Beneficial Effects of Valsartan on Target Lesion Revascularization After Percutaneous Coronary Interventions With Bare-Metal Stents

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Background: Angiotensin II receptor blockers (ARB) have been shown to reduce cardiovascular events in patients at risk. The effect of valsartan on outcomes after percutaneous coronary interventions (PCI) with bare-metal stents (BMS) was investigated.

Methods and Results: The prospective, randomized study included 191 patients at 5 participating institutions, who were randomly assigned to either a 40–80 mg valsartan add-on or non-ARB treatment. The primary endpoint was a composite of all-cause death, non-fatal myocardial infarction, and target lesion revascularization (TLR) at 18 months. Enrollment was stopped when the use of drug-eluting stents has been expanded in Japan. No significant differences existed between the groups in terms of primary endpoint (18.9% vs. 24.8%; hazard ratio [HR], 0.84; 95% confidence interval [CI], 0.61–1.14; $P=0.26$). In the valsartan group, as compared with the non-ARB group, the secondary endpoint of TLR was significantly reduced at a median follow-up 4.4 years; the rate of TLR was from 27.8% to 14.5% (HR, 0.69; 95%CI, 0.49–0.96; $P=0.024$).

Conclusions: Valsartan treatment was not superior to non-ARB treatment in reducing the primary endpoint after PCI at 18 months. The pre-specified secondary endpoint of TLR was lower in the valsartan group, but this needs to be proved statistically with an adequate study sampling. (*Circ J* 2011; **75**: 1641–1648)

Key Words: Percutaneous coronary intervention; Restenosis; Revascularization; Stents

The growing use of coronary stents has improved the results of percutaneous coronary intervention (PCI) over the last decade.¹ However, in-stent restenosis continues to limit the long-term success of this procedure.² Drug-eluting stents (DES) coated with strong antiproliferative agents such as sirolimus or paclitaxel have dramatically reduced the need for repeat revascularization procedures due to reduction in restenosis rates after PCI.^{3–6}

Notwithstanding this tremendous progression in antirestenotic therapies, with the use of DES, target lesion revascularization (TLR) remains necessary in approximately 12% of patients at 2 years after PCI.⁷ Moreover, there is increasing concern about the safety of DES, in light of reports that they are associated with a slightly increased rate of late stent throm-

bosis and possibly increased rates of myocardial infarction (MI) and death after PCI.⁸ Although the efficacy of DES lies in reducing restenosis-related TLR, lesions at low risk of restenosis might still be considered suitable for bare-metal stents (BMS) in the contemporary DES era.⁹

Previous studies have shown the benefits of angiotensin converting enzyme (ACE) inhibitors in patients with coronary artery disease.^{10,11} In contrast, the effects of angiotensin II receptor blockers (ARBs) with coronary artery disease remain to be determined. While 2 open-label studies suggested beneficial effects of ARBs on neointimal proliferation at 6 months,^{12,13} a smaller randomized open-label study did not show a reduction in neointimal proliferation for ARB-related patients after coronary stent implantation at 6 months.¹⁴

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The purpose of the present study was to investigate the effects of valsartan on long-term outcomes after PCI with BMS in coronary artery disease patients.

Methods

Patient Population

This study was a prospective randomized, open, and non-placebo-controlled trial performed at 5 participating institutions. It was approved by the ethics committee at each participating institution, and all patients gave written informed consent.

Patients were eligible for the study if they were 30–80 years old and had received a coronary stent implantation. Clinical exclusion criteria included a left ventricular ejection fraction of less than 30%, a serum creatinine concentration >2.0 mg/dl, pregnancy, hemorrhagic diatheses, contraindication or allergy to aspirin, ticlopidine, or stainless steel, a history of anaphylaxis in response to iodinated contrast medium, and treatment with an ARB 4 weeks or less before randomization. Angiographic eligibility criteria were the presence of at least 1 target lesion in a native coronary artery with a reference vessel diameter (RVD) between 2.5 and 4.0 mm suitable for stent implantation. There were no limitations on the number of treated lesions and vessels, or lesion length. Angiographic exclusion criteria included: a left main lesion, ostial lesion, severe calcification of the target lesion, or use of atherectomy before stenting.

Patients were randomly assigned to receive either valsartan (valsartan add-on group) or conventional treatment by non-ARB antihypertensives (non-ARB group). Patients in the valsartan add-on group were prescribed 40–80 mg/day starting the next morning following PCI and continuing for at least 3 years. **Figure 1** shows that 1 patient (0.52%) withdrew consent after eligibility.

Randomization was undertaken using the minimization method controlling for the following 2 factors: acute MI and participating institution.

Evaluation of Renal Function

The glomerular filtration rate was calculated for each patient according to the simplified Modification of Diet in Renal

Disease equation for Japanese,¹⁵ using the value of serum creatinine closest to the time of, but before, the index PCI. Patients were then stratified in 2 groups using the cut-off value $60 \text{ ml} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$ below which chronic kidney disease (moderate to severe renal impairment) is defined according to the latest National Kidney Foundation practice guidelines.¹⁶

Patient Follow up

Clinical follow up was scheduled for all patients at 6 months, 12 months, 18 months, 24 months, and then yearly for a total of 4 years after the procedure by office visit or direct telephone call to the patients. A follow-up angiography with quantitative coronary angiography (QCA) was systematically performed at 180 ± 30 days. The decision to perform further TLR after the 6-month angiographic follow up was left to the investigators' discretion.

PCI

Lesions were treated with the use of standard interventional techniques, and stenting without predilatation was allowed. After the stent had been implanted, further dilatation was performed as necessary to ensure that there was less than 20% residual stenosis, with a Thrombolysis In Myocardial Infarction grade III flow rate. Postprocedural dual antiplatelet therapy consisted of 81–250 mg/day aspirin, indefinitely, and 200 mg/day ticlopidine, for at least 4 weeks.

Coronary Lesion Analysis

Lesions were classified according to the modified American Heart Association/American College of Cardiology (AHA/ACC) classification.¹⁷ Lesions were measured on angiograms by experienced cardiologists. Lesion length, RVD, minimal lumen diameter (MLD), and percent diameter stenosis were measured in the Cardiovascular Measurement System (CMS, MEDIS, Leiden, The Netherlands).¹⁸

Clinical Outcomes

The primary endpoint was a composite of death from any cause, non-fatal acute MI, or TLR at 18 months. Secondary endpoints included the individual rates of death from any cause, non-fatal acute MI, TLR, stroke (hospitalization and

diagnosed by CT and/or MRI), heart failure (hospitalization, clinical symptoms, clinical signs, and the need for treatment with intravenous diuretics, vasodilators, or inotropic drugs), and the need for non-TLR at a long-term clinical follow up (median 4.4 years; interquartile range, 3.9–5.0). Elective angiographic control at 6 months was specified as a secondary endpoint.

Binary restenosis was considered as the occurrence of stenosis of >50% diameter in the stented lesions. Late lumen loss was defined as MLD at follow up minus post-procedural MLD measured by QCA. TLR was defined as a repeat intervention (PCI or coronary artery bypass graft) to treat a luminal stenosis within the stent or in the 5-mm distal or proximal segments adjacent to the stent. Non-TLR was defined as clinically driven revascularization of the lesions other than the target lesion. The diagnosis of MI during follow up was established whenever a Q-wave in at least 2 contiguous leads appeared on the electrocardiogram, or there was an elevation in serum creatine kinase-MB fraction levels >3 times the upper limit of the normal range.

Statistical Analysis

On the basis of the study in Japan, we had hypothesized that Japanese patients with coronary artery disease might have approximately 30% of composite cardiovascular events (death, non-fatal MI and TLR) in 18 months follow up after PCI with BMS. We estimated the number of enrolled patients as 240 (120 in each group) to validate the hypothesis under the assumption that the valsartan add-on group achieves a 40% risk reduction compared with the non-ARB group and gives 80% statistical power for detecting a clinical significance with a 2-tailed 5% statistical significant level. All analyses were based on the intention-to-treat principle. For continuous variables, data are presented as mean $\pm$ SD and were compared by the Student's t-test. For categorical numbers, data are shown as number and percentage, and were compared by the chi-square test. An event rate was estimated by the Kaplan-Meier approach. A Cox proportional hazard model was used to assess the risk of adverse events at long term clinical follow up after the index PCI. Multivariate analysis were performed to identify independent predictors of TLR, using clinical and angiographic variables of age, gender, diabetes status, concomitant antihypertensive treatment (use of valsartan, use of

Table 1. Baseline Clinical Characteristics

	Valsartan (n=90)	Non-ARB (n=101)	P value
Age (years)	64 $\pm$ 10	65 $\pm$ 9	0.31
Male gender	71 (79)	79 (78)	0.91
Hypertension	63 (70)	75 (74)	0.51
Dyslipidemia	63 (70)	72 (71)	0.85
Diabetes mellitus	36 (40)	46 (46)	0.44
Current smoker	45 (50)	51 (50)	0.95
Body mass index	24 $\pm$ 2.8	24 $\pm$ 2.6	0.31
SBP (mmHg)	134 $\pm$ 17	133 $\pm$ 19	0.96
DBP (mmHg)	76 $\pm$ 12	74 $\pm$ 13	0.43
Triple vessel disease	15 (17)	14 (14)	0.60
Prior MI	9 (10)	9 (9)	0.80
Prior PCI	15 (17)	15 (15)	0.73
Prior CABG	4 (4)	2 (2)	0.33
LVEF (%)	61 $\pm$ 11	62 $\pm$ 11	0.51
Acute MI	36 (40)	36 (36)	0.54
Q wave MI	17 (19)	15 (15)	0.46
CKD	23 (26)	34 (34)	0.22

Values are number of patients (%) or mean $\pm$ SD.

ARB, angiotensin II receptor blockers; SBP, systolic blood pressure; DBP, diastolic blood pressure; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; LVEF, left ventricular ejection fraction; CKD, chronic kidney disease.

ACE inhibitors, and use of calcium-channel blockers), small vessel size ($\leq$ 2.75 mm), and long lesion (>20 mm). A probability of <0.05 was considered significant. All statistical analyses were performed using the JMP for Windows, version 5.1 (SAS Institute, Cary, NC, USA).

Results

Baseline Characteristics

From August 2002 through December 2004, a total of 191 patients were randomized in this study. In December 2004, the enrollment was stopped because the use of DES had been expanded in Japan. **Table 1** shows the baseline clinical char-

Table 2. Medical Treatment

	Valsartan (n=90)	Non-ARB (n=101)	P value
Medical treatment before randomization			
Statins (%)	27 (30)	30 (30)	0.96
ACE inhibitors (%)	11 (12)	12 (12)	0.94
β -adrenergic blockers (%)	9 (10)	7 (7)	0.45
Calcium-channel blockers (%)	39 (43)	46 (46)	0.76
Nitrates (%)	27 (30)	30 (30)	0.96
Nicorandil (%)	12 (13)	20 (20)	0.23
Medical treatment at discharge			
Statins (%)	54 (60)	58 (57)	0.72
ACE inhibitors (%)	12 (13)	39 (39)	<0.001
β -adrenergic blockers (%)	14 (16)	16 (16)	0.96
Calcium-channel blockers (%)	30 (33)	53 (52)	0.008
Nitrates (%)	30 (33)	33 (33)	0.26
Nicorandil (%)	26 (29)	31 (31)	0.79

Values are number of patients (%) or mean $\pm$ SD.

ARB, angiotensin II receptor blockers; ACE, angiotensin-converting enzyme.

Lesions	Valsartan (n=111)	Non-ARB (n=127)	P value
Type B2 or C lesion*	68 (61)	67 (53)	0.19
Treated vessel			
Right coronary artery	42 (38)	49 (39)	0.83
Left anterior descending artery	40 (36)	49 (39)	
Left circumflex artery	29 (26)	29 (22)	
Restenotic lesion	4 (4)	2 (2)	0.32
Chronic total occlusion	5 (5)	3 (2)	0.36
Calcified lesion	14 (13)	18 (14)	0.72
Eccentric lesion	57 (51)	70 (55)	0.56
Diffuse lesion	17 (15)	19 (15)	0.94
Stents/patient	1.1±0.2	1.1±0.3	0.66
Stent diameter (mm)	3.2±0.4	3.2±0.5	0.95
Small-size stent use (≤2.75 mm)	26 (23)	29 (23)	0.91
Thin-strut stent use (≤0.10 mm)	89 (80)	93 (73)	0.21
Total stent length/lesion (mm)	19±8	19±8	0.77
Maximal balloon pressure (atm)	14±3	14±4	0.63
Bifurcation with kissing balloon technique	5 (5)	5 (4)	0.83
Direct stenting	19 (17)	14 (11)	0.18

Values are number of patients (%) or mean±SD. *American College of Cardiology/American Heart Association lesion classification.

ARB, angiotensin II receptor blockers.

acteristics for all the patients who were assigned to treatment. The 2 groups were similar with respect to all variables examined; all patients were Japanese, with a mean age of 64 years, a mean body mass index of 24 kg/m², and a mean systolic and diastolic blood pressure of 134/75 mmHg. About two-thirds were male. Clinical presentation at index PCI included 72 cases of acute MI (36 cases in the valsartan add-on group and 36 cases in the non-ARB group, P=0.54). As shown in Table 2, medical treatment before randomization was similar for the 2 groups; 30% of patients were receiving

statins, 12% ACE inhibitors, 7–10% β -adrenergic blockers, and 43–46% calcium-channel blockers. However, at discharge, approximately 60% of the patients were treated with statins in both groups (60% vs. 57%, P=0.72) and there was more use of ACE inhibitors (13% vs. 39%, P<0.001) and calcium-channel blockers (33% vs. 52%, P=0.008) in the non-ARB group than in the valsartan add-on group. At follow up, the mean systolic and diastolic blood pressure levels were 128±16/74±9.8 mmHg in the valsartan add-on group and 130±13/73±9.4 mmHg in the non-ARB group. Blood pressure

Table 4. Angiographic Results

	Valsartan (n=90)	Non-ARB (n=101)	P value
Lesion, n	111	127	
Lesion length (mm)	12.6±6.7	12.4±7.1	0.80
Reference vessel diameter (mm)	2.77±0.67	2.81±0.67	0.60
Pre-procedural MLD (mm)	0.54±0.46	0.59±0.46	0.36
Post-procedural MLD (mm)	2.91±0.56	2.99±0.67	0.26
Complete revascularization (%)	65 (72)	69 (68)	0.56
Angiographic follow-up (per lesion)	98 (88)	117 (92)	0.32
Follow-up MLD (mm)	1.98±0.85	1.80±0.90	0.13
Late lumen loss (mm)	0.95±0.76	1.20±0.92	0.037
Binary restenosis	22 (22)	30 (26)	0.59

Values are number of patients (%) or mean±SD.

ARB, angiotensin II receptor blockers; MLD, minimal lumen diameter.

Figure 3. Hazard ratios (closed square) with 95% confidential intervals (CI; bar) for primary and secondary endpoints. ARB, angiotensin II receptor blockers; MI, myocardial infarction; TLR, target lesion revascularization.

levels were not significantly different between the groups during follow up (systolic blood pressure, $P=0.23$; diastolic blood pressure, $P=0.38$)

The angiographic and procedural characteristics are shown in [Table 3](#). The lesions in the 2 groups were treated similarly with the use of conventional techniques. The choice of BMS was at the discretion of the operator; however, the distribution of commercially available stents in the 2 groups was similar. The valsartan add-on group consisted of 111 lesions and the non-ARB group consisted of 127 lesions.

Primary Endpoint

At 18 months, the incidence of the primary endpoint was 18.9% in the valsartan add-on group and 24.8% in the non-ARB group. The reduction of primary outcome did not

achieve statistical significance (hazard ratio [HR], 0.84; 95% confidence interval [CI], 0.61–1.14; $P=0.26$; [Figure 2A](#)).

Secondary Endpoints

Angiographic data at 6 months were available for 79 of the 90 patients (88%) in the valsartan add-on group and 91 of the 101 patients (90%) in the non-ARB group. The mean RVD of the target vessel and the mean length of the lesion at baseline were similar in the 2 groups. The mean MLDs of the stented segment before and after the procedure were similar between the 2 groups. At 6 months, the mean in-stent late luminal loss was significantly smaller (0.95 ± 0.76 mm vs. 1.20 ± 0.92 mm; $P=0.037$) in the valsartan add-on group than in the non-ARB group ([Table 4](#)). However, the binary restenosis rate was not significantly different between the 2 groups

Table 5. Multivariate Predictors of TLR at a Long-Term Follow-up

	HR	95%CI	P value
Age	0.98	0.46–0.94	0.32
Female gender	0.80	0.95–1.02	0.29
Diabetes mellitus	1.18	0.86–1.62	0.32
Use of valsartan	0.67	0.46–0.94	0.020
Use of ACE inhibitors	0.81	0.55–1.16	0.25
Use of calcium-channel blockers	0.96	0.69–1.33	0.80
Small vessel size (≤ 2.75 mm)	1.47	1.02–2.06	0.038
Long lesion (>20 mm)	1.76	1.29–2.45	<0.001

TLR, target lesion revascularization; HR, hazard ratio; CI, confidence interval; ACE, angiotensin-converting enzyme.

(22% vs. 26%; $P=0.59$).

There were no significant differences between the valsartan and the non-ARB groups in terms of all-cause death (7.9 vs. 6.2%), acute MI (4.7 vs. 7.2%), heart failure (1.1 vs. 3.0%), stroke (3.8 vs. 1.1%), non-TLR (20.4 vs. 22.3%) (Figure 3). No patients died from a cardiac cause in either group. However, at a median follow up at 4.4 years, TLR was performed in 14.5% in the valsartan add-on group and 27.8% of the patients in the non-ARB group (HR, 0.69; 95%CI, 0.49–0.96; $P=0.024$) (Figure 2B). Using a multivariate analysis after adjusting for confounders, valsartan add-on treatment (HR, 0.67; 95%CI, 0.46–0.94; $P=0.020$), small vessel size (HR, 1.47; 95%CI, 1.02–2.06; $P=0.038$), and long lesion (HR, 1.76; 95%CI, 1.29–2.45; $P<0.001$) were found to be the independent predictors of TLR after PCI with BMS (Table 5).

Among the patients who were randomly assigned to the valsartan add-on group, 86% were still taking valsartan at the end of the study. There were side effects that resulted in discontinuation (hypotension, 2%; renal dysfunction, 1%) in the valsartan add-on group. In addition, 2 patients (2%) were switched to other ARBs. In 7 patients (7%) from the non-ARB group, ARBs were prescribed at the end of the study.

Discussion

Valsartan treatment was not superior to non-ARB treatment in reducing the primary endpoint at 18 months after PCI. In a recent major trial in Japanese patients with hypertension and/or coronary artery disease, candesartan was similar to standard non-ARB treatment in reducing rates of cardiovascular events among patients with angiographically documented coronary artery disease.¹⁹ However, in the JIKEI-Heart Study, which included hypertensive patients with coronary artery disease and/or heart failure, valsartan add-on treatment significantly inhibited the incidence of cardiovascular mortality and morbidity.²⁰ At the time of this study, which was designed with a target of 120 patients in each group, the incidence of composite cardiovascular events was expected to be 30% in the non-ARB group. Because the study patients did not reach the target, and the incidence of the primary endpoint was lower than expected, the statistical power was considered insufficient for verification of the efficacy of valsartan. In addition, no patients died of a cardiac cause in either group at a long-term follow up (>4 years); this implies a selection for a very low-risk clinical population. Moreover, because the patients in the non-ARB group had received more ACE inhibitors and calcium-channel blockers than those in

the valsartan group, these drugs seemed to reduce the cardiovascular events after PCI.

This trend might be attributable to the previous studies regarding these agents.^{10,21} Because various kinds and doses of agents including ACE inhibitors and calcium-channel blockers were used, the assessment of such agents might be limited in the present study.

ARB and In-Stent Restenosis

Although the rate of binary restenosis revealed no statistically significant differences between the 2 groups, late lumen loss was significantly reduced in the valsartan add-on group compared with the non-ARB group at the 6-month follow up period.

In-stent restenosis occurs mainly from excessive neointimal formation.²² Neointimal formation after stent placement results from deep focal injury caused by the penetration of stent struts and the chronic presence of foreign body material. The amount of neointimal area is proportional to the severity of the injury inflicted on the arterial wall by the stent struts.²³ It has been reported that an ARB inhibits neointimal formation in the rat carotid injury model.²⁴ Patients receiving a low-dose oral administration of valsartan (80 mg/day), compared with placebo and ACE inhibitors in previous trials, showed a preventive effect on in-stent restenosis after BMS implantation.^{25,26} Conflicting results have been demonstrated with the use of other ARBs such as candesartan cilexetil²⁷ and losartan.²⁸ The effect of valsartan is likely to be, at least in part, a decrease in markers of inflammation.²⁸

Valsartan Dosage

Our study demonstrated that low-dose valsartan treatment (average of 60.7 mg/day) had a favorable effect on reducing TLR after coronary stenting. It has been previously shown that administration of a high-dose oral valsartan (160–320 mg/day) after implantation of BMS in type B2/C coronary artery lesions reduces angiographic in-stent restenosis, TLR, late lumen loss, and major cardiovascular event rates more effectively than a low-dose valsartan (80 mg/day).²⁹ However, several studies in Japanese patients have shown that a treatment with a daily dose of 80 mg valsartan has similar antihypertensive effects to that of 20 mg nifedipine³⁰ or 5 mg amlodipine.³¹ Doses of all antihypertensive drugs, including valsartan, were based on the guidelines of the Japanese Hypertension Society.³² In addition, our study was designed for coronary artery disease patients, including normotensive patients. The mean blood pressure at baseline was 134/75 mmHg, and therefore we considered that the dose of valsartan in the present study was adequate.

TLR

The prespecified secondary endpoint of TLR was lower in the valsartan add-on treatment group compared with the conventional non-ARB treatment at a median follow-up period of 4.4 years. Kaplan-Meier curves of probability of TLR have suggested that most of the difference in TLR was driven by surveillance angiography rather than clinical indications. Because ischemia testing was not required before follow-up angiography in this open study, revascularization decisions at angiographic follow-up might have been affected by treatment assignment. Moreover, Cutlip et al³³ reported that in multicenter trials, a follow-up angiography led to 44% more repeated interventions than studies without mandated angiography. This suggests that non-ischemia-producing lesions were treated at the time of follow-up angiography.

We identified valsartan add-on treatment, small vessel, and long lesion as independent predictors of TLR. The patients in the non-ARB group were treated with ACE inhibitors more frequently than those in the valsartan add-on group. In the large studies, ACE inhibitor therapy was shown to significantly increase the rate of in-stent restenosis after PCI with BMS.^{34,35} From our data, however, it appears unlikely that ACE inhibitor therapy could offer the same results as those obtained in these studies.

After coronary stent implantation, recognized predictors of increased restenosis include diabetes mellitus, small vessel diameter and long lesion. The effect of these variables could not be analyzed because of the sample size and study design. Whether the positive effect of valsartan on TLR rate is pronounced in diabetics and patients with small vessels or long lesions must be re-evaluated with a large number of study patients.

Study Limitations

Major limitations of the present study are the small sample size in both groups as well as the lack of mechanistic insight of valsartan's effect on reducing the need for TLR. Moreover, the present study was randomized, but was neither placebo-controlled nor blinded. Therefore, larger studies are needed to further elucidate the antirestenotic effect of valsartan. If larger trials can confirm the beneficial effects on reducing the need for TLR, this treatment with an orally taken drug might be a promising tool to modulate restenosis after coronary stenting. This might also be important with respect to DES, for which the restenosis rate is significantly lower compared with BMS. However, in more complex lesions, the binary restenosis rate is approximately 15% and is as high as 31% in small vessels, despite the use of DES, as shown in the TAXUS-V study.³⁶ Finally, intravascular ultrasound data were not available in this study and therefore it was not possible to analyze optimal stent expansion. In addition, we could not assess the shear stress at the site of the target lesion.

Conclusion

The valsartan treatment was not superior to the non-ARB treatment in reducing the primary endpoint at 18 months after the PCI with BMS. The pre-specified secondary endpoint of TLR was lower in the valsartan group compared with the non-ARB group. The angiographic data at 6 months supported this finding, with a significantly lower late lumen loss. Finally, the beneficial effects of valsartan on TLR need to be proven statistically with an adequate study sample.

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References

- Serruys PW, de Jaegere P, Kiemeneij F, Macaya C, Rutsch W, Heyndrickx G, et al. A comparison of balloon-expandable-stent implantation with balloon angioplasty in patients with coronary artery disease. *N Engl J Med* 1994; **331**: 489–495.
- Dussaillant GR, Mintz GS, Pichard AD, Kent KM, Salter LF, Popma JJ, et al. Small stent size and intimal hyperplasia contribute to restenosis: A volumetric intravascular ultrasound analysis. *J Am Coll Cardiol* 1995; **26**: 720–724.
- Morice MC, Serruys PW, Sousa JE, Fajadet J, Ban Hayashi E, Perin M, et al. A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. *N Engl J Med* 2002; **346**: 1773–1780.
- Stone GW, Ellis SG, Cox DA, Hermiller J, O'shaughnessy C, Mann JT, et al; TAXUS-IV Investigators. A polymer-based, paclitaxel-eluting stent in patients with coronary artery disease. *N Engl J Med* 2004; **350**: 221–231.
- Cheng CI, Lee FY, Chang JP, Hsueh SK, Hsieh YK, Fang CY, et al. Long-term outcomes of intervention for unprotected left main coronary artery stenosis: Coronary stenting vs coronary artery bypass grafting. *Circ J* 2009; **73**: 705–712.
- Park KW, Kang SH, Chung WY, Lee HY, Park JS, Kang HJ, et al. 'Real world' comparison of drug-eluting stents vs bare metal stents in the treatment of unselected patients with acute ST-segment elevation myocardial infarction. *Circ J* 2010; **74**: 1111–1120.
- Tamekiyo H, Hayashi Y, Toyofuku M, Ueda H, Tadamichi S, Okimoto T, et al. Clinical outcomes of sirolimus-eluting stenting after rotational atherectomy. *Circ J* 2009; **73**: 2042–2049.
- Takahashi S, Kaneda H, Tanaka S, Miyashita Y, Shiono T, Taketani Y, et al. Late angiographic stent thrombosis after sirolimus-eluting stent implantation. *Circ J* 2007; **71**: 226–228.
- Kaiser C, Brunner-La Rocca HP, Buser PT, Bonetti PO, Osswald S, Linka A, et al; BASKET investigators. Incremental cost-effectiveness of drug-eluting stents compared with a third-generation bare-metal stent in a real-world setting: Randomised Basal stent Kosten Effektivitäts trial (BASKET). *Lancet* 2005; **366**: 921–929.
- Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G. Effects of an angiotensin-converting enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients: The Heart Outcomes Prevention Evaluation Study Investigators. *N Engl J Med* 2000; **342**: 145–153.
- Otsuka M, Yamamoto H, Okimoto T, Dohi Y, Mito S, Gomyo Y, et al. Long-term effects of quinapril with high affinity for tissue angiotensin-converting enzyme after coronary intervention in Japanese. *Am Heart J* 2004; **147**: 662–668.
- Peters S, Götting B, Trümmel M, Rust H, Brattström X. Valsartan for prevention of restenosis after stenting of type B2/C lesions: The Val-PREST trial. *J Invasive Cardiol* 2001; **13**: 93–97.
- Yoshida O, Hirayama H, Nanasato M, Watanabe T, Murohara T. The angiotensin II receptor blocker candesartan cilexetil reduced neointimal proliferation after coronary stent implantation: A prospective randomized study under intravascular ultrasound guidance. *Am Heart J* 2005; **149**: e1–e6.
- Wakayama T, Ogawa H, Iida H, Takaki A, Iwami T, Mochizuki M, et al. Effects of candesartan and probucol on restenosis after coronary stenting: Results of stent intimal hyperplasia inhibition by new angiotensin II receptor antagonist (ISHIN) Trial. *Circ J* 2003; **67**: 519–524.
- Imai E, Horio M, Nitta K, Yamagata K, Iseki K, Hara S, et al. Estimation of glomerular filtration rate by the MDRD study equation modified for Japanese patients with chronic kidney disease. *Clin Exp Nephrol* 2007; **11**: 41–50.
- Levy AS, Coresh J, Balk E, Kausz AT, Levin A, Steffes MW, et al; National Kidney Foundation. National Kidney Foundation practice guidelines for chronic kidney disease: Evaluation, classification, and stratification. *Ann Intern Med* 2003; **139**: 137–147.
- Ellis SG, Vandormael MG, Cowley MJ, DiSciascio G, Deligonul U, Topol EJ, et al. Coronary morphologic and clinical determinants of procedural outcome with angioplasty for multivessel coronary disease: Implications for patient selection: Multivessel Angioplasty Prognosis Study Group. *Circulation* 1990; **82**: 1193–1202.
- van der Zwet PM, Reiber JH. A new approach for the quantification of complex lesion morphology: The gradient field transform; basic principles and validation results. *J Am Coll Cardiol* 1994; **24**: 216–224.
- Kasanuki H, Hagiwara N, Hosoda S, Sumiyoshi T, Honda T, Haze K, et al. 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.

20. Mochizuki S, Dahlöf B, Shimizu M, Ikewaki K, Yoshikawa M, Taniguchi I, et al. 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.
21. Bestenhorn HP, Neumann FJ, Büttner HJ, Betz P, Strüzenhofecker P, von Hondenberg E, et al. Evaluation of the effect of oral verapamil on clinical outcome and angiographic restenosis after percutaneous coronary intervention: The randomized, double-blind, placebo-controlled, multicenter verapamil slow-release for prevention of cardiovascular events after angioplasty (VESPA) trial. *J Am Coll Cardiol* 2004; **43**: 2160–2165.
22. Komatsu R, Ueda M, Naruko T, Kojima A, Becker AE. Neointimal tissue response at sites of coronary stenting in humans: Macroscopic, histological, and immunohistochemical analyses. *Circulation* 1998; **98**: 224–233.
23. Schwartz RS, Huber KC, Murphy JG, Edwards WD, Camrud AR, Vlietstra RE, et al. Restenosis and the proportional neointimal response to coronary artery injury: Results in a porcine model. *J Am Coll Cardiol* 1992; **19**: 267–274.
24. Nozawa Y, Matsuura N, Miyake H, Yamada S, Kimura R. Effects of TH-142177 on angiotensin II-induced proliferation, migration and intracellular signaling in vascular smooth muscle cells and on neointimal thickening after balloon injury. *Life Sci* 1999; **64**: 2061–2070.
25. Peters S, Götting B, Trümmel M, Rust H, Brattström A. Valsartan for prevention of restenosis after stenting of type B2/C lesions: The Val PREST trial. *J Invasive Cardiol* 2001; **13**: 93–97.
26. Peters S, Trümmel M, Meyners W, Koehler B, Westermann K, Trümmel Valsartan versus ACE inhibition after bare metal stent implantation: Results of the VALVLACE trial. *Int J Cardiol* 2005; **98**: 331–335.
27. Radke PW, Figulla HR, Drexler H, Klues HG, Mügge A, Silber S, et al; AACHEN Trial Investigators. A double-blind, randomized, placebo-controlled multicenter clinical trial to evaluate the effects of the angiotensin II receptor blocker candesartan cilexetil on intimal hyperplasia after coronary stent implantation. *Am Heart J* 2006; **152**: 761.e1–e6.
28. Iwata A, Miura S, Imaizumi S, Kiya Y, Nishikawa H, Zhang B, et al. Do valsartan and losartan have the same effects in the treatment of coronary artery disease? *Circ J* 2007; **71**: 32–38.
29. Peters S. Comparison of efficacy of low- (80 mg/day) and high- (160–320 mg/day) dose valsartan in the prevention of in-stent restenosis after implantation of bare-metal stents in type B2/C coronary artery lesions. *Am J Cardiovasc Drugs* 2008; **8**: 83–87.
30. Munakata M, Nagasaki A, Nunokawa T, Sakuma T, Kato H, Yoshinaga K, et al. Effects of valsartan and nifedipine coat-core on systemic arterial stiffness in hypertensive patients. *Am J Hypertens* 2004; **17**: 1050–1055.
31. Yasunari K, Maeda K, Watanabe T, Nakamura M, Yoshikawa J, Asada A. Comparative effects of valsartan versus amlodipine on left ventricular mass and reactive oxygen species formation by monocytes in hypertensive patients with left ventricular hypertrophy. *J Am Coll Cardiol* 2004; **43**: 2116–2123.
32. Ogihara T, Kikuchi K, Matsuoka H, Fujita T, Higaki J, Horiuchi M, et al; Japanese Society of Hypertension Committee. The Japanese Society of Hypertension Guidelines for the Management of Hypertension (JSH 2009). *Hypertens Res* 2009; **32**: 3–107.
33. Cutlip DE, Chauhan MS, Baim DS, Ho K, Popma JJ, Bachinsky W, et al. Clinical restenosis after coronary stenting: Perspectives from multicenter clinical trials. *J Am Coll Cardiol* 2002; **40**: 2082–2089.
34. Ribichini F, Wijns W, Ferreo V, Matullo G, Camilla T, Feola M, et al. Effect of angiotensin-converting enzyme inhibition on restenosis after coronary stenting. *Am J Cardiol* 2003; **91**: 154–158.
35. Jørgensen E, Kelbæk H, Helqvist S, Jensen GV, Saunamäki K, Kastrup J, et al. Predictors of coronary in-stent restenosis: Importance of angiotensin-converting enzyme gene polymorphism and treatment with angiotensin-converting enzyme inhibitors. *J Am Coll Cardiol* 2001; **38**: 1434–1439.
36. Stone GW, Ellis SG, Cannon L, Mann JT, Greenberg JD, Spriggs D, et al; TAXUS V Investigators. Comparison of a polymer-based paclitaxel-eluting stent with a bare metal stent in patients with complex coronary artery disease: A randomized controlled trial. *JAMA* 2005; **294**: 1215–1223.