TABLE 3. Cox hazards analysis for all-cause mortality

Variables	All-cause mortality		
	Hazard ratio	95% CI	*P* value
Age	1.08	1.06-1.10	<.0001
CRF (hemodialysis dependent)	4.39	2.72-7.06	<.0001
CRF (non–hemodialysis dependent)	3.31	1.70-6.41	<.0001
Extracardiac arteriopathy	1.79	1.29-2.49	.001
No. of anastomoses	0.77	0.64-0.93	.005
LVEF, %	0.98	0.97-0.99	.005
Diabetes mellitus (insulin use)	1.80	1.17-2.77	.007
Incomplete revascularization	1.80	1.15-2.81	.010
SVG	1.51	1.01-2.24	.043
3-Vessel disease	0.66	0.41-1.06	.086
GEA	1.44	0.93-2.20	.099
COPD	1.76	0.89-3.48	.104
BITA	1.40	0.92-2.12	.117
Hypercholesterolemia	0.79	0.58-1.09	.149
CHF	1.30	0.87-1.94	.196
CVA	1.24	0.87-1.76	.229
Diabetes mellitus (diet or oral drug use)	1.22	0.86-1.71	.262
Conversion to CCAB	2.19	0.51-9.44	.292
Previous MI	0.86	0.62-1.21	.387
≥1 Total occluded lesion(s)	0.86	0.61-1.21	.397
Previous cardiac surgery	1.53	0.55-4.27	.415
Female sex	1.18	0.76-1.85	.460
BSA	0.73	0.20-2.64	.625
AF	1.16	0.62-2.18	.651
Left main disease	0.94	0.68-1.30	.705
Hypertension	1.05	0.74-1.48	.789
Emergency operation	0.95	0.57-1.59	.850
Previous PCI	0.98	0.72-1.34	.883

CI, Confidence interval; *CRF*, chronic renal failure; *LVEF*, left ventricular ejection fraction; *SVG*, saphenous vein graft; *GEA*, right gastroepiploic artery; *COPD*, chronic obstructive pulmonary disease; *BITA*, bilateral internal thoracic arteries; *CHF*, congestive heart failure; *CVA*, cerebrovascular accident; *CCAB*, conventional coronary artery bypass; *MI*, myocardial infarction; *BSA*, body surface area; *AF*, atrial fibrillation; *PCI*, percutaneous coronary intervention.

line with these previous studies, and the Kaplan-Meier curves diverged over time, although the follow-up was relatively short. On the other hand, 2 investigators reported no difference in survival between CR and IR patients.[19,20] This discrepancy may be partly the result of the difference in patient selection. Rastan et al[19] limited the study subjects to patients with left internal thoracic artery-LAD bypasses.

This retrospective study could not identify the reason why IR is associated with midterm survival. However, one possible explanation is that the poorer outcome of the IR group might be ascribed to the differences in patient characteristics. Osswald et al[21] noted that advanced coronary artery disease and other comorbidities might account for the higher risk of death after IR. Inasmuch as multivariable logistic regression analysis revealed that the predictors for IR were 1 or more total occluded lesion(s), lower BSA, 3-vessel disease, emergency operation, diabetes mellitus (diet or oral drug use), and female sex (Table 2), IR might serve as a surrogate variable for previous MI. Ischemic cardiomyopathy is well recognized as a predictor of long-term survival after coronary artery bypass grafting.[22] It is also possible that higher-risk profiles of the IR group account for the decreased survival.

O'Connor et al[23] reported that lower BSA and female sex are associated with coronary diameter. Although IR could result from a difficulty of anastomoses in small coronary arteries, myocardial viability may also account for its influence on midterm survival.[5] In this study, most segments left unbypassed were in the RCA and LCx systems (98%). This might partly reflect our grafting strategy. Some of these arteries were left unbypassed because of an occlusion on preoperative angiography. However, they may have been more important than originally recognized.[6] In addition, patients with poor left ventricular function and predominantly viable myocardium may have a better outcome after revascularization than those with less viability.[24] However, assessments, such as positron emission tomography,[25] were not routinely undertaken preoperatively in our series. Outcomes might be expected to improve if the diseased vessels were revascularized in their territories with "hibernating myocardium."[25]

Graft Patency

Several studies[10,11] reported that reintervention at follow-up was more frequent among patients undergoing OPCAB than among those undergoing CCAB. Wijeysundera et al,[13] in their meta-analysis, reported that the mean graft number was 0.19 lower in the OPCAB arm in the randomized studies, and both the randomized and the retrospective studies showed trends toward increased repeated revascularization. The possible causes are IR and the lower patency rate in OPCAB patients. However, the relative contributions of the 2 possible causes have not been determined.[10,12,13] Lopes et al[9] have recently reported that vein graft failure is associated with repeat revascularization after an angiographic follow-up of the Project of Ex Vivo Vein Graft Engineering via Transfection (PRVENT) IV cohort. In our study, similar to their results, the event-free rates for MACCE or reintervention were both significantly lower in the occlusion group ($P < .001$ for both). Twenty-four patients received PCI, and 1 patient underwent a redo operation immediately after graftgraphy (18 PCIs and 1 surgery in the occlusion group), whereas there were 63 PCIs and 3 redo surgeries after discharge. The differences in the event-free rates for MACCE or reintervention between the occlusion and patent groups were mainly due to the early PCI procedures. However, even if in-hospital repeated interventions were excluded, the event-free rate for reintervention was still lower in the occlusion group ($P = .038$). Achievement of higher patency, in addition to CR, might be expected to lower the rate of adverse cardiac events. It

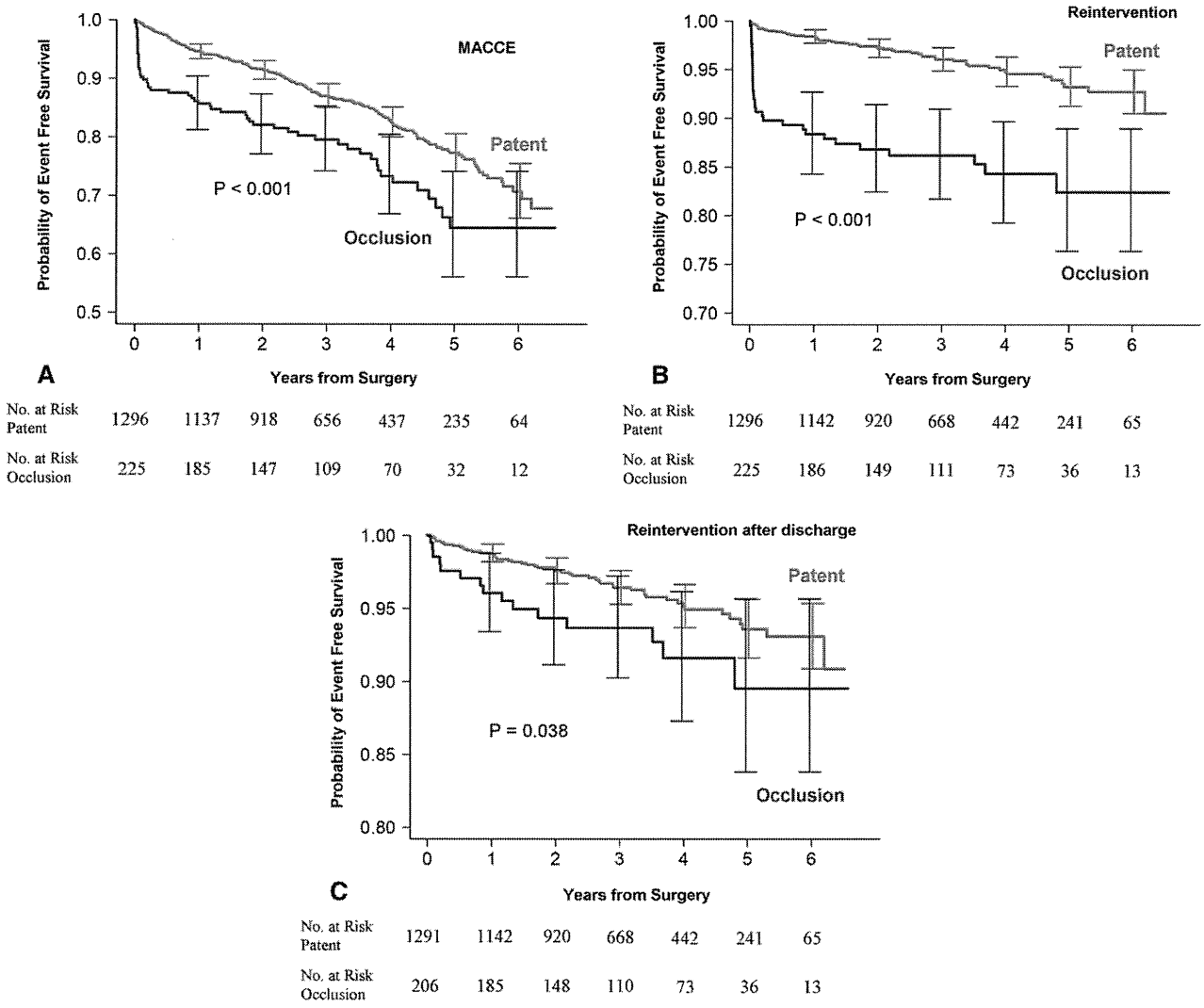

FIGURE 2. Kaplan-Meier estimates for the patent and occlusion groups. A, Event-free survival curve for MACCE. B, Event-free survival curve for reintervention. C, Event-free survival curve for reintervention after discharge. *MACCE*, Major adverse cardiac and cerebrovascular event.

is mandatory to explore the optimal graft and target selection in OPCAB surgery.[9,16]

Limitations

First, because this was a retrospective observational study, confounding biases might not have been eliminated. Multivariable analyses were used in the study to control for differences in prognostic factors. Also, our propensity score analyses did not suggest any substantial selection bias; nevertheless, some unmeasured factors (eg, more complex coronary pathology) were inevitable,[8] and any causal effects cannot be stated. Second, this study was from a single surgeon and a single center, limiting the generalizability of these results. Third, graftgraphy was performed using 2 modalities: catheter-based angiography and multidetector CT. MDCT is generally used in daily practice, but catheter-based coronary angiography remains the gold standard. In addition, the results of those 2 examinations were read by 2 different teams. Although times 0 of the Kaplan-Meier curves for the occlusion and patent groups should be the time of angiographic evaluation, the actual dates of the angiography were not available from our database. Fourth, although interaction between IR and occlusion was not significant, it might be owing to the few patients in the IR and occlusion groups. Fifth, the dominancy of coronary systems or the number of class C lesions was not noted in our database, and the assessment of infarcted area viability was not routinely performed. Sixth, each patient could not be identified as too small or diffusely diseased, because several patients had more than one reason for incomplete revascularization and some others had no reason given in the operator's note. Finally, because only

77 patients underwent on-pump CABG in our institution during the study period, we could not compare the angiographic results between OPCAB and on-pump CABG.

CONCLUSIONS

Incomplete revascularization was relevant to higher mid-term mortality after OPCAB, whereas the risks of MACCE and reintervention were higher for patients with occluded grafts. The surgical mantra of CR remains pertinent, even in OPCAB. CR, coupled with achievement of a higher patency rate, could be expected to improve outcomes at follow-up after OPCAB surgery.

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ACD

000 The impact of incomplete revascularization and angiographic patency on midterm results after off-pump coronary artery bypass grafting

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This study assessed the relationships among incomplete revascularization, angiographic patency, and midterm results after OPCAB surgery. Completeness of revascularization was relevant to survival, whereas graft patency was associated with freedom from reintervention. Complete revascularization, coupled with achievement of a higher patency rate, could be expected to improve follow-up outcomes.

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Sex-Based Differences in Clinical Practice and Outcomes for Japanese Patients With Acute Myocardial Infarction Undergoing Primary Percutaneous Coronary Intervention

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on behalf of the CREDO-Kyoto Investigators

Background: Limited data are available for sex-based differences in Japanese patients with acute myocardial infarction (AMI) undergoing primary percutaneous coronary intervention (PCI).

Methods and Results: The study patients comprised 1,197 women and 3,182 men who underwent primary PCI for AMI in 2005–2007. Compared with the men, the women were significantly older, and had significantly longer onset-to-balloon time and lower rate of follow-up coronary angiography. In-hospital mortality was higher among women than men (8.7% vs. 4.9%, P<0.001). Although the cumulative incidence of all-cause death at 3 years was also higher for women (17.7% vs. 10.7%, P<0.001), the adjusted risk for all-cause death was comparable [hazard ratio (HR, women vs. men)=0.94, 95% confidence interval (CI): 0.71–1.24, P=0.66]. The incidence (12.1% vs. 12.4%, P=0.77) and the adjusted risk (HR=0.99, 95% CI 0.78–1.24, P=0.92) for any clinically-driven coronary revascularization were both comparable. However, regarding any non-clinically-driven coronary revascularization, the incidence (19.6% vs. 27.8%, P<0.001) and the adjusted risk (HR=0.79, 95% CI 0.65–0.95, P=0.012) were both lower in women relative to men.

Conclusions: In current Japanese clinical practice for AMI, onset-to-balloon time was significantly longer in women than in men. Female sex was associated with lower follow-up coronary angiography rate and lower incidence of any non-clinically-driven coronary revascularization, whereas the incidence of any clinically-driven coronary revascularization was comparable between the sexes.

Key Words: Acute myocardial infarction; Outcomes; Percutaneous coronary intervention; Women.

Higher unadjusted risks for mortality and major complications have been demonstrated in female relative to male patients with acute myocardial infarction (AMI). However, there remains controversy with respect to sex differences in adjusted clinical outcomes.[1–4] The inconsistency in unadjusted and adjusted results of comparisons of clinical outcome between women and men has been often ascribed to women's older age, accumulated comorbidities, and less frequent application of evidence-based treatments. However, there are a few studies suggesting that female sex is an independent predictor of better long-term survival after coronary revascularization.[5–7] In addition, because the low rate of

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restenosis achieved with drug-eluting stents (DES) has enabled percutaneous coronary intervention (PCI) for lesions with smaller reference diameters, female patients benefit more from DES implantation, partly because of their smaller coronary artery diameters than in male patients.[8,9] Other factors that could cause sex-based differences in outcome include differences in prehospital case fatality,[10] access to emergency care and unawareness among women of the importance of secondary prevention for coronary artery diseases (CADs).[11,12]

The purpose of this study was to clarify sex-based differences in risk factor profiles, treatments and outcomes among Japanese patients with AMI undergoing primary PCI in the DES era.

Methods

Study Subjects

The Coronary REvascularization Demonstrating Outcome study in Kyoto (CREDO-Kyoto) percutaneous coronary intervention (PCI)/coronary artery bypass grafting (CABG) registry cohort-2 is a physician-initiated, non-company sponsored multicenter registry that enrolled patients from 26 centers in Japan during January 2005 to December 2007 after the approval of sirolimus-eluting stents.[13] The relevant review boards or ethics committees in all 26 participating centers (**Appendix S1**) approved the research protocol. Because of the retrospective enrollment, written informed consent from the patients was waived, although we excluded those patients who refused participation in the study when contacted for follow-up. This strategy is in accordance with the guidelines for epidemiological studies issued by the Ministry of Health, Labor and Welfare of Japan.

During the 3 years of the enrollment, 5,486 patients with AMI were enrolled. After excluding 57 patients who refused study participation, and patients with malignant disease or prior PCI/CABG, and those treated with CABG, 4,379 patients were analyzed in the current study. Baseline characteristics, comorbidity, treatments, and in-hospital as well as long-term outcome measures including death, cardiovascular death, MI, stroke and any coronary revascularization procedures were compared between women and men.

Data Collection, Definitions and Follow-up

Clinical and analytical data for the study subjects were collected from hospital charts or databases in each center by independent clinical research coordinators (**Appendix S2**). The baseline data for the patients included: age, sex, smoking habit, body mass index, systolic blood pressure on admission, heart rate on admission, and comorbidities such as hypertension, diabetes mellitus, dyslipidemia (low-density lipoprotein-cholesterol [LDL-C] ≥140 mg/dl, triglycerides [TGs] ≥150 mg/dl, high-density lipoprotein-cholesterol [HDL-C] <40 mg/dl), chronic kidney disease, high white blood cell (WBC) count (>11×10^9/L),[14] anemia (blood hemoglobin level <11 g/dl), hyperglycemia on admission (blood glucose level >198 mg/dl),[15] peripheral arterial disease (PAD: patient being treated for carotid, aortic and/or other peripheral vascular diseases or scheduled for interventions), atrial fibrillation (AF), history of heart failure (HF), prior MI, prior cerebrovascular accident, Thrombolysis In Myocardial Infarction (TIMI) flow grade at initial coronary angiography (CAG), and whether the index PCI was successful or not. Diabetes was diagnosed by each physician, based on the diagnosis and classification of diabetes mellitus of the expert committee.[16] Estimated glomerular filtration rate (eGFR) was calculated by the Modification of Diet in Renal Disease formula modified for Japanese patients,[17] and chronic kidney disease was defined as an eGFR <30 ml·min^{-1}·1.73 m^{-2}. The initial perfusion status of the infarct-related artery was assessed according to the TIMI study classification.[18] Successful PCI was defined as procedural success for the culprit lesion determined by the physician without slow flow/no reflow phenomenon in the infarct-related artery, equivalent to final TIMI flow grade 3. The patients were followed up with respect to mortality for a median of 3.0 years. All deaths were confirmed by medical records or telephone interviews with the patients' families, and death was regarded as being cardiovascular in origin unless obvious non-cardiovascular causes were identified. MI was defined according to the Arterial Revascularization Therapy Study.[19] In the present study, major adverse cardiovascular events (MACE) were defined as a composite of cardiovascular death, MI and stroke. Bleeding events were evaluated with respect to intracranial bleeding, severe bleeding as defined by Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) classification, and gastrointestinal bleeding.[20] CAG was not performed routinely, but left to the discretion of the attending physician. In the current analysis, follow-up CAG includes both scheduled follow-up CAG and unscheduled clinically-driven CAG. Any coronary revascularization included any PCI or CABG performed during follow-up. In this registry, clinically-driven coronary revascularizations were distinguished from non-clinically-driven revascularizations. Any clinically-driven coronary revascularizations were defined by the existence of at least one of the following: angina symptoms (chest pain at rest, AMI, unstable angina pectoris, and stable effort angina) or objective ischemia shown by a stress test.

Statistical Analysis

Continuous variables are expressed as the mean±standard deviation, except for the time from symptom onset to admission, onset-to-balloon time, door-to-balloon time, and highest creatinine phosphokinase, expressed as the median (interquartile range). Differences in the baseline clinical characteristics and treatments between women and men were evaluated by Pearson chi-square test for categorical variables and Student's t-test for continuous variables. Cumulative incidences were estimated by the Kaplan-Meier method and differences between women and men were examined by log-rank test. A Cox proportional hazards model was used to estimate hazard ratios (HR) of sex, adjusting for baseline differences. We listed the following 46 clinically relevant factors as potential independent risk-adjusting variables for clinical outcomes: age ≥75 years; sex; body mass index ≥25 kg/m^2; hypertension; diabetes on insulin therapy; LDL-C ≥140 mg/dl; TG ≥150 mg/dl; HDL-C <40 mg/dl; current smoking; prior MI; prior stroke; history of HF; mitral regurgitation ≥grade 3; AF; dialysis; eGFR <30 ml·min^{-1}·1.73 m^{-2}, not on dialysis; anemia; WBC count >11×10^9/L; platelets <100×10^9/L; blood glucose level >198 mg/dl; chronic obstructive pulmonary disease; liver cirrhosis; PAD; highest creatinine phosphokinase ≥3,000 IU/L; cardiogenic shock at presentation; multivessel CAD; target of left main coronary artery (LMCA); target of proximal left anterior descending artery; target of chronic total occlusion; target of bifurcation; TIMI flow grade 0 at initial CAG; successful PCI; total stent length ≥28 mm; minimal stent diameter <3.0 mm; DES use; aspirin; cilostazol; statins; angiotensin-converting enzyme inhibitors (ACEI)/angiotensin II receptor blockers (ARB); β-adrenergic blockers; calcium-channel blockers; nitrates; nicorandil; warfarin; proton-pump inhibitors; and

Table 1. Comparisons of the Baseline Characteristics of the AMI Patients by Sex

	Women	Men	P value
No. of patients	1,197	3,182	
Age (years±SD)	74.1±10.9	64.5±11.7	<0.001
Age ≥75 years (%)	624 (52.1)	670 (21.1)	<0.001
BMI (mean±SD)	22.9±3.7	23.9±3.4	<0.001
BMI ≥25 kg/m^2 (%)	285 (23.8)	993 (31.2)	<0.001
SBP on admission (mmHg)	134.5±31.7	135.4±29.6	0.38
Heart rate on admission (beats/min)	77.6±20.4	77.7±21.7	0.91
Hypertension (%)	966 (81.0)	2,442 (76.7)	0.005
Diabetes (%)	380 (31.8)	1,046 (32.9)	0.48
Oral hypoglycemic medication	237 (19.8)	619 (19.5)	0.80
Insulin use	56 (4.7)	129 (4.1)	0.36
No medical treatment	104 (8.7)	341 (10.7)	0.048
LDL-C ≥140 mg/dl (%)	272 (27.9)	643 (24.9)	0.068
Triglyceride ≥150 mg/dl (%)	138 (13.1)	578 (20.7)	<0.001
HDL-C <40 mg/dl (%)	240 (23.7)	1,012 (37.1)	<0.001
Current smoking (%)	175 (14.6)	1,652 (51.9)	<0.001
LVEF (mean±SD)	54.6±13.4	53.1±12.5	0.003
≤40% (%)	153 (16.8)	384 (15.5)	0.36
Prior MI (%)	28 (2.3)	106 (3.3)	0.089
Prior stroke (%)	128 (10.7)	270 (8.5)	0.024
Heart failure (%)	44 (3.7)	36 (1.1)	<0.001
Mitral regurgitation ≥3 (%)	59 (4.9)	65 (2.0)	<0.001
Atrial fibrillation (%)	138 (11.5)	261 (8.2)	<0.001
Dialysis (%)	22 (1.8)	39 (1.2)	0.12
eGFR <30 ml·min^{-1}·1.73 m^{-2}, not on dialysis (%)	84 (7.0)	98 (3.1)	<0.001
White blood cell count (mean±SD)	9,493±3,480	10,562±3,682	<0.001
>11×10^9/L (%)	288 (24.8)	1,188 (38.0)	<0.001
Anemia (hemoglobin <11 g/dl) (%)	232 (19.4)	166 (5.2)	<0.001
Platelets <100×10^9/L (%)	19 (1.6)	52 (1.6)	0.91
Blood glucose level (mean±SD)	182.4±88.4	176.7±88.9	0.059
>198 mg/dl (%)	341 (29.1)	824 (26.4)	0.077
Chronic obstructive pulmonary disease (%)	51 (4.3)	90 (2.8)	0.017
Liver cirrhosis (%)	25 (2.1)	64 (2.0)	0.87
Peripheral arterial disease (%)	30 (2.5)	95 (3.0)	0.40
Time from symptom onset to admission (h)*	4.0 (1.8–11.4)	3.0 (1.4–9.2)	0.016
Medications before admission (%)			
Aspirin	161 (13.5)	402 (12.6)	0.47
Thienopyridine	69 (5.8)	201 (6.3)	0.50
Ticlopidine	60 (87.0)	187 (93.0)	0.12
Clopidogrel	9 (13.0)	14 (7.0)	0.12
Cilostazol	12 (1.0)	29 (0.9)	0.78
Statins	220 (18.4)	361 (11.4)	<0.001
Antihypertensive drugs	669 (69.3)	1,274 (52.2)	<0.001

*Data are median (interquartile range).
AMI, acute myocardial infarction; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; LVEF, Left ventricular ejection fraction; MI, myocardial infarction; SD, standard deviation; SBP, systolic blood pressure.

H2 blockers. We then selected risk-adjusting variables that showed univariate P-values <0.05 as those to include simultaneously in each multivariate model. The continuous variables were dichotomized by clinically meaningful reference values. All analyses were conducted using JMP version 5 (SAS Institute Inc, Cary, NC, USA). All reported P-values are 2-sided and P<0.05 was considered to indicate statistical significance.

Results

Baseline Characteristics

The baseline clinical characteristics of the women and men are listed in **Table 1**. The women were approximately 10 years older than the men, and 52% of the female patients as compared with 21% of the men were ≥75 years of age. Compared with the men, the women more frequently had hypertension, eGFR <30 ml·min^{-1}·1.73 m^{-2} and not on dialysis, prior stroke,

Table 2. Characteristics of the Index AMI

	Women	Men	P value
Onset-to-balloon time (h)*	6.1 (3.5–15.4)	4.9 (3.1–12.6)	0.030
>180 min (%)	860 (81.5)	2,159 (75.8)	<0.001
Door-to-balloon time (h)*	1.7 (1.1–2.8)	1.7 (1.1–2.5)	0.80
>90 min (%)	579 (55.9)	1,503 (53.9)	0.27
Highest creatinine phosphokinase (IU/L)*	1,531 (695–3,173)	2,230 (999–4,212)	<0.001
>3,000 IU/L (%)	311 (26.3)	1,196 (38.0)	<0.001
Killip class ≥3 (%)	230 (19.2)	464 (14.6)	<0.001
Cardiogenic shock at presentation (%)	197 (16.5)	410 (12.9)	0.002
Cardiopulmonary arrest at presentation (%)	29 (2.4)	108 (3.4)	0.100
Use of intra-aortic balloon counter pulsation (%)	161 (13.5)	495 (15.6)	0.082
Use of percutaneous cardiopulmonary support (%)	24 (2.0)	95 (3.0)	0.075
Infarcted region (%)			
Anterior wall	537 (44.9)	1,503 (47.2)	0.26
Inferior wall	453 (37.8)	1,138 (35.8)	
Lateral wall	57 (4.8)	123 (3.9)	
Posterior wall	150 (12.5)	418 (13.1)	
TIMI flow grade 0 at initial CAG (%)	666 (55.6)	1,790 (56.3)	0.71
Successful PCI (%)	1,054 (88.1)	2,862 (89.9)	0.070
Major complications (%)			
Severe arrhythmia	189 (15.8)	567 (17.8)	0.11
Ventricular tachycardia	93 (7.8)	317 (10.0)	0.026
Ventricular fibrillation	55 (4.6)	200 (6.3)	0.033
Complete atrioventricular block	65 (5.4)	163 (5.1)	0.68
Other arrhythmia	15 (1.3)	26 (0.8)	0.18
Right ventricular infarction	24 (2.0)	53 (1.7)	0.45
Cardiac tamponade	14 (1.2)	14 (0.44)	0.007
Cardiac rupture	20 (1.7)	7 (0.22)	<0.001
Mitral regurgitation grade ≥3	8 (0.67)	11 (0.35)	0.15
Ventricular septal perforation	5 (0.42)	1 (0.03)	0.002

*Data are median (interquartile range).
AMI, acute myocardial infarction; CAG, coronary angiography; PCI, percutaneous coronary intervention; TIMI, Thrombolysis In Myocardial Infarction.

history of HF, AF, and anemia, whereas higher prevalences of body mass index ≥25 kg/m^2, untreated diabetes, TG ≥150 mg/dl, HDL-C <40 mg/dl, current smoking status and WBC count >11×10^9/L were seen in the men. There were no significant differences in the prevalences of diabetes, diabetes on insulin therapy, diabetes on oral hypoglycemic medication, LDL-C ≥140 mg/dl, prior MI, hemodialysis, and PAD between the women and men. The time from symptom onset to admission was significantly longer in the women than in the men.

Characteristics of Index MI

The characteristics of the index MI are shown in **Table 2**. The median time from the onset of MI to balloon was significantly longer in the women than in the men (6.1 vs. 4.9 h), but the door-to-balloon time was comparable. Distribution of infarct location was comparable between the sexes, although the men had larger infarcts estimated by highest creatinine phosphokinase level: median highest creatinine phosphokinase was 1,531 IU/L for the women and 2,230 IU/L for the men. The female patients were more likely to be in a higher Killip class at admission, and had a higher prevalence of cardiogenic shock than the male patients. However, frequency of the use of intra-aortic balloon pumping or percutaneous cardiopulmonary support device was not different by sex. The rates of patients with TIMI flow grade 0 at initial CAG and those with successful PCI were comparable between sexes. The severe acute complications of AMI, such as cardiac tamponade, cardiac rupture, and ventricular septal perforation, occurred more frequently in the women than in the men, although the prevalence of ventricular tachycardia and ventricular fibrillation was lower in the women. The prevalences of complete atrioventricular block, right ventricular infarction, and severe mitral regurgitation were comparable.

Lesion Characteristics and Treatments

Comparisons of the lesion characteristics and of treatments during hospitalization between the women and men are shown in **Table 3**. There were no significant differences in the rates of multivessel disease, unprotected LMCA, and chronic total occlusion between the women and men. Regarding the diseased vessel, it was less commonly the proximal left anterior descending artery in the women than in the men.

The rate of using a stent was lower in the women than in the men (89.3% vs. 92.3%, P=0.002) and the difference arose from the significantly lower rate of use of bare metal stents (BMS) in the women than in the men (68.4% vs. 73.9%, P<0.001); the rate of DES use was comparable between the women and men. The success rate of stent implantation was very high in both the women and the men, although the BMS implantation success rate was slightly lower in the women than in the men

Table 3. Lesion Characteristics, Revascularization Procedures, and Medications

	Women	Men	P value
Lesion characteristics (%)			
Multivessel disease	615 (51.4)	1,609 (50.6)	0.63
Unprotected left main coronary artery	48 (4.0)	143 (4.5)	0.48
Chronic total occlusion	113 (9.4)	347 (10.9)	0.16
Revascularization procedures (%)			
Target of left anterior descending artery	669 (55.9)	1,852 (58.2)	0.17
Target of left main coronary artery	32 (2.7)	122 (3.8)	0.063
Target of proximal left anterior descending artery	622 (52.0)	1,761 (55.3)	0.045
Target of chronic total occlusion	28 (2.3)	128 (4.0)	0.007
Target of bifurcation	317 (26.5)	871 (27.4)	0.56
Stent use	1,069 (89.3)	2,936 (92.3)	0.002
BMS (%)	819 (68.4)	2,350 (73.9)	<0.001
BMS only	691 (64.9)	1,980 (67.5)	0.13
DES	374 (35.1)	955 (32.5)	0.13
SES only	223 (24.4)	540 (21.4)	0.064
Stent deployment success (%)	1,065 (99.6)	2,935 (100)	0.01
BMS	815 (99.5)	2,348 (99.9)	0.022
SES	339 (99.7)	887 (99.9)	0.48
Side-branch stenting (%)	37 (3.1)	105 (3.3)	0.73
No. of implanted stents (mean±SD)	1.73±0.03	1.72±0.02	0.81
Total stent length (mm; mean±SD)	35.4±0.47	36.1±0.79	0.46
>28mm (%)	457 (42.9)	1,289 (43.9)	0.57
Minimal stent diameter (mm; mean±SD)	2.91±0.01	3.04±0.008	<0.001
<3.0mm (%)	465 (43.7)	945 (32.2)	<0.001
Medications at discharge (%)			
Aspirin	1,175 (98.2)	3,142 (98.7)	0.15
Thienopyridine	1,127 (94.2)	3,063 (96.3)	0.002
Ticlopidine	1,016 (90.2)	2,798 (91.4)	0.42
Clopidogrel	109 (9.7)	262 (8.6)	0.42
Other thienopyridine	2 (0.18)	3 (0.1)	0.42
Cilostazol	383 (32.0)	1,131 (35.5)	0.029
Statins	624 (52.1)	1,724 (54.2)	0.23
ACEI/ARB	830 (69.3)	2,321 (72.9)	0.018
β-adrenergic blocker	416 (34.8)	1,334 (41.9)	<0.001
Calcium-channel blocker	265 (22.1)	615 (19.3)	0.039
Nitrates	376 (31.4)	909 (28.6)	0.065
Nicorandil	294 (24.6)	915 (28.8)	0.006
Warfarin	121 (10.1)	319 (10.0)	0.93
Proton-pump inhibitor	441 (36.8)	1,058 (33.3)	0.026
H2 blocker	373 (31.2)	1,075 (33.8)	0.10
Follow-up CAG (%)	689 (64.2)	2,364 (78.9)	<0.001

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BMS, bare metal stent; CAG, coronary angiography; DES, drug-eluting stent; SES, sirolimus-eluting stent; SD, standard deviation.

(99.5% vs. 99.9%, P=0.022).

With respect to the medications at discharge, there were no significant differences between the women and men in the proportions of patients treated with aspirin (98.2% vs. 98.7%), statins (52.1% vs. 54.2%), nitrates (31.4% vs. 28.6%), and H2-blockers (31.2% vs. 33.8%). Cardioprotective drugs such as ACEI/ARB (69.3% vs. 72.9%, P=0.018) and β-adrenergic blockers (34.8% vs. 41.9%, P=0.001) were less frequently prescribed to women than to men, while calcium-channel blockers (22.1% vs. 19.3%, P=0.039) and proton-pump inhibitors (36.8% vs. 33.3%, P=0.026) were more frequently prescribed to women.

The rate of follow-up CAG was significantly lower in the women than in the men (64.2% vs. 78.9%, P<0.001).

In-Hospital Mortality and Long-Term Clinical Outcomes

The in-hospital mortality rate was significantly higher in the women than in the men (8.7% vs. 4.9%, P<0.001) (**Table 4**). At 3 years, female sex was associated with significantly higher unadjusted incidences of all-cause death (17.7% vs. 10.7%, P<0.001), cardiovascular death (14.4% vs. 7.8%, P<0.001), and MACE (21.0% vs. 13.9%, P<0.001) (**Figure 1**). Detailed analyses of the causes of death revealed that female sex was associated with higher unadjusted incidences of death by acute coronary syndrome (9.7% vs. 5.2%, P<0.001) and non-cardiac death (4.8% vs. 3.3%, P=0.019) relative to male sex. The in-

Table 4. Crude In-Hospital Mortality and Long-Term Outcomes for Women and Men Undergoing PCI for AMI

	Women	Men	P value
In-hospital outcome (%)			
All-cause death	104 (8.7)	155 (4.9)	<0.001
MACE	135 (11.3)	220 (6.9)	<0.001
Bleeding (%)			
Intracranial bleeding	4 (0.3)	5 (0.2)	0.25
GUSTO severe	34 (2.8)	59 (1.9)	0.044
Gastrointestinal bleeding	16 (1.3)	31 (1.0)	0.30
Long-term outcome (%)			
All-cause death	192 (17.7)	313 (10.7)	<0.001
Cardiovascular death	159 (14.4)	238 (7.8)	<0.001
Death by ACS	113 (9.7)	163 (5.2)	<0.001
Non-cardiac death	41 (4.8)	82 (3.3)	0.019
Sudden death	8 (1.0)	33 (1.2)	0.22
MACE	233 (21.0)	414 (13.9)	<0.001
Bleeding			
Intracranial bleeding	18 (1.9)	26 (1.1)	0.11
GUSTO severe	51 (4.7)	100 (3.6)	0.11
Gastrointestinal bleeding	31 (3.1)	70 (2.5)	0.32
Coronary revascularization			
Any	294 (29.3)	1,039 (36.7)	<0.001
TLR	199 (19.7)	678 (23.6)	0.033
Non-TLR	162 (16.8)	574 (20.9)	0.012
Clinically-driven revascularization			
Any	108 (12.1)	293 (12.4)	0.77
TLR	70 (7.3)	196 (7.5)	0.79
Non-TLR	59 (6.6)	157 (6.6)	0.77
Non-clinically-driven revascularization			
Any	186 (19.6)	746 (27.8)	<0.001
TLR	129 (13.4)	482 (17.4)	0.006
Non-TLR	103 (10.9)	417 (15.3)	0.001

MACE was defined as a composite of cardiovascular death, MI and stroke.
ACS, acute coronary syndrome; AMI, acute myocardial infarction; GUSTO, Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries; MACE, major adverse cardiovascular events; PCI, percutaneous coronary intervention; TLR, target lesion revascularization.

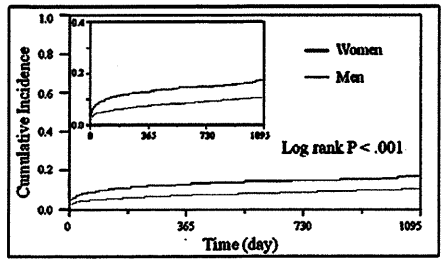
cidence of sudden death was comparable between the women and the men (**Table 4**). The multivariate Cox proportional hazards models indicated no significant differences between women and men in the long-term adjusted risks of all-cause death [HR 0.94; 95% confidence interval (CI) 0.71–1.24], cardiovascular death (HR 1.06; 95% CI 0.77–1.47), and MACE (HR 1.06; 95% CI 0.83–1.34). The factors that showed a significant effect on long-term all-cause mortality in our analyses included age ≥75 years, LDL-C ≥140 mg/dl, HDL-C <40 mg/dl, AF, dialysis, eGFR <30 ml·min^{-1}·1.73 m^{-2} and not on dialysis, WBC count >11×10^9/L, platelets <100×10^9/L, blood glucose level >198 mg/dl, history of PAD, highest creatinine phosphokinase ≥3,000 IU/L, cardiogenic shock on admission, and multivessel coronary disease (**Table S1**). The in-hospital incidences of intracranial bleeding and gastrointestinal bleeding were comparable between the women and the men; however, GUSTO severe bleeding occurred more frequently in the women (2.8% vs. 1.8%, P=0.044). The long-term incidences of intracranial, gastrointestinal, and GUSTO severe bleeding at 3 years were all comparable between the sexes (**Table 4**).

Coronary Revascularization During Follow-up

The incidence of any coronary revascularization was significantly lower in the women than in the men (at 3 years: 29.3% vs. 36.7%, log-rank P<0.001; **Figure 2**). There was no significant difference in the incidence of any clinically-driven coronary revascularization, and the difference in the incidence of any coronary revascularization was derived from the difference in the incidence of any non-clinically-driven coronary revascularization (at 3 years: 19.6% in the women vs. 27.8% in the men, P<0.001). The significantly lower incidence of the any non-clinically-driven coronary revascularization in the women was seen both in the setting of target lesion revascularization (TLR) (at 3 years: 13.4% vs. 17.4%, P=0.006) and in non-TLR (at 3 years: 10.9% vs. 15.3%, P=0.001) (**Table 4**).

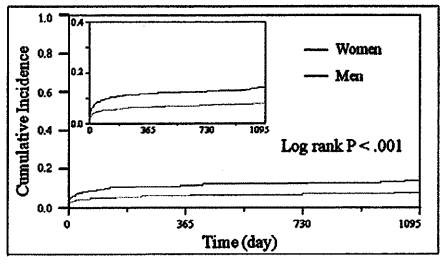
In a multivariate Cox proportional hazards model in all patients, female sex was associated with significantly lower incidence of any coronary revascularization (HR 0.83; 95% CI 0.72–0.96, P=0.010). Other factors that had a significant effect on the incidence of any coronary revascularization were dialysis, multivessel disease, target of unprotected LMCA, total stent length ≥28 mm, and minimal stent diameter <3.0 mm (**Table S2**). Female sex also had significant effect on the incidence of any non-clinically-driven coronary revascularization (HR 0.79; 95% CI 0.65–0.95, P=0.012), although in the analysis of any clinically-driven coronary revascularization, the

A All-cause Death



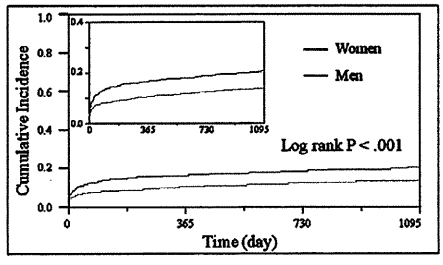
Interval	0 day	30 days	1 year	2 years	3 years
Women					
Incidence		7.6%	13.0%	15.0%	17.7%
N of events		91	153	175	192
N of patients at risk	1197	1092	978	765	416
Men					
Incidence		4.3%	7.6%	9.3%	10.7%
N of events		137	238	286	313
N of patients at risk	3182	3005	2817	2223	1213

B Cardiovascular Death



Interval	0 day	30 days	1 year	2 years	3 years
Women					
Incidence		7.6%	11.7%	12.6%	14.4%
N of events		91	138	148	159
N of patients at risk	1197	1092	978	765	416
Men					
Incidence		4.3%	6.6%	7.3%	7.8%
N of events		137	207	227	238
N of patients at risk	3182	3005	2817	2223	1213

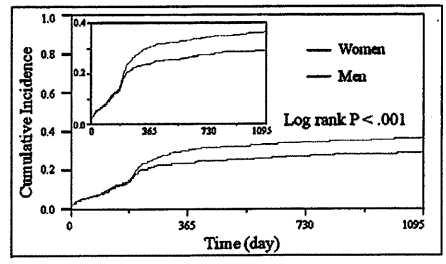
C MACE



Interval	0 day	30 days	1 year	2 years	3 years
Women					
Incidence		10.6%	16.5%	18.8%	21.0%
N of events		126	195	218	233
N of patients at risk	1197	1058	930	716	392
Men					
Incidence		6.8%	10.7%	12.4%	13.9%
N of events		215	336	385	414
N of patients at risk	3182	2928	2697	2100	1140

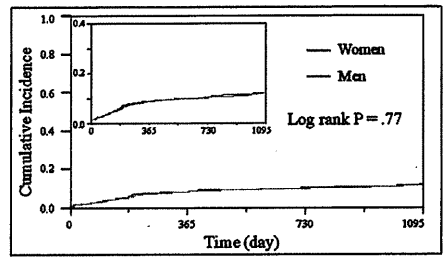
Figure 1. Cumulative incidences of (**A**) all-cause death, (**B**) cardiovascular death, and (**C**) major adverse cardiovascular events (MACE) defined as a composite of cardiovascular death, myocardial infarction and stroke were all significantly higher in the women than in the men who underwent primary percutaneous coronary intervention for acute myocardial infarction.

A Any Coronary Revascularization



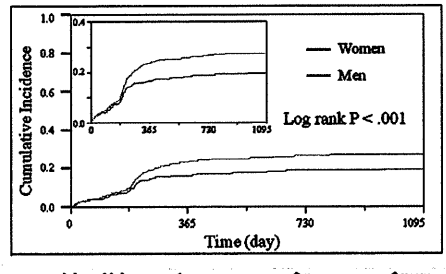
Interval	0 day	30 days	1 year	2 years	3 years
Women					
Incidence		4.7%	23.9%	27.4%	29.3%
N of events		54	250	282	294
N of patients at risk	1197	1043	745	547	290
Men					
Incidence		5.1%	30.5%	34.6%	36.7%
N of events		159	895	1003	1039
N of patients at risk	3182	2856	1960	1466	777

B Any Clinically-driven Coronary Revascularization



Interval	0 day	30 days	1 year	2 years	3 years
Women					
Incidence		2.0%	8.9%	10.3%	12.1%
N of events		23	88	99	108
N of patients at risk	1197	1043	745	547	290
Men					
Incidence		2.2%	8.8%	10.6%	12.4%
N of events		68	238	273	293
N of patients at risk	3182	2856	1960	1466	777

C Any Non-clinically-driven Coronary Revascularization



Interval	0 day	30 days	1 year	2 years	3 years
Women					
Incidence		2.8%	16.5%	19.0%	19.6%
N of events		31	162	183	186
N of patients at risk	1197	1043	745	547	290
Men					
Incidence		3.0%	23.8%	26.8%	27.8%
N of events		91	657	730	746
N of patients at risk	3182	2856	1960	1466	777

Figure 2. Cumulative incidences of (**A**) any coronary revascularization, (**B**) any clinically-driven coronary revascularization and (**C**) any non-clinically-driven coronary revascularization were all significantly lower in the women than in the men who underwent primary percutaneous coronary intervention for acute myocardial infarction.

risks were similar between the women and men (**Table S3**).

Discussion

The main findings of the present study are as follows: (1) coronary risk factor profiles differed between female and male Japanese AMI patients undergoing primary PCI in the DES era: the prevalence of older age, hypertension and chronic kidney disease were significantly higher in the women, whereas obesity, high TG and low HDL-C levels, and current smoking were more prevalent in the men; (2) significant differences in patient treatment/management: the onset-to-balloon time was longer and the incidence of non-clinically-driven coronary revascularization was lower in women than in men; (3) unadjusted incidences of all-cause death, cardiovascular death, and MACE were all higher in the women, whereas these outcome measures became comparable between the women and the men after adjustment.

Differences in Baseline Characteristics Between Female and Male Patients

In our previous study that analyzed the differences in risk factor profiles between female and male Japanese patients with CAD, excluding AMI, the prevalences of diabetes and high LDL-C level were significantly higher in the women than in the men, whereas the prevalence of obesity was comparable.[21] However, in the present study of Japanese AMI patients, the prevalence of obesity was significantly higher in the men than in the women, and the prevalences of diabetes and high LDL-C level were comparable. Because the prevalences of obesity and metabolic syndrome are higher in young AMI patients, particularly young male patients, than in stable CAD patients, our study's distinctive sex-based differences in the risk factor profiles of AMI and stable CAD patients may be concordant with the results of previous studies.[1–4,22–27] Greater difference in age between the two sexes among the AMI patients (approximately 10 years) than in the more stable CAD patients (approximately 5 years) may partly account for this observation.

Despite such differences in the risk factor profiles, no significant differences were found between the two sexes in the severity of CAD assessed as multivessel disease, unprotected LMCA and chronic total occlusion.

Characteristics Related to MI and Revascularization Procedures, and In-Hospital Mortality

It is still uncertain how sex itself affects the in-hospital outcome of AMI patients. As shown in this study, higher age and higher prevalence of chronic kidney disease were frequently found in the female AMI patients, which could be related to higher in-hospital mortality. In the current study analyzing a recent AMI cohort treated by primary PCI, in-hospital mortality was higher among the women than the men, which is in accordance with a previous study showing higher in-hospital mortality despite lower peak creatinine phosphokinase levels in Japanese female patients with ST-elevation MI (STEMI).[26] Thus, in-hospital mortality was still higher among the women in a more recent cohort with more frequent use of cardioprotective agents and higher success rate of PCI.[26–28] Contrary to this, including the current study, a population-based study of 201,114 people in Scotland showed that the 30-day case fatality rate was lower in women than in men, when deaths from AMI that occur without hospital admission were taken into consideration.[10] Because the current study could not assess prehospital information, our results should be carefully interpreted.

When the timing of revascularization therapy was compared, onset-to-balloon time was significantly longer in the women than in the men, whereas door-to-balloon time was comparable between the sexes. Namely, there was a longer time from onset to presentation at hospital for women. Several previous reports have also demonstrated more frequent time delay to treatment in female AMI patients relative to male. The possible reasons for this sex-related difference include a higher prevalence of atypical symptoms in female AMI patients.[26,29,30] Although the time to primary PCI could be associated with the incidence of in-hospital mortality, the relative importance of onset-to-balloon time and of door-to-balloon time has not been clarified.[31,32]

Previous studies performed outside Japan have suggested that less intensive treatment for women than for men might be a possible explanation for the higher mortality rate among female AMI patients.[25,33] However, in our study there were no significant procedural differences between the women and men in the treatment of AMI, such as in the numbers of stents used. Thus, it is unlikely that procedural differences in the index PCI resulted in the worse in-hospital outcomes in the women.

Sex-Based Differences in Long-Term Outcomes

Unadjusted survival analyses revealed significantly higher incidences among the female AMI patients with respect to all-cause death, cardiovascular death, and MACE during long-term follow-up, which was in sharp contrast to our previous observation in Japanese stable CAD patients suggesting comparable outcomes for these endpoints.[21] After adjustment for possible confounding factors, risks for mortality and MACE became comparable between the female and male AMI patients after primary PCI. This is also a distinctive finding compared with the result that the adjusted risk for mortality was significantly lower among female than male Japanese patients with stable CAD.[21] The Kaplan-Meier curves indicate sex-based differences in all-cause and cardiovascular deaths, and in MACE, which derives from the higher rate of early mortality among the women. Thus, poorer early outcomes for women after AMI appear to account for the distinctive sex-based differences in long-term outcome. There were also several differences between the women and men that might have also affected the long-term outcomes. Consistent with previous observations, evidence-based medications for patients after MI such as ACEI/ARB and β-adrenergic blockers were less frequently prescribed for female patients as compared with male patients.[1,11,12] The higher age of the women analyzed in the present study may have affected the prescribing of ACEI/ARB and β-adrenergic blockers, but better evidence-based medical treatment may be needed to improve the long-term outcome for female AMI patients. The difference in the timing of primary PCI might also affect the long-term outcome according to sex. We have recently shown that shorter onset-to-balloon time was associated with better long-term clinical outcomes in Japanese patients with STEMI.[34] The significantly longer onset-to-balloon time seen in female patients could lead to deterioration in the outcome for female AMI patients.

The risk for any coronary revascularization was lower in the women than in the men, which was a consistent observation with our previous study in stable CAD patients in the BMS era.[21] In the Kaplan-Meier analyses comparing any clinically-driven and any non-clinically-driven coronary revascularization, TLR and non-TLR between the sexes clearly showed that the difference in the risk for any coronary revascularization

was caused by the significantly lower incidences of both non-clinically-driven TLR and non-clinically-driven non-TLR in the women. The differences remained significant after adjustment by Cox proportional hazards model. The significantly lower rate of follow-up CAG in the women could account for the lower incidence of non-clinically-driven coronary revascularization based on the angiographic findings at follow-up CAG. Indeed, the divergence in Kaplan-Meier curves for any coronary revascularization and for any non-clinically-driven coronary revascularization appeared at the timing of routine follow-up CAG in this study. It has been previously shown that routine follow-up CAG significantly increases the incidence of any non-clinically-driven coronary revascularization.[35–37] Atypical symptoms, difficulty in identifying myocardial ischemia, less willingness to undergo invasive investigations, and physician-based prejudices about female patients could contribute to the lower rate of follow-up CAG in the women.[38–41] In addition, although the rate of DES use in the current cohort was relatively low, the use of DES might have enhanced the lower risk of any coronary revascularization in the women that was also shown in the cohort in the BMS era.[21] A recent study showed that DES can be used safely and will effectively reduce restenosis and repeat coronary revascularization after PCI.[42] Because women have coronary arteries with smaller diameters and thus a potentially high risk of restenosis, female patients may benefit more than the men from the use of DES.

Study Limitations

Several limitations must be noted in addition to the limitations that are common to all observational studies caused by differences in the patients' background characteristics. Data for blood tests, smoking habit and medical therapies were only assessed at 1 time point. Therefore, lifestyle modifications after hospitalization and adherence to medical therapies were not considered in the analyses. For instance, the incidence of current smoker was remarkably higher in the men relative to the women, but the rate and effect of discontinuation of smoking were not taken into consideration in the current study. Our database did not include detailed information of patients' clinical histories such as the presence of pre-infarction angina, which might affect patients' in-hospital, as well as long-term, outcomes. In this observational study, indications for revascularization therapies were not defined but depended on the decision of each attending physician. Therefore, a sex-based selection bias might exist in the indication of treatment strategies.

Conclusions

This observational study revealed sex-related differences in the management of Japanese AMI patients, such as longer onset-to-balloon time and lower follow-up CAG rate among women. Unadjusted long-term clinical outcomes were worse in female than in male patients, but became comparable after adjustment. A lower incidence of non-clinically-driven coronary revascularization might account for the lower risk for any coronary revascularization in the women. The use of cardioprotective drugs, including ACEI/ARB and β-adrenergic blockers, was less prevalent among the women than the men, and better evidence-based medications may be needed to further improve the outcomes of female AMI patients after primary PCI.

Acknowledgments

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Supplementary Files

Supplementary File 1

Appendix S1. List of Participating Centers and Investigators

Appendix S2. List of Clinical Research Coordinators

Table S1. Multivariate Analysis for Factors Associated With the Incidence of Long-Term All-Cause Mortality in Women and Men Undergoing PCI for AMI

Table S2. Multivariate Analysis for Factors Associated With the Incidence of Any Coronary Revascularization in Women and Men Undergoing PCI for AMI

Table S3. Relative Adjusted Risk in the Female AMI Patients for Clinically-Driven or Non-Clinically-Driven Any Coronary Revascularization

Please find supplementary file(s);
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Renal Function and Effect of Statin Therapy on Cardiovascular Outcomes in Patients Undergoing Coronary Revascularization (from the CREDO-Kyoto PCI/CABG Registry Cohort-2)

Masahiro Natsuaki, MD[a], Yutaka Furukawa, MD[c,*], Takeshi Morimoto, MD[d], Ryuzo Sakata, MD[b], and Takeshi Kimura, MD[a]; on Behalf of the CREDO-Kyoto PCI/CABG Registry Cohort-2 Investigators

Although statin therapy is essential for secondary cardiovascular prevention, the therapeutic effect of statins on cardiovascular outcomes in patients with advanced chronic kidney disease (CKD) after coronary revascularization has not been fully elucidated. In the CREDO-Kyoto Registry Cohort-2, 14,706 patients who underwent first coronary revascularization were divided into 4 strata based on estimated glomerular filtration rate (eGFR) or status of hemodialysis (HD). Patients in each stratum were further divided into 2 groups based on statin therapy at discharge: non-CKD stratum (eGFR ≥60 ml/min/1.73 m^2), 8,959 patients (statin, n = 4,747; no statin, n = 4,212); mild CKD stratum (eGFR ≥30 to <60 ml/min/1.73 m^2), 4,567 patients (statin, n = 2,135; no statin, n = 2,432); severe CKD stratum (eGFR <30 ml/min/1.73 m^2), 608 patients (statin, n = 229; no statin, n = 379); and HD stratum, 572 patients (statin, n = 117; no statin, n = 455). Median follow-up duration was 956 days (interquartile range 699 to 1,245). Adjusted risk for major adverse cardiovascular events (MACEs; composite of cardiovascular death, myocardial infarction, or stoke) was significantly lower in the statin group than in the no-statin group in the non-CKD (hazard ratio 0.8, 95% confidence interval 0.68 to 0.95, p = 0.01) and mild CKD (hazard ratio 0.69, 95% confidence interval 0.56 to 0.84, p = 0.0002) strata. However, a significant association of statin therapy and lower risk for MACEs was not seen in the severe CKD (hazard ratio 0.91, 95% confidence interval 0.6 to 1.38, p = 0.65) and HD (hazard ratio 1.04, 95% confidence interval 0.64 to 1.69, p = 0.87) strata. In conclusion, statin therapy was associated with significantly lower risk for MACEs in patients with non-CKD and mild CKD undergoing coronary revascularization. However, therapeutic benefits of statins were not apparent in patients with severe CKD and HD. **(Am J Cardiol 2012;110:1568–1577)**

Chronic kidney disease (CKD) is one of the strongest prognostic factors in patients with coronary artery disease,[1,2] and primary and secondary preventions are important for patients with CKD. Beneficial effects of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) on cardiovascular outcomes have been shown in a wide range of patient groups.[3–6] However, previous studies have suggested that effects of statins in patients with CKD might differ according to severity of renal dysfunction. It has been repeatedly demonstrated that statin therapy decreases the risk for cardiovascular events in patients with mild CKD,[7–9] whereas statin therapy has been found to not decrease cardiovascular risk in patients on hemodialysis (HD) in randomized controlled trials.[10,11] Recently, the Study of Heart and Renal Protection (SHARP) trial showed that coadministration of simvastatin plus ezetimibe decreased the incidence of major atherosclerotic events in a wide range of patients with advanced CKD.[12] However, the SHARP trial excluded patients with a history of myocardial infarction or coronary revascularization. In addition, effects of simvastatin and ezetimibe could not be individually evaluated in this trial. Thus, further investigations to evaluate the effect of statin therapy on cardiovascular outcomes in patients with advanced CKD and coronary artery disease would be warranted. In the present study, we analyzed the impact of statin therapy on cardiovascular outcomes in patients with or without CKD in a large Japanese observational database of patients who underwent first coronary revascularization.

Methods

The design and patient enrollment (from January 2005 to December 2007) of the Coronary Revascularization Demonstrating Outcome Study in Kyoto Percutaneous Coronary Intervention/Coronary Artery Bypass Grafting (CREDO-Kyoto PCI/CABG) Registry Cohort-2 (Supplementary Appendix A) has been described previously.[13–16] Of the 15,939 patients registered, 14,706 patients (PCI, 12,588; isolated CABG, 2,118) constituted the study population for the pres-

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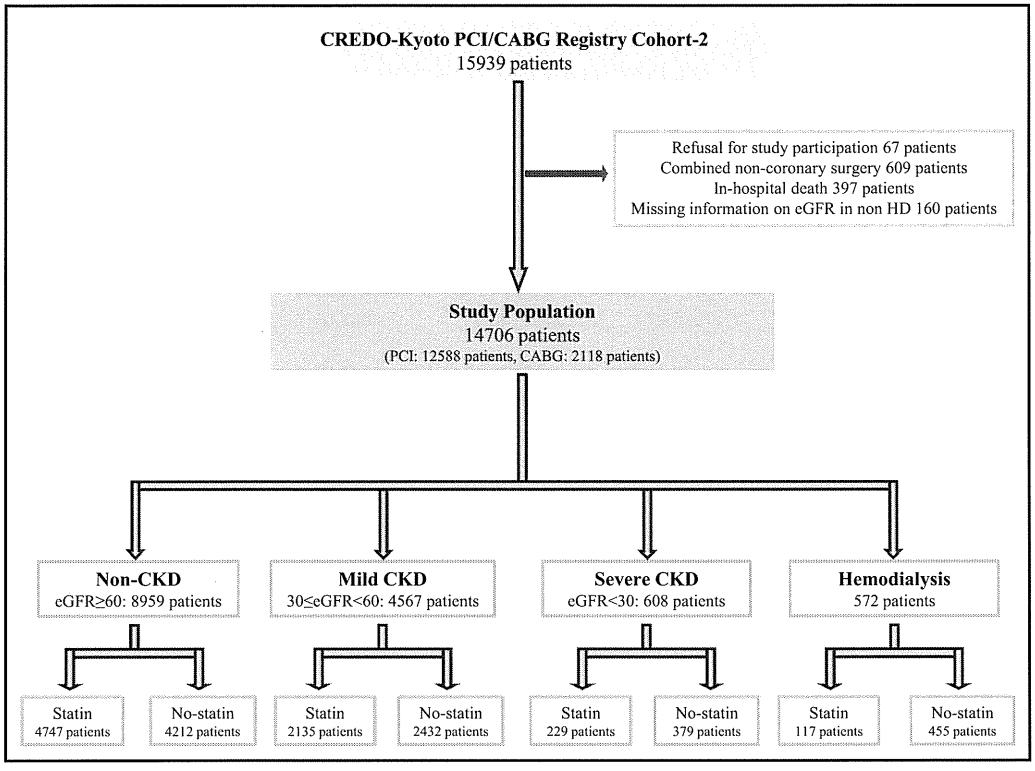


Figure 1. Study flow chart.

ent analyses. Patients were divided into 4 strata based on estimated glomerular filtration rate (eGFR) or status of HD and patients in each stratum were further divided into 2 groups based on statin therapy at discharge: non-CKD stratum (eGFR $\geq$60 ml/min/1.73 m^2), 8,959 patients (statin group, n = 4,747; no-statin group, n = 4,212); mild CKD stratum (eGFR $\geq$30 to $<$60 ml/min/1.73 m^2), 4,567 patients (statin group, n = 2,135; no-statin group, n = 2,432): severe CKD stratum (eGFR $<$30 ml/min/1.73 m^2), 608 patients (statin group, n = 229; no-statin group, n = 379); and HD stratum, 572 patients (statin group, n = 117; no-statin group, n = 455; Figure 1).

Definitions of baseline characteristics/events and data collection by experienced clinical research coordinators in the independent research organization (Research Institute for Production Development, Kyoto, Japan; Supplementary Appendix B) were described previously.[13] Low-density lipoprotein cholesterol concentrations were calculated by the Friedewald formula.[17] For triglyceride levels $\geq$400 mg/dl, low-density lipoprotein cholesterol was judged as missing information. Renal function was expressed as eGFR calculated by the Modification of Diet in Renal Disease formula modified for Japanese patients.[18] The primary outcome measurement in the present analysis was major adverse cardiovascular events (MACEs; composite of cardiovascular death, myocardial infarction, or stroke). Cardiovascular death, myocardial infarction, and stroke were adjudicated against original source documents by a clinical event committee (Supplementary Appendix C).

Median follow-up duration was 956 days (interquartile range 699 to 1,245). Serum lipid levels and eGFR during follow-up were measured optionally in 8,987 patients (61%) and in 12,382 patients (84%), respectively, and median interval from the index procedure to the measurement was 357 days (interquartile range 254 to 398).

Categorical variables were compared with chi-square test. Continuous variables were expressed as mean $\pm$ SD or median and interquartile range and 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 with log-rank test. We used Cox proportional hazard models to estimate risk for MACEs in each stratum adjusting the differences in patient characteristics, procedural factors, and medications. Consistent with our previous reports, we chose 31 clinically relevant factors listed in Table 1 as risk-adjusting variables.[13–16] Continuous variables were dichotomized by clinically meaningful reference values or median values. Statin therapy and the 31 risk-adjusting variables were simultaneously included in the Cox proportional hazard model. Twenty-six centers were included in the model as stratification variables. Effect of statin therapy (statin compared to no-statin group) was expressed as hazard ratios and their 95% confidence intervals. Statistical analyses were conducted by a physician (M.N.) and by 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.

Relevant review boards or ethics committees in all participating centers approved the research protocol. Because of retrospective enrollment, written informed consent from patients was waived; however, we excluded those patients who refused participation in the study when contacted for

Table 1
Baseline characteristics between statin versus no-statin group in patients with nonchronic kidney disease or mild chronic kidney disease

Variable	Non-CKD (eGFR ≥60 ml/min/1.73 m^2)			Mild CKD (eGFR ≥30–<60 ml/min/1.73 m^2)		
	Statin (n = 4,747)	No statin (n = 4,212)	p Value	Statin (n = 2,135)	No statin (n = 2,432)	p Value
Clinical characteristics						
Age (years)	64.4 ± 10.7	67.0 ± 10.5	<0.0001	71.4 ± 9.4	73.4 ± 9.0	<0.0001
Age ≥75*	888 (19%)	1,086 (26%)	<0.0001	854 (40%)	1,190 (49%)	<0.0001
Men*	3,414 (72%)	3,257 (77%)	<0.0001	1,438 (67%)	1,767 (73%)	<0.0001
Body mass index (kg/m^2)	24.3 ± 3.4	23.3 ± 3.3	<0.0001	24.3 ± 3.4	23.3 ± 3.6	<0.0001
Body mass index <25.0*	2,998 (63%)	3,051 (72%)	<0.0001	1,322 (62%)	1,771 (73%)	<0.0001
Baseline lipid levels						
Total cholesterol (mg/dl)	200 ± 42.4	186 ± 35.0	<0.0001	192 ± 41.7	184 ± 37.3	<0.0001
High-density lipoprotein cholesterol (mg/dl)	48.7 ± 13.3	48.0 ± 13.5	0.01	47.2 ± 13.5	45.5 ± 13.1	<0.0001
Triglyceride (mg/dl)	114 (79–169)	103 (71–150)	<0.0001	114 (81–165)	106 (73–148)	<0.0001
Low-density lipoprotein cholesterol (mg/dl)	124 ± 37.9	114 ± 30.2	<0.0001	119 ± 37.6	115 ± 31.5	0.0005
Estimated glomerular filtration rate (ml/min/1.73 m^2)	79.2 ± 23.8	78.3 ± 16.8	0.04	49.1 ± 7.7	48.5 ± 8.0	0.006
Acute myocardial infarction*	1,759 (37%)	1,289 (31%)	<0.0001	607 (28%)	606 (25%)	0.007
Hypertension*	3,863 (81%)	3,272 (78%)	<0.0001	1,879 (88%)	2,076 (85%)	0.009
Diabetes mellitus*	1,799 (38%)	1,540 (37%)	0.19	864 (40%)	926 (38%)	0.10
On insulin therapy	287 (6.1%)	285 (6.8%)	0.16	198 (9.3%)	229 (9.4%)	0.87
Current smoking*	1,778 (37%)	1,432 (34%)	0.0007	496 (23%)	616 (25%)	0.10
Heart failure*	537 (11%)	607 (14%)	<0.0001	477 (22%)	702 (29%)	<0.0001
Shock at presentation	124 (2.6%)	103 (2.5%)	0.62	134 (6.3%)	175 (7.2%)	0.22
Mitral regurgitation grade 3/4*	93 (2.0%)	122 (2.9%)	0.004	88 (4.1%)	148 (6.1%)	0.003
Ejection fraction	60.1 ± 12.3	59.1 ± 12.7	0.0004	58.9 ± 13.4	57.0 ± 14.2	<0.0001
Previous myocardial infarction*	444 (9.4%)	412 (9.8%)	0.49	316 (15%)	382 (16%)	0.40
Previous stroke*	324 (6.8%)	435 (10%)	<0.0001	282 (13%)	363 (15%)	0.10
Peripheral vascular disease*	231 (4.9%)	296 (7.0%)	<0.0001	202 (9.5%)	282 (12%)	0.02
Multivessel disease	2,672 (56%)	2,365 (56%)	0.89	1,398 (65%)	1,587 (65%)	0.87
Target of proximal left anterior descending artery*	2,950 (62%)	2,626 (62%)	0.84	1,260 (59%)	1,519 (62%)	0.02
Unprotected left main coronary artery disease*	263 (5.5%)	362 (8.6%)	<0.0001	154 (7.2%)	281 (12%)	<0.0001
Target of chronic total occlusion*	636 (13%)	670 (16%)	0.0008	342 (16%)	477 (20%)	0.002
Revascularization by coronary artery bypass grafting*	347 (7.3%)	713 (17%)	<0.0001	234 (11%)	553 (23%)	<0.0001
Atrial fibrillation*	277 (5.8%)	378 (9.0)%	<0.0001	210 (9.8%)	385 (16%)	<0.0001
Anemia (hemoglobin <11 g/dl)*	194 (4.1%)	307 (7.3%)	<0.0001	234 (11%)	421 (17%)	<0.0001
Platelet count $<100 \times 10^9/L$*	33 (0.7%)	66 (1.6%)	<0.0001	18 (0.8%)	49 (2.0%)	0.0008
Chronic obstructive pulmonary disease*	160 (3.4%)	158 (3.8%)	0.33	75 (3.5%)	88 (3.6%)	0.88
Liver cirrhosis*	91 (1.9%)	139 (3.3%)	<0.0001	33 (1.6%)	78 (3.2%)	0.0002
Malignancy*	315 (6.6%)	423 (10%)	<0.0001	215 (10%)	271 (11%)	0.24
Baseline medication						
Medication at hospital discharge						
Antiplatelet therapy						
Thienopyridine	4,366 (92%)	3,475 (83%)	<0.0001	1,881 (88%)	1,877 (77%)	<0.0001
Ticlopidine	3,852 (89%)	3,204 (92%)	<0.0001	1,657 (88%)	1,734 (93%)	<0.0001
Clopidogrel	498 (11%)	264 (7.6%)	<0.0001	221 (12%)	140 (7.5%)	<0.0001
Aspirin	4,721 (99%)	4,166 (99%)	0.004	2,107 (99%)	2,391 (98%)	0.30
Cilostazol*	946 (20%)	708 (17%)	0.0001	361 (17%)	352 (14%)	0.02
Other medications						
β Blockers*	1,608 (34%)	1,015 (24%)	<0.0001	780 (37%)	671 (28%)	<0.0001
Angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers*	2,893 (61%)	2,069 (49%)	<0.0001	1,316 (62%)	1,265 (52%)	<0.0001
Nitrates*	1,495 (31%)	1,669 (40%)	<0.0001	728 (34%)	973 (40%)	<0.0001
Calcium channel blockers*	1,776 (37%)	1,754 (42%)	<0.0001	970 (45%)	1,112 (46%)	0.84
Nicorandil*	1,200 (25%)	1,117 (27%)	0.18	592 (28%)	687 (28%)	0.70
Warfarin*	443 (9.3%)	556 (13%)	<0.0001	245 (11%)	427 (18%)	<0.0001
Proton pump inhibitors*	1,245 (26%)	1,069 (25%)	0.36	617 (29%)	686 (28%)	0.61
H_2 blockers*	1,322 (28%)	1,186 (28%)	0.75	617 (29%)	667 (27%)	0.27

Table 1
(continued)

Variable	Non-CKD (eGFR ≥60 ml/min/1.73 m^2)			Mild CKD (eGFR ≥30–<60 ml/min/1.73 m^2)		
	Statin (n = 4,747)	No statin (n = 4,212)	p Value	Statin (n = 2,135)	No statin (n = 2,432)	p Value
Serum levels during follow-up†						
Total cholesterol (mg/dl)	176 ± 34.2	188 ± 33.3	<0.0001	174 ± 33.7	186 ± 35.3	<0.0001
High-density lipoprotein cholesterol (mg/dl)	53.0 ± 14.1	52.0 ± 15.1	0.01	51.1 ± 14.3	49.8 ± 14.2	0.02
Triglyceride (mg/dl)	120 (87–170)	118 (84–168)	0.1	125 (91–173)	120 (86–169)	0.04
Low-density lipoprotein cholesterol (mg/dl)	95.3 ± 28.3	110 ± 29.9	<0.0001	94.7 ± 28.8	109 ± 30.6	<0.0001
Low-density lipoprotein cholesterol change (mg/dl)	−30.9 ± 39.1	−6.3 ± 33.4	<0.0001	−26.2 ± 39.9	−7.9 ± 34.6	<0.0001
Low-density lipoprotein cholesterol change (%)	−19.8 ± 28.9	−1.4 ± 31.7	<0.0001	−15.9 ± 33.0	−1.9 ± 37.6	<0.0001
Estimated glomerular filtration rate (ml/min/1.73 m^2)	71.0 ± 16.8	70.9 ± 16.8	0.82	48.8 ± 13.4	49.0 ± 14.1	0.64
Estimated glomerular filtration rate change (ml/min/1.73 m^2)	−8.2 ± 24.9	−7.1 ± 15.9	0.02	−0.28 ± 11.6	0.34 ± 11.8	0.10
Estimated glomerular filtration rate change/year (ml/min/1.73 m^2)	−11.3 ± 63.3	−8.0 ± 53.1	0.01	2.1 ± 39.8	2.5 ± 37.7	0.77

Values are expressed as number of patients (percentage), mean ± SD, or median (interquartile range).

* Potential independent variables selected for multivariate analysis.

† Values for serum lipid levels during follow-up were available in 3,271 patients in the statin group and in 2,457 patients in the no-statin group in the nonchronic kidney disease stratum and 1,387 patients in the statin group and 1,318 patients in the no-statin group in the mild chronic kidney disease stratum. Values for estimated glomerular filtration rate levels during follow-up were available in 4,152 patients in the statin group and 3,479 patients in the no-statin group in the nonchronic kidney disease stratum, 1,848 patients in the statin group and 1,985 patients in the no-statin group in the mild chronic kidney disease stratum.

follow-up. This strategy is concordant with guidelines for epidemiologic studies issued by the Ministry of Health, Labor and Welfare of Japan.

Results

In the non-CKD and mild CKD strata, patients in the statin group were younger and had higher body mass index than those in the no-statin group. Female gender, acute myocardial infarction, and hypertension were found more often in the statin group than in the no-statin group, whereas heart failure, moderate to severe mitral regurgitation, peripheral vascular disease, unprotected left main coronary artery disease, target of chronic total occlusion, revascularization by CABG, atrial fibrillation, anemia, low platelet count, and liver cirrhosis were more common in the no-statin than in the statin group. Ejection fraction and eGFR were significantly lower in the no-statin than in the statin group. Baseline lipid profile and medications were also significantly different between the 2 groups in the 2 strata (Table 1).

In the severe CKD stratum, patients in the statin group were younger and had higher body mass index and eGFR than those in the no-statin group. Female gender and hypertension were found more often in the statin group than in the no-statin group, whereas revascularization by CABG, atrial fibrillation, and anemia were more common in the no-statin than in the statin group. Baseline lipid profile and medications were also significantly different between the 2 groups (Table 2).

In the HD stratum, patients in the statin group had higher body mass index than those in the no-statin group. Female gender, insulin-treated diabetes mellitus, and previous myocardial infarction were found more often in the statin group than in the no-statin group, whereas revascularization by CABG and malignancy were more common in the no-statin than in the statin group. Baseline lipid profile and medications were also significantly different between the 2 groups (Table 2).

In the non-CKD and mild CKD strata, cumulative incidences of MACEs, all-cause death, cardiovascular death, and stroke through 3 years were significantly lower in the statin group than in the no-statin group (Figure 2). However, incidences of myocardial infarction and any coronary revascularization showed no significant differences between the 2 groups (Table 3). In the severe CKD and HD strata, there was no significant difference in cumulative incidence of MACEs between the statin and no-statin groups (Figure 3).

After adjusting confounders by multivariable analysis, risk for MACEs was significantly lower in the statin group than in the no-statin group in the non-CKD and mild CKD strata, whereas significant risk decrease for MACEs with use of statins was not found in the severe CKD and HD strata (Figure 4). Also, there were no significant differences in cumulative incidences of all-cause death, individual components of MACEs, and any coronary revascularization between the 2 groups in the severe CKD and HD strata (Table 3).

Regarding renal outcome, decrease of eGFR as represented by eGFR change per year was significantly greater in the statin group than in the no-statin group in the non-CKD stratum. There was no significant difference in eGFR change per year between the statin and no-statin groups in the mild CKD and severe CKD strata (Tables 1 and 2).

Table 2
Baseline characteristics between statin versus no-statin group in patients with severe chronic kidney disease or hemodialysis

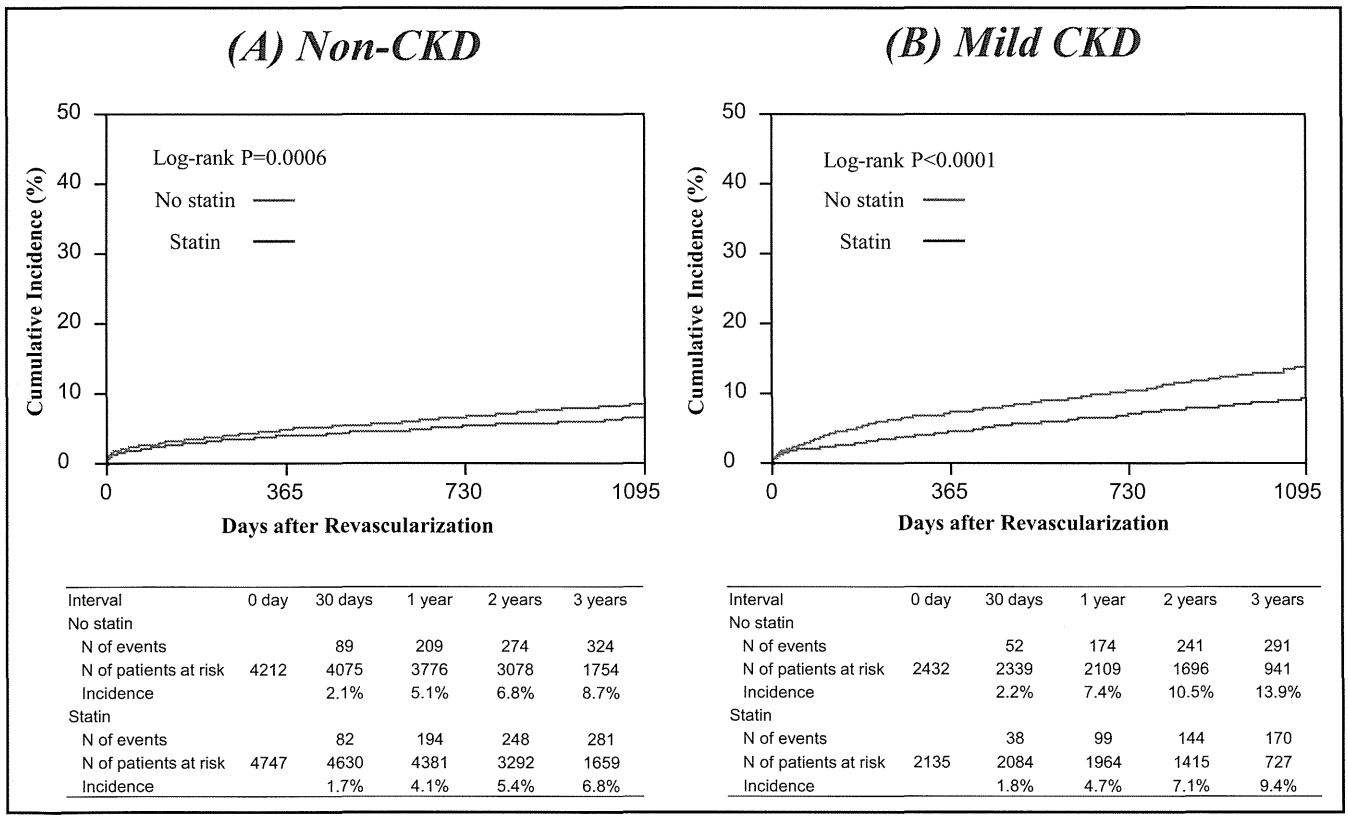
Variable	Severe CKD (eGFR <30 ml/min/1.73 m^2)			HD		
	Statin (n = 229)	No statin (n = 379)	p Value	Statin (n = 117)	No statin (n = 455)	p Value
Clinical characteristics						
Age (years)	72.0 ± 10.1	74.6 ± 9.7	0.002	65.6 ± 11.0	65.5 ± 9.7	0.94
Age ≥75 years	106 (46%)	203 (54%)	0.08	28 (24%)	82 (18%)	0.16
Men	119 (52%)	247 (65%)	0.001	68 (58%)	363 (80%)	<0.0001
Body mass index (kg/m^2)	23.9 ± 3.9	23.0 ± 3.5	0.004	22.8 ± 4.6	21.9 ± 3.2	0.02
Body mass index <25.0	153 (67%)	289 (76%)	0.01	88 (75%)	384 (84%)	0.02
Baseline lipid levels						
Total cholesterol (mg/dl)	187 ± 45.1	175 ± 43.7	0.001	170 ± 42.4	162 ± 39.9	0.04
High-density lipoprotein cholesterol (mg/dl)	44.6 ± 14.0	41.5 ± 12.2	0.01	46.4 ± 14.9	43.2 ± 13.0	0.04
Triglyceride (mg/dl)	121 (85–188)	107 (72–154)	0.02	97 (74–153)	100 (70–141)	0.46
Low-density lipoprotein cholesterol (mg/dl)	114 ± 38.7	109 ± 35.2	0.14	102 ± 35.1	94.4 ± 29.6	0.04
Estimated glomerular filtration rate (ml/min/1.73 m^2)	22.0 ± 6.2	20.8 ± 6.7	0.04	NA	NA	
Acute myocardial infarction	58 (25%)	109 (29%)	0.36	18 (15%)	46 (10%)	0.12
Hypertension	221 (97%)	342 (90%)	0.003	105 (90%)	392 (86%)	0.29
Diabetes mellitus	128 (56%)	203 (54%)	0.58	72 (62%)	274 (60%)	0.79
On insulin therapy	50 (22%)	87 (23%)	0.75	44 (38%)	127 (28%)	0.04
Current smoking	48 (21%)	93 (25%)	0.31	20 (17%)	96 (21%)	0.33
Heart failure	96 (42%)	183 (48%)	0.13	43 (37%)	144 (32%)	0.30
Shock at presentation	22 (9.6%)	44 (12%)	0.44	3 (2.6%)	11 (2.4%)	0.93
Mitral regurgitation grade 3/4	18 (7.9%)	30 (7.9%)	0.98	10 (8.6%)	35 (7.7%)	0.76
Ejection fraction	55.5 ± 14.2	54.0 ± 14.7	0.26	53.2 ± 14.1	54.1 ± 13.8	0.54
Previous myocardial infarction	41 (18%)	75 (20%)	0.57	24 (21%)	59 (13%)	0.046
Previous stroke	41 (18%)	86 (23%)	0.16	11 (9.4%)	71 (16%)	0.07
Peripheral vascular disease	23 (10%)	46 (12%)	0.43	17 (15%)	90 (20%)	0.18
Multivessel disease	165 (72%)	284 (75%)	0.43	83 (71%)	311 (68%)	0.59
Target of proximal left anterior descending artery	136 (59%)	227 (60%)	0.90	64 (55%)	266 (58%)	0.46
Unprotected left main coronary artery disease	23 (10%)	45 (12%)	0.49	12 (10%)	55 (12%)	0.58
Target of chronic total occlusion	43 (19%)	72 (19%)	0.95	22 (19%)	86 (19%)	0.98
Revascularization by coronary artery bypass grafting	38 (17%)	109 (29%)	0.0005	12 (10%)	112 (25%)	0.0003
Atrial fibrillation	21 (9.2%)	65 (17%)	0.005	15 (13%)	60 (13%)	0.92
Anemia (hemoglobin <11 g/dl)	105 (46%)	214 (56%)	0.01	70 (60%)	270 (59%)	0.92
Platelet count <100 × 10^9/L	4 (1.8%)	10 (2.6%)	0.47	6 (5.1%)	27 (5.9%)	0.74
Chronic obstructive pulmonary disease	14 (6.1%)	15 (4.0%)	0.23	1 (0.9%)	7 (1.5%)	0.55
Liver cirrhosis	6 (2.6%)	16 (4.2%)	0.29	4 (3.4%)	31 (6.8%)	0.15
Malignancy	23 (10%)	56 (15%)	0.09	4 (3.4%)	47 (10%)	0.01
Baseline medication						
Medication at hospital discharge						
Antiplatelet therapy						
Thienopyridine	188 (82%)	273 (72%)	0.004	103 (88%)	345 (76%)	0.003
Ticlopidine	173 (92%)	252 (93%)	0.70	93 (90%)	321 (93%)	0.37
Clopidogrel	15 (8.0%)	19 (7.0%)	0.70	10 (9.7%)	24 (7.0%)	0.37
Aspirin	226 (99%)	377 (99%)	0.31	115 (98%)	444 (98%)	0.64
Cilostazol	30 (13%)	56 (15%)	0.56	11 (9.4%)	59 (13%)	0.28
Other medications						
β Blockers	100 (44%)	122 (32%)	0.005	43 (37%)	100 (22%)	0.001
Angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers	149 (65%)	167 (44%)	<0.0001	63 (54%)	198 (44%)	0.046
Nitrates	86 (38%)	150 (40%)	0.62	44 (38%)	160 (35%)	0.62
Calcium channel blockers	135 (59%)	222 (59%)	0.93	50 (43%)	233 (51%)	0.10
Nicorandil	61 (27%)	115 (30%)	0.33	36 (31%)	115 (25%)	0.23
Warfarin	26 (11%)	68 (18%)	0.03	17 (15%)	70 (15%)	0.82
Proton pump inhibitors	90 (39%)	175 (46%)	0.10	48 (41%)	185 (41%)	0.94
H_2 blockers	53 (23%)	66 (17%)	0.09	25 (21%)	119 (26%)	0.28

Table 2
(continued)

Variable	Severe CKD (eGFR <30 ml/min/1.73 m^2)			HD		
	Statin (n = 229)	No statin (n = 379)	p Value	Statin (n = 117)	No statin (n = 455)	p Value
Serum levels during follow-up*						
Total cholesterol (mg/dl)	174 ± 36.6	173 ± 39.6	0.88	163 ± 40.2	164 ± 37.6	0.98
High-density lipoprotein cholesterol (mg/dl)	48.0 ± 14.4	44.4 ± 12.9	0.03	46.1 ± 15.0	44.3 ± 13.2	0.34
Triglyceride (mg/dl)	128 (88–188)	112 (85–156)	0.1	126 (80–176)	113 (83–162)	0.60
Low-density lipoprotein cholesterol (mg/dl)	97.0 ± 30.3	103 ± 33.6	0.17	90.5 ± 33.4	93.3 ± 30.0	0.51
Low-density lipoprotein cholesterol change (mg/dl)	−18.8 ± 42.6	−7.7 ± 41.5	0.047	−5.4 ± 30.7	−1.7 ± 31.9	0.43
Low-density lipoprotein cholesterol change (%)	−7.6 ± 41.1	0.004 ± 39.2	0.15	−1.5 ± 33.2	4.6 ± 39.9	0.29
Estimated glomerular filtration rate (ml/min/1.73 m^2)	23.1 ± 12.2	22.6 ± 13.4	0.67	Not applicable	Not applicable	
Estimated glomerular filtration rate change (ml/min/1.73 m^2)	1.1 ± 10.9	1.7 ± 11.4	0.56	Not applicable	Not applicable	
Estimated glomerular filtration rate change/year (ml/min/1.73 m^2)	3.6 ± 24.0	5.5 ± 29.2	0.47	Not applicable	Not applicable	

Values are expressed as number of patients (percentage), mean ± SD, or median (interquartile range).

* Values for serum lipid levels during follow-up were available in 111 patients in the statin group and 158 patients in the no-statin group in the severe chronic kidney disease stratum, 66 patients in the statin group and 219 patients in the no-statin group in the hemodialysis stratum. Values for estimated glomerular filtration rate levels during follow-up were available in 185 patients in the statin group and 287 patients in the no-statin group in the severe chronic kidney disease stratum.



Interval	0 day	30 days	1 year	2 years	3 years
No statin					
N of events		89	209	274	324
N of patients at risk	4212	4075	3776	3078	1754
Incidence		2.1%	5.1%	6.8%	8.7%
Statin					
N of events		82	194	248	281
N of patients at risk	4747	4630	4381	3292	1659
Incidence		1.7%	4.1%	5.4%	6.8%

Interval	0 day	30 days	1 year	2 years	3 years
No statin					
N of events		52	174	241	291
N of patients at risk	2432	2339	2109	1696	941
Incidence		2.2%	7.4%	10.5%	13.9%
Statin					
N of events		38	99	144	170
N of patients at risk	2135	2084	1964	1415	727
Incidence		1.8%	4.7%	7.1%	9.4%

Figure 2. 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)* nonchronic kidney disease stratum (estimated glomerular filtration rate ≥60 ml/min/1.73 m^2) and in *(B)* mild chronic kidney disease stratum (estimated glomerular filtration rate ≥30 to <60 ml/min/1.73 m^2).