



BMJ Open Demographics, practice patterns and long-term outcomes of patients with non-ST-segment elevation acute coronary syndrome in the past two decades: the CREDO-Kyoto Cohort-2 and Cohort-3

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ABSTRACT

Objectives To evaluate patient characteristics and long-term outcomes in patients with non-ST-segment elevation acute coronary syndrome (NSTEMI) in the past two decades.

Design Multicenter retrospective study.

Setting The Coronary REvascularization Demonstrating Outcome Study in Kyoto (CREDO-Kyoto) percutaneous coronary intervention (PCI)/coronary artery bypass grafting (CABG) Registry Cohort-2 (2005–2007) and Cohort-3 (2011–2013).

Participants 3254 patients with NSTEMI who underwent first coronary revascularisation.

Primary and secondary outcome measures The primary outcome was all-cause death. The secondary outcomes were cardiovascular death, cardiac death, sudden cardiac death, non-cardiovascular death, non-cardiac death, myocardial infarction, definite stent thrombosis, stroke, hospitalisation for heart failure, major bleeding, any coronary revascularisation and target vessel revascularisation.

Results Patients in Cohort-3 were older and more often had heart failure at admission than those in Cohort-2. The prevalence of PCI, emergency procedure and guideline-directed medical therapy was higher in Cohort-3 than in Cohort-2. In patients who received PCI, the prevalence of transradial approach, drug-eluting stent use and intravascular ultrasound use was higher in Cohort-3 than in Cohort-2. There was no change in 3-year adjusted mortality risk from Cohort-2 to Cohort-3 (HR 1.00, 95% CI 0.83 to 1.22, $p=0.97$). Patients in Cohort-3 compared with those in Cohort-2 were associated with lower adjusted risks for stroke (HR 0.65, 95% CI 0.46 to 0.92, $p=0.02$) and any coronary revascularisation (HR 0.76, 95% CI 0.66 to 0.87, $p<0.001$), but with higher risk for major bleeding (HR 1.25, 95% CI 1.06 to 1.47, $p=0.008$). The unadjusted

Strengths and limitations of this study

- The present study is the first study evaluating changes in demographics, clinical practices and long-term clinical outcomes in patients with non-ST-segment elevation acute coronary syndrome (NSTEMI) enrolled beyond 2010 (Cohort-3) compared with those enrolled before 2010 (Cohort-2).
- The 3-year adjusted risk of patients in Cohort-3 relative to those in Cohort-2 was not significantly different for all-cause death.
- Patients in Cohort-3 as compared with those in Cohort-2 were associated with lower risks for definite stent thrombosis, stroke and any coronary revascularisation, but with higher risk for major bleeding.
- This study was a historical comparison and should result in systematic differences in selection of patients and acquisition of outcomes.

risk for definite stent thrombosis was lower in Cohort-3 than in Cohort 2 (HR 0.29, 95% CI 0.11 to 0.67, $p=0.003$).

Conclusions In the past two decades, we did not find improvement for mortality in patients with NSTEMI. We observed a reduction in the risks for definite stent thrombosis, stroke and any coronary revascularisation, but an increase in the risk for major bleeding.

INTRODUCTION

Non-ST-segment elevation acute coronary syndrome (NSTEMI), consisting of non-ST-segment elevation myocardial infarction (NSTEMI) and unstable angina (UA), has

been one of the main causes of death from cardiovascular disease.¹ Several studies also demonstrated that the early mortality of patients with NSTEMACS have improved from 1990s to 2000s.^{2–4} However, there was a scarcity of studies evaluating the long-term clinical outcomes in patients with NSTEMACS enrolled beyond 2010 compared with those enrolled before 2010.⁵ Therefore, we aimed to evaluate changes in demographics, practice patterns and long-term clinical outcomes in patients with NSTEMACS in the past two decades using data from a series of large Japanese cohorts of patients who underwent first coronary revascularisation enrolled in 2005–2007 and 2011–2013.

METHODS

Study population

The Coronary REvascularization Demonstrating Outcome Study in Kyoto (CREDO-Kyoto) percutaneous coronary intervention (PCI)/coronary artery bypass grafting (CABG) Registry Cohort-2 and Cohort-3 are a series of physician-initiated, non-company sponsored, multicentre registry enrolling consecutive patients who underwent first coronary revascularisation, either PCI or isolated CABG. Cohort-2 enrolled patients between January 2005 and December 2007 among 26 centres in Japan after the introduction of drug-eluting stents (DES) in 2004 (online supplemental appendix A).⁶ Cohort-3 enrolled patients between January 2011 and December 2013 among 22 centres in Japan after approval of the new-generation DES in 2010 (online supplemental appendix A). We enrolled a total of 30 257 consecutive patients who had undergone first coronary revascularisation with PCI or isolated CABG in Cohort-2 (N=15 330) and Cohort-3 (N=14 927). The annual volume of first coronary revascularisation

procedures for stable coronary artery disease and acute coronary syndrome in each participating centre was described in online supplemental table 1. There were 3386 patients with NSTEMACS, after excluding patients with refusal for study participation, patients with stable coronary artery disease and patients with ST elevation myocardial infarction (STEMI). To make the two cohorts comparable, we further excluded 124 patients in Cohort-2 who were enrolled from four cardiology divisions and five cardiovascular surgery divisions not participating in Cohort-3, and 8 patients in Cohort-3 who were enrolled from one cardiovascular surgery division not participating in Cohort-2. Finally, we retrieved 3254 patients with NSTEMACS for the current study (Cohort-2: 1683 patients and Cohort-3: 1571 patients) from 22 centres (both PCI and CABG available: 15 centres and only PCI available: 7 centres) (figure 1).

The relevant institutional review boards at all participating hospitals approved the study protocols, and we performed the study in accordance with the Declaration of Helsinki. Written informed consent for both registries were waived because of the retrospective nature of the study; however, we excluded those patients who refused participation in the study when contacted at follow-up. This strategy is concordant with the guidelines of the Japanese Ministry of Health, Labor and Welfare.

Definitions and clinical outcome measures

NSTEMACS consisted of NSTEMI and UA. NSTEMI was defined as acute coronary syndrome (ACS) other than STEMI, with elevating cardiac biomarkers, consisting of at least a value exceeding the upper reference limit for troponin, or $>3\times$ of the upper reference limit for creatine kinase MB (CK-MB). UA was defined as ACS meeting

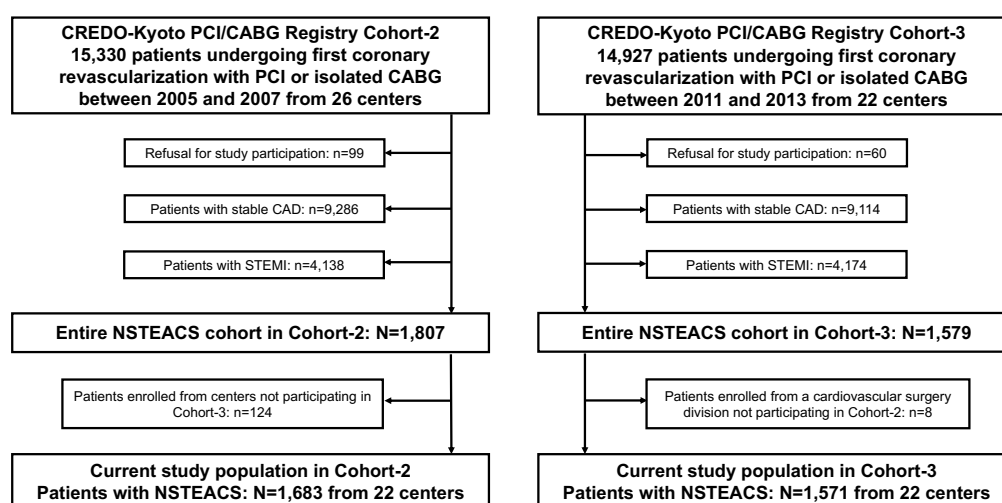


Figure 1 Study flowchart. CABG, coronary artery bypass grafting; CAD, coronary artery disease; CREDO-Kyoto, Coronary REvascularization Demonstrating Outcome study in Kyoto; NSTEMACS, non-ST-segment elevation acute coronary syndrome; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.

Braunwald classification type 3 without elevation of cardiac biomarkers. Experienced clinical research coordinators from the independent clinical research organisation (Research Institute for Production Development, Kyoto, Japan; online supplemental appendix B) collected data on baseline clinical, angiographic and procedural characteristics from the hospital charts or hospital databases according to the prespecified definitions that were identical in Cohort-2 and Cohort-3.

The primary outcome measure of this study was all-cause death at 3 years. The secondary outcome measures included cardiovascular death, cardiac death, sudden cardiac death, non-cardiovascular death, non-cardiac death, myocardial infarction, definite stent thrombosis, stroke, hospitalisation for heart failure, major bleeding, any coronary revascularisation and target vessel revascularisation. The definition of baseline characteristics and endpoints were described in online supplemental appendix C.

Data collection and follow-up

Collection of follow-up information was mainly conducted through review of hospital charts by the clinical research coordinators, and additional follow-up information was collected through contact with patients, relatives and/or referring physicians by sending mail with questions regarding vital status, subsequent hospitalisations and status of antiplatelet therapy.

Given the difference of follow-up durations between the two cohorts, follow-up was censored at 3 years after the index procedure to ensure >90% of clinical follow-up rate in both cohorts. Complete 3-year follow-up information was obtained for 95.9% of patients in Cohort-2 and 93.5% in Cohort-3, respectively. The clinical event committee adjudicated those endpoint events including death, myocardial infarction, stroke and major bleeding (online supplemental appendix D).

Statistical analysis

Continuous variables were expressed as mean±SD or median with IQR. We used the Student's t-test or Wilcoxon rank-sum test based on their distributions for comparing continuous variables. Categorical variables were expressed as frequencies and percentages and were compared using χ^2 test. We estimated cumulative incidence by the Kaplan-Meier method and assess the differences with the log-rank test. To estimate the adjusted HR and the 95% CI of Cohort-3 compared with Cohort-2, we used multivariable Cox proportional hazard models by incorporating the 16 clinically relevant factors. Clinically relevant factors were age ≥75 years, sex, body mass index <25.0 kg/m², hypertension, diabetes mellitus, current smoking, heart failure, prior myocardial infarction, prior stroke, peripheral vascular disease, estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m² without haemodialysis, haemodialysis, anaemia, malignancy, target of proximal left anterior descending coronary artery and PCI strategy

(table 1). The risk-adjusting variables included demographic factors, but not included the factors related to management during the index hospitalisation, because differences in management converged into the changes between Cohort-2 and Cohort-3. Continuous risk-adjusting variables were dichotomised according to the clinically meaningful reference values to make proportional hazard assumptions robust and to be consistent with previous reports.⁷ Proportional hazard assumptions for the risk-adjusting variables were assessed on the plots of log(time) versus log[-log(survival)] stratified by the variable, and the assumptions were verified to be acceptable for all variables. We conducted a landmark analysis for all-cause death within and beyond 30 days after the index procedure to distinguish early death related to the index NSTEMI event from late death during long-term follow-up. We also conducted a landmark analysis for major bleeding within and beyond 30 days to distinguish periprocedural bleeding from non-periprocedural bleeding. We also evaluated the cumulative incidence of major bleeding and persistent dual antiplatelet therapy (DAPT) discontinuation only in patients who received PCI as the index coronary revascularisation procedure.

All analyses were performed using R V.3.6.1 (R Foundation for Statistical Computing, Vienna, Austria). All reported p values were two-tailed, and p values less than 0.05 were considered statistically significant.

Patient and public involvement

In this study, patients were not involved in the design, or conduct, or reporting or dissemination plans of our research.

RESULTS

Baseline characteristics and medications

The prevalence of NSTEMI among NSTEMI patients was significantly higher in Cohort-3 compared with Cohort-2 (table 1). Baseline clinical characteristics were generally similar between the two cohorts except for a few aspects. Patients in Cohort-3 were older and more often had heart failure and malignancy, but less often had current smoking and prior myocardial infarction than those in Cohort-2 (table 1). Regarding procedural characteristics, the prevalence of emergency procedures, transradial approach and intravascular ultrasound (IVUS) use increased significantly from Cohort-2 to Cohort-3. The prevalence of DES use was much higher in Cohort-3 than in Cohort-2, with new-generation DES use in the vast majority of DES cases in Cohort-3 (table 1). In terms of baseline medications, patients in Cohort-3 more often took thienopyridine, statins, beta-blockers, ACE inhibitors/angiotensin receptor blockers and proton pump inhibitors than those in Cohort-2. Thienopyridines used in the vast majority of patients were ticlopidine in Cohort-2 and clopidogrel in Cohort-3 (table 1).

Table 1 Baseline characteristics of patients with NSTEMI comparing Cohort-2 and Cohort-3

	Cohort-2 (N=1683)	Cohort-3 (N=1571)	P value
NSTEMI	703 (42%)	1329 (85%)	<0.001
UA	980 (58%)	242 (15%)	
(A) Clinical characteristics			
Age (years)	68.9±11.4	69.8±11.6	0.02
Age≥75 years*	589 (35%)	594 (38%)	0.10
Men*	1207 (72%)	1167 (74%)	0.11
Body mass index (kg/m ²)	23.5±3.4	23.7±3.6	0.07
Body mass index <25.0 kg/m ² *	1186 (70%)	1078 (69%)	0.27
Hypertension*	1385 (82%)	1303 (83%)	0.66
Systolic blood pressure on admission	140±28	140±29	0.62
Diastolic blood pressure on admission	78±19	79±19	0.07
Diabetes mellitus*	640 (38%)	569 (36%)	0.30
On insulin therapy	119 (7.1%)	102 (6.5%)	0.56
Current smoking*	608 (36%)	484 (31%)	0.002
Heart failure*	384 (23%)	428 (27%)	0.004
Current heart failure	354 (21%)	411 (26%)	<0.001
LVEF	57.5±13	57.9±13	0.41
LVEF ≤40%	138 (12%)	134 (10%)	0.12
Prior myocardial infarction*	123 (7.3%)	60 (3.8%)	<0.001
Prior stroke (symptomatic)*	209 (12%)	219 (14%)	0.22
Peripheral vascular disease*	76 (4.5%)	67 (4.3%)	0.79
eGFR <30 mL/min/1.73 m ² , without haemodialysis*	89 (5.3%)	98 (6.2%)	0.28
Haemodialysis*	59 (3.5%)	68 (4.3%)	0.26
ESRD (eGFR <30 mL/min/1.73 m ² or haemodialysis)	148 (8.8%)	166 (11%)	0.10
Atrial fibrillation	156 (9.3%)	154 (9.8%)	0.65
Anaemia (haemoglobin <11.0 g/dL)*	240 (14%)	214 (14%)	0.64
Thrombocytopenia (platelet <100 000)	31 (1.8%)	36 (2.3%)	0.44
Chronic obstructive pulmonary disease	69 (4.1%)	59 (3.8%)	0.68
Liver cirrhosis	43 (2.6%)	35 (2.2%)	0.62
Malignancy*	146 (8.7%)	179 (11%)	0.01
ARC-HBR	773 (46%)	748 (48%)	0.35
(B) Angiographic characteristics			
No of target lesions or anastomoses	1.7±1.0	1.7±1.0	0.20
Multivessel disease	1016 (60%)	939 (60%)	0.76
Target of proximal LAD*	949 (56%)	913 (58%)	0.34
(C) Procedural characteristic			
Emergency procedure†	1110 (66%)	1156 (74%)	<0.001
PCI*	1453 (86%)	1440 (92%)	<0.001
Transradial approach	262 (18%)	438 (30%)	<0.001
Transfemoral approach	1035 (71%)	913 (63%)	<0.001
IVUS use	494 (34%)	981 (68%)	<0.001
Staged PCI	333 (23%)	339 (24%)	0.72
Stent use	1348 (93%)	1356 (94%)	0.13
Bare metal stent	699 (52%)	320 (24%)	<0.001

Continued

Table 1 Continued

	Cohort-2 (N=1683)	Cohort-3 (N=1571)	P value
Drug-eluting stent	649 (48%)	1036 (76%)	<0.001
First-generation DES use	649 (100%)	19 (1.8%)	<0.001
Sirolimus-eluting stent (CYPHER)	614 (95%)	14 (74%)	–
Paclitaxel-eluting stent (TAXUS)	46 (7.1%)	5 (26%)	–
New-generation DES use	–	1026 (99%)	–
Everolimus-eluting stent (XIENCE)	–	584 (57%)	–
Everolimus-eluting stent (PROMUS)	–	232 (23%)	–
Biolimus-eluting stent (NOBORI)	–	251 (24%)	–
Zotarolimus-eluting stent (RESOL)	–	24 (2.3%)	–
Zotarolimus-eluting stent (ENDEAVOR)	–	98 (9.6%)	–
CABG	230 (14%)	131 (8.3%)	<0.001
Off pump	118 (51%)	64 (49%)	0.65
ITA use	217 (94%)	121 (92%)	0.46
(D) Medication at hospital discharge			
Antiplatelet therapy			
Thienopyridine	1439 (86%)	1457 (93%)	<0.001
Ticlopidine	1300 (91%)	38 (2.7%)	
Clopidogrel	127 (8.9%)	1389 (97%)	
Aspirin	1662 (99%)	1544 (98%)	0.33
Cilostazol	404 (24%)	45 (2.9%)	<0.001
Statins	811 (48%)	1229 (78%)	<0.001
High-intensity statins therapy†	26 (1.5%)	29 (1.8%)	0.60
Beta-blockers	493 (29%)	678 (43%)	<0.001
ACE inhibitor/ARB	969 (58%)	1052 (67%)	<0.001
Nitrates	657 (39%)	290 (18%)	<0.001
Calcium channel blockers	643 (38%)	547 (35%)	0.049
Nicorandil	461 (27%)	296 (19%)	<0.001
Warfarin	166 (9.9%)	162 (10%)	0.71
DOAC	–	24 (1.5%)	–
Proton pump inhibitors	581 (35%)	1089 (69%)	<0.001
Histamine type-2 receptor blockers	465 (28%)	211 (13%)	<0.001

Continuous variables were expressed as mean±SD or median (IQR). Categorical variables were expressed as number (percentage). Number of missing values were described in online supplemental appendix E.

*Risk-adjusting variables for the Cox proportional hazard models.

†Emergency procedure was defined as the procedure which was performed on the index admission date for patients with acute myocardial infarction and/or the procedure which was recorded as emergency procedure through review of hospital charts.

‡High-intensity statin therapy in this study was defined as the statin doses greater than or equal to atorvastatin 20 mg, pitavastatin 4 mg or rosuvastatin 10 mg.

ARC-HBR, Academic Research Consortium-High Bleeding Risk; CABG, coronary artery bypass grafting; DOAC, direct oral anticoagulants; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; ACE inhibitor/ARB, angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker; ITA, internal thoracic artery; LAD, left anterior descending coronary artery; NSTEMI, non-ST-segment elevation acute coronary syndrome; PCI, percutaneous coronary intervention.

Clinical outcomes

The cumulative 3-year incidence of all-cause death was not significantly different between Cohort-2 and Cohort-3 (13.1% and 13.8%, log-rank $p=0.50$) (table 2 and figure 2A). After adjusting for confounders, the risk of

all-cause death in Cohort-3 relative to Cohort-2 remained insignificant at 3 years (HR 1.00, 95% CI 0.83 to 1.22, $p=0.97$) (table 2). In the 30-day landmark analysis, cumulative incidence of all-cause death was also not significantly different between Cohort-2 and Cohort-3, both within 30

Table 2 Clinical outcomes compared between Cohort-2 and Cohort-3

Endpoints	Cohort-2 (N=1683)	Cohort-3 (N=1571)				
	Number of patients with event (Cumulative 3-year incidence)		Crude HR (95% CI)	P value	Adjusted HR (95% CI)	P value
All-cause death	216 (13.1%)	210 (13.8%)	1.07 (0.88 to 1.29)	0.5	1.00 (0.83 to 1.22)	0.97
Cardiovascular death	140 (8.6%)	125 (8.3%)	0.98 (0.77 to 1.24)	0.85	0.91 (0.71 to 1.16)	0.43
Cardiac death	126 (7.7%)	114 (7.5%)	0.99 (0.77 to 1.27)	0.94	0.91 (0.70 to 1.18)	0.48
Sudden cardiac death	17 (1.1%)	19 (1.4%)	1.23 (0.64 to 2.37)	0.53	–	–
Non-cardiovascular death	76 (4.9%)	85 (6.1%)	1.23 (0.91 to 1.68)	0.18	1.17 (0.85 to 1.60)	0.33
Non-cardiac death	90 (5.8%)	96 (6.8%)	1.18 (0.88 to 1.57)	0.27	1.13 (0.84 to 1.52)	0.41
Myocardial infarction	56 (3.6%)	57 (4.0%)	1.12 (0.77 to 1.62)	0.55	1.09 (0.75 to 1.59)	0.65
Definite stent thrombosis*	21 (1.7%)	6 (0.5%)	0.29 (0.11 to 0.67)	0.003	–	–
Stroke	90 (5.8%)	54 (3.8%)	0.65 (0.47 to 0.91)	0.01	0.65 (0.46 to 0.92)	0.02
Hospitalisation for heart failure	119 (7.7%)	94 (6.7%)	0.86 (0.66 to 1.13)	0.28	0.82 (0.62 to 1.08)	0.16
Major bleeding	315 (19.1%)	300 (19.7%)	1.02 (0.87 to 1.20)	0.79	1.25 (1.06 to 1.47)	0.008
Any coronary revascularisation	458 (29.4%)	353 (24.9%)	0.81 (0.70 to 0.93)	0.003	0.76 (0.66 to 0.87)	<0.001
Target vessel revascularisation	351 (22.4%)	255 (18.0%)	0.76 (0.65 to 0.90)	0.001	0.71 (0.60 to 0.84)	<0.001

The risk of Cohort-3 relative to Cohort-2 was expressed as HR with 95% CI. The covariates for the multivariate Cox proportional hazard models were indicated in [table 1](#). Myocardial infarction was adjudicated based on the ARTS definition.

Major bleeding was defined as GUSTO moderate/severe bleeding.

*Definite stent thrombosis was adjudicated based on the ARC definition and was analysed only for patients who underwent PCI with stent implantation (1348 patients in Cohort-2 and 1356 patients in Cohort-3).

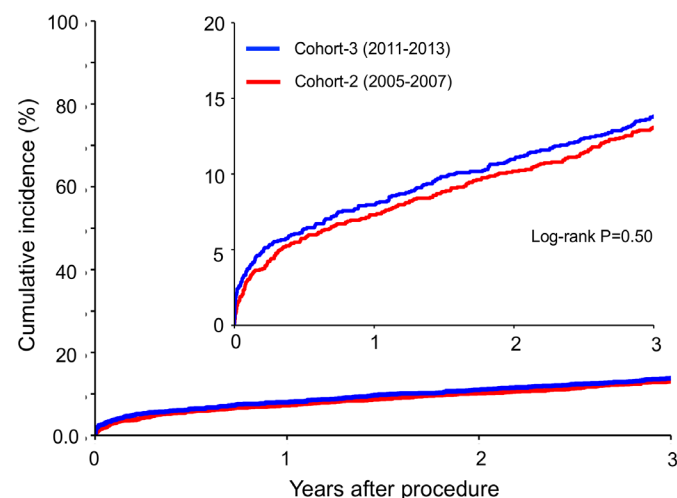
ARC, Academic Research Consortium; ARTS, arterial revascularisation therapy study; GUSTO, Global Utilisation of Streptokinase and Tissue plasminogen activator for Occluded coronary arteries; NSTEACS, non-ST-segment elevation acute coronary syndrome.

days (2.9% vs 3.5%, log-rank $p=0.27$) and beyond 30 days (10.5% vs 10.7%, log-rank $p=0.88$). The risk of Cohort-3 relative to Cohort-2 remained insignificant both within 30 days (HR 1.02, 95% CI 0.68 to 1.52, $p=0.92$) and beyond 30 days (HR 0.99, 95% CI 0.80 to 1.24, $p=0.96$) (online supplemental figure 1). There also was no difference in other mortality outcomes such as cardiovascular and non-cardiovascular death between the two cohorts ([table 2](#) and [figure 2B](#)). The cumulative 3-year incidence was significantly lower in Cohort 3 than in Cohort-2 for definite stent thrombosis (1.7% vs 0.5%, log-rank $p=0.004$), stroke (5.8% vs 3.8%, log-rank $p=0.01$), target vessel revascularisation (22.4% vs 18.0%, log-rank $p=0.001$) and any coronary revascularisation (29.4% vs 24.9%, log-rank $p=0.003$), while it was not different for myocardial infarction between Cohort-2 and Cohort-3 (3.6% vs 4.0%, log-rank $p=0.55$) ([table 2](#) and [figure 3](#)). Even after adjusting for confounders, the lower risk of Cohort-3 relative to Cohort-2 remained significant for stroke (HR 0.65, 95% CI 0.46 to 0.92, $p=0.02$), any coronary revascularisation (HR 0.76, 95% CI 0.66 to 0.87, $p<0.001$) and target vessel revascularisation (HR 0.71, 95% CI 0.60 to 0.84, $p<0.001$),

but not for myocardial infarction (HR 1.09, 95% CI 0.75 to 1.59, $p=0.65$) ([table 2](#)).

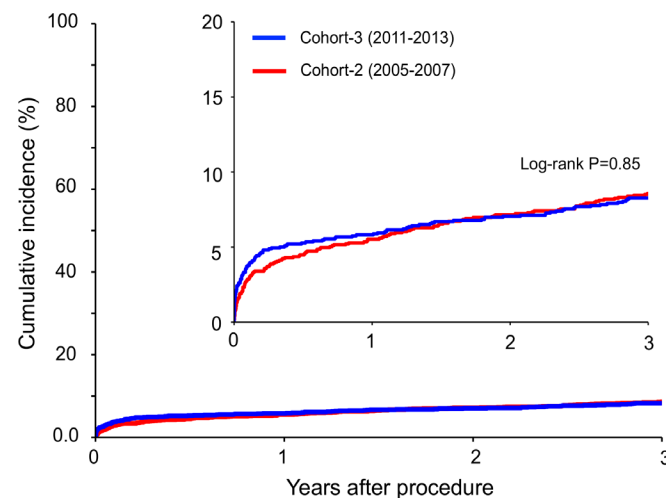
The cumulative incidence of major bleeding was not significantly different between Cohort-2 and Cohort-3 (19.1% and 19.7%, log-rank $p=0.78$) ([table 2](#) and [figure 3](#)). However, after adjusting for confounders, the excess risk of Cohort-3 relative to Cohort-2 turned out to be significant for major bleeding (HR 1.25, 95% CI 1.06 to 1.47, $p=0.008$) ([table 2](#)). In the 30-day landmark analysis, there was a trend towards increased adjusted risk of Cohort-3 relative to Cohort-2 for major bleeding both within 30 days and beyond 30 days (online supplemental figure 2). Considering the differences in the patterns of major bleeding between PCI and CABG, we evaluated the risk of major bleeding only in patients who received PCI; the cumulative incidence of major bleeding was significantly higher in Cohort-3 compared with Cohort-2, and after adjusting confounders, the excess risk of Cohort-3 relative to Cohort-2 remained significant for major bleeding (online supplemental figure 3). These results were consistent in both within and beyond 30 days after index procedure (online supplemental figure 3). The

A All-cause death



Interval	0 day	30 days	1 year	2 years	3 years
Cohort-3					
N of patients at risk	1571	1498	1389	1326	1254
N of patients with event		55	123	168	210
Cumulative incidence		3.5%	8.0%	11.0%	13.8%
Cohort-2					
N of patients at risk	1683	1630	1524	1464	1400
N of patients with event		48	122	169	216
Cumulative incidence		2.9%	7.3%	10.2%	13.1%

B Cardiovascular death



Interval	0 day	30 days	1 year	2 years	3 years
Cohort-3					
N of patients at risk	1571	1498	1389	1326	1254
N of patients with event		55	90	108	125
Cumulative incidence		3.5%	5.8%	7.1%	8.3%
Cohort-2					
N of patients at risk	1683	1630	1524	1464	1400
N of patients with event		45	92	118	140
Cumulative incidence		2.7%	5.5%	7.2%	8.6%

Figure 2 Kaplan-Meier curves comparing mortality outcomes between Cohort-2 and Cohort-3: (A) all-cause death and (B) cardiovascular death.

cumulative incidence of persistent DAPT discontinuation in patients who received PCI was significantly lower in Cohort-3 than in Cohort-2, indicating significantly longer DAPT duration in Cohort-3 than in Cohort-2 (online supplemental figure 4).

DISCUSSION

The main findings of this study were as follows: (1) Patients with NSTEMACS in Cohort-3 were older and more often had heart failure than those in Cohort-2. (2) The prevalence of PCI, emergency procedure, transradial approach, DES use, IVUS use and guideline-directed medical therapy were higher with longer duration of DAPT in Cohort-3 than in Cohort-2. (3) There was no change in 3-year mortality risk from Cohort-2 to Cohort-3. (4) Patients in Cohort-3 as compared with those in Cohort-2 were associated with lower risks for definite stent thrombosis, stroke and any coronary revascularisation, but with higher risk for major bleeding.

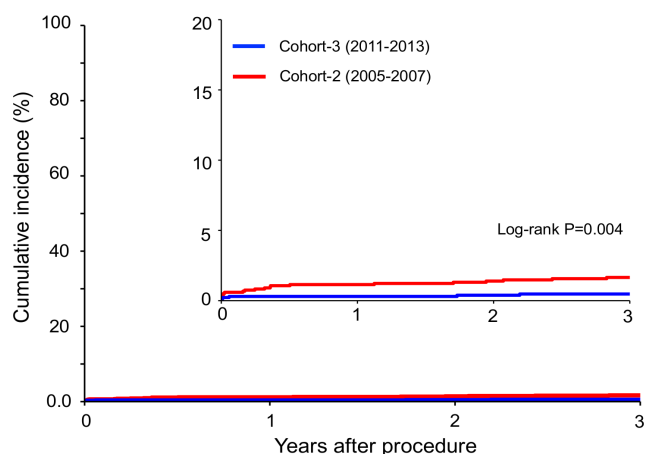
The American Heart Association (AHA)/American College of Cardiology (ACC) and European Society of Cardiology (ESC) guidelines have regularly updated and recommended appropriate interventional and pharmacological strategies.⁸⁻¹⁰ Several studies demonstrated the improvement of early and long-term outcome in patients with NSTEMACS from 1990s to 2000s.²⁻⁴ Meanwhile, there was little data which evaluated long-term clinical outcomes in patients with NSTEMACS after 2010s,⁵ and it is unknown whether these guideline recommendations have led to an

improvement of clinical outcomes. Given the higher risk of long-term mortality in patients with NSTEMACS than in patients with STEMI, evaluating long-term clinical outcome and adherence to evidence-based practice in the real-world clinical practice would be important. Here, we evaluated long-term clinical outcomes in patients with NSTEMACS enrolled between 2011 and 2013 and between 2005 and 2007 using a series of Japanese registry of consecutive patients who underwent first coronary revascularisation.

The proportion of NSTEMI among NSTEMACS was much higher in Cohort-3 than in Cohort-2, which could be related to the fact that high sensitivity troponin measurement was introduced in Japan from 2010, and therefore, was not available in Cohort-2.

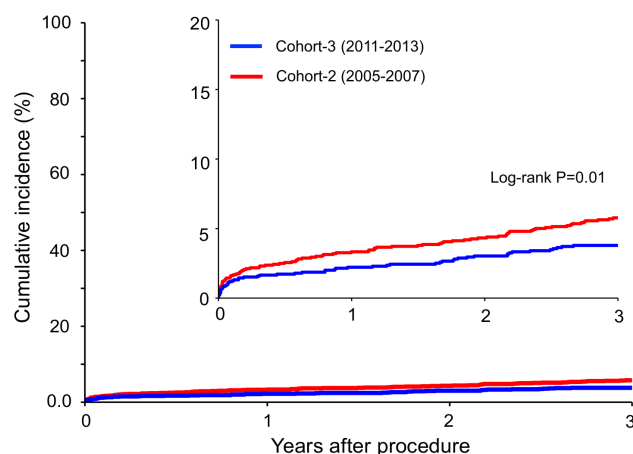
Nevertheless, patients in Cohort-3 were older and more often treated in emergency, and more often had current heart failure than those in Cohort-2. We observed substantial changes in practice patterns which might have contributed to improve clinical outcomes from Cohort-2 to Cohort-3. First, we demonstrated that more patients took guideline-directed medical therapy including a P2Y12 inhibitor, beta-blockers, ACE inhibitors and statins which were recommended by both the AHA/ACC and ESC guidelines.^{18 10} Second, for patients who underwent PCI, more patients were treated with transradial approach, which was recommend in the ESC guideline because of lower risk of bleeding and a trend towards favourable outcomes.^{10 11} Third, much larger proportion of patients

A Definite stent thrombosis



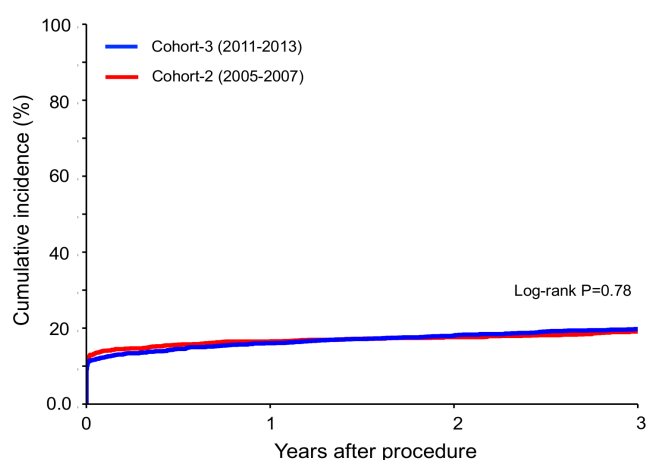
Interval	0 day	30 days	1 year	2 years	3 years
Cohort-3					
N of patients at risk	1356	1295	1209	1154	1088
N of patients with event		4	4	5	6
Cumulative incidence		0.3%	0.3%	0.4%	0.5%
Cohort-2					
N of patients at risk	1348	1298	1218	1167	1114
N of patients with event		8	15	18	21
Cumulative incidence		0.6%	1.1%	1.4%	1.7%

B Stroke



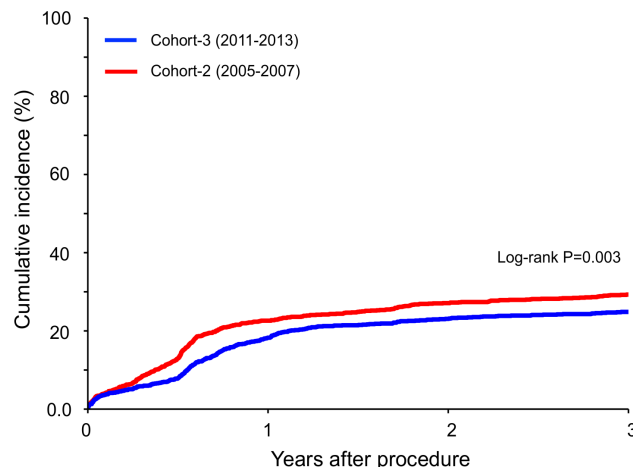
Interval	0 day	30 days	1 year	2 years	3 years
Cohort-3					
N of patients at risk	1571	1481	1369	1301	1226
N of patients with event		18	33	44	54
Cumulative incidence		1.2%	2.2%	3.0%	3.8%
Cohort-2					
N of patients at risk	1683	1611	1489	1417	1340
N of patients with event		24	54	69	90
Cumulative incidence		1.4%	3.3%	4.3%	5.8%

C Major bleeding



Interval	0 day	30 days	1 year	2 years	3 years
Cohort-3					
N of patients at risk	1571	1340	1216	1150	1074
N of patients with event		191	248	276	300
Cumulative incidence		12.2%	16.0%	18.0%	19.7%
Cohort-2					
N of patients at risk	1683	1422	1318	1256	1189
N of patients with event		234	276	293	315
Cumulative incidence		13.9%	16.5%	17.6%	19.1%

D Any coronary revascularization



Interval	0 day	30 days	1 year	2 years	3 years
Cohort-3					
N of patients at risk	1571	1447	1139	1023	940
N of patients with event		54	264	330	353
Cumulative incidence		3.5%	18.3%	23.1%	24.9%
Cohort-2					
N of patients at risk	1683	1566	1181	1063	980
N of patients with event		64	359	426	458
Cumulative incidence		3.9%	22.6%	27.1%	29.4%

Figure 3 Kaplan-Meier curves comparing other secondary outcome measures between Cohort-2 and Cohort-3: (A) definite stent thrombosis, (B) stroke, (C) major bleeding and (D) any coronary revascularisation. Definite stent thrombosis was adjudicated based on the ARC definition and was analysed only for patients who underwent PCI with stent implantation (1348 patients in Cohort-2 and 1356 patients in Cohort-3). Major bleeding was defined as GUSTO moderate/severe bleeding. ARC, Academic Research Consortium; GUSTO, Global Utilisation of Streptokinase and Tissue plasminogen activator for Occluded coronary arteries.

were treated with DES, particularly new-generation DES, in Cohort-3 than in Cohort-2. Several randomised clinical trials and meta-analysis have demonstrated reduction in cardiovascular death or non-fatal MI with new-generation

DES compared with bare metal stent (BMS).^{12 13} Fourth, more patients underwent IVUS-guided PCI which was reported to be associated with favourable outcomes compared with angio-guided PCI.¹⁴ Despite these changes

in practice patterns, we could not demonstrate significant improvement in mortality outcomes from Cohort-2 to Cohort-3. Nevertheless, the adjusted risk for cardiac or cardiovascular death numerically favoured Cohort-3 relative to Cohort-2, although the present study was underpowered for the mortality outcomes. The changes in practice patterns from Cohort-2 to Cohort-3 might be qualitatively appropriate, but quantitatively insufficient. We should further promote guideline-directed medical therapy, high intensity statin therapy in particular, which might lead to improvement in mortality outcomes. Moreover, it might be important to minimise the difference in adherence to evidence-based practice across facilities.^{15 16}

We demonstrated substantial reduction in stroke from Cohort-2 to Cohort-3, which could be partially explained by the higher prevalence of guideline-directed medical therapy. Control of blood pressure, which is crucial in preventing stroke, might have improved from Cohort-2 to Cohort-3, although we did not have data on blood pressure during follow-up.¹⁷ We also found significant reduction in the risks for definite stent thrombosis, and any coronary revascularisation from Cohort-3 to Cohort-2, which could mostly be explained by the more widespread use of DES and predominant use of new-generation DES in Cohort-3 than in Cohort-2,¹⁸ although we could not deny the contribution of the higher prevalence of guideline-directed medical therapy.

In the mean time, we observed the higher risk of bleeding in Cohort-3 relative to Cohort-2 in patients who underwent PCI. The reasons for the higher bleeding risk in Cohort-3 than in Cohort-2 were considered to be the difference in the types of thienopyridine used and longer DAPT duration in Cohort-3 than in Cohort-2. In Cohort-2, ticlopidine was predominantly used with a dose regimen of 100 mg two times per day as the standard dose in Japan, which was much lower than the dose used globally (250 mg two times per day), while in Cohort-3, clopidogrel was predominantly used with a dose regimen of 75 mg once daily which was the same dose as that used globally. Recently, several randomised trials have demonstrated very short DAPT after PCI reduced major bleeding without increase in cardiovascular events.^{19 20} Given the ageing society with higher risk of bleeding, we should further explore the optimal DAPT duration and optimal maintenance antithrombotic regimen in patients with NSTEMI.

Limitations

This study has several limitations. First, historical comparison should result in systematic differences in selection of patients and acquisition of outcomes. To minimise this difference, we enrolled only patients from facilities that participated in both Cohort-2 and Cohort-3, standardised the follow-up duration at 3 years, and adopted the identical methodology for baseline and follow-up data collection and definitions of baseline characteristics and clinical outcome measures in Cohort-2 and Cohort-3. We found numerically higher risk for myocardial infarction

in Cohort-3 than in Cohort-2, despite significantly lower incidence of definite stent thrombosis in Cohort-3 than in Cohort-2. We could not deny the ascertainment bias for myocardial infarction. The less widespread use of troponin for the diagnosis of myocardial infarction in Cohort-2 compared with Cohort-3 might have underestimated the incidence of myocardial infarction as an outcome measure in Cohort-2. Second, changes in practice pattern beyond 2014 were not available and the present study results did not represent the contemporary clinical practice. Moreover, the thienopyridines used were mainly ticlopidine in Cohort-2 and mainly clopidogrel in Cohort-3, which was quite different from the current antiplatelet therapy (ticagrelor or prasugrel) in patients with NSTEMI. Third, we included only patients who had undergone first coronary revascularisation, which could be a selection bias in this study. Fourth, we did not have data on control of blood pressure during follow-up, which might have improved over time, leading to reduction of stroke from Cohort-2 to Cohort-3. Fifth, the present study was underpowered for mortality outcomes. Finally, although we made extensive statistical risk adjustment, there might be some residual unmeasured confounders, especially unnoticed changes between cohorts.

CONCLUSIONS

In the past two decades, we did not find any significant difference in mortality outcomes in patients with NSTEMI. We observed significant reduction in the risks for definite stent thrombosis, stroke and any coronary revascularisation, but significant increase in the risk for major bleeding.

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Contributors T Kimura conceptualised the CREDO-Kyoto PCI/CABG Registry Cohort-3. YT prepared the original draft of the manuscript. H Shiomi, TM and T Kimura reviewed and edited the original draft of the manuscript. YT, H Shiomi, Y Yoshikawa, YMN, K Yamamoto and K Yamaji curated the data. YT, TM and T Kimura constructed the methodology for this study. YT and TM performed the statistical analysis. H Shiomi, TM, RT, K Yamaji, JT, SS, MI, T Takeda, MS, NE, KI, TI, TO, ES, TY, T Tamura, H Sakamoto, KA, YS, YF, YS, YN, KK, T Komiya, KM and T Kimura are investigators of the CREDO-Kyoto PCI/CABG Registry Cohort-3. YT, H Shiomi, Y, YMN, K Yamamoto and KN assessed and validated events within the CREDO-Kyoto PCI/CABG Registry Cohort-3. T Kimura is the guarantor.

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Competing interests HS reports personal fees from Abbott Vascular, Boston Scientific and Daiichi Sankyo. TM reports lecturer's fees from Bayer, Daiichi Sankyo, Japan Lifeline, Kyocera, Mitsubishi Tanabe, Novartis and Toray; the manuscript fees from Bristol-Myers Squibb and Kowa; served advisory boards for Asahi Kasei, Boston Scientific, Bristol-Myers Squibb and Sanofi. NE reports personal fees from Abbott Vascular, Medtronic, Terumo, Bayer, Boston Scientific, Daiichi-Sankyo, Edwards Lifescience, Pfizer, Bristol Myers Squibb, Takeda and Boehringer Ingelheim. YF reports personal fees from Daiichi Sankyo, Bayer, Sanofi, Kowa, Pfizer, Bristol-Myers Squibb, Otsuka Pharmaceutical, Sumitomo Dainippon Pharma, Takeda and Ono Pharmaceutical. YN reports grant from Abbott Vascular and Boston Scientific, and reports personal fees from Abbott Vascular, Bayer, Boston Scientific, Bristol-Myers Squibb, Daiichi Sankyo. TK reports personal fees from Abbott Vascular, MSD, Eisai, Edwards Lifescience, Ono Pharmaceutical, Tsumura, Medical Review, Kowa, Sanofi, Daiichi Sankyo, Takeda Pharmaceutical, Pharmaceuticals and Medical Devices Agency, Abiomed, Bayer, Bristol-Myers Squibb, Boston Scientific, Lifescience, Toray, Astellas Amgen Biopharma, Astellas, AstraZeneca, Otsuka Pharmaceutical, OrbusNeich, MSD Life Science Foundation, Public Health Research Foundation, Chugai Pharmaceutical, Boehringer Ingelheim, Japan Society for the Promotion of Science, Interscience, Philips, Kowa Pharmaceutical, Mitsubishi Tanabe Pharma, Terumo, Novartis Pharma and Sumitomo Dainippon Pharma.

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Ethics approval The protocol for CREDO Kyoto PCI/CABG Registry Cohort-2 and Cohort-3 were approved by the human research ethics committees of the Kyoto University Graduate School of Medicine (E42,E2400).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information.

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SUPPLEMENTARY MATERIAL

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Supplemental Appendix A: List of participating centers and investigators

The CREDO-Kyoto PCI/CABG Registry Cohort-2

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Uchida, Yuko Yamamoto, Satoko Nishida, Mai Yoshimoto, Sachiko Maeda, Izumi Miki,

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The CREDO-Kyoto PCI/CABG Registry Cohort-3

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Kumiko Kitagawa, Masayo Kitamura, Takahiro Kuwahara, Satoko Nishida, Naoko Okamoto,

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Yamazaki

Supplemental Appendix C: Definitions of baseline characteristics and endpoints

Diabetes was defined as treatment with oral hypoglycemic agents or insulin, prior clinical diagnosis of diabetes, glycated hemoglobin level $\geq 6.5\%$, or non-fasting blood glucose level ≥ 200 mg/dL. Left ventricular ejection fraction was measured either by contrast left ventriculography or echocardiography. Prior stroke was defined as ischemic or hemorrhagic stroke with neurological symptoms lasting >24 hours. Peripheral vascular disease was regarded as present when carotid, aortic, or other peripheral vascular diseases were being treated or scheduled for surgical or endovascular interventions. Renal function was expressed as estimated glomerular filtration rate (eGFR) calculated by the Modification of Diet in Renal Disease formula modified for Japanese patients.¹ High-intensity statins therapy in this study was defined as the statin doses greater than or equal to atorvastatin 20 mg, pitavastatin 4 mg, or rosuvastatin 10 mg.

Death was regarded as cardiac in origin unless obvious non-cardiac causes could be identified. Cardiovascular death included cardiac death, and other vascular death related to stroke, renal disease, and vascular disease. Any death during the index hospitalization and death of unknown cause were regarded as cardiac death. Sudden death was defined as unexplained death in previously stable patients. Myocardial infarction was defined according to the definition in the Arterial Revascularization Therapy Study (ARTS)², and only Q-wave myocardial infarction was regarded as myocardial infarction when it occurred within 7 days of the index procedure.³ Definite stent thrombosis was defined according to the Academic Research Consortium (ARC) definition.⁴ Stroke during follow up was defined as ischemic or hemorrhagic stroke requiring hospitalization with symptoms lasting >24 hours. Hospitalization for heart failure was defined as hospitalization due to worsening heart failure requiring intravenous drug therapy. Major bleeding was defined as the global utilization of streptokinase and tissue plasminogen activator for occluded coronary arteries (GUSTO)

moderate/severe bleeding.^{3, 5} TVR was defined as either PCI or CABG related to the original target vessel. Any coronary revascularization was defined as either 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 included in the index procedure. Duration of dual antiplatelet therapy (DAPT) in patients who underwent PCI was left to the discretion of each attending physician. Persistent discontinuation of DAPT was defined as withdrawal of either thienopyridines or aspirin for at least 2 months.

Supplemental Appendix D: List of the clinical event committee members**The CREDO-Kyoto PCI/CABG Registry Cohort-2**

Mitsuru Abe (Kyoto Medical Center), Hiroki Shiomi (Kyoto University Hospital), Tomohisa Tada (Deutsches Herzzentrum), Junichi Tazaki (Kyoto University Hospital), Yoshihiro Kato (Saiseikai Noe Hospital), Mamoru Hayano (Gunma Cardiovascular Center), Akihiro Tokushige (Kagoshima University Hospital), Masahiro Natsuaki (Kyoto University Hospital), Tetsu Nakajima (Kyoto University Hospital).

The CREDO-Kyoto PCI/CABG Registry Cohort-3

Masayuki Fuki (Kyoto University Hospital), Eri Toda Kato (Kyoto University Hospital), Yukiko Matsumura-Nakano (Kyoto University Hospital), Kenji Nakatsuma (Mitsubishi Kyoto Hospital), Hiroki Shiomi (Kyoto University Hospital), Yasuaki Takeji (Kyoto University Hospital), Hidenori Yaku (Mitsubishi Kyoto Hospital), Erika Yamamoto (Kyoto University Hospital), Ko Yamamoto (Kyoto University Hospital), Yugo Yamashita (Kyoto University Hospital), Yusuke Yoshikawa (Kyoto University Hospital), Hiroki Watanabe (Japanese Red Cross Wakayama Medical Center)

Supplemental Appendix E: Missing values about baseline characteristics

There were missing values for body mass index in 125 patients (Cohort-2: 103 [6.1%] and Cohort-3: 22 [2.1%]), for systolic blood pressure in 28 patients (Cohort-2: 22 [1.3%] and Cohort-3: 6 [0.4%]), for diastolic blood pressure in 31 patients (Cohort-2: 22 [1.3%] and Cohort-3: 9 [0.6%]), for LVEF in 813 patients (Cohort-2: 558 [33%] and Cohort-3: 255 [16%]), for eGFR in 31 patients (Cohort-2: 29 [1.7%] and Cohort-3: 2 [0.1%]), for hemoglobin level in 35 patients (Cohort-2: 33 [2.0%] and Cohort-3: 2 [0.1%]), for platelet count in 17 patients (Cohort-2: 16 [1.0%] and Cohort-3: 1 [0.6%]).

Supplementary figure legends

Supplemental Figure 1. Landmark analysis within and beyond 30 days for all-cause death comparing between Cohort-2 and Cohort-3

HR=hazard ratio; CI=confidence interval.

Supplemental Figure 2. Landmark analysis within and beyond 30 days for major bleeding comparing between Cohort-2 and Cohort-3

Major bleeding was defined as GUSTO moderate/severe bleeding.

HR=hazard ratio; CI=confidence interval; GUSTO=global utilization of streptokinase and tissue plasminogen activator for occluded coronary arteries.

Supplemental Figure 3. Kaplan-Meier curves for major bleeding comparing between Cohort-2 and Cohort-3 in patients who received PCI as the index coronary revascularization procedure

(A) Entire follow-up period and (B) Landmark analysis within and beyond 30 days

Supplemental Figure 4. Kaplan-Meier curves for persistent DAPT discontinuation comparing between Cohort-2 and Cohort-3 in patients who received PCI as the index coronary revascularization procedure

Persistent discontinuation of DAPT was defined as withdrawal of either thienopyridines or aspirin for at least 2 months.

DAPT=dual antiplatelet therapy.

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Supplemental Figure 1. Landmark analysis within and beyond 30 days for all-cause death comparing between Cohort-2 and Cohort-3

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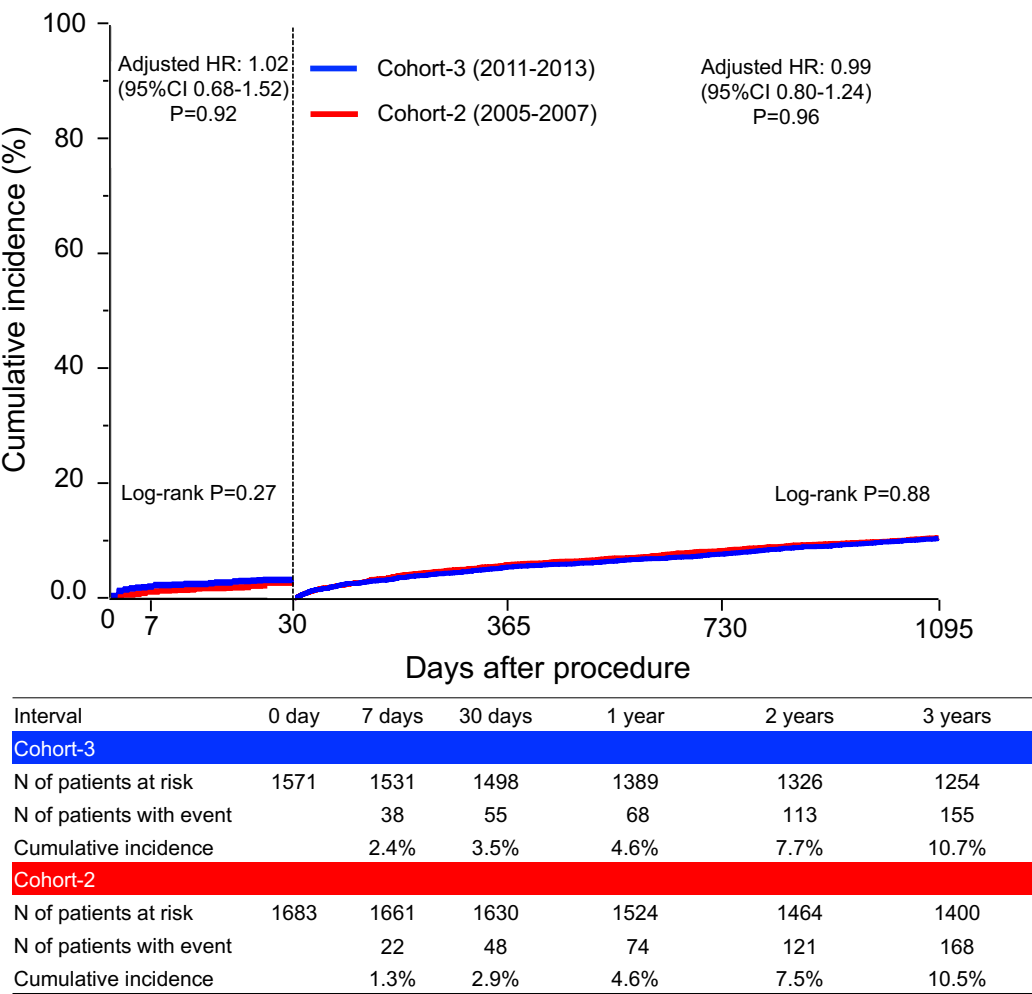
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All-cause death within and beyond 30 days



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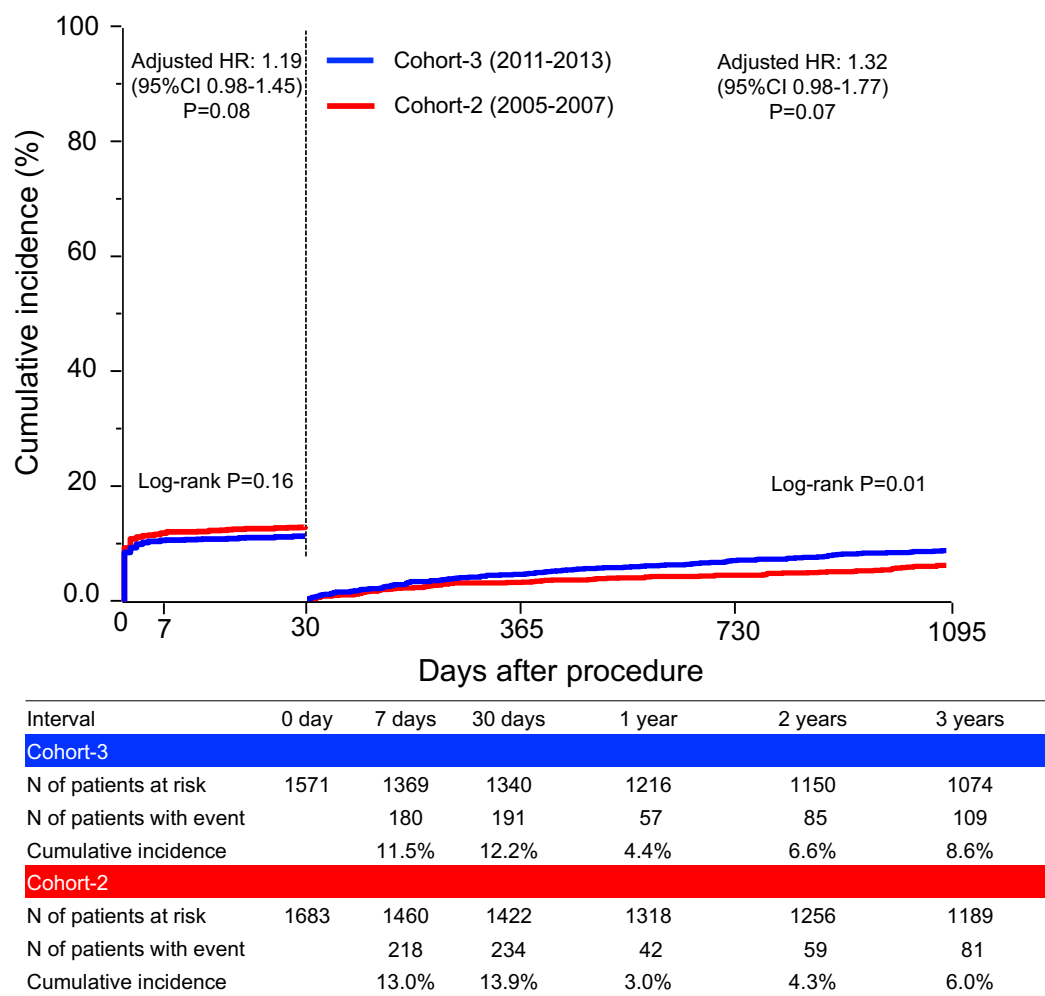
Supplemental Figure 2. Landmark analysis within and beyond 30 days for major

2

bleeding comparing between Cohort-2 and Cohort-3

3

Major bleeding within and beyond 30 days

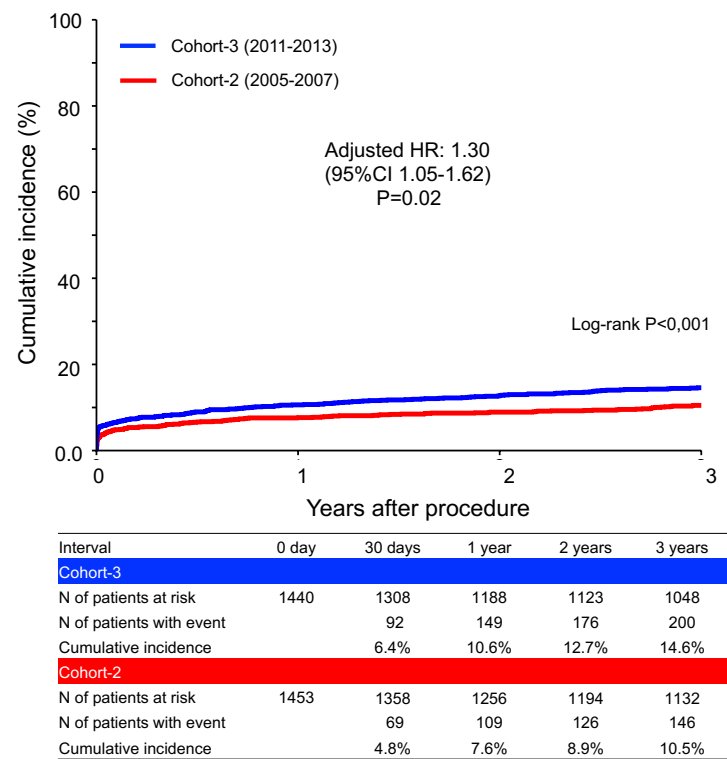


1 Supplemental Figure 3. Kaplan-Meier curves for major bleeding comparing between Cohort-2 and Cohort-3 in patients who received

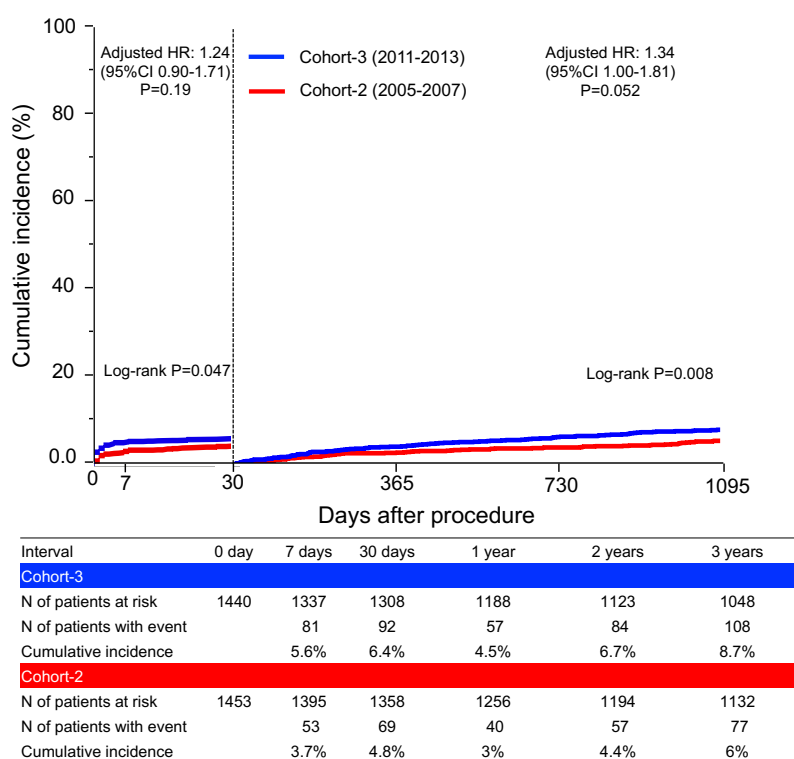
2 PCI as the index coronary revascularization procedure

3

(A) Entire follow-up period

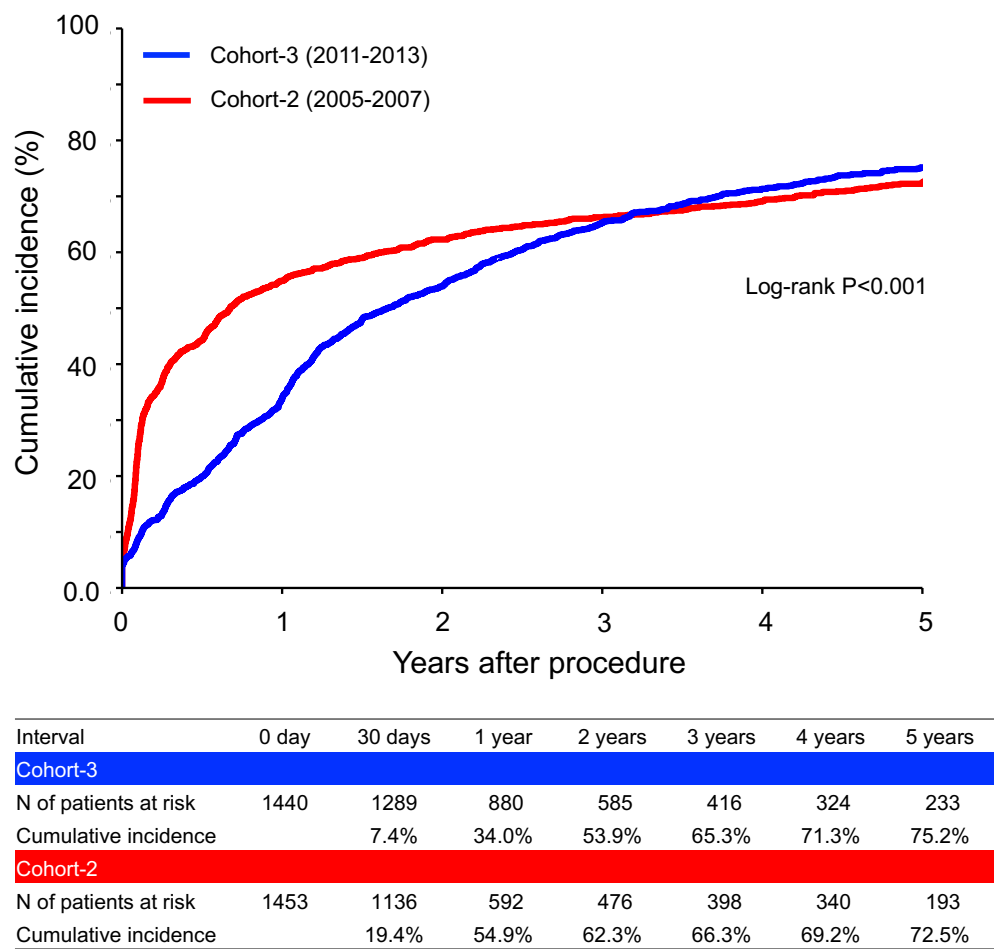


(B) Landmark analysis within and beyond 30 days



1 **Supplemental Figure 4. Kaplan-Meier curves for persistent DAPT discontinuation**
2 **comparing between Cohort-2 and Cohort-3 in patients who received PCI as the index**
3 **coronary revascularization procedure**
4

Persistent DAPT discontinuation



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1 Supplemental Table 1. The annual volume of first coronary revascularization

2 procedures for stable coronary artery disease and acute coronary syndrome in each

3 participating center in the Cohort-2 and Cohort-3

<Cohort-2>	2005		2006		2007	
	PCI	CABG	PCI	CABG	PCI	CABG
Kansai Denryoku Hospital	38	0	62	0	51	0
Kishiwada City Hospital	104	14	115	16	136	10
Kyoto University Hospital	163	18	201	6	158	1
Nara Hospital, Kinki University Faculty of Medicine	115	102	99	87	77	78
Kumamoto University Hospital	60	26	55	26	83	11
Koto Memorial Hospital	70	0	140	0	186	0
Mitsubishi Kyoto Hospital	100	26	105	24	123	31
Shimada Municipal Hospital	46	0	73	0	118	0
Shiga University of Medical Science Hospital	72	0	84	0	58	0
Kagoshima University Medical and Dental Hospital	27	64	34	53	33	49
Juntendo University Shizuoka Hospital	247	34	254	28	247	21
Kokura Memorial Hospital	709	109	674	123	822	127
Kobe City Medical Center General Hospital	203	35	217	45	235	43
Nishi-Kobe Medical Center	93	0	69	0	95	0
Shizuoka General Hospital	175	16	188	21	187	18
Shizuoka City Shizuoka Hospital	183	103	173	87	185	92
Kurashiki Central Hospital	663	53	600	34	538	48
Osaka Red Cross Hospital	147	18	157	24	129	22
Tenri Hospital	146	29	134	14	245	24
Shimabara Hospital	94	12	96	8	126	4
Japanese Red Cross Wakayama Medical Center	215	32	233	39	183	25
Hamamatsu Rosai Hospital	97	30	73	38	80	33
Maizuru Kyosai Hospital	145	15	136	16	89	7
University of Fukui Hospital	58	13	68	17	109	7
Hyogo Prefectural Amagasaki Hospital	148	23	184	24	209	20
Kitano Hospital	80	0	64	0	70	0

<Cohort-3>	2011		2012		2013	
	PCI	CABG	PCI	CABG	PCI	CABG
Kansai Denryoku Hospital	96	0	63	0	75	0
Kyoto University Hospital	145	13	138	14	172	5
Nara Hospital, Kinki University Faculty of Medicine	103	81	94	85	79	76
Koto Memorial Hospital	219	0	187	0	204	0
Mitsubishi Kyoto Hospital	119	29	114	30	151	31
Kishiwada City Hospital	124	18	98	11	112	12
Shimada Municipal Hospital	152	0	147	0	130	0
Shiga University of Medical Science Hospital	106	0	100	0	113	0
Juntendo University Shizuoka Hospital	240	13	261	35	258	29
Kokura Memorial Hospital	825	94	767	115	767	97
Kobe City Medical Center General Hospital	196	26	172	38	194	41
Nishi-Kobe Medical Center	84	0	91	0	78	0
Shizuoka General Hospital	183	17	137	19	137	21
Shizuoka City Shizuoka Hospital	255	66	263	69	286	67
Kurashiki Central Hospital	662	24	601	54	601	47
Osaka Red Cross Hospital	156	17	157	17	162	18
Tenri Hospital	201	24	240	30	240	27
Shimabara Hospital	79	0	77	0	77	0
Japanese Red Cross Wakayama Medical Center	195	27	203	19	173	26
Hamamatsu Rosai Hospital	108	22	110	14	132	15
Hyogo Prefectural Amagasaki Hospital	198	13	182	10	203	8
Kitano Hospital	82	17	85	12	99	16

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