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Demographics, Clinical Practices, and Long-term Outcomes of Patients with ST-segment-elevation Myocardial Infarction in the Past Two Decades: CREDO-Kyoto Acute Myocardial Infarction Registry Wave-1 and Wave-2

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Title: Demographics, Clinical Practices, and Long-term Outcomes of Patients with ST-segment-elevation Myocardial Infarction in the Past Two Decades: CREDO-Kyoto Acute Myocardial Infarction Registry Wave-1 and Wave-2

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Abstract

Objectives: To evaluate changes in demographics, clinical practices, and long-term clinical outcomes of STEMI patients between before and beyond 2010.

Design: Multicenter retrospective study

Setting: The Coronary REvascularization Demonstrating Outcome Study in Kyoto (CREDO-Kyoto) AMI Registries Wave-1 (2005-2007, 26 centers) and Wave-2 (2011-2013, 22 centers).

Participants: 9001 patients with STEMI who underwent coronary revascularization (Wave-1: 4278 patients; Wave-2: 4723 patients).

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, hospitalization for heart failure, major bleeding, target vessel revascularization, ischemia-driven target vessel revascularization, any coronary revascularization, ischemia-driven any coronary revascularization.

Results: Patients in Wave-2 were older, more often had comorbidities, and more often presented with cardiogenic shock than those in Wave-1. Patients in Wave-2 had shorter onset-to-balloon time, and door-to-balloon time, were more frequently used drug-eluting stents, and received guideline-directed medication than those in Wave-1. The cumulative 3-year incidence of all-cause death was not significantly different between Wave-1 and Wave-2 (15.5% and 15.7%, P=0.77). The adjusted risk for all-cause death in Wave-2 relative to Wave-1 was not significant at 3 yeas (HR: 0.92, 95%CI: 0.83-1.03, P=0.14), but lower beyond 30 days (HR: 0.86, 95%CI: 0.75–0.98, P=0.03). The adjusted risks of Wave-2 relative to Wave-1 were significantly lower for definite stent thrombosis (HR 0.59, 95%CI:

0.43-0.81, P=0.001), and for any coronary revascularization (HR 0.75, 95%CI: 0.69-0.81, P<0.001), but higher for major bleeding (HR 1.34, 95%CI: 1.20-1.51, P=0.005).

Conclusions: We could not demonstrate improvement in 3-year mortality risk from Wave-1 to Wave-2, but we found reduction in mortality risk beyond 30 days. We also found reduction in the risks for definite stent thrombosis and any coronary revascularization, but increase in the risk for major bleeding from Wave-1 to Wave-2.

Strengths and limitations of this study

・The present study is the first study evaluating changes of demographics, clinical practices, and long-term clinical outcomes in STEMI patients enrolled beyond 2010 (Wave-2) compared with those enrolled before 2010 (Wave-1).

・The 3-year adjusted risks of patients in Wave-2 relative to those in Wave-1 were not significantly different for all-cause death, myocardial infarction, and stroke, and significantly lower for definite stent thrombosis and any coronary revascularization, but higher for major bleeding

・The 3-year adjusted risks of patients in Wave-2 relative to those in Wave-1 was lower for all-cause death beyond 30 days.

・This study was a historical comparison should result in systematic differences in selection of patients and acqisition of outcomes

Introduction

The early mortality of patients with ST-segment-elevation myocardial infarction (STEMI) has been steadily declining over the last several decades. [1-5] This trend appeared to have been driven by many factors, including demographic change, better pharmacologic management, widespread penetration of thrombolysis and/or primary percutaneous coronary intervention (PCI), shorter door-to-balloon time, and improvement in secondary prevention.[4, 6-10] Several large studies had demonstrated improvement of early mortality for patients with STEMI from 1990s to 2000s.[1-3, 10] Treatment based on the updated guidelines might have further improved the clinical outcomes of STEMI patients beyond 2000s.[11, 12] However there could be a gap between guideline and real-world clinical practice. It is currently unknown whether the changes in the guidelines have contributed to change real-world clinical practice and to improve clinical outcomes; in particular, there is a scarcity of data evaluating the long-term clinical outcomes in STEMI patients enrolled beyond 2010 compared with those enrolled before 2010. [10, 13-15] Therefore, we sought to evaluate changes in demographics, clinical practices, and long-term clinical outcomes of STEMI patients using data from the 2 large Japanese cohorts of patients with acute myocardial infarction (AMI) enrolled in 2005-2007 and 2011-2013.

Methods

Study Population

The Coronary REvascularization Demonstrating Outcome Study in Kyoto (CREDO-Kyoto) AMI Registries Wave-1 and Wave-2 are a series of physician-initiated, non-company sponsored, multi-center registry enrolling consecutive patients with AMI who underwent coronary revascularization, either PCI or isolated coronary artery bypass grafting (CABG), within seven days of the onset of symptoms. Wave-1 enrolled patients between January 2005 and December 2007 among 26 centers (both PCI and CABG available: 20

centers, and only PCI available: 6 centers) in Japan after the introduction of drug-eluting stents (DES) in 2004 (supplementary appendix A).[16] Wave-2 enrolled patients between January 2011 and December 2013 among 22 centers (both PCI and CABG available: 16 centers, and only PCI available: 6 centers) in Japan after approval of the new-generation DES in 2010 (supplementary appendix A). We made a historical comparison on demographics, clinical practices, and long-term clinical outcomes of STEMI patients between Wave-1 and Wave-2.

We enrolled a total of 11899 consecutive AMI patients who had undergone coronary revascularization with PCI or isolated CABG from Wave-1 (N=5429) and Wave-2 (N=6470). In the present study, we excluded patients with refusal for study participation (Wave-1: N=9, and Wave-2: N=21), and non-ST-segment elevation myocardial infarction (NSTEMI) (Wave-1: N=875, and Wave-2: N=1720). To make Wave-1 and Wave-2 comparable, we further excluded 267 patients in Wave-1 who were enrolled from 4 cardiology divisions and 5 cardiovascular surgery divisions not participating in Wave-2 and 6 patients in Wave-2 who were enrolled from 1 cardiovascular surgery division not participating in Wave-1. Finally, we retrieved 9001 patients with STEMI for the current study (Wave-1: 4278 patients and Wave-2: 4723 patients) from 22 centers (both PCI and CABG available: 15 centers, and only PCI available: 7 centers) (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

Experienced clinical research coordinators from the independent clinical research organization (Research Institute for Production Development, Kyoto, Japan; Supplementary Appendix B) collected baseline clinical, angiographic and procedural characteristics from the hospital charts or hospital databases according to the pre-specified definitions that were identical in Wave-1 and Wave-2.

Diabetes was defined as treatment with oral hypoglycemic agents or insulin, prior clinical diagnosis of diabetes, glycated hemoglobin level ≥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. [17] 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.

The primary outcome measure of this study was all-cause death. The secondary outcome measures included cardiovascular death, cardiac death, sudden cardiac death, non-cardiovascular death, non-cardiac death, myocardial infarction, definite stent thrombosis, stroke, hospitalization for heart failure, major bleeding, target vessel revascularization (TVR), ischemia-driven target vessel revascularization, any coronary revascularization, ischemia-driven any coronary revascularization. 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) [18], and only Q-wave myocardial infarction was regarded as myocardial infarction when it occurred within 7 days of the index procedure. [19] Definite stent thrombosis was defined according to the Academic Research Consortium (ARC) definition. [20] 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. [19, 21] 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) 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.

Data Collection and Follow-up

Collection of follow-up information was mainly conducted through review of the 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 hospitalizations, and status of antiplatelet therapy.

Follow-up was censored at 3 years after the index procedure to ensure >90% of clinical follow-up rate in both Wave-1 and Wave-2. Complete 3-year follow-up information was obtained for 96.2% of patients in Wave-1, and 93.2% of patients in Wave-2, respectively. The clinical event committee adjudicated those endpoint events including death, myocardial infarction, stroke and major bleeding (Supplementary Appendix C).

Statistical Analysis

Continuous variables were expressed as mean ± standard deviation (SD) or median with interquartile range (IQR). Continuous variables were compared using the Student's t-test or Wilcoxon rank sum test based on their distributions. Categorical variables are expressed as frequencies and percentages and were compared using χ^2 test. Cumulative incidence was estimated by the Kaplan-Meier method and differences were assessed with the log-rank test. To estimate the adjusted hazard ration (HR) and their 95% confidence intervals (CI) of Wave-2 compared to Wave-1, we used multivariable Cox proportional hazard models by incorporating the 17 clinically relevant factors listed in Table 1. The risk-adjusting variables included demographic factors, but not included the factors related to management during the index hospitalization, because differences in management converged into the changes between Wave-1 and Wave 2. Continuous risk-adjusting variables were dichotomized according to the clinically meaningful reference values to make proportional hazard assumptions robust and to be consistent with previous reports.[22] 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. The missing values for the risk-adjusting variables were imputed as "normal" in the binary classification, because data should have been available if abnormalities were suspected. We performed subgroup analysis for major bleeding stratified

by the Academic Research Consortium High Bleeding Risk (ARC-HBR) criteria.[23] 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 STEMI 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.

All analyses were performed using R version 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

Clinical and Procedural Characteristics

Patients in Wave-2 were older and were more often living alone than those in Wave-1. Patients in Wave-2 more often had diabetes, end-stage renal failure, prior stroke, peripheral vascular disease, prior PCI, and malignancy, and less often had ejection fraction ≤40%, and current smoking than those in Wave-1 (Table 1).

Regarding presentation, Wave-2 as compared with Wave-1 included more patients who directly admitted to the participating centers without inter-facility transfer, and who presented with cardiogenic shock and/or Killip class III/IV. Regarding angiographic characteristics, the prevalence of left anterior descending artery culprit was not different between Wave-1 and Wave-2. Patients in Wave-2 more often had multivessel disease than those in Wave-1 (Table 1).

Regarding procedural characteristics, onset-to-balloon time and door-to-balloon time were significantly shorter in Wave-2 than in Wave-1. Prevalence of transradial approach increased significantly, but only slightly, from Wave-1 to Wave-2. Prevalence of DES use was much higher in Wave-2 than in Wave-1, with new-generation DES use in the vast majority of DES cases in Wave-2 (Table 1). Intra-aortic balloon pumping was more often used in Wave-2 than in in Wave-1 (Table 1).

In terms of baseline medications, patients in Wave-2 more often took thienopyridine, statins, beta-blockers, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, and proton pump inhibitors than those in Wave-1, while patients in Wave-2 less often took cilostazol than those in Wave-1. The prevalence of high-intensity statins therapy was very low in both Wave-1 and Wave-2. Regarding the kind of thienopyridine, the vast majority of patients in Wave-1 took ticlopidine, while the vast majority of patients in Wave-2 took clopidogrel (Table 1).

Clinical Outcomes

The cumulative 3-year incidence of all-cause death was not significantly different between Wave-1 and Wave-2 (15.5% versus 15.7%, log-rank P=0.77) (Table 2, and Figure 2A). The adjusted risk of Wave-1 relative to Wave-2 remained insignificant for all-cause death (HR: 0.92, 95%CI: 0.83–1.03, P=0.14) (Table 2). In the 30-day landmark analysis, cumulative incidence of all-cause death was not significantly different between Wave-1 and Wave-2 both within 30 days (5.5% versus 5.9%, log-rank P=0.37), and beyond 30 days (10.6% versus 10.4%, log-rank P=0.74). However, after adjusting confounders, the lower mortality risk of Wave-2 relative to Wave-1 was significant beyond 30 days after index procedure (HR: 0.86, 95%CI: 0.75–0.98, P=0.03), although it was not significant within 30 days (HR: 1.04, 95%CI: 0.87–1.23, P=0.69) (Figure I in the online-only Data Supplement).

The results of the 30-day landmark analysis were consistent in patients with and without cardiogenic shock (Figure I in the online-only Data Supplement).

The lower crude and adjusted risks of Wave-2 relative to Wave-1 were significant for definite stent thrombosis, target vessel revascularization, and any coronary revascularization, while those were insignificant for cardiovascular death, myocardial infarction, and stroke (Table 2, and Figure 3).

Meanwhile, the cumulative 3-year incidence of major bleeding was significantly higher in Wave-2 than in Wave-1 (16.5% and 12.0%, log-rank P<0.001) (Table 2, and Figure 3). The excess adjusted risk of Wave-2 relative to Wave-1 remained significant for major bleeding (HR: 1.34, 95%CI: 1.20–1.51, P=0.005) (Table 2). In the 30-day landmark analysis, the excess crude and adjusted risks of Wave-2 relative to Wave-1 for major bleeding were significant both within 30 days and beyond 30 days (Figure II in the online-only Data Supplement). In the subgroup analysis, the higher risk of Wave-2 relative to Wave-1 for major bleeding was consistent in patients with and without ARC-HBR (Figure III in the online-only Data Supplement). The cumulative incidence of persistent DAPT discontinuation was significantly lower in Wave-2 than in Wave-1, indicating significantly longer DAPT duration in Wave-2 than in Wave-1 (Figure IV in the online-only Data Supplement).

Discussion

The main findings of this study were as follows; 1) Regarding demographics, STEMI patients in Wave-2 were older, more often had comorbidities, and more often presented with serious hemodynamic conditions than those in Wave-1; 2) Regarding clinical practice, patients in Wave-2 had shorter onset-to-balloon time and door-to-balloon time, were more frequently treated with DES, and more often received guideline-directed medical therapy at baseline, and longer duration of DAPT during follow-up than those in Wave-1; 3)

The 3-year adjusted risks of patients in Wave-2 relative to those in Wave-1 were not significantly different for all-cause death, myocardial infarction, and stroke, and significantly lower for definite stent thrombosis and any coronary revascularization, but significantly higher for major bleeding; 4) We witnessed a lower adjusted mortality risk of Wave-2 relative to Wave-1 beyond 30 days, but not within 30 days.

This was the first study to evaluate demographics, clinical practices, and long-term clinical outcomes in STEMI patients enrolled beyond 2010 compared with those enrolled before 2010. In the present study, we could not demonstrate significant improvement in mortality risk from Wave-1 to Wave-2. The morality rates at 30 days were still around 5-6% in both Wave-1 and Wave-2, which was in line with the previous studies.[5, 24] It was true that patients in Wave-2 were older and sicker than those in Wave-1. However, even the adjusted analysis did not suggest improvement in 30-day morality risk from Wave-1 to Wave-2. We did observe significantly shorter onset-to-balloon time and door-to-balloon time with less frequent inter-facility transfer, and more frequent use of DES in Wave-2 than in Wave-1. However, these changes in clinical practice did not lead to improvement in 30-day morality rate. Further shorteninig of onset-to-balloon time, more widespread use of transradial approach, and improved management of cardiogenic shock might be important to improve 30-day morality rate.[16, 25-32]

On the other hands, beyond 30 days after the index procedure, we found a significantly lower adjusted mortality risk of patients in Wave-2 relative to those in Wave-1. The changes in clinical practices that might have contributed to lower mortality risk in Wave-2 relative to Wave-1 included shorter onset-to-balloon time, introduction of new-generation DES, and higher prevalence of guideline-directed medications use, particularly statins. Indeed, in the present study, the rates of definite stent thrombosis and any coronary revascularization were significantly lower in Wave-2 than in Wave-1, which was in line with

the previous studies comparing new-generation DES with first-generation DES.[33] Moereover, we did find substantial increase in the prevalence of statins use. Nevertheless, the prescription rate of high-intensity statins therapy was extremely low in both Wave-1 and Wave-2. The efficacy of high-intensity statins therapy has been firmly established in preventing cardiovascular events in patients with coronary artery disease.[34 35] We should make every effort to promote wider penetration of high-intensity statins therapy in Japan.

Meanwhile, we have demonstrated that the cumulative 3-year incidence of major bleeding was significantly higher in Wave-2 than in Wave-1. Patients in Wave-2 were older and sicker than those in Wave-1. However, even after adjusting confounders, the excess risk of Wave-2 relative to Wave-1 remained significant for major bleeding. Moreover, the excess bleeding risk of Wave-2 relative to Wave-1 was significant regardless of ARC-HBR. Furthermore, the excess bleeding risk of Wave-2 relative to Wave-1 was significant both within 30 days and beyond 30 days. One of the reasons for the higher bleeding risk within 30 days in Wave-2 than in Wave-1 might be the different types of thienopyridine used in Wave-1 and Wave-2. In Wave-1, the vast majority of patients took ticlopidine 100 mg twice daily as the standard dose in Japan, which was much lower than the dose used globally (250 mg twice daily), while in Wave-2, the vast majority of patients took clopidogrel 75 mg once daily, which was the the dose used globally. The 30-day rate of major bleeding in Wave-2 was substantial (Entire cohort: 9.8%, ARC-HBR: 14.8%, and non-ARC-HBR: 5.4%), warranting to explore the optimal antiplatelet regimen in STEMI patients minimizing bleeding events while maintaining efficacy in preventing thrombotic events. For the higher bleeding risk beyond 30 days in Wave-2 than in Wave-1, one of the reasons in addition to the difference in the types of thienopyridine might be the longer DAPT duration in Wave-2 than in Wave-1. Recent studies have suggested clinical benefit with very short DAPT after PCI in reducing major bleeding without increase in cardiovascular events, although STEMI patients

constituded only a small proportion in the STOPDAPT-2 (ShorT and OPtimal duration of Dual AntiPlatelet Therapy after everolimus-eluting cobalt-chromium stent-2) trial, and were excluded in the TWILIGHT (Ticagrelor with Aspirin or Alone in High-Risk Patients after Coronary Intervention) trial. [36 37] We should continue to pursue the optimal DAPT duration and optimal maintenance antithrombotic regimen in STEMI patients.

Limitations

There are several limitations of this study. First, historical comparison should result in systematic differences in selection of patients and acqisition of outcomes, although we were careful in using data only from those centers that participated in both Wave-1 and Wave-2, standardizing the follow-up duration at 3 years, and adopting the identical methodology for baseline and follow-up data collection, and definitions of baseline characteristics and clinical outcome measures in Wave-1 and Wave-2. It is noteworthy that cumulative incidence of myocardial infarction was numerically higher in Wave-2 than in Wave-1, despite significantly lower incidence of definite stent thrombosis in Wave-2 than in Wave-1. We could not deny the possibility of ascertainment bias for myocardial infarction, although we adopted the identical definition of myocardial infarction in Wave-1 and Wave-2. The less widespread use of troponin for the diagnosis of myocardial infarction in Wave-1 compared with Wave-2 might have underestimated the incidence of myocardial infarction in Wave-1, as reflected by the fact that there were much larger number of patients with NSTEMI in Wave-2 than in Wave-1. Moreover, we could not deny the possibility of ascertainment bias for major bleeding, although we adopted the identical definition in Wave-1 and Wave-2. It could be posible that more major bleeding events were recorded in the hospital charts due to the growing interest in bleeding events in later time period. Second, there might be some residual unmeasured confounders, although we made extensive risk adjustment.

Conclusions

We could not demonstrate significant improvement in 3-year mortality risk from Wave-1 to Wave-2, but we found significant reduction in mortality risk beyond 30 days. There were significant reduction in the risks for definite stent thrombosis and any coronary revascularization, but significant increase in the risk for major bleeding from Wave-1 to Wave-2.

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Footnotes

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Contributors:

T.Kimura conceptualizated the CREDO-Kyoto AMI Registry. YT, prepared the original draft of the manuscript. H.Shiomi, TM, T.Kimura reviewed and edited the the original draft of the manuscript. YT, H.Shiomi, Y.Yoshikawa, YMN, K.Yamamoto, K.Yamaji curated data. YT, TM, T.Kimura constructed methodology for this study. YT, TM performed the statistical analysis. H.Shiomi, TM, RT, K.Yamaji, JT, Hirotoshi Watanabe, SS, MI, TT, MS, NE, KI, TI, TO, ES, TY, H.Sakamoto, KA, YS, YF, YS, YN, KK, T.Komiya, KM, T.Kimura are investigaters of the CREDO-Kyoto AMI Registry. YT, H.Shiomi, YY, YMN, K.Yamamoto, ETK, EY, Y.Yamashita, MF, Hiroki Watanabe, HY, KN assessed and validated events within the CREDO-Kyoto AMI Registry. T.Kimura is the Guarantor.

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Competing interest statement:

All authors have completed the Unified Competing Interest form and declare: Dr. Shiomi reports personal fees from Abbott Vascular, Boston Scientific, and Daiichi Sankyo. Dr. Morimoto reports lecturer's fees from Bayer, Daiichi Sankyo, Japan Lifeline, Kyocera, Mitsubishi Tanabe, Novartis, and Toray; the manuscript fees from Bristol-Myers Squibb and

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Ethical approval:

The protocol for CREDO-Kyoto AMI Registry Wave-1 and Wave-2 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 sharing statement:

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

Figure legends

Figure 1. Study flowchart

CREDO-Kyoto=Coronary REvascularization Demonstrating Outcome study in Kyoto; AMI=acute myocardial infarction; PCI=percutaneous coronary intervention, CABG=coronary artery bypass grafting; NSTEMI=non-ST-segment elevation myocardial infarction; STEMI=ST-segment elevation myocardial infarction.

Figure 2. Kaplan-Meier curves (A) for all-cause death and (B) for cardiovascular death comparing between Wave-1 and Wave-2

Figure 3. Kaplan-Meier curves comparing between Wave-1 and Wave-2 for (A) myocardial infarction, (B) definite stent thrombosis, (C) major bleeding, and (D) any coronary revascularization

Definite stent thrombosis was based on the ARC definition, and was analyzed only for patients who underwent PCI with stent implantation (3739 patients in Wave-1 and 4241 patients in Wave-2).

Major bleeding was defined as GUSTO moderate/severe bleeding.

CREDO-Kyoto==Coronary REvascularization Demonstrating Outcome study in Kyoto; AMI=acute myocardial infarction; STEMI=ST-segment elevation myocardial infarction; NSTEMI=non-ST-segment elevation myocardial infarction; ARC=academic research consortium; GUSTO=global utilization of streptokinase and tissue plasminogen activator for occluded coronary arteries .

Table 1. Baseline characteristics comparing between Wave-1 and Wave-2

	Wave-1 (N=4278)	Wave-2 (N=4723)	P value
(A) Clinical characteristics			
Age (years)	67.6 ± 12.2	68.8 ± 12.5	<0.001
Age ≥75 years*	1336 (31%)	1694 (36%)	<0.001
Men*	3156 (74%)	3538 (75%)	0.23
Body mass index (kg/m^2)	23.6 ± 3.5	23.7 ± 3.6	0.40
Body mass index <25.0 kg/m^2*	3058 (72%)	3269 (69%)	0.02
Hypertension*	3343 (78%)	3768 (80%)	0.06
Diabetes mellitus*	1395 (33%)	1664 (35%)	0.009
on insulin therapy	205 (4.8%)	270 (5.7%)	0.06
Current smoking*	1730 (40%)	1702 (36%)	<0.001
Heart failure*	1350 (32%)	1566 (33%)	0.11
LVEF	52.5±12.9	53.8±12.4	<0.001
LVEF ≤40%	596 (18%)	595 (14%)	<0.001
Prior PCI	364 (8.5%)	523 (11%)	<0.001
Prior CABG	53 (1.2%)	59 (1.2%)	1.00
Prior myocardial infarction*	381 (8.9%)	427 (9.0%)	0.85
Prior stroke (symptomatic)*	394 (9.2%)	521 (11%)	0.005
Peripheral vascular disease*	138 (3.2%)	209 (4.4%)	0.004
eGFR<30mL/min/1.73m^2, without hemodialysis*	202 (4.7%)	288 (6.1%)	0.005
Hemodialysis*	73 (1.7%)	131 (2.8%)	0.001
eGFR <30 ml/min/1.73m^2 or hemodialysis	275 (6.4%)	419 (8.9%)	<0.001
Atrial fibrillation	418 (9.8%)	419 (8.9%)	0.15
Anemia (Hemoglobin <11.0g/dl)*	438 (10%)	531 (11%)	0.13
Thrombocytopenia (Platelet <100×10^9/L)	84 (2.0%)	102 (2.2%)	0.56
Chronic obstructive pulmonary disease	140 (3.3%)	173 (3.7%)	0.34
Liver cirrhosis	101 (2.4%)	101 (2.1%)	0.52
Malignancy*	337 (7.9%)	516 (11%)	<0.001
(B) Presentation			
Living alone	509 (13%)	780 (17%)	<0.001
Direct admission	2215 (54%)	2603 (57%)	0.02
Inter-facility transfer	1866 (44%)	1983 (42%)	0.12

Killip class III/IV	725 (17%)	915 (19%)	0.003
Cardiogenic shock	596 (14%)	757 (16%)	0.005
Cardiopulmonary arrest*	142 (3.3%)	193 (4.1%)	0.06
Maximum CK	3100 ± 3616	2801 ± 4328	<0.001
(C)Angiographic characteristics			
Infarct related artery location:			
Left anterior descending coronary artery*	1976 (46%)	2171 (46%)	0.79
Left circumflex coronary artery	419 (9.8%)	464 (9.8%)	1.00
Right coronary artery	1730 (41%)	1893 (40%)	0.70
Left main coronary artery	107 (2.5%)	170 (3.6%)	0.003
Coronary artery bypass graft	19 (0.4%)	24 (0.5%)	0.78
Multivessel disease	2222 (52%)	2655 (56%)	<0.001
(D) Procedural characteristics			
Onset-to-balloon time (hours)	4.2 (2.8-7.2)	4.0 (2.7-6.6)	<0.001
Door-to-balloon time (minutes)	90 (60-132)	79 (59-110)	<0.001
Intra-aortic balloon pump use	738 (17%)	994 (21%)	<0.001
Percutaneous cardiopulmonary support use	116 (2.7%)	149 (3.2%)	0.24
PCI*	4180 (98%)	4625 (98%)	0.48
Transradial approach	498 (12%)	733 (16%)	<0.001
Transfemoral approach	3432 (82%)	3640 (79%)	<0.001
IVUS use for the culprit lesion	1260 (30%)	2653 (57%)	<0.001
Stent use for the culprit lesion	3739 (89%)	4241 (92%)	<0.001
Bare metal stent	2946 (79%)	1735 (41%)	<0.001
Drug-eluting stent	793 (21%)	2506 (59%)	<0.001
Staged PCI	932 (22%)	1018 (22%)	0.77
Stent use including staged PCI	3802 (91%)	4295 (93%)	0.001
Bare metal stent	2542 (67%)	1491 (35%)	<0.001
Drug-eluting stent	1260 (33%)	2804 (65%)	<0.001
First-generation DES use	1257 (99%)	47 (1.7%)	<0.001
Sirolimus-eluting stent (CYPHER™)	1174 (93%)	27 (57%)	
Paclitaxel-eluting stent (TAXUS™)	115 (9.1%)	21 (45%)	
New-generation DES use	-	2776 (99%)	
Everolimus-eluting stent (XIENCE™)	-	2054 (74%)	
Everolimus-eluting stent (PROMUS™)	-	1616 (58%)	

Biolimus-eluting stent (NOBORI™)	-	725 (26%)	
Zotarolimus-eluting stent (RESOLUTE™)	-	255 (9.2%)	
Zotarolimus-eluting stent (ENDEAVOR™)	-	49 (1.8%)	
CABG	98 (2.3%)	98 (2.1%)	0.48
Off pump	34 (35%)	43 (44%)	0.19
ITA use	82 (84%)	80 (82%)	0.71
(E) Baseline Medications			
Antiplatelet therapy			
Thienopyridine	3993 (93%)	4521 (96%)	<0.001
Ticlopidine	3652 (85%)	124 (2.6%)	<0.001
Clopidogrel	340 (7.9%)	4339 (92%)	<0.001
Aspirin	4209 (98%)	4636 (98%)	0.45
Cilostazol	1501 (35%)	116 (2.5%)	<0.001
Statins	2281 (53%)	3885 (82%)	<0.001
High-intensity statins therapy§	67 (1.6%)	78 (1.7%)	0.81
Beta-blockers	1747 (41%)	2555 (54%)	<0.001
ACE inhibitors/ARB	3040 (71%)	3554 (75%)	<0.001
Nitrates	1269 (30%)	832 (18%)	<0.001
Calcium channel blockers	885 (21%)	970 (21%)	0.88
Nicorandil	1198 (28%)	966 (20%)	<0.001
Warfarin	495 (12%)	591 (13%)	0.18
DOAC	-	61 (1.3%)	-
Proton pump inhibitors	1470 (34%)	3505 (74%)	<0.001
Histamine type-2 receptor blockers	1393 (33%)	553 (12%)	<0.001

Continuous variables were expressed as mean ± standard deviation, or median (interquartile range). Categorical variables were expressed as number (percentage).

There were missing values for body mass index in 341 patients (Wave-1: 232 [5.4%] and Wave-2: 109 [2.3%]), for LVEF in 1385 patients (Wave-1: 951 [22%] and Wave-2: 434 [9.2%]), for eGFR in 94 patients (Wave-1: 80 [1.9%] and Wave-2: 14 [0.3%]), for hemoglobin level in 110 patients (Wave-1: 99 [2.3%] and Wave-2: 11 [0.2%]), for platelet count in 47 patients (Wave-1: 29 [0.7%] and Wave-2: 18 [0.4%]), for max CK in 91 patients (Wave-1: 39 [0.9%] and Wave-2: 52 [1.1%]),. The numbers of missing values for body mass

index, eGFR, hemoglobin level, and platelet count were negligibly small. The missing values for these variables were imputed as "normal" in the binary classification, because data should have been available if abnormalities were suspected. On the other hands, the missing values for LVEF were not imputed in the categorical classification, because the numbers of missing values were substantial for these variables. Onset to balloon time and door to balloon time were analyzed only for patients who underwent PCI within 24 hours of the onset of symptoms excluding nosocomial onset (onset to balloon time: 3271 patients in Wave-1 and 3372 patients in Wave-2; door to balloon time: 3228 patients in Wave-1 and 3242 patients in Wave-2).

*Risk-adjusting variables for the Cox proportional hazard models

§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.

PCI=percutaneous coronary intervention; CABG=coronary artery bypass grafting; ESRD=end-stage renal disease; eGFR=estimated glomerular filtration rate; ITA=internal thoracic artery; CK=creatine kinase; ACE inhibitor/ARB=angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; DOAC=direct oral anticoagulants.

Table 2. Clinical outcomes comparing between Wave-1 and Wave-2

Endpoints	Wave-1 (N=4278) N of patients with event (Cumulative 3-year incidence)	Wave-2 (N=4723) N of patients with event (Cumulative 3-year incidence)	Crude HR (95% CI)	P value	Adjusted HR (95% CI)	P value
All-cause death	654 (15.5%)	722 (15.7%)	1.02 (0.91-1.13)	0.77	0.92 (0.83-1.03)	0.14
Cardiovascular death	475 (11.3%)	524 (11.4%)	1.01 (0.89-1.15)	0.86	0.93 (0.82-1.06)	0.26
Cardiac death	448 (10.7%)	489 (10.7%)	1.00 (0.88-1.14)	1.00	0.93 (0.81-1.05)	0.24
Sudden cardiac death	47 (1.2%)	45 (1.1%)	0.88 (0.59-1.33)	0.54	0.76 (0.50-1.15)	0.19
Non-cardiovascular death	179 (4.7%)	198 (4.8%)	1.03 (0.84-1.26)	0.80	0.90 (0.73-1.10)	0.29
Non-cardiac death	206 (5.4%)	233 (5.7%)	1.05 (0.87-1.27)	0.61	0.91 (0.75-1.10)	0.34
Myocardial infarction	169 (4.3%)	202 (4.8%)	1.10 (0.90-1.35)	0.36	1.04 (0.85-1.28)	0.72
Definite stent thrombosis*	81 (2.3%)	60 (1.5%)	0.65 (0.47-0.91)	0.01	0.59 (0.43-0.81)	0.001
Stroke	191 (4.9%)	243 (5.7%)	1.17 (0.97-1.42)	0.10	1.09 (0.90-1.31)	0.40
Hospitalization for heart failure	267 (7.0%)	305 (7.4%)	1.06 (0.90-1.25)	0.50	0.97 (0.82-1.14)	0.68
Major bleeding	492 (12.0%)	741 (16.5%)	1.39 (1.25-1.56)	<0.001	1.34 (1.20-1.51)	0.005
Any coronary revascularization	1277 (33.0%)	1112 (26.6%)	0.76 (0.70-0.83)	<0.001	0.75 (0.69-0.81)	<0.001
Ischemia-driven any coronary revascularization	472 (12.3%)	522 (12.6%)	1.02 (0.90-1.15)	0.80	0.99 (0.87-1.12)	0.87
Target vessel revascularization	1017 (26.3%)	816 (19.5%)	0.70 (0.64-0.77)	<0.001	0.69 (0.63-0.76)	<0.001
Ischemia-driven target vessel revascularization	353 (9.1%)	364 (8.7%)	0.94 (0.81-1.09)	0.43	0.92 (0.79-1.06)	0.25

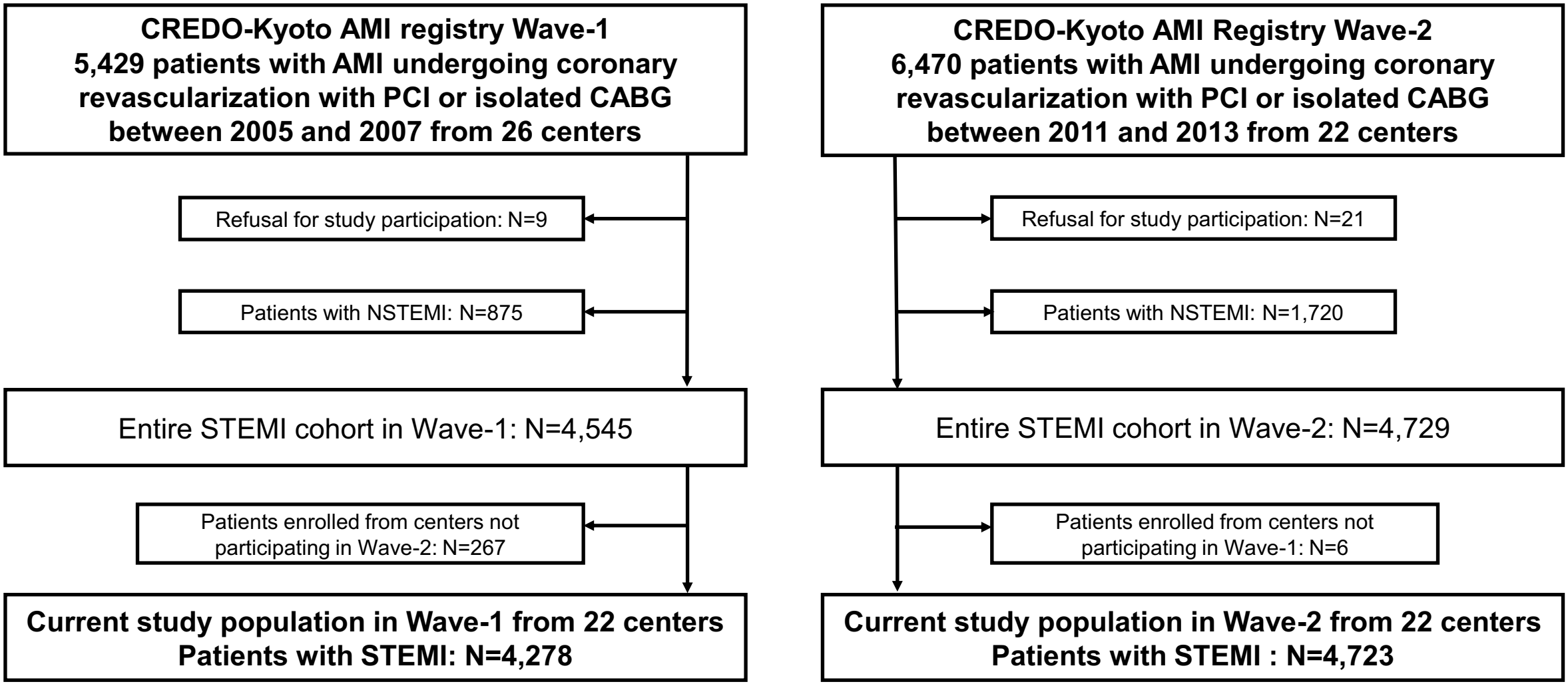
The risk of Wave-2 relative to Wave-1was expressed as HR with 95%CI. The covariates for the multivariate Cox proportional hazard models were indicated in Table 1.

Myocardial infarction was based on the ARTS definition.

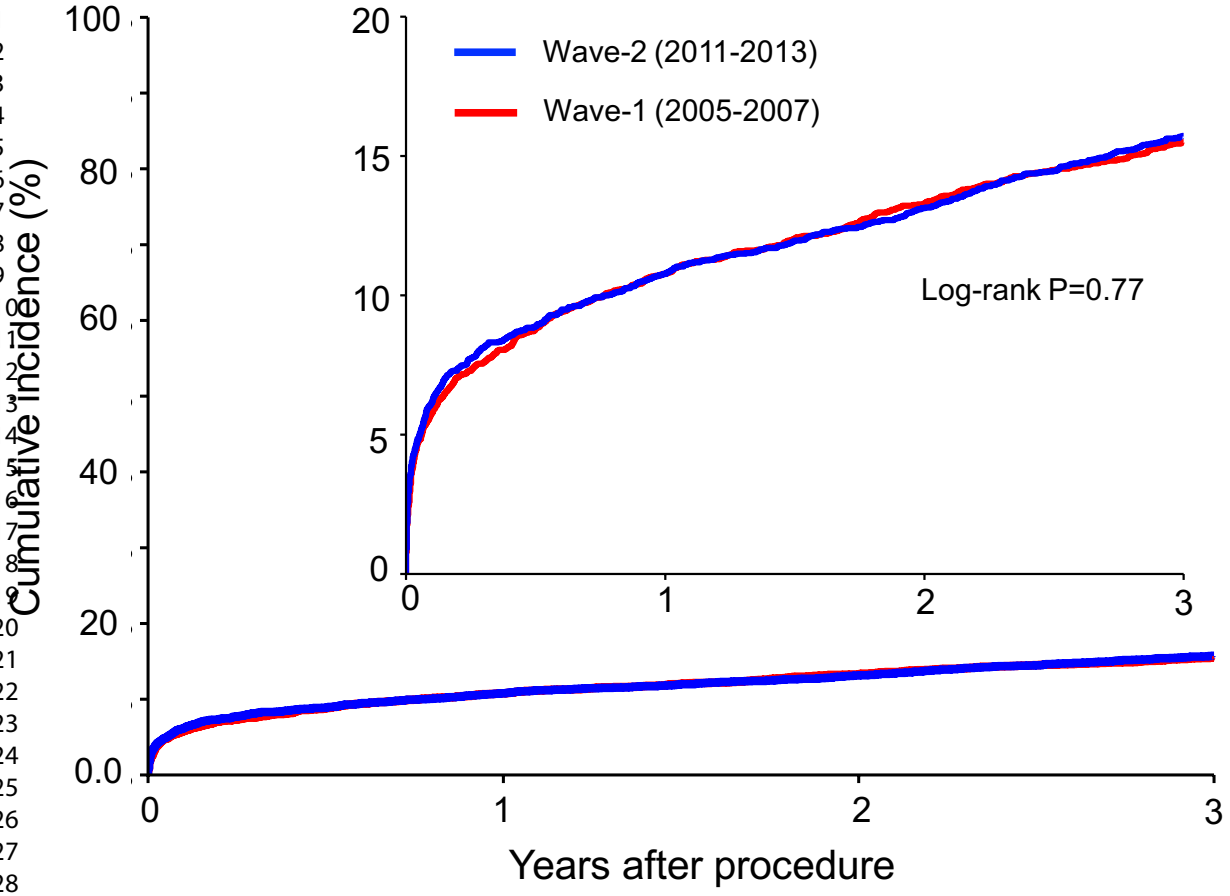
*Definite stent thrombosis was based on the ARC definition, and was analyzed only for patients who underwent PCI with stent implantation (3739 patients in Wave-1 and 4241 patients in Wave-2).

Major bleeding was defined as GUSTO moderate/severe bleeding.

HR=hazard ratio; CI=confidence interval; ARTS=arterial revascularization therapy study; ARC=academic research consortium; GUSTO=global utilization of streptokinase and tissue plasminogen activator for occluded coronary arteries.

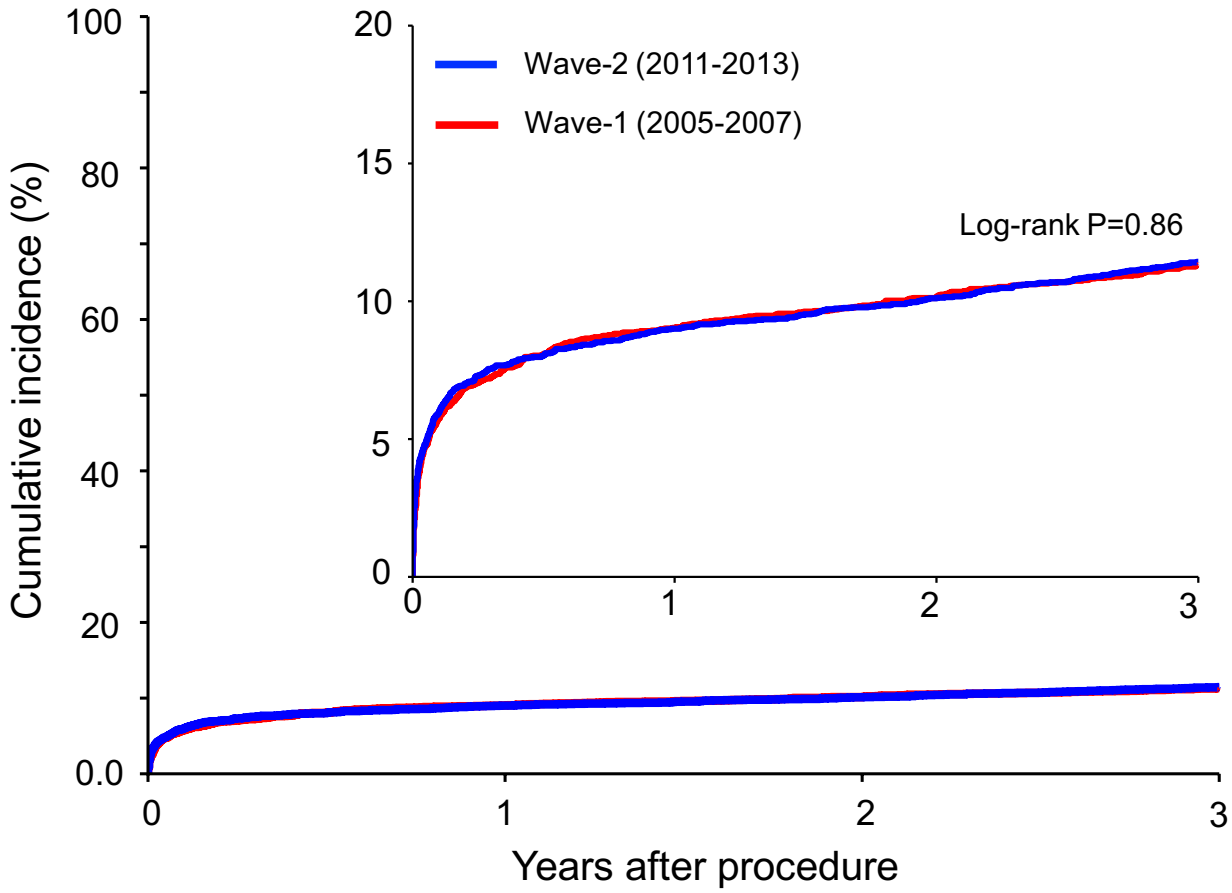

CREDO-Kyoto AMI registry Wave-1
5,429 patients with AMI undergoing coronary revascularization with PCI or isolated CABG between 2005 and 2007 from 26 centers
Refusal for study participation: N=9
Patients with NSTEMI: N=875
Entire STEMI cohort in Wave-1: N=4,545
Patients enrolled from centers not participating in Wave-2: N=267
Current study population in Wave-1 from 22 centers
Patients with STEMI: N=4,278
CREDO-Kyoto AMI Registry Wave-2
6,470 patients with AMI undergoing coronary revascularization with PCI or isolated CABG between 2011 and 2013 from 22 centers
Refusal for study participation: N=21
Patients with NSTEMI: N=1,720
Entire STEMI cohort in Wave-2: N=4,729
Patients enrolled from centers not participating in Wave-1: N=6
Current study population in Wave-2 from 22 centers
Patients with STEMI : N=4,723

(A) All-cause death



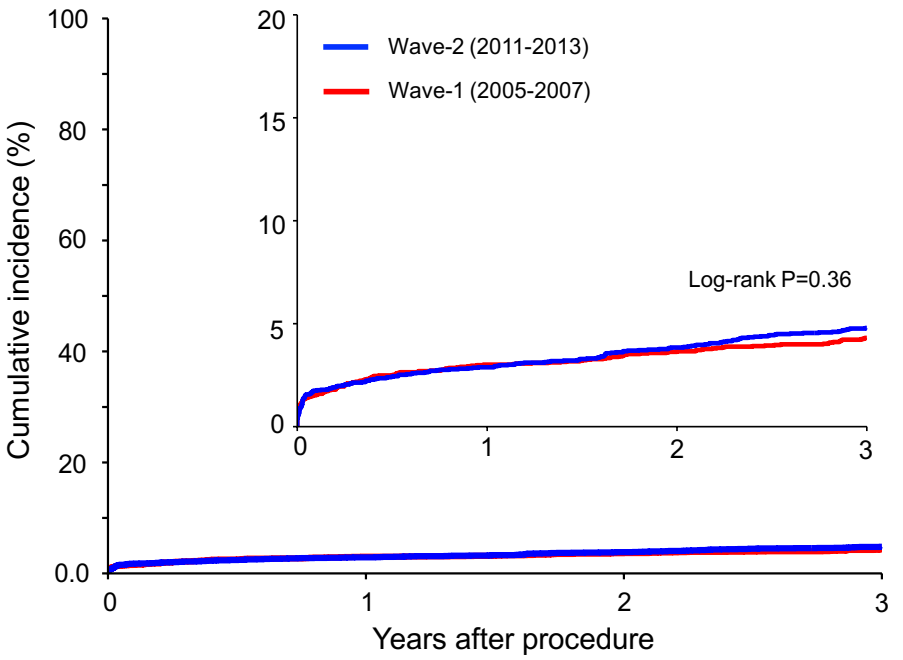
Interval	0 day	30 days	1 year	2 years	3 years
Wave-2					
N of patients at risk	4723	4395	4041	3858	3685
N of patients with event		280	502	608	722
Cumulative incidence		5.9%	10.8%	13.1%	15.7%
Wave-1					
N of patients at risk	4278	4023	3744	3602	3454
N of patients with event		235	458	564	654
Cumulative incidence		5.5%	10.8%	13.3%	15.5%

(B) Cardiovascular death



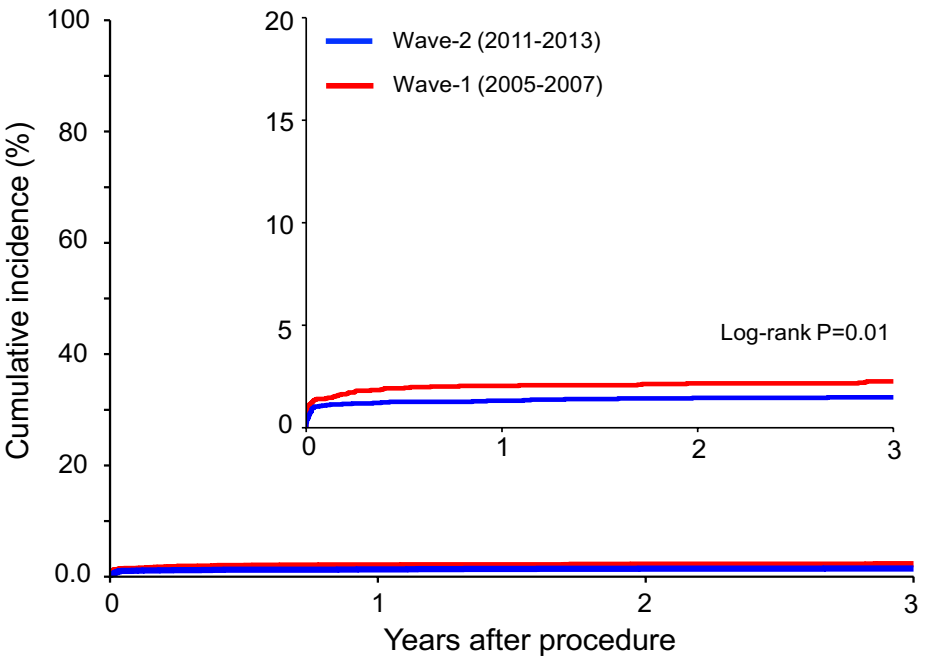
Interval	0 day	30 days	1 year	2 years	3 years
Wave-2					
N of patients at risk	4723	4395	4041	3858	3685
N of patients with event		272	420	468	524
Cumulative incidence		5.8%	9%	10.1%	11.4%
Wave-1					
N of patients at risk	4278	4023	3744	3602	3454
N of patients with event		234	384	430	475
Cumulative incidence		5.5%	9%	10.2%	11.3%

(A) Myocardial infarction



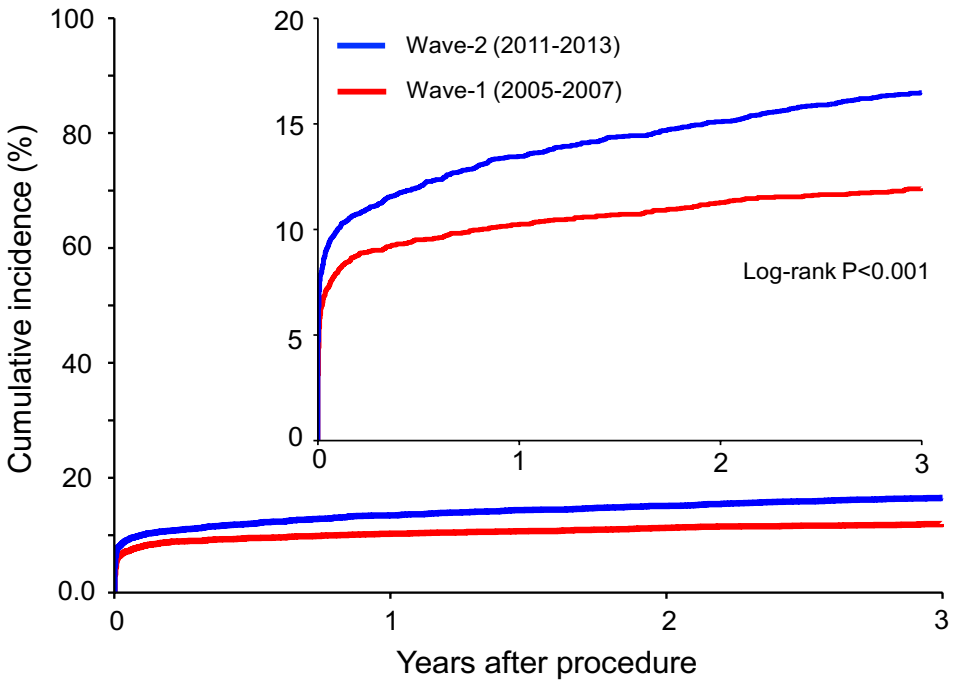
Interval	0 day	30 days	1 year	2 years	3 years
Wave-2					
N of patients at risk	4723	4332	3940	3729	3539
N of patients with event		79	128	166	202
Cumulative incidence		1.7%	2.9%	3.8%	4.8%
Wave-1					
N of patients at risk	4278	3967	3651	3499	3337
N of patients with event		64	122	146	169
Cumulative incidence		1.5%	3.0%	3.7%	4.3%

(B) Definite stent thrombosis



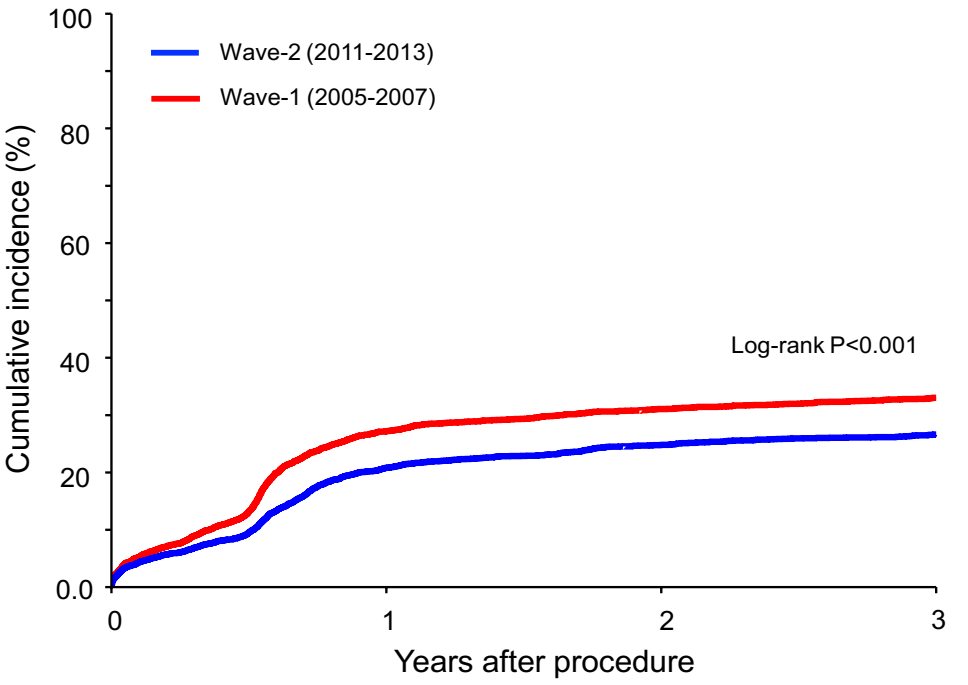
Interval	0 day	30 days	1 year	2 years	3 years
Wave-2					
N of patients at risk	4241	3945	3642	3476	3335
N of patients with event		45	54	59	60
Cumulative incidence		1.1%	1.3%	1.5%	1.5%
Wave-1					
N of patients at risk	3739	3494	3257	3137	3012
N of patients with event		52	74	78	81
Cumulative incidence		1.4%	2.0%	2.2%	2.3%

(C) Major bleeding



Interval	0 day	30 days	1 year	2 years	3 years
Wave-2					
N of patients at risk	4723	4067	3665	3453	3276
N of patients with event		457	618	686	741
Cumulative incidence		9.8%	13.5%	15.1%	16.5%
Wave-1					
N of patients at risk	4278	3773	3485	3333	3189
N of patients with event		331	428	467	492
Cumulative incidence		7.8%	10.3%	11.3%	12.0%

(D) Any coronary revascularization



Interval	0 day	30 days	1 year	2 years	3 years
Wave-2					
N of patients at risk	4723	4236	3210	2894	2690
N of patients with event		178	885	1043	1112
Cumulative incidence		3.9%	20.8%	24.8%	26.6%
Wave-1					
N of patients at risk	4278	3836	2735	2487	2298
N of patients with event		206	1066	1209	1277
Cumulative incidence		5.0%	27.2%	31.1%	33.0%

SUPPLEMENTARY MATERIAL

Table of contents

Supplemental Appendix A: List of participating centers and investigators

The CREDO-Kyoto AMI Registry Wave-1

Cardiology

Kyoto University Hospital: Takeshi Kimura, Hiroki Shiomi

Kishiwada City Hospital: Mitsuo Matsuda, Hirokazu Mitsuoka

Tenri Hospital: Yoshihisa Nakagawa

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Kitano Hospital: Ryuji Nohara

Koto Memorial Hospital: Tomoyuki Murakami, Teruki Takeda

Kokura Memorial Hospital: Masakiyo Nobuyoshi, Masashi Iwabuchi

Maizuru Kyosai Hospital: Ryozo Tatami

Nara Hospital, Kinki University Faculty of Medicine: Manabu Shirotani

Kobe City Medical Center General Hospital: Toru Kita, Yutaka Furukawa, Natsuhiko Ehara

Nishi-Kobe Medical Center: Hiroshi Kato, Hiroshi Eizawa

Kansai Denryoku Hospital: Katsuhisa Ishii

Osaka Red Cross Hospital: Masaru Tanaka

University of Fukui Hospital: Jong-Dae Lee, Akira Nakano

Shizuoka City Shizuoka Hospital: Akinori Takizawa

Hamamatsu Rosai Hospital: Masaaki Takahashi

Shiga University of Medical Science Hospital: Minoru Horie, Hiroyuki Takashima

Japanese Red Cross Wakayama Medical Center: Takashi Tamura

Shimabara Hospital: Mamoru Takahashi

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Juntendo University Shizuoka Hospital: Keiichi Tanbara

The CREDO-Kyoto AMI Registry Wave-2

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The CREDO-Kyoto AMI Registry Wave-1

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The CREDO-Kyoto AMI Registry Wave-2

Research Institute for Production Development

Sakiko Arimura, Yumika Fujino, Miya Hanazawa, Chikako Hibi, Risa Kato, Yui Kinoshita, Kumiko Kitagawa, Masayo Kitamura, Takahiro Kuwahara, Satoko Nishida, Naoko Okamoto, Yuki Sato, Saori Tezuka, Marina Tsuda, Miyuki Tsumori, Misato Yamauchi, Itsuki Yamazaki

Supplemental Appendix C: List of the clinical event committee members

The CREDO-Kyoto AMI Registry Wave-1

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The CREDO-Kyoto AMI Registry Wave-2

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)

Supplementary figure legends

Supplemental Figure I. Landmark analysis within and beyond 30 days for all-cause death comparing between Wave-1 and Wave-2 in (A) entire study population, (B) patients with cardiogenic shock, and (C) patients without cardiogenic shock

HR=hazard ratio; CI=confidence interval.

Supplemental Figure II. Landmark analysis within and beyond 30 days for major bleeding comparing between Wave-1 and Wave-2

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 III . Kaplan-Meier curves for major bleeding comparing between Wave-1 and Wave-2 (A) in patients with ARC-HBR and (B) in patients without ARC-HBR

ARC-HBR=academic research consortium-high bleeding risk; HR=hazard ratio; CI=confidence interval.

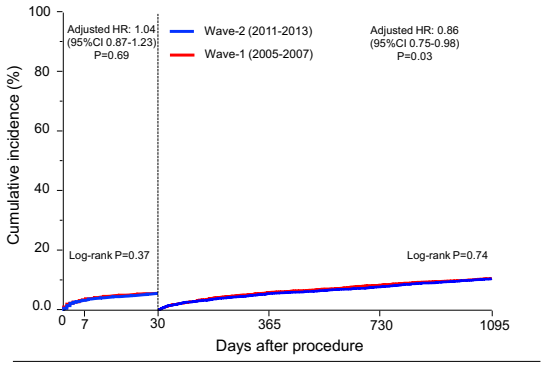
Supplemental Figure IV. Kaplan-Meier curves for persistent DAPT discontinuation comparing between Wave-1 and Wave-2

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

DAPT=dual antiplatelet therapy.

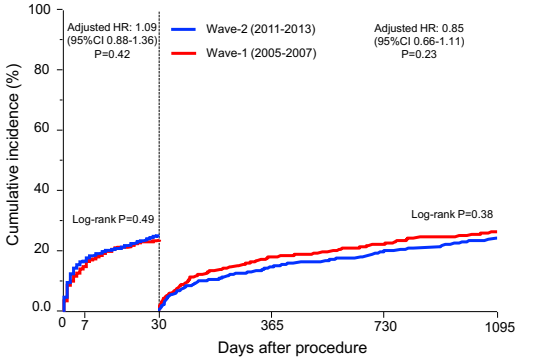
Supplemental Figure I. Landmark analysis within and beyond 30 days for all-cause death comparing between Wave-1 and Wave-2 (A) in entire study population, (B) in patients with cardiogenic shock, and (C) in patients without cardiogenic shock

(A) All-cause death in entire study population



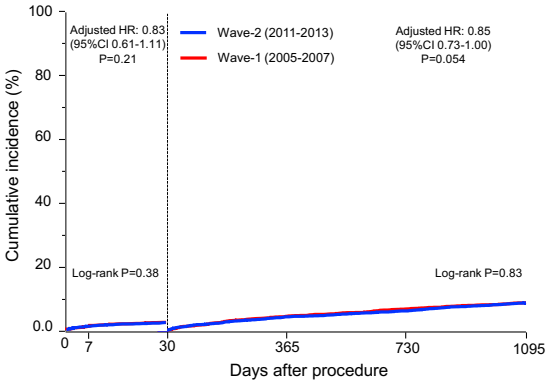
Interval	0 day	7 days	30 days	1 year	2 years	3 years
Wave-2						
N of patients at risk	4723	4551	4395	4041	3858	3685
N of patients with event		183	280	222	328	442
Cumulative incidence		3.9%	5.9%	5.1%	7.6%	10.4%
Wave-1						
N of patients at risk	4278	4137	4023	3744	3602	3454
N of patients with event		154	235	223	329	419
Cumulative incidence		3.6%	5.5%	5.6%	8.3%	10.6%

(B) All-cause death in patients with cardiogenic shock



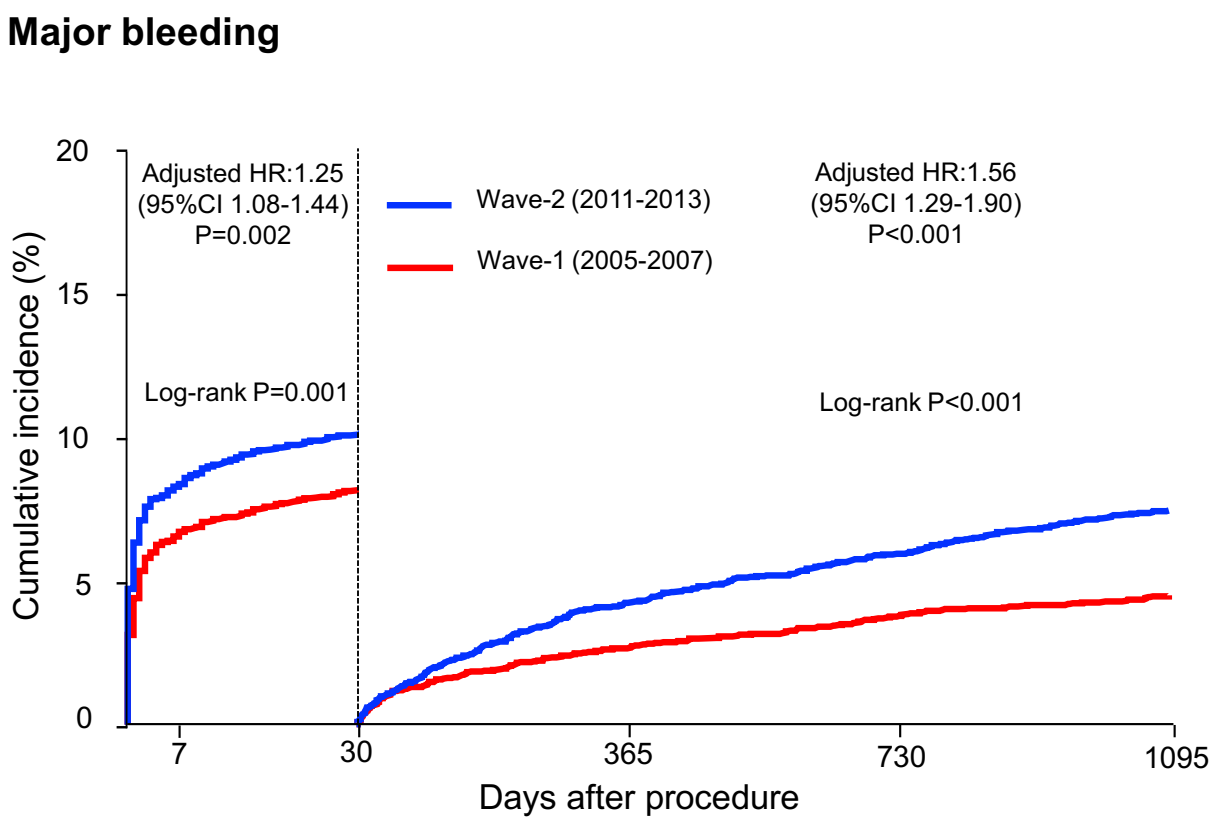
Interval	0 day	7 days	30 days	1 year	2 years	3 years
Wave-2						
N of patients at risk	757	629	556	446	407	375
N of patients with event		136	193	73	100	123
Cumulative incidence		18.0%	25.6%	13.7%	19.0%	23.6%
Wave-1						
N of patients at risk	596	506	450	370	346	317
N of patients with event		100	143	74	96	114
Cumulative incidence		16.8%	24.0%	16.6%	21.5%	25.7%

(C) All-cause death in patients without cardiogenic shock



Interval	0 day	7 days	30 days	1 year	2 years	3 years
Wave-2						
N of patients at risk	3966	3922	3839	3595	3451	3310
N of patients with event		47	87	149	228	319
Cumulative incidence		1.2%	2.2%	3.9%	6.1%	8.6%
Wave-1						
N of patients at risk	3682	3631	3573	3374	3256	3137
N of patients with event		54	92	149	233	305
Cumulative incidence		1.5%	2.5%	4.2%	6.6%	8.7%

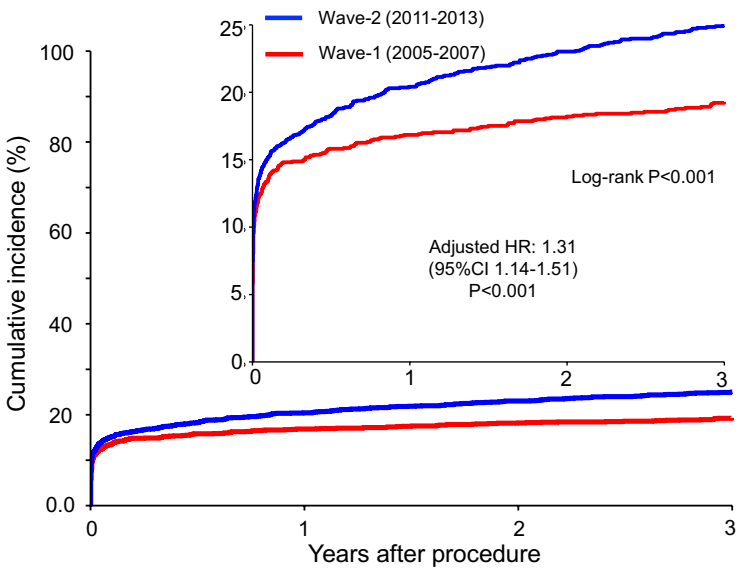
Supplemental Figure II. Landmark analysis within and beyond 30 days for major bleeding comparing between Wave-1 and Wave-2



Interval	0 day	7 days	30 days	1 year	2 years	3 years
Wave-2						
N of patients at risk	4723	4234	4067	3665	3453	3276
N of patients with event		383	457	161	229	284
Cumulative incidence		8.2%	9.8%	4.1%	5.9%	7.4%
Wave-1						
N of patients at risk	4278	3909	3773	3485	3333	3189
N of patients with event		272	331	97	136	161
Cumulative incidence		6.4%	7.8%	2.6%	3.7%	4.5%

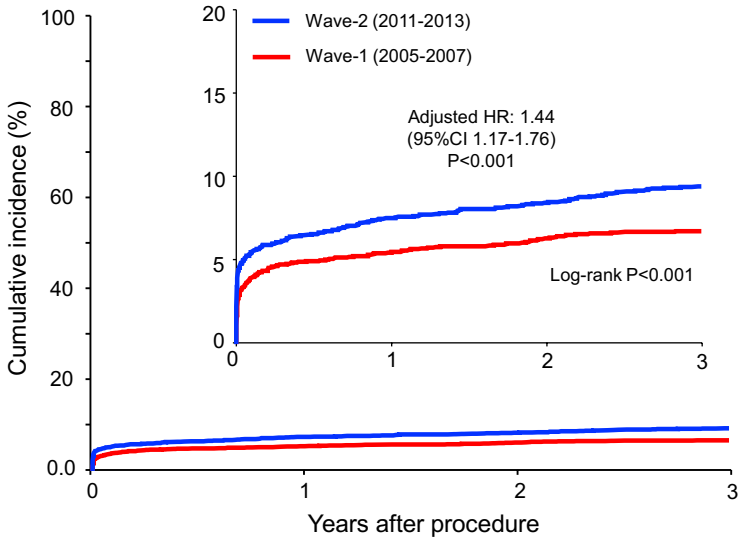
Supplemental Figure III. Kaplan-Meier curves for major bleeding comparing between Wave-1 and Wave-2 for major bleeding (A) in patients with ARC-HBR and (B) in patients without ARC-HBR

(A) Major bleeding in patients with ARC-HBR



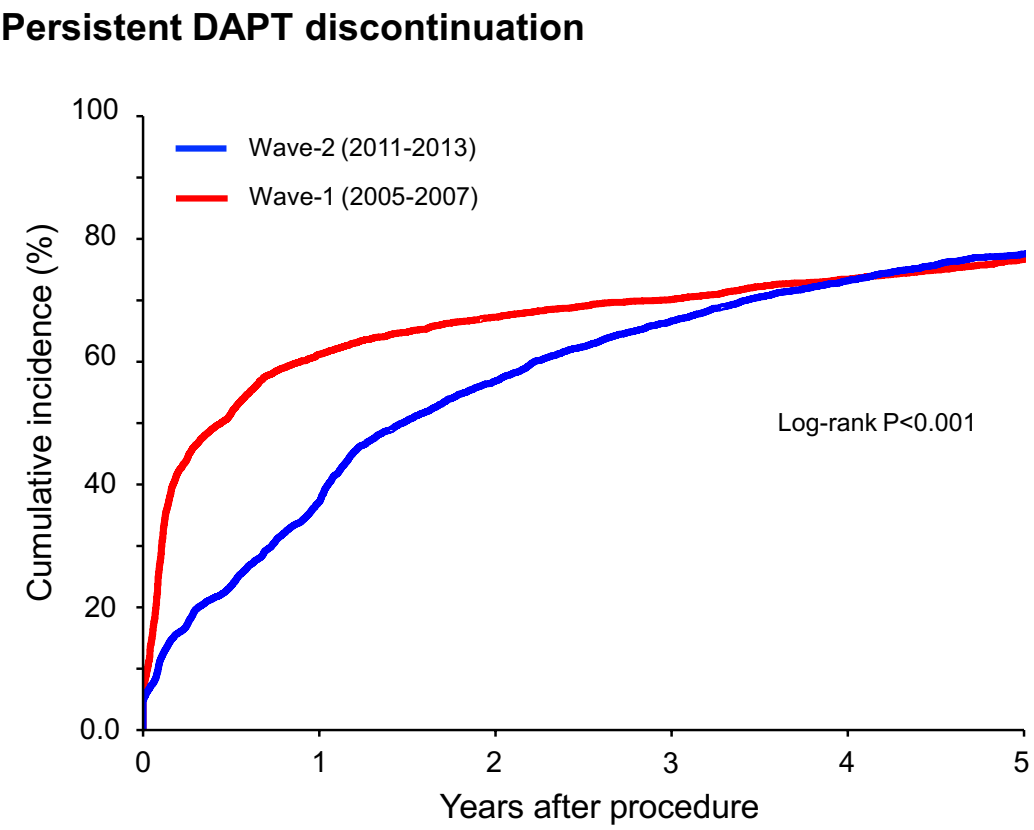
Interval	0 day	30 days	1 year	2 years	3 years
Wave-2					
N of patients at risk	2213	1736	1454	1308	1199
N of patients with event		322	430	476	508
Cumulative incidence		14.8%	20.4%	23.0%	25.0%
Wave-1					
N of patients at risk	1811	1451	1259	1170	1082
N of patients with event		237	293	313	328
Cumulative incidence		13.4%	16.8%	18.2%	19.3%

(B) Major bleeding in patients without ARC-HBR



Interval	0 day	30 days	1 year	2 years	3 years
Wave-2					
N of patients at risk	2510	2331	2211	2145	2077
N of patients with event		135	188	210	233
Cumulative incidence		5.4%	7.6%	8.5%	9.5%
Wave-1					
N of patients at risk	2467	2322	2226	2163	2107
N of patients with event		94	135	154	164
Cumulative incidence		3.8%	5.5%	6.4%	6.8%

Supplemental Figure IV. Kaplan-Meier curves for persistent DAPT discontinuation comparing between Wave-1 and Wave-2



Interval	0 day	30 days	1 year	2 years	3 years	4 years	5 years
Wave-2							
N of patients at risk	4625	3987	2603	1716	1272	971	700
Cumulative incidence		9.6%	37.2%	56.9%	66.7%	73.2%	77.5%
Wave-1							
N of patients at risk	4180	3093	1457	1186	1029	849	442
Cumulative incidence		23.7%	61.2%	67.3%	70.1%	73.4%	76.7%

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	7
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	9
Bias	9	Describe any efforts to address potential sources of bias	10
Study size	10	Explain how the study size was arrived at	7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9
		(*b*) Describe any methods used to examine subgroups and interactions	10
		(*c*) Explain how missing data were addressed	9
		(*d*) If applicable, explain how loss to follow-up was addressed	9
		(*e*) Describe any sensitivity analyses	N/A
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	7
		(c) Consider use of a flow diagram	7
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10
		(b) Indicate number of participants with missing data for each variable of interest	10
		(c) Summarise follow-up time (eg, average and total amount)	10
Outcome data	15*	Report numbers of outcome events or summary measures over time	11

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	11 11 11
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	12
Discussion			
Key results	18	Summarise key results with reference to study objectives	12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	13-14
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	17

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

BMJ Open

Changes of Demographics, Clinical Practices, and Long-term Outcomes of Patients with ST-segment-elevation Myocardial Infarction who Underwent Coronary Revascularization in the Past Two Decades: Cohort Study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-043683.R1
Article Type:	Original research
Date Submitted by the Author:	28-Jan-2021
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Primary Subject Heading:	Cardiovascular medicine
Secondary Subject Heading:	Cardiovascular medicine
Keywords:	Myocardial infarction < CARDIOLOGY, Coronary intervention < CARDIOLOGY, Coronary heart disease < CARDIOLOGY

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Title: Changes of Demographics, Clinical Practices, and Long-term Outcomes of Patients with ST-segment-elevation Myocardial Infarction who Underwent Coronary Revascularization in the Past Two Decades: Cohort Study

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Abstract

Objectives: To evaluate changes in demographics, clinical practices, and long-term clinical outcomes of STEMI patients before and beyond 2010.

Design: Multicenter retrospective cohort study

Setting: The Coronary REvascularization Demonstrating Outcome Study in Kyoto (CREDO-Kyoto) AMI Registries Wave-1 (2005-2007, 26 centers) and Wave-2 (2011-2013, 22 centers).

Participants: 9001 patients with STEMI who underwent coronary revascularization (Wave-1: 4278 patients; Wave-2: 4723 patients).

Primary and secondary outcome measures: The primary outcome was all-cause death at 3 years. The secondary outcomes were cardiovascular death, cardiac death, sudden cardiac death, non-cardiovascular death, non-cardiac death, myocardial infarction, definite stent thrombosis, stroke, hospitalization for heart failure, major bleeding, target vessel revascularization, ischemia-driven target vessel revascularization, any coronary revascularization, ischemia-driven any coronary revascularization.

Results: Patients in Wave-2 were older, more often had comorbidities, and more often presented with cardiogenic shock than those in Wave-1. Patients in Wave-2 had shorter onset-to-balloon time, door-to-balloon time, and were more frequently implanted drug-eluting stents, and received guideline-directed medication than those in Wave-1. The cumulative 3-year incidence of all-cause death was not significantly different between Wave-1 and Wave-2 (15.5% and 15.7%, P=0.77). The adjusted risk for all-cause death in Wave-2 relative to Wave-1 was not significant at 3 years (HR: 0.92, 95%CI: 0.83-1.03, P=0.14), but lower beyond 30 days (HR: 0.86, 95%CI: 0.75–0.98, P=0.03). The adjusted risks of Wave-2 relative to Wave-1 were significantly lower for definite stent thrombosis (HR 0.59, 95%CI:

0.43-0.81, P=0.001), and for any coronary revascularization (HR 0.75, 95%CI: 0.69-0.81, P<0.001), but higher for major bleeding (HR 1.34, 95%CI: 1.20-1.51, P=0.005).

Conclusions: We could not demonstrate improvement in 3-year mortality risk from Wave-1 to Wave-2, but we found reduction in mortality risk beyond 30 days. We also found risk reduction for definite stent thrombosis and any coronary revascularization, but increase in the risk for major bleeding from Wave-1 to Wave-2.

Strengths and limitations of this study

- Evaluating changes of demographics, clinical practices, and long-term clinical outcomes in STEMI patients enrolled beyond 2010 compared with those enrolled before 2010.
- Multicenter registry with large sample size enrolled consecutive patients who underwent revascularization for AMI
- Historical comparison which should result in systematic differences in selection of patients and acquisition of outcomes

Introduction

The early mortality of patients with ST-segment-elevation myocardial infarction (STEMI) has been steadily declining over the last several decades. [1-5] This trend appeared to have been driven by many factors, including demographic change, better pharmacologic management, widespread distribution of thrombolysis and/or primary percutaneous coronary intervention (PCI), shorter door-to-balloon time, and improvement in secondary prevention.[4, 6-10] Several large studies had demonstrated improvement of early mortality for patients with STEMI from 1990s to 2000s.[1-3, 10] Treatment based on the updated guidelines might have further improved the clinical outcomes of STEMI patients beyond 2000s.[11, 12] It is currently unknown whether the changes in the guidelines have contributed to change real-world clinical practice and to improve clinical outcomes; in particular, there is a scarcity of data evaluating the long-term clinical outcomes in STEMI patients enrolled beyond 2010 compared with those enrolled before 2010, when the new-generation DES was approved in Japan. [10, 13-15] Therefore, we sought to evaluate changes in demographics, clinical practices, and long-term clinical outcomes of STEMI patients using data from 2 large Japanese cohorts of patients with acute myocardial infarction (AMI) enrolled in 2005-2007 and 2011-2013.

Methods

Study Population

The Coronary REvascularization Demonstrating Outcome Study in Kyoto (CREDO-Kyoto) AMI Registries Wave-1 and Wave-2 are a series of physician-initiated, non-company sponsored, multi-center registry enrolling consecutive patients with AMI who underwent coronary revascularization, either PCI or isolated coronary artery bypass grafting (CABG), within seven days of the onset of symptoms. Wave-1 enrolled patients between January 2005 and December 2007 among 26 centers (both PCI and CABG available: 20 centers, and only PCI available: 6 centers) in Japan after the introduction of drug-eluting stents (DES) in 2004

(supplementary appendix A).[16] Wave-2 enrolled patients between January 2011 and December 2013 among 22 centers (both PCI and CABG available: 16 centers, and only PCI available: 6 centers) in Japan after approval of the new-generation DES in 2010 (supplementary appendix A). We made a historical comparison on demographics, clinical practices, and long-term clinical outcomes of STEMI patients between Wave-1 and Wave-2.

We enrolled a total of 11899 consecutive AMI patients who had undergone coronary revascularization with PCI or isolated CABG from Wave-1 (N=5429) and Wave-2 (N=6470). In the present study, we excluded patients with refusal for study participation (Wave-1: N=9, and Wave-2: N=21), and non-ST-segment elevation myocardial infarction (NSTEMI) (Wave-1: N=875, and Wave-2: N=1720). To make Wave-1 and Wave-2 comparable, we further excluded 267 patients in Wave-1 who were enrolled from 4 cardiology divisions and 5 cardiovascular surgery divisions not participating in Wave-2 and 6 patients in Wave-2 who were enrolled from 1 cardiovascular surgery division not participating in Wave-1. Finally, we retrieved 9001 patients with STEMI for the current study (Wave-1: 4278 patients and Wave-2: 4723 patients) from 22 centers (both PCI and CABG available: 15 centers, and only PCI available: 7 centers) (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

STEMI patients were defined by the electrocardiograms as patients with ≥0.1 mV of ST-segment elevation in ≥2 limb leads or ≥0.2 mV in ≥2 contiguous precordial leads, accompanied by chest pain lasting at least 30 minutes or increased serum levels of cardiac biomarkers such as troponin and/or creatine kinase MB fraction. Experienced clinical research coordinators from the independent clinical research organization (Research Institute for Production Development, Kyoto, Japan; Supplementary Appendix B) collected baseline clinical, angiographic and procedural characteristics from the hospital charts or hospital databases according to the pre-specified definitions that were identical in Wave-1 and Wave-2.

Diabetes was defined as treatment with oral hypoglycemic agents or insulin, prior clinical diagnosis of diabetes, glycated hemoglobin level ≥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.[17] 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.

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, hospitalization for heart failure, major bleeding, target vessel revascularization, ischemia-driven target vessel revascularization, any coronary

revascularization and ischemia-driven any coronary revascularization. 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) [18], and only Q-wave myocardial infarction was regarded as myocardial infarction when it occurred within 7 days of the index procedure. [19] Definite stent thrombosis was defined according to the Academic Research Consortium (ARC) definition. [20] 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. [19, 21] 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) 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.

Data Collection and Follow-up

Collection of follow-up information was mainly conducted through review of the 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 hospitalizations, and status of antiplatelet therapy.

Follow-up was censored at 3 years after the index procedure to ensure >90% of clinical follow-up rate in both Wave-1 and Wave-2. Complete 3-year follow-up information was obtained for 96.2% of patients in Wave-1, and 93.2% of patients in Wave-2, respectively. The clinical event committee adjudicated those endpoint events including death, myocardial infarction, stroke and major bleeding (Supplementary Appendix C).

Statistical Analysis

Continuous variables were expressed as mean ± standard deviation (SD) or median with interquartile range (IQR). Continuous variables were compared using the Student's t-test or Wilcoxon rank sum test based on their distributions. Categorical variables are expressed as frequencies and percentages and were compared using χ^2 test. To calculate the survival functions, follow-up periods were separately calculated for each outcome with censoring due to death or the last visit. The non-fatal outcomes other than the analyzed outcomes in the survival analyses were ignored. Cumulative incidence was estimated by the Kaplan-Meier method and differences were assessed with the log-rank test. To estimate the adjusted hazard ratio (HR) and their 95% confidence intervals (CI) of Wave-2 compared to Wave-1, we used multivariable Cox proportional hazard models by incorporating the 17 clinically relevant factors listed in Table 1. The risk-adjusting variables included demographic factors, but not included the factors related to management during the index hospitalization, because differences in management converged into the changes between Wave-1 and Wave 2. Continuous risk-adjusting variables were dichotomized according to the clinically meaningful reference values to make proportional hazard assumptions robust and to be consistent with

previous reports.[22] 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. The missing values for the risk-adjusting variables were imputed as "normal" in the binary classification, because data should have been available if abnormalities were suspected. We performed subgroup analysis for major bleeding stratified by the Academic Research Consortium High Bleeding Risk (ARC-HBR) criteria.[23] 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 STEMI 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.

All analyses were performed using R version 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

Clinical and Procedural Characteristics

Patients in Wave-2 were older and were more often living alone than those in Wave-1. Patients in Wave-2 more often had diabetes, end-stage renal failure, prior stroke, peripheral vascular disease, prior PCI, and malignancy, and less often had ejection fraction ≤40%, and current smoking than those in Wave-1 (Table 1).

Regarding presentation, Wave-2 as compared with Wave-1 included more patients who directly admitted to the participating centers without inter-facility transfer, and who presented with cardiogenic shock and/or Killip class III/IV. Regarding angiographic characteristics, the prevalence of left anterior descending artery culprit was not different between Wave-1 and Wave-2. Patients in Wave-2 more often had multivessel disease than those in Wave-1 (Table 1).

Regarding procedural characteristics, onset-to-balloon time and door-to-balloon time were significantly shorter in Wave-2 than in Wave-1. Prevalence of transradial approach increased significantly, but only slightly, from Wave-1 to Wave-2. Prevalence of DES use was much higher in Wave-2 than in Wave-1, with new-generation DES use in the vast majority of DES cases in Wave-2 (Table 1). Intra-aortic balloon pumping was more often used in Wave-2 than in in Wave-1 (Table 1).

In terms of baseline medications, patients in Wave-2 more often took thienopyridine, statins, beta-blockers, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, and proton pump inhibitors than those in Wave-1, while patients in Wave-2 less often took cilostazol than those in Wave-1. The prevalence of high-intensity statins therapy was very low in both Wave-1 and Wave-2. Regarding the kind of thienopyridine, the vast majority of patients in Wave-1 took ticlopidine, while the vast majority of patients in Wave-2 took clopidogrel (Table 1).

Clinical Outcomes

The cumulative 3-year incidence of all-cause death was not significantly different between Wave-1 and Wave-2 (15.5% versus 15.7%, log-rank P=0.77) (Table 2, and Figure 2A). The adjusted risk of Wave-2 relative to Wave-1 remained insignificant for all-cause death (HR: 0.92, 95%CI: 0.83–1.03, P=0.14) (Table 2). In the 30-day landmark analysis,

cumulative incidence of all-cause death was not significantly different between Wave-1 and Wave-2 both within 30 days (5.5% versus 5.9%, log-rank P=0.37), and beyond 30 days (10.6% versus 10.4%, log-rank P=0.74). However, after adjusting confounders, the lower mortality risk of Wave-2 relative to Wave-1 was significant beyond 30 days after index procedure (HR: 0.86, 95%CI: 0.75–0.98, P=0.03), although it was not significant within 30 days (HR: 1.04, 95%CI: 0.87–1.23, P=0.69) (Supplementary figure 1). The results of the 30-day landmark analysis were consistent in patients with and without cardiogenic shock (Supplementary figure I).

The lower crude and adjusted risks of Wave-2 relative to Wave-1 were significant for definite stent thrombosis and any coronary revascularization, while those were insignificant for cardiovascular death, myocardial infarction, and stroke (Table 2, Figure 2B, Figure 3).

Meanwhile, the cumulative 3-year incidence of major bleeding was significantly higher in Wave-2 than in Wave-1 (16.5% and 12.0%, log-rank P<0.001) (Table 2, and Figure 3). The excess adjusted risk of Wave-2 relative to Wave-1 remained significant for major bleeding (HR: 1.34, 95%CI: 1.20–1.51, P=0.005) (Table 2). In the 30-day landmark analysis, the excess crude and adjusted risks of Wave-2 relative to Wave-1 for major bleeding were significant both within 30 days and beyond 30 days (Supplementary figure II). In the subgroup analysis, the higher risk of Wave-2 relative to Wave-1 for major bleeding was consistent in patients with and without ARC-HBR (Supplementary figure III). The cumulative incidence of persistent DAPT discontinuation was significantly lower in Wave-2 than in Wave-1, indicating significantly longer DAPT duration in Wave-2 than in Wave-1 (Supplementary figure IV).

Discussion

The main findings of this study were as follows; 1) Regarding demographics, STEMI patients in Wave-2 were older, more often had comorbidities, and more often presented with serious hemodynamic conditions than those in Wave-1; 2) Regarding clinical practice, patients in Wave-2 had shorter onset-to-balloon time and door-to-balloon time, were more frequently treated with DES, and more often received guideline-directed medical therapy at baseline, and longer duration of DAPT during follow-up than those in Wave-1; 3) The 3-year adjusted risks of patients in Wave-2 relative to those in Wave-1 were not significantly different for all-cause death, myocardial infarction, and stroke, and significantly lower for definite stent thrombosis and any coronary revascularization, but significantly higher for major bleeding; 4) We witnessed a lower adjusted mortality risk of Wave-2 relative to Wave-1 beyond 30 days, but not within 30 days.

There was scarce of data evaluating demographics, clinical practices, and long-term clinical outcomes in STEMI patients enrolled beyond 2010 compared with those enrolled before 2010. [10, 24] In the present study, we could not demonstrate significant improvement in mortality risk from Wave-1 to Wave-2. The mortality rates at 30 days were still around 5-6% in both Wave-1 and Wave-2, which was in line with the previous studies. [25, 26] It was true that patients in Wave-2 were older and sicker than those in Wave-1. However, even the adjusted analysis did not suggest improvement in 30-day morality risk from Wave-1 to Wave-2. We did observe significantly shorter onset-to-balloon time and door-to-balloon time with less frequent inter-facility transfer, and more frequent use of DES in Wave-2 than in Wave-1. However, these changes in clinical practice did not lead to improvement in 30-day mortality rate. Further shortening of onset-to-balloon time, more widespread use of transradial approach, and improved management of cardiogenic shock might be important to improve 30-day mortality rate.[16, 27-34]

On the other hand, beyond 30 days after the index procedure, we found a significantly lower adjusted mortality risk of patients in Wave-2 relative to those in Wave-1. The changes in clinical practices that might have contributed to lower mortality risk in Wave-2 relative to Wave-1 included shorter onset-to-balloon time, introduction of new-generation DES, and higher prevalence of guideline-directed medications use, particularly statins. Indeed, in the present study, the rates of definite stent thrombosis and any coronary revascularization were significantly lower in Wave-2 than in Wave-1, which was in line with the previous study comparing new-generation DES with first-generation DES.[35] Moreover, we did find substantial increase in the prevalence of statins use. Nevertheless, the prescription rate of high-intensity statin therapy was extremely low in both Wave-1 and Wave-2. The efficacy of high-intensity statin therapy has been firmly established in preventing cardiovascular events in patients with coronary artery disease.[36 37] We should make every effort to promote wider penetration of high-intensity statins therapy in Japan.

Meanwhile, we have demonstrated that the cumulative 3-year incidence of major bleeding was significantly higher in Wave-2 than in Wave-1. Patients in Wave-2 were older and sicker than those in Wave-1. However, even after adjusting confounders, the excess risk of Wave-2 relative to Wave-1 remained significant for major bleeding. Moreover, the excess bleeding risk of Wave-2 relative to Wave-1 was significant regardless of ARC-HBR. Furthermore, the excess bleeding risk of Wave-2 relative to Wave-1 was significant both within 30 days and beyond 30 days. One of the reasons for the higher bleeding risk within 30 days in Wave-2 than in Wave-1 might be the different types of thienopyridine used in Wave-1 and Wave-2. In Wave-1, the vast majority of patients took ticlopidine 100 mg twice daily as the standard dose in Japan, which was much lower than the dose used globally (250 mg twice daily), while in Wave-2, the vast majority of patients took clopidogrel 75 mg once daily, which was the the dose used globally. The 30-day rate of major bleeding in Wave-2 was

substantial (Entire cohort: 9.8%, ARC-HBR: 14.8%, and non-ARC-HBR: 5.4%), warranting to explore the optimal antiplatelet regimen in STEMI patients minimizing bleeding events while maintaining efficacy in preventing thrombotic events. For the higher bleeding risk beyond 30 days in Wave-2 than in Wave-1, one of the reasons in addition to the difference in the types of thienopyridine might be the longer DAPT duration in Wave-2 than in Wave-1. Recent studies have suggested clinical benefit with very short DAPT after PCI in reducing major bleeding without increase in cardiovascular events, although STEMI patients constituded only a small proportion in the STOPDAPT-2 (ShorT and OPtimal duration of Dual AntiPlatelet Therapy after everolimus-eluting cobalt-chromium stent-2) trial, and were excluded in the TWILIGHT (Ticagrelor with Aspirin or Alone in High-Risk Patients after Coronary Intervention) trial. [38 39] We should continue to pursue the optimal DAPT duration and optimal maintenance antithrombotic regimen in STEMI patients. Our study was based on the multicenter registry with large sample size enrolled consecutive patients who underwent revascularization for AMI and the follow-up rate was high enough. Threfore, we believe our findings should be applicable in Japan or other similar settings outside Japan, but the changes in clinical pictures of STEMI should be investigated in other settings with different healthcare systems.

Limitations

There are several limitations of this study. First, historical comparison should result in systematic differences in selection of patients and acqisition of outcomes, although we were careful in using data only from those centers that participated in both Wave-1 and Wave-2, standardizing the follow-up duration at 3 years, and adopting the identical methodology for baseline and follow-up data collection, and definitions of baseline characteristics and clinical

outcome measures in Wave-1 and Wave-2. It is noteworthy that cumulative incidence of myocardial infarction was numerically higher in Wave-2 than in Wave-1, despite significantly lower incidence of definite stent thrombosis in Wave-2 than in Wave-1. We could not deny the possibility of ascertainment bias for myocardial infarction, although we adopted the identical definition of myocardial infarction in Wave-1 and Wave-2. The less widespread use of troponin for the diagnosis of myocardial infarction in Wave-1 compared with Wave-2 might have underestimated the incidence of myocardial infarction in Wave-1, as reflected by the fact that there were much larger number of patients with NSTEMI in Wave-2 than in Wave-1. Moreover, we could not deny the possibility of ascertainment bias for major bleeding, although we adopted the identical definition in Wave-1 and Wave-2. It could be possible that more major bleeding events were recorded in the hospital charts due to the growing interest in bleeding events in later time period. Second, we chose several outcomes as secondary outcomes carrying the risk of multiple comparisons. Third, we only included patients who underwent coronary revascularization, which might have lead to selection bias. However, it is quite rare for a STEMI patient not undergoing primary PCI. Finally, there might be some residual unmeasured confounders, although we made extensive risk adjustment.

Conclusions

We could not demonstrate significant improvement in 3-year mortality risk from Wave-1 to Wave-2, but we found significant reduction in mortality risk beyond 30 days. There were significant reduction in the risks for definite stent thrombosis and any coronary revascularization, but significant increase in the risk for major bleeding from Wave-1 to Wave-2.

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Contributors:

T.Kimura conceptualizated the CREDO-Kyoto AMI Registry. YT, prepared the original draft of the manuscript. H.Shiomi, TM, T.Kimura reviewed and edited the the original draft of the manuscript. YT, H.Shiomi, Y.Yoshikawa, YMN, K.Yamamoto, K.Yamaji curated data. YT, TM, T.Kimura constructed methodology for this study. YT, TM performed the statistical analysis. H.Shiomi, TM, RT, K.Yamaji, JT, Hirotoshi Watanabe, SS, MI, Teruki Takeda, MS, NE, KI, TI, Toshihiro Tamura, TO, ES, TY, H.Sakamoto, KA, YS, YF, YS, YN, KK, T.Komiya, KM, T.Kimura are investigaters of the CREDO-Kyoto AMI Registry. YT, H.Shiomi, YY, YMN, K.Yamamoto, ETK, EY, Y.Yamashita, MF, Hiroki Watanabe, HY, KN assessed and validated events within the CREDO-Kyoto AMI Registry. T.Kimura is the Guarantor.

Competing interest statement:

All authors have completed the Unified Competing Interest form and declare: Dr. Shiomi reports personal fees from Abbott Vascular, Boston Scientific, and Daiichi Sankyo. Dr. Morimoto 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. Dr. Kato reports grant from Ono Pharmaceutical, and reports personal fees from Daiichi Sankyo, AstraZeneca, Bristol-Myers Squibb, Tanabe-Mitsubishi Pharma, Ono Pharmaceutical, MSD KK, Pfizer. Dr. Ehara reports personal fees from Abbott Vascular, Medtronic, Terumo, Bayer, Boston Scientific, Daiichi-Sankyo, Edwards Lifescience, Pfizer, Bristol Myers Squibb, Takeda, Boehringer Ingelheim. Dr. Furukawa reports personal fees from Daiichi Sankyo, Bayer, Sanofi, Kowa, Pfizer, Bristol-Myers Squibb, Otsuka Parmaceutical, Sumitomo Dainippon Pharma, Takeda and Ono Pharmaceutical. Dr.

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Data sharing statement:

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

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Footnotes

Acknowledgments:

We appreciate the support and collaboration of the coinvestigators participating in the CREDO Kyoto PCI/CABG Registry Wave-1 and the CREDO Kyoto PCI/CABG Registry Wave-2. We are indebted to the outstanding effort of the clinical research coordinators for data collection.

Ethical approval:

The protocol for CREDO-Kyoto AMI Registry Wave-1 and Wave-2 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.

Figure legends

Figure 1. Study flowchart

CREDO-Kyoto=Coronary REvascularization Demonstrating Outcome study in Kyoto; AMI=acute myocardial infarction; PCI=percutaneous coronary intervention, CABG=coronary artery bypass grafting; NSTEMI=non-ST-segment elevation myocardial infarction; STEMI=ST-segment elevation myocardial infarction.

Figure 2. Kaplan-Meier curves (A) for all-cause death and (B) for cardiovascular death comparing between Wave-1 and Wave-2

Figure 3. Kaplan-Meier curves comparing between Wave-1 and Wave-2 for (A) myocardial infarction, (B) definite stent thrombosis, (C) major bleeding, and (D) any coronary revascularization

Definite stent thrombosis was based on the ARC definition, and was analyzed only for patients who underwent PCI with stent implantation (3739 patients in Wave-1 and 4241 patients in Wave-2).

Major bleeding was defined as GUSTO moderate/severe bleeding.

CREDO-Kyoto==Coronary REvascularization Demonstrating Outcome study in Kyoto; AMI=acute myocardial infarction; STEMI=ST-segment elevation myocardial infarction; NSTEMI=non-ST-segment elevation myocardial infarction; ARC=academic research consortium; GUSTO=global utilization of streptokinase and tissue plasminogen activator for occluded coronary arteries .

1 **Table 1. Baseline characteristics comparing between Wave-1 and Wave-2**

	Wave-1 (N=4278)	Wave-2 (N=4723)	P value
(A) Clinical characteristics			
Age (years)	67.6 ± 12.2	68.8 ± 12.5	<0.001
Age ≥75 years*	1336 (31%)	1694 (36%)	<0.001
Men*	3156 (74%)	3538 (75%)	0.23
Body mass index (kg/m^2)	23.6 ± 3.5	23.7 ± 3.6	0.40
Body mass index <25.0 kg/m^2*	3058 (72%)	3269 (69%)	0.02
Hypertension*	3343 (78%)	3768 (80%)	0.06
Diabetes mellitus*	1395 (33%)	1664 (35%)	0.009
on insulin therapy	205 (4.8%)	270 (5.7%)	0.06
Current smoking*	1730 (40%)	1702 (36%)	<0.001
Heart failure*	1350 (32%)	1566 (33%)	0.11
LVEF	52.5±12.9	53.8±12.4	<0.001
LVEF ≤40%	596 (18%)	595 (14%)	<0.001
Prior PCI	364 (8.5%)	523 (11%)	<0.001
Prior CABG	53 (1.2%)	59 (1.2%)	1.00
Prior myocardial infarction*	381 (8.9%)	427 (9.0%)	0.85
Prior stroke (symptomatic)*	394 (9.2%)	521 (11%)	0.005
Peripheral vascular disease*	138 (3.2%)	209 (4.4%)	0.004
eGFR<30mL/min/1.73m^2, without hemodialysis*	202 (4.7%)	288 (6.1%)	0.005
Hemodialysis*	73 (1.7%)	131 (2.8%)	0.001
eGFR <30 ml/min/1.73m^2 or hemodialysis	275 (6.4%)	419 (8.9%)	<0.001
Atrial fibrillation	418 (9.8%)	419 (8.9%)	0.15
Anemia (Hemoglobin <11.0g/dl)*	438 (10%)	531 (11%)	0.13
Thrombocytopenia (Platelet <100×10^9/L)	84 (2.0%)	102 (2.2%)	0.56
Chronic obstructive pulmonary disease	140 (3.3%)	173 (3.7%)	0.34
Liver cirrhosis	101 (2.4%)	101 (2.1%)	0.52
Malignancy*	337 (7.9%)	516 (11%)	<0.001
(B) Presentation			
Living alone	509 (13%)	780 (17%)	<0.001
Direct admission	2215 (54%)	2603 (57%)	0.02
Inter-facility transfer	1866 (44%)	1983 (42%)	0.12

Killip class III/IV	725 (17%)	915 (19%)	0.003
Cardiogenic shock	596 (14%)	757 (16%)	0.005
Cardiopulmonary arrest*	142 (3.3%)	193 (4.1%)	0.06
Maximum CK	2133 (1002-4077)	1836 (767-3663)	<0.001
(C) Angiographic characteristics			
Infarct related artery location:			
Left anterior descending coronary artery*	1979 (46%)	2191 (46%)	0.91
Left circumflex coronary artery	443 (10%)	479 (10%)	0.76
Right coronary artery	1732 (40%)	1898 (40%)	0.78
Left main coronary artery	107 (2.5%)	172 (3.6%)	0.002
Coronary artery bypass graft	19 (0.4%)	24 (0.5%)	0.77
Multivessel disease	2222 (52%)	2655 (56%)	<0.001
(D) Procedural characteristics			
Onset-to-balloon time (hours)	4.2 (2.8-7.2)	4.0 (2.7-6.6)	<0.001
Door-to-balloon time (minutes)	90 (60-132)	79 (59-110)	<0.001
Intra-aortic balloon pump use	738 (17%)	994 (21%)	<0.001
Percutaneous cardiopulmonary support use	116 (2.7%)	149 (3.2%)	0.24
PCI*	4180 (98%)	4625 (98%)	0.48
Transradial approach	498 (12%)	733 (16%)	<0.001
Transfemoral approach	3432 (82%)	3640 (79%)	<0.001
IVUS use for the culprit lesion	1260 (30%)	2653 (57%)	<0.001
Stent use for the culprit lesion	3739 (89%)	4241 (92%)	<0.001
Bare metal stent	2946 (79%)	1735 (41%)	<0.001
Drug-eluting stent	793 (21%)	2506 (59%)	<0.001
Staged PCI	932 (22%)	1018 (22%)	0.77
Stent use including staged PCI	3802 (91%)	4295 (93%)	0.001
Bare metal stent	2542 (67%)	1490 (35%)	<0.001
Drug-eluting stent	1260 (33%)	2805 (65%)	<0.001
First-generation DES use	1257 (99%)	47 (1.7%)	<0.001
Sirolimus-eluting stent (CYPHER™)	1174 (93%)	27 (57%)	
Paclitaxel-eluting stent (TAXUS™)	115 (9.1%)	21 (45%)	
New-generation DES use	-	2776 (99%)	
Everolimus-eluting stent (XIENCE™)	-	2054 (74%)	
Everolimus-eluting stent (PROMUS™)	-	1616 (58%)	

Biolimus-eluting stent (NOBORI™)	-	725 (26%)	
Zotarolimus-eluting stent (RESOLUTE™)	-	255 (9.2%)	
Zotarolimus-eluting stent (ENDEAVOR™)	-	49 (1.8%)	
CABG	98 (2.3%)	98 (2.1%)	0.48
Off pump	34 (35%)	43 (44%)	0.19
ITA use	82 (84%)	80 (82%)	0.71
(E) Baseline Medications			
Antiplatelet therapy			
Thienopyridine	3993 (93%)	4521 (96%)	<0.001
Ticlopidine	3652 (85%)	124 (2.6%)	<0.001
Clopidogrel	340 (7.9%)	4339 (92%)	<0.001
Aspirin	4209 (98%)	4636 (98%)	0.45
Cilostazol	1501 (35%)	116 (2.5%)	<0.001
Statins	2281 (53%)	3885 (82%)	<0.001
High-intensity statins therapy§	67 (1.6%)	78 (1.7%)	0.81
Beta-blockers	1747 (41%)	2555 (54%)	<0.001
ACE inhibitors/ARB	3040 (71%)	3554 (75%)	<0.001
Nitrates	1269 (30%)	832 (18%)	<0.001
Calcium channel blockers	885 (21%)	970 (21%)	0.88
Nicorandil	1198 (28%)	966 (20%)	<0.001
Warfarin	495 (12%)	591 (13%)	0.18
DOAC	-	61 (1.3%)	-
Proton pump inhibitors	1470 (34%)	3505 (74%)	<0.001
Histamine type-2 receptor blockers	1393 (33%)	553 (12%)	<0.001

1 Continuous variables were expressed as mean ± standard deviation, or median (interquartile
2 range). Categorical variables were expressed as number (percentage).
3 There were missing values for body mass index in 341 patients (Wave-1: 232 [5.4%] and
4 Wave-2: 109 [2.3%]), for LVEF in 1385 patients (Wave-1: 951 [22%] and Wave-2: 434
5 [9.2%]), for eGFR in 94 patients (Wave-1: 80 [1.9%] and Wave-2: 14 [0.3%]), for
6 hemoglobin level in 110 patients (Wave-1: 99 [2.3%] and Wave-2: 11 [0.2%]), for platelet
7 count in 47 patients (Wave-1: 29 [0.7%] and Wave-2: 18 [0.4%]), for max CK in 91 patients
8 (Wave-1: 39 [0.9%] and Wave-2: 52 [1.1%]),. The numbers of missing values for body mass

index, eGFR, hemoglobin level, and platelet count were negligibly small. The missing values for these variables were imputed as "normal" in the binary classification, because data should have been available if abnormalities were suspected. On the other hands, the missing values for LVEF were not imputed in the categorical classification, because the numbers of missing values were substantial for these variables. Onset to balloon time and door to balloon time were analyzed only for patients who underwent PCI within 24 hours of the onset of symptoms excluding nosocomial onset (onset to balloon time: 3271 patients in Wave-1 and 3372 patients in Wave-2; door to balloon time: 3228 patients in Wave-1 and 3242 patients in Wave-2).

*Risk-adjusting variables for the Cox proportional hazard models

§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.

PCI=percutaneous coronary intervention; CABG=coronary artery bypass grafting; ESRD=end-stage renal disease; eGFR=estimated glomerular filtration rate; ARC-HBR= ARC-HBR=academic research consortium-high bleeding risk; CK=creatine kinase; ITA=internal thoracic artery; ACE inhibitor/ARB=angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; DOAC=direct oral anticoagulants.

Table 2. Clinical outcomes comparing between Wave-1 and Wave-2

Endpoints	Wave-1 (N=4278) N of patients with event (Cumulative 3-year incidence)	Wave-2 (N=4723) N of patients with event (Cumulative 3-year incidence)	Crude HR (95% CI)	P value	Adjusted HR (95% CI)	P value
All-cause death	654 (15.5%)	722 (15.7%)	1.02 (0.91-1.13)	0.77	0.92 (0.83-1.03)	0.14
Cardiovascular death	475 (11.3%)	524 (11.4%)	1.01 (0.89-1.15)	0.86	0.93 (0.82-1.06)	0.26
Cardiac death	448 (10.7%)	489 (10.7%)	1.00 (0.88-1.14)	1.00	0.93 (0.81-1.05)	-
Sudden cardiac death	47 (1.2%)	45 (1.1%)	0.88 (0.59-1.33)	0.54	0.76 (0.50-1.15)	-
Non-cardiovascular death	179 (4.7%)	198 (4.8%)	1.03 (0.84-1.26)	0.80	0.90 (0.73-1.10)	0.29
Non-cardiac death	206 (5.4%)	233 (5.7%)	1.05 (0.87-1.27)	0.61	0.91 (0.75-1.10)	-
Myocardial infarction	169 (4.3%)	202 (4.8%)	1.10 (0.90-1.35)	0.36	1.04 (0.85-1.28)	0.72
Definite stent thrombosis*	81 (2.3%)	60 (1.5%)	0.65 (0.47-0.91)	0.01	0.59 (0.43-0.81)	0.001
Stroke	191 (4.9%)	243 (5.7%)	1.17 (0.97-1.42)	0.10	1.09 (0.90-1.31)	0.40
Hospitalization for heart failure	267 (7.0%)	305 (7.4%)	1.06 (0.90-1.25)	0.50	0.97 (0.82-1.14)	0.68
Major bleeding	492 (12.0%)	741 (16.5%)	1.39 (1.25-1.56)	<0.001	1.34 (1.20-1.51)	0.005
Target vessel revascularization	1017 (26.3%)	816 (19.5%)	0.70 (0.64-0.77)	<0.001	0.69 (0.63-0.76)	-
Ischemia-driven target vessel revascularization	353 (9.1%)	364 (8.7%)	0.94 (0.81-1.09)	0.43	0.92 (0.79-1.06)	-
Any coronary revascularization	1277 (33.0%)	1112 (26.6%)	0.76 (0.70-0.83)	<0.001	0.75 (0.69-0.81)	-
Ischemia-driven any coronary revascularization	472 (12.3%)	522 (12.6%)	1.02 (0.90-1.15)	0.80	0.99 (0.87-1.12)	-

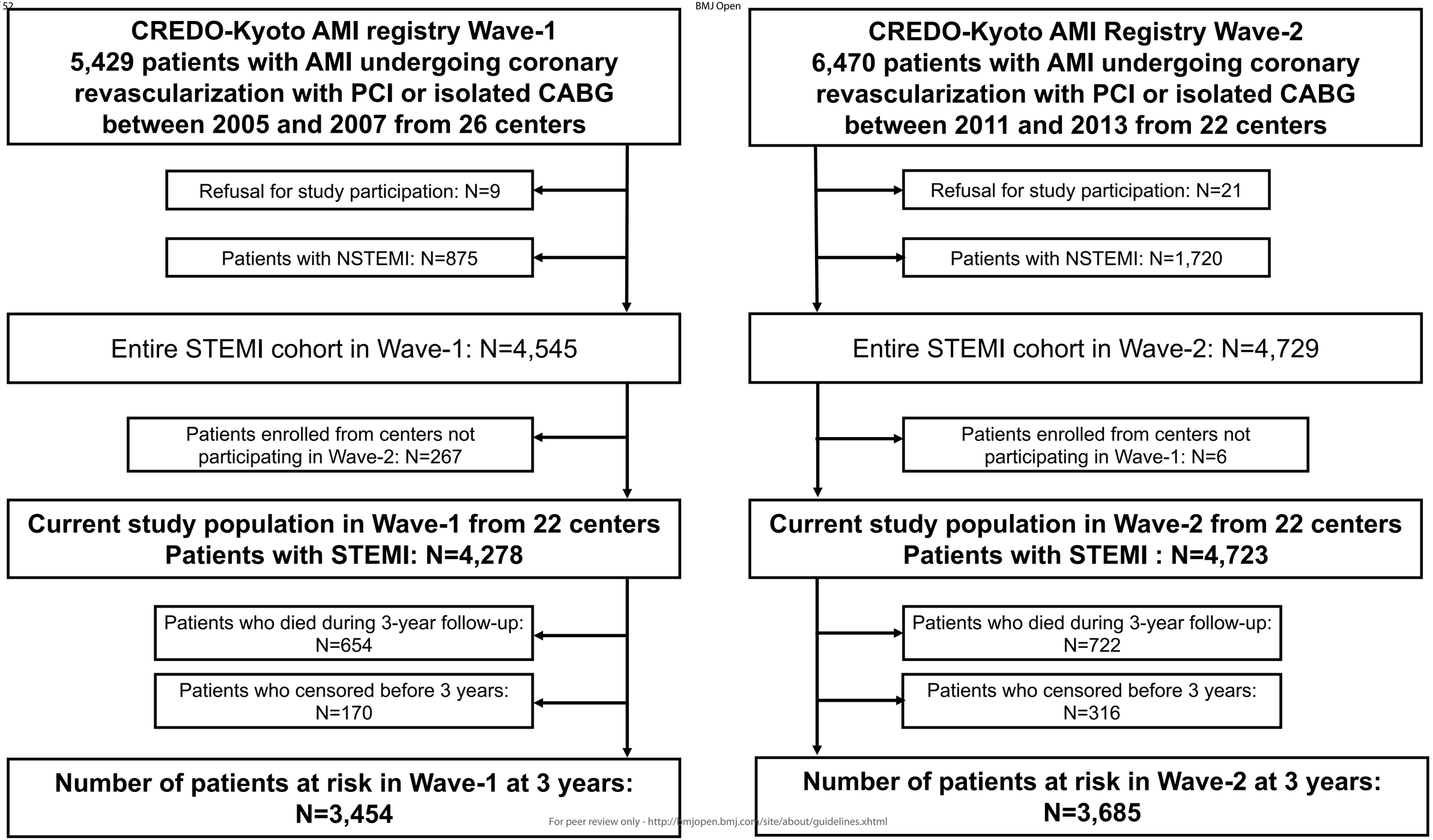
The risk of Wave-2 relative to Wave-1was expressed as HR with 95%CI. The covariates for the multivariate Cox proportional hazard models were indicated in Table 1.

Myocardial infarction was based on the ARTS definition.

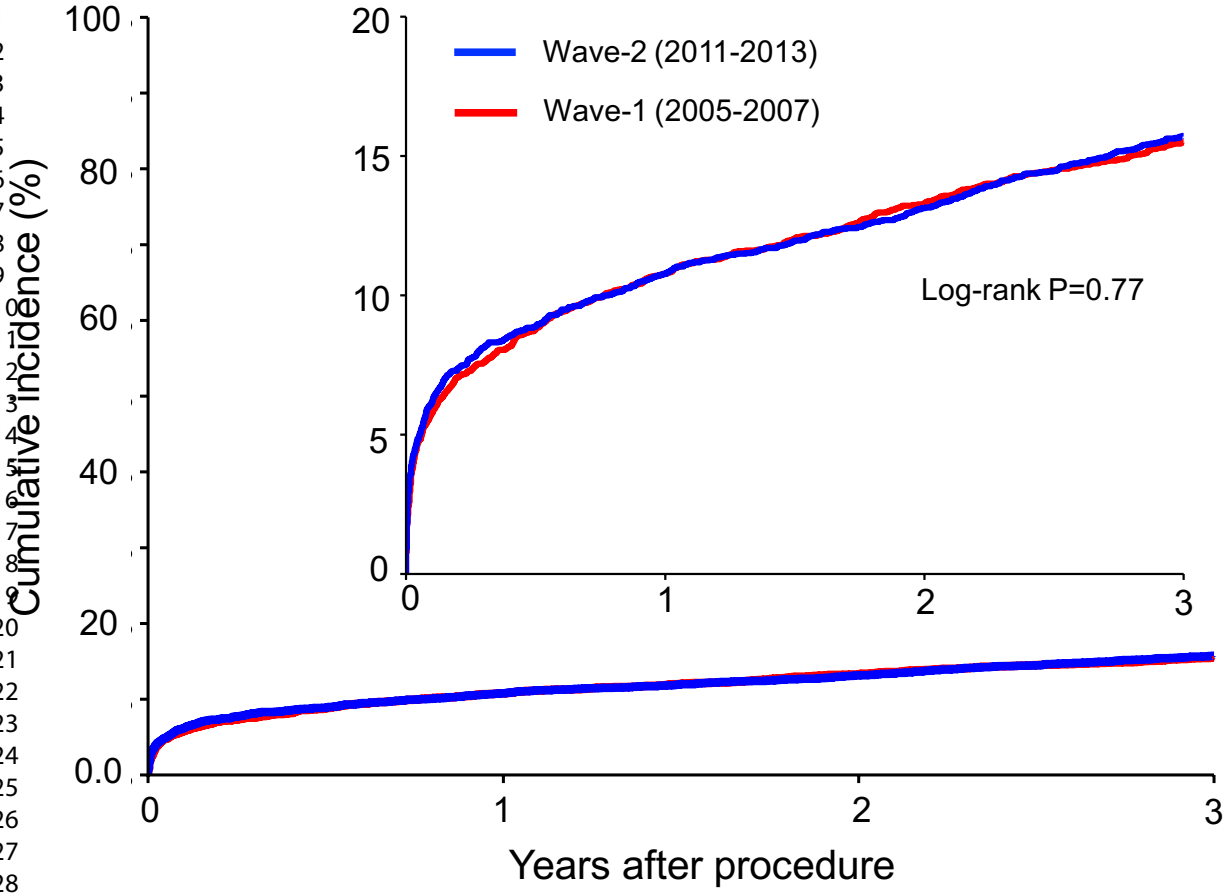
*Definite stent thrombosis was based on the ARC definition, and was analyzed only for patients who underwent PCI with stent implantation (3739 patients in Wave-1 and 4241 patients in Wave-2).

Major bleeding was defined as GUSTO moderate/severe bleeding.

HR=hazard ratio; CI=confidence interval; ARTS=arterial revascularization therapy study; ARC=academic research consortium; GUSTO=global utilization of streptokinase and tissue plasminogen activator for occluded coronary arteries.

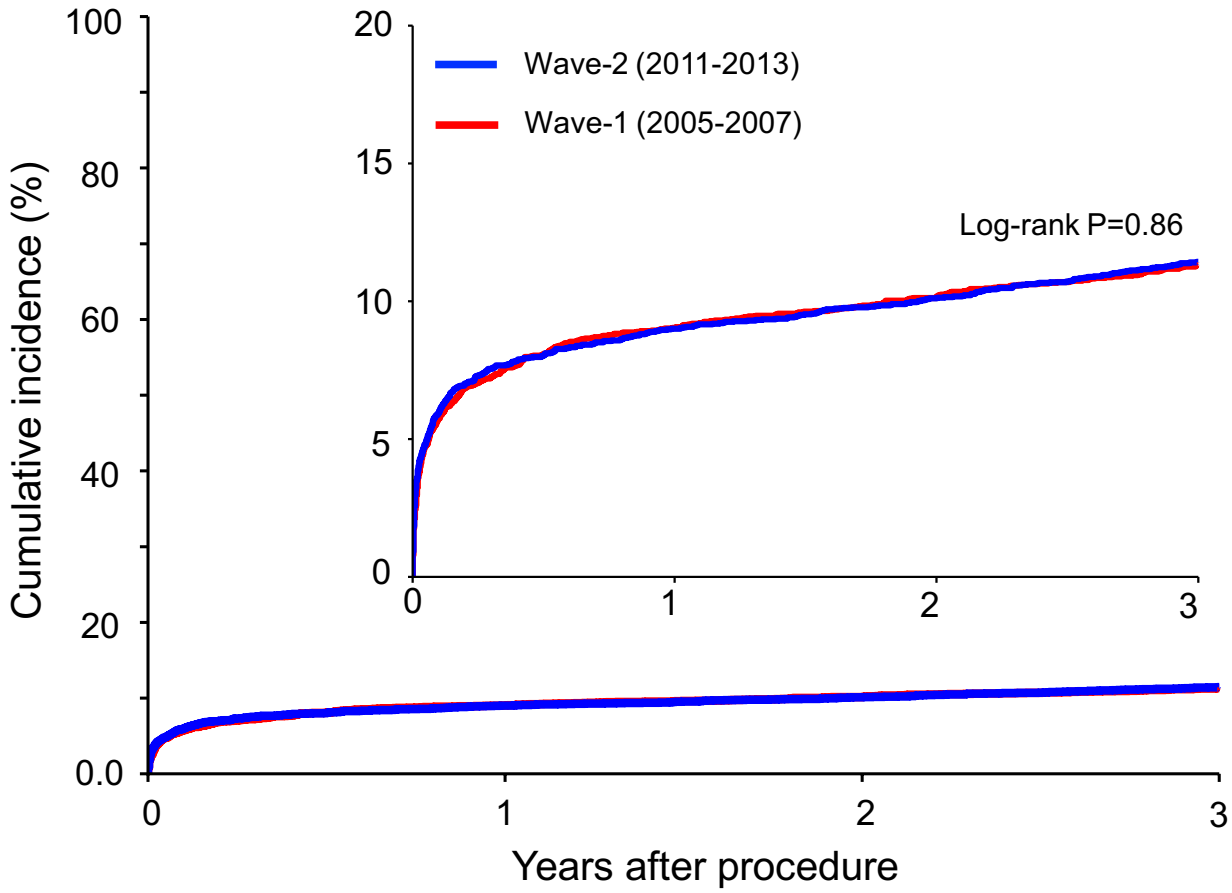


(A) All-cause death



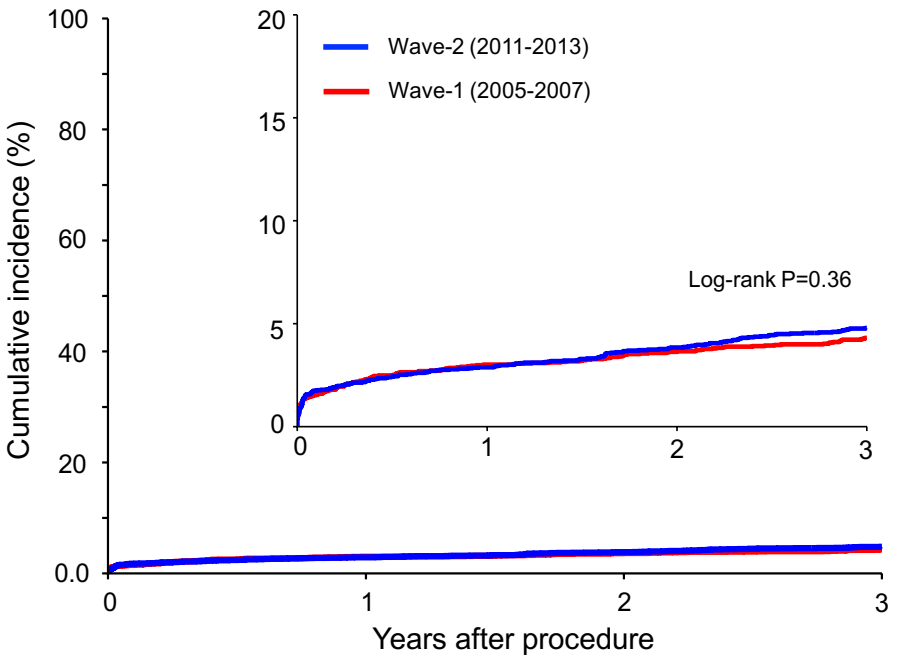
Interval	0 day	30 days	1 year	2 years	3 years
Wave-2					
N of patients at risk	4723	4395	4041	3858	3685
N of patients with event		280	502	608	722
Cumulative incidence		5.9%	10.8%	13.1%	15.7%
Wave-1					
N of patients at risk	4278	4023	3744	3602	3454
N of patients with event		235	458	564	654
Cumulative incidence		5.5%	10.8%	13.3%	15.5%

(B) Cardiovascular death



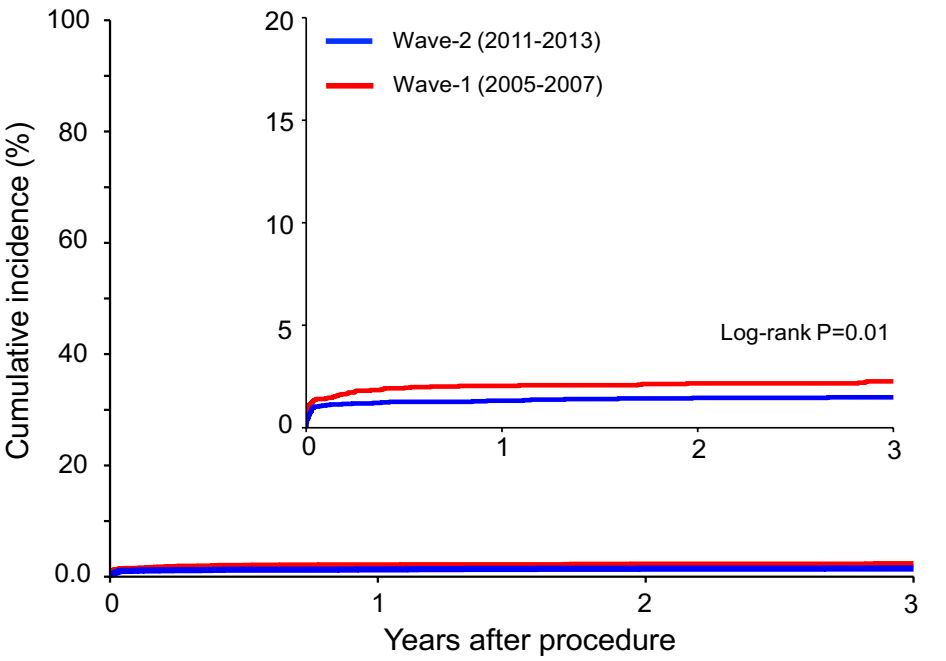
Interval	0 day	30 days	1 year	2 years	3 years
Wave-2					
N of patients at risk	4723	4395	4041	3858	3685
N of patients with event		272	420	468	524
Cumulative incidence		5.8%	9%	10.1%	11.4%
Wave-1					
N of patients at risk	4278	4023	3744	3602	3454
N of patients with event		234	384	430	475
Cumulative incidence		5.5%	9%	10.2%	11.3%

(A) Myocardial infarction



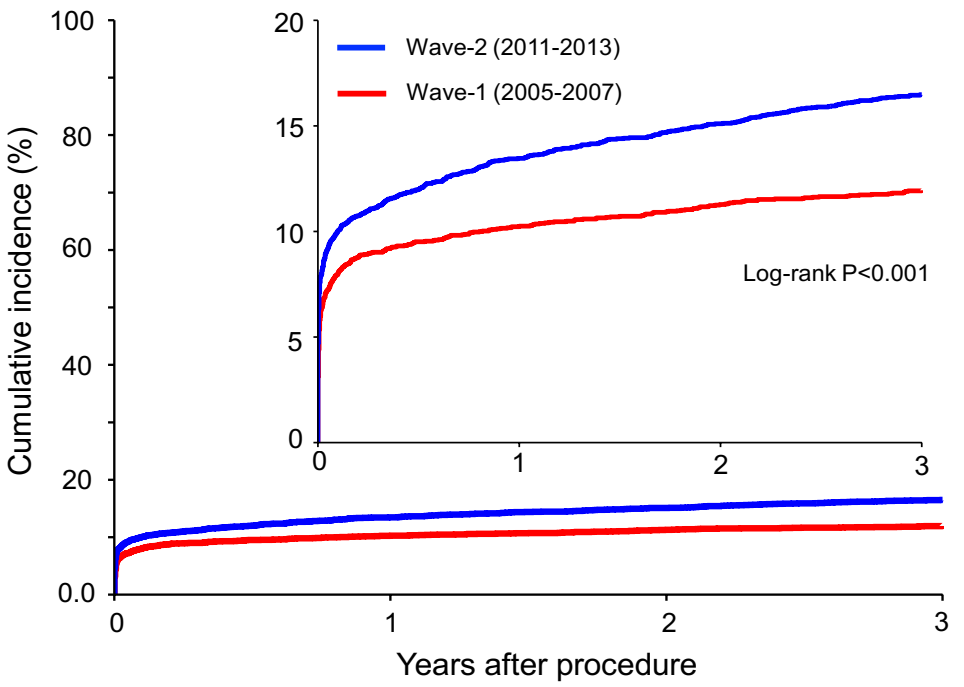
Interval	0 day	30 days	1 year	2 years	3 years
Wave-2					
N of patients at risk	4723	4332	3940	3729	3539
N of patients with event		79	128	166	202
Cumulative incidence		1.7%	2.9%	3.8%	4.8%
Wave-1					
N of patients at risk	4278	3967	3651	3499	3337
N of patients with event		64	122	146	169
Cumulative incidence		1.5%	3.0%	3.7%	4.3%

(B) Definite stent thrombosis



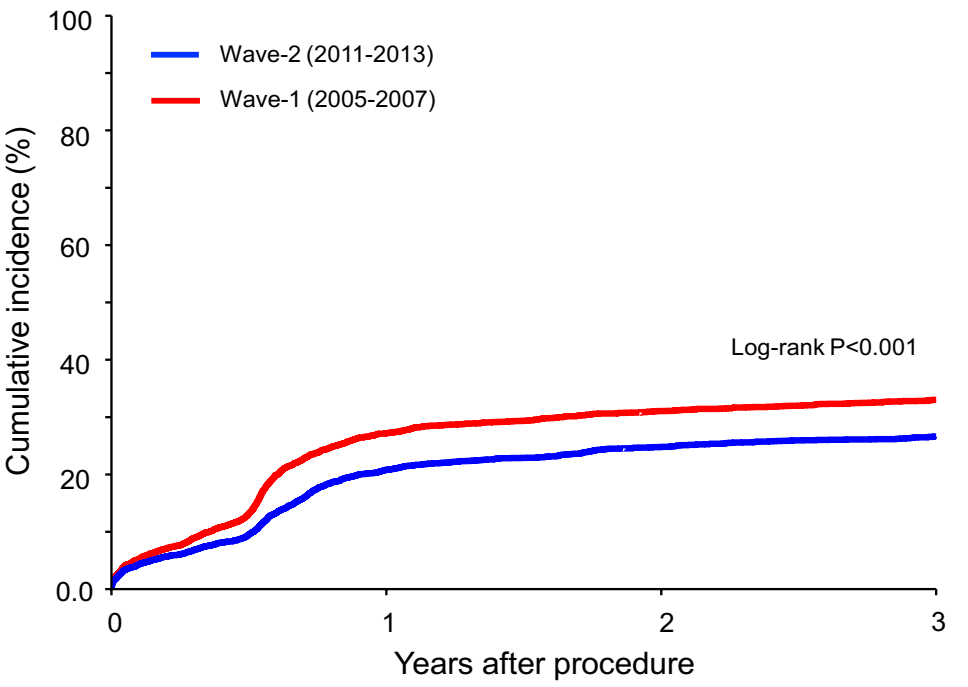
Interval	0 day	30 days	1 year	2 years	3 years
Wave-2					
N of patients at risk	4241	3945	3642	3476	3335
N of patients with event		45	54	59	60
Cumulative incidence		1.1%	1.3%	1.5%	1.5%
Wave-1					
N of patients at risk	3739	3494	3257	3137	3012
N of patients with event		52	74	78	81
Cumulative incidence		1.4%	2.0%	2.2%	2.3%

(C) Major bleeding



Interval	0 day	30 days	1 year	2 years	3 years
Wave-2					
N of patients at risk	4723	4067	3665	3453	3276
N of patients with event		457	618	686	741
Cumulative incidence		9.8%	13.5%	15.1%	16.5%
Wave-1					
N of patients at risk	4278	3773	3485	3333	3189
N of patients with event		331	428	467	492
Cumulative incidence		7.8%	10.3%	11.3%	12.0%

(D) Any coronary revascularization



Interval	0 day	30 days	1 year	2 years	3 years
Wave-2					
N of patients at risk	4723	4236	3210	2894	2690
N of patients with event		178	885	1043	1112
Cumulative incidence		3.9%	20.8%	24.8%	26.6%
Wave-1					
N of patients at risk	4278	3836	2735	2487	2298
N of patients with event		206	1066	1209	1277
Cumulative incidence		5.0%	27.2%	31.1%	33.0%

SUPPLEMENTARY MATERIAL

Table of contents

Supplemental Appendix A: List of participating centers and investigators

The CREDO-Kyoto AMI Registry Wave-1

Cardiology

Kyoto University Hospital: Takeshi Kimura, Hiroki Shiomi

Kishiwada City Hospital: Mitsuo Matsuda, Hirokazu Mitsuoka

Tenri Hospital: Yoshihisa Nakagawa

Hyogo Prefectural Amagasaki Hospital: Hisayoshi Fujiwara, Yoshiki Takatsu, Ryoji Taniguchi

Kitano Hospital: Ryuji Nohara

Koto Memorial Hospital: Tomoyuki Murakami, Teruki Takeda

Kokura Memorial Hospital: Masakiyo Nobuyoshi, Masashi Iwabuchi

Maizuru Kyosai Hospital: Ryozo Tatami

Nara Hospital, Kinki University Faculty of Medicine: Manabu Shirotani

Kobe City Medical Center General Hospital: Toru Kita, Yutaka Furukawa, Natsuhiko Ehara

Nishi-Kobe Medical Center: Hiroshi Kato, Hiroshi Eizawa

Kansai Denryoku Hospital: Katsuhisa Ishii

Osaka Red Cross Hospital: Masaru Tanaka

University of Fukui Hospital: Jong-Dae Lee, Akira Nakano

Shizuoka City Shizuoka Hospital: Akinori Takizawa

Hamamatsu Rosai Hospital: Masaaki Takahashi

Shiga University of Medical Science Hospital: Minoru Horie, Hiroyuki Takashima

Japanese Red Cross Wakayama Medical Center: Takashi Tamura

Shimabara Hospital: Mamoru Takahashi

Kagoshima University Medica and Dental Hospital: Chuwa Tei, Shuichi Hamasaki

Shizuoka General Hospital: Hirofumi Kambara, Osamu Doi, Satoshi Kaburagi

Kurashiki Central Hospital: Kazuaki Mitsudo, Kazushige Kadota

Mitsubishi Kyoto Hospital: Shinji Miki, Tetsu Mizoguchi

Kumamoto University Hospital: Hisao Ogawa, Seigo Sugiyama

Shimada Municipal Hospital: Ryuichi Hattori, Takeshi Aoyama, Makoto Araki

Juntendo University Shizuoka Hospital: Satoru Suwa

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Tenri Hospital: Kazuo Yamanaka

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Kokura Memorial Hospital: Michiya Hanyu

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The CREDO-Kyoto AMI Registry Wave-2

Cardiology

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Tenri Hospital: Toshihiro Tamura

Hyogo Prefectural Amagasaki General Medical Center: Yukihito Sato, Ryoji Taniguchi

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Koto Memorial Hospital: Tomoyuki Murakami, Teruki Takeda

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Kurashiki Central Hospital: Kazushige Kadota, Takeshi Tada

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Shimada Municipal Hospital: Takeshi Aoyama

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Kokura Memorial Hospital: Yoshiharu Soga, Akira Marui

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Supplemental Appendix B: List of clinical research coordinators

The CREDO-Kyoto AMI Registry Wave-1

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The CREDO-Kyoto AMI Registry Wave-2

Research Institute for Production Development

Sakiko Arimura, Yumika Fujino, Miya Hanazawa, Chikako Hibi, Risa Kato, Yui Kinoshita, Kumiko Kitagawa, Masayo Kitamura, Takahiro Kuwahara, Satoko Nishida, Naoko Okamoto, Yuki Sato, Saori Tezuka, Marina Tsuda, Miyuki Tsumori, Misato Yamauchi, Itsuki Yamazaki

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The CREDO-Kyoto AMI Registry Wave-1

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The CREDO-Kyoto AMI Registry Wave-2

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Supplementary figure legends

Supplemental Figure I. Landmark analysis within and beyond 30 days for all-cause death comparing between Wave-1 and Wave-2 in (A) entire study population, (B) patients with cardiogenic shock, and (C) patients without cardiogenic shock

HR=hazard ratio; CI=confidence interval.

Supplemental Figure II. Landmark analysis within and beyond 30 days for major bleeding comparing between Wave-1 and Wave-2

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 III . Kaplan-Meier curves for major bleeding comparing between Wave-1 and Wave-2 (A) in patients with ARC-HBR and (B) in patients without ARC-HBR

ARC-HBR=academic research consortium-high bleeding risk; HR=hazard ratio; CI=confidence interval.

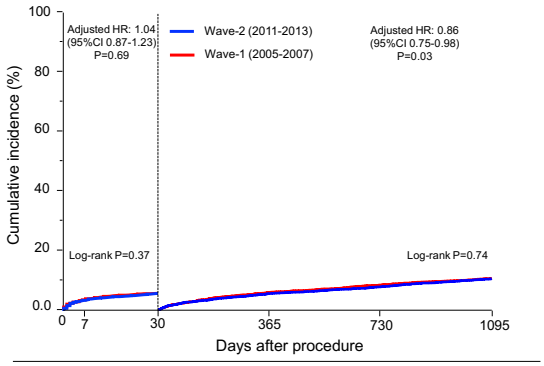
Supplemental Figure IV. Kaplan-Meier curves for persistent DAPT discontinuation comparing between Wave-1 and Wave-2

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

DAPT=dual antiplatelet therapy.

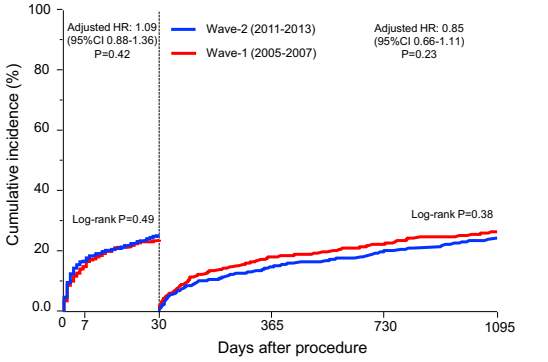
Supplemental Figure I. Landmark analysis within and beyond 30 days for all-cause death comparing between Wave-1 and Wave-2 (A) in entire study population, (B) in patients with cardiogenic shock, and (C) in patients without cardiogenic shock

(A) All-cause death in entire study population



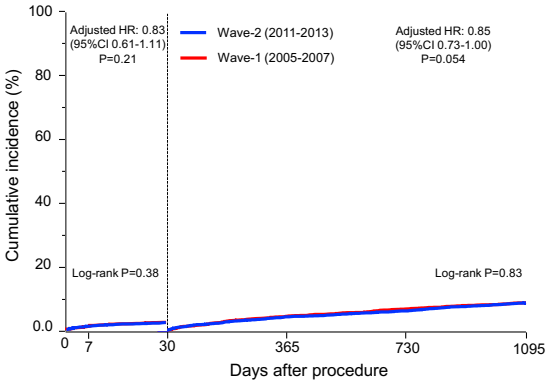
Interval	0 day	7 days	30 days	1 year	2 years	3 years
Wave-2						
N of patients at risk	4723	4551	4395	4041	3858	3685
N of patients with event		183	280	222	328	442
Cumulative incidence		3.9%	5.9%	5.1%	7.6%	10.4%
Wave-1						
N of patients at risk	4278	4137	4023	3744	3602	3454
N of patients with event		154	235	223	329	419
Cumulative incidence		3.6%	5.5%	5.6%	8.3%	10.6%

(B) All-cause death in patients with cardiogenic shock



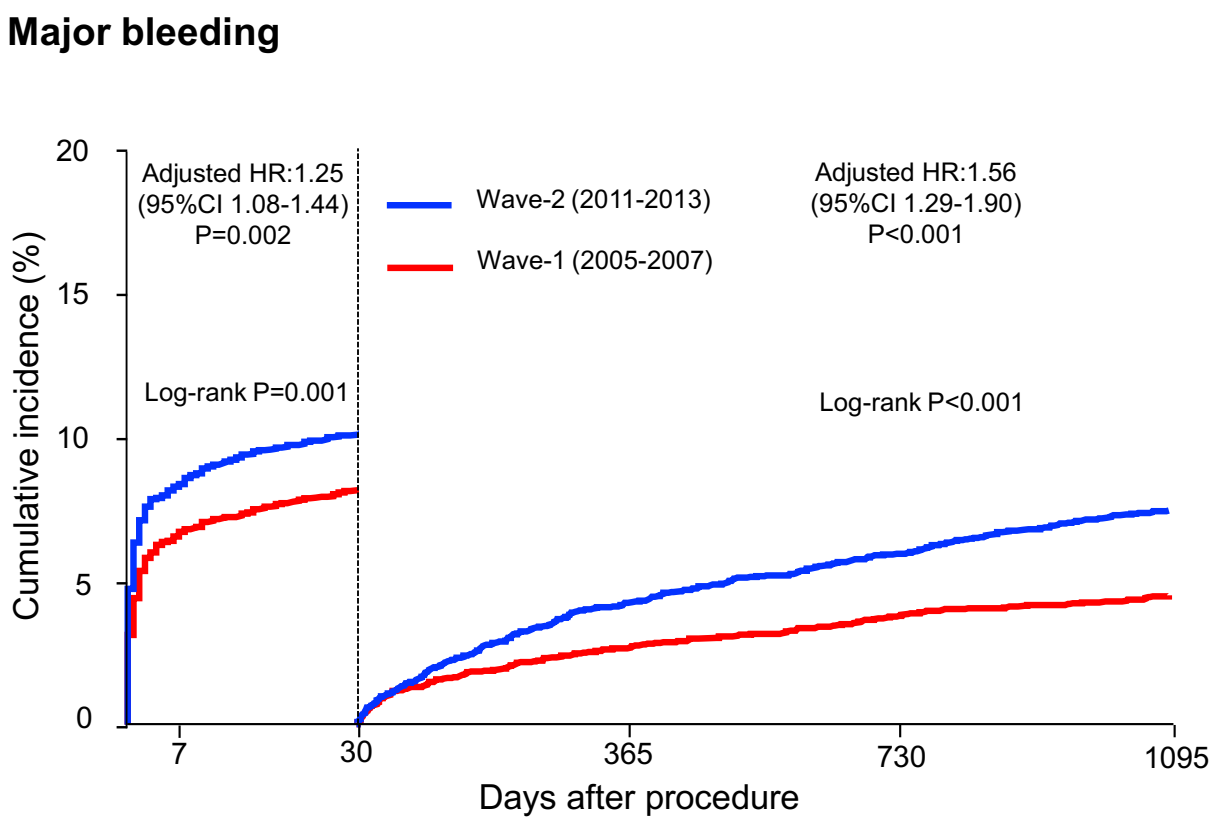
Interval	0 day	7 days	30 days	1 year	2 years	3 years
Wave-2						
N of patients at risk	757	629	556	446	407	375
N of patients with event		136	193	73	100	123
Cumulative incidence		18.0%	25.6%	13.7%	19.0%	23.6%
Wave-1						
N of patients at risk	596	506	450	370	346	317
N of patients with event		100	143	74	96	114
Cumulative incidence		16.8%	24.0%	16.6%	21.5%	25.7%

(C) All-cause death in patients without cardiogenic shock



Interval	0 day	7 days	30 days	1 year	2 years	3 years
Wave-2						
N of patients at risk	3966	3922	3839	3595	3451	3310
N of patients with event		47	87	149	228	319
Cumulative incidence		1.2%	2.2%	3.9%	6.1%	8.6%
Wave-1						
N of patients at risk	3682	3631	3573	3374	3256	3137
N of patients with event		54	92	149	233	305
Cumulative incidence		1.5%	2.5%	4.2%	6.6%	8.7%

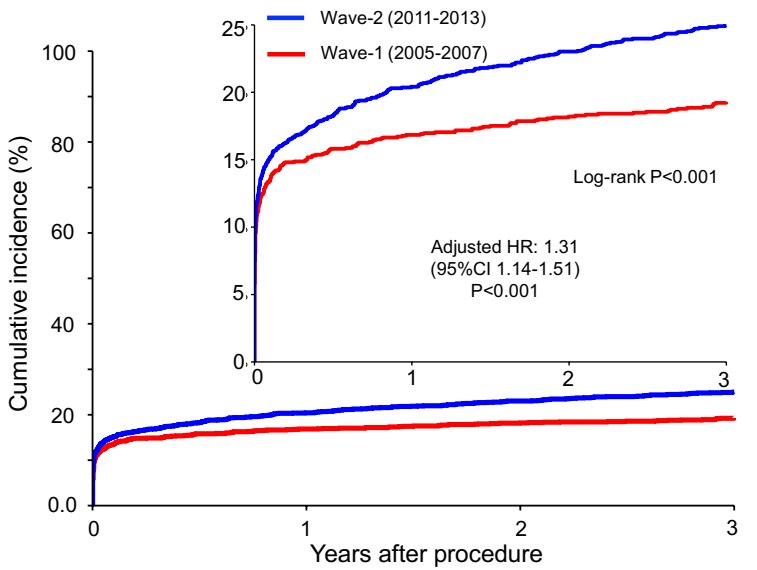
Supplemental Figure II. Landmark analysis within and beyond 30 days for major bleeding comparing between Wave-1 and Wave-2



Interval	0 day	7 days	30 days	1 year	2 years	3 years
Wave-2						
N of patients at risk	4723	4234	4067	3665	3453	3276
N of patients with event		383	457	161	229	284
Cumulative incidence		8.2%	9.8%	4.1%	5.9%	7.4%
Wave-1						
N of patients at risk	4278	3909	3773	3485	3333	3189
N of patients with event		272	331	97	136	161
Cumulative incidence		6.4%	7.8%	2.6%	3.7%	4.5%

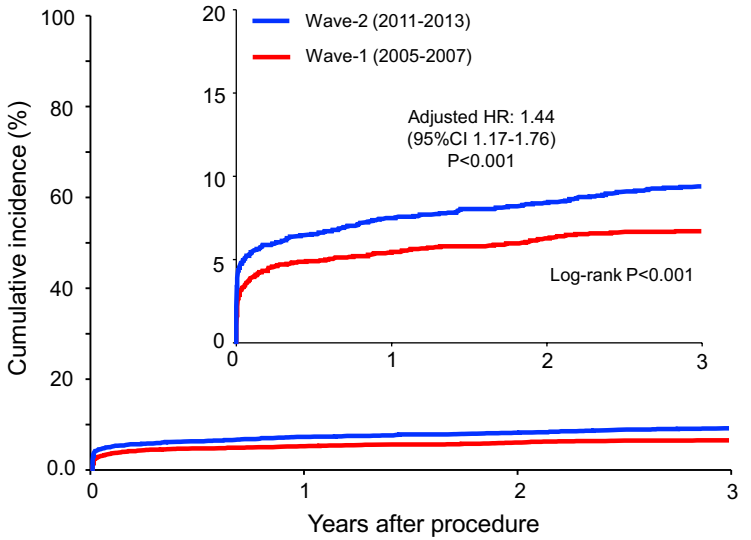
Supplemental Figure III. Kaplan-Meier curves for major bleeding comparing between Wave-1 and Wave-2 for major bleeding (A) in patients with ARC-HBR and (B) in patients without ARC-HBR

(A) Major bleeding in patients with ARC-HBR



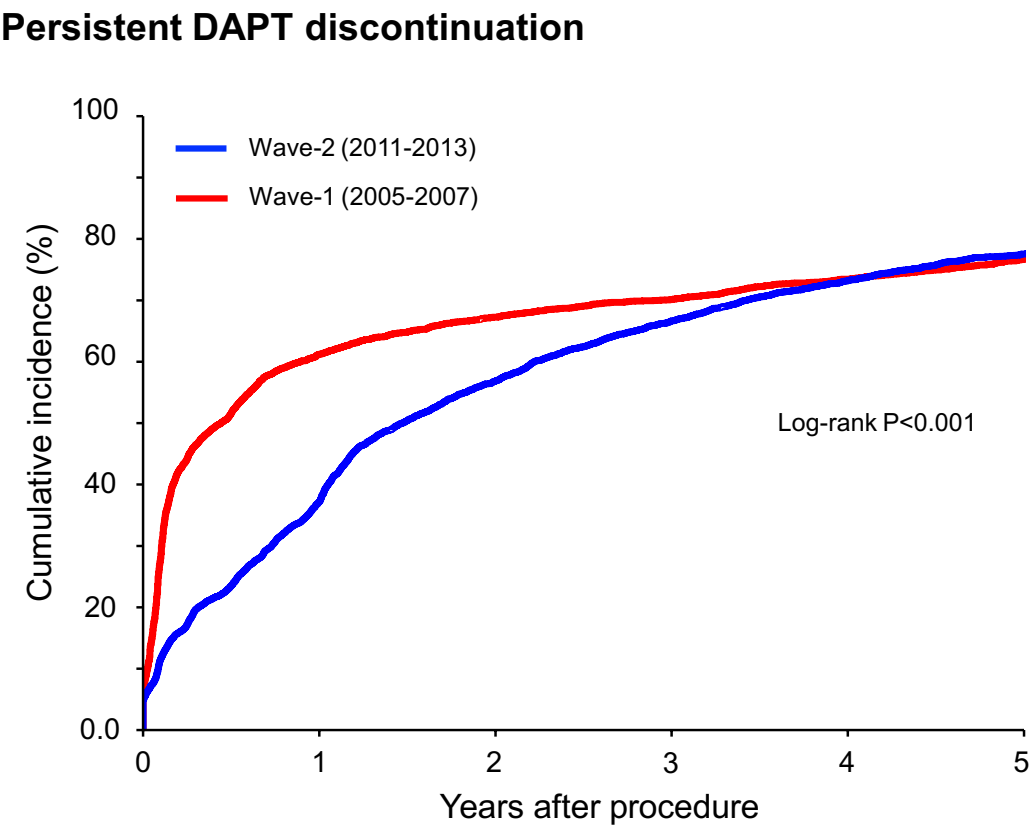
Interval	0 day	30 days	1 year	2 years	3 years
Wave-2					
N of patients at risk	2213	1736	1454	1308	1199
N of patients with event		322	430	476	508
Cumulative incidence		14.8%	20.4%	23.0%	25.0%
Wave-1					
N of patients at risk	1811	1451	1259	1170	1082
N of patients with event		237	293	313	328
Cumulative incidence		13.4%	16.8%	18.2%	19.3%

(B) Major bleeding in patients without ARC-HBR



Interval	0 day	30 days	1 year	2 years	3 years
Wave-2					
N of patients at risk	2510	2331	2211	2145	2077
N of patients with event		135	188	210	233
Cumulative incidence		5.4%	7.6%	8.5%	9.5%
Wave-1					
N of patients at risk	2467	2322	2226	2163	2107
N of patients with event		94	135	154	164
Cumulative incidence		3.8%	5.5%	6.4%	6.8%

Supplemental Figure IV. Kaplan-Meier curves for persistent DAPT discontinuation comparing between Wave-1 and Wave-2



Interval	0 day	30 days	1 year	2 years	3 years	4 years	5 years
Wave-2							
N of patients at risk	4625	3987	2603	1716	1272	971	700
Cumulative incidence		9.6%	37.2%	56.9%	66.7%	73.2%	77.5%
Wave-1							
N of patients at risk	4180	3093	1457	1186	1029	849	442
Cumulative incidence		23.7%	61.2%	67.3%	70.1%	73.4%	76.7%

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	7
Objectives	3	State specific objectives, including any prespecified hypotheses	7
Methods			
Study design	4	Present key elements of study design early in the paper	8
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	8
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	8-9
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	8-9
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	9
Bias	9	Describe any efforts to address potential sources of bias	9
Study size	10	Explain how the study size was arrived at	9
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	11
		(*b*) Describe any methods used to examine subgroups and interactions	11
		(*c*) Explain how missing data were addressed	11
		(*d*) If applicable, explain how loss to follow-up was addressed	11
		(*e*) Describe any sensitivity analyses	N/A
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	8
		(c) Consider use of a flow diagram	8
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	13
		(b) Indicate number of participants with missing data for each variable of interest	13
		(c) Summarise follow-up time (eg, average and total amount)	11
Outcome data	15*	Report numbers of outcome events or summary measures over time	14

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	14 14 14
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	14
Discussion			
Key results	18	Summarise key results with reference to study objectives	15
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	17
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	16-17
Generalisability	21	Discuss the generalisability (external validity) of the study results	17
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	24

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

BMJ Open

Changes in Demographics, Clinical Practices, and Long-term Outcomes of Patients with ST-segment-elevation Myocardial Infarction who Underwent Coronary Revascularization in the Past Two Decades: Cohort Study

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Primary Subject Heading:	Cardiovascular medicine
Secondary Subject Heading:	Cardiovascular medicine
Keywords:	Myocardial infarction < CARDIOLOGY, Coronary intervention < CARDIOLOGY, Coronary heart disease < CARDIOLOGY

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Title: Changes in Demographics, Clinical Practices, and Long-term Outcomes of Patients with ST-segment-elevation Myocardial Infarction who Underwent Coronary Revascularization in the Past Two Decades: Cohort Study

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Abstract

Objectives: To evaluate changes in demographics, clinical practices, and long-term clinical outcomes of STEMI patients before and beyond 2010.

Design: Multicenter retrospective cohort study

Setting: The Coronary REvascularization Demonstrating Outcome Study in Kyoto (CREDO-Kyoto) AMI Registries Wave-1 (2005-2007, 26 centers) and Wave-2 (2011-2013, 22 centers).

Participants: 9001 patients with STEMI who underwent coronary revascularization (Wave-1: 4278 patients; Wave-2: 4723 patients).

Primary and secondary outcome measures: The primary outcome was all-cause death at 3 years. The secondary outcomes were cardiovascular death, cardiac death, sudden cardiac death, non-cardiovascular death, non-cardiac death, myocardial infarction, definite stent thrombosis, stroke, hospitalization for heart failure, major bleeding, target vessel revascularization, ischemia-driven target vessel revascularization, any coronary revascularization, ischemia-driven any coronary revascularization.

Results: Patients in Wave-2 were older, more often had comorbidities, and more often presented with cardiogenic shock than those in Wave-1. Patients in Wave-2 had shorter onset-to-balloon time, door-to-balloon time, and were more frequently implanted drug-eluting stents, and received guideline-directed medication than those in Wave-1. The cumulative 3-year incidence of all-cause death was not significantly different between Wave-1 and Wave-2 (15.5% and 15.7%, P=0.77). The adjusted risk for all-cause death in Wave-2 relative to Wave-1 was not significant at 3 years (HR: 0.92, 95%CI: 0.83-1.03, P=0.14), but lower beyond 30 days (HR: 0.86, 95%CI: 0.75–0.98, P=0.03). The adjusted risks of Wave-2 relative to Wave-1 were significantly lower for definite stent thrombosis (HR 0.59, 95%CI:

0.43-0.81, P=0.001), and for any coronary revascularization (HR 0.75, 95%CI: 0.69-0.81, P<0.001), but higher for major bleeding (HR 1.34, 95%CI: 1.20-1.51, P=0.005).

Conclusions: We could not demonstrate improvement in 3-year mortality risk from Wave-1 to Wave-2, but we found reduction in mortality risk beyond 30 days. We also found risk reduction for definite stent thrombosis and any coronary revascularization, but increase in the risk for major bleeding from Wave-1 to Wave-2.

Strengths and limitations of this study

- Evaluating changes of demographics, clinical practices, and long-term clinical outcomes between STEMI patients enrolled beyond 2010 and those enrolled before 2010.
- Multicenter registry with large sample size enrolled consecutive patients who underwent revascularization for AMI
- Systematic differences between two cohorts in selection of patients and collection of events

Introduction

The early mortality of patients with ST-segment-elevation myocardial infarction (STEMI) has been steadily declining over the last several decades. [1-5] This trend appears to have been driven by many factors, including demographic change, better pharmacologic management, widespread distribution of thrombolysis and/or primary percutaneous coronary intervention (PCI), shorter door-to-balloon time, and improvement in secondary prevention. [4, 6-10] Several large studies had demonstrated improvement of early mortality for patients with STEMI from 1990s to 2000s. [1-3 10] Treatment based on the updated guidelines might have further improved the clinical outcomes of STEMI patients beyond 2000s. [11, 12] It is currently unknown whether the changes in the guidelines have contributed to change real-world clinical practice and to improve clinical outcomes; in particular, there is a few data evaluating the long-term clinical outcomes in STEMI patients enrolled beyond 2010 compared with those enrolled before 2010, when the new-generation DES was approved in Japan. [10, 13-15] Therefore, we sought to evaluate changes in demographics, clinical practices, and long-term clinical outcomes of STEMI patients using data from 2 large Japanese cohorts of patients with acute myocardial infarction (AMI) enrolled in 2005-2007 and 2011-2013.

Methods

Study Population

The Coronary REvascularization Demonstrating Outcome Study in Kyoto (CREDO-Kyoto) AMI Registries Wave-1 and Wave-2 are a series of physician-initiated, non-company sponsored, multi-center registry enrolling consecutive patients with AMI who underwent coronary revascularization, either PCI or isolated coronary artery bypass grafting (CABG), within seven days of the onset of symptoms. Wave-1 enrolled patients between January 2005 and December 2007 among 26 centers (both PCI and CABG available: 20 centers, and only PCI available: 6 centers) in Japan after the introduction of drug-eluting stents (DES) in 2004

(supplementary appendix A).[16] Wave-2 enrolled patients between January 2011 and December 2013 among 22 centers (both PCI and CABG available: 16 centers, and only PCI available: 6 centers) in Japan after approval of the new-generation DES in 2010 (supplementary appendix A). We made a historical comparison on demographics, clinical practices, and long-term clinical outcomes of STEMI patients between Wave-1 and Wave-2.

We enrolled a total of 11899 consecutive AMI patients who had undergone coronary revascularization with PCI or isolated CABG within 7 days from onset from Wave-1 (N=5429) and Wave-2 (N=6470). In the present study, we excluded patients with refusal for study participation (Wave-1: N=9, and Wave-2: N=21), and non-ST-segment elevation myocardial infarction (NSTEMI) (Wave-1: N=875, and Wave-2: N=1720). To make Wave-1 and Wave-2 comparable, we further excluded 267 patients in Wave-1 who were enrolled from 4 cardiology divisions and 5 cardiovascular surgery divisions not participating in Wave-2 and 6 patients in Wave-2 who were enrolled from 1 cardiovascular surgery division not participating in Wave-1. Finally, the current study population was 9001 patients with STEMI (Wave-1: 4278 patients and Wave-2: 4723 patients) from 22 centers (both PCI and CABG available: 15 centers, and only PCI available: 7 centers) (Figure 1).

The relevant institutional review boards at all participating hospitals approved the study protocols. As described previously, we waived written informed consent for both registries because of the retrospective nature of the study; however, we excluded those patients who refused participation in the study when contacted at follow-up, which is concordant with the guidelines of the Japanese Ministry of Health, Labor and Welfar [17].

Definitions and Clinical Outcome Measures

STEMI patients were defined by the electrocardiograms as patients with ≥0.1 mV of ST-segment elevation in ≥2 limb leads or ≥0.2 mV in ≥2 contiguous precordial leads,

accompanied by chest pain lasting at least 30 minutes or increased serum levels of cardiac biomarkers such as troponin and/or creatine kinase MB fraction. Baseline clinical, angiographic and procedural characteristics were collected by the experienced clinical research coordinators from the independent clinical research organization (Research Institute for Production Development, Kyoto, Japan; Supplementary Appendix B) from the hospital charts or hospital databases according to the pre-specified definitions.

Diabetes was defined as treatment with oral hypoglycemic agents or insulin, prior clinical diagnosis of diabetes, glycated hemoglobin level ≥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. [18]

The primary outcome measure of this study was all-cause death at 3 years. The secondary outcome measures were cardiovascular death, cardiac death, sudden cardiac death, non-cardiovascular death, non-cardiac death, myocardial infarction, definite stent thrombosis, stroke, hospitalization for heart failure, major bleeding, target vessel revascularization, ischemia-driven target vessel revascularization, any coronary revascularization and ischemia-driven any coronary revascularization. The definition of death was described in detail previously. [19, 20] Myocardial infarction was defined according to the definition in the Arterial Revascularization Therapy Study (ARTS) [21], and Only Q-wave myocardial infarction was regarded as myocardial infarction when it occurred within 7 days of the index procedure. [22] Definite stent thrombosis was defined according to the Academic Research Consortium

(ARC) definition. [23] 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. [22, 24] 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) 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.

Data Collection and Follow-up

The methods for collecting follow-up information were described in detail previously [17]. Follow-up started at the time of revascularization for STEMI and was censored at 3 years after the index procedure to ensure >90% of clinical follow-up rate in both Wave-1 and Wave-2. Complete 3-year follow-up information was obtained for 96.2% of patients in Wave-1, and 93.2% of patients in Wave-2, respectively. Death, myocardial infarction, stroke and major bleeding were adjudicated by the clinical event committee (Supplementary Appendix C).

Statistical Analysis

We expressed continuous variables as mean ± standard deviation (SD) or median with interquartile range (IQR) and used the Student's t-test or Wilcoxon rank sum test based

on their distributions for comparing continuous variables. We expressed categorical variables as frequencies and percentages and used χ^2 test for comparing categorical variables. To calculate the survival functions, follow-up periods were separately calculated for each outcome with censoring due to death or the last visit. The non-fatal outcomes other than the analyzed outcomes in the survival analyses were ignored. Cumulative incidence was estimated by the Kaplan-Meier method and differences were assessed with the log-rank test. To estimate the overall and cause-specific hazard ratio (HR) and their 95% confidence intervals (CI) of Wave-2 compared to Wave-1, we used multivariable Cox proportional hazard models by incorporating the 17 clinically relevant factors listed in Table 1. The variables did not include the factors related to management during the index hospitalization, because differences in management converged into the changes between Wave-1 and Wave 2. Continuous risk-adjusting variables were dichotomized according to the clinically meaningful reference values to make proportional hazard assumptions robust and to be consistent with previous reports. [17, 25] We assessed proportional hazard assumptions for the risk-adjusting variables on the plots of log (time) versus log [-log (survival)] stratified by the variable, and verified the assumptions were acceptable for all variables. The missing values for the risk-adjusting variables were imputed as "normal" in the binary classification, because data should have been available if abnormalities were suspected. We performed subgroup analysis for major bleeding stratified by the Academic Research Consortium High Bleeding Risk (ARC-HBR) criteria. [26] We conducted landmark analyses for all-cause death and major bleeding within and beyond 30 days to distinguish perioperative and non-perioperative events.

All analyses were performed using R version 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

Clinical and Procedural Characteristics

Patients in Wave-2 were older and were more often living alone than those in Wave-1. Patients in Wave-2 more often had diabetes, end-stage renal failure, prior stroke, peripheral vascular disease, prior PCI, and malignancy, and less often had ejection fraction ≤40%, and current smoking than those in Wave-1 (Table 1).

Regarding presentation, Wave-2 as compared with Wave-1 included more patients who directly admitted to the participating centers without inter-facility transfer, and who presented with cardiogenic shock and/or Killip class III/IV. Regarding angiographic characteristics, the prevalence of left anterior descending artery culprit was not different between Wave-1 and Wave-2. Patients in Wave-2 more often had multivessel disease than those in Wave-1 (Table 1).

Regarding procedural characteristics, onset-to-balloon time and door-to-balloon time were significantly shorter in Wave-2 than in Wave-1. Prevalence of transradial approach increased significantly, but only slightly, from Wave-1 to Wave-2. Prevalence of DES use was much higher in Wave-2 than in Wave-1, with new-generation DES use in the vast majority of DES cases in Wave-2 (Table 1). Intra-aortic balloon pumping was more often used in Wave-2 than in in Wave-1 (Table 1).

In terms of baseline medications, patients in Wave-2 more often took thienopyridine, statins, beta-blockers, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, and proton pump inhibitors than those in Wave-1, while patients in Wave-

2 less often took cilostazol than those in Wave-1. The prevalence of high-intensity statins therapy was very low in both Wave-1 and Wave-2. Regarding the kind of thienopyridine, the vast majority of patients in Wave-1 took ticlopidine, while the vast majority of patients in Wave-2 took clopidogrel (Table 1).

Clinical Outcomes

The cumulative 3-year incidence of all-cause death was not significantly different between Wave-1 and Wave-2 (15.5% versus 15.7%, log-rank P=0.77) (Table 2, and Figure 2A). The adjusted risk of Wave-2 relative to Wave-1 remained insignificant for all-cause death (HR: 0.92, 95%CI: 0.83–1.03, P=0.14) (Table 2). In the 30-day landmark analysis, cumulative incidence of all-cause death was not significantly different between Wave-1 and Wave-2 both within 30 days (5.5% versus 5.9%, log-rank P=0.37), and beyond 30 days (10.6% versus 10.4%, log-rank P=0.74). However, after adjusting confounders, the lower mortality risk of Wave-2 relative to Wave-1 was significant beyond 30 days after index procedure (HR: 0.86, 95%CI: 0.75–0.98, P=0.03), although it was not significant within 30 days (HR: 1.04, 95%CI: 0.87–1.23, P=0.69) (Supplementary figure 1). The results of the 30-day landmark analysis were consistent in patients with and without cardiogenic shock (Supplementary figure I).

The lower crude and adjusted risks of Wave-2 relative to Wave-1 were significant for definite stent thrombosis and any coronary revascularization, while those were insignificant for cardiovascular death, myocardial infarction, and stroke (Table 2, Figure 2B, Figure 3).

Meanwhile, the cumulative 3-year incidence of major bleeding was significantly higher in Wave-2 than in Wave-1 (16.5% and 12.0%, log-rank P<0.001) (Table 2, and Figure 3). The excess adjusted risk of Wave-2 relative to Wave-1 remained significant for major

bleeding (HR: 1.34, 95%CI: 1.20–1.51, P=0.005) (Table 2). In the 30-day landmark analysis, the excess crude and adjusted risks of Wave-2 relative to Wave-1 for major bleeding were significant both within 30 days and beyond 30 days (Supplementary figure II). In the subgroup analysis, the higher risk of Wave-2 relative to Wave-1 for major bleeding was consistent in patients with and without ARC-HBR (Supplementary figure III). The cumulative incidence of persistent DAPT discontinuation was significantly lower in Wave-2 than in Wave-1, indicating significantly longer DAPT duration in Wave-2 than in Wave-1 (Supplementary figure IV).

Discussion

The main findings of this study were as follows; 1) Regarding demographics, STEMI patients in Wave-2 were older, more often had comorbidities, and more often presented with serious hemodynamic conditions than those in Wave-1; 2) Regarding clinical practice, patients in Wave-2 had shorter onset-to-balloon time and door-to-balloon time, were more frequently treated with DES, and more often received guideline-directed medical therapy at baseline, and longer duration of DAPT during follow-up than those in Wave-1; 3) The 3-year adjusted risks of patients in Wave-2 relative to those in Wave-1 were not significantly different for all-cause death, myocardial infarction, and stroke, and significantly lower for definite stent thrombosis and any coronary revascularization, but significantly higher for major bleeding; 4) We witnessed a lower adjusted mortality risk of Wave-2 relative to Wave-1 beyond 30 days, but not within 30 days.

There was scarce of data evaluating demographics, clinical practices, and long-term clinical outcomes in STEMI patients enrolled beyond 2010 compared with those enrolled before 2010. [10, 27] In the present study, we could not demonstrate significant improvement in mortality risk from Wave-1 to Wave-2. The mortality rates at 30 days were still around 5-6%

in both Wave-1 and Wave-2, which was in line with the previous studies. [28, 29] It was true that patients in Wave-2 were older and sicker than those in Wave-1. However, even the adjusted analysis did not suggest improvement in 30-day morality risk from Wave-1 to Wave-2. We did observe significantly shorter onset-to-balloon time and door-to-balloon time with less frequent inter-facility transfer, and more frequent use of DES in Wave-2 than in Wave-1. However, these changes in clinical practice did not lead to improvement in 30-day mortality rate. Further shortening of onset-to-balloon time, more widespread use of transradial approach, and improved management of cardiogenic shock might be important to improve 30-day mortality rate. [16, 30-37]

On the other hand, beyond 30 days after the index procedure, we found a significantly lower adjusted mortality risk of patients in Wave-2 relative to those in Wave-1. The changes in clinical practices that might have contributed to lower mortality risk in Wave-2 relative to Wave-1 included shorter onset-to-balloon time, introduction of new-generation DES, and higher prevalence of guideline-directed medications use, particularly statins. Indeed, in the present study, the rates of definite stent thrombosis and any coronary revascularization were significantly lower in Wave-2 than in Wave-1, which was in line with the previous study comparing new-generation DES with first-generation DES. [38] Moreover, we did find substantial increase in the prevalence of statins use. Nevertheless, the prescription rate of high-intensity statin therapy was extremely low in both Wave-1 and Wave-2. The efficacy of high-intensity statin therapy has been firmly established in preventing cardiovascular events in patients with coronary artery disease.[39, 40] We should make every effort to promote wider penetration of high-intensity statins therapy in Japan.

Meanwhile, we have demonstrated that the cumulative 3-year incidence of major bleeding was significantly higher in Wave-2 than in Wave-1. Patients in Wave-2 were older and sicker than those in Wave-1. However, even after adjusting confounders, the excess risk

of Wave-2 relative to Wave-1 remained significant for major bleeding. Moreover, the excess bleeding risk of Wave-2 relative to Wave-1 was significant regardless of ARC-HBR. Furthermore, the excess bleeding risk of Wave-2 relative to Wave-1 was significant both within 30 days and beyond 30 days. One of the reasons for the higher bleeding risk within 30 days in Wave-2 than in Wave-1 might be the different types of thienopyridine used in Wave-1 and Wave-2. In Wave-1, the vast majority of patients took ticlopidine 100 mg twice daily as the standard dose in Japan, which was much lower than the dose used globally (250 mg twice daily), while in Wave-2, the vast majority of patients took clopidogrel 75 mg once daily, which was the the dose used globally. The 30-day rate of major bleeding in Wave-2 was substantial (Entire cohort: 9.8%, ARC-HBR: 14.8%, and non-ARC-HBR: 5.4%), warranting to explore the optimal antiplatelet regimen in STEMI patients minimizing bleeding events while maintaining efficacy in preventing thrombotic events. For the higher bleeding risk beyond 30 days in Wave-2 than in Wave-1, one of the reasons in addition to the difference in the types of thienopyridine might be the longer DAPT duration in Wave-2 than in Wave-1. Recent studies have suggested clinical benefit with very short DAPT after PCI in reducing major bleeding without increase in cardiovascular events, although STEMI patients constituded only a small proportion in the STOPDAPT-2 (ShorT and OPtimal duration of Dual AntiPlatelet Therapy after everolimus-eluting cobalt-chromium stent-2) trial, and were excluded in the TWILIGHT (Ticagrelor with Aspirin or Alone in High-Risk Patients after Coronary Intervention) trial. [41, 42] We should continue to pursue the optimal DAPT duration and optimal maintenance antithrombotic regimen in STEMI patients. Our study was based on the multicenter registry with large sample size enrolled consecutive patients who underwent revascularization for AMI and the follow-up rate was high enough. Threfore, we believe our findings should be applicable in Japan or other similar settings outside Japan, but the changes

in clinical pictures of STEMI should be investigated in other settings with different healthcare systems.

Limitations

There are several limitations of this study. First, historical comparison should result in differences in selection of patients and collection of events, although we were careful in using data only from those centers that participated in both Wave-1 and Wave-2, standardizing the follow-up duration at 3 years, and adopting the identical methodology for baseline and follow-up data collection, and definitions of baseline characteristics and clinical outcome measures in Wave-1 and Wave-2. We could not deny the possibility of ascertainment bias for myocardial infarction, although we adopted the identical definition of myocardial infarction in Wave-1 and Wave-2. The less widespread use of troponin for the diagnosis of myocardial infarction in Wave-1 compared with Wave-2 might have underestimated the incidence of myocardial infarction in Wave-1, as reflected by the fact that there were much larger number of patients with NSTEMI in Wave-2 than in Wave-1. Moreover, we could not deny the possibility of ascertainment bias for major bleeding, although we adopted the identical definition in Wave-1 and Wave-2. It could be possible that more major bleeding events were recorded in the hospital charts due to the growing interest in bleeding events in later time period. Second, the incidence of various end-points during 3-year follow-up is probably overestimated, because not accounting for competing risks. Third, we chose several outcomes as secondary outcomes carrying the risk of multiple comparisons. Fourth, we only included patients who underwent coronary revascularization, which might have lead to selection bias. However, it is quite rare for a STEMI patient not undergoing primary PCI. Finally, residual unmeasured confounders might exist.

Conclusions

We could not demonstrate improvement in 3-year mortality risk from Wave-1 to Wave-2, but we found significant reduction in mortality risk beyond 30 days. We also found significant risk reduction for definite stent thrombosis and any coronary revascularization, but increase in the risk for major bleeding from Wave-1 to Wave-2.

Contributors:

T.Kimura conceptualizated the CREDO-Kyoto AMI Registry. YT, prepared the original draft of the manuscript. H.Shiomi, TM, T.Kimura reviewed and edited the the original draft of the manuscript. YT, H.Shiomi, Y.Yoshikawa, YMN, K.Yamamoto, K.Yamaji curated data. YT, TM, T.Kimura constructed methodology for this study. YT, TM performed the statistical analysis. H.Shiomi, TM, RT, K.Yamaji, JT, Hirotoshi Watanabe, SS, MI, Teruki Takeda, MS, NE, KI, TI, Toshihiro Tamura, TO, ES, TY, H.Sakamoto, KA, YS, YF, YS, YN, KK, T.Komiya, KM, T.Kimura are investigaters of the CREDO-Kyoto AMI Registry. YT, H.Shiomi, YY, YMN, K.Yamamoto, ETK, EY, Y.Yamashita, MF, Hiroki Watanabe, HY, KN assessed and validated events within the CREDO-Kyoto AMI Registry. T.Kimura is the Guarantor.

Competing interest statement:

All authors have completed the Unified Competing Interest form and declare: Dr. Shiomi reports personal fees from Abbott Vascular, Boston Scientific, and Daiichi Sankyo. Dr. Morimoto 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. Dr. Kato reports grant from Ono Pharmaceutical, and reports personal fees from Daiichi Sankyo, AstraZeneca, Bristol-Myers Squibb, Tanabe-Mitsubishi Pharma, Ono Pharmaceutical, MSD KK, Pfizer. Dr. Ehara reports personal fees from Abbott Vascular, Medtronic, Terumo, Bayer, Boston Scientific, Daiichi-Sankyo, Edwards Lifescience, Pfizer, Bristol Myers Squibb, Takeda, Boehringer Ingelheim. Dr. Furukawa reports personal fees from Daiichi Sankyo, Bayer, Sanofi, Kowa, Pfizer, Bristol-Myers Squibb, Otsuka Parmaceutical, Sumitomo Dainippon Pharma, Takeda and Ono Pharmaceutical. Dr.

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Data sharing statement:

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

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Footnotes

Acknowledgments:

We appreciate the support and collaboration of the coinvestigators participating in the CREDO Kyoto PCI/CABG Registry Wave-1 and the CREDO Kyoto PCI/CABG Registry Wave-2. We are indebted to the outstanding effort of the clinical research coordinators for data collection.

Ethical approval:

The protocol for CREDO-Kyoto AMI Registry Wave-1 and Wave-2 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.

Figure legends

Figure 1. Study flowchart

CREDO-Kyoto=Coronary REvascularization Demonstrating Outcome study in Kyoto; AMI=acute myocardial infarction; PCI=percutaneous coronary intervention, CABG=coronary artery bypass grafting; NSTEMI=non-ST-segment elevation myocardial infarction; STEMI=ST-segment elevation myocardial infarction.

Figure 2. Kaplan-Meier curves (A) for all-cause death and (B) for cardiovascular death comparing between Wave-1 and Wave-2

Figure 3. Kaplan-Meier curves comparing between Wave-1 and Wave-2 for (A) myocardial infarction, (B) definite stent thrombosis, (C) major bleeding, and (D) any coronary revascularization

Definite stent thrombosis was based on the ARC definition, and was analyzed only for patients who underwent PCI with stent implantation (3739 patients in Wave-1 and 4241 patients in Wave-2).

Major bleeding was defined as GUSTO moderate/severe bleeding.

CREDO-Kyoto==Coronary REvascularization Demonstrating Outcome study in Kyoto; AMI=acute myocardial infarction; STEMI=ST-segment elevation myocardial infarction; NSTEMI=non-ST-segment elevation myocardial infarction; ARC=academic research consortium; GUSTO=global utilization of streptokinase and tissue plasminogen activator for occluded coronary arteries .

1 **Table 1. Baseline characteristics comparing between Wave-1 and Wave-2**

	Wave-1 (N=4278)	Wave-2 (N=4723)	P value
(A) Clinical characteristics			
Age (years)	67.6 ± 12.2	68.8 ± 12.5	<0.001
Age ≥75 years*	1336 (31%)	1694 (36%)	<0.001
Men*	3156 (74%)	3538 (75%)	0.23
Body mass index (kg/m^2)	23.6 ± 3.5	23.7 ± 3.6	0.40
Body mass index <25.0 kg/m^2*	3058 (72%)	3269 (69%)	0.02
Hypertension*	3343 (78%)	3768 (80%)	0.06
Diabetes mellitus*	1395 (33%)	1664 (35%)	0.009
on insulin therapy	205 (4.8%)	270 (5.7%)	0.06
Current smoking*	1730 (40%)	1702 (36%)	<0.001
Heart failure*	1350 (32%)	1566 (33%)	0.11
LVEF	52.5±12.9	53.8±12.4	<0.001
LVEF ≤40%	596 (18%)	595 (14%)	<0.001
Prior PCI	364 (8.5%)	523 (11%)	<0.001
Prior CABG	53 (1.2%)	59 (1.2%)	1.00
Prior myocardial infarction*	381 (8.9%)	427 (9.0%)	0.85
Prior stroke (symptomatic)*	394 (9.2%)	521 (11%)	0.005
Peripheral vascular disease*	138 (3.2%)	209 (4.4%)	0.004
eGFR<30mL/min/1.73m^2, without hemodialysis*	202 (4.7%)	288 (6.1%)	0.005
Hemodialysis*	73 (1.7%)	131 (2.8%)	0.001
eGFR <30 ml/min/1.73m^2 or hemodialysis	275 (6.4%)	419 (8.9%)	<0.001
Atrial fibrillation	418 (9.8%)	419 (8.9%)	0.15
Anemia (Hemoglobin <11.0g/dl)*	438 (10%)	531 (11%)	0.13
Thrombocytopenia (Platelet <100×10^9/L)	84 (2.0%)	102 (2.2%)	0.56
Chronic obstructive pulmonary disease	140 (3.3%)	173 (3.7%)	0.34
Liver cirrhosis	101 (2.4%)	101 (2.1%)	0.52
Malignancy*	337 (7.9%)	516 (11%)	<0.001
(B) Presentation			
Living alone	509 (13%)	780 (17%)	<0.001
Direct admission	2215 (54%)	2603 (57%)	0.02
Inter-facility transfer	1866 (44%)	1983 (42%)	0.12

Killip class III/IV	725 (17%)	915 (19%)	0.003
Cardiogenic shock	596 (14%)	757 (16%)	0.005
Cardiopulmonary arrest*	142 (3.3%)	193 (4.1%)	0.06
Maximum CK	2133 (1002-4077)	1836 (767-3663)	<0.001
(C) Angiographic characteristics			
Infarct related artery location:			
Left anterior descending coronary artery*	1979 (46%)	2191 (46%)	0.91
Left circumflex coronary artery	443 (10%)	479 (10%)	0.76
Right coronary artery	1732 (40%)	1898 (40%)	0.78
Left main coronary artery	107 (2.5%)	172 (3.6%)	0.002
Coronary artery bypass graft	19 (0.4%)	24 (0.5%)	0.77
Multivessel disease	2222 (52%)	2655 (56%)	<0.001
(D) Procedural characteristics			
Onset-to-balloon time (hours)	4.2 (2.8-7.2)	4.0 (2.7-6.6)	<0.001
Door-to-balloon time (minutes)	90 (60-132)	79 (59-110)	<0.001
Intra-aortic balloon pump use	738 (17%)	994 (21%)	<0.001
Percutaneous cardiopulmonary support use	116 (2.7%)	149 (3.2%)	0.24
PCI*	4180 (98%)	4625 (98%)	0.48
Transradial approach	498 (12%)	733 (16%)	<0.001
Transfemoral approach	3432 (82%)	3640 (79%)	<0.001
IVUS use for the culprit lesion	1260 (30%)	2653 (57%)	<0.001
Stent use for the culprit lesion	3739 (89%)	4241 (92%)	<0.001
Bare metal stent	2946 (79%)	1735 (41%)	<0.001
Drug-eluting stent	793 (21%)	2506 (59%)	<0.001
Staged PCI	932 (22%)	1018 (22%)	0.77
Stent use including staged PCI	3802 (91%)	4295 (93%)	0.001
Bare metal stent	2542 (67%)	1490 (35%)	<0.001
Drug-eluting stent	1260 (33%)	2805 (65%)	<0.001
First-generation DES use	1257 (99%)	47 (1.7%)	<0.001
Sirolimus-eluting stent (CYPHER™)	1174 (93%)	27 (57%)	
Paclitaxel-eluting stent (TAXUS™)	115 (9.1%)	21 (45%)	
New-generation DES use	-	2776 (99%)	
Everolimus-eluting stent (XIENCE™)	-	2054 (74%)	
Everolimus-eluting stent (PROMUS™)	-	1616 (58%)	

Biolimus-eluting stent (NOBORI™)	-	725 (26%)	
Zotarolimus-eluting stent (RESOLUTE™)	-	255 (9.2%)	
Zotarolimus-eluting stent (ENDEAVOR™)	-	49 (1.8%)	
CABG	98 (2.3%)	98 (2.1%)	0.48
Off pump	34 (35%)	43 (44%)	0.19
ITA use	82 (84%)	80 (82%)	0.71
(E) Baseline Medications			
Antiplatelet therapy			
Thienopyridine	3993 (93%)	4521 (96%)	<0.001
Ticlopidine	3652 (85%)	124 (2.6%)	<0.001
Clopidogrel	340 (7.9%)	4339 (92%)	<0.001
Aspirin	4209 (98%)	4636 (98%)	0.45
Cilostazol	1501 (35%)	116 (2.5%)	<0.001
Statins	2281 (53%)	3885 (82%)	<0.001
High-intensity statins therapy§	67 (1.6%)	78 (1.7%)	0.81
Beta-blockers	1747 (41%)	2555 (54%)	<0.001
ACE inhibitors/ARB	3040 (71%)	3554 (75%)	<0.001
Nitrates	1269 (30%)	832 (18%)	<0.001
Calcium channel blockers	885 (21%)	970 (21%)	0.88
Nicorandil	1198 (28%)	966 (20%)	<0.001
Warfarin	495 (12%)	591 (13%)	0.18
DOAC	-	61 (1.3%)	-
Proton pump inhibitors	1470 (34%)	3505 (74%)	<0.001
Histamine type-2 receptor blockers	1393 (33%)	553 (12%)	<0.001

1 Continuous variables were expressed as mean ± standard deviation, or median (interquartile
2 range). Categorical variables were expressed as number (percentage).
3 There were missing values for body mass index in 341 patients (Wave-1: 232 [5.4%] and
4 Wave-2: 109 [2.3%]), for LVEF in 1385 patients (Wave-1: 951 [22%] and Wave-2: 434
5 [9.2%]), for eGFR in 94 patients (Wave-1: 80 [1.9%] and Wave-2: 14 [0.3%]), for
6 hemoglobin level in 110 patients (Wave-1: 99 [2.3%] and Wave-2: 11 [0.2%]), for platelet
7 count in 47 patients (Wave-1: 29 [0.7%] and Wave-2: 18 [0.4%]), for max CK in 91 patients
8 (Wave-1: 39 [0.9%] and Wave-2: 52 [1.1%]),. The numbers of missing values for body mass

index, eGFR, hemoglobin level, and platelet count were negligibly small. The missing values for these variables were imputed as "normal" in the binary classification, because data should have been available if abnormalities were suspected. On the other hands, the missing values for LVEF were not imputed in the categorical classification, because the numbers of missing values were substantial for these variables. Onset to balloon time and door to balloon time were analyzed only for patients who underwent PCI within 24 hours of the onset of symptoms excluding nosocomial onset (onset to balloon time: 3271 patients in Wave-1 and 3372 patients in Wave-2; door to balloon time: 3228 patients in Wave-1 and 3242 patients in Wave-2).

*Risk-adjusting variables for the Cox proportional hazard models

§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.

PCI=percutaneous coronary intervention; CABG=coronary artery bypass grafting; ESRD=end-stage renal disease; eGFR=estimated glomerular filtration rate; ARC-HBR= ARC-HBR=academic research consortium-high bleeding risk; CK=creatine kinase; ITA=internal thoracic artery; ACE inhibitor/ARB=angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; DOAC=direct oral anticoagulants.

Table 2. Clinical outcomes comparing between Wave-1 and Wave-2

Endpoints	Wave-1 (N=4278) N of patients with event (Cumulative 3-year incidence)	Wave-2 (N=4723) N of patients with event (Cumulative 3-year incidence)	Crude HR (95% CI)	P value	Adjusted HR (95% CI)	P value
All-cause death	654 (15.5%)	722 (15.7%)	1.02 (0.91-1.13)	0.77	0.92 (0.83-1.03)	0.14
Cardiovascular death	475 (11.3%)	524 (11.4%)	1.01 (0.89-1.15)	0.86	0.93 (0.82-1.06)	0.26
Cardiac death	448 (10.7%)	489 (10.7%)	1.00 (0.88-1.14)	1.00	0.93 (0.81-1.05)	-
Sudden cardiac death	47 (1.2%)	45 (1.1%)	0.88 (0.59-1.33)	0.54	0.76 (0.50-1.15)	-
Non-cardiovascular death	179 (4.7%)	198 (4.8%)	1.03 (0.84-1.26)	0.80	0.90 (0.73-1.10)	0.29
Non-cardiac death	206 (5.4%)	233 (5.7%)	1.05 (0.87-1.27)	0.61	0.91 (0.75-1.10)	-
Myocardial infarction	169 (4.3%)	202 (4.8%)	1.10 (0.90-1.35)	0.36	1.04 (0.85-1.28)	0.72
Definite stent thrombosis*	81 (2.3%)	60 (1.5%)	0.65 (0.47-0.91)	0.01	0.59 (0.43-0.81)	0.001
Stroke	191 (4.9%)	243 (5.7%)	1.17 (0.97-1.42)	0.10	1.09 (0.90-1.31)	0.40
Hospitalization for heart failure	267 (7.0%)	305 (7.4%)	1.06 (0.90-1.25)	0.50	0.97 (0.82-1.14)	0.68
Major bleeding	492 (12.0%)	741 (16.5%)	1.39 (1.25-1.56)	<0.001	1.34 (1.20-1.51)	0.005
Target vessel revascularization	1017 (26.3%)	816 (19.5%)	0.70 (0.64-0.77)	<0.001	0.69 (0.63-0.76)	-
Ischemia-driven target vessel revascularization	353 (9.1%)	364 (8.7%)	0.94 (0.81-1.09)	0.43	0.92 (0.79-1.06)	-
Any coronary revascularization	1277 (33.0%)	1112 (26.6%)	0.76 (0.70-0.83)	<0.001	0.75 (0.69-0.81)	-
Ischemia-driven any coronary revascularization	472 (12.3%)	522 (12.6%)	1.02 (0.90-1.15)	0.80	0.99 (0.87-1.12)	-

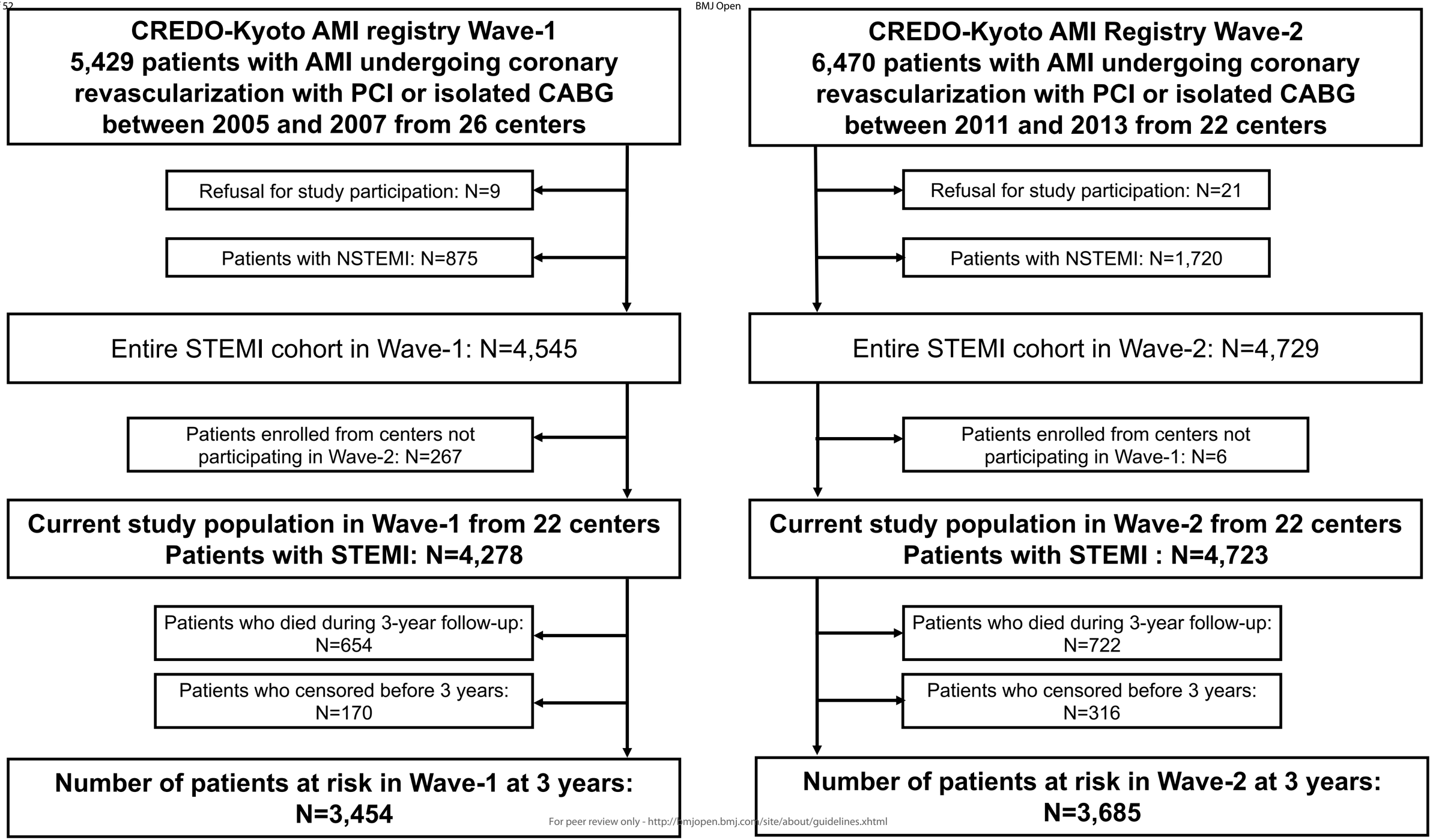
The risk of Wave-2 relative to Wave-1was expressed as HR with 95%CI. The covariates for the multivariate Cox proportional hazard models were indicated in Table 1.

Myocardial infarction was based on the ARTS definition.

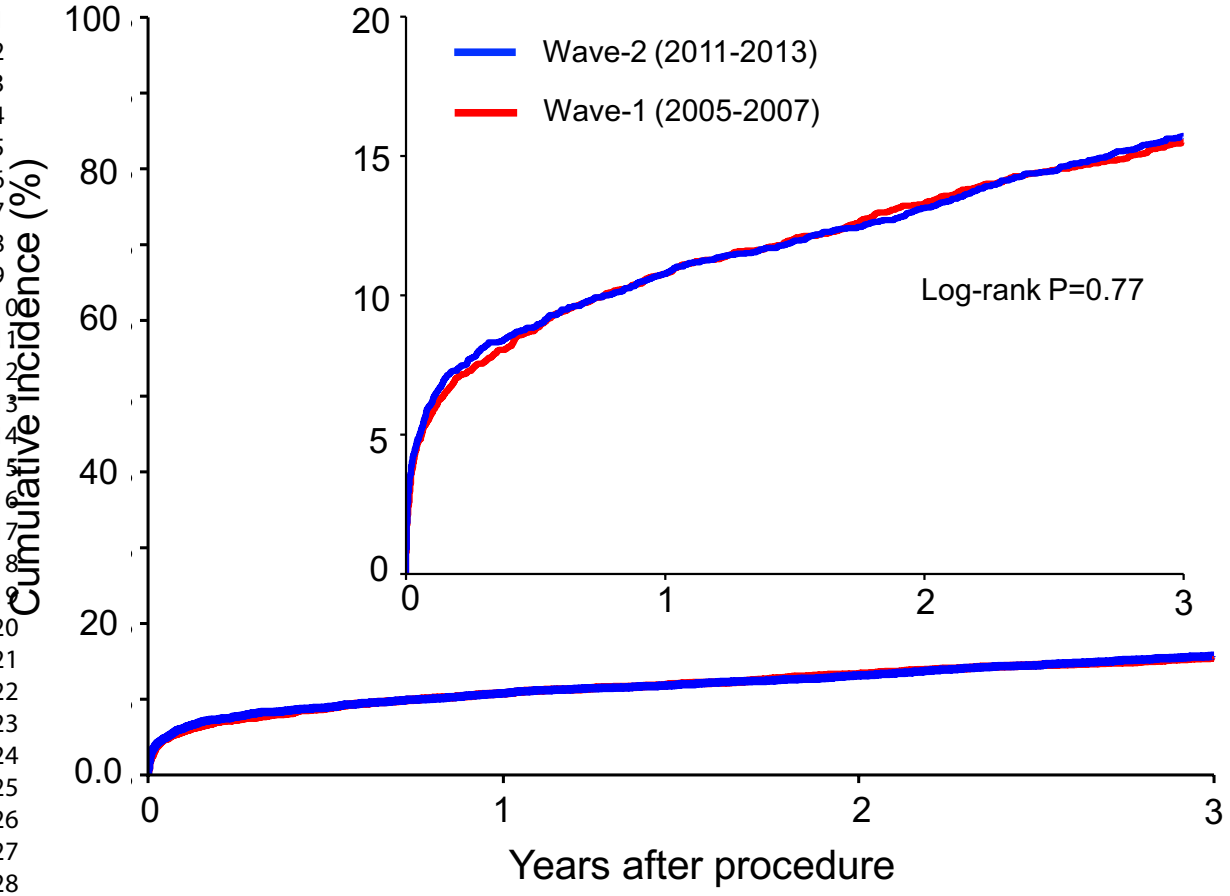
*Definite stent thrombosis was based on the ARC definition, and was analyzed only for patients who underwent PCI with stent implantation (3739 patients in Wave-1 and 4241 patients in Wave-2).

Major bleeding was defined as GUSTO moderate/severe bleeding.

HR=hazard ratio; CI=confidence interval; ARTS=arterial revascularization therapy study; ARC=academic research consortium; GUSTO=global utilization of streptokinase and tissue plasminogen activator for occluded coronary arteries.

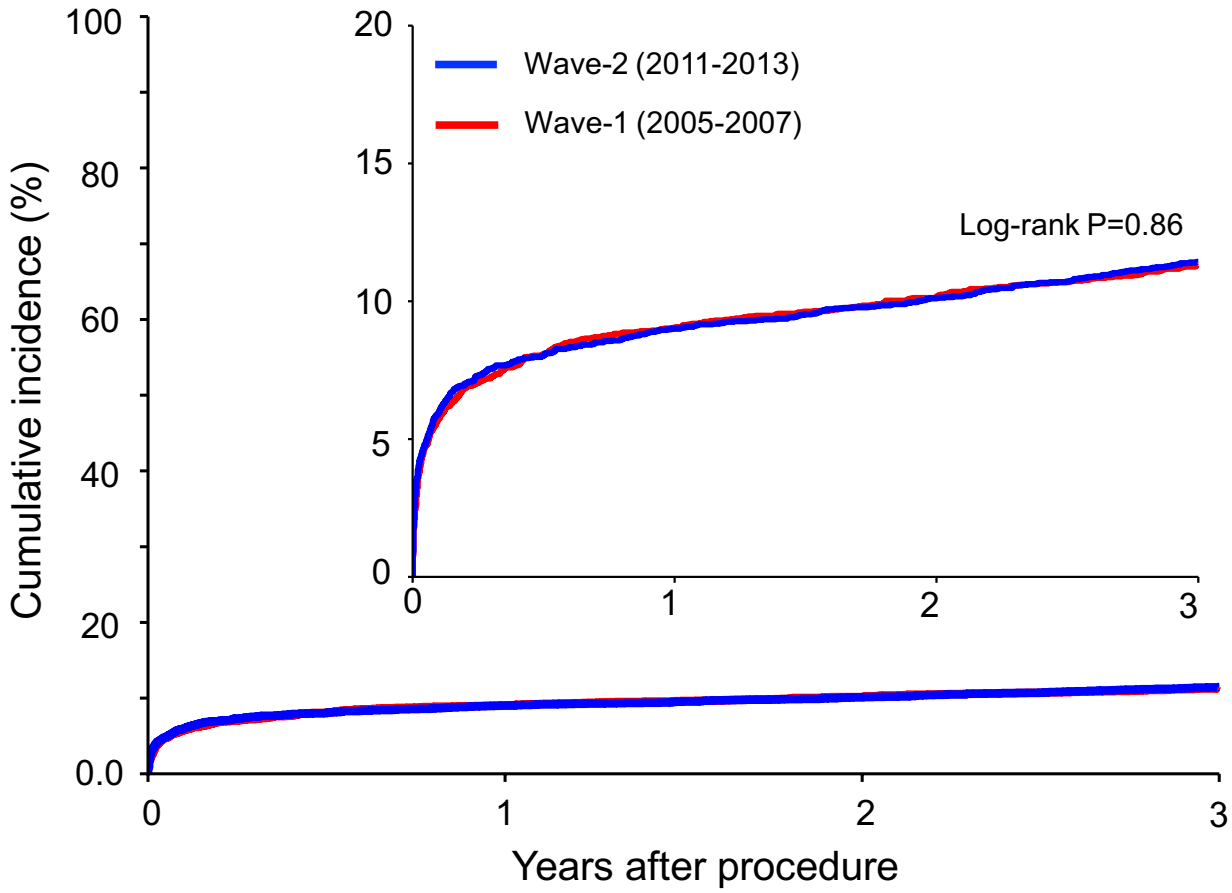


(A) All-cause death



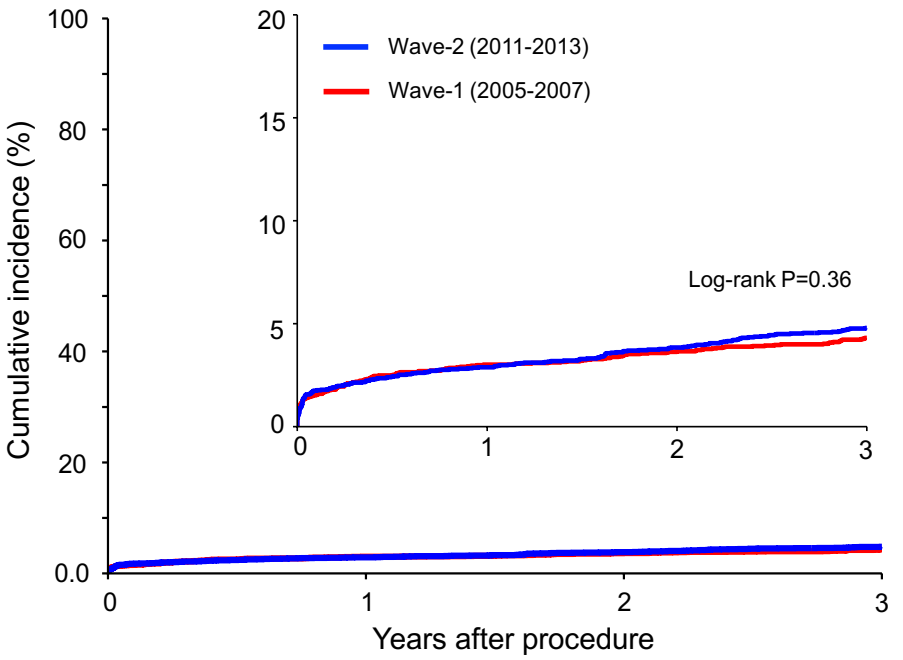
Interval	0 day	30 days	1 year	2 years	3 years
Wave-2					
N of patients at risk	4723	4395	4041	3858	3685
N of patients with event		280	502	608	722
Cumulative incidence		5.9%	10.8%	13.1%	15.7%
Wave-1					
N of patients at risk	4278	4023	3744	3602	3454
N of patients with event		235	458	564	654
Cumulative incidence		5.5%	10.8%	13.3%	15.5%

(B) Cardiovascular death



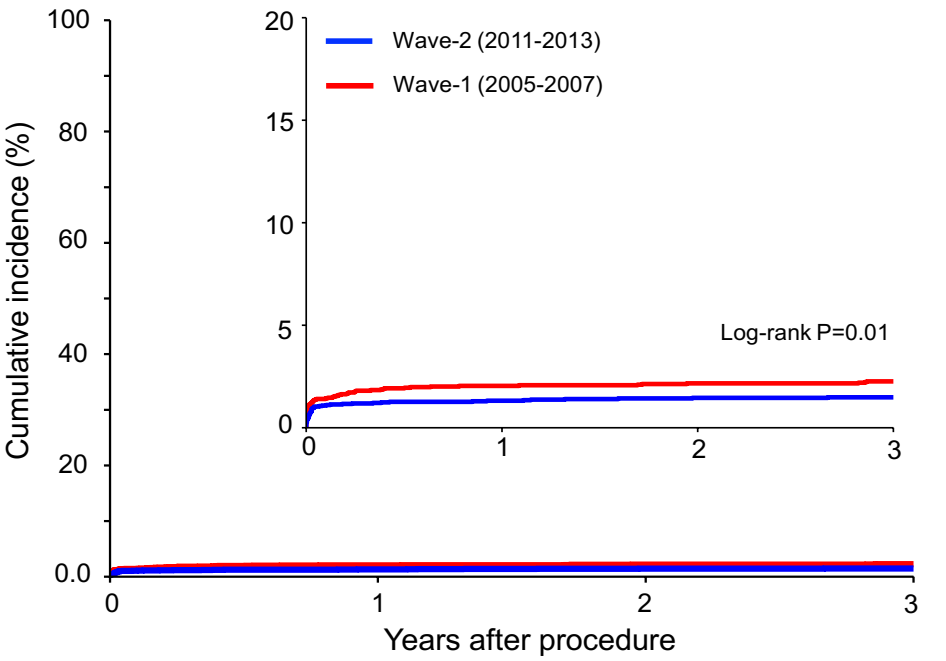
Interval	0 day	30 days	1 year	2 years	3 years
Wave-2					
N of patients at risk	4723	4395	4041	3858	3685
N of patients with event		272	420	468	524
Cumulative incidence		5.8%	9%	10.1%	11.4%
Wave-1					
N of patients at risk	4278	4023	3744	3602	3454
N of patients with event		234	384	430	475
Cumulative incidence		5.5%	9%	10.2%	11.3%

(A) Myocardial infarction



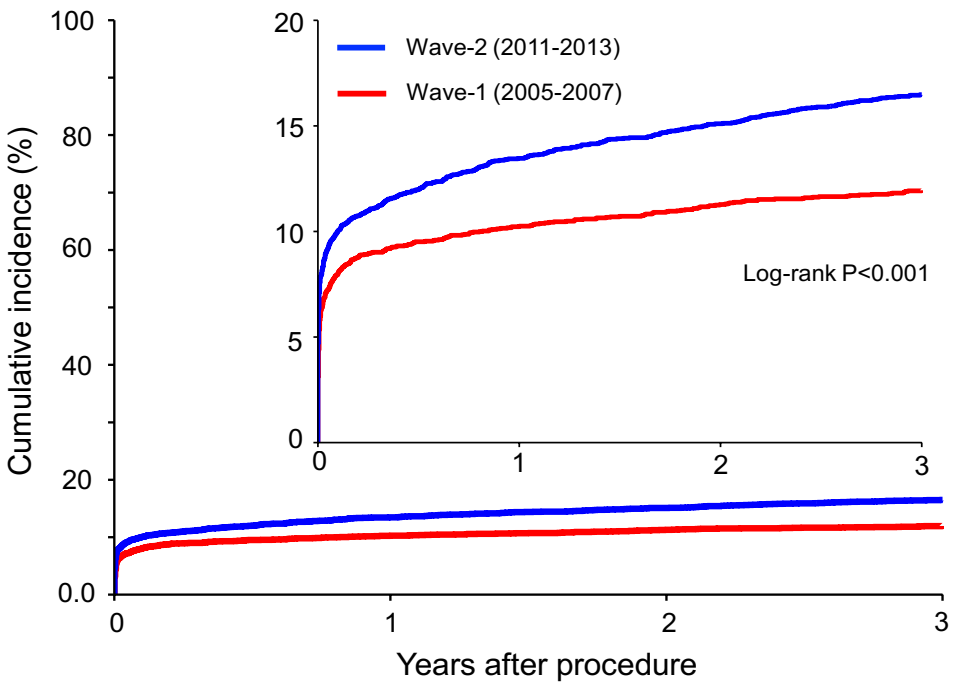
Interval	0 day	30 days	1 year	2 years	3 years
Wave-2					
N of patients at risk	4723	4332	3940	3729	3539
N of patients with event		79	128	166	202
Cumulative incidence		1.7%	2.9%	3.8%	4.8%
Wave-1					
N of patients at risk	4278	3967	3651	3499	3337
N of patients with event		64	122	146	169
Cumulative incidence		1.5%	3.0%	3.7%	4.3%

(B) Definite stent thrombosis



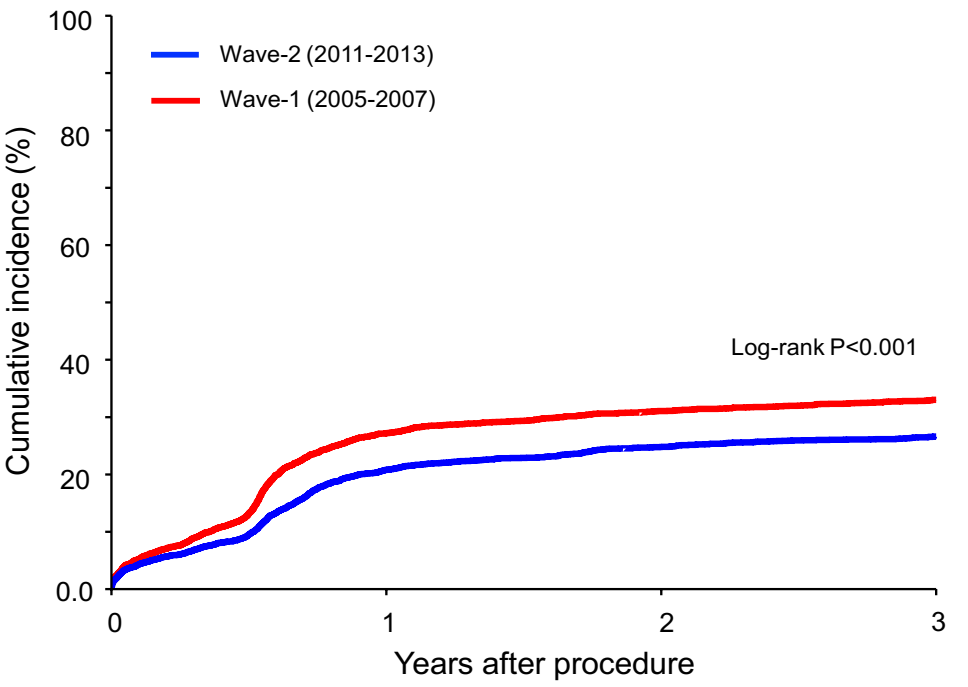
Interval	0 day	30 days	1 year	2 years	3 years
Wave-2					
N of patients at risk	4241	3945	3642	3476	3335
N of patients with event		45	54	59	60
Cumulative incidence		1.1%	1.3%	1.5%	1.5%
Wave-1					
N of patients at risk	3739	3494	3257	3137	3012
N of patients with event		52	74	78	81
Cumulative incidence		1.4%	2.0%	2.2%	2.3%

(C) Major bleeding



Interval	0 day	30 days	1 year	2 years	3 years
Wave-2					
N of patients at risk	4723	4067	3665	3453	3276
N of patients with event		457	618	686	741
Cumulative incidence		9.8%	13.5%	15.1%	16.5%
Wave-1					
N of patients at risk	4278	3773	3485	3333	3189
N of patients with event		331	428	467	492
Cumulative incidence		7.8%	10.3%	11.3%	12.0%

(D) Any coronary revascularization



Interval	0 day	30 days	1 year	2 years	3 years
Wave-2					
N of patients at risk	4723	4236	3210	2894	2690
N of patients with event		178	885	1043	1112
Cumulative incidence		3.9%	20.8%	24.8%	26.6%
Wave-1					
N of patients at risk	4278	3836	2735	2487	2298
N of patients with event		206	1066	1209	1277
Cumulative incidence		5.0%	27.2%	31.1%	33.0%

SUPPLEMENTARY MATERIAL

Table of contents

Supplemental Appendix A: List of participating centers and investigators

The CREDO-Kyoto AMI Registry Wave-1

Cardiology

Kyoto University Hospital: Takeshi Kimura, Hiroki Shiomi

Kishiwada City Hospital: Mitsuo Matsuda, Hirokazu Mitsuoka

Tenri Hospital: Yoshihisa Nakagawa

Hyogo Prefectural Amagasaki Hospital: Hisayoshi Fujiwara, Yoshiki Takatsu, Ryoji Taniguchi

Kitano Hospital: Ryuji Nohara

Koto Memorial Hospital: Tomoyuki Murakami, Teruki Takeda

Kokura Memorial Hospital: Masakiyo Nobuyoshi, Masashi Iwabuchi

Maizuru Kyosai Hospital: Ryozo Tatami

Nara Hospital, Kinki University Faculty of Medicine: Manabu Shirotani

Kobe City Medical Center General Hospital: Toru Kita, Yutaka Furukawa, Natsuhiko Ehara

Nishi-Kobe Medical Center: Hiroshi Kato, Hiroshi Eizawa

Kansai Denryoku Hospital: Katsuhisa Ishii

Osaka Red Cross Hospital: Masaru Tanaka

University of Fukui Hospital: Jong-Dae Lee, Akira Nakano

Shizuoka City Shizuoka Hospital: Akinori Takizawa

Hamamatsu Rosai Hospital: Masaaki Takahashi

Shiga University of Medical Science Hospital: Minoru Horie, Hiroyuki Takashima

Japanese Red Cross Wakayama Medical Center: Takashi Tamura

Shimabara Hospital: Mamoru Takahashi

Kagoshima University Medica and Dental Hospital: Chuwa Tei, Shuichi Hamasaki

Shizuoka General Hospital: Hirofumi Kambara, Osamu Doi, Satoshi Kaburagi

Kurashiki Central Hospital: Kazuaki Mitsudo, Kazushige Kadota

Mitsubishi Kyoto Hospital: Shinji Miki, Tetsu Mizoguchi

Kumamoto University Hospital: Hisao Ogawa, Seigo Sugiyama

Shimada Municipal Hospital: Ryuichi Hattori, Takeshi Aoyama, Makoto Araki

Juntendo University Shizuoka Hospital: Satoru Suwa

Cardiovascular Surgery

Kyoto University Hospital: Ryuzo Sakata, Tadashi Ikeda, Akira Marui

Kishiwada City Hospital: Masahiko Onoe

Tenri Hospital: Kazuo Yamanaka

Hyogo Prefectural Amagasaki Hospital: Keiichi Fujiwara, Nobuhisa Ohno

Kokura Memorial Hospital: Michiya Hanyu

Maizuru Kyosai Hospital: Tsutomu Matsushita

Nara Hospital, Kinki University Faculty of Medicine: Noboru Nishiwaki, Yuichi Yoshida

Kobe City Medical Center General Hospital: Yukikatsu Okada, Michihiro Nasu

Osaka Red Cross Hospital: Shogo Nakayama

University of Fukui Hospital: Kuniyoshi Tanaka, Takaaki Koshiji, Koichi Morioka

Shizuoka City Shizuoka Hospital: Mitsuomi Shimamoto, Fumio Yamazaki

Hamamatsu Rosai Hospital: Junichiro Nishizawa

Japanese Red Cross Wakayama Medical Center: Masaki Aota

Shimabara Hospital: Takafumi Tabata

Kagoshima University Medica and Dental Hospital: Yutaka Imoto, Hiroyuki Yamamoto

Shizuoka General Hospital: Katsuhiko Matsuda, Masafumi Nara

Kurashiki Central Hospital: Tatsuhiko Komiya

Mitsubishi Kyoto Hospital: Hiroyuki Nakajima

Kumamoto University Hospital: Michio Kawasuji, Syuji Moriyama

Juntendo University Shizuoka Hospital: Keiichi Tanbara

The CREDO-Kyoto AMI Registry Wave-2

Cardiology

Kyoto University Hospital: Takeshi Kimura, Hiroki Shiomi

Kishiwada City Hospital: Mitsuo Matsuda, Takashi Uegaito

Tenri Hospital: Toshihiro Tamura

Hyogo Prefectural Amagasaki General Medical Center: Yukihito Sato, Ryoji Taniguchi

Kitano Hospital: Moriaki Inoko

Koto Memorial Hospital: Tomoyuki Murakami, Teruki Takeda

Kokura Memorial Hospital: Kenji Ando, Takenori Domei

Kindai University Nara Hospital: Manabu Shirotani

Kobe City Medical Center General Hospital: Yutaka Furukawa, Natsuhiko Ehara

Kobe City Nishi-Kobe Medical Center: Hiroshi Eizawa

Kansai Denryoku Hospital: Katsuhisa Ishii, Eiji Tada

Osaka Red Cross Hospital: Masaru Tanaka, Tsukasa Inada

Shizuoka City Shizuoka Hospital: Tomoya Onodera, Ryuzo Nawada

Hamamatsu Rosai Hospital: Eiji Shinoda, Miho Yamada

Shiga University of Medical Science Hospital: Takashi Yamamoto, Hiroshi Sakai

Japanese Red Cross Wakayama Medical Center: Takashi Tamura, Mamoru Toyofuku

Shimabara Hospital: Mamoru Takahashi

Shizuoka General Hospital: Hiroki Sakamoto, Tomohisa Tada

Kurashiki Central Hospital: Kazushige Kadota, Takeshi Tada

Mitsubishi Kyoto Hospital: Shinji Miki, Kazuhisa Kaneda

Shimada Municipal Hospital: Takeshi Aoyama

Juntendo University Shizuoka Hospital: Satoru Suwa

Cardiovascular Surgery

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Kishiwada City Hospital: Tatsuya Ogawa

Tenri Hospital: Atsushi Iwakura

Hyogo Prefectural Amagasaki General Medical Center: Nobuhisa Ohno

Kitano Hospital: Michiya Hanyu

Kokura Memorial Hospital: Yoshiharu Soga, Akira Marui

Kindai University Nara Hospital: Nobushige Tamura

Kobe City Medical Center General Hospital: Tadaaki Koyama

Osaka Red Cross Hospital: Shogo Nakayama

Shizuoka City Shizuoka Hospital: Fumio Yamazaki, Yasuhiko Terai

Hamamatsu Rosai Hospital: Junichiro Nishizawa

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Shizuoka General Hospital: Hiroshi Tsuneyoshi

Kurashiki Central Hospital: Tatsuhiko Komiya

Mitsubishi Kyoto Hospital: Jiro Esaki

Juntendo University Shizuoka Hospital: Keiichi Tambara

Supplemental Appendix B: List of clinical research coordinators

The CREDO-Kyoto AMI Registry Wave-1

Research Institute for Production Development

Kumiko Kitagawa, Misato Yamauchi, Naoko Okamoto, Yumika Fujino, Saori Tezuka, Asuka Saeki, Miya Hanazawa, Yuki Sato, Chikako Hibi, Hitomi Sasae, Emi Takinami, Yuriko Uchida, Yuko Yamamoto, Satoko Nishida, Mai Yoshimoto, Sachiko Maeda, Izumi Miki, Saeko Minematsu

The CREDO-Kyoto AMI Registry Wave-2

Research Institute for Production Development

Sakiko Arimura, Yumika Fujino, Miya Hanazawa, Chikako Hibi, Risa Kato, Yui Kinoshita, Kumiko Kitagawa, Masayo Kitamura, Takahiro Kuwahara, Satoko Nishida, Naoko Okamoto, Yuki Sato, Saori Tezuka, Marina Tsuda, Miyuki Tsumori, Misato Yamauchi, Itsuki Yamazaki

Supplemental Appendix C: List of the clinical event committee members

The CREDO-Kyoto AMI Registry Wave-1

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 AMI Registry Wave-2

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)

Supplementary figure legends

Supplemental Figure I. Landmark analysis within and beyond 30 days for all-cause death comparing between Wave-1 and Wave-2 in (A) entire study population, (B) patients with cardiogenic shock, and (C) patients without cardiogenic shock

HR=hazard ratio; CI=confidence interval.

Supplemental Figure II. Landmark analysis within and beyond 30 days for major bleeding comparing between Wave-1 and Wave-2

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 III . Kaplan-Meier curves for major bleeding comparing between Wave-1 and Wave-2 (A) in patients with ARC-HBR and (B) in patients without ARC-HBR

ARC-HBR=academic research consortium-high bleeding risk; HR=hazard ratio; CI=confidence interval.

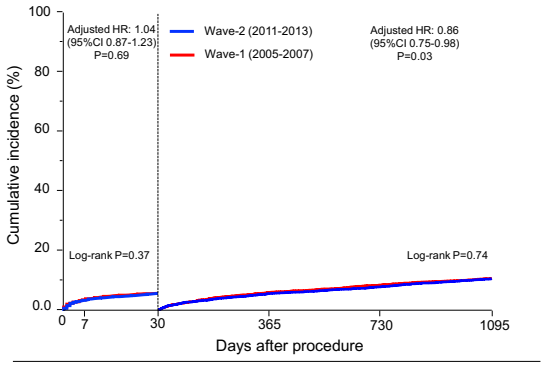
Supplemental Figure IV. Kaplan-Meier curves for persistent DAPT discontinuation comparing between Wave-1 and Wave-2

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

DAPT=dual antiplatelet therapy.

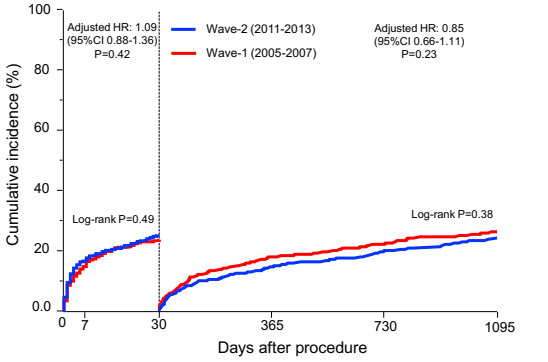
Supplemental Figure I. Landmark analysis within and beyond 30 days for all-cause death comparing between Wave-1 and Wave-2 (A) in entire study population, (B) in patients with cardiogenic shock, and (C) in patients without cardiogenic shock

(A) All-cause death in entire study population



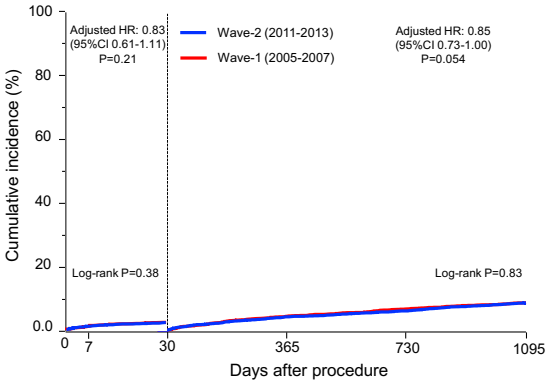
Interval	0 day	7 days	30 days	1 year	2 years	3 years
Wave-2						
N of patients at risk	4723	4551	4395	4041	3858	3685
N of patients with event		183	280	222	328	442
Cumulative incidence		3.9%	5.9%	5.1%	7.6%	10.4%
Wave-1						
N of patients at risk	4278	4137	4023	3744	3602	3454
N of patients with event		154	235	223	329	419
Cumulative incidence		3.6%	5.5%	5.6%	8.3%	10.6%

(B) All-cause death in patients with cardiogenic shock



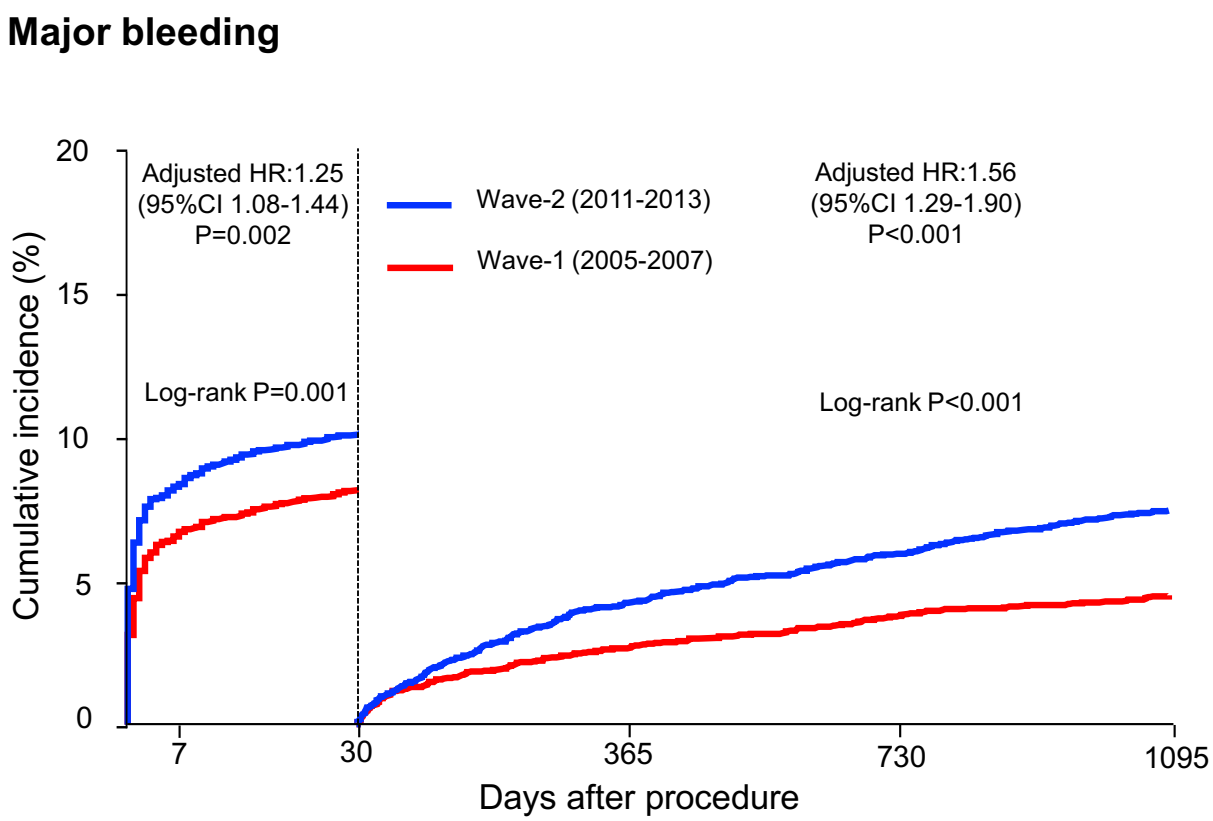
Interval	0 day	7 days	30 days	1 year	2 years	3 years
Wave-2						
N of patients at risk	757	629	556	446	407	375
N of patients with event		136	193	73	100	123
Cumulative incidence		18.0%	25.6%	13.7%	19.0%	23.6%
Wave-1						
N of patients at risk	596	506	450	370	346	317
N of patients with event		100	143	74	96	114
Cumulative incidence		16.8%	24.0%	16.6%	21.5%	25.7%

(C) All-cause death in patients without cardiogenic shock



Interval	0 day	7 days	30 days	1 year	2 years	3 years
Wave-2						
N of patients at risk	3966	3922	3839	3595	3451	3310
N of patients with event		47	87	149	228	319
Cumulative incidence		1.2%	2.2%	3.9%	6.1%	8.6%
Wave-1						
N of patients at risk	3682	3631	3573	3374	3256	3137
N of patients with event		54	92	149	233	305
Cumulative incidence		1.5%	2.5%	4.2%	6.6%	8.7%

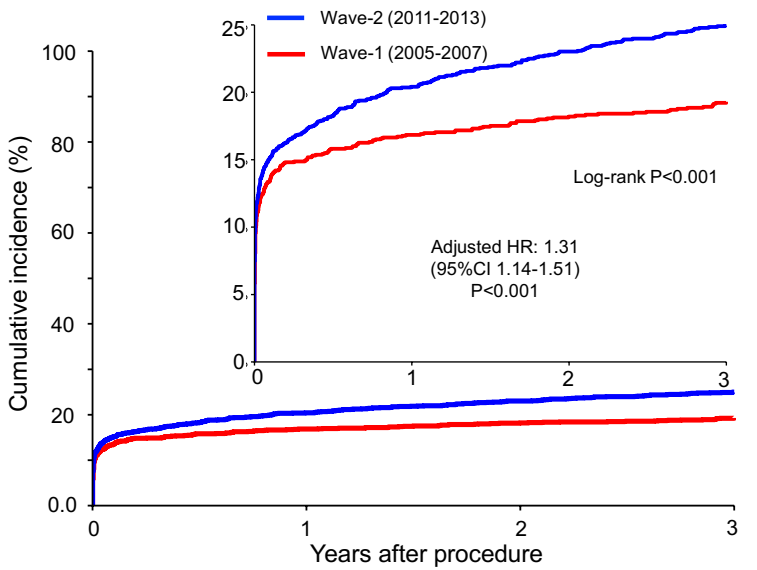
Supplemental Figure II. Landmark analysis within and beyond 30 days for major bleeding comparing between Wave-1 and Wave-2



Interval	0 day	7 days	30 days	1 year	2 years	3 years
Wave-2						
N of patients at risk	4723	4234	4067	3665	3453	3276
N of patients with event		383	457	161	229	284
Cumulative incidence		8.2%	9.8%	4.1%	5.9%	7.4%
Wave-1						
N of patients at risk	4278	3909	3773	3485	3333	3189
N of patients with event		272	331	97	136	161
Cumulative incidence		6.4%	7.8%	2.6%	3.7%	4.5%

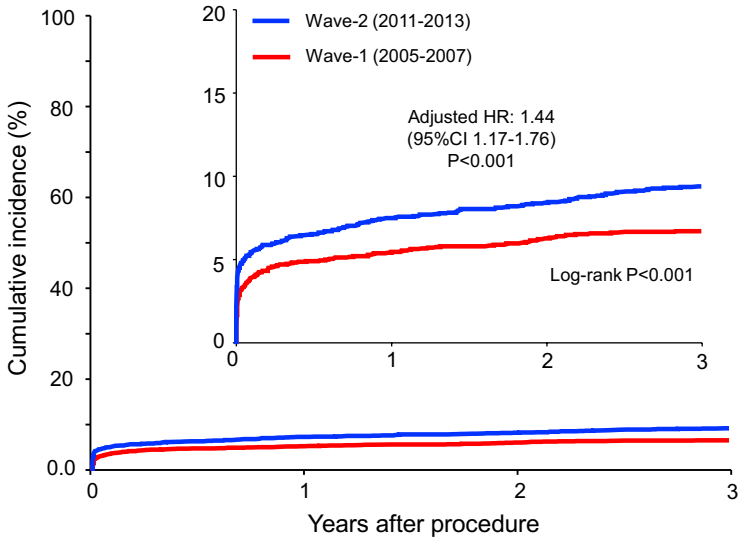
Supplemental Figure III. Kaplan-Meier curves for major bleeding comparing between Wave-1 and Wave-2 for major bleeding (A) in patients with ARC-HBR and (B) in patients without ARC-HBR

(A) Major bleeding in patients with ARC-HBR



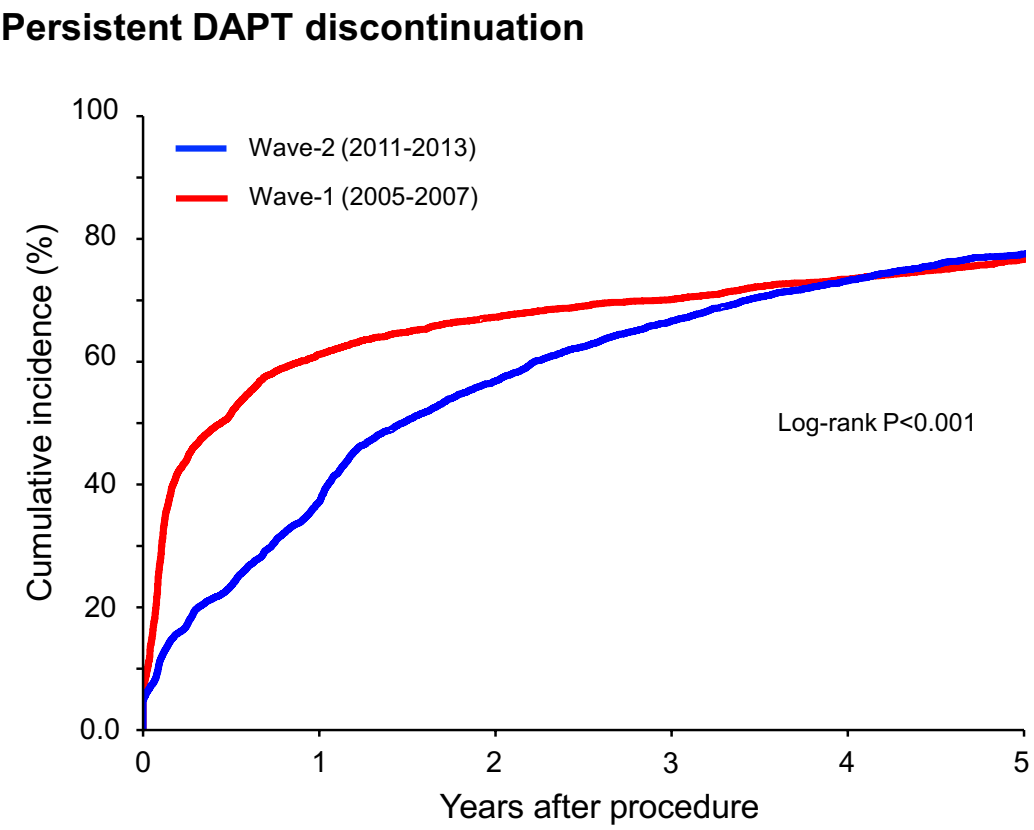
Interval	0 day	30 days	1 year	2 years	3 years
Wave-2					
N of patients at risk	2213	1736	1454	1308	1199
N of patients with event		322	430	476	508
Cumulative incidence		14.8%	20.4%	23.0%	25.0%
Wave-1					
N of patients at risk	1811	1451	1259	1170	1082
N of patients with event		237	293	313	328
Cumulative incidence		13.4%	16.8%	18.2%	19.3%

(B) Major bleeding in patients without ARC-HBR



Interval	0 day	30 days	1 year	2 years	3 years
Wave-2					
N of patients at risk	2510	2331	2211	2145	2077
N of patients with event		135	188	210	233
Cumulative incidence		5.4%	7.6%	8.5%	9.5%
Wave-1					
N of patients at risk	2467	2322	2226	2163	2107
N of patients with event		94	135	154	164
Cumulative incidence		3.8%	5.5%	6.4%	6.8%

Supplemental Figure IV. Kaplan-Meier curves for persistent DAPT discontinuation comparing between Wave-1 and Wave-2



Interval	0 day	30 days	1 year	2 years	3 years	4 years	5 years
Wave-2							
N of patients at risk	4625	3987	2603	1716	1272	971	700
Cumulative incidence		9.6%	37.2%	56.9%	66.7%	73.2%	77.5%
Wave-1							
N of patients at risk	4180	3093	1457	1186	1029	849	442
Cumulative incidence		23.7%	61.2%	67.3%	70.1%	73.4%	76.7%

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	7
Objectives	3	State specific objectives, including any prespecified hypotheses	7
Methods			
Study design	4	Present key elements of study design early in the paper	8
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	8
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	8-9
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	8-9
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	9
Bias	9	Describe any efforts to address potential sources of bias	9
Study size	10	Explain how the study size was arrived at	9
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	11
		(*b*) Describe any methods used to examine subgroups and interactions	11
		(*c*) Explain how missing data were addressed	11
		(*d*) If applicable, explain how loss to follow-up was addressed	11
		(*e*) Describe any sensitivity analyses	N/A
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	8
		(c) Consider use of a flow diagram	8
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	13
		(b) Indicate number of participants with missing data for each variable of interest	13
		(c) Summarise follow-up time (eg, average and total amount)	11
Outcome data	15*	Report numbers of outcome events or summary measures over time	14

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	14 14 14
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	14
Discussion			
Key results	18	Summarise key results with reference to study objectives	15
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	17
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	16-17
Generalisability	21	Discuss the generalisability (external validity) of the study results	17
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	24

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.