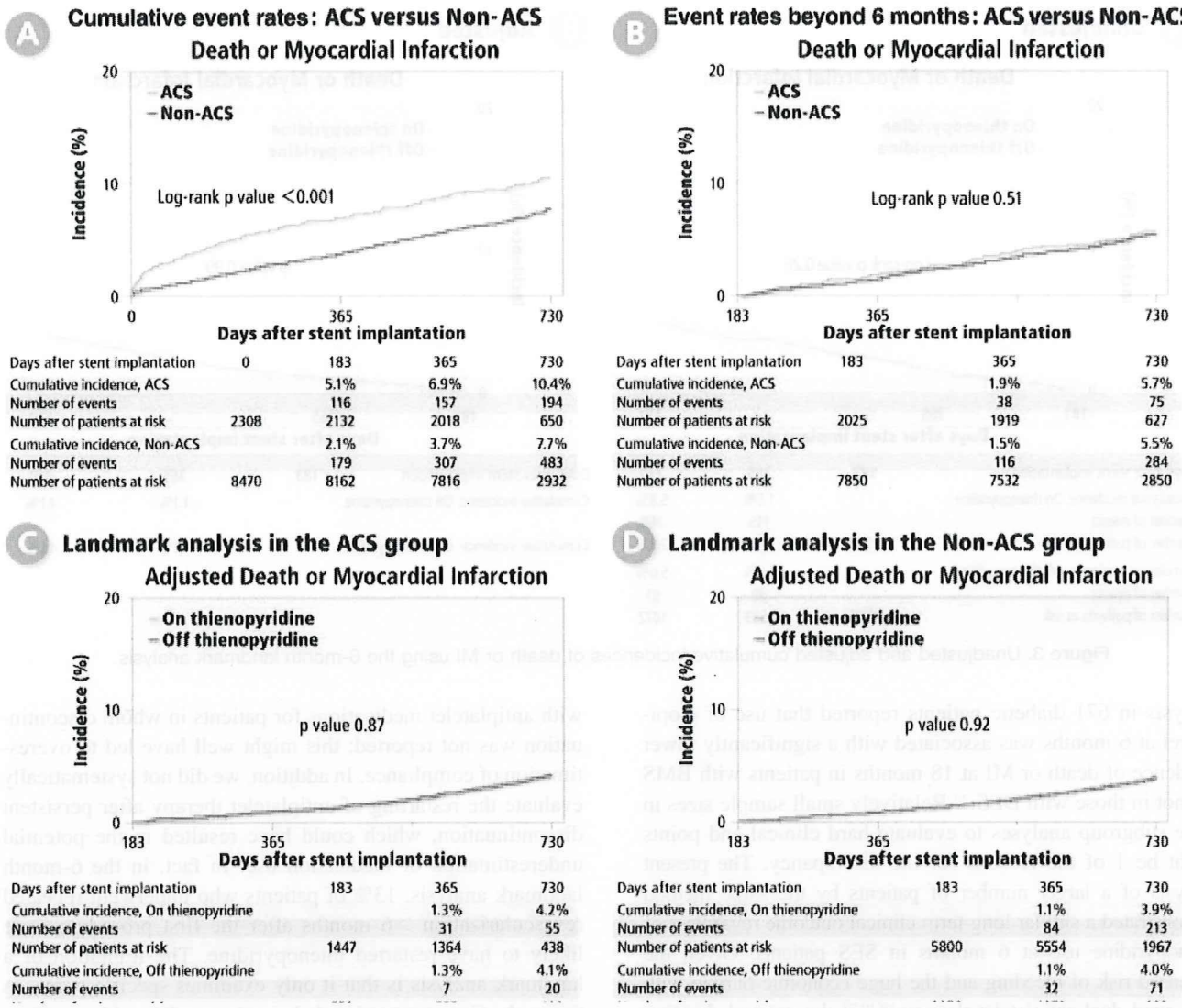

Days after stent implantation	0	183	365	730
Cumulative incidence, ACS		5.1%	6.9%	10.4%
Number of events		116	157	194
Number of patients at risk	2308	2132	2018	650
Cumulative incidence, Non-ACS		2.1%	3.7%	7.7%
Number of events		179	307	483
Number of patients at risk	8470	8162	7816	2932

Days after stent implantation	183	365	730
Cumulative incidence, ACS		1.9%	5.7%
Number of events		38	75
Number of patients at risk	2025	1919	627
Cumulative incidence, Non-ACS		1.5%	5.5%
Number of events		116	284
Number of patients at risk	7850	7532	2850

Days after stent implantation	183	365	730
Cumulative incidence, On thienopyridine		1.3%	4.2%
Number of events		31	55
Number of patients at risk	1447	1364	438
Cumulative incidence, Off thienopyridine		1.3%	4.1%
Number of events		7	20

Days after stent implantation	183	365	730
Cumulative incidence, On thienopyridine		1.1%	3.9%
Number of events		84	213
Number of patients at risk	5800	5554	1967
Cumulative incidence, Off thienopyridine		1.1%	4.0%
Number of events		32	71

Figure 4. A, Cumulative rates of death or MI in patients with or without ACS. B, Rates of death or MI beyond 6 months in patients with or without ACS. C and D, Adjusted cumulative incidences of death or MI using the 6-month landmark analysis in patients with and without ACS.

Despite these limitations, we would conclude that discontinuation of both thienopyridine and aspirin, but not discontinuation of thienopyridine therapy alone, was associated with an increased risk of ST. Landmark analysis did not suggest an apparent clinical benefit of thienopyridine use beyond 6 months after SES implantation.

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Disclosures

Dr Kimura serves as an advisory board member and member of the speakers' bureau for Cordis Cardiology and has received honoraria from Cordis Cardiology. Dr Nakagawa is a member of the speakers' bureau and has received honoraria from Cordis Cardiology. Dr Miyazaki is an advisory board member and receives honoraria from Cordis Cardiology. Drs Shiode and Mitsudo both report receipt of honoraria from Cordis Cardiology. The remaining authors report no conflicts.

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CLINICAL PERSPECTIVE

Randomized data are lacking on the optimal duration of dual-antiplatelet therapy after drug-eluting stent implantation and on the risks associated with discontinuation of dual-antiplatelet therapy. Despite the absence of randomized data, the use of dual-antiplatelet therapy beyond 1 year has become commonplace in clinical practice. In the j-Cypher registry, 10 778 Japanese patients treated exclusively by sirolimus-eluting stents were followed up for up to 2 years with prospective data collection on the status of antiplatelet therapy during follow-up. Incidences of definite stent thrombosis were 0.34% at 30 days, 0.54% at 1 year, and 0.77% at 2 years. Thienopyridine use was maintained in 97%, 62%, and 50% of patients at 30 days, 1 year, and 2 years, respectively. The main findings of the present study were that discontinuation of both aspirin and thienopyridine, but not discontinuation of thienopyridine therapy only, was associated with an increased stent thrombosis risk and that no apparent clinical benefit of thienopyridine use could be seen beyond 6 months after sirolimus-eluting stent implantation, according to the 6-month landmark analysis. Given the increased risk of bleeding and huge economic burden associated with prolonged dual-antiplatelet therapy, the optimal duration of dual-antiplatelet therapy should be defined by prospective randomized trials evaluating its net clinical benefit after consideration of both ischemic events and bleeding complications.

Temporal Pattern of Strokes After On-Pump and Off-Pump Coronary Artery Bypass Graft Surgery

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Background. The incidence of strokes has not decreased after coronary artery bypass graft surgery (CABG). The purpose of this study is to identify incidence, risk factors, and temporal pattern of strokes after on-pump and off-pump CABG.

Methods. We analyzed 2,516 consecutive patients who underwent first elective isolated CABG. The primary endpoint was strokes within 30 days. The temporal onset of the deficits was classified by consensus as either an "early stroke," which is present just after emergence from anesthesia, or a "delayed stroke," which is present after first awaking from surgery without a neurologic deficit.

Results. More than half of strokes (29 of 46; 63%) were delayed strokes. Patients undergoing off-pump CABG had significantly lower risk of early stroke (0.1% versus 1.1%, $p = 0.0009$), whereas the incidence of delayed strokes was not different significantly (0.9% versus 1.4%, $p = 0.3484$) between patients undergoing on-pump and off-pump CABG. In multivariate analyses, undergoing off-pump CABG was an independent protective factor for all strokes (relative risk 0.29, 95% confidence interval: 0.14 to 0.56, $p = 0.0005$) and early strokes (relative risk 0.05, 95% confidence interval: 0.003 to 0.24, $p < 0.0001$), but it was not an independent protective factor for delayed strokes (relative risk 0.54, 95% confidence interval: 0.24 to 1.17, $p = 0.1210$).

Conclusions. Undergoing off-pump CABG reduces the incidence of perioperative stroke mainly by minimizing early strokes; however, the risk of delayed strokes is not different between patients undergoing on-pump and off-pump CABG.

(Ann Thorac Surg 2009;87:1839–45)

Despite advances in surgical techniques and improvements in perioperative care, the incidence of perioperative strokes after cardiac surgery has not decreased, and observation that reflects the aging of the population and an increase in the number of elderly patients with coexisting conditions who undergo cardiac surgery. Perioperative strokes result in prolonged hospital stay, increased disability rates, discharge to long-term care facilities, and death after surgery [1]. Many studies have previously compared off-pump coronary artery bypass graft surgery (CABG) with on-pump CABG surgery, and many of these studies have revealed that off-pump CABG has superior outcomes, particularly with regard to short-term mortality and complication rates, including strokes [2–15]. However, how off-pump CABG reduces the incidence of strokes is unclear.

Previous studies have demonstrated that perioperative strokes are predominantly ischemic and embolic, and the timing of embolic strokes after surgery shows a bimodal distribution. Approximately half of the perioperative strokes are identified within the first day after surgery [16, 17]; these events result from manipulations of the heart and aorta or from the release of particulate matter from the cardiopulmonary bypass pump [1, 16, 18]. The remaining half occur after uneventful recovery from anesthesia [16, 17]; these strokes are often attributed to postoperative atrial fibrillation, myocardial infarction, and coagulopathy [18]. Therefore, an investigation into the temporal pattern of strokes has important implications for risk stratification and modification of strokes after CABG.

The purpose of this study is to identify the incidence and risk factors of strokes, including strokes detected early and those detected at a later stage after CABG, and to examine the temporal pattern of strokes according to the type of surgical procedure.

Material and Methods

The Coronary Revascularization Demonstrating Outcome Study in Kyoto (CREDO-Kyoto) registry has collected in-

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hospital and long-term data (median follow-up period, 42.8 months) on the potential risk factors and outcomes in 2,516 consecutive patients who underwent their first isolated CABG at 21 institutions between 2000 and 2002 in Japan. Patients who had had an acute myocardial infarction within 1 week before the index procedure were excluded. The details of the CREDO-Kyoto registry design and main outcomes have been published [19]. The study protocol is concordant with the guidelines for epidemiologic studies issued by the Ministry of Health, Labor, and Welfare of Japan. The relevant review boards or ethics committees in all 21 participating centers approved the research protocol.

In each center, preoperative baseline characteristics and intraoperative data were collected from hospital charts or databases by independent clinical research coordinators according to prespecified definitions. Data in this registry include patient demographics (for example, age and sex), potential risk factors, comorbidities (for example, history of stroke, hypertension, and current smoking status), and intraoperative data (such as internal thoracic artery utilization) that have been demonstrated to be related to clinical outcomes.

To identify the incidence, risk factors, and temporal pattern of strokes, including strokes detected early after on-pump or off-pump CABG, we performed post hoc analysis. Patients were categorized into off-pump CABG and on-pump CABG groups according to the operation that they ultimately underwent. Patients undergoing surgery for cardiac valves or aortic disease simultaneously with CABG were excluded from this study. All procedural decisions and adjunctive pharmacotherapy were made at the discretion of the patient and the surgeon performing CABG, and either off-pump or on-pump CABG was performed at the discretion of the surgeons.

The primary endpoint was stroke occurrence within 30 days, and the temporal onset of the deficits was classified by consensus as follows: "early stroke," if new neurologic deficit was discovered when the patient emerged from anesthesia, and "delayed stroke," if the patient had a neurologic deficit after first awakening from surgery without a neurologic deficit.

Follow-up data after discharge were obtained from hospital charts or by contacting patients or referring physicians. An independent clinical events committee adjudicated events.

Definition of Stroke

Stroke was defined as any new permanent global or focal neurologic deficit that could not be attributed to other neurologic (for example, dementia) or medical (namely, metabolic abnormalities, hypoxia, or drugs) processes. Reversible cerebral ischemic events (transient ischemic attacks, which were defined clinically by the temporary nature of the associated neurologic symptoms that last less than 24 hours) were not included in the analysis because the occurrence of these events cannot be identified under general anesthesia, and their detection is hindered postoperatively by the residual effects of anesthetics, analgesics, and sedatives. In the majority of patients, strokes were diagnosed by neurologists and confirmed by computed tomography or magnetic resonance imaging head scans.

Table 1. Preoperative Baseline Characteristics and Intraoperative Variables of Patients Undergoing On-Pump and Off-Pump Coronary Artery Bypass Graft Surgery

	Overall (n = 2,516)		On Pump (n = 1,399)		Off Pump (n = 1,117)		
	n	%	n	%	n	%	*p* Value
History of stroke	562	22.3%	251	17.9%	311	27.8%	<0.0001
Hypertension	1768	70.3%	930	66.5%	838	75.0%	<0.0001
LVEF ≤40%	264	10.5%	175	12.5%	89	8.0%	<0.0001
Age, years	67.3 ± 9.5		68.6 ± 9.4		66.3 ± 9.5		<0.0001
Peripheral arterial disease	493	19.6%	239	17.1%	254	22.7%	0.0005
Hyperlipidemia	1345	53.5%	715	51.1%	630	56.4%	0.0089
Previous myocardial infarction	846	33.6%	493	35.2%	353	31.6%	0.0558
Serum creatinine ≥2.0 mg/dL	431	17.1%	225	16.1%	206	18.4%	0.0984
Current smoking status	621	24.7%	360	25.7%	261	23.4%	0.1238
Aneurysm	146	5.8%	74	5.3%	72	6.4%	0.2300
Female sex	704	28.0%	384	27.4%	320	28.6%	0.5315
Diabetes mellitus	1155	45.9%	647	46.2%	508	45.5%	0.7473
Dialysis	125	5.0%	69	4.9%	56	5.0%	0.9267
Atrial fibrillation	145	5.8%	80	5.7%	65	5.8%	0.9316
Internal thoracic artery use	2358	93.7%	1346	96.2%	1012	90.6%	<0.0001
Number of anastomoses	3.3 ± 1.1		3.3 ± 1.0		3.2 ± 1.2		0.0047
Emergent procedure	154	6.1%	78	5.6%	76	6.8%	0.2095
CPB time, minutes			123.1 ± 40.1				
Aorta clamp time, minutes			72.5 ± 33.7				

CPB = cardiopulmonary bypass; LVEF = left ventricular ejection fraction.

Table 2. Discharge Medication Regimens of Patients Undergoing On-Pump and Off-Pump Coronary Artery Bypass Graft Surgery

	Overall (n = 2,516)		On Pump (n = 1,399)		Off Pump (n = 1,117)		
	n	%	n	%	n	%	*p* Value
Aspirin	2089	83.0%	1097	78.4%	992	88.8%	<0.0001
Warfarin	749	29.8%	568	40.6%	181	16.2%	<0.0001
Statin	503	20.0%	208	14.9%	295	26.4%	<0.0001
Beta-blocker	249	9.9%	127	9.1%	119	10.7%	0.0005
ACEI/ARB	532	21.1%	242	17.3%	290	26.0%	<0.0001
Type I AAD	423	16.8%	275	19.7%	148	13.2%	<0.0001
Type III AAD	3	0.1%	7	0.5%	10	0.9%	0.1025

AAD = antiarrhythmia drug; ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin-receptor antagonist.

Diagnosis of Associated Conditions

Documentation of a prior stroke required verification by each patient's primary care physician, review of medical records, and review of the results of computed tomography and magnetic resonance imaging if available. Diabetes mellitus or hypertension was considered to be present if the patients were previously diagnosed, or if they were being treated with either insulin or oral antidiabetic drugs or antihypertensive drugs. Patients were considered to have a history of myocardial infarction if infarction had been previously diagnosed on electrocardiographs or coronary angiography. The criteria for the diagnosis of perioperative myocardial infarction were the appearance of new Q waves and an increase in creatine kinase to 2.0 times or more the upper limit of normal occurring 24 hours or less after CABG.

Table 3. Univariate Relationships of Clinical Variables With All Strokes

Variable	Relative Risk	95% CI	*p* Value
Off-pump CABG	0.39	0.18–0.74	0.0065
History of stroke	5.13	2.85–9.44	<0.0001
Atrial fibrillation	4.17	1.86–8.45	0.0002
Age[a]	1.03	1.00–1.07	0.0604
Peripheral arterial disease	1.82	0.93–3.36	0.0660
Hyperlipidemia	1.64	0.90–3.10	0.1113
Hypertension	1.75	0.88–3.89	0.1329
Current smoking status	1.49	0.78–2.75	0.2109
Internal thoracic artery utilization	0.53	0.22–1.54	0.2176
Diabetes mellitus	1.41	0.79–2.55	0.2505
Aneurysm	1.56	0.46–3.93	0.4018
Serum creatinine ≥ 2.0 mg/dL	1.33	0.62–2.61	0.4259
Previous myocardial infarction	1.27	0.69–2.29	0.4343
Emergent procedure	1.44	0.44–8.90	0.6134
LVEF ≤ 40%	0.81	0.24–2.04	0.6970
Number of anastomoses[b]	0.96	0.74–1.23	0.7293
Female	0.91	0.45–1.71	0.7728
Dialysis	0.87	0.14–2.86	0.8452

[a] Hazard ratio for 1 increase in age. [b] Hazard ratio for 1 increase in the number of anastomoses.

CABG = coronary artery bypass graft surgery; CI = confidence interval; LVEF = left ventricular ejection fraction.

Peripheral arterial disease was considered to be present when patients were being treated for carotid, aortic, or other peripheral vascular diseases or were scheduled for surgical or endovascular interventions. Left ventricular ejection fraction (LVEF) was measured either by contrast left ventriculography or echocardiography. Atrial fibrillation contained paroxysmal, persistent, and permanent atrial fibrillation.

Statistical Analysis

Statistical analysis of categorical variables was carried out using cross tables with the Pearson χ^2 test. Survival curves were estimated using the Kaplan-Meier method. To determine the baseline risk factors for the incidence of all strokes, early strokes, and delayed strokes, we developed a Cox proportional hazard model for the following potential variables: off-pump CABG, emergency procedure, history of stroke, atrial fibrillation, aneurysm, peripheral arterial disease, hypertension, age, LVEF 40% or less, hyperlipidemia, serum creatinine greater than 2.0 mg/dL, history of myocardial infarction, current smoking status, diabetes mellitus, dialysis, female sex, internal thoracic artery utilization, and number of anastomoses. All statistical tests were two-tailed; a *p* value less than 0.05 was considered statisti-

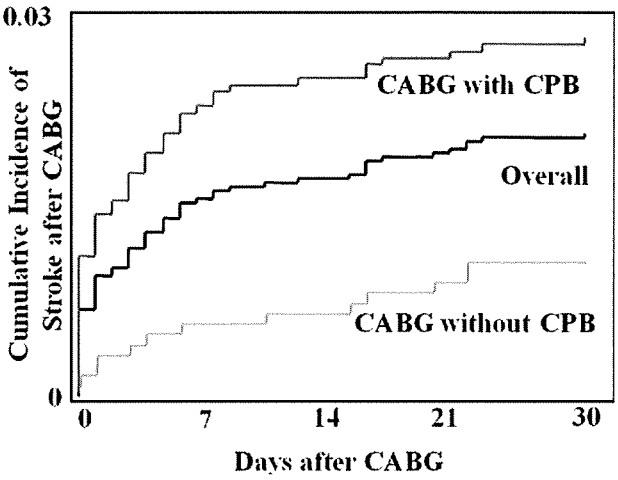

Fig 1. Cumulative incidence of stroke after coronary artery bypass graft surgery (CABG). Postoperative day 0 refers to the day of surgery. (CPB = cardiopulmonary bypass.)

Table 4. Number and Temporal Pattern of Strokes Based on Type of Surgical Procedure

	All Strokes		Early Strokes		Delayed Strokes	
	n	%	n	%	n	%
Overall (n = 2516)	46	1.8%	17	0.7%	29	1.1%
On-pump CABG (n = 1,399)	35	2.5%	16	1.1%	19	1.4%
Off-pump CABG (n = 1,117)	11	1.0%	1	0.1%	10	0.9%
p Value	0.0043		0.0009		0.3484	

CABG = coronary artery bypass graft surgery.

cally significant, and a *p* value less than 0.1 was considered to indicate a statistical tendency. The variables for which *p* values were less than 0.1 in univariate analyses were included in multivariate analyses. All analyses were performed with JMP version 6.0.3 (SAS Institute, Cary, NC).

Results

Preoperative baseline characteristics and intraoperative variables of patients undergoing on-pump and off-pump CABG are shown in Table 1. As indicated, patients undergoing on-pump CABG appeared to have a higher prevalence of reduced left ventricular function (LVEF 40% or less) and internal thoracic artery utilization. Patients undergoing on-pump CABG had also tendency to have history of myocardial infarction more frequently. Conversely, patients undergoing off-pump CABG were older, had a history of stroke more frequently, had lower average number of anastomoses, and showed greater prevalence of hypertension, peripheral arterial disease, and hyperlipidemia. Patients undergoing off-pump CABG also had tendency to have chronic kidney disease (serum creatinine greater than 2.0 mg/dL) more frequently. The discharge medication regimens are shown in Table 2.

All patients continued to attend follow-up examinations at 30 days. Within 30 days after CABG, 46 patients (1.8%) had a stroke. Univariate analyses indicated that undergoing off-pump CABG, history of stroke, and atrial fibrillation were significant predictors of stroke (Table 3).

The number and temporal pattern of strokes based on the type of surgical procedure is shown in Figure 1 and Table 4. The incidence of stroke was sustained for 30 days after CABG. Eighteen strokes were detected early after surgery (37% of strokes, 0.7% of the 2,516 patients); 29 strokes were delayed (63% of strokes, 1.1% of patients). Among patients who underwent off-pump CABG (n = 1,117), 1 stroke occurred early after surgery (9% of strokes, 0.1% of patients); 10 strokes were delayed (91% of strokes, 0.9% of patients). Among patients who underwent on-pump CABG (n = 1,399), 16 strokes were detected early after surgery (46% of strokes, 1.1% of patients); 19 strokes were delayed (54% of strokes, 1.4% of patients; Table 4, Fig 1). Compared with patients undergoing off-pump CABG, patients undergoing on-pump CABG more frequently had early strokes. However, the incidence of delayed strokes did not differ between patients undergoing on-pump and off-pump CABG.

Multivariate analyses (considering the baseline characteristics and results of univariate analyses) indicated that undergoing off-pump CABG was an independent protective factor for stroke, and history of stroke and atrial fibrillation were independent risk factors for stroke (Table 5). Furthermore, undergoing off-pump CABG was an independent protective factor for early stroke, and history of stroke and age was an independent risk factor of early stroke. History of stroke and atrial fibrillation were independent risk factors for delayed stroke (Table 5).

Within 30 days after CABG, 3 and 8 deaths occurred among patients with early and delayed strokes, respectively. This 30-day mortality rate (early strokes, 18%; delayed strokes, 28%) was higher than that observed among patients without perioperative stroke (1.9%, $p < 0.0001$). Perioperative Q-wave myocardial infarction incidence (on-pump 1.5% versus off-pump 1.2%, $p = 0.4704$) did not differ between patients undergoing on-pump and off-pump CABG.

Comment

The temporal pattern of strokes based on the type of surgical procedure was a novel finding of this study. More than half of the strokes (29 of 46; 63%) occurred after initial, uneventful neurologic recovery from cardiac surgery and were defined as delayed strokes. Patients undergoing off-pump CABG had significantly lower risk of early stroke compared with patients undergoing on-pump CABG. In contrast, the incidence of delayed stroke did not significantly differ between patients undergoing on-pump and off-pump CABG. Multivariate analyses in this study also demonstrated that undergoing off-pump CABG was an independent protective factor for all strokes and early

Table 5. Multivariate Relationships of Clinical Variables With All, Early, and Delayed Strokes

Variables	Relative Risk	95% CI	*p* Value
All strokes			
Off-pump CABG	0.29	0.14–0.56	0.0005
History of stroke	5.18	2.80–9.74	<0.0001
Atrial fibrillation	3.28	1.42–6.87	0.0029
Age[a]	1.03	0.99–1.07	0.1393
PAD	1.26	0.63–2.41	0.4991
Early strokes			
Off-pump CABG	0.05	0.003–0.24	<0.0001
History of stroke	7.27	2.67–21.69	0.0001
Age[a]	1.11	1.03–1.19	0.0029
Atrial fibrillation	2.82	0.61–9.46	0.1619
PAD	0.55	0.12–1.79	0.3415
Delayed strokes			
Off-pump CABG	0.54	0.24–1.17	0.1210
History of stroke	4.03	1.86–8.86	0.0005
Atrial fibrillation	3.54	1.26–8.53	0.0189
PAD	1.84	0.81–3.99	0.1395
Age[a]	0.99	0.96–1.04	0.7936

[a] Hazard ratio for 1 increase in age.

CABG = coronary artery bypass graft surgery; CI = confidence interval; PAD = peripheral arterial disease.

strokes, but not for delayed strokes. From this study, we conclude that undergoing off-pump CABG may reduce the incidence of perioperative stroke mainly by minimizing early strokes; however, the risk of delayed strokes does not differ between patients undergoing on-pump and off-pump CABG.

Early strokes are mainly caused by manipulations of the heart and aorta or by the release of particulate matter from the cardiopulmonary bypass pump [1, 16, 18]. Some studies that used transcranial doppler ultrasonography demonstrated the production of aortic emboli on cannulation and application of aortic clamps [20–22] and the production of large quantities of aortic emboli during cardiopulmonary bypass without manipulation of the aorta [23]. Aortic manipulation was also reported to be an independent risk factor for postoperative stroke. Indeed, in this study, only 1 stroke (9% of strokes, 0.1% of patients) was detected early after surgery among patients who underwent off-pump CABG of this study (n = 1,117). Thus, it follows that among patients undergoing off-pump CABG, the incidence of early strokes could be reduced by avoiding cardiopulmonary bypass or by minimizing the manipulation of the aorta. Moreover, for reducing the incidence of stroke, it is important that the surgical technique is selected according to the patient's risk profile.

In this study, the risk of delayed stroke did not significantly differ between patients undergoing on-pump and off-pump CABG. Delayed stroke, which is often attributed to postoperative atrial fibrillation, myocardial infarction, and coagulopathy, remains a problem after both on-pump and off-pump CABG. Multivariate analyses of this study also indicated that atrial fibrillation was independent risk factors for delayed stroke. Atrial fibrillation, which was reported to occur in 30% to 50% of patients after cardiac surgery and to increase the risk of perioperative stroke in some studies [16, 18, 24–28], was found to be a significant predictor of delayed strokes after CABG in this study. No controlled trials have specifically addressed the use of anticoagulation therapy for new-onset postoperative atrial fibrillation; however, the American College of Chest Physicians recommends the consideration of heparin therapy for patients in whom atrial fibrillation develops after surgery, and the continuation of anticoagulation therapy for 30 days after the return of a normal sinus rhythm [29]. It was reported that the incidence of postoperative atrial fibrillation and stroke may be reduced by the prophylactic administration of amiodarone and beta-blockers before cardiac surgery [30]. Because, in this study, we do not have precise information about the in-hospital adjunctive pharmacotherapy that might affect the incidence of perioperative stroke, we excluded the information about the adjunctive pharmacotherapy from the analyses of perioperative strokes. Further studies are required to investigate whether these pharmacologic interventions reduce the incidence of delayed strokes.

Study Limitations

This study was not a randomized observational study. We had no precise information about the mechanism of the strokes, in-hospital adjunctive pharmacotherapy, and the incidence of atrial fibrillation after surgery. Previously, it was reported that delayed stroke also may be related to intimal injury to the ascending aorta due to clamping [31]; however, we also do not have precise intraoperative information (for example, use of intra-aortic balloon pump, intraoperative echocardiography of the ascending aorta, use of single or multiple applications of the aortic cross-clamp) that might affect the incidence of both early and delayed strokes. The study population was not very large, and hence, we could not properly examine the precise predictors of stroke and the protective effects of risk modification to prevent stroke and morbidity.

In conclusion, this is the first study of a large prospective cohort analyzing the temporal pattern of perioperative strokes based on the type of surgical procedure in patients undergoing CABG. We found that more than half of the perioperative strokes after CABG were delayed strokes that occurred after initial uneventful neurologic recovery from surgery. This study also demonstrated that undergoing off-pump CABG might reduce the incidence of perioperative stroke, mainly by minimizing early strokes, when neurologic deficit was detected after the patient's emergence from anesthesia; the risk of delayed strokes did not differ between patients undergoing on-pump and off-pump CABG. Delayed stroke, which is often attributed to postoperative atrial fibrillation, myocardial infarction, and coagulopathy, remains a problem after both on-pump and off-pump CABG.

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Appendix

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Effect of Intensive Statin Therapy on Regression of Coronary Atherosclerosis in Patients With Acute Coronary Syndrome

A Multicenter Randomized Trial Evaluated by Volumetric Intravascular Ultrasound Using Pitavastatin Versus Atorvastatin (JAPAN-ACS [Japan Assessment of Pitavastatin and Atorvastatin in Acute Coronary Syndrome] Study)

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Objectives The objective of this study was to evaluate whether the regressive effects of aggressive lipid-lowering therapy with atorvastatin on coronary plaque volume (PV) in patients with acute coronary syndrome (ACS) are generalized for other statins in multicenter setting.

Background A previous single-center study reported beneficial regressive effects of atorvastatin in patients with ACS on PV of the nonculprit site by intravascular ultrasound (IVUS) evaluation. The effect of statins other than atorvastatin on PV has not been evaluated in the setting of ACS.

Methods The JAPAN-ACS (Japan Assessment of Pitavastatin and Atorvastatin in Acute Coronary Syndrome) study was a prospective, randomized, open-label, parallel group study with blind end point evaluation conducted at 33 centers in Japan. A total of 307 patients with ACS undergoing IVUS-guided percutaneous coronary intervention were randomized, and 252 patients had evaluable IVUS examinations at baseline and 8 to 12 months' follow-up. Patients were randomly assigned to receive either 4 mg/day of pitavastatin or 20 mg/day of atorvastatin. The primary end point was the percentage change in nonculprit coronary PV.

Results The mean percentage change in PV was −16.9 ± 13.9% and −18.1 ± 14.2% ($p = 0.5$) in the pitavastatin and atorvastatin groups, respectively, which was associated with negative vessel remodeling. The upper limit of 95% confidence interval of the mean difference in percentage change in PV between the 2 groups (1.11%, 95% confidence interval: −2.27 to 4.48) did not exceed the pre-defined noninferiority margin of 5%.

Conclusions The administration of pitavastatin or atorvastatin in patients with ACS equivalently resulted in significant regression of coronary PV (Japan Assessment of Pitavastatin and Atorvastatin in Acute Coronary Syndrome; NCT00242944).
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JACC Vol. 54, No. 4, 2009
July 21, 2009:293–302

Abbreviations and Acronyms

ACS = acute coronary syndrome
CRP = C-reactive protein
EEM = external elastic membrane
FAS = full analysis set
HDL-C = high-density lipoprotein cholesterol
IVUS = intravascular ultrasound
LDL-C = low-density lipoprotein cholesterol
PCI = percutaneous coronary intervention
PV = plaque volume

Many large-scale pivotal clinical trials (1–3) have shown that 3-hydroxy-3-methyl-glutaryl coenzyme A reductase inhibitors (statins) reduce both atherogenic lipoproteins as well as cardiovascular morbidity and mortality. In addition, several previous multicenter studies in which the authors used intravascular ultrasound (IVUS) imaging revealed that statins attenuate the progression of atherosclerosis or even diminish plaque volume (4,5). An IVUS study in patients with acute coronary syndrome (ACS) demonstrated that statin therapy with 20 mg/day of atorvastatin could reduce nonculprit coronary plaque volume (6). However, this study was a relatively small trial conducted at a single center. This observation, if confirmed in a larger multicenter study, could address one of the mechanisms of improvement of clinical outcome provided by administration of statins in patients with ACS (7–10).

The effect of statins other than atorvastatin on plaque volume (PV) has not been evaluated in the setting of ACS. Pitavastatin is a statin that is commonly used in Japan, South Korea, and Thailand. It has been demonstrated that its ability to lower levels of low-density lipoprotein cholesterol (LDL-C) is comparable with that of atorvastatin (11). Therefore, a multicenter study using a central IVUS core laboratory was designed to assess the effect of pitavastatin on coronary PV compared with that of atorvastatin in patients with ACS.

Methods

Study design and ethical considerations. The JAPAN-ACS (Japan Assessment of Pitavastatin and Atorvastatin in Acute Coronary Syndrome) study was a prospective, randomized, open-label, parallel group study with blind endpoint evaluation at 33 centers to examine the effect of 8 to 12 months' treatment with pitavastatin versus atrovastatin in coronary plaque regression in nonpercutaneous coronary intervention (PCI) sites of the culprit vessel in patients with ACS. A documentation of the present study design was published before the dataset was locked (12). This study was conducted according to the Declaration of Helsinki and with the approval of the institutional review boards of all 33 participating institutions. Written informed consent to participate was obtained from all of the patients enrolled.

Patient enrollment and randomization. Patients with ACS who satisfied all criteria for inclusion were selected after having a successful PCI under IVUS guidance. We defined ACS as unstable angina pectoris, non–ST-segment elevation myocardial infarction (MI) or ST-segment elevation MI. These diagnoses were made if patients met at least 2 of the following 3 conditions: 1) ischemic ECG changes; 2) the increase (≥2 times) in serum creatine kinase or creatine kinase, myocardial band, or a positive troponin T result; and 3) the presence of symptoms suggestive of ACS. A standard antiplatelet therapy and other medications for ACS were provided.

The patients were randomized within 72 h after PCI to receive either pitavastatin (4 mg) or atorvastatin (20 mg) daily. The dose of 20 mg/day of atorvastatin was selected because when such doses were used in the ESTABLISH (Demonstration of the Beneficial Effect on Atherosclerotic Lesions by Serial Volumetric Intravascular Ultrasound Analysis During Half a Year After Coronary Event) study they significantly reduced coronary PV in patients with ACS (6) and because this dose was the most intensive permitted one to reduce LDL-C in Japan at the beginning of this trial. In addition, the pitavastatin dosage of 4 mg/day was selected because it causes a similar LDL-C–lowering effect to 20 mg/day of atorvastatin (11). We did not include a control group of patients not receiving statin treatment because of ethical reasons. The randomization was stratified by the presence of diabetes mellitus, sex, and total cholesterol level by use of a web response system, which generated association sequence. The IVUS examination was performed at baseline and repeated after 8 to 12 months' administration of the allocated drugs.

Blood examinations for lipid levels and inflammatory markers were performed at baseline and follow-up at 8 to 12 months. Lipid profiles and other biomarkers were measured at SRL Co., Ltd., Tokyo, Japan, and pentraxin3 at Perseus Proteomics Inc., Tokyo, Japan. Safety was evaluated by regular medical examination and laboratory tests at 1, 3, and 8 to 12 months after enrollment. The independent event assessment committee evaluated major adverse cardiac events and any other adverse events.

Examination with IVUS. After IVUS-guided PCI of the culprit lesion of ACS, IVUS examination was performed in both the longest and least angulated culprit vessel segment meeting inclusion criteria. After 200 μg of intracoronary nitroglycerin was administered, a 40-MHz, 2.6-F (0.87-mm) IVUS catheter (Atlantis SR Pro2, Boston Scientific, Natick, Massachusetts) was advanced into the culprit vessel,

honoraria for lectures from Kowa Pharmaceutical, Pfizer, and Astellas Pharma. Dr. Yamagishi has received honoraria for lectures from Kowa Pharmaceutical, Pfizer, and Astellas Pharma and has received a research grant from Kowa Pharmaceutical and Astellas Pharma. Dr. Ozaki is an advisory member of Kowa Pharmaceutical and has received honoraria for lectures from Pfizer and Kowa Pharmaceutical. Dr. Kimura is an advisory member of Kowa Pharmaceutical and has received honoraria for the lectures from Kowa Pharmaceutical and Astellas Pharma. Dr. Saito has received honoraria for lectures from Kowa Pharmaceutical. Dr. Daida is an advisory member of Kowa Pharmaceutical and has received honoraria for lectures and research grants from Kowa Pharmaceutical, Pfizer, and Astellas Pharma. Dr. Matsuzaki is an advisory member of Kowa Pharmaceutical and Pfizer and has received honoraria for lectures and research grants from Kowa Pharmaceutical, Pfizer, and Astellas Pharma.

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and the transducer was positioned as far distally as could be safely reached. This procedure was designed to select the longest-possible vessel segment for analysis. A motorized pullback device withdrew the transducer at a speed of 0.5 mm/s. The consoles used were ClearView or Galaxy 2 systems (Boston Scientific). The same imaging system with the same type of IVUS catheter was used for both the baseline and the follow-up examinations When the angular span of the acoustic shadow of calcification or attenuation by some noncalcified tissues was >90°, the case was excluded. After an 8- to 12-month treatment period, IVUS examinations were performed under the conditions identical to the baseline.

Core laboratory analysis of IVUS. Two independent experienced investigators who were unaware of the patient group allocation performed the quantitative IVUS analysis at the central core laboratory. Baseline and follow-up IVUS images were reviewed together on a display, and target segments were selected. The target segment was determined at a non-PCI site (>5 mm proximal or distal to the PCI site) of culprit vessel with a reproducible index, usually a branch site, on the PCI vessel. Spotty calcification, side vein, and distances from side branch, orifice, left anterior descending-left circumflex branch bifurcation, and stent edge also were referred. Subsequently, every 6th image (0.1 mm apart) was manually traced on a commercially available IVUS measurement software (echoPlaque2, INDEC systems Inc., Santa Clara, California). Moreover, this software automatically interpolated the tracing of 5 cross sections in between the 2 manually traced images. Therefore, the volume was calculated from each of 0.017-mm spaced segments. The final cross section for measurement was obtained at a proximal fiduciary site.

The IVUS measurements were performed according to the standards of the American College of Cardiology and the European Society of Cardiology (13). These measurements are present in the standard manner, for which accuracy and reproducibility have been well established (14). The primary end point was the percent change in coronary PV during the observation period:

$$\frac{\text{PV (follow-up)} - \text{(baseline)}}{\text{PV (baseline)}} \times 100$$

Coronary PV was calculated as the sum of the differences between the external elastic membrane (EEM) and lumen area across all evaluated frames as: $PV = \Sigma(EEM_{CSA} - LUMEN_{CSA})$, where EEM_{CSA} = external elastic membrane cross-sectional area and $LUMEN_{CSA}$ = luminal cross-sectional area.

Major secondary end points include nominal change in percent PV (%PV) and nominal change in normalized plaque volume (NPV) (follow-up minus baseline, respectively):

$$NPV = PV \times \frac{L_{MED}}{L_{MEASURED}}$$

where L_{MED} = median value of observed length in all subjects and $L_{MEASURED}$ = observed length of each plaque.

Statistical analysis. A detailed structure of statistical analyses in the current study was described elsewhere (12). In brief, this study aims to evaluate whether the effect of pitavastatin on coronary PV would not be inferior to that of atorvastatin and vice versa. Two-sided noninferiority was evaluated by analysis of variance with adjustment for sex, the presence of diabetes mellitus, and total cholesterol level on admission as previously described (12). We decided noninferiority margin as follows: 1) in the ESTABLISH study, the % change in PV of atorvastatin was 13.1 ± 12.8%; 2) standard deviation (±12.8) multiplied by 0.36 (15) yielded 4.608, rounded to 5; and 3) the noninferiority margin was decided as 5%. We calculated 150 subjects in each group with an alpha level of 5%, a power of 80%, and a dropout rate of 30%.

We used full analysis set (FAS) of data for primary analyses. Data of patients were included in FAS if patients had ACS and measurable IVUS both at the enrollment and at follow-up. We prepared per-protocol analysis set of data if enrolled patients completely met the inclusion and exclusion criteria and followed the protocol as it was. If patients received the study drug at least once, they were included in the safety analysis set of data.

After the descriptive statistics, comparisons of continuous variables between the 2 groups were performed by the 2-sample *t* test or Wilcoxon rank sum test, and those between the baseline and the follow-up by 1-sample *t* tests or Wilcoxon sign rank test according to their distributions. Comparisons of categorical values between the 2 groups were performed by chi-square tests and Fisher exact tests. We used general linear models to assess relationships between the percent change in coronary PV and several factors, including serum lipid profile at 8 to 12 months, or to assess interobserver and intraobserver variabilities for measuring plaque area. The numbers of adverse events were assessed to determine safety profiles. The significance level was 5% 2-sided (2.5% 1-sided), and all statistical analyses were performed by the use of the SAS system version 9.1 (SAS Institute, Cary, North Carolina).

Results

Patient population. The grouping of patients in the present study is shown in Figure 1. Between November 1, 2005, and October 31, 2006, 307 patients were enrolled at 33 centers in Japan, and 153 patients were randomly assigned to receive pitavastatin and 154 to atorvastatin. The IVUS images qualified for evaluation both at baseline and at follow-up were obtained in 125 patients (82%) in the pitavastatin group and in 127 patients (82%) in the atorvastatin group. The median follow-up time with intraquartile

JACC Vol. 54, No. 4, 2009
July 21, 2009:293–302

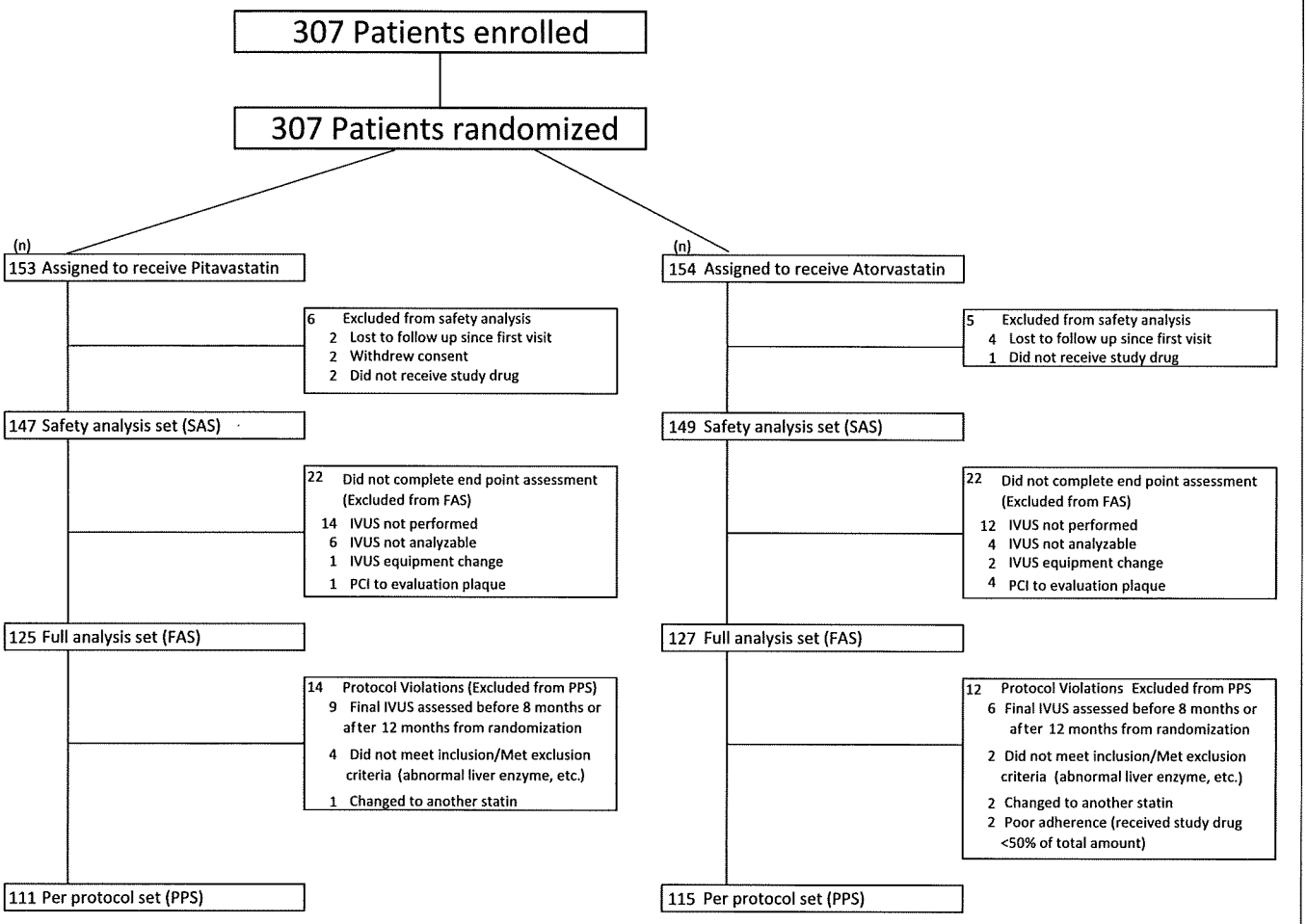

Figure 1 Disposition of Patients

FAS = full analysis set; IVUS = intravascular ultrasound; PCI = percutaneous coronary intervention; PPS = per protocol set; SAS = safety analysis set.

range in the pitavastatin group was 9.3 (range 8.5 to 10.3) months and 9.6 (range 8.6 to 10.5) months in the atorvastatin group, respectively.

There was no significant difference in baseline demographics and characteristics between the 2 groups (Table 1). Eighty-two percent of patients were men, and 29% of total patients had diabetes. Sixty-four percent of patients had ST-segment elevation MI, and drug-eluting stents were used in 32% and bare-metal stents in 66%. Plaques proximal to the PCI sites were analyzed in 70% of patients.

Laboratory results. We found that LDL-C decreased from 130.9 ± 33.3 mg/dl (3.39 ± 0.86 mmol/l) at baseline to 81.1 ± 23.4 mg/dl (2.10 ± 0.61 mmol/l) at 8 to 12 months' follow-up ($p < 0.001$) in the pitavastatin group and from 133.8 ± 31.4 mg/dl (3.47 ± 0.81 mmol/l) to 84.1 ± 27.4 mg/dl (2.18 ± 0.71 mmol/l; $p < 0.001$) in the atorvastatin group (Table 2). We found that high-density lipoprotein cholesterol (HDL-C) as well as triglycerides showed comparable increase between the 2 groups. The inflammatory markers, high-sensitivity C-reactive protein, pentraxin3, and white blood cell counts were markedly increased at baseline and were not different between the 2 groups in terms of percent change.

Efficacy analysis with IVUS. We randomly selected 93 IVUS cross-sectional images from 31 patients to assess the intraobserver and interobserver variabilities for measuring plaque area by 2 independent technicians. The correlation coefficient and mean difference ± SD were 0.99 and 0.02 ± 0.24 mm^2 (of the absolute mean value, 6.97 ± 4.33 mm^2, of the samples) for intraobserver variability and 0.98 and 0.13 ± 0.32 mm^2 for interobserver variability.

As a primary end point, the percent change in coronary PV showed a significant regression for both groups (−16.9 ± 13.9% in the pitavastatin group, −18.1 ± 14.2% in the atorvastatin group, and −17.5 ± 14.0% for total patients) (Table 3). Noninferiority of pitavastatin to atorvastatin and also atorvastatin to pitavastatin in terms of percent change in PV was proved (Fig. 2). The mean difference of drug effects on percent change in PV ($\mu p - \mu a$), adjusted for sex, the presence of diabetes mellitus, and total cholesterol level, was 1.11% (95% confidence interval [CI]: −2.27% to 4.48%). The upper limit of 95% CI of this

Table 1 Baseline Patient Characteristics and Concomitant Drugs

Characteristic	Pitavastatin (n = 125)	Atorvastatin (n = 127)
Age (yrs)	62.5 ± 11.5	62.4 ± 10.6
Male	103 (82.4)	103 (81.1)
BMI (kg/m^2)	24.5 ± 3.7	24.2 ± 3.3
Waist circumference (cm)	87.2 ± 9.5	87.0 ± 8.6
Diabetes	36 (28.8)	38 (29.9)
Hypertension	73 (58.4)	84 (66.1)
Family history of CAD	24 (19.2)	21 (16.5)
Smoking	57 (45.6)	62 (48.8)
Alcohol drinker	59 (47.2)	62 (48.8)
Type of ACS		
STEMI	75 (60.0)	87 (68.5)
NSTEMI	18 (14.4)	18 (14.2)
UAP	32 (25.6)	22 (17.3)
Abnormal Q-wave	46 (36.8)	40 (31.5)
Max CK (IU/l), median (IQR)	1,173 (206–2,664)	1,400 (349–2,806)
Culprit vessel		
RCA	33 (26.4)	48 (37.8)
LAD	75 (60.0)	61 (48.0)
LCx	16 (12.8)	18 (14.2)
LMT	1 (0.8)	0
Analysis segment		
Proximal to the treated site	86 (68.8)	90 (70.9)
Disital to the treated site	39 (31.2)	37 (29.1)
BMS	77 (61.6)	89 (70.1)
DES	45 (36.0)	35 (27.6)
Other than stent (POBA)	3 (2.4)	3 (2.4)
Concomitant drugs		
Aspirin	124 (99.2)	124 (97.6)
Ticlopidine	102 (81.6)	107 (84.3)
Clopidogrel	9 (7.2)	8 (6.3)
Beta-blocker	55 (44.0)	61 (48.0)
ACE inhibitor	35 (28.0)	39 (30.7)
ARB	57 (45.6)	68 (53.5)
PPAR-γ agonist	4 (3.2)	6 (4.7)
Sulfonylurea	12 (9.6)	8 (6.3)
α-GI	10 (8.0)	11 (8.7)
Calcium blocker	25 (20.0)	24 (18.9)
Nitrate	21 (16.8)	17 (13.4)
Diuretic	10 (8.0)	9 (7.1)
Aldosterone blocker	3 (2.4)	2 (1.6)
Digitalis	3 (2.4)	2 (1.6)
Other antiplatelet agents	10 (8.0)	7 (5.5)
Warfarin	5 (4.0)	2 (1.6)
Antiarrhythmic agent	1 (0.8)	1 (0.8)

Data are expressed as n (%) unless otherwise specified. Continuous variables were represented by mean ± SD or median (IQR). There were no significant differences of any characteristics between the 2 groups.

ACE = angiotensin-converting enzyme; ACS = acute coronary syndrome; ARB = angiotensin receptor blocker; α-GI = alpha-glucosidase inhibitor; BMI = body mass index; BMS = bare-metal stent; CAD = coronary artery disease; CK = creatine kinase; DES = drug-eluting stent; IQR = intraquartile range; LAD = left anterior descending; LCx = left circumflex branch; LMT = left main trunk; NSTEMI = non–ST-elevation myocardial infarction; POBA = plain old balloon angioplasty; RCA = right coronary artery; STEMI = ST-elevation myocardial infarction; UAP = unstable angina pectoris.

difference did not exceed the pre-defined noninferiority margin of 5%. The direction of difference in per-protocol analysis set setting, mean value of 1.36% (95% CI: −2.15% to 4.88%), was consistent with FAS setting. Secondary efficacy end points such as %PV and normalized PV were significantly reduced in both groups (Table 3).

These benefits were associated with significant negative vessel remodeling in both groups (113.0 ± 59.3 mm^3 to 105.4 ± 55.0 mm^3), which consequently provided slight but significant lumen enlargement (56.1 ± 59.3 mm^3 to 57.8 ± 30.5 mm^3). Reduction in EEM volume correlated with the decreased PV (r = 0.7), but there was no correlation between change in lumen volume and change in PV (Fig. 3). Figure 4 showed representative examples of IVUS in a single patient with ACS at the baseline and the follow-up period in pitavastatin group.

Plaque regression and biomarkers. Because there was no significant difference in percent change in PV between the 2 groups, the correlation between LDL-C level and percent change in PV was evaluated in the whole FAS patients. There were no significant correlations between LDL-C level at follow-up or at baseline and percent change in PV. Percent change in LDL-C level during the study period also did not significant correlate with percent change in PV (Fig. 5). In addition, there were no significant correlations between high-sensitivity C-reactive protein level at follow-up or at baseline and percent change in PV.

Adverse events. There were no significant differences in the prevalence of these major adverse cardiac events and adverse events between the pitavastatin group and the atorvastatin group (Table 4). The study drugs were discontinued because of either adverse reactions or abnormality of laboratory value only in 2.7% and 4.7% of the pitavastatin group and the atorvastatin group, respectively.

Discussion

Our study demonstrated that aggressive lipid-lowering therapy with either pitavastatin 4 mg/day or atorvastatin 20 mg/day achieved significant regression of the coronary PV with negative vessel remodeling in patients with ACS based on a randomized, large-scale, multicenter, central IVUS core laboratory evaluation study. Therefore, the results provided support to the hypothesis that administration of statins after the onset of ACS has the potential to reverse the process of atherosclerosis, thereby improving clinical outcome (7–10). Moreover, the results showed that pitavastatin as well as atorvastatin provided a comparable benefit to reduce PV in such patients. This observation also generalized the effect of statins other than atorvastatin on PV in the setting of ACS.

The degree of percent change in PV was −17.5% for total patients in this study. This beneficial regressive effect was similar to that reported by the ESTABLISH single-center study (−13.1%) (6), even more than that of the REVERSAL trial (−0.4%, median in the atorvastatin group) that used a similar primary end point. One of the potential reasons for this might be the difference in clinical presentation (ACS vs. stable coronary artery disease). Evidence has accumulated that shows

Table 2 Laboratory Results

	Baseline		Follow-Up		Percent Change (%)				
	Pitavastatin (n = 125)	Atorvastatin (n = 127)	Pitavastatin (n = 125)	Atorvastatin (n = 127)	Pitavastatin (n = 125)	p Value Compared With Baseline	Atorvastatin (n = 127)	p Value Compared With Baseline	p Value Between Groups
TC	196.5 ± 35.6	197.9 ± 36.4	151.3 ± 28.0	152.8 ± 33.1	−21.6 ± 16.0	<0.001	−21.9 ± 17.7	<0.001	0.9
LDL-C	130.9 ± 33.3	133.8 ± 31.4	81.1 ± 23.4	84.1 ± 27.4	−36.2 ± 19.5	<0.001	−35.8 ± 22.9	<0.001	0.9
TG	119.2 ± 53.2	116.7 ± 58.1	126.8 ± 80.3	120.7 ± 59.1	16.2 ± 59.9	0.003	21.2 ± 75.5	0.002	0.6
HDL-C	45.0 ± 10.1	43.9 ± 9.4	48.8 ± 12.7	47.1 ± 11.7	9.9 ± 23.5	<0.001	8.0 ± 21.4	<0.001	0.5
HDL-C baseline <40 mg/dl	34.6 ± 3.4	34.5 ± 4.0	41.4 ± 7.2	37.8 ± 7.5	20.6 ± 24.6 (n = 39)	<0.001	10.8 ± 25.4 (n = 46)	0.006	0.08
HDL_2-C	30.4 ± 10.0	29.5 ± 8.6	33.0 ± 12.3	31.7 ± 10.5	10.8 ± 31.4	<0.001	8.7 ± 28.0	<0.001	0.6
HDL_3-C	18.5 ± 3.6	18.0 ± 3.8	17.9 ± 3.2	17.4 ± 3.5	−0.5 ± 21.9	0.8	−1.4 ± 21.5	0.5	0.7
RLP-C	4.5 ± 2.7	4.2 ± 2.4	4.1 ± 3.6	3.7 ± 2.5	4.7 ± 87.9	0.6	6.2 ± 80.9	0.4	0.9
Small dense LDL (RM value)	0.35 ± 0.04	0.36 ± 0.05	0.34 ± 0.04	0.34 ± 0.03	−2.6 ± 11.1	0.01	−3.4 ± 11.9	0.002	0.6
Non-HDL-C	151.1 ± 33.1	153.5 ± 33.7	102.6 ± 25.2	105.7 ± 32.2	−30.5 ± 18.9	<0.001	−30.1 ± 20.8	<0.001	0.9
LDL-C/HDL-C	3.0 ± 0.9	3.2 ± 0.9	1.8 ± 0.6	1.9 ± 0.7	−40.3 ± 19.4	<0.001	−38.8 ± 23.1	<0.001	0.6
ApoA-I	111.8 ± 19.8	109.8 ± 19.2	130.9 ± 24.8	124.5 ± 24.1	18.5 ± 21.6	<0.001	14.0 ± 19.4	<0.001	0.1
ApoB	103.6 ± 23.3	104.8 ± 23.2	73.3 ± 17.0	74.6 ± 21.3	−27.6 ± 18.3	<0.001	−27.6 ± 20.2	<0.001	0.99
ApoE	4.1 ± 1.2	4.2 ± 1.1	3.6 ± 1.0	3.5 ± 1.0	−9.4 ± 23.5	<0.001	−12.7 ± 23.5	<0.001	0.3
ApoB/ApoA-I	0.95 ± 0.25	0.97 ± 0.24	0.58 ± 0.16	0.62 ± 0.22	−37.7 ± 16.1	<0.001	−35.7 ± 18.2	<0.001	0.4
MDA-LDL (U/l)	130.2 ± 43.6	128.9 ± 49.1	88.1 ± 27.4	93.9 ± 34.6	−28.4 ± 25.3	<0.001	−22.1 ± 28.2	<0.001	0.1
Phospholipid	200.4 ± 30.8	199.0 ± 33.1	183.7 ± 31.1	177.4 ± 29.8	−7.4 ± 15.8	<0.001	−10.1 ± 14.4	<0.001	0.2
Lp(a)	20.2 ± 16.7	22.9 ± 21.9	22.7 ± 22.0	24.2 ± 25.8	5.9 ± 45.6	0.2	9.8 ± 54.9	0.049	0.5
hs-CRP (mg/l), median (IQR)	19.9 (7.1–71.1)	14.9 (4.7–62.4)	0.54 (0.36–1.1)	0.53 (0.26–1.2)	−97.3 (−99.1 to −89.6)	<0.001*	−95.4 (−99.0 to −84.5)	<0.001*	0.4†
PTX3 (ng/ml), median (IQR)	5.9 (3.8–8.9)	5.6 (3.8–9.0)	2.1 (1.5–2.8)	1.9 (1.3–2.6)	−64.3 (−77.5 to −45.1)	<0.001*	−68.9 (−79.1 to −52.4)	<0.001*	0.9†
WBC (cells/l), median (IQR)	8,820 (7,015–11,400)	9,300 (7,580–11,200)	6,000 (5,300–7,200)	6,000 (5,005–7,268)	−31.6 (−44.9 to −16.6)	<0.001*	−33.6 (−45.1 to −17.2)	<0.001*	0.7†
HbA1c (%)	5.9 ± 1.3	6.0 ± 1.1	5.9 ± 1.1	5.9 ± 0.89	0.6 ± 10.5	0.5	0.6 ± 10.5	0.5	0.98

Values are mg/dl unless otherwise indicated. Continuous variables were represented by mean ± SD or median (IQR). The last column indicates the comparison of percent change in valuables between pitavastatin and atorvastatin group. SI conversions: To convert total cholesterol, LDL-C, HDL-C, HDL_2-C, HDL_3-C, remnant lipoprotein-C (RLP-C), non-HDL-C to mmol/l, multiply by 0.0259; apolipoprotein (apo)A-I, apoB, apoE to g/l, multiply by 10; malonyl-dialdehyde (MDA)-low-density lipoprotein (LDL), phospholipid and lipoprotein (a) [Lp(a)] to mg/l, multiply by 10; PTX3 to μg/l, multiply values by 1. *Wilcoxon sign rank test. †Wilcoxon rank sum test.

CRP = C-reactive protein; Hb = hemoglobin; HDL-C = high-density lipoprotein cholesterol; hs-CRP = high-sensitivity C-reactive protein; IQR = intraquartile range; IVUS = intravascular ultrasound; LDL-C = low-density lipoprotein cholesterol; PCI = percutaneous coronary intervention; PTX3 = pentraxin 3; RM = relative migration; TC = total cholesterol; WBC = white blood cell counts.

Table 3 IVUS Results

	Baseline				Follow-Up			
	Both Groups (n = 252)	Pitavastatin (n = 125)	Atorvastatin (n = 127)	p Value Between Groups	Both Groups (n = 252)	Pitavastatin (n = 125)	Atorvastatin (n = 127)	p Value Between Groups
Plaque volume (mm^3)	56.9 ± 32.2	49.8 ± 28.8	63.9 ± 33.9	<0.001	47.5 ± 29.1	41.6 ± 25.0	53.3 ± 31.7	0.0013
Percent plaque volume (%)	50.0 ± 10.3	49.4 ± 10.8	50.5 ± 9.7	0.4	44.0 ± 10.8	43.7 ± 11.0	44.3 ± 10.7	0.7
Normalized plaque volume (mm^3)	54.6 ± 18.9	52.7 ± 19.4	56.4 ± 18.3	0.1	45.3 ± 18.0	43.9 ± 17.7	46.6 ± 18.3	0.2
Vessel volume (mm^3)	113.0 ± 59.3	100.2 ± 54.2	125.6 ± 61.5	<0.001	105.4 ± 55.0	93.3 ± 48.7	117.2 ± 58.3	<0.001
Lumen volume (mm^3)	56.1 ± 31.5	50.5 ± 29.7	61.6 ± 32.3	0.0046	57.8 ± 30.5	51.7 ± 27.9	63.9 ± 31.7	0.0013
IVUS lesion length (mm)	6.7 ± 3.0	6.1 ± 2.8	7.3 ± 3.1	0.0021	S/B	S/B	S/B	—

	Nominal Change						
	Both Groups (n = 252)	p Value Compared With Baseline	Pitavastatin (n = 125)	p Value Compared With Baseline	Atorvastatin (n = 127)	p Value Compared With Baseline	p Value Between Groups
Plaque volume (mm^3)	−9.4 ± 9.8	<0.001	−8.2 ± 8.9	<0.001	−10.6 ± 10.6	<0.001	0.05
Percent plaque volume (%)	−6.0 ± 6.2	<0.001	−5.7 ± 6.3	<0.001	−6.3 ± 6.1	<0.001	0.5
Normalized plaque volume (mm^3)	−9.3 ± 8.4	<0.001	−8.7 ± 8.2	<0.001	−9.8 ± 8.6	<0.001	0.3
Vessel volume (mm^3)	−7.7 ± 14.9	<0.001	−7.0 ± 15.2	<0.001	−8.3 ± 14.7	<0.001	0.5
Lumen volume (mm^3)	1.8 ± 10.6	0.0093	1.2 ± 10.5	0.2	2.3 ± 10.5	0.019	0.4
IVUS lesion length (mm)	S/B	—	—	—	—	—	—

	Percent Change (%)						
	Both Groups (n = 252)	p Value Compared With Baseline	Pitavastatin (n = 125)	p Value Compared With Baseline	Atorvastatin (n = 127)	p Value Compared With Baseline	p Value Between Groups
Plaque volume (mm^3)	−17.5 ± 14.0	<0.001	−16.9 ± 13.9	<0.001	−18.1 ± 14.2	<0.001	0.5
Percent plaque volume (%)	NA	<0.001	NA	<0.001	NA	<0.001	0.5
Normalized plaque volume (mm^3)	NA	<0.001	NA	<0.001	NA	<0.001	0.3
Vessel volume (mm^3)	−6.0 ± 11.4	<0.001	−5.9 ± 11.8	<0.001	−6.2 ± 11.1	<0.001	0.8
Lumen volume (mm^3)	6.5 ± 20.4	<0.001	6.4 ± 21.5	0.0012	6.6 ± 19.4	<0.001	0.9
IVUS lesion length (mm)	S/B	—	—	—	—	—	—

Continuous variables were represented by mean ± SD.
IVUS = intravascular ultrasound; NA = not applicable; S/B = same as the baseline.

patients with ACS have many greater-risk nonculprit plaques (16–19). The plaques in the most-diseased 10-mm segments showed more regression than whole coronary artery in the REVERSAL trials (4), and the %PV at the baseline in this study was relatively large compared with those in both trials (JAPAN-ACS, ~50%; REVERSAL, ~40%). Furthermore, there was relatively greater proportion of the patients who were administered statins de novo after the entry of this trial. It is also possible there are genetic, racial, or ethnic differences in terms of response to statins.

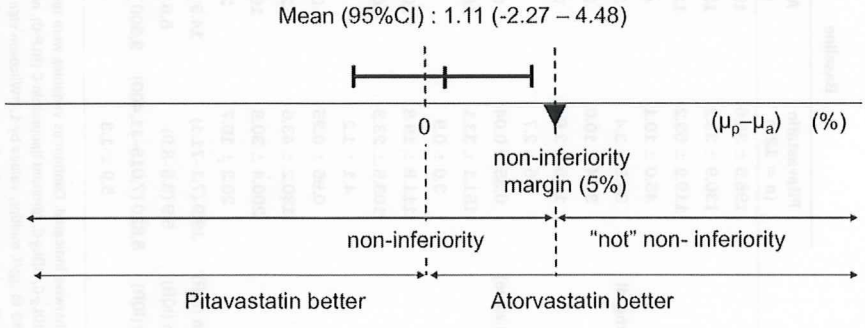

Figure 2 Primary End Point (Noninferiority Test)

The difference of drug effects on percent change in plaque volume ($\mu p - \mu a$) adjusted for sex, the presence of diabetes mellitus, and total cholesterol level, where μp represents percent change in plaque volume of the pitavastatin group and μa represents that of the atorvastatin group. Noninferiority of pitavastatin to atorvastatin was evident for this end point.

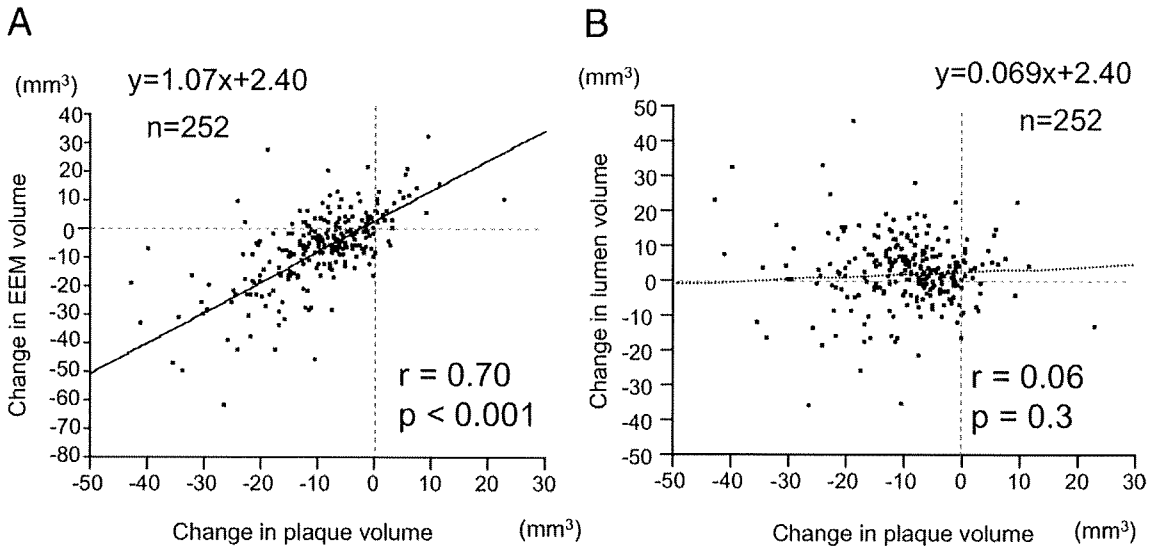

Figure 3 **Correlation Between the Change in Plaque Volume and the Change in Lumen Volume and EEM Volume**

There were significant correlations between the change in plaque volume and the change in external elastic membrane (EEM) volume **(A)**, whereas no significant correlation was observed between the change in plaque volume and the change in lumen volume **(B)**. The regression of plaque volume was associated with negative vessel remodeling.

The correlation between the reduction of LDL-C and the regression of PV was not significant in the present study as compared with previous placebo-controlled studies (Fig. 5) (6,20). One of the reasons might be that this study did not have a placebo arm of patients not receiving lipid-lowering therapy, which was not included for ethical reasons. Regression in PV was observed in a broad spectrum of patients regardless of the baseline LDL-C level. Pleiotropic

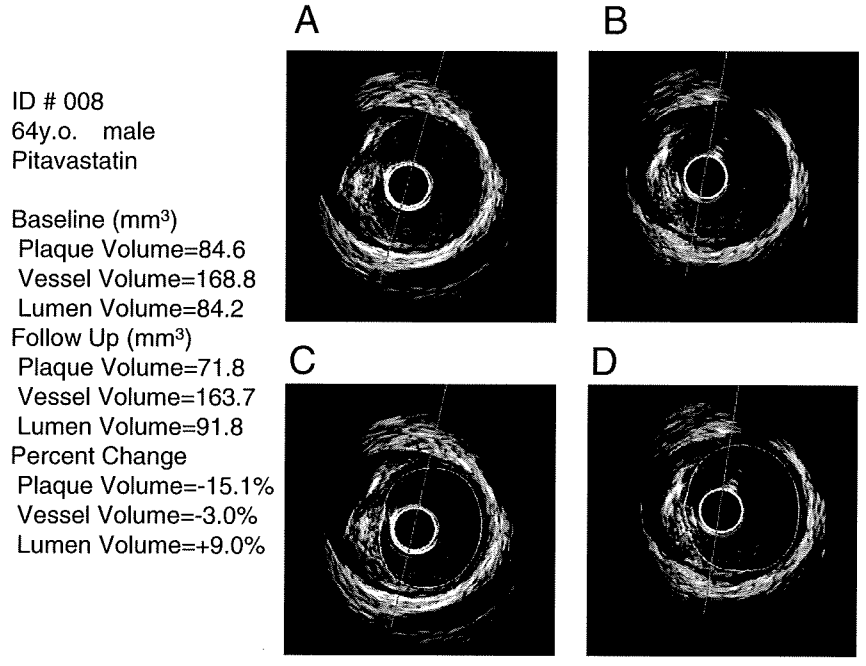

Figure 4 **Representative Cases of IVUS Analysis**

Shown are intravascular ultrasound (IVUS) images of the same cross section at the baseline **(A)** and at the follow-up **(B)**. **C** and **D** correspond to **A** and **B** with outlined leading edges of lumen and external elastic membrane. There is substantial reduction in plaque area observed for the cross-sectional images.

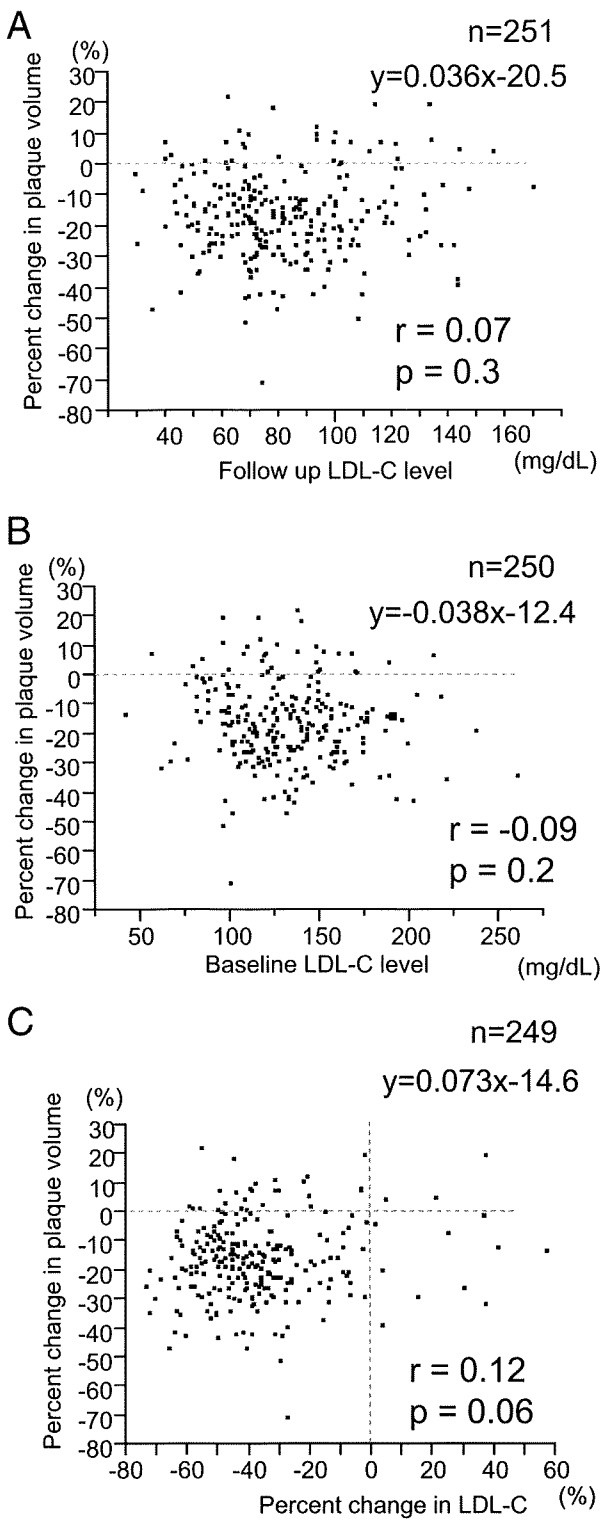

Figure 5 Relationship Between LDL-C and Percent Change in Plaque Volume

(A) Relationship between the follow-up low-density lipoprotein (LDL)-C level and percent change in plaque volume during 8- to 12-month follow-up. **(B)** Relationship between the baseline LDL-C level and percent change in plaque volume during 8- to 12-month follow-up. **(C)** Relationship between percent change in LDL-C and percent change in plaque volume during 8- to 12-month follow-up. There was no or slightly week correlation in these relationships.

Table 4 MACE and Adverse Events

	Pitavastatin (n = 147)	Atorvastatin (n = 149)	p Value
MACE	30 (20.4)	34 (22.8)	0.6
Myocardial Infarction	0	3 (2.0)	0.2‡
Coronary revascularization	30 (20.4)	31 (20.8)	0.9
TLR	16 (10.9)	19 (12.8)	0.6
TVR	9 (6.1)	8 (5.4)	0.8
Other vessel revascularization	8 (5.4)	9 (6.0)	0.8
Death from any cause	0	0	—
Adverse drug reaction	3 (2.0)	3 (2.0)	0.99
Myalgia	0	1 (0.7)	0.99‡
Eczema	2 (1.4)	3 (2.0)	0.99‡
Depression	1 (0.7)	0	0.5‡
Vomiting	1 (0.7)	0	0.5‡
Abnormality of laboratory value	19 (12.9)	17 (11.4)	0.7
AST/ALT*	11 (7.5)	11 (7.4)	0.97
CK†	8 (5.4)	8 (5.4)	0.98
Discontinuation	4 (2.7)	7 (4.7)	0.4
Adverse drug reaction	1 (0.7)	2 (1.3)	0.99‡
Abnormality of laboratory value	3 (2.0)	5 (3.4)	0.7‡
100% adherence	118 (80.3)	110 (73.8)	0.2

Data are expressed as n (%) unless otherwise specified. The chi-square test was used unless otherwise specified. *Upper than 100 (IU/l); in these, causes independent from trial drugs were suspected in 3 cases of the pitavastatin group and 3 of the atorvastatin group respectively. †Upper than 350 (IU/l); in these, causes independent from trial drugs were suspected in 1 cases of the pitavastatin group and 1 of the atorvastatin group respectively. ‡Fisher exact test.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CK = creatine kinase; MACE = major adverse cardiac events; TLR = target lesion revascularization; TVR = target vessel revascularization.

effects unrelated to LDL-C reduction might be one of the mechanisms of plaque regression. Other pharmacologic and lifestyle interventions applied after the onset of ACS might contribute to the modification of the plaque. In addition, PV regression observed in our study was associated with negative vessel remodeling, which might suggest that nonculprit plaques in patients with ACS were stabilized by statins (21).

Study limitations. The observation of a single plaque in the culprit vessel may not represent the pan-coronary nature of a plaque. Meanwhile, it has been documented that the ACS may represent the pan-coronary process of vulnerable plaque development, suggesting that a single plaque can reflect the general feature of whole coronary artery (19). Another criticism may be that arteries undergoing mechanical interventions were included, which could have affected atheroma measurements. However, IVUS examination for nonculprit vessel in emergent patients with ACS was not possible because of ethical reasons. IVUS might not be appropriate to identify thrombosis. It has been reported that thrombosis can be identified by IVUS with a sensitivity of <50% (22). However, fresh thrombus, which is frequently seen in ACS, can be detected with a true-positive rate of 80% (23). Therefore, meticulous care was taken to exclude thrombus in the present study as strictly as possible with criteria that thrombus in an IVUS image is usually mobile and relatively low echoic, with a uniform texture having

some scintillations, some microchannels, and a soft wavy surface.

Conclusions

Intensive statin therapy with 4 mg/day of pitavastatin or 20 mg/day of atorvastatin in patients with ACS resulted in significant regression of atheroma burden with negative vessel remodeling in a large-scale, multicenter trial using a central IVUS core laboratory in which the noninferiority of pitavastatin to atorvastatin was proved.

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Key Words: acute coronary syndrome ▪ plaque ▪ statins ▪ intravascular ultrasound.

APPENDIX

For a list of JAPAN-ACS Investigators, please see the online version of this article.

Three-Year Outcomes After Sirolimus-Eluting Stent Implantation for Unprotected Left Main Coronary Artery Disease

Insights From the j-Cypher Registry

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Background—Long-term outcomes after stenting of an unprotected left main coronary artery (ULMCA) with drug-eluting stents have not been addressed adequately despite the growing popularity of this procedure.

Methods and Results—j-Cypher is a multicenter prospective registry of consecutive patients undergoing sirolimus-eluting stent implantation in Japan. Among 12 824 patients enrolled in the j-Cypher registry, the unadjusted mortality rate at 3 years was significantly higher in patients with ULMCA stenting (n=582) than in patients without ULMCA stenting (n=12 242; 14.6% versus 9.2%, respectively; $P<0.0001$); however, there was no significant difference between the 2 groups in the adjusted risk of death (hazard ratio 1.23, 95% confidence interval 0.95 to 1.60, $P=0.12$). Among 476 patients whose ULMCA lesions were treated exclusively with a sirolimus-eluting stent, patients with ostial/shaft lesions (n=96) compared with those with bifurcation lesions (n=380) had a significantly lower rate of target-lesion revascularization for the ULMCA lesions (3.6% versus 17.1%, $P=0.005$), with similar cardiac death rates at 3 years (9.8% versus 7.6%, $P=0.41$). Among patients with bifurcation lesions, patients with stenting of both the main and side branches (n=119) had significantly higher rates of cardiac death (12.2% versus 5.5%; $P=0.02$) and target-lesion revascularization (30.9% versus 11.1%; $P<0.0001$) than those with main-branch stenting alone (n=261).

Conclusions—The higher unadjusted mortality rate of patients undergoing ULMCA stenting with a sirolimus-eluting stent did not appear to be related to ULMCA treatment itself but rather to the patients' high-risk profile. Although long-term outcomes in patients with ostial/shaft ULMCA lesions were favorable, outcomes in patients with bifurcation lesions treated with stenting of both the main and side branches appeared unacceptable. (***Circulation.* 2009;120:1866-1874.**)

Key Words: stents ■ revascularization ■ coronary disease ■ ischemia ■ restenosis

Although coronary artery bypass graft surgery has long been considered the "gold standard" for revascularization of patients with unprotected left main coronary artery (ULMCA) disease, drug-eluting stents (DES) have been used with increasing frequency for the percutaneous coronary intervention (PCI) of ULMCA disease.[1,2] However, recent reports have questioned the long-term safety of DES on the basis of a concern about increased rates of very late stent thrombosis (ST) compared with that found with bare-metal stents (BMS).[3] In patients undergoing ULMCA stenting, stent failure manifesting as restenosis or thrombosis may be associated with a large area of myocardium in jeopardy and subsequent fatal myocardial infarction or sudden death; therefore, the long-term performance of DES in ULMCA disease is considered to be more closely linked to survival outcome than in non-ULMCA disease. To assess long-term outcomes of ULMCA PCI with sirolimus-eluting stents (SES) in the real world, we investigated the 3-year clinical

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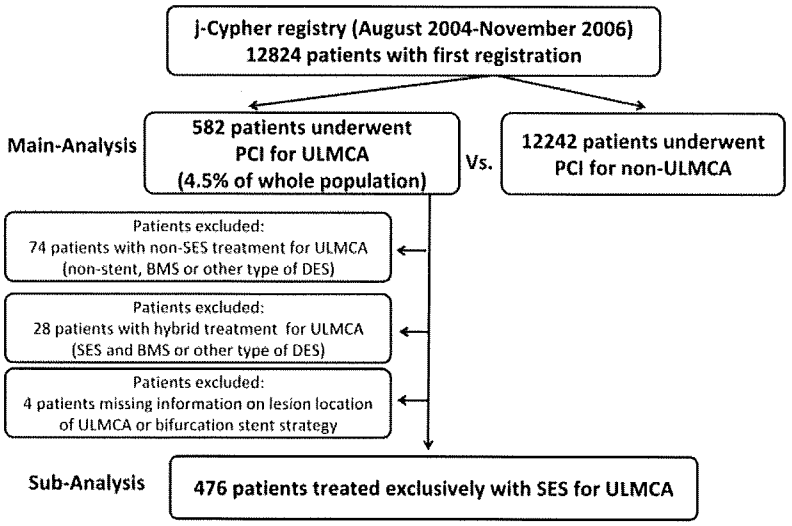

Figure 1. Study flow chart.

outcomes of patients undergoing SES implantation for ULMCA lesions in a large multicenter registry.

Clinical Perspective on p 1874

Methods

Study Design and Patient Population

The study design and patient enrollment for the j-Cypher registry has been described in detail elsewhere.[4] In brief, the j-Cypher registry is a physician-directed prospective multicenter registry in Japan enrolling consecutive patients undergoing SES implantation. From August 2004 to November 2006, 12 824 patients were enrolled in the j-Cypher registry for the first time, and 10 784 patients were treated exclusively with SES. The recommended antiplatelet regimen was aspirin (≥81 mg/d) indefinitely and a thienopyridine (200 mg of ticlopidine or 75 mg of clopidogrel daily) for at least 3 months. The duration of dual-antiplatelet therapy was left to the discretion of each attending physician.

The relevant review boards in all 37 participating centers approved the study protocol. Written informed consent was obtained from all patients enrolled.

Among the 12 824 patients enrolled in the j-Cypher registry, 582 underwent PCI for ULMCA disease (ULMCA group), and 12 242 patients underwent PCI for non-ULMCA lesions only (non-ULMCA group; Figure 1). Baseline characteristics, clinical outcomes, and causes of death in the ULMCA group were compared with those in the non-ULMCA group. Patients undergoing PCI for protected left main coronary artery lesions (n=101) were included in the non-ULMCA group.

Subgroup analysis was also conducted in 476 patients whose ULMCA lesion was treated exclusively by SES (Figure 1). Clinical outcomes in the subgroup study population were analyzed according to lesion location (ostial/shaft or bifurcation), stenting strategy (bifurcation 1-stent strategy or bifurcation 2-stent strategy), and number of diseased vessels other than ULMCA.

Definitions

The left main coronary artery was defined as "unprotected" when no surgical grafts to the left coronary system were patent. Renal insufficiency was defined as estimated glomerular filtration rate <30 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$ according to the Modification of Diet in Renal Disease study equation modified for Japanese patients.[5] Coronary angiographic parameters were assessed in each participating center either by visual assessment or by quantitative angiographic measurement. Bifurcation lesion was defined as that which involved a side branch ≥2.2 mm in diameter. Bifurcation 2-stent treatment was defined as stenting of both the main and side branches and 1-stent treatment as stenting of the main branch alone. When stenting for the side-branch ostium (circumflex in the vast majority of the cases) was performed before stenting of the main branch, the procedure was regarded as an elective 2-stent strategy. When stenting for the side-branch ostium was performed after stenting of the main branch, the procedure was regarded as a provisional 2-stent strategy.

During follow-up, death was regarded as cardiac in origin unless obvious noncardiac causes could be identified. Any death during the index hospitalization was regarded as cardiac death. Myocardial infarction was adjudicated according to the definition in the Arterial Revascularization Therapy Study.[6] ST was defined according to the Academic Research Consortium definition.[7] Both Academic Research Consortium "definite ST" and "definite/probable ST" on a patient basis were used as the end points for ST. Definite ST of the ULMCA lesion was also assessed separately. Target-lesion revascularization (TLR) was defined as either PCI or coronary artery bypass graft surgery due to restenosis or thrombosis of the target lesion that included the proximal and distal edge segments and the ostium of the side branches.

Statistical Analysis

Categorical variables are presented as counts and/or percentages and were compared with the χ^2 test. Continuous variables were expressed as mean±SD unless otherwise indicated. Continuous variables were compared with the Student t test, ANOVA, or Wilcoxon rank sum test on the basis of their distribution. Cumulative incidences of adverse events were estimated by the Kaplan–Meier method, and curves were compared with the log-rank test.

We used the Cox proportional hazard model to identify risk factors for end points such as death, cardiac death, and TLR. Proportional hazard assumptions were assessed by the plot of log (time) versus log [−log (survival)] stratified by risk factor variables. All variables in Table 1 were used as candidates for risk factors, and we selected those with $P<0.10$. We then conducted a backward-selection procedure on the multivariable Cox proportional hazard model with all selected risk factors and identified the independent risk factors with $P<0.05$. Lastly, we added ULMCA intervention as a risk factor and developed the final model.

We conducted a similar backward selection for multivariable Cox proportional hazard models to assess the effect of lesion location and bifurcation stenting strategy on all-cause death, cardiac death, or TLR in the subgroup of patients with ULMCA stenting. Then, we reached the final model with independent risk factors and bifurcation lesion or 2-stent strategy.

Adjusted survival curves were drawn for the 2 groups of patients with or without ULMCA stenting by use of the Cox proportional hazard model in conjunction with methods described by Ghali et al,[8] with adjustment for the above-mentioned variables selected by the backward-selection procedure.