Prevalence and Clinical Outcome of Polyvascular Atherosclerotic Disease in Patients Undergoing Coronary Intervention

Takashi Miura, MD; Yoshimitsu Soga, MD; Tatsuki Doijiri, MD; Hideaki Aihara, MD; Hiroyoshi Yokoi, MD; Masashi Iwabuchi, MD; Masakiyo Nobuyoshi, MD

Background: The goal of this study was to evaluate the prevalence and outcomes of polyvascular disease (polyVD; defined as lower extremity artery disease, carotid artery disease, renal artery disease, or abdominal aortic aneurysm) in patients undergoing percutaneous coronary intervention (PCI).

Methods and Results: The subjects were 1,597 patients who underwent PCI and who were prospectively enrolled in the study. The carotid, renal and peripheral arteries and abdominal aorta were simultaneously evaluated using duplex ultrasound and ankle-brachial index to evaluate the presence of polyVD. The primary endpoint was major adverse cardiovascular events (MACE: cardiovascular death, myocardial infarction [MI], and stroke). PolyVD was found in 446 of 1,597 patients (27.9%). MACE were significantly higher in the polyVD group compared to those with coronary artery disease (CAD) alone ($n=1,151$; 12.1% vs. 3.8%, $P<0.0001$). The incidence of cardiovascular death and stroke were significantly higher in the polyVD group (7.9% vs. 1.6%, $P<0.0001$; 3.6% vs. 1.2%, $P=0.006$, respectively). The incidence of MI was similar in the 2 groups (3.7% vs. 1.3%, $P=0.08$). The adjusted hazard ratios for MACE in patients with 1, 2, and 3 arterial beds (compared with CAD alone) increased from 1.64 to 1.74 to 10.62 ($P<0.0001$).

Conclusions: There was a high incidence of MACE in patients with polyVD undergoing PCI and this incidence increased with the number of arterial beds. (*Circ J* 2013; **77**: 89–95)

Key Words: Coronary intervention; Outcome; Polyvascular disease; Prevalence

The postoperative incidence of cardiovascular events is high after revascularization in patients with coronary artery disease (CAD).^{1,2} The major causes of death in these patients are cardiac death and vascular (excluding cardiac) death.³ Patients with CAD with one or more atherosclerotic lesions have a poor prognosis^{4,5} that is not improved by revascularization in patients with stable angina.¹ Little is known, however, about the long-term outcomes of CAD in patients with one or more atherosclerotic lesions after revascularization. Therefore, we investigated the prevalence and outcome of patients with and without polyvascular disease (polyVD) after successful percutaneous coronary intervention (PCI).

ative atherosclerotic lesions in patients with CAD requiring revascularization. Duplex ultrasound and ankle-brachial index (ABI) are safe and practical methods for detection of polyVD in screening of the carotid, renal and lower extremity arteries, and the abdominal aorta.^{6,7} Therefore, these approaches were used in the present study. The prevalence of polyVD has not been systematically evaluated in patients undergoing PCI. Therefore, the goal of the study was to determine this prevalence and to evaluate the impact of polyVD on prognosis in this patient group.

Methods

Study Design

This study was performed at a single center over 24 months. The subjects were patients with CAD who underwent successful PCI (defined as $<30\%$ of residual stenosis without any complications). The prevalence of polyVD and the outcome for

Editorial p43

PolyVD was defined as lower extremity artery disease (LEAD), carotid artery disease (CaAD), renal artery disease (RAD), or abdominal aortic aneurysm (AAA), as representa-

Received April 23, 2012; revised manuscript received July 29, 2012; accepted August 29, 2012; released online September 26, 2012 Time for primary review: 13 days

Department of Cardiology, Kokura Memorial Hospital, Kitakyushu (T.M., Y.S., H.A., H.Y., M.I., M.N.); Department of Cardiology, Yamatoseiwa Hospital, Yamato (T.D.), Japan

Mailing address: Takashi Miura, MD, Department of Cardiology, Kokura Memorial Hospital, 1-2-3 Asano, Kokurakita-ku, Kitakyushu 802-0001, Japan. E-mail: miuramen10miuramen@yahoo.co.jp

ISSN-1346-9843 doi:10.1253/circj.CJ-12-0535

All rights are reserved to the Japanese Circulation Society. For permissions, please e-mail: cj@j-circ.or.jp

patients with and without polyVD were examined. Exclusion criteria included symptomatic heart failure, dementia, inability to adopt a supine position due to orthopedic or neurological limitations, access site-related complications, persistent chest pain, new ST-segment deviation, or a major life-threatening illness. Patients who were unwilling or unable to provide informed consent were also excluded.

The carotid and renal arteries and abdominal aorta were simultaneously examined by 6 experienced sonographers who were trained to achieve inter-rater consistency. The results were verified by 2 or more sonographers. Study enrollment was performed after approval of the hospital ethics committee and after informed consent was obtained. This study (Prevalence of Peripheral Artery Disease) is registered with the University Hospital Medical Information Network-Clinical Trials Registry (UMIN-CTR), as accepted by the International Committee of Medical Journal Editors (No. UMIN000002486).

Study Endpoints

The goals of the study were to determine the prevalence of polyVD (defined as LEAD, CaAD, RAD or AAA) in patients undergoing PCI and to examine the impact of polyVD on prognosis. The primary endpoint was the incidence of major adverse cardiovascular events (MACE: cardiovascular death, myocardial infarction [MI] and stroke). The secondary endpoints were cardiovascular death, non-fatal MI, and stroke.

Study Procedure

All patients were pretreated with ticlopidine (200 mg daily) or clopidogrel (75 mg daily), in addition to aspirin (100–200 mg daily). A loading dose of 300 mg of clopidogrel was given to patients who had not previously taken this drug. Aspirin and ticlopidine were started at least 2 days before elective stenting. After discharge from hospital, lifelong oral aspirin was recommended, with oral thienopyridine for at least 1 month after placement of a bare-metal stent (BMS) or lifelong after placement of a drug-eluting stent (DES), but without oral thienopyridine after balloon angioplasty. Clinical follow-up was performed at 1, 6, 12, and 24 months. When a subject was judged to have reached the study endpoint, the event was validated by the Event Advisory Committee.

Definitions

The presence of LEAD was defined as ABI <0.9⁸ or a history

of endovascular or surgical revascularization. CaAD was defined as a peak systolic velocity (PSV) >125 cm/s⁹ or a history of endovascular or surgical treatment. No detectable signal was graded as complete or near occlusion. RAD was defined as PSV >180 cm/s in the renal artery and a PSV ratio for the renal artery and the aorta (renal aorta ratio; RAR) >3.5,¹⁰ or a history of endovascular or surgical revascularization. AAA was defined as aortic diameter >30 mm¹¹ or a history of endovascular or surgical repair.

B-mode grayscale images of the abdominal aorta were obtained in transverse and longitudinal projections. Hypertension was defined as systolic blood pressure (BP) ≥140 mmHg, diastolic BP ≥90 mmHg, or ongoing therapy for hypertension. Dyslipidemia was defined as a serum total cholesterol concentration ≥220 mg/dl, a low-density lipoprotein-cholesterol concentration ≥140 mg/dl, or current treatment with lipid-lowering therapy. Diabetes was defined as HbA_{1c} >6.5%, a casual plasma glucose >200 mg/dl, or current treatment with oral hypoglycemic agents or insulin injection. Smoking was defined as being a current smoker. CAD was defined as >75% reduction of lumen diameter on coronary angiography. The number of diseased vessels was classified as 1-vessel disease (VD), 2-VD or 3-VD. Left main trunk disease was classified as 2-VD. Body mass index was defined as weight in kilograms divided by height in meters squared. Elderly patients were defined as those aged ≥70 years old. Left ventricular ejection fraction (LVEF) was measured on echocardiography and LVEF <40% was regarded as LV dysfunction. Chronic kidney disease (CKD) was defined as creatinine clearance <30 ml/min estimated using the Cockcroft-Gould formula.

Patients in whom any lesion was found were treated if they met the current guidelines and consented to treatment. Medication with oral drugs was given at discharge. The composite outcome of ischemic events was defined as cardiovascular death, MI, and stroke. The definition of cardiovascular death included any deaths with an immediate cardiovascular cause, sudden deaths with unknown cause. MI was typically defined as creatine kinase (CK) or CK-MB above the upper limit of normal at Kokura Memorial Hospital or as development of significant Q waves in at least 2 contiguous leads of an electrocardiogram, and stroke was defined as ischemic stroke diagnosed by a neurologist.

Table 1. Patient Characteristics

	Total (n=1,597)	PolyVD(+) (n=446)	CAD alone (n=1,151)	P-value
Age (years)	71.0±10.0	73.3±9.0	68.9±10.1	0.0001
≥70	836 (52.3)	303 (67.9)	553 (46.3)	<0.0001
Male gender	1,201 (75.3)	346 (77.6)	855 (74.2)	0.17
BMI (kg/m ²)	23.8±3.4	23.3±3.7	24.0±3.2	0.14
Hypertension	1,303 (81.6)	387 (86.7)	916 (79.6)	0.001
Dyslipidemia	926 (60.0)	239 (53.6)	688 (59.8)	0.027
Diabetes mellitus	739 (46.3)	220 (49.3)	519 (45.0)	0.13
Insulin use	90 (5.6)	40 (9.0)	50 (4.3)	0.0003
Current smoker	356 (22.3)	115 (25.8)	241 (20.9)	0.037
Previous PCI	776 (48.6)	222 (49.8)	554 (48.1)	0.56
Previous CABG	97 (6.1)	43 (9.6)	54 (4.7)	0.0002
Previous stroke	149 (9.3)	63 (14.1)	86 (7.5)	<0.0001
Previous MI	431 (27.0)	113 (25.3)	318 (27.6)	0.35
History of HF	142 (8.9)	58 (13.0)	84 (7.3)	0.0003
LV dysfunction	103 (6.5)	47 (10.5)	56 (4.9)	<0.0001
Chronic kidney disease	164 (10.3)	90 (20.2)	74 (6.4)	<0.0001
Hemodialysis (%)	105 (6.6)	54 (12.1)	51 (4.4)	<0.0001
CKD non-HD (%)	70 (4.4)	40 (9.0)	30 (2.6)	<0.0001
Medication				
Aspirin	1,519 (95.1)	427 (95.7)	1,091 (86.7)	0.43
Thienopyridines	1,401 (87.7)	403 (90.4)	998 (86.7)	0.26
β-blockers	441 (27.6)	128 (28.7)	313 (27.2)	0.55
ACEI/ARB	878 (55.0)	265 (59.4)	613 (53.3)	0.026
Statins	870 (54.5)	234 (52.5)	636 (55.3)	0.32
Diuretics	272 (17.0)	108 (24.2)	164 (14.2)	<0.0001
Lesion				
Use of DES	591 (37.0)	177 (39.6)	414 (36.0)	0.17
ACS	242 (15.2)	61 (13.7)	181 (15.7)	0.31
2 vessels	305 (19.1)	92 (20.6)	213 (18.5)	0.33
3 vessels	70 (4.4)	24 (5.4)	46 (4.0)	0.23

Data given as mean ± SD or n (%).

ACEI, angiotensin-converting enzyme inhibitor; ACS, acute coronary syndrome; ARB, angiotensin receptor blocker; BMI, body mass index; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CKD, chronic kidney disease; DES, drug-eluting stent; HD, hemodialysis; HF, heart failure; LV, left ventricular; MI, myocardial infarction; PCI, percutaneous coronary intervention; polyVD, polyvascular disease.

Statistical Analysis

Continuous variables are reported as mean ± SD unless otherwise indicated. Continuous variables were compared using unpaired t-test or Wilcoxon rank sum test on the basis of the normality of the distribution. Categorical variables were compared by chi-squared test. A multivariate logistic regression model was used to identify independent risk factors for polyVD. The model included pre-specified risk factors of old age, hypertension, hyperlipidemia, current smoker, previous coronary artery bypass grafting (CABG), previous stroke, history of heart failure, CKD, LV dysfunction, use of angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs), use of insulin, and use of diuretics. The results of this analysis are expressed as hazard ratios (HR) for the comparison of risk with 95% confidence intervals (CI). P<0.05 was considered to be significant.

Survival curves were estimated using the Kaplan-Meier method and compared by log-rank test. All analyses were based on an intention-to-treat (ITT) principle. HR, 95% CI, and P-values were calculated using models adjusted for age, gender, hypertension, hyperlipidemia, current smoker, previous CABG,

previous stroke, history of heart failure, CKD, use of ACEI/ARBs, and use of insulin. P<0.05 was also considered to be significant in this analysis.

Results

Subjects

A total of 1,711 patients treated between November 2007 and October 2009 were considered eligible for the study, of whom 114 (6.6%) were subsequently excluded based on the exclusion criteria or failure to obtain consent. Therefore, 1,597 patients were enrolled, including 446 diagnosed with polyVD and 1,151 with CAD alone (Figure 1).

Baseline Demographics

Patient baseline demographics are listed in Table 1. Patients with polyVD were older and had higher rates of hypertension, dyslipidemia, current smoking, CKD, history of heart failure, LV dysfunction, history of CABG, history of stroke, and use of ACEI/ARBs, diuretics and insulin compared to patients without polyVD.

Table 2. Univariate and Multivariate Predictors of PolyVD

	Unadjusted		Adjusted	
	HR (95%CI)	P-value	HR (95%CI)	P-value
Old age	2.46 (1.95–3.09)	<0.0001	2.80 (2.18–3.60)	<0.0001
Hypertension	1.68 (1.24–2.29)	0.001	1.50 (1.07–2.10)	0.02
Current smoker	1.31 (1.02–1.69)	0.037	1.78 (1.34–2.36)	<0.0001
Previous CABG	2.17 (1.43–3.29)	0.0003	2.07 (1.32–3.24)	0.016
Previous stroke	2.04 (1.44–2.88)	<0.0001	1.76 (1.22–2.55)	0.003
CKD	3.68 (2.65–5.12)	<0.0001	3.75 (2.63–5.37)	<0.0001
Use of insulin	2.17 (1.41–3.34)	0.0004	1.80 (1.12–2.89)	0.002

Adjusted result were adjusted for old age, hypertension, hyperlipidemia, current smoker, CKD, history of HF, previous CABG, previous stroke, use of ACEIs or ARBs, use of insulin, and use of diuretics.
CI, confidence interval; HR, hazard ratio. Other abbreviations as in Table 1.

Endpoints

During the observation period, 38 patients dropped out or withdrew informed consent. Therefore, clinical follow-up was completed in 1,559/1,597 patients (97.6%). PolyVD was found in 446 (27.9%) of the 1,597 patients: PAD in 301 (18.8%), CaAD in 115 (7.2%), RAD in 64 (4.1%), and AAA in 96 (6.0%). Thus, 1,151 patients (72.1%) had CAD alone, and 331 (20.7%), 97 (6.1%), 17 (1.1%) and 1 (0.1%) had 1, 2, 3 and 4 arterial beds, respectively, in addition to CAD. The prevalence of polyVD based on the number of diseased cardiac vessels was 27.0% (333/1,233), 30.3% (91/300), and 34.4% (22/64) in patients with 1-, 2- and 3-VD, respectively. There was a trend for an increase in prevalence with an increased number of VD, but no significant difference among these groups.

Multivariate logistic analysis was performed using 12 pre-specified potential risk factors to estimate the determinants of polyVD. Old age (HR, 2.80; 95% CI: 2.18–3.60, $P<0.0001$), hypertension (HR, 1.50; 95% CI: 1.07–2.10, $P=0.02$), current smoker (HR, 1.78; 95% CI: 1.34–2.36, $P<0.0001$), previous CABG (HR, 2.07; 95% CI: 1.32–3.24, $P=0.016$), previous stroke (HR, 1.76; 95% CI: 1.22–2.55, $P=0.003$), CKD (HR, 3.75; 95% CI: 2.63–5.37, $P<0.0001$), and use of insulin (HR, 1.80; 95% CI: 1.12–2.89, $P=0.002$) were independent determinants of polyVD (Table 2). CKD had the strongest association with polyVD in this study.

The incidence of MACE was significantly higher in patients with polyVD than in patients with CAD alone (12.1% vs. 3.8%, $P<0.0001$). There was a significant difference in the incidence of MACE between the polyVD and CAD alone groups on ITT analysis (12.1% vs. 3.8%, $P<0.0001$). The incidences of stroke and cardiovascular death were significantly higher in the polyVD group on ITT analysis (3.6% vs. 1.2%, $P=0.006$; 7.9% vs. 1.6%, $P<0.0001$, respectively). The incidence of MI had a trend toward increase in the polyVD group, but was not significantly different between the 2 groups (3.7% vs. 1.3%, $P=0.08$; Figure 2).

All-cause mortality was significantly higher in the polyVD group (14.1% vs. 4.3%, $P<0.0001$). The major cause of death was cardiovascular death in both groups. The incidence of MACE significantly increased with the number of vascular beds. The adjusted HR for MACE in patients with 1, 2, or 3 arterial beds (compared with CAD alone) increased from 1.64 to 1.74 to 10.62 ($P<0.0001$). After correction of each endpoint for age, gender, hypertension, dyslipidemia, current smoker, CKD, history of heart failure, history of CABG, history of stroke, and use of insulin, the polyVD group had a significantly higher incidence of MACE (HR, 2.09; 95% CI: 1.32–3.30, adjusted $P=0.0017$), cardiovascular death (HR, 2.82; 95%

CI: 1.60–5.3, adjusted $P=0.0013$), and stroke (HR, 2.08; 95% CI: 0.94–4.59, adjusted $P=0.069$). In contrast, the incidence of MI was similar in the 2 groups (HR, 1.43; 95% CI: 0.64–3.19, adjusted $P=0.38$; Table 3).

Discussion

Severe CAD

The Japanese CAD (JCAD) study identified baseline characteristics and prognosis of all patients with CAD.¹² With regard to risk factors, prevalence of dyslipidemia and hypertension and diabetes mellitus was 57.6%, 54.6%, and 40.3%, respectively in the JCAD study and 60%, 81.6%, and 46.3%, respectively in the current study. This suggests that prevalence of risk factors may increase with severity of CAD. The rate of all-cause death and cardiovascular death and MI at 2-year follow-up was 3.5%, 1.8%, and 1.4%, respectively in the JCAD study and 7.1%, 3.3%, and 1.9%, respectively in the current study. This suggests that the rate of cardiovascular events increases with severity of CAD.

PolyVD

Atherosclerosis is the leading cause of morbidity and mortality worldwide^{13,14} and is expected to be the primary cause of death until the year 2020, despite ongoing efforts to extend primary and secondary prevention to high-risk individuals.¹⁵ Atherothrombotic diseases are currently referred to as “polyvascular disease”, and most reports of polyVD discuss LEAD, cerebrovascular disease, and CAD. In addition to these conditions, we included RAD and AAA in our definition of polyVD. RAD (especially that with $\geq 75\%$ stenosis and bilateral RAD) is an independent prognostic factor¹⁶ with extremely poor 5-year survival rates: 45.5% and 36.4% for RAD complicated with CAD and with both CAD and LEAD, respectively.¹⁷ Screening on duplex ultrasound is effective for reduction of AAA-related mortality, but not for reduction of all-cause mortality, because AAA contributes to $<3\%$ of all deaths. The main cause of death is a cardiovascular cause (44%) in patients with AAA >30 mm,¹¹ which suggests that these patients tend to have more polyVD.

Prevalence of PolyVD

Approximately 1 out of 4 CAD patients who underwent PCI had polyVD in the present study. The Reduction of Atherothrombosis for Continued Health (REACH) registry in Japan found a prevalence of 22.4% for polyVD (excluding RAS and AAA) in stable outpatients with CAD,¹⁸ and we found a prevalence of 22.9% for polyVD (excluding RAS and AAA) in

Figure 2. Cumulative incidence of (A) major adverse cardiovascular events (MACE; includes cardiovascular death, myocardial infarction [MI], and stroke), (B) cardiovascular death, (C) stroke and (D) MI between patients with polyvascular disease (polyVD) and those with coronary artery disease (CAD) alone. On intention-to-treat analysis: (A) the incidence of MACE was significantly higher in the polyVD group (12.1% vs. 3.8%, $P < 0.0001$); (B) the incidence of cardiovascular death and (C) stroke were significantly higher in the polyVD group (7.9% vs. 1.6%, $P < 0.0001$; 3.1% vs. 1.2%, $P = 0.006$, respectively); and (D) the incidence of MI was similar in both groups (2.7% vs. 1.6%, $P = 0.08$). PCI, percutaneous coronary intervention.

Table 3. Primary and Secondary Endpoints

Outcome	PolyVD(+) (n=446), n (%)	CAD alone (n=1,151), n (%)	Unadjusted		Adjusted	
			HR (95%CI)	P-value	HR (95%CI)	P-value
Primary endpoints						
MACE (cardiovascular death, MI, or stroke)	54 (12.1)	44 (3.8)	3.47 (2.29–5.25)	<0.0001	2.09 (1.32–3.30)	0.0017
Secondary endpoints						
Cardiovascular death	35 (7.9)	18 (1.6)	5.36 (3.00–9.57)	<0.0001	2.82 (1.60–5.31)	0.0013
Stroke	16 (3.6)	14 (1.2)	3.02 (1.46–6.25)	0.003	2.08 (0.94–4.59)	0.069
MI	12 (2.7)	18 (1.6)	1.74 (0.83–3.64)	0.14	1.43 (0.64–3.19)	0.38

Results were adjusted for age, gender, hypertension, hyperlipidemia, current smoker, CKD, history of HF, history of CABG, history of stroke, and use of insulin.

MACE, major adverse cardiovascular events. Other abbreviations as in Tables 1,2.

patients who underwent PCI. These results suggest that the prevalence of polyVD in patients who undergo PCI, including those with acute coronary syndrome (ACS), is similar to that in stable outpatients.

A history of treatment for polyVD was found in 133/446 (29.8%) of the present patients with polyVD, while de novo lesions were detected using ABI and duplex ultrasound in 313/446 (70.2%). This indicates that approximately 70% of the patients with polyVD had been underdiagnosed and were asymptomatic or had atypical symptoms, despite being at increased risk for morbidity and mortality. This suggests that systematic screening on duplex ultrasound and ABI may be useful to detect polyVD and identify patients at a high risk for cardiovascular events.

Predictors of PolyVD

A prior report found that the incidence of smoking and hypertension, and the presence of cerebrovascular disease were predictors of polyVD.¹⁹ In the current study, we found that old age, hypertension, current smoker, previous CABG, previous stroke, CKD, and use of insulin were predictors of polyVD in patients undergoing PCI. Thus, systematic screening using duplex ultrasound and ABI may be useful in patients with one or more of these risk factors.

Incidence of MACE in PolyVD Patients

Patients with polyVD had a significantly higher rate of cardiovascular events. The incidence of MACE in patients with and without polyVD (excluding AAA, RAS) was 12.7% and 6.1%, respectively, at 2-year follow-up in the European REACH registry,²⁰ and 12.1% and 3.8%, respectively, in the current study. The rate of MACE in all patients with polyVD was similar between the 2 registries. The cardiovascular event rate in patients with polyVD who underwent PCI and in stable outpatients with polyVD was similar, which suggests that screening for polyVD should be performed carefully in both groups.

The incidences of stroke and cardiovascular death were significantly higher in the present polyVD group. This is similar to that of other large-scale registries,^{4,20} but a different result was obtained for the incidence of MI. MI most frequently evolves from mild to moderate stenotic lesions, but 30–40% of cases of MI evolve from severe stenotic lesions.²¹ It is generally accepted that PCI for severe stenotic lesions reduces recurrent ACS in patients with unstable disease.²² In the present study, almost all patients had undergone complete revascularization up to at least 1 month after enrollment and all received follow-up on coronary angiography or computed tomographic angiography at 6 and 12 months after PCI. Thus,

we could have detected and performed revascularization on progressive lesions before the onset of ACS.

The incidence of MACE significantly increased with the number of arterial beds. In particular, the adjusted HR for MACE significantly increased from 2 to 3 arterial beds (from 1.74 to 10.62, $P<0.0001$). This indicates that cardiovascular events dramatically increase with the number of arterial beds in patients undergoing PCI. Therefore, early detection and more aggressive therapeutic intervention are recommended for patients with polyVD in this high-risk group.

Therapy for PolyVD

It has been shown that dual antiplatelet therapy with thienopyridines and aspirin has no significant benefit in patients at high risk for atherothrombotic events, compared with aspirin alone.²³ In the present study, after discharge from hospital, lifelong oral aspirin was recommended, with oral thienopyridine for at least 1 month after placement of a BMS or lifelong after placement of a DES. The incidence of MACE did not differ significantly between patients treated with DESs and BMSs (6.5% vs. 5.9%, $P=0.87$). In the polyVD group alone, there was also no significant difference in MACE between DES and BMS treatment (8.1% vs. 8.4%, $P=0.87$). This suggested that dual antiplatelet therapy with thienopyridines and aspirin had no significant benefit for atherothrombotic events in the present study, compared with aspirin alone. It has been shown that intensive lipid-lowering therapy with statins has significant clinical benefit in patients with stable CAD,²⁴ and cerebrovascular disease.²⁵ Therefore, aggressive therapy using statins may be useful for reducing ischemic events in patients with polyVD.

Limitations and Conclusion

This study had several limitations. First, although it was performed as a large-scale prospective observational study, it was also a single high-volume center study. Therefore, patients with more severe CAD may have been recruited to this study as compared to standard city hospitals. Second, the subjects were patients with CAD who underwent PCI successfully, excluding the patients who underwent PCI unsuccessfully. Third, there are severe restrictions on the indications for medication in Japan. Although Japanese guidelines clearly recommend use of statins and ACEI/ARBs for the secondary prevention of CAD, these medications are not covered by health insurance for atherosclerosis alone and CAD alone in Japan. It was difficult to use statins for CAD without dyslipidemia and ACEI/ARB for CAD without hypertension or congestive heart failure in Japan. Therefore use of these medications was relatively lower in this study

than in studies from other countries. These results are similar to that of the REACH registry⁵ and other Japanese studies.^{26,27} Fourth, there were no data on DAPT continuation at 2-year follow-up, or on medication such as cilostazol and sarpogrelate at baseline.

Within these limitations, we conclude that the incidence of MACE is significantly increased by polyVD in patients undergoing PCI and is further increased in those with a greater number of arterial beds.

Disclosures

Financial Support: None. Conflict of Interest: None of the authors have a real or perceived conflict of interest regarding the work in the manuscript.

References

1. Boden WE, O'Rourke RA, Teo KK, Hartigan PM, Maron DJ, Kostuk WJ, et al; COURAGE Trial Research Group. Optimal medical therapy with or without PCI for stable coronary disease. *N Engl J Med* 2007; **356**: 1503–1516.
2. Kimura T, Morimoto T, Furukawa Y, Nakagawa Y, Shizuta S, Ehara N, et al. Long-term outcomes of coronary-artery bypass graft surgery versus percutaneous coronary intervention for multivessel coronary artery disease in the bare-metal stent era. *Circulation* 2008; **118**: S199–S209.
3. Yamaji K, Kimura T, Morimoto T, Nakagawa Y, Inoue K, Soga Y, et al. Very long-term (15 to 20 years) clinical and angiographic outcome after coronary bare metal stent implantation. *Circ Cardiovasc Interv* 2010; **3**: 468–475.
4. Bhatt DL, Eagle KA, Ohman EM, Hirsch AT, Goto S, Mahoney EM, et al; REACH Registry Investigators. Comparative determinants of 4-year cardiovascular event rates in stable outpatients at risk of or with atherothrombosis. *JAMA* 2010; **304**: 1350–1357.
5. Steg PG, Bhatt DL, Wilson PW, D'Agostino R Sr, Ohman EM, Röther J, et al; REACH Registry Investigators. One-year cardiovascular event rates in outpatients with atherothrombosis. *JAMA* 2007; **297**: 1197–1206.
6. Olin JW, Kaufman JA, Bluemke DA, Bonow RO, Gerhard MD, Jaff MR, et al; American Heart Association. Atherosclerotic vascular disease conference: Writing Group IV: Imaging. *Circulation* 2004; **109**: 2626–2633.
7. Hirsch AT, Criqui MH, Treat-Jacobson D, Regensteiner JG, Creager MA, Olin JW, et al. Peripheral arterial disease detection, awareness, and treatment in primary care. *JAMA* 2001; **286**: 1317–1324.
8. Criqui MH, Denenberg JO, Bird CE, Fronek A, Klauber MR, Langer RD. The correlation between symptoms and non-invasive test results in patients referred for peripheral arterial disease testing. *Vasc Med* 1996; **1**: 65–71.
9. Steinvil A, Sadeh B, Arbel Y, Justo D, Belei A, Borenstein N, et al. Prevalence and predictors of concomitant carotid and coronary artery atherosclerotic disease. *J Am Coll Cardiol* 2011; **57**: 779–783.
10. Hoffmann U, Edwards JM, Carter S, Goldman ML, Harley JD, Zaccardi MJ, et al. Role of duplex scanning for the detection of atherosclerotic renal artery disease. *Kidney Int* 1991; **39**: 1232–1239.
11. Ashton HA, Buxton MJ, Day NE, Kim LG, Marteau TM, Scott RA, et al; Multicentre Aneurysm Screening Study Group. The Multicentre Aneurysm Screening Study (MASS) into the effect of abdominal aortic aneurysm screening on mortality in men: A randomised controlled trial. *Lancet* 2002; **360**: 1531–1539.
12. Japanese Coronary Artery Disease (JCAD) Study Investigators. Current status of the background of patients with coronary artery disease in Japan. *Circ J* 2006; **70**: 1256–1262.
13. Viles-Gonzalez JF, Fuster V, Badimon JJ. Atherothrombosis: A widespread disease with unpredictable and life-threatening consequences. *Eur Heart J* 2004; **25**: 1197–1207.
14. The World Health Report. Reducing risks, promoting healthy lives. Geneva: World Health Organization, 2002.
15. Murray CJ, Lopez AD. Alternative projections of mortality and disability by cause 1990–2020: Global Burden of Disease Study. *Lancet* 1997; **349**: 1498–1504.
16. Conlon PJ, Little MA, Pieper K, Mark DB. Severity of renal vascular disease predicts mortality in patients undergoing coronary angiography. *Kidney Int* 2001; **60**: 1490–1497.
17. Conlon PJ, O'Riordan E, Kalra PA. New insights into the epidemiologic and clinical manifestations of atherosclerotic renovascular disease. *Am J Kidney Dis* 2000; **35**: 573–587.
18. Yamazaki T, Goto S, Shigematsu H, Shimada K, Uchiyama S, Nagai R, et al. Prevalence, awareness and treatment of cardiovascular risk factors in patients at high risk of atherothrombosis in Japan. *Circ J* 2007; **71**: 995–1003.
19. Elsharawy MA, Alkhadra AH, Ibrahim MFA, Selim F, Hassan K, Elsaid AS, et al. Impact of atherosclerosis risk factors on the clinical presentation of arterial occlusive disease in Arabic patients. *Int J Angiol* 2008; **17**: 203–206.
20. Suarez C, Zeymer U, Limbourg T, Baumgartner I, Cacoub P, Poldermans D, et al. Influence of polyvascular disease on cardiovascular event rates: Insights from the REACH Registry. *Vasc Med* 2010; **15**: 259–265.
21. Falk E, Shah PK, Fuster V. Coronary plaque disruption. *Circulation* 1995; **92**: 657–671.
22. Nishigaki K, Yamazaki T, Kitabatake A, Yamaguchi T, Kanmatsuse K, Kodama I, et al. Percutaneous coronary intervention plus medical therapy reduces the incidence of acute coronary syndrome more effectively than initial medical therapy only among patients with low-risk coronary artery disease: A randomized, comparative, multicenter study. *JACC Cardiovasc Interv* 2008; **1**: 469–479.
23. Bhatt DL, Fox KA, Hacke W, Berger PB, Black HR, Boden WE, et al. Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. *N Engl J Med* 2006; **354**: 1706–1717.
24. LaRosa JC, Grundy SM, Waters DD, Shear C, Barter P, Fruchart JC, et al. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. *N Engl J Med* 2005; **352**: 1425–1435.
25. Amarenco P, Bogousslavsky J, Callahan A 3rd, Goldstein LB, Hennerici M, Rudolph AE, et al. High-dose atorvastatin after stroke or transient ischemic attack. *N Engl J Med* 2006; **355**: 549–559.
26. Funakoshi S, Furukawa Y, Ehara N, Morimoto T, Kaji S, Kimura T, et al. Clinical characteristics and outcomes of Japanese women undergoing coronary revascularization therapy. *Circ J* 2011; **75**: 1358–1367.
27. Ogita M, Miyauchi K, Kurata T, Yokoyama K, Dohi T, Tuboi S, et al. Clinical impact of angiographic restenosis after bare-metal stent implantation on long-term outcomes in patients with coronary artery disease. *Circ J* 2011; **75**: 2566–2572.