and severe accumulation of oxidized low-density lipoprotein[9]. The effects of valsartan on restenosis have been attributed to its anti-inflammatory effects on plaque[10] and its inhibition of low-density lipoprotein oxidation[11]. Furthermore, in the AMI myocardium, a cathepsin G-like enzyme and chymase predominantly produce AII at an early stage and on day 5 or later after AMI, respectively, and the ability to produce ACE-dependent AII is slightly increased at the margin of the infarction[12]. These findings lead us to speculate that various pathways for AII production are present in the parietal walls in AMI. We believe this interpretation provides a basis for the finding that valsartan, an ARB, prevents restenosis in patients with AMI.

Furthermore, the AII type 2 (AT_2) receptor, whose existence has been clarified together with that of the AT_1 receptor[13], is believed to be present at only low levels in the cardiovascular system until a pathological state arises. The blockade of the AT_1 receptor by ARBs stimulates the AT_2 receptor. Binding to the AT_2 receptor is thought to induce antihypertensive and cardioprotective activity by activating cyclic guanine monophosphate through the production of nitric oxide and by dilating blood vessels[14,15]. In addition, the AT_2 receptor may inhibit vascular proliferation[16] and has recently been found to appear in areas of cardiovascular remodeling after myocardial infarction[17]. Because valsartan is highly selective for the AT_1 receptor, the inhibited AT_2 receptor might exert a restenosis-inhibiting effect. However, much remains unknown about AII receptor subtypes.

We consider the results of the present study to be clinically applicable, although DESs are now in use. PCI is the most common treatment for coronary artery disease. However, questions remain about PCI's success rate, safety, and restenosis rate. Questions also remain about DESs. However, because a decreased rate of restenosis[18-22] is perhaps the main reason for using DESs, their success rate and safety should be considered separately. Especially for emergent PCI in patients with AMI, the success rate and safety are the most important issues. From this point of view, DESs, especially the sirolimus-eluting stent, which is the only DES available now in Japan, do not have an excellent delivery profile. Furthermore, ticlopidine is unsafe for use in emergencies, when the patient's history and medical information are often unavailable. In addition, restenosis-preventing effects of DESs themselves have been reported in AMI lesions among acute coronary syndrome (ACS) lesions. However, this issue remains controversial. For these reasons, the bare metal stent is often chosen for PCI in patients with AMI. However, the restenosis rate remains an issue for the bare metal stent, which is used when the success rate and safety are considered more important than the restenosis rate. By applying the results of the present study, the issues of success rate and safety can be emphasized in emergent PCI for AMI patients through the use of an appropriate bare metal stent and oral valsartan, while also decreasing the restenosis rate.

Moreover,[23] valsartan has been reported to increase the survival rate after myocardial infarction and to be useful for decreasing the incidence of cardiovascular disorders. In conclusion, the results of the present study indicate that valsartan is extremely useful for treating patients with AMI.

The limitations of the present study include: 1) the small number of patients; 2) the use of the envelop method to assign patients to groups; and 3) different PCI strategies used by surgeons. Further observation of the clinical course of AMI patients will be required to overcome these limitations.

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