Table 3
Event rates at three years in statin versus no-statin group in each stratum

Variable	Statin	No Statin	p Value
Nonchronic kidney disease (estimated glomerular filtration rate ≥60 ml/min/1.73 m^2)			
All-cause death	139/4,747 (3.7%)	201/4,212 (5.7%)	<0.0001
Major adverse cardiovascular events	281/4,747 (6.8%)	324/4,212 (8.7%)	0.0006
Cardiovascular death	62/4,747 (1.6%)	98/4,212 (2.8%)	0.0004
Myocardial infarction	117/4,747 (2.8%)	116/4,212 (3.0%)	0.37
Stroke	125/4,747 (3.0%)	151/4,212 (4.2%)	0.005
Any coronary revascularization	1,322/4,747 (29.9%)	1,140/4,212 (29.3%)	0.75
Mild chronic kidney disease (estimated glomerular filtration rate ≥30–<60 ml/min/1.73 m^2)			
All-cause death	122/2,135 (7.1%)	240/2,432 (11.8%)	<0.0001
Major adverse cardiovascular events	170/2,135 (9.4%)	291/2,432 (13.9%)	<0.0001
Cardiovascular death	61/2,135 (3.4%)	129/2,432 (6.4%)	<0.0001
Myocardial infarction	53/2,135 (2.8%)	78/2,432 (3.7%)	0.18
Stroke	81/2,135 (4.6%)	130/2,432 (6.4%)	0.01
Any coronary revascularization	552/2,135 (27.9%)	583/2,432 (26.5%)	0.29
Severe chronic kidney disease (estimated glomerular filtration rate <30 ml/min/1.73 m^2)			
All-cause death	43/229 (21.5%)	86/379 (26.4%)	0.24
Major adverse cardiovascular events	41/229 (21.1%)	81/379 (25.7%)	0.34
Cardiovascular death	26/229 (13.5%)	55/379 (18.1%)	0.34
Myocardial infarction	14/229 (8.1%)	10/379 (3.9%)	0.055
Stroke	13/229 (6.2%)	28/379 (8.9%)	0.39
Any coronary revascularization	49/229 (23.2%)	67/379 (21.7%)	0.23
Hemodialysis			
All-cause death	25/117 (27.2%)	104/455 (28.6%)	0.60
Major adverse cardiovascular events	26/117 (28.2%)	91/455 (25.4%)	0.49
Cardiovascular death	14/117 (16.2%)	68/455 (19.9%)	0.43
Myocardial infarction	8/117 (8.2%)	17/455 (4.8%)	0.17
Stroke	10/117 (11.2%)	30/455 (9.0%)	0.25
Any coronary revascularization	43/117 (44.7%)	167/455 (44.6%)	0.59

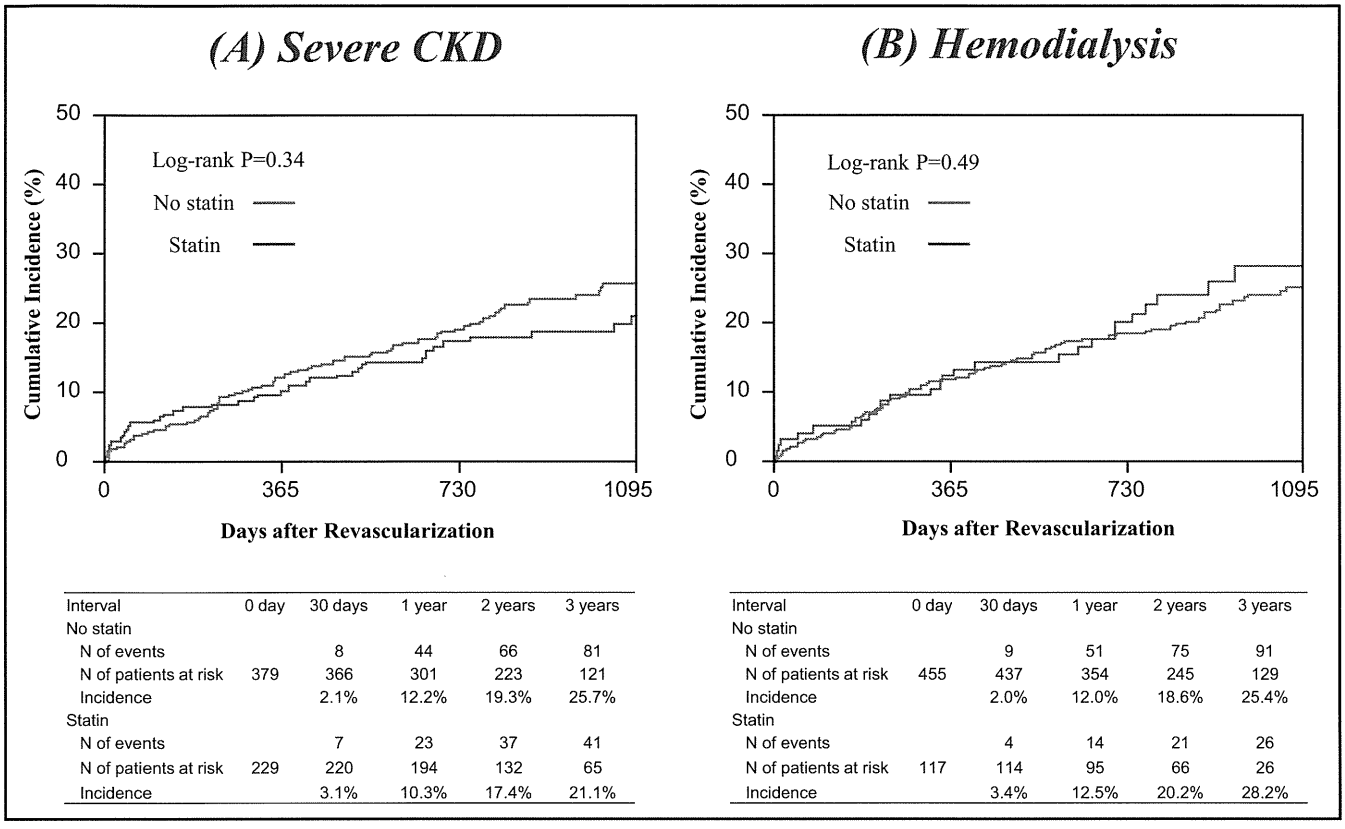
Data are presented as number of events/number of patients (incidence). Major adverse cardiovascular events were a composite of cardiovascular death, myocardial infarction, or stroke.

Discussion

The main findings of the present study are as follows: (1) statin therapy after coronary revascularization was associated with lower cardiovascular risk in patients with non-CKD and mild CKD but not in those with severe CKD and HD; (2) there was no significant difference in changes in eGFR at 1-year follow-up between the statin and no-statin group in patients with CKD.

Post hoc analysis of the Cholesterol and Recurrent Events (CARE) study revealed that statin therapy for secondary prevention decreased the risk for death from coronary disease or symptomatic nonfatal myocardial infarction in patients with mild CKD and creatinine clearance ≤75 ml/min (mean creatinine clearance 61.3 ± 10.1 ml/min).[8] Post hoc analysis of the Aggressive Lipid-Lowering Initiation Abates New Cardiac Events (ALLIANCE) study also showed that statin therapy for secondary prevention decreased the risk for cardiovascular events in patients with mild CKD and eGFR ≤60 ml/min/1.73 m^2 (mean eGFR 51.2 ± 8.1 ml/min/1.73 m^2).[9] Consistent with these reports, risk for cardiovascular events was significantly lower in the statin group compared to the no-statin group in patients with mild CKD (eGFR ≥30 to <60 ml/min/1.73 m^2) in this study. Thus, statin therapy should be strongly recommended in patients with mild CKD and those with non-CKD after coronary revascularization. When we look at each outcome, statin therapy was associated with lower risks for cardiovascular death and stroke but not for myocardial infarction and coronary revascularization. The number of study patients might be underpowered to test the difference in each outcome measurement in each stratum. Lower prevalence of myocardial infarction compared to stroke in a Japanese population could also contribute to a lack of significant effects of statins to prevent myocardial infarction. A comparable prevalence of any coronary revascularization between the statin and no-statin groups was not a surprising finding because randomized trials have failed to show the effects of statins to decrease restenosis.[19]

Patients with HD are a representative patient population who are resistant to cardiovascular preventive medication. Statins have failed to prove benefits by randomized trials in patients with HD.[10,11] The SHARP trial showed that simvastatin plus ezetimibe significantly decreased the first major atherosclerotic events in patients with severe CKD (eGFR ≥15 to <30 ml/min/1.73 m^2).[12] The study patients of the SHARP trial included 27% patients on HD and 5% on peritoneal dialysis and was designed to evaluate the effect of intensive lowering of low-density lipoprotein cholesterol in patients without known coronary artery disease. If the effects of intensive lowering therapy of low-density lipo-



Interval	0 day	30 days	1 year	2 years	3 years
No statin					
N of events		8	44	66	81
N of patients at risk	379	366	301	223	121
Incidence		2.1%	12.2%	19.3%	25.7%
Statin					
N of events		7	23	37	41
N of patients at risk	229	220	194	132	65
Incidence		3.1%	10.3%	17.4%	21.1%

Interval	0 day	30 days	1 year	2 years	3 years
No statin					
N of events		9	51	75	91
N of patients at risk	455	437	354	245	129
Incidence		2.0%	12.0%	18.6%	25.4%
Statin					
N of events		4	14	21	26
N of patients at risk	117	114	95	66	26
Incidence		3.4%	12.5%	20.2%	28.2%

Figure 3. Cumulative incidence of major adverse cardiovascular events (composite of cardiovascular death, myocardial infarction, and stoke) in the statin versus no-statin group in the *(A)* severe chronic kidney disease stratum (estimated glomerular filtration rate <30 ml/min/1.73 m^2) and *(B)* hemodialysis stratum.

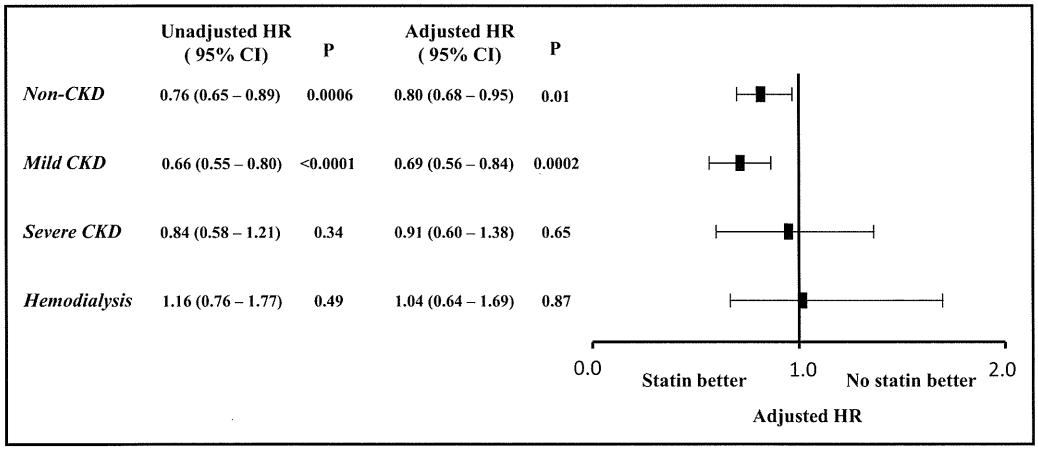


Figure 4. Unadjusted and adjusted risks of statin use for major adverse cardiovascular events (composite of cardiovascular death, myocardial infarction, and stoke) in the nonchronic kidney disease (estimated glomerular filtration rate ≥60 ml/min/1.73 m^2), mild chronic kidney disease (estimated glomerular filtration rate ≥30 to <60 ml/min/1.73 m^2), severe chronic kidney disease (estimated glomerular filtration rate <30 ml/min/1.73 m^2), and hemodialysis strata. CI = confidence interval; HR = hazard ratio.

protein cholesterol were evaluated separately in patient not on dialysis and in patients on dialysis, the relative risk decrease by simvastatin plus ezetimibe appeared to be attenuated in patients on dialysis. Because individual effects of simvastatin and ezetimibe were not assessed in SHARP, effects of statins in cardiovascular prevention in patients not on dialysis with severe CKD remain uncertain. In the present analysis studying a secondary prevention cohort, association of statin therapy with lower risk for MACEs was not found in patients not on HD with severe CKD (eGFR <30 ml/min/1.73 m^2) or in patients on HD. These findings corroborated previous studies that could not prove benefits of statins for cardiovascular prevention in patients on HD[10,11] and suggested that the threshold of renal dysfunction regarding a potential cardiovascular preventive benefit of statins may lie between mild and severe renal dysfunction.

Therefore, statins should be considered more important as preventive medication in the early stage of CKD, whereas the effect of statins may be attenuated in patients with severe CKD or those on HD at high cardiovascular risk. Patients with advanced CKD generally have advanced atherosclerosis, typically characterized by heavy calcification, and statins may no longer provide significant benefits in patients with end-stage vascular pathology. Other possible factors associated with lack of risk decreased by low-density lipoprotein cholesterol lowering in patients with advanced CKD may include defective high-density lipoprotein and high oxidation rates of low-density lipoprotein.[20] Thus, in general, statin therapy should be started at earlier stage of CKD to improve cardiovascular outcomes in patients with renal dysfunction. In contrast, post hoc analysis of the 4D (Die Deutsche Diabetes Dialyze) study revealed that statin therapy decreased rates of adverse outcomes in the highest quartile of low-density lipoprotein cholesterol (≥145 mg/dl) in patients on HD.[21] Statin therapy might be effective in selected patients on HD in whom increased low-density lipoprotein might be playing a major role in the pathogenesis of cardiovascular events. In an aging society, the number of patients with coronary artery disease and advanced CKD is expected to increase, and more effective strategies for secondary cardiovascular prevention in patients with advanced CKD need to be established.

With respect to renal outcomes, eGFR level was decreased in the 2 groups in patients without CKD and decrease of eGFR was greater in the statin than in the no-statin group. Because a significant association between statin therapy and change in eGFR was not shown in any other CKD stratum, difference in eGFR decrease between the 2 groups might result from differences in patients' background characteristics rather than the effects of statins. In accord with our reports, Strippoli et al[22] reported that statin therapy did not improve eGFR in a meta-analysis. In contrast, another meta-analysis by Sandhu et al[23] showed that statin therapy achieved a small decrease in the rate of kidney function loss especially in populations with cardiovascular disease. Although the results of these 2 meta-analyses were different regarding the effects of statins on eGFR, the 2 studies consistently indicated a significant decrease in proteinuria by statin therapy.[22,23] Because proteinuria is an independent risk factor for coronary artery disease, potential benefits of statin therapy on renal dysfunction may augment the beneficial effects of statins in secondary cardiovascular prevention in patients with CKD.[24] Although we could not evaluate the relation between proteinuria and cardiovascular events, risk decrease for MACEs in patients with mild CKD might be associated with a decrease of proteinuria. Further investigations are needed to elucidate the association of statin therapy with decrease of proteinuria or improvement of eGFR level.

Some limitations to our study should be considered. This study was an observational study and had limitations that are common to all observational studies caused by differences in patients' background characteristics among groups. Because information about medical therapy was obtained only at hospital discharge, adherence of patients to medications and crossover of medications was not considered in this study. Statin-treated patients included statin-naive patients and patients treated with statins before the index hospitalization. Therefore, statin-treated patients include patients who required coronary revascularization despite primary preventive statin therapy. We could not assess the side effects of statins in our database, although they might be another important issue to be addressed, particularly in patients with CKD. The number of patients in the severe CKD and HD strata was relatively small compared with that in the non-CKD and mild CKD strata.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.amjcard.2012.07.021.

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Comparison of Long-Term Outcome After Percutaneous Coronary Intervention Versus Coronary Artery Bypass Grafting in Patients With Unprotected Left Main Coronary Artery Disease (from the CREDO-Kyoto PCI/CABG Registry Cohort-2)

Hiroki Shiomi, MD[a], Takeshi Morimoto, MD, PhD[c], Mamoru Hayano, MD[d], Yutaka Furukawa, MD[e], Yoshihisa Nakagawa, MD[f], Junichi Tazaki, MD[a], Masao Imai, MD[a], Kyohei Yamaji, MD[g], Tomohisa Tada, MD[i], Masahiro Natsuaki, MD[a], Sayaka Saijo, MD[a], Shunsuke Funakoshi, MD[a], Kazuya Nagao, MD[j], Koji Hanazawa, MD[f], Natsuhiko Ehara, MD[e], Kazushige Kadota, MD[k], Masashi Iwabuchi, MD[g], Satoshi Shizuta, MD[a], Mitsuru Abe, MD[l], Ryuzo Sakata, MD[b], Hitoshi Okabayashi, MD[m], Michiya Hanyu, MD[h], Fumio Yamazaki, MD[n], Mitsuomi Shimamoto, MD[n], Noboru Nishiwaki, MD[o], Yutaka Imoto, MD[p], Tatsuhiko Komiya, MD[q], Minoru Horie, MD[r], Hisayoshi Fujiwara, MD[s], Kazuaki Mitsudo, MD[k], Masakiyo Nobuyoshi, MD[g], Toru Kita, MD[e], and Takeshi Kimura, MD[a,*], on Behalf of the CREDO-Kyoto PCI/CABG Registry Cohort-2 Investigators

The long-term outcome of percutaneous coronary intervention (PCI) compared to coronary artery bypass grafting (CABG) for unprotected left main coronary artery disease (ULMCAD) remains to be investigated. We identified 1,005 patients with ULMCAD of 15,939 patients with first coronary revascularization enrolled in the CREDO-Kyoto PCI/CABG Registry Cohort-2. Cumulative 3-year incidence of a composite of death/myocardial infarction (MI)/stroke was significantly higher in the PCI group than in the CABG group (22.7% vs 14.8%, p = 0.0006, log-rank test). However, the adjusted outcome was not different between the PCI and CABG groups (hazard ratio [HR] 1.30, 95% confidence interval [CI] 0.79 to 2.15, p = 0.30). Stratified analysis using the SYNTAX score demonstrated that risk for a composite of death/MI/stroke was not different between the 2 treatment groups in patients with low (<23) and intermediate (23 to 33) SYNTAX scores (adjusted HR 1.70, 95% CI 0.77 to 3.76, p = 0.19; adjusted HR 0.86, 95% CI 0.37 to 1.99, p = 0.72, respectively), whereas in patients with a high SYNTAX score (≥33), it was significantly higher after PCI than after CABG (adjusted HR 2.61, 95% CI 1.32 to 5.16, p = 0.006). In conclusion, risk of PCI for serious adverse events seemed to be comparable to that after CABG in patients with ULMCAD with a low or intermediate SYNTAX score, whereas PCI compared with CABG was associated with a higher risk for serious adverse events in patients with a high SYNTAX score. **(Am J Cardiol 2012;110:924–932)**

In recent years, several observational studies have reported favorable clinical outcomes of percutaneous coronary intervention (PCI) using drug-eluting stents (DESs) in patients with unprotected left main coronary artery disease (ULMCAD).[1–3] The Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery (SYNTAX) randomized trial reported comparable safety and efficacy outcomes of PCI compared to coronary artery bypass grafting (CABG) in the ULMCAD subset.[4–6] Reflecting these study results, updated clinical guidelines for ULM-

[a]Departments of Cardiovascular Medicine and [b]Cardiovascular Surgery, Graduate School of Medicine, Kyoto University, Kyoto, Japan; [c]Center for General Internal Medicine and Emergency Care, Kinki University School of Medicine, Osaka, Japan; [d]Division of Cardiology, Gunma Cardiovascular Center, Gumma, Japan; [e]Department of Cardiovascular Medicine, Kobe City Medical Center General Hospital, Kobe, Japan; [f]Division of Cardiology, Tenri Hospital, Tenri, Japan; Divisions of [g]Cardiology and [h]Cardiovascular Surgery, Kokura Memorial Hospital, Kitakyushu, Japan; [i]Deutsches Herzzentrum, Technische Universität, Munich, Germany; [j]Division of Cardiology, Osaka Red Cross Hospital, Osaka, Japan; [k]Division of Cardiology, Kurashiki Central Hospital, Kurashiki, Japan; [l]Division of Cardiology, Kyoto Medical Center, Kyoto, Japan; [m]Department of Cardiovascular Surgery, Iwate Medical University, Iwate, Japan; [n]Division of Cardiovascular Surgery, Shizuoka City Shizuoka Hospital, Shizuoka, Japan; [o]Division of Cardiovascular Surgery, Nara Hospital, Kinki University Faculty of Medicine, Nara, Japan; [p]Department of Cardiovascular Surgery, Graduate School of Medicine, Kagoshima University, Kagoshima, Japan; [q]Division of Cardiovascular Surgery, Kurashiki Central Hospital, Kurashiki, Japan; [r]Department of Cardiovascular and Respiratory Medicine, Shiga University of Medical Science Hospital, Shiga, Japan; [s]Division of Cardiology, Hyogo Prefectural Amagasaki Hospital, Amagasaki, Japan. Manuscript received March 14, 2012; revised manuscript received and accepted May 23, 2012.

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*Corresponding author: Tel: 81-75-751-4254; fax: 81-75-751-3289.
E-mail address: taketaka@kuhp.kyoto-u.ac.jp (T. Kimura).

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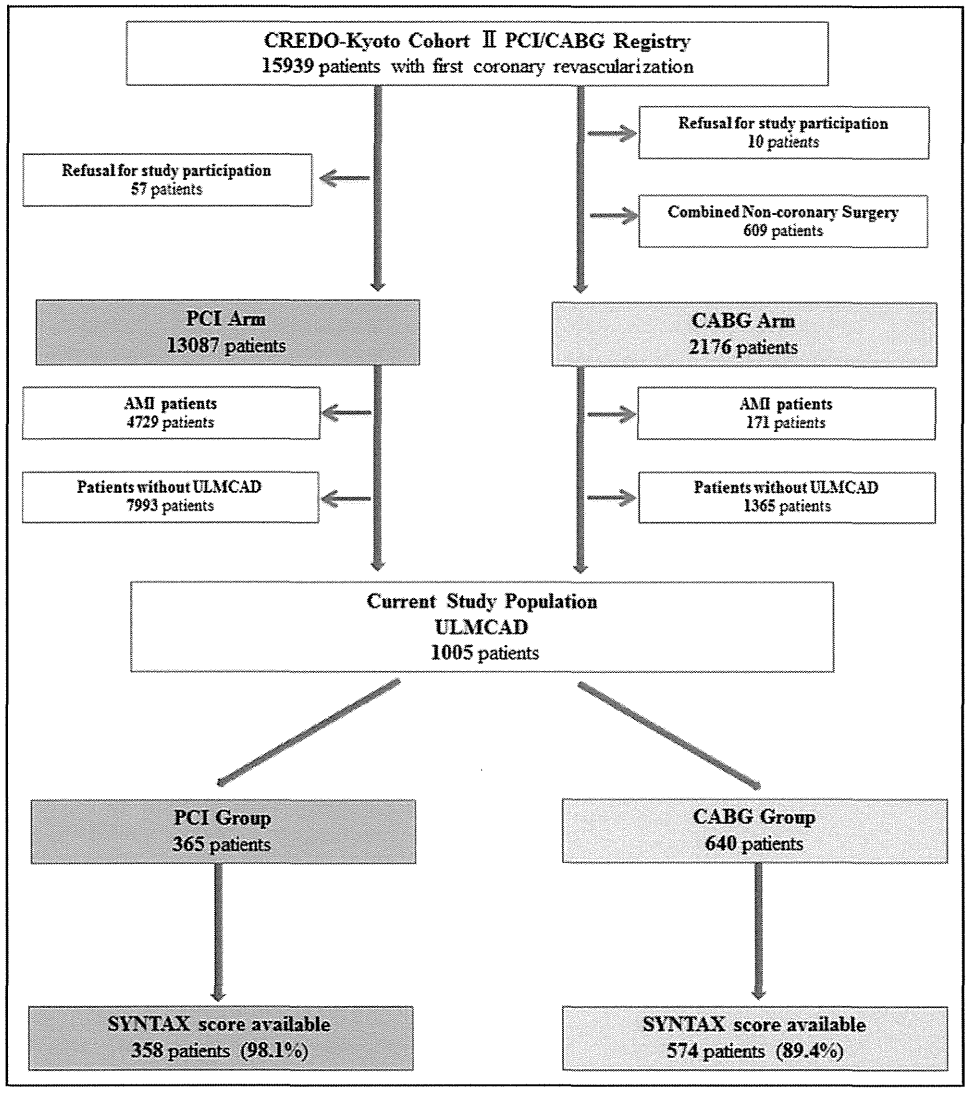


Figure 1. Study flowchart. AMI = acute myocardial infarction.

CAD regarded PCI as an alternative to CABG in patients with less complex coronary anatomy or in patients with high surgical risk.[7,8] However, the number of patients enrolled in these trials was insufficient in drawing definitive conclusions on the role of PCI in treating patients with ULMCAD. Therefore, we evaluated the long-term clinical outcome of PCI compared to CABG and the utility of the SYNTAX score for risk stratification in patients with ULMCAD in a large observational database in Japan.

Methods

The Coronary Revascularization Demonstrating Outcome Study in Kyoto (CREDO-Kyoto) PCI/CABG Registry Cohort-2 is a physician-initiated, noncompany-sponsored, multicenter registry that enrolled consecutive patients undergoing first coronary revascularization in 26 centers in Japan from January 2005 through December 2007. The relevant ethics committees in all 26 participating centers (Supplementary Appendix A) approved the research protocol. Because of retrospective enrollment, written informed consent from the patients was waived. However, patients who refused participation in the study when contacted for follow-up were excluded.

The study design and patient enrollment in the registry have been described in detail previously.[9] Of 15,939 patients enrolled in the registry, the study population for the present prespecified subanalysis of the CREDO-Kyoto PCI/CABG Registry Cohort-2 consisted of 1,005 patients with ULMCAD (365 patients with PCI and 640 patients with CABG) excluding those patients who refused study participation, had concomitant noncoronary surgery, and had acute myocardial infarction (MI; Figure 1).

Demographic, angiographic, and procedural data were collected from hospital charts according to prespecified definitions by experienced research coordinators in an independent research organization (Research Institute for Production Development, Kyoto, Japan; Supplementary Appendix B). Patients with ULMCAD were identified using angiographic information recorded in their hospital charts. Therefore, the present study population included those patients in

Table 1
Comparison of baseline characteristics between percutaneous and coronary artery bypass grafting groups

	PCI (n = 365)	CABG (n = 640)	p Value
Clinical characteristics			
Age (years)	71.4 ± 10.1	69.4 ± 9.2	0.001
Age ≥75 years*†	151 (41%)	208 (33%)	0.005
Men*	259 (71%)	490 (77%)	0.051
Body mass index (kg/m^2)	23.4 ± 3.4	23.2 ± 3.0	0.35
Body mass index <25.0 kg/m^2*	271 (74%)	467 (73%)	0.66
Unstable angina pectoris	52 (14%)	71 (11%)	0.15
Hypertension*	313 (86%)	542 (85%)	0.65
Diabetes mellitus*	155 (42%)	291 (45%)	0.36
On insulin therapy	35 (9.6%)	93 (15%)	0.02
Current smoker*	79 (22%)	157 (25%)	0.30
Heart failure*	76 (21%)	131 (20%)	0.89
Ejection fraction (%)	59.3 ± 14.7	60.2 ± 13.4	0.34
Ejection fraction ≤40%	34 (12%)	56 (9.5%)	0.30
Mitral regurgitation grade 3/4*	25 (6.9%)	17 (2.7%)	0.002
Previous myocardial infarction*	70 (19%)	105 (16%)	0.27
Previous stroke (symptomatic)*	54 (15%)	75 (12%)	0.16
Peripheral vascular disease*	45 (12%)	76 (12%)	0.83
Estimated glomerular filtration rate (ml/min/1.73 m^2)	62.2 (45.7–74.5)	61.0 (46.6–72.1)	0.20
Estimated glomerular filtration rate <30 ml/min/1.73 m^2 without hemodialysis*†	19 (5.2%)	38 (5.9%)	0.63
Hemodialysis*†	26 (7.1%)	44 (6.9%)	0.88
Anemia (hemoglobin <11.0 g/dl)*	72 (20%)	128 (20%)	0.92
Platelet count <100 × 10^9/L*	3 (0.8%)	19 (3.0%)	0.02
Chronic obstructive pulmonary disease*	12 (3.3%)	17 (2.7%)	0.57
Liver cirrhosis*	9 (2.5%)	19 (3.0%)	0.64
Malignancy*	58 (16%)	69 (11%)	0.02
Procedural characteristics			
Number of target lesions or anastomoses	2.00 ± 1.03	3.09 ± 1.04	<0.0001
Extent of coronary artery disease			<0.0001
Isolated unprotected left main coronary artery disease	31 (8.5%)	57 (8.9%)	
Unprotected left main coronary artery + 1-vessel disease	89 (24.4%)	108 (16.9%)	
Unprotected left main coronary artery + 2-vessel disease	132 (36.2%)	182 (28.4%)	
Unprotected left main coronary artery + 3-vessel disease	113 (31.0%)	293 (45.8%)	
Target of proximal left anterior descending coronary artery*	174 (48%)	451 (70%)	<0.0001
Target of chronic total occlusion*	45 (12%)	166 (26%)	<0.0001
Emergency procedure	34 (9.3%)	50 (7.8%)	0.41
SYNTAX score	26.5 (21–34)	30 (22–40)	<0.0001
Low <23	123 (34.4%)	154 (26.8%)	
Intermediate 23–33	131 (36.6%)	177 (30.8%)	0.0002
High ≥33	104 (29.1%)	243 (42.3%)	
Total number of stents	2.78 ± 1.70	—	—
Total stent length (mm)	58.7 ± 41.0	—	—
Stent use	357 (98%)	—	—
Drug-eluting stent use	277 (78%)	—	—
Internal thoracic artery use	—	629 (98%)	—
Off pump	—	414 (65%)	—
Baseline medications			
Antiplatelet therapy			
Thienopyridine	362 (99%)	72 (11%)	<0.0001
Ticlopidine	316 (87%)	67 (94%)	0.07
Clopidogrel	46 (13%)	4 (5.6%)	
Aspirin	361 (99%)	632 (99%)	0.83
Cilostazol*	45 (12%)	41 (6.4%)	0.002
Other medications			
Statins*	184 (50%)	199 (31%)	<0.0001
β Blockers*	110 (30%)	174 (27%)	0.32
Angiotensin-converting enzyme inhibitor/angiotensin receptor blocker*	191 (52%)	211 (33%)	<0.0001
Nitrates*	170 (47%)	230 (36%)	0.001
Calcium channel blockers*	171 (47%)	332 (52%)	0.13
Nicorandil*	94 (26%)	277 (43%)	<0.0001

Table 1
(*continued*)

	PCI (n = 365)	CABG (n = 640)	p Value
Warfarin*	30 (8.2%)	244 (38%)	<0.0001
Proton pump inhibitors*†	92 (25%)	263 (41%)	<0.0001
H_2 blockers*	78 (21%)	204 (32%)	0.0003

Continuous variables are presented as mean ± SD or median (interquartile range).
* Risk-adjusting variables selected for Cox proportional hazard models.
† Risk-adjusting variables selected for multivariable models (parsimonious models for subgroup analysis).

whom PCI was not attempted for the LMCA lesions based on clinical judgments. Definitions for clinical characteristics are described in the Supplemental Text.

The SYNTAX score was calculated using the SYNTAX score calculator (available at: http://www.syntaxscore.com) by a dedicated SYNTAX score committee (Supplementary Appendix C) in a blinded fashion to the clinical data. Intra- and interobserver variabilities of the SYNTAX score calculation in our group were previously reported.[10] Cut-off values for SYNTAX score tertiles (low <23, intermediate 23 to 33, and high ≥33) were defined according to analysis in the SYNTAX trial.[4,5]

The primary outcome measurement for the present analysis was defined as a composite of all-cause death, MI, and stroke. Other prespecified end points included all-cause death, cardiac death, MI, stroke, and coronary revascularization. Death was regarded as cardiac in origin unless obvious noncardiac causes could be identified. Any death during the index hospitalization for coronary revascularization was regarded as cardiac death. MI was defined according to the definition in the Arterial Revascularization Therapy Study.[11] Stroke was defined as ischemic or hemorrhagic stroke requiring hospitalization with symptoms lasting >24 hours. Coronary revascularization was defined as PCI or CABG for any reason. Scheduled staged coronary revascularization procedures performed within 3 months of the initial procedure were not regarded as follow-up events but were included in the index procedure.

Collection of follow-up information was conducted mainly through review of inpatient and outpatient hospital charts by clinical research coordinators in the independent research organization. Additional follow-up information was collected through contact with patients, relatives, and/or referring physicians by sending mail with questions on vital status, additional hospitalizations, and status of antiplatelet therapy. Death, MI, stent thrombosis, and stroke were adjudicated by the clinical event committee (Supplementary Appendix D).

Because final data collection for follow-up events was initiated on July 1, 2009, follow-up events were censored on this date. Median follow-up duration for surviving patients was 1,027 days (interquartile range 734 to 1,311). Complete 1-year follow-up information was obtained in 95.4% of patients (96.4% in PCI group and 94.8% in CABG group, p = 0.24).

Categorical variables were presented as number and percentage and were compared with chi-square test. Continuous variables were expressed as mean ± SD or median with interquartile range. Continuous variables were compared using Student's *t* test or Wilcoxon rank-sum test based on their distributions.

Cumulative incidence was estimated by the Kaplan–Meier method and differences were assessed using log-rank test. Effects of PCI compared to CABG for individual end points were expressed as hazard ratios (HRs) with 95% confidence intervals (CIs). In the entire study population, HR was estimated using nonparsimonious multivariable Cox proportional hazard models adjusted for the 30 clinically relevant factors listed in Table 1, which was consistent with previous reports from the current registry. Continuous variables were dichotomized using clinically meaningful reference values or median values. Proportional hazard assumptions for potential independent risk-adjusting variables were assessed on log (time) versus log(−log) (survival) plots stratified by the variable, and assumptions were verified as acceptable for all variables. We incorporated the 26 participating centers in the Cox proportional hazard models as the stratification variable.

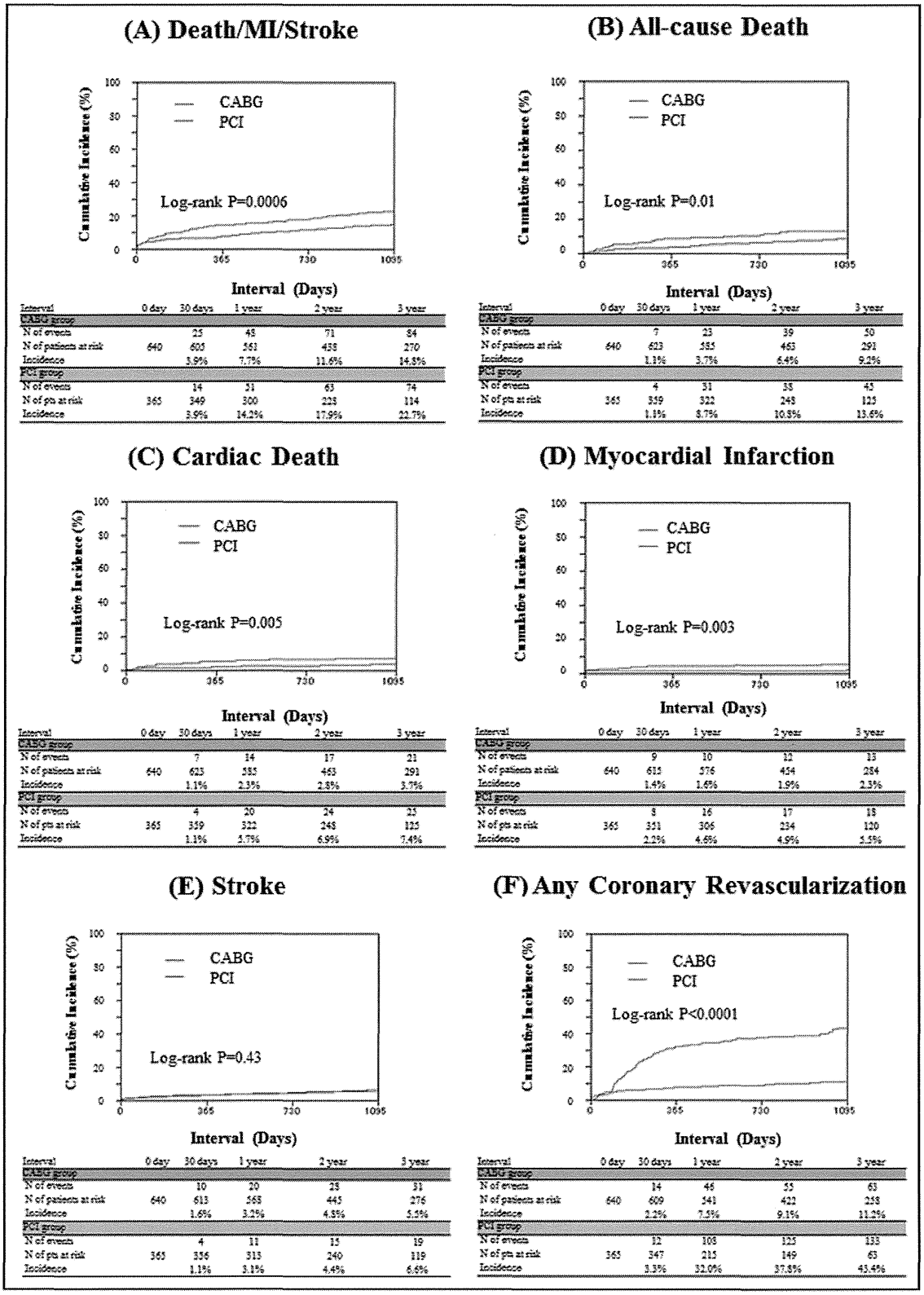
Unadjusted and adjusted risks of PCI compared to CABG for the primary outcome measurement were evaluated in each SYNTAX score category as a subgroup analysis to assess utility of the SYNTAX score for risk stratification. In addition to modes of coronary revascularization (PCI vs CABG), 4 variables with a p value <0.05 in the previously described full model (age ≥75 years, estimated glomerular filtration rate <30 ml/min/1.73 m^2 without hemodialysis, hemodialysis, and proton pump inhibitors) were included in multivariable models for subgroup analysis reflecting our preference for parsimonious models to avoid overfitting.

Statistical analyses were conducted by a physician (H.S.) and a statistician (T.M.) using JMP 8.0 and SAS 9.2 (SAS Institute, Cary, North Carolina). All statistical analyses were 2-tailed and p values <0.05 were considered statistically significant.

Results

Patients in the PCI group were older and more often had malignancy and severe mitral regurgitation, whereas patients in the CABG group more often had diabetes on insulin therapy and thrombocytopenia (Table 1).

The CABG group included more patients with complex coronary anatomy and larger numbers of target lesions or anastomoses (Table 1). SYNTAX scores were available in 932 patients (92.7%). Median SYNTAX score was significantly higher in the CABG group than in the PCI group. Stents were used in 98% of patients in the PCI group and



Interval	0 day	30 days	1 year	2 year	3 year
CABG group					
N of events		25	48	71	84
N of patients at risk	640	605	561	458	270
Incidence		3.9%	7.7%	11.6%	14.5%
PCI group					
N of events		14	31	63	74
N of pts at risk	365	349	300	225	114
Incidence		3.9%	14.2%	17.9%	22.7%

Interval	0 day	30 days	1 year	2 year	3 year
CABG group					
N of events		7	23	39	50
N of patients at risk	640	623	585	463	293
Incidence		1.1%	3.7%	6.4%	9.2%
PCI group					
N of events		4	31	35	43
N of pts at risk	365	359	322	248	125
Incidence		1.1%	8.7%	10.5%	13.6%

Interval	0 day	30 days	1 year	2 year	3 year
CABG group					
N of events		7	14	17	21
N of patients at risk	640	623	585	463	293
Incidence		1.1%	2.3%	2.8%	3.7%
PCI group					
N of events		4	20	24	25
N of pts at risk	365	359	322	248	125
Incidence		1.1%	5.7%	6.9%	7.4%

Interval	0 day	30 days	1 year	2 year	3 year
CABG group					
N of events		9	10	12	13
N of patients at risk	640	615	576	454	284
Incidence		1.4%	1.6%	1.9%	2.3%
PCI group					
N of events		8	16	17	18
N of pts at risk	365	351	306	234	120
Incidence		2.2%	4.6%	4.9%	5.5%

Interval	0 day	30 days	1 year	2 year	3 year
CABG group					
N of events		10	20	28	31
N of patients at risk	640	613	565	445	276
Incidence		1.6%	3.2%	4.5%	5.5%
PCI group					
N of events		4	11	15	19
N of pts at risk	365	356	313	240	119
Incidence		1.1%	3.1%	4.4%	6.6%

Interval	0 day	30 days	1 year	2 year	3 year
CABG group					
N of events		14	46	55	63
N of patients at risk	640	609	541	422	258
Incidence		2.2%	7.5%	9.1%	11.2%
PCI group					
N of events		12	108	125	133
N of pts at risk	365	347	215	149	63
Incidence		3.3%	32.0%	37.5%	45.4%

Figure 2. Kaplan–Meier event curves of percutaneous coronary intervention versus coronary artery bypass grafting for *(A)* a composite of all-cause death, myocardial infarction, and stroke, *(B)* all-cause death, *(C)* cardiac death, *(D)* stroke, *(E)* myocardial infarction, and *(F)* any revascularization.

≥1 DES was used in 78% of patients. In the PCI group, PCI targeting of an ULMCA lesion was performed in 306 patients (83.4%), in whom a left main distal bifurcation was involved in 210 patients (68.6%) and DES was used for the left main lesion in 209 patients (68.3%). At least 1 internal thoracic artery was used in 98.3% of patients in the CABG

Table 2
Univariate and multivariable analyses for three-year clinical outcomes: percutaneous coronary intervention versus coronary artery bypass grafting

	PCI* (n = 365)	CABG* (n = 640)	Univariate HR (95% CI)	p Value	Multivariable HR (95% CI)	p Value
Death/myocardial infarction/stroke	74 (22.7%)	84 (14.8%)	1.67 (1.24–2.24)	0.0006	1.30 (0.79–2.15)	0.30
Death	45 (13.6%)	50 (9.2%)	1.61 (1.10–2.34)	0.01	0.79 (0.40–1.57)	0.50
Cardiac death	25 (7.4%)	21 (3.7%)	2.20 (1.26–3.86)	0.005	1.80 (0.64–5.09)	0.27
Myocardial infarction	18 (5.5%)	13 (2.3%)	2.72 (1.38–5.51)	0.003	2.47 (0.81–7.54)	0.11
Stroke	19 (6.6%)	31 (5.5%)	1.25 (0.72–2.12)	0.43	0.79 (0.30–2.08)	0.63
Coronary revascularization	133 (43.4%)	63 (11.2%)	4.43 (3.31–5.98)	<0.0001	5.83 (3.74–9.09)	<0.0001

* Number of events (incidence).

group and prevalence of off-pump CABG was high (64.7%). Baseline medications were significantly different in several aspects between the 2 groups (Table 1).

Cumulative 3-year incidence of the primary outcome measurement (death/MI/stroke) in the PCI group was significantly higher than that in the CABG group (22.7% vs 14.8%, p = 0.0006, log-rank test; Figure 2). However, after adjusting for potential confounders, risk of PCI compared to CABG for the primary outcome measurement was not significantly different (adjusted HR 1.30, 95% CI 0.79 to 2.15, p = 0.30; Table 2). Regarding survival outcome, cumulative 3-year incidence of all-cause death and cardiac death were higher in the PCI group than in the CABG group (13.6% vs 9.2%, p = 0.01, log-rank test; 7.4% vs 3.7%, p = 0.005, log-rank test, respectively; Figure 2). However, adjusted risks for all-cause death and cardiac death were not different between the 2 groups (adjusted HR 0.79, 95% CI 0.40 to 1.57, p = 0.50; adjusted HR 1.80, 95% CI 0.64 to 5.09, p = 0.27, respectively; Table 2). Cumulative 3-year incidence of MI was significantly higher in the PCI group compared to the CABG group (5.5% vs 2.3%, p = 0.003, log-rank test; Figure 2). However, adjusted risk of PCI compared to CABG for MI was not significantly different (adjusted HR 2.47, 95% CI 0.81 to 7.54, p = 0.11), although the point estimate strongly favored CABG (Table 2). Cumulative 3-year incidence of definite stent thrombosis in the PCI group was low (1.5%). Risk for stroke was not different between the 2 groups (6.6% vs 5.5%, p = 0.43, log-rank test, adjusted HR 0.79, 95% CI 0.30 to 2.08, p = 0.63; Figure 2 and Table 2). PCI was associated with a markedly higher risk for any coronary revascularization compared to CABG (43.4% vs 11.2%, p <0.0001, log-rank test, adjusted HR 5.83, 95% CI 3.74 to 9.09, p <0.0001; Figure 2 and Table 2).

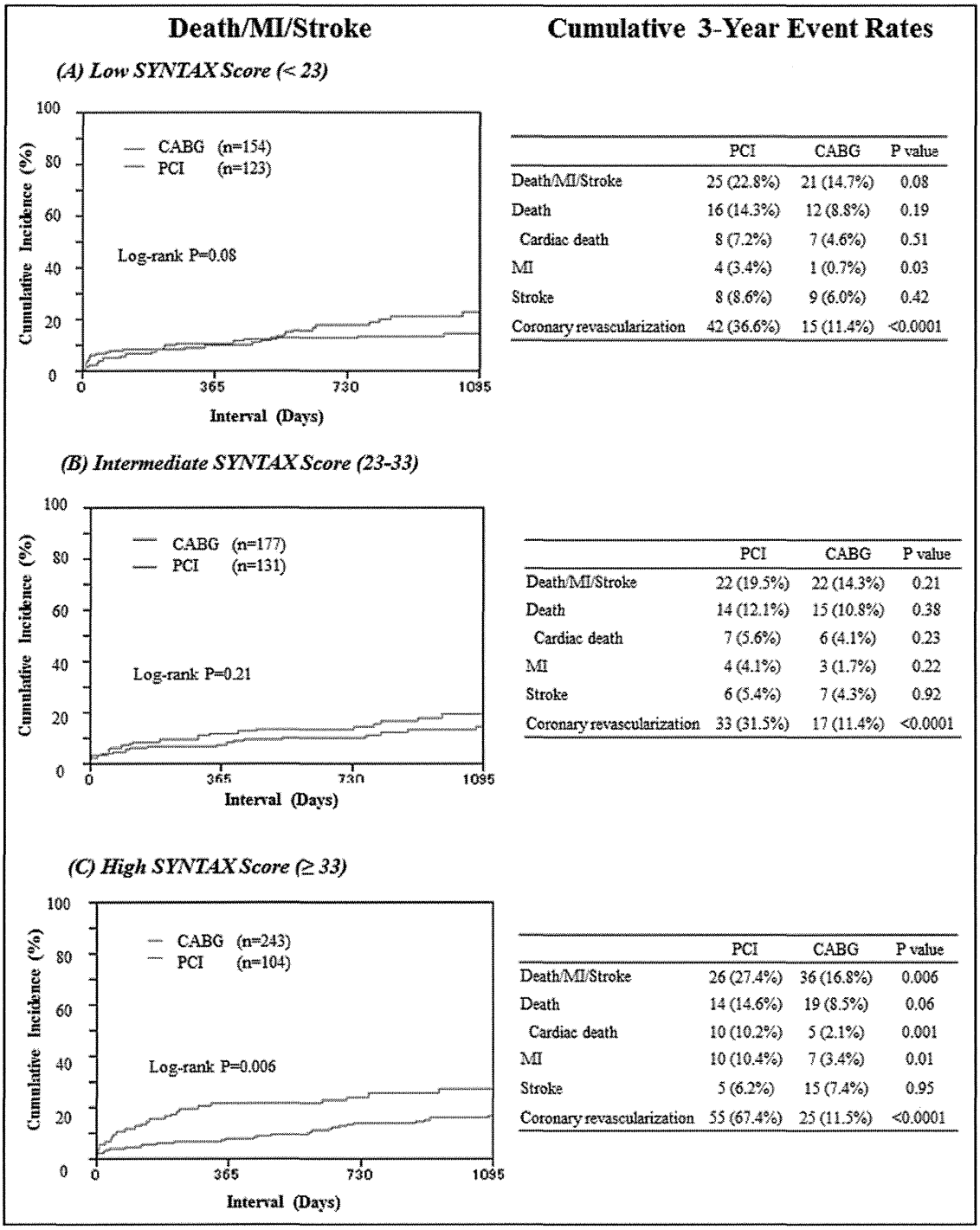
Clinical outcome was compared between the PCI and CABG groups among the 3 categories of coronary anatomic complexities stratified by the SYNTAX score. Cumulative 3-year incidences of the primary outcome measurement were not different between the PCI and CABG groups in patients with low and intermediate SYNTAX scores (22.8% vs 14.7%, p = 0.08, log-rank test; 19.5% vs 14.3%, p = 0.21, log-rank test). However, cumulative 3-year incidence of the primary outcome measurement was markedly higher in the PCI group than in the CABG group in patients with a high SYNTAX score (27.4% vs 16.8%, p = 0.006, log-rank test; Figure 3). After adjustment for potential confounders, risk of PCI compared to CABG for the primary outcome measurement remained significantly higher in patients with a high SYNTAX score (adjusted HR 2.61, 95% CI 1.32 to 5.16, p = 0.006), whereas it was not significantly different in patients with low and intermediate SYNTAX scores (adjusted HR 1.70, 95% CI 0.77 to 3.76, p = 0.19; adjusted HR 0.86, 95% CI 0.37 to 1.99, p = 0.72).

Discussion

The main findings in the present study were as follows. (1) Three-year clinical outcome of PCI was comparable to CABG for serious cardiovascular events in patients with ULMCAD. (2) Risk for serious cardiovascular events was not significantly different between PCI and CABG in patients with a low or intermediate SYNTAX score but was markedly higher after PCI compared to CABG in patients with a high SYNTAX score.

The favorable outcome of PCI for the treatment of ULMCAD as demonstrated in the ULMCAD subset of the SYNTAX trial led to the recently updated recommendation of PCI for ULMCAD.[1–6] However, evidence from randomized trials comparing PCI using DESs to CABG in patients with ULMCAD is quite limited. Indeed, Boudriot et al[12] failed to demonstrate noninferiority of PCI using sirolimus-eluting stents compared to CABG with respect to major adverse cardiac events in patients with ULMCAD in their randomized trial, whereas Park et al[13] showed noninferiority of PCI compared to CABG with respect to major adverse cardiac and cerebrovascular events in the Premier of Randomized Comparison of Bypass Surgery versus Angioplasty Using Sirolimus-Eluting Stent in Patients with Left Main Coronary Artery Disease (PRECOMBAT) trial. Moreover, results from randomized trials should be interpreted cautiously for application to daily clinical practice because selected patients with relatively low risk profiles were generally enrolled in these randomized trials. Therefore, results from large-scale observational studies are also important. The present analysis from a multicenter registry in Japan suggested comparable long-term clinical outcome for a composite of death/MI/stroke between PCI and CABG in patients with ULMCAD, which is consistent with previous observational studies and the SYNTAX and PRECOMBAT randomized trials.[1,4–6,13,14]

Appropriate selection of patients with ULMCAD for PCI is the most important consideration while expanding the use of PCI for ULMCAD. Risk stratification using the SYNTAX score has drawn attention for the selection of revascularization procedures in complex coronary artery diseases such as ULMCAD or 3-vessel CAD.[4] However, the utility



	PCI	CABG	P value
Death/MI/Stroke	25 (22.8%)	21 (14.7%)	0.08
Death	16 (14.3%)	12 (8.8%)	0.19
Cardiac death	8 (7.2%)	7 (4.6%)	0.51
MI	4 (3.4%)	1 (0.7%)	0.03
Stroke	8 (8.6%)	9 (6.0%)	0.42
Coronary revascularization	42 (36.6%)	15 (11.4%)	<0.0001

	PCI	CABG	P value
Death/MI/Stroke	22 (19.5%)	22 (14.3%)	0.21
Death	14 (12.1%)	15 (10.8%)	0.38
Cardiac death	7 (5.6%)	6 (4.1%)	0.23
MI	4 (4.1%)	3 (1.7%)	0.22
Stroke	6 (5.4%)	7 (4.3%)	0.92
Coronary revascularization	33 (31.5%)	17 (11.4%)	<0.0001

	PCI	CABG	P value
Death/MI/Stroke	26 (27.4%)	36 (16.8%)	0.006
Death	14 (14.6%)	19 (8.5%)	0.06
Cardiac death	10 (10.2%)	5 (2.1%)	0.001
MI	10 (10.4%)	7 (3.4%)	0.01
Stroke	5 (6.2%)	15 (7.4%)	0.95
Coronary revascularization	55 (67.4%)	25 (11.5%)	<0.0001

Figure 3. Kaplan–Meier event curves comparing percutaneous coronary intervention to coronary artery bypass grafting for a composite of all-cause death, myocardial infarction, and stroke stratified by *(A)* low (<23), *(B)* intermediate (23 to 33), and *(C)* high (≥33) SYNTAX score tertiles.

of the SYNTAX score for risk stratification in ULMCAD is still controversial.[15–17] Capodanno et al[15] reported that PCI was associated with a higher mortality than CABG in patients with ULMCAD and a SYNTAX score ≥34 in 2 Italian centers. In contrast, Kim et al[16] and Park et al[17] reported the SYNTAX score failed to stratify clinical outcome in patients with ULMCAD in a subanalysis of the Revascularization for Unprotected Left Main Coronary Artery Stenosis: Comparison of Percutaneous Coronary Angioplasty versus Surgical Revascularization (MAIN-COMPARE) registry study, although they demonstrated the utility of the SYNTAX score for risk stratification in patients who received DESs. The present study provided additional support for the utility of the SYNTAX score for risk stratification in patients with ULMCAD. Results stratified by the SYNTAX tertiles in the present study were consistent with results of the SYNTAX randomized trial.[5] Therefore, PCI for patients with ULMCAD and a high SYNTAX score

should be discouraged unless the operative risk is prohibitively high. In contrast, long-term clinical outcome of PCI seemed to be comparable to that of CABG in patients with a low or intermediate SYNTAX score, supporting the recent trend for expanding the use of PCI in this category of patients with ULMCAD. However, the number of patients studied was still insufficient to advocate widespread use of PCI in patients with ULMCAD and less complex coronary anatomy. Results of the Evaluation of Xience Prime versus coronary artery bypass surgery for effectiveness of left main revascularization (EXCEL) trial, which is an ongoing randomized trial comparing PCI using everolimus-eluting stents to CABG in 2,600 patients with ULMCAD and a SYNTAX score <33, would provide further guidance for PCI use in this important subset of patients.

There are several important limitations in this study. First and most importantly, the observational study design precluded definitive conclusions regarding the superiority of PCI or CABG because of selection bias and unmeasured confounders. Because CABG had been considered the gold standard for patients with ULMCAD, selection bias could be greater in patients with ULMCAD compared to other subsets of severe CAD such as 3-vessel CAD. Therefore, the present results should be interpreted very carefully. Furthermore, the results from the SYNTAX subgroup analyses should be regarded as hypothesis generating. Second, the number of patients enrolled was still small and SYNTAX score data were not available for all patients. Third, duration of follow-up might not be sufficient to evaluate the long-term outcome of coronary revascularization. Fourth, we did not exclude those patients in whom PCI was not attempted for the LMCA lesions based on clinical judgments. The present study population might include patients with less severe LMCA lesions in the PCI and CABG groups.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.amjcard.2012.05.022.

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ORIGINAL ARTICLE
Cardiovascular Intervention

Intensity of Statin Therapy, Achieved Low-Density Lipoprotein Cholesterol Levels and Cardiovascular Outcomes in Japanese Patients After Coronary Revascularization

– Perspectives From the CREDO-Kyoto Registry Cohort-2 –

Masahiro Natsuaki, MD; Yutaka Furukawa, MD; Takeshi Morimoto, MD; Yoshihisa Nakagawa, MD; Koh Ono, MD; Satoshi Kaburagi, MD; Tsukasa Inada, MD; Hirokazu Mitsuoka, MD; Ryoji Taniguchi, MD; Akira Nakano, MD; Toru Kita, MD; Ryuzo Sakata, MD; Takeshi Kimura, MD on behalf of the CREDO-Kyoto PCI/CABG registry cohort-2 investigators

Background: Association of the type of statin and the achieved level of low-density lipoprotein cholesterol (LDL-C) with cardiovascular outcome has not been fully elucidated.

Methods and Results: The study included 14,866 patients who underwent a first coronary revascularization in 2005–2007. We identified 7,299 patients with statin therapy at discharge (so-called strong statins [atorvastatin, rosuvastatin, and pitavastatin]: 4,742 patients; standard statins [pravastatin, simvastatin, and fluvastatin]: 2,557 patients). Unadjusted 3-year incidence of major adverse cardiovascular events (MACE: composite of cardiovascular death, myocardial infarction and stoke) was significantly lower (7.5% vs. 9.6%, P=0.0008) in the strong statin group, and there was a trend in adjusted risk of MACE favoring strong statins (hazard ratio [HR] 0.87, [95% confidence interval (CI) 0.73–1.04], P=0.13). Among 4,846 patients with follow-up LDL-C data available, outcomes were evaluated according to achieved LDL-C level (<80, 80–99 [reference], 100–119, ≥120 mg/dl). Compared with the reference group, the risk for MACE was significantly higher in the ≥120 mg/dl group (adjusted HR 1.74 [95%CI 1.11–2.71], P=0.01), although it was comparable in the 100–119 mg/dl group (adjusted HR 1.23 [95%CI 0.78–1.94], P=0.38) and in the <80 mg/dl group (adjusted HR 1.15 [95%CI 0.75–1.75], P=0.52).

Conclusions: Strong statin therapy was associated with a trend toward lower cardiovascular risk compared with standard statin therapy. When LDL-C <120 mg/dl was achieved, risks for cardiovascular events were comparable irrespective of achieved LDL-C level. (*Circ J* 2012; **76:** 1369–1379)

Key Words: Cholesterol; Coronary artery disease; Outcomes; Statins

The 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) have been reported as effective in primary and secondary prevention of cardiovascular disease.[1–5] However, the influence of the intensity of statin therapy as represented by the type of statin and the achieved level of low-density lipoprotein cholesterol (LDL-C) on cardiovascular outcome in patients with coronary artery disease (CAD) has not been fully addressed. Regarding the types of statins, the PROVE-IT[6] and IDEAL[7] studies respectively compared cardiovascular outcomes between atorvastatin 80 mg and pravastatin 40 mg, and between atorvastatin 80 mg and simvastatin 20 mg. Atorvastatin, which is more potent in reducing

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Department of Cardiovascular Medicine (M.N., K.O., T. Kimura), Department of Cardiovascular Surgery (R.S.), Kyoto University Graduate School of Medicine, Kyoto; Department of Cardiovascular Medicine, Kobe City Medical Center General Hospital, Kobe (Y.F., T. Kita.); Center for General Internal Medicine and Emergency Care, Kinki University School of Medicine, Osaka-Sayama (T.M.); Division of Cardiology, Tenri Hospital, Tenri (Y.N.); Division of Cardiology, Shizuoka General Hospital, Shizuoka (S.K.); Division of Cardiology, Osaka Red Cross Hospital, Osaka (T.I.); Division of Cardiology, Kishiwada City Hospital, Kishiwada (H.M.); Division of Cardiology, Hyogo Prefectural Amagasaki Hospital, Amagasaki (R.T.); and Division of Cardiology, University of Fukui Hospital, Fukui (A.N.), Japan
Mailing address: Yutaka Furukawa, MD, Department of Cardiovascular Medicine, Kobe City Medical Center General Hospital, 2-1-1 Minatojima-minamimachi, Chuo-ku, Kobe 650-0047, Japan. E-mail: furukawa@kcho.jp

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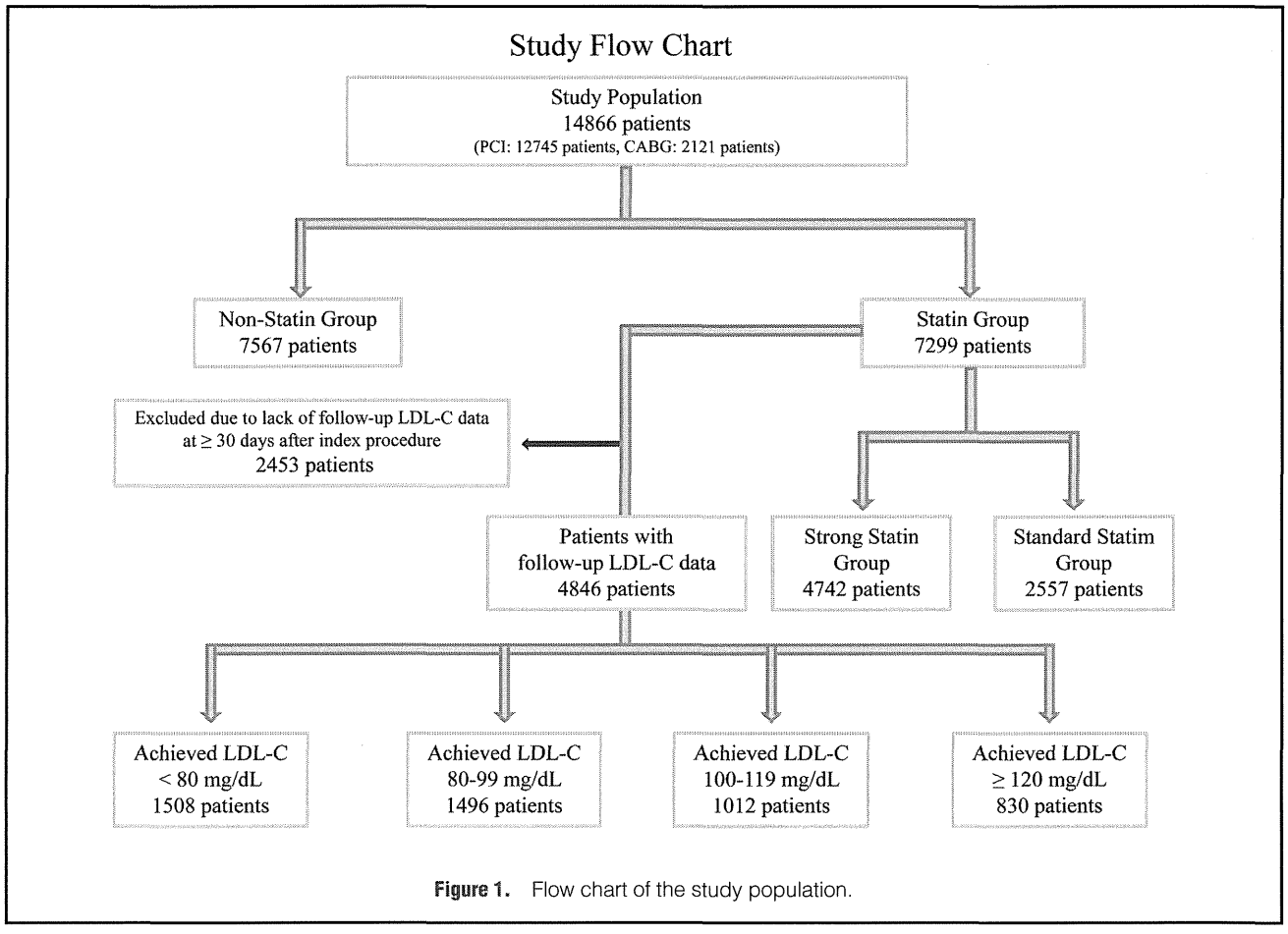

Figure 1. Flow chart of the study population.

LDL-C than comparators, provided better cardiovascular outcomes in those studies. However, the 2 trials enrolled patients either with acute coronary syndrome or with prior myocardial infarction (MI). The effect of the type of statins on cardiovascular outcomes needs to be further elucidated in stable CAD patients without prior MI, who often receive life-long statin therapy. Also, it is not known whether the same conclusion is applicable to ethnicities other than those evaluated in the trials, such as Japanese patients. In the MEGA trial, which tested the effects of pravastatin in the setting of primary prevention in Japan, administration of pravastatin 10–20 mg daily resulted in 33% relative risk reduction for major cardiovascular events with only 18% mean LDL-C reduction.[8]

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Regarding the association between achieved LDL-C level and cardiovascular outcome, an increase in atorvastatin dose from 10 mg to 80 mg achieved a lower on-treatment LDL-C level and improved cardiovascular outcomes in the TNT study.[9] However, it is still controversial whether the observed improvement in cardiovascular outcomes in the TNT study was causally related to the lower level of achieved LDL-C or related to the greater magnitude of pleiotropic effects associated with higher statin dose. It is also unclear whether the difference in the on-treatment LDL-C level within the range usually achieved with contemporary statin therapy could still be an independent risk factor for cardiovascular events.[10–13]

In this study, we analyzed the influence of the intensity of statin therapy, as represented by the type of statins and achieved LDL-C level during statin therapy, on cardiovascular outcomes in a large Japanese observational database of patients who underwent their first coronary revascularization.

Methods

Study Population

The CREDO-Kyoto (Coronary REvascularization Demonstrating Outcome study in Kyoto) percutaneous coronary intervention (PCI)/coronary artery bypass grafting (CABG) registry cohort-2 is a multicenter registry enrolling consecutive patients undergoing their first coronary revascularization procedures among 26 centers in Japan between January 2005 and December 2007 (**Appendix S1**). The relevant review boards or ethics committees in all participating centers approved the research protocol. Because of retrospective enrollment, written informed consent from the patients was waived; however, we excluded those patients who refused participation in the study when contacted for follow-up. This strategy is concordant with the guidelines for epidemiological studies issued by the Ministry of Health, Labor and Welfare of Japan.

The design and patient enrollment of the CREDO-Kyoto PCI/CABG registry cohort-2 has been described previously.[14] A total of 15,939 patients underwent PCI or CABG as their first coronary revascularization procedure during the 3 years of enrollment. Excluding 67 patients who refused study participation, 609 patients who underwent combined non-coronary surgery, and 397 patients who died during the index hospital-

Table 1. Baseline Characteristics and Achieved Lipid Levels in Strong vs. Standard Statin Group

	Strong statins (n=4,742)	Standard statins (n=2,557)	P value
Clinical characteristics			
Age (years)	65.7±10.9	68.4±10.6	<0.0001
≥75 years*	23%	31%	<0.0001
Male*	70%	69%	0.38
BMI	24.4±3.5	23.9±3.4	<0.0001
<25.0*	61%	67%	<0.0001
Baseline lipid levels			
Total cholesterol (mg/dl)	200±45.8	190±35.1	<0.0001
HDL-C (mg/dl)	47.8±13.3	48.8±13.6	0.005
TG (mg/dl)	118 (81–174)	110 (75–156)	<0.0001
LDL-C (mg/dl)	125±41.2	116±30.3	<0.0001
Statins before hospitalization	56%	60%	0.0003
Acute myocardial infarction	35%	31%	0.0003
Hypertension*	84%	84%	0.96
Diabetes mellitus*	39%	40%	0.80
On insulin therapy	7.9%	8.1%	0.75
Current smoking*	35%	28%	<0.0001
Heart failure*	16%	16%	0.94
Shock at presentation	4.3%	3.3%	0.03
Mitral regurgitation grade 3/4*	2.6%	3.4%	0.04
Ejection fraction	59.3±12.8	59.8±12.7	0.12
Prior myocardial infarction*	11%	13%	0.01
Prior stroke*	8.6%	10%	0.053
Peripheral vascular disease*	6.2%	7.0%	0.17
Multivessel disease	59%	61%	0.13
Target of proximal LAD*	62%	60%	0.06
Unprotected LMCA*	6.1%	6.5%	0.55
Target of CTO*	15%	13%	0.09
Mode of revascularization: CABG*	9.5%	7.0%	0.0002
eGFR <30, not on dialysis*	3.2%	3.1%	0.75
Dialysis*	1.3%	2.1%	0.01
Atrial fibrillation*	6.7%	8.1%	0.03
Anemia (Hb <11 g/dl)*	7.8%	9.2%	0.05
Platelets <100×10^9/L*	0.8%	0.9%	0.66
COPD*	3.3%	3.6%	0.47
Liver cirrhosis*	1.6%	2.2%	0.10
Malignancy*	6.9%	9.1%	0.001
Baseline medication			
Medication at hospital discharge			
Antiplatelet therapy:			
Thienopyridine	90%	92%	0.0002
Ticlopidine	87%	91%	<0.0001
Clopidogrel	13%	9.1%	<0.0001
Aspirin	99%	99%	0.92
Cilostazole*	20%	17%	0.005
Other medications			
β-blocker*	36%	34%	0.25
ACEI/ARB*	62%	60%	0.12
Nitrates*	31%	35%	0.001
Calcium-channel blocker*	39%	43%	0.0003
Nicorandil*	25%	28%	0.04
Warfarin*	10%	9.8%	0.56
Proton-pump inhibitor*	29%	25%	<0.0001
H2-blocker*	28%	27%	0.27

(Table 1 continued the next page.)

	Strong statins (n=4,742)	Standard statins (n=2,557)	P value
Achieved lipid levels			
Total cholesterol (mg/dl)	172.5±35.9	182.3±31.9	<0.0001
HDL-C (mg/dl)	51.6±14.0	52.8±14.7	0.003
TG (mg/dl)	124 (89–178)	123 (88–174)	0.43
LDL-C (mg/dl)	92.0±29.2	101±26.1	<0.0001
LDL-C change (mg/dl)	−34.7 (−62.8 to −5.4)	−16.9 (−38.4 to 4.0)	<0.0001
% LDL-C change	−28.9 (−44.3 to −5.3)	−15.1 (−30.0 to 3.9)	<0.0001

Values are mean±SD or median (interquartile range).
*Potential independent variables selected for multivariate analysis.
**Values for achieved lipid levels were available in 3,668 patients with strong statin therapy and in 2,058 patients with standard statin therapy.
ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers; BMI, body mass index; CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; CTO, chronic total occlusion; eGFR, estimated glomerular filtration rate; Hb, hemoglobin; HDL-C, high-density lipoprotein cholesterol; LAD, left anterior descending artery; LDL-C, low-density lipoprotein cholesterol; LMCA, left main coronary artery disease; TG, triglycerides.

ization, 14,866 patients (PCI: 12,745; isolated CABG: 2,121) constituted the study population for the current analyses.

Patients were divided into 2 groups according to the use of statins at discharge: 7,299 patients with statin therapy (statin group) and 7,567 without statin therapy (non-statin group). To analyze the association of the type of statin therapy and cardiovascular outcome, we divided the 7,299 statin-treated patients into 2 groups according to the type of statins: (1) strong statin group (4,742 patients) comprising atorvastatin (3,347 patients; median daily dose 10 mg), rosuvastatin (735 patients; median daily dose 2.5 mg) and pitavastatin (660 patients; median daily dose 2 mg); (2) standard statin group (2,557 patients) comprising pravastatin (1,815 patients; median daily dose 10 mg), simvastatin (434 patients; median daily dose 5 mg) and fluvastatin (308 patients; median daily dose 20 mg) (**Figure 1**).

Among the 7,299 patients in the statin group, follow-up LDL-C data at ≥30 days after the index procedure were available for 4,846 patients. To assess the association between the LDL-C level achieved with statin therapy and cardiovascular outcome, the 4,846 patients were subdivided into 4 groups according to the LDL-C level at follow-up: <80 mg/dl group (1,508 patients), 80–99 mg/dl group (reference group; 1,496 patients), 100–119 mg/dl group (1,012 patients) and ≥120 mg/dl group (830 patients) (**Figure 1**).

Definitions

Definitions of baseline clinical characteristics have been described previously.[14] LDL-C concentrations were calculated by the Friedewald formula.[15] In cases of triglyceride ≥400 mg/dl, LDL-C was judged as missing information.

The primary outcome measure in the current analysis was major adverse cardiovascular events (MACE; composite of cardiovascular death, MI, and stroke). Death was regarded as cardiac in origin unless obvious non-cardiac causes could be identified. Vascular death was defined as death related to aortic, cerebral, renal and peripheral vascular disease. MI was defined according to the definition in the Arterial Revascularization Therapy Study.[16] Within 1 week of the index procedure, only Q-wave MI was adjudicated as MI. Stroke during follow-up was defined as ischemic or hemorrhagic stroke requiring hospitalization with symptoms lasting >24 h.

Data Collection and Follow-up

Demographic, angiographic, and procedural data were collected from hospital charts or databases according to prespecified definitions by experienced clinical research coordinators in the independent research organization (Research Institute for Production Development, Kyoto, Japan) (**Appendix S2**). Follow-up data were obtained from hospital charts or by contacting patients or referring physicians. Cardiovascular death, MI and stroke were adjudicated against original source documents by a Clinical Event Committee (**Appendix S3**).

Median follow-up duration was 960 (interquartile range [IQR]: 699–1,246) days. Follow-up LDL-C levels were measured optionally and the median interval from the index procedure to the measurement of LDL-C was 357 (IQR: 254–398) days. Median follow-up duration after measurement of LDL-C level was 624 (IQR: 372–897) days.

Statistical Analysis

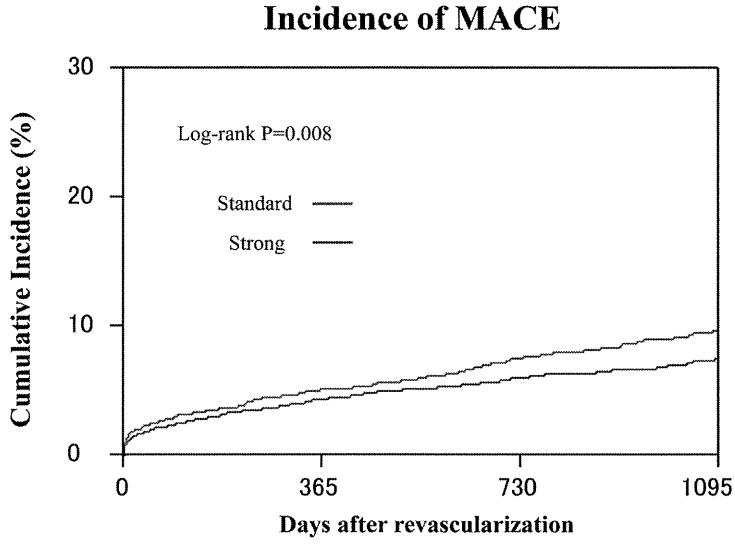
Categorical variables were compared with the chi-square test. Continuous variables are expressed as mean value±standard deviation or median and IQR, and compared using Student's t-test or the Wilcoxon rank sum test, based on their distributions. Variables in each LDL-C group were compared with analysis of variance. Cumulative incidence was estimated by the Kaplan-Meier method and differences were assessed with the log-rank test. Regarding the comparison according to the achieved LDL-C level, the 80–99 mg/dl group was used as the reference group, because the current Japanese guidelines recommend to controlling LDL-C <100 mg/dl as secondary prevention of CAD.

We used Cox proportional hazard models to estimate the risk for MACE, adjusting for differences in patient characteristics, procedural factors, and medications. We chose 32 clinically relevant factors (**Table 1**) as the risk-adjusting variables. The continuous variables were dichotomized by clinically meaningful reference values or median values. Proportional hazard assumption for the comparison between the strong and standard statin groups was assessed on the plots of log (time) vs. log [-log (survival)] stratified by statin therapy and was justified. The type of statin and the 32 risk-adjusting variables were simultaneously included in the Cox proportional hazard model. The 26 centers were included in the model as stratification variables because of their non-proportional property and possible association with treatment selection and MACE. The effect of the strong statin (the strong vs. standard statin group) was expressed as the hazard ratio (HR) and 95% confidence interval (CI). The same analysis was conducted to estimate the risk for MACE in the statin group compared with the non-

Table 2. Event Rates at 3 Years in Strong vs. Standard Statin Group

	No. of events/No. of patients (incidence)		P value
	Strong statins	Standard statins	
All-cause death	187/4,742 (5.0%)	143/2,557 (6.7%)	0.006
MACE	306/4,742 (7.5%)	214/2,557 (9.6%)	0.008
Cardiovascular death	93/4,742 (2.4%)	70/2,557 (3.2%)	0.08
Myocardial infarction	111/4,742 (2.6%)	82/2,557 (3.7%)	0.02
Stroke	139/4,742 (3.4%)	91/2,557 (4.2%)	0.19

MACE, major adverse cardiovascular events (cardiovascular death, myocardial infarction or stroke).



Interval	0 day	30 days	1 year	2 years	3 years
Standard					
N of events		53	128	182	214
N of patients at risk	2557	2477	2335	1798	952
Incidence		2.1%	5.1%	7.5%	9.6%
Strong					
N of events		80	204	270	306
N of patients at risk	4742	4635	4364	3154	1552
Incidence		1.7%	4.4%	6.0%	7.5%

Figure 2. Incidence of major adverse cardiovascular events (MACE: composite of cardiovascular death, myocardial infarction and stoke): strong vs. standard statin group.

statin group.

To evaluate the relationship between achieved LDL-C level and cardiovascular outcome, we used landmark analysis. The day of follow-up LDL-C measurement was set as the landmark point and cardiovascular outcomes were evaluated from this point. Those patients who had experienced each cardiovascular event before obtaining follow-up LDL-C levels were excluded from this analysis. The adjusted risk for MACE was estimated by the Cox proportional hazard model by incorporating the achieved LDL-C level categories together with the 32 risk-adjusting variables stratified by the 26 centers. In the Cox proportional hazard model, we developed dummy codes for LDL-C ≥120 mg/dl, 100–119 mg/dl and <80 mg/dl, with LDL-C level of 80–99 mg/dl as the reference. The effect of each achieved LDL-C level category compared with the reference category was expressed as HR and 95%CI.

Statistical analyses were conducted by a physician (M. Natsuaki) and by a statistician (T. Morimoto) using JMP 8.0 (SAS Institute Inc, Cary, NC, USA) and SAS 9.2 (SAS Institute Inc) software. All the statistical analyses were two-tailed. $P<0.05$ was considered statistically significant.

Results

Baseline Characteristics and Clinical Outcomes: Statin vs. Non-Statin Group

Because of the large number of patients and the observational study design, significant differences were observed in many variables in the baseline characteristics of the statin and the non-statin groups. Patients in the non-statin group were older and more often had comorbidities such as diabetes mellitus on insulin therapy, heart failure, prior stroke, peripheral vascular disease, and renal failure, than patients in the statin group. Baseline levels of total cholesterol, LDL-C, high-density lipoprotein cholesterol (HDL-C) and triglycerides were all higher in the statin group than in the non-statin group (Table S1).

During the 3-year follow-up, the incidence of MACE was significantly lower in the statin group than in the non-statin

Table 3. Baseline Characteristics and Achieved Lipid Levels According to the LDL-C Level During Statin Therapy

	LDL-C <80 mg/dl (n=1,508)	LDL-C 80–99 mg/dl (n=1,496)	LDL-C 100–119 mg/dl (n=1,012)	LDL-C ≥120 mg/dl (n=830)	P value
Clinical characteristics					
Age (years)	66.7±10.6	66.4±10.3	66.2±10.5	66.3±11.4	0.70
≥75 years	25%	24%	25%	27%	0.38
Male	76%	70%	69%	61%	<0.0001
BMI	24.3±3.5	24.3±3.5	24.3±3.3	24.5±3.6	0.57
<25.0	62%	63%	62%	59%	0.40
Baseline lipid levels					
Total cholesterol (mg/dl)	186±40.0	198±40.2	203±38.7	214±45.0	<0.0001
HDL-C (mg/dl)	48.8±14.0	49.2±13.4	47.8±13.3	47.6±12.7	0.02
TG (mg/dl)	110 (74–165)	112 (77–161)	121 (84–168)	119 (86–166)	0.0005
LDL-C (mg/dl)	112±34.1	123±35.9	130±34.9	139±40.8	<0.0001
Statins before hospitalization	49%	56%	60%	61%	<0.0001
Acute myocardial infarction	39%	37%	31%	31%	<0.0001
Hypertension	82%	83%	85%	84%	0.31
Diabetes mellitus	38%	38%	38%	38%	0.99
On insulin therapy	7.2%	6.5%	6.6%	7.7%	0.68
Current smoking	33%	32%	31%	33%	0.68
Heart failure	17%	14%	12%	14%	0.009
Shock at presentation	5.0%	3.5%	2.3%	3.4%	0.004
Mitral regurgitation grade 3/4	2.7%	2.1%	3.0%	3.5%	0.26
Ejection fraction	59.4±12.6	59.6±12.4	59.5±12.0	59.0±12.5	0.76
Prior myocardial infarction	10%	10%	11%	11%	0.80
Prior stroke	7.8%	8.4%	8.7%	10%	0.26
Peripheral vascular disease	4.9%	5.8%	5.9%	9.4%	0.0004
Multivessel disease	57%	58%	56%	60%	0.35
Target of proximal LAD	63%	58%	60%	60%	0.03
Unprotected LMCA	5.2%	4.8%	4.1%	6.0%	0.26
Target of CTO	11%	14%	15%	16%	0.004
Mode of revascularization: CABG	4.5%	4.6%	4.5%	4.7%	0.99
eGFR <30, not on dialysis	2.2%	2.1%	2.4%	2.7%	0.87
Dialysis	1.7%	1.0%	1.5%	1.0%	0.25
Atrial fibrillation	6.4%	6.8%	7.6%	5.9%	0.49
Anemia (Hb <11 g/dl)	7.6%	6.4%	6.6%	8.0%	0.37
Platelets <100×10^9/L	1.1%	0.7%	0.8%	0.6%	0.58
COPD	3.5%	2.8%	3.6%	4.5%	0.23
Liver cirrhosis	2.4%	1.5%	1.5%	1.1%	0.08
Malignancy	8.6%	6.4%	7.8%	6.6%	0.10
Baseline medication					
Medication at hospital discharge					
Strong statins	78%	62%	55%	56%	<0.0001
Antiplatelet therapy					
Thienopyridine	95%	95%	95%	95%	0.96
Ticlopidine	85%	89%	90%	91%	<0.0001
Clopidogrel	15%	11%	10%	8.6%	<0.0001
Aspirin	99%	99%	99%	99%	0.24
Cilostazole	19%	21%	19%	23%	0.15
Other medications					
β-blockers	36%	35%	33%	38%	0.18
ACEI/ARB	66%	63%	62%	61%	0.05
Nitrates	28%	31%	34%	38%	<0.0001
Calcium-channel blocker	38%	41%	41%	43%	0.09
Nicorandil	27%	24%	23%	22%	0.007
Warfarin	9.1%	9.0%	8.2%	8.3%	0.83
Proton-pump inhibitor	28%	29%	26%	24%	0.10
H2 blocker	29%	26%	28%	28%	0.24

(Table 3 continued the next page.)

	LDL-C <80 mg/dl (n=1,508)	LDL-C 80–99 mg/dl (n=1,496)	LDL-C 100–119 mg/dl (n=1,012)	LDL-C ≥120 mg/dl (n=830)	P value
Achieved lipid levels					
Total cholesterol (mg/dl)	145±20.0	169±17.1	188±16.4	223±26.4	<0.0001
HDL-C (mg/dl)	51.8±15.0	53.4±14.5	51.6±13.6	51.8±13.1	0.002
TG (mg/dl)	120 (82–177)	116 (85–160)	122 (89–174)	135 (101–176)	<0.0001
LDL-C (mg/dl)	65.6±11.1	89.6±5.7	109±5.8	142±20.6	<0.0001
LDL-C change (mg/dl)	−44.9 (−69.6 to −21.6)	−29.2 (−55.2 to −6.6)	−16.6 (−43.7 to 6.0)	4.7 (−19.6 to 26.1)	<0.0001
% LDL-C change	−40.8 (−52.1 to −24.5)	−24.5 (−38.8 to −6.8)	−13.4 (−28.5 to 6.0)	3.8 (−12.5 to 22.9)	<0.0001

Values are mean±SD or median (interquartile range).
Abbreviations see in Table 1.

Table 4. Event Rates at 2 Years After Measurement of LDL-C According to the LDL-C Level During Statin Therapy

	No. of events/No. of patients (incidence)				P value
	LDL-C <80 mg/dl	LDL-C 80–99 mg/dl	LDL-C 100–119 mg/dl	LDL-C ≥120 mg/dl	
All-cause death	52/1,504 (4.4%)	36/1,486 (3.2%)	26/1,006 (3.2%)	26/829 (3.9%)	0.11
MACE	44/1,458 (3.8%)	37/1,429 (3.5%)	29/970 (4.0%)	35/810 (5.0%)	0.08
Cardiovascular death	24/1,504 (1.8%)	16/1,486 (1.3%)	15/1,006 (1.9%)	14/829 (2.0%)	0.13
Myocardial infarction	11/1,476 (0.8%)	8/1,450 (0.7%)	9/991 (1.6%)	9/817 (1.3%)	0.42
Stroke	20/1,484 (1.9%)	18/1,464 (1.8%)	11/985 (1.4%)	17/820 (2.4%)	0.43

LDL-C, low-density lipoprotein cholesterol; MACE, major adverse cardiovascular events (cardiovascular death, myocardial infarction or stroke).

Table 5. Univariate and Multivariable Risks for MACE According to the Achieved LDL-C Level

LDL-C	Univariate		Multivariable	
	HR (95%CI)	P value	HR (95%CI)	P value
<80 mg/dl	1.22 (0.81–1.85)	0.34	1.15 (0.75–1.75)	0.52
100–119 mg/dl	1.29 (0.82–2.00)	0.26	1.23 (0.78–1.94)	0.38
≥120 mg/dl	1.74 (1.14–2.68)	0.01	1.74 (1.11–2.71)	0.01

Patients with achieved LDL-C 80–99 mg/dl were used as the reference.
LDL-C, low-density lipoprotein cholesterol; MACE, major adverse cardiovascular events (cardiovascular death, myocardial infarction or stroke); HR, hazard ratio; CI, confidence interval.

group (8.3% vs. 12.1%, log-rank P<0.0001). The incidence of MACE was also significantly lower in the statin group than in the non-statin group even in patients with baseline LDL-C <100 mg/dl (8.9% vs. 13.0%, log-rank P<0.0001). After adjusting confounders by multivariable analysis, patients with statin therapy was associated with a lower risk for MACE as compared with those without statin therapy (HR 0.8 [95%CI 0.71–0.90], P=0.0001).

Baseline Characteristics and Clinical Outcomes: Strong vs. Standard Statin Group

Patients in the strong statin group were younger and had a higher body mass index than the standard statin group. Acute MI, current smoker, shock at presentation and revascularization by CABG were more often found in the strong than in the standard statin group. Conversely, mitral regurgitation grade 3/4, prior MI, hemodialysis, atrial fibrillation, anemia and malignancy were more common in the standard than in the strong statin group. Patients who had received statins before the index hospitalization for coronary revascularization were also more common in the standard statin group. In terms of baseline lipid profile, total cholesterol, triglycerides and LDL-C levels were higher and HDL-C was lower in the strong statin group compared with the standard statin group. Baseline medications were also significantly different between the 2 groups (Table 1).

Throughout the 3-year follow-up, the incidence of MACE was significantly lower in the strong statin group than in the standard statin group (7.5% vs. 9.6%, log-rank P=0.008) (Table 2, Figure 2). The incidence of MACE tended to be lower in the strong statin group than in the standard statin group even in patients with baseline LDL-C <100 mg/dl (7.7% vs. 10.8%, log-rank P=0.07). The incidence of the individual components of MACE, such as cardiovascular death, MI, and stroke, also tended to be lower in the strong statin group. After adjusting confounders by multivariable analysis, the use of strong statins was associated with a non-significant trend toward a lower risk of MACE as compared with the use of standard statins (HR 0.87 [95%CI 0.73–1.04], P=0.13). The absolute difference of mean achieved LDL-C level between the strong and the standard statin groups was relatively small (92.0±29.2 vs. 101±26.1 mg/dl), although the difference was statistically highly significant (Table 1).

Baseline Characteristics and Clinical Outcomes According to the Achieved LDL-C Level

Baseline characteristics and medications were significantly different across the 4 categories of achieved LDL-C level. Female sex, peripheral vascular disease, chronic total occlusion as a target lesion and prescription of statins before the index hospitalization were more often found in the higher achieved LDL-C levels. Acute MI, heart failure, shock at presentation