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Initial reduction of oxidative stress by angiotensin receptor blocker
contributes long term outcomes after percutaneous coronary intervention
(経皮的冠動脈インターベンション施行患者へのアンジオテンシン受容体拮抗薬
による早期の酸化ストレスの抑制は、長期予後に寄与する)

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野呂 忠孝

(竹原有史、住友和弘、竹内利治、石井良直、
加藤淳一、川辺淳一、長谷部直幸)

Original Article

Initial reduction of oxidative stress by angiotensin receptor blocker contributes long term outcomes after percutaneous coronary intervention

Tadanori Noro¹, Naofumi Takehara², Kazuhiro Sumitomo¹, Toshiharu Takeuchi¹, Yoshinao Ishii³, Jun-ichi Kato⁴, Jun-ichi Kawabe², Naoyuki Hasebe¹

Departments of ¹Cardiology, ²Cardiovascular Regeneration and Innovation, Asahikawa Medical University, Japan; ³Department of Cardiology, Asahikawa City Hospital, Japan; ⁴Department of Cardiology, Asahikawa Kosei General Hospital, Japan

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Abstract: Background: It remains unclear whether administration of ARB with reactive oxygen species (ROS) scavenging effects improves the prognosis of patients undergoing PCI. Objectives: This study investigated whether the pre-intervention antioxidant effect of angiotensin receptor blocker (ARB) affects long-term outcomes in patients after successful percutaneous coronary intervention (PCI) without early adverse events. Methods: Fifty-two patients who underwent elective PCI were randomly assigned for treatment with or without ARB, which was administered within 48 hours before PCI. ROS levels in mononuclear cells (MNCs) and serum superoxide dismutase (SOD) activity were measured pre-PCI and 6 months post-PCI. After exclusion of unexpected early adverse events during angiographic follow-up period, the long-term outcome (major adverse cerebro-cardiovascular event; MACCE) was assessed in eligible patients. Results: Forty-three patients (non-ARB n = 22, ARB n = 21) were followed up in this study. During angiographic follow-up period, ROS formation in MNCs was significantly increased in the non-ARB group (from 29.4 [21.6-35.2] to 37.2 [30.7-45.1] arbitrary units; p = 0.031) compared to that in the ARB group. Meanwhile, SOD activity was significantly impaired in the non-ARB group alone (from 24.0 ± 17.0 to 16.3 ± 13.8%, p = 0.004). During the follow-up period (median, 63.3 months), MACCEs were observed in 6 patients. The cumulative event ratio of MACCE was significantly higher in the non-ARB group than in the ARB group (p = 0.018). Conclusions: Concomitant administration of ARB effectively reduced ROS production of PCI patients during angiographic follow-up period. Initial ROS inhibition following ARB administration may contribute to improvement of worse outcomes in patients who have undergone successful PCI.

Keywords: Angiotensin receptor blocker, oxidative stress, mononuclear cells, PCI, ROS

Introduction

Cardiovascular disease remains the most important cause of morbidity and mortality in developed countries, based on widespread risk factors such as hypertension, diabetes mellitus, and dyslipidemia [1-3]. Oxidative stress occurs as a result of the generation of reactive oxygen species (ROS) such as hydrogen peroxide (H₂O₂), peroxynitrite, and free radicals. ROS production is increased by several stimuli, including hyperglycemia, high blood pressure, and shear stress, and is closely associated with the progression of atherosclerosis and vulnerable plaques [4, 5]. Angiotensin II which acts as a ROS inducer by an NADPH-dependent

mechanism increases ROS formation in the peripheral circulation as a resulting of vessel injury and percutaneous coronary intervention (PCI) of coronary artery disease (CAD) patients [6, 7]. On the other hand, oxidative stress can be counteracted by redox systems such as manganese superoxide dismutase (MnSOD), catalase, and pertussis toxin. Recent reports have indicated that angiotensin receptor blockers (ARB) have not only anti-hypertensive effects but also modulation of oxidative stress by directly inhibiting the angiotensin II type-1 receptor, resulting in reduced restenosis of coronary arteries following PCI [8, 9]. However, it remains unclear whether the antioxidant effects of ARB administered prior to the PCI are corre-

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lated with clinical outcomes in patients who have undergone PCI, especially in patients who have undergone successful PCI without early adverse events.

Mononuclear cells (MNCs) and leukocytes in the peripheral blood are well known modulators of chronic inflammation associated with the atherosclerotic plaques found in the vascular wall. Oxidative stress, which generates ROS in MNCs and leukocytes, mediates the progress of atherosclerotic lesions in the vascular wall [10]. Leu *et al.* reported the correlation between ROS formation in peripheral blood MNCs and the long-term cardiovascular outcome of patients with cardiac syndrome X [11]. Therefore, ROS in MNCs is viewed as a surrogate marker of the pathophysiological stage and cardiovascular outcome of CAD patients.

Here, we assessed whether ARB administration prior to the PCI through its antioxidant effect to MNCs affected the long-term outcomes of patients undergoing PCI, especially after successful PCI without early adverse events.

Materials and methods

Participants

This study was conducted as a multicenter, open randomized, prospective cohort trial. Eligible patients, enrolled at 3 hospitals (Asahikawa Medical University Hospital, Asahikawa City Hospital, and Asahikawa Kosei General Hospital), had the following characteristics: 1) age 18-90 years with stable or provokable myocardial ischemia; 2) scheduled PCI for a single *de novo* lesion in a native coronary artery; 3) well-controlled blood pressure (BP < 140/90 mmHg); and 4) no use of angiotensin-converting enzyme inhibitor (ACE-I) or ARB therapy. The exclusion criteria included the following: 1) resistant hypertension (BP > 140/90 mmHg using triple anti-hypertensive drugs); 2) pregnancy; and 3) drug allergy and/or contra-indications to ACE-I and ARB. Patients provided written informed consent and the study protocols were approved by the institutional review board at each participating center.

Study design

Patients were randomly assigned into 2 groups using the concealed allocation: the ARB group or non-ARB group. Patients in the ARB group

were administered 20-80 mg of valsartan beginning 48 h to the elective PCI through to the angiographic follow-up (6 months after stenting). If the patients did not have well-controlled blood pressure within the angiographic follow-up, the ARB group was treated for hypertension with an increased dose of valsartan (max 160 mg), whereas the non-ARB group was treated for hypertension with additional anti-hypertension drugs-excluding ACE-I and/or ARB-or an increased dose of anti-hypertension drugs.

Coronary artery stenosis was evaluated by well-trained cardiologists at each hospital by quantitative coronary analysis (QCA) followed by classification according to the American College of Cardiology and American Heart Association. Coronary stenting was performed on culprit lesions using bare metal stents (BMSs) or drug-eluting stent (DESs) when coronary arteries had a stenosis diameter of $\geq 75\%$, according to the QCA analysis using either electrocardiographic changes with typical chest pain at rest or a positive exercise-induced ischemic finding in the area of the culprit lesion. In-stent restenosis (ISR) was defined as a restenosis diameter of $\geq 50\%$ after stenting (either within the stent or at its margins) at the angiographic follow-up examination. Target lesion revascularization (TLR) was defined as either repeat PCI or coronary artery bypass grafting for a lesion within the stent or at the 5-mm borders proximal or distal to the stent.

Clinical outcomes

The outcome investigated in this study was a major adverse cerebro- cardiovascular event (MACCE) such as cardiovascular death, resuscitated cardiac arrest, non-fatal myocardial infarction, non-fatal stroke, hospitalization for heart failure, revascularization in peripheral artery disease, hospitalization for unstable angina with objective evidence of ischemia, or coronary revascularization including TLR. To assess the patients without initial MACCE associated with primary PCI within angiographic follow-up period, who were defined as patients with successful PCI, the patients experiencing MACCE which were classified as unexpected early adverse events prior to angiographic follow-up were excluded. Lastly, the primary outcomes were defined as the first occurrence of MACCEs after angiographic follow-up and were assessed in patients with successful PCI. No restrictions in ARB administration after angio-

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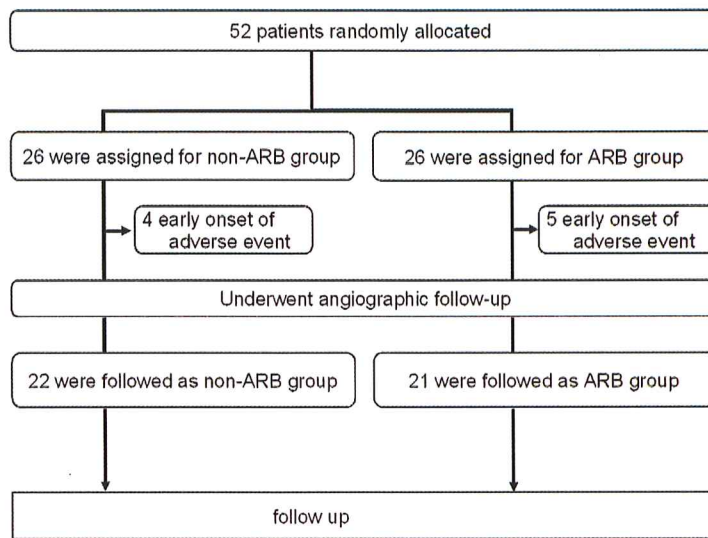


Figure 1. Study design scheme. ARB = angiotensin receptor blocker; MACCE = major cerebro-cardiovascular event; CAG = coronary angiography; TLR = target lesion revascularization.

Table 1. Angiographic findings and TLR at angiographic follow-up

		non-ARB (n = 25)	ARB (n = 22)	p
Target lesion in CAG		41	38	
Lesion	LAD	17	18	0.6
	LCX	11	10	0.96
	RCA	13	10	0.6
STENT	BMS	23	16	0.22
	DES	13	13	0.82
% stenosis in QCA	pre-PCI	86.4	81.5	0.19
	post PCI	14.6	14.5	0.97
	6 month after	41.8	31.3	0.10
ISR		22.0 (9/41)	15.8 (6/38)	0.49
TLR		3 (7.3%)	1 (2.6%)	0.34

LAD = left descending artery; LCX = left circumflex artery; RCA = right coronary artery; BMS = bare metal stent; DES = drug eluting stent; QCA = quantitative coronary analysis; PCI = percutaneous coronary angioplasty; ISR = in-stent restenosis; TLR = target lesion revascularization.

graphic follow-up were implemented in either the ARB or non-ARB group.

Intracellular oxidative stress and SOD assay

Fasting blood samples were collected before coronary angiography performed for the primary PCI and during angiographic follow-up period. To isolate peripheral blood MNCs, venous peripheral blood was extracted and incubated in a solution containing NH_4Cl , KHCO_3 , and tetrasodium ethylenediaminetetraacetic acid in Chelex 100-treated water (pH 7.3) for 10 min

for erythrocyte hemolysis. The blood samples were then washed with ice-cold 2-[4-(2-hydroxyethyl)-1-piperazinyl] ethanesulfonic acid (HEPES) buffer (pH 7.4) and centrifuged at 1,000 g at 4°C for 5 min, and the supernatant was subsequently discarded. To measure the intracellular H_2O_2 produced in MNCs, the cells were resuspended in 1 mL of HEPES buffer (pH 7.4) and 6-carboxy-2',7'-dichlorodihydrofluorescein diacetate (CDCFH-DA; Molecular Probes, Netherlands; 10 μM final concentration) were added to each sample and incubated at 37°C for 30 min, as described previously [12]. After adjusting to a cell density of 2×10^5 cells/mL, the levels of H_2O_2 in the MNCs were determined using gated flow cytometry with a fluorescence-activated cell sorter (EPICS XL/XL-MCL System II v3.0, Bton Dickinson). For each aliquot of cell suspension, an appropriate electronic gate was generated, and 5,000 events were collected in live mode. H_2O_2 levels were calculated as relative fluorescence units, namely, the median channel value of the fluorescing cell population. Serum SOD activity was measured as the super-oxide inhibition rate using the NBT method (SOD Activity Detection Kit, BioVision).

Statistical analysis

Continuous variables were presented as means \pm standard deviation (SD). The unpaired-*t* test and Mann-Whitney *U* test were used to analyze the 2 independent groups. The absolute change in ROS formation between baseline and the 6-month angiographic follow-up examination was compared using paired *t* tests or Wilcoxon signed-rank tests. Chi-square tests were used for the analysis of categorical variables. To investigate the differences between groups in the cumulative event ratio for MACCE, the

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Table 2. Baseline patient characteristics, medication, and laboratory values

	non-ARB (n = 22)	ARB (n = 21)	p value
age (y)	68.4 ± 8.5	66.6 ± 8.2	0.487
male	20	13	0.034
BMI (kg/cm ²)	25.1 ± 2.5	26.3 ± 3.5	0.188
Systolic blood pressure (mmHg)	131.8 ± 15.4	130.6 ± 19.8	0.818
HR (bpm)	67.1 ± 7.9	64.3 ± 11.7	0.378
History			
Hypertension	17	13	0.332
glucose tolerance insufficiency	9	12	0.366
Dyslipidemia	20	20	0.999
smoking history	21	13	0.009
current smoking	4	2	0.664
Brinkman index	973.6 ± 156.0	688.1 ± 159.7	0.2081
Pre-procedural medications			
Ticlopidine	20	20	0.999
Statin	18	20	0.345
CCB	17	10	0.062
β-blocker	10	11	0.763
ARB	0	21	
Pre-procedural laboratory			
FBS (mg/dl)	115.3 ± 28.2	112.1 ± 24.6	0.696
HbA1c (%)	6.0 ± 1.2	6.1 ± 1.0	0.716
LDL-cholesterol (F) (mg/dl)	111.9 ± 36.2	118.2 ± 23.8	0.509
HDL-cholesterol (mg/dl)	48.7 ± 13.2	50.8 ± 12.8	0.589
Triglycerides (mg/dl)	134.5 ± 87.9	143.2 ± 105.6	0.768
Lp(a) (mg/dl)	23.4 ± 12.8	29.1 ± 21.0	0.295
eGFR	66.4 ± 17.6	63.7 ± 20.5	0.649
Clinical presentation			
Previous myocardial infarction	6	7	0.747
Previous angioplasty	7	6	0.999

occurrence of MACCEs was presented using the Kaplan-Meier cumulative survival curve and compared using the log-rank test. Multiple regression analysis was used for ARB-treatment, sex, age, and smoking history to evaluate the independent variables for MACCE incidents. Group differences were considered statistically significant at $p < 0.05$. Statistical analysis was performed using SPSS software.

Results

Patient characteristics at enrolment

Between September 2003 and September 2006, 52 patients with stable angina pectoris undergoing PCI were enrolled and assigned into 2 groups. A diagram illustrating the study

design is shown in **Figure 1**. The mean time between primary PCI and the angiographic follow-up examination was 196 ± 37 days. Five patients presented with early onset MACCEs including cerebral infarction, hospitalization for heart failure, femoral-tibia artery bypass grafting following the onset of peripheral artery disease, onset of unstable angina pectoris and effort angina pectoris. Procedural characteristics and angiographic analyses from primary PCI to angiographic follow-up are shown in **Table 1**. Forty-one lesions in 25 patients in the ARB group and 38 lesions in 22 patients in the non-ARB group were analyzed using QCA. The number and location of coronary stenosis in patients undergoing PCI were comparable between the 2 groups (non-ARB vs. ARB: 17 vs. 18 lesions in the left anterior descending artery, $p = 0.6$; 11 vs. 10 lesions in the left circumflex artery, $p = 0.96$; and 13 vs. 10 lesions in the right coronary artery, $p = 0.82$). Furthermore, no significant difference in stenting with BMSs (a total of 39 lesions in the non-ARB vs. ARB groups: 23 vs. 16, $p = 0.22$) or DESs (a total of 26 lesions in non-ARB vs. ARB, 13 vs. 13, $p = 0.82$) was observed between the groups. The primary success of coronary intervention was similar in the 2 groups. At the angiographic follow-up examination, the incidence of coronary stenosis in stent-implanted lesions tended to be higher in the non-ARB group than in the ARB group (41.8% vs. 31.3%, $p = 0.10$). TLR was performed in 3 patients in the non-ARB group and one patient in the ARB group. The proportion of patients undergoing TLR was comparable in the 2 study groups.

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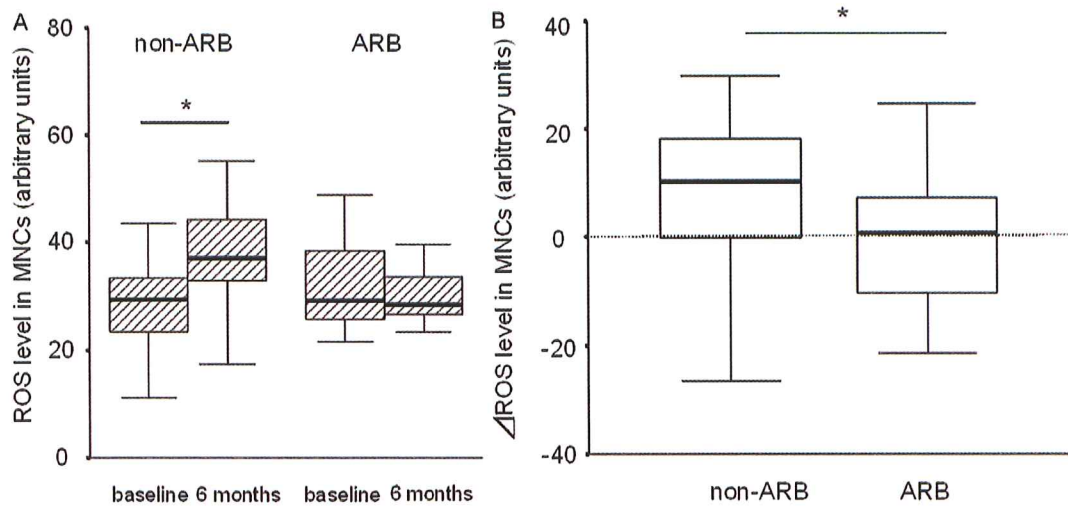


Figure 2. Levels of reactive oxygen species (ROS) formation in mononuclear cells (MNCs) at baseline and 6 months after percutaneous coronary angioplasty, with or without angiotensin receptor blocker (ARB). A: ROS levels in MNCs in coronary artery disease (CAD) patients. B: The absolute change in MNC ROS formation in CAD patients from baseline to 6 months (non-ARB group, n = 22; ARB group, n = 21; *p < 0.05).

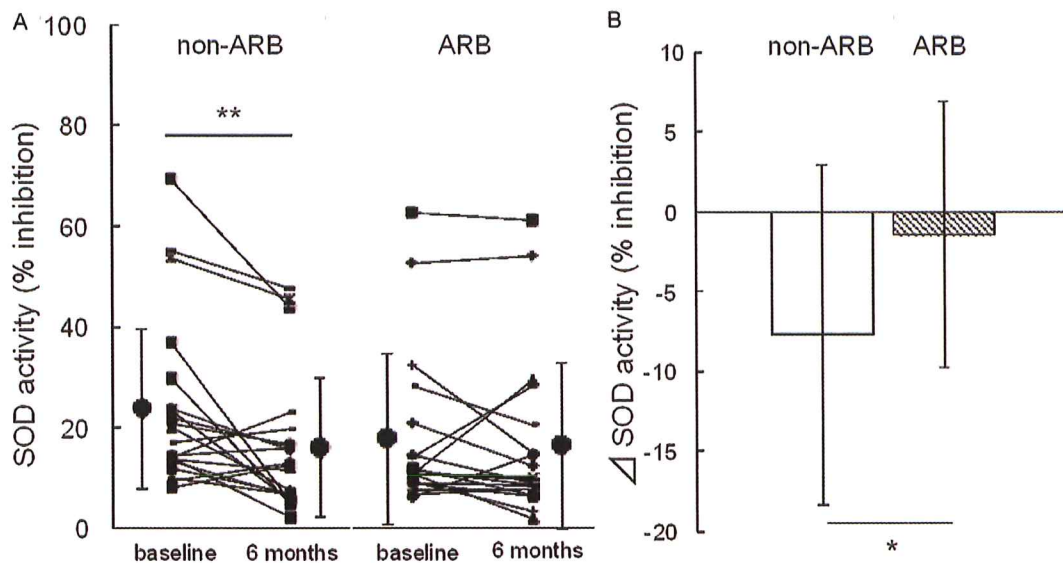


Figure 3. Superoxide dismutase (SOD) activity at baseline and 6 months after PCI with or without angiotensin receptor blocker (ARB). A: Serum SOD activity (% inhibition) in CAD patients. B: Absolute change in serum SOD activity in CAD patients from baseline to 6 months (non-ARB group, n = 22; ARB group, n = 21; *p < 0.05; **p < 0.01).

Therefore, 43 patients who underwent successful PCI (non-ARB group, n = 22; ARB group, n = 21) were followed up and assessed for primary outcomes after angiographic follow-up examination (median time, 56 months). Baseline characteristics are shown in **Table 2**. Patient's BP was not significantly different

between the 2 groups (ARB vs. non-ARB: $130.6 \pm 1.9/73.5 \pm 9.6$ vs. $131.8 \pm 3.3/70.6 \pm 1.8$ mmHg, p = N.S.). No differences between the 2 groups were observed in most parameters (age, body mass index, hypertension, glucose tolerance insufficiency, dyslipidemia, previous myocardial infarction and angioplasty, and lab-

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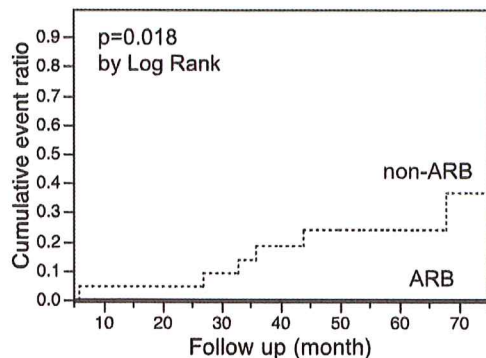


Figure 4. Cumulative event ratio of cardio-cerebrovascular death, myocardial infarction, unstable angina, stroke, heart failure, and target lesion revascularization after angiographic follow-up examination.

oratory data), with the exception of the proportion of male patients and smoking history. Smoking history was different between 2 groups (ARB vs. non-ARB: 13/21 vs. 21/22, $p < 0.01$), however, the ratio of current smoker (ARB vs. non-ARB: 2/22 vs. 4/21, $p = 0.6640$) and brinkman index (ARB vs. non-ARB: 688.1 ± 159.7 vs. 973.6 ± 156.0 , $p = 0.2081$) were no significantly different in 2 groups.

Intracellular oxidative stress in mononuclear cells and SOD activity in peripheral blood

ROS formation (intracellular hydrogen peroxidase) in MNCs was evaluated at baseline (before PCI) and at the angiographic follow-up examination (6 months after PCI; **Figure 2A**). ROS formation in the MNCs was similar between the groups at baseline (non-ARB, $n = 22$ vs. ARB, $n = 21$; median (IQR), 29.4 (21.6-35.2) arbitrary units vs. 29.3, (24.8-42.4) arbitrary units, $p = 0.419$). In the non-ARB group, ROS formation in the MNCs at 6 months was significantly higher than that at baseline (37.2 [30.7-45.1] vs. 29.4 [21.6-35.2] arbitrary units; $p = 0.031$). However, no difference in ROS formation in the MNCs was detected between baseline and 6 months in the ARB group (29.3 [24.8-42.4] vs. 28.5 [25.9-34.8] arbitrary units; $p = 0.829$). The absolute change in ROS formation in the MNCs from baseline to 6 months was significantly lower in the ARB group than in the non-ARB group (**Figure 2B**, $p = 0.035$). MnSOD, which is a well-known redox enzyme that counteracts oxidative stress, was evaluated to determine serum SOD activity. Baseline serum SOD activity and ROS formation in the MNCs

(non-ARB vs. ARB: $24.0 \pm 17.0\%$ vs. $17.9 \pm 15.8\%$, $p = 0.256$) were not significantly different (**Figure 3A**). In the non-ARB group, SOD activity was significantly impaired at the angiographic follow-up examination compared to that at baseline ($16.3 \pm 13.8\%$ vs. $24.0 \pm 17.0\%$, $p = 0.004$); however, SOD activity in the ARB group was preserved until the angiographic follow-up examination (from $17.9 \pm 15.8\%$ to $16.6 \pm 16.3\%$, $p = 0.476$). As shown in **Figure 3B**, the attenuation of SOD activity observed in the non-ARB group (from baseline to angiographic follow-up) was significantly inhibited in the ARB-group (non-ARB vs. ARB: $-7.7 \pm 10.6\%$ vs. $-1.4 \pm 8.4\%$, $p = 0.046$).

Long-term outcomes of patients who underwent successful PCI

Primary outcomes were assessed in 43 patients who underwent successful PCI. During the median follow-up examination at 63.3 months from October 2004 to August 2010, the following MACCEs occurred in 6 non-ARB patients: TLR due to unstable angina pectoris ($n = 2$), hospitalization for new onset of unstable angina pectoris with typical chest pain and ST-segment deviation in the precordial leads ($n = 2$), hospitalization for congestive heart failure ($n = 1$), and cerebral infarction ($n = 1$). However, no patient in the ARB group experienced MACCEs. The cumulative event ratio for MACCE was significantly higher in the non-ARB group than in the ARB group (**Figure 4**; log-rank test; $p = 0.018$). There were differences in the distribution of sex and smoking history in the 2 groups; however, multiple logistic regression analysis using sex, aging, and smoking history as covariates indicated that only the initial ARB administration showed a statistically significant correlation with MACCEs ($p = 0.0119$).

Discussion

The present study demonstrated that administration of ARB immediately prior to PCI improves long-term outcomes in patients who underwent successful PCI without experience early onset of MACCEs. In addition, our findings showed that administration of ARB to PCI patients prevented increase in ROS formation of peripheral blood MNCs and preserved MnSOD activity until 6 month after PCI. This beneficial effect of ARB might contribute, at least in part, to improvement of worse outcomes in PCI patients.

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Several reports have indicated that ARB treatment is effective in the primary prevention of cerebro-cardiovascular events in CAD patients. The Val-PREST trial reported that valsartan inhibited post-PCI ISR in type B/C coronary lesions [13]. Subsequently, trials using candesartan [14] and telmisartan [15] also showed similar effects in CAD patients and a post-hoc analysis of the HIJ-CREATE trial data also indicated that an ARB-based therapy might reduce the risk of coronary events in hypertensive patients with CAD and impaired renal function [16]. On the other hand, Sugihara *et al.* reported that the incidence of ISR in PCI patients was comparable between the non-ARB and ARB hypertensive treatment groups [17]. We also could not confirm the protective effect of an ARB on neo-intima formation in the coronary arteries of PCI patients at the angiographic follow-up examination. However, the cerebro-cardiovascular outcome of PCI patients is affected by not only the restenosis of the target lesion but also the progression of neo-intima formation in non-target lesions. In the present study, if no administration of ARB to PCI patients, even patients who underwent successful PCI had a 32% increased risk of MACCEs as a long-term outcome after angiographic follow-up, with the exception of patients in the ARB group. Recently, Hirohata *et al.* reported that pre-loading with olmesartan in stable angina patients planning to undergo elective PCI prevented the progression of coronary atherosclerotic plaques without target lesions that were assessed using serial intravascular ultrasound [9], and this beneficial effect significantly inhibited the incidence of MACCEs in a long-term follow-up study (OLIVUS trial) [18].

Angioplasty of coronary arteries generates NADPH-oxidase-dependent ROS formation and elevates inflammatory cytokine levels in the target atherosclerotic plaques through activation of the renin-angiotensin system [6, 7, 19]. Then, ischemic reperfusion injuries accompanied with coronary angioplasty activate leukocytes and MNCs in the peripheral blood, which is an additional source of ROS production [20] and stimulates the migration and adhesion of activated leukocytes to atherosclerotic plaques [10]. The oxidative-stress accompanying coronary angioplasty aggravates injured target vessels as well as systemic atherosclerosis through the activation of the renin-angiotensin system, especially in the angiotensin II type 1 receptor cascade, in the tissues and peripheral circula-

tion by ROS formation. It is known that the pre-loading of ARB inhibits neo-intima formation in the experimental balloon injury model [21, 22], and reduces early adhesion of MNCs in the biphasic recruitment to atherosclerotic plaques within 24 h and 1 week [10, 23]. In the present study, we have demonstrated that the administration of ARB prior to PCI procedure attenuated ROS formation of circulating-MNCs and preserved serum SOD activity until 6 month after primary PCI. This beneficial effects of ARB may be attributed to a mechanism involving the direct inhibition of oxidative stress via angiotensin II type 1 receptor-mediated NADPH-oxidase activation in both tissues [8, 9, 24, 25] and circulating MNCs [10, 26], as well as the activation of the redox system following oxidative stress [27]. Therefore, this is a first report that the initial reduction of ROS in circulating-MNCs by the administration of ARB might contribute the reduction of the cumulative event ratio in MACCE of successful PCI patients.

The first limitation of this study was the difference between the experimental groups with respect to sex and smoking rates. We were unable to avoid these group differences due to the limited number of patients eligible for the study. However, the ratio of current smoker in enrollment and follow-up period was rare, and then, no difference was seen in brinkman index between 2 groups. Furthermore, according to a multiple logistic regression analysis, smoking history and sex did not influence the incidence of MACCEs in the groups (smoking, $p = 0.3910$; male patients, $p = 0.2320$). The second limitation was the small sample size of enrollment in 3 years. In the RITA-2 trial, the event ratio for cardiac death, or definite MI, and coronary angioplasty in the evaluation of outcomes 7 years after primary PCI was 44% in patients with stable angina pectoris [28]. Even in small sample size, our results in the non-ARB group were also shown the high incidence of MACCEs (34%) in long-term, such as BMS stenting or balloon angioplasty in CAD patients like the RITA-2 trial. Therefore, followed larger scale trials will be able to confirm our observation of the beneficial effect of ARB in the current clinical setting.

Conclusion

Administration of ARB prior to the PCI effectively prevented increase in ROS formation of the MNCs in PCI patients during angiographic fol-

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low-up period. Initial ROS inhibition using ARB may improve long-term clinical outcomes in patients who have undergone successful PCI without early adverse events.

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Disclosure of conflict of interest

None to disclose.

Abbreviations

ROS, reactive oxygen species; PCI, percutaneous coronary intervention; MNC, mononuclear cell; SOD, superoxide dismutase; MACCE, major adverse cerebro-cardiovascular event; DES, drug-eluting stent.

Address correspondence to: Dr. Naofumi Takehara, Department of Cardiovascular Regeneration and Innovation, Asahikawa Medical University, 2-1-1-1 Midorigaokahigashi, Asahikawa, 075-8510, Japan. Tel: +81-166-68-2442; Fax: +81-166-68-2449; E-mail: takenao1@mac.com

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