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CITATION:

Takeji, Yasuaki ...[et al]. Changes in demographics, clinical practices and long-term outcomes of patients with ST segment-elevation myocardial infarction who underwent coronary revascularisation in the past two decades: cohort study. BMJ Open 2021, 11(3): e043683.

ISSUE DATE:

2021-03

URL:

http://hdl.handle.net/2433/276761

Open access Original research

BMJ Open

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To cite: Takeji Y, Shiomi H, Morimoto T, *et al*. Changes in demographics, clinical practices and long-term outcomes of patients with ST segment-elevation myocardial infarction who underwent coronary revascularisation in the past two decades: cohort study. *BMJ Open* 2021;**11**:e043683. doi:10.1136/bmjopen-2020-043683

► Prepublication history and additional materials for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2020-043683).

Received 12 August 2020
Revised 20 February 2021
Accepted 04 March 2021

Check for updates

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ABSTRACT

Objective To evaluate changes in demographics, clinical practices and long-term clinical outcomes of patients with ST segment-elevation myocardial infarction (STEMI) before and beyond 2010.

Design Multicentre retrospective cohort study.

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

Participants 9001 patients with STEMI who underwent coronary revascularisation (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, hospitalisation for heart failure, major bleeding, target vessel revascularisation, ischaemia-driven target vessel revascularisation, any coronary revascularisation and any ischaemia-driven coronary revascularisation.

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 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 of all-cause death in Wave-2 relative to Wave-1 was not significant at 3 years (HR 0.92, 95% CI 0.83 to 1.03, p=0.14), but lower beyond 30 days (HR 0.86, 95% CI 0.75 to 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 to 0.81, p=0.001) and for any coronary revascularisation (HR 0.75, 95% CI 0.69 to 0.81, p<0.001), but higher for major bleeding (HR 1.34, 95% CI 1.20 to 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

Strengths and limitations of this study

- Evaluating changes of demographics, clinical practices and long-term clinical outcomes between patients with ST segment-elevation myocardial infarction enrolled beyond 2010 and those enrolled before 2010.
- Multicentre registry with large sample size enrolled consecutive patients who underwent revascularisation for acute myocardial infarction.
- Systematic differences between two cohorts in the selection of patients and collection of events.

coronary revascularisation, but an increase in the risk of major bleeding from Wave-1 to Wave-2.

INTRODUCTION

The early mortality of patients with ST segment-elevation myocardial infarction (STEMI) has been steadily declining over the past several decades.[1–5] This trend appears to have been driven by many factors, including demographic change, better pharmacological 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 patients with STEMI 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 patients with STEMI 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 patients with STEMI using data from two 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, multicentre registry enrolling consecutive patients with AMI who underwent coronary revascularisation, either PCI or isolated coronary artery bypass grafting (CABG), within 7 days of the onset of symptoms. Wave-1 enrolled patients between January 2005 and December 2007 among 26 centres (both PCI and CABG available: 20 centres, and only PCI available: 6 centres) in Japan after the introduction of drug-eluting stents (DESs) in 2004 (online supplemental appendix A).[16] Wave-2 enrolled patients between January 2011 and December 2013 among 22 centres (both PCI and CABG available: 16 centres, and only PCI available: 6 centres) in Japan after approval of the new-generation DES in 2010 (online supplemental appendix A). We made a historical comparison on demographics, clinical practices and long-term clinical outcomes of patients with STEMI between Wave-1 and Wave-2.

We enrolled a total of 11 899 consecutive patients with AMI who had undergone coronary revascularisation 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 four cardiology divisions and five cardiovascular surgery divisions not participating in Wave-2 and 6 patients in Wave-2 who were enrolled from one 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 centres (both PCI and CABG available: 15 centres and only PCI available: 7 centres) (figure 1).

Definitions and clinical outcome measures

Patients with STEMI 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 min 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 organisation (Research Institute for Production Development, Kyoto, Japan; online supplemental appendix B) from the hospital charts or hospital databases according to the prespecified definitions.

Diabetes was defined as treatment with oral hypoglycaemic agents or insulin, prior clinical diagnosis of diabetes, glycated haemoglobin level of ≥6.5% or non-fasting blood glucose level of ≥200 g/L. Left ventricular ejection fraction was measured either by contrast left ventriculography or echocardiography. Prior stroke was defined as ischaemic or haemorrhagic 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 calculated by the Modification of Diet in Renal Disease formula modified for Japanese patients.[17]

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, hospitalisation for heart failure, major bleeding, target vessel revascularisation, ischaemia-driven target vessel revascularisation, any coronary revascularisation and ischaemia-driven any coronary revascularisation. The definition of death was described in detail previously.[18 19] Myocardial infarction was defined according to the definition in the Arterial Revascularisation Therapy Study,[20] and only Q-wave myocardial infarction was regarded as myocardial infarction when it occurred within 7 days of the index procedure.[21] Definite stent thrombosis was

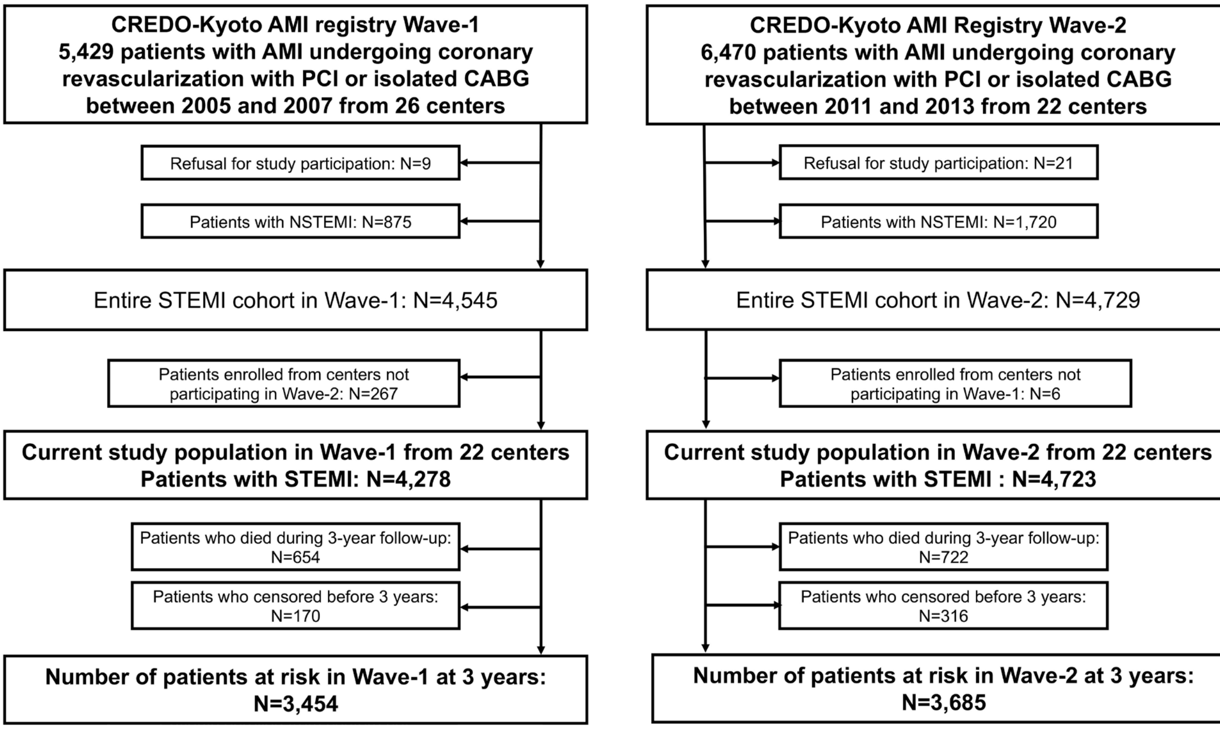


Figure 1 Study flowchart. AMI, acute myocardial infarction; CABG, coronary artery bypass grafting; CREDO-Kyoto, Coronary Revascularization Demonstrating Outcome Study in Kyoto; NSTEMI, non-ST segment-elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST segment-elevation myocardial infarction.

defined according to the Academic Research Consortium (ARC) definition.[22] Stroke during follow-up was defined as ischaemic or haemorrhagic stroke requiring hospitalisation with symptoms lasting >24 hours. Hospitalisation for heart failure was defined as hospitalisation 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 moderate/severe bleeding.[21 23] Target vessel revascularisation (TVR) was defined as either PCI or CABG related to the original target vessel. Any coronary revascularisation was defined as either PCI or CABG for any reason. Scheduled staged coronary revascularisation 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.[24] Follow-up started at the time of revascularisation for STEMI and were 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 (online supplemental appendix C).

Statistical analysis

We expressed continuous variables as mean±SD or median with IQR and used Student's t-test or Wilcoxon's 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 analysed 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 HR and their 95% CIs of Wave-2 compared with 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 hospitalisation because differences in management converged into the changes between Wave-1 and Wave-2. Continuous risk-adjusting variables were dichotomised according to the clinically meaningful reference values to make proportional hazard assumptions robust and to be consistent with previous reports.[24 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

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

	Wave-1 (n=4278)	Wave-2 (n=4723)	P value
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<30 mL/min/1.73 m^2, without haemodialysis*	202 (4.7%)	288 (6.1%)	0.005
Hemodialysis*	73 (1.7%)	131 (2.8%)	0.001
eGFR <30 mL/min/1.73 m^2 or haemodialysis	275 (6.4%)	419 (8.9%)	<0.001
Atrial fibrillation	418 (9.8%)	419 (8.9%)	0.15
Anaemia (haemoglobin<11.0 g/L)*	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
Presentation			
Living alone	509 (13%)	780 (17%)	<0.001
Direct admission	2215 (54%)	2603 (57%)	0.02
Interfacility 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
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
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 (min)	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

Continued

Table 1 Continued

	Wave-1 (n=4278)	Wave-2 (n=4723)	P value
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
DES	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
DES	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
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 statin 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±SD or median (IQR). 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 haemoglobin 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, haemoglobin 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 hand, 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 analysed 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 statin therapy in this study was defined as the statin doses greater than or equal to atorvastatin 20 mg, pitavastatin 4 mg or rosuvastatin 10 mg.
ARB, angiotensin receptor blocker; CABG, coronary artery bypass grafting; CK, creatine kinase; DES, drug-eluting stent; DOAC, direct oral anticoagulants; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; ITA, internal thoracic artery; IVUS, intravascular ultrasound; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention.

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

Patient and public involvement

In this study, patients were not involved in the design, conduct, 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 fractions ≤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 centres without interfacility 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, ACE 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 statin 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

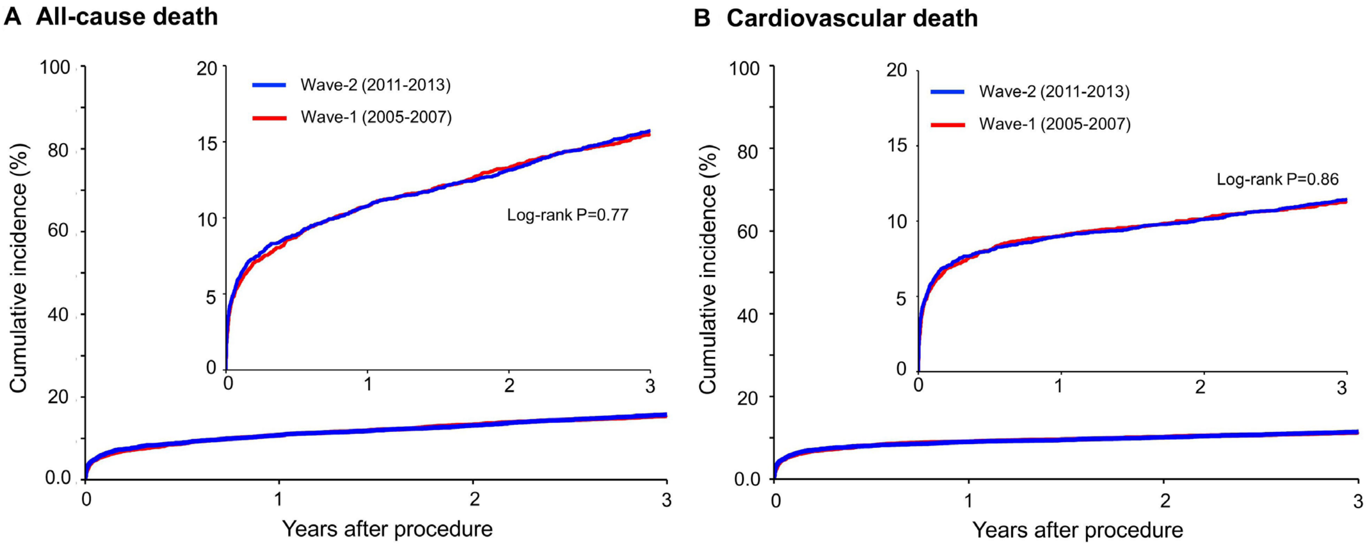
The cumulative 3-year incidence of all-cause death was not significantly different between Wave-1 and Wave-2 (15.5% vs 15.7%, log-rank p=0.77) (figure 2A and table 2). The adjusted risk of Wave-2 relative to Wave-1 remained insignificant for all-cause death (HR 0.92, 95% CI 0.83 to 1.03, p=0.14) (table 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% vs 5.9%, log-rank p=0.37) and beyond 30 days (10.6% vs 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 to 0.98, p=0.03), although it was not significant within 30 days (HR 1.04, 95% CI 0.87 to 1.23, p=0.69) (online supplemental figure 1). The results of the 30-day landmark analysis were consistent in patients with and without cardiogenic shock (online supplemental figure 1).

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

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) (figure 3 and table 2). The excess adjusted risk of Wave-2 relative to Wave-1 remained significant for major bleeding (HR 1.34, 95% CI 1.20 to 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 (online supplemental figure 2). 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 (online supplemental figure 3). 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 (online supplemental figure 4).

DISCUSSION

The main findings of this study were as follows: (1) regarding demographics, patients with STEMI in Wave-2 were older, more often had comorbidities and more often presented with serious haemodynamic 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, more often received guideline-directed medical therapy at baseline, and had 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 revascularisation, 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.



A

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

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%

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

There was scarcity of data evaluating demographics, clinical practices and long-term clinical outcomes in patients with STEMI 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 interfacility 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]

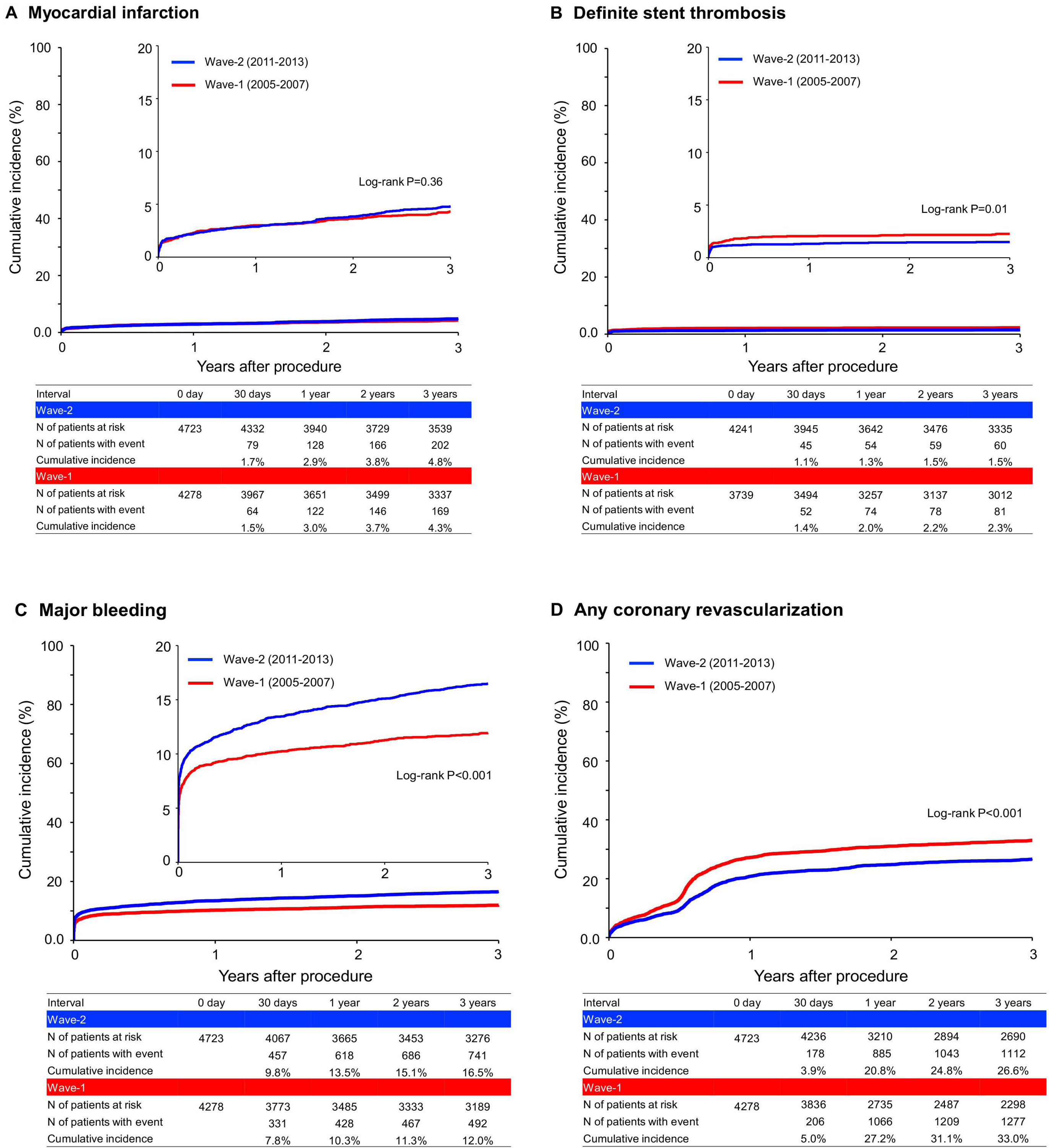
On the other hand, beyond 30 days after the index procedure, we found a significantly lower adjusted mortality risk of patients in Wave-2 relative to those in Wave-1. The changes in clinical practices that might have contributed to lower mortality risk in Wave-2 relative to Wave-1 included shorter onset-to-balloon 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 revascularisation 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 statin 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 two times per day as the standard dose in Japan, which was much lower than the dose used globally (250 mg two times per day), while in Wave-2, the vast majority of patients took clopidogrel 75 mg once per day, which was the the dose used globally. The 30-day rate of major bleeding in Wave-2

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

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

The risk of Wave-2 relative to Wave-1 was expressed as HR with 95% CI. The covariates for the multivariate Cox proportional hazard models are indicated in table 1.
Myocardial infarction was based on the ARTS definition.
Major bleeding was defined as GUSTO moderate/severe bleeding.
*Definite stent thrombosis was based on the ARC definition and was analysed only for patients who underwent PCI with stent implantation (3739 patients in Wave-1 and 4241 patients in Wave-2).
ARC, Academic Research Consortium; ARTS, Arterial Revascularisation Therapy Study; GUSTO, Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries; PCI, percutaneous coronary intervention.



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%

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 revascularisation. Definite stent thrombosis was based on the ARC definition and was analysed 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. ARC, Academic Research Consortium; GUSTO, Global Utilisation of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries.

was substantial (entire cohort: 9.8%, ARC-HBR: 14.8% and non-ARC-HBR: 5.4%), warranting to explore the optimal antiplatelet regimen in patients with STEMI minimising 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 patients with STEMI constituded only a small proportion in the Short and Optimal duration of Dual Antiplatelet Therapy after Everolimus-eluting Cobalt-Chromium Stent-2 trial, and were excluded in the 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 patients with STEMI. Our study, which was based on the multicentre registry with large sample size, enrolled consecutive patients who underwent revascularisation for AMI, and the follow-up rate was high enough. Therefore, 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 centres that participated in both Wave-1 and Wave-2, standardising 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 endpoints during the 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 revascularisation, which might have lead to selection bias. However, it is quite rare for a patient with STEMI 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 a significant risk reduction for definite stent thrombosis and any coronary revascularisation but an increase in the risk of major bleeding from Wave-1 to Wave-2.

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Acknowledgements We appreciate the support and collaboration of the coinvestigators participating in theCoronary Revascularization Demonstrating Outcome Study in Kyoto (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.

Contributors TKi conceptualised the Coronary Revascularization Demonstrating Outcome Study in Kyoto (CREDO-Kyoto) AMI Registry. YT prepared the original draft of the manuscript. HSh, TM and TKi reviewed and edited the the original draft of the manuscript. YT, HSh, YYo, YM-N, KYamam and KYamaj curated data. YT, TM and TKi constructed methodology for this study. YT and TM performed the statistical analysis. HSh, TM, RT, KYamaj, JT, HW, SS, MI, TTak, MS, NE, KI, TI, TTam, TO, ES, TY, HSa, KA, YS, YF, YS, YN, KK, TKo, KM and TKi are investigators of the CREDO-Kyoto AMI Registry. YT, HSh, YY, YM-N, KYam, ETK, EY, YYa, MF, HW, HY and KN assessed and validated events within the CREDO-Kyoto AMI Registry. TKi is the guarantor.

Funding This study was supported by an educational grant from the Research Institute for Production Development (Kyoto, Japan) and the Pharmaceuticals and Medical Devices Agency in Japan (Tokyo, Japan). Grant numbers were not applicable.

Competing interests All authors have completed the Unified Competing Interest form and declare the following: HSh reports personal fees from Abbott Vascular, Boston Scientific and Daiichi Sankyo. TM reports lecturer's fees from Bayer, Daiichi Sankyo, Japan Lifeline, Kyocera, Mitsubishi Tanabe, Novartis and Toray; the manuscript fees from Bristol-Myers Squibb and Kowa; serving on advisory boards for Asahi Kasei, Boston Scientific, Bristol-Myers Squibb and Sanofi. ETK reports grant from Ono Pharmaceutical and reports personal fees from Daiichi Sankyo, AstraZeneca, Bristol-Myers Squibb, Tanabe-Mitsubishi Pharma, Ono Pharmaceutical, MSD KK and Pfizer. NE reports personal fees from Abbott Vascular, Medtronic, Terumo, Bayer, Boston Scientific, Daiichi-Sankyo, Edwards Lifescience, Pfizer, Bristol Myers Squibb, Takeda and Boehringer Ingelheim. YF reports personal

fees from Daiichi Sankyo, Bayer, Sanofi, Kowa, Pfizer, Bristol-Myers Squibb, Otsuka Parmaceutical, Sumitomo Dainippon Pharma, Takeda and Ono Pharmaceutical. YN reports grant from Abbott Vascular and Boston Scientific, and reports personal fees from Abbott Vascular, Bayer, Boston Scientific, Bristol-Myers Squibb, Daiichi Sankyo. TKi reports personal fees from Abbott Vascular, MSD, Eisai, Edwards Lifescience, Ono Pharmaceutical, Tsumura, Medical Review, Kowa, Sanofi, Daiichi Sankyo, Takeda Pharmaceutical, Pharmaceuticals and Medical Devices Agency, Abiomed, Bayer, Bristol-Myers Squibb, Boston Scientific, Lifescience, Toray, Astellas Amgen Biopharma, Astellas, AstraZeneca, Otsuka Parmaceutical, OrbusNeich, MSD Life Science Foundation, Public Health Research Foundation, Chugai Pharmaceutical, Boehringer Ingelheim, Japan Society for the Promotion of Science, Interscience, Philips, Kowa Pharmaceutical, Mitsubishi Tanabe Pharma, Terumo, Novartis Pharma and Sumitomo Dainippon Pharma.

Patient consent for publication Not required.

Ethics 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). The relevant institutional review boards at all participating hospitals approved the study protocols. 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 Welfare.

Provenance and peer review Not commissioned; externally peer reviewed.

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

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SUPPLEMENTARY MATERIAL

Table of contents

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Supplemental Appendix A: List of participating centers and investigators

<u>The CREDO-Kyoto AMI Registry Wave-1</u>

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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

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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

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Mitsubishi Kyoto Hospital: Hiroyuki Nakajima

Kumamoto University Hospital: Michio Kawasuji, Syuji Moriyama

Juntendo University Shizuoka Hospital: Keiichi Tanbara

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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

Kyoto University Hospital: Kenji Minatoya, Kazuhiro Yamazaki

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

Japanese Red Cross Wakayama Medical Center: Naoki Kanemitsu, Hiroyuki Hara

Shizuoka General Hospital: Hiroshi Tsuneyoshi

Kurashiki Central Hospital: Tatsuhiko Komiya

Mitsubishi Kyoto Hospital: Jiro Esaki

Juntendo University Shizuoka Hospital: Keiichi Tambara

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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

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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.

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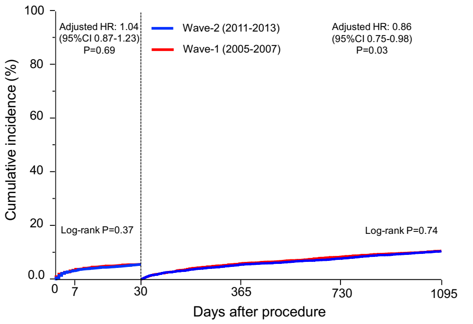
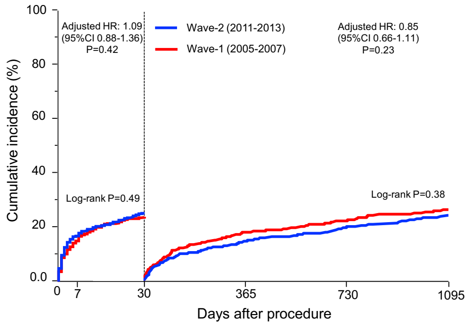
Supplemental Figure I. Landmark analysis within and beyond 30 days for all-cause death comparing between Wave-1 and Wave-2 (A) in entire study population, (B) in patients with cardiogenic shock, and (C) in patients without cardiogenic shock

(A) All-cause death in entire study population



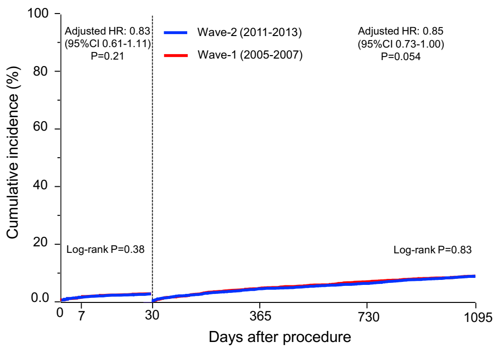
Interval	0 day	7 days	30 days	1 year	2 years	3 years
Wave-2						
N of patients at risk	4723	4551	4395	4041	3858	3685
N of patients with event		183	280	222	328	442
Cumulative incidence		3.9%	5.9%	5.1%	7.6%	10.4%
Wave-1						
N of patients at risk	4278	4137	4023	3744	3602	3454
N of patients with event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

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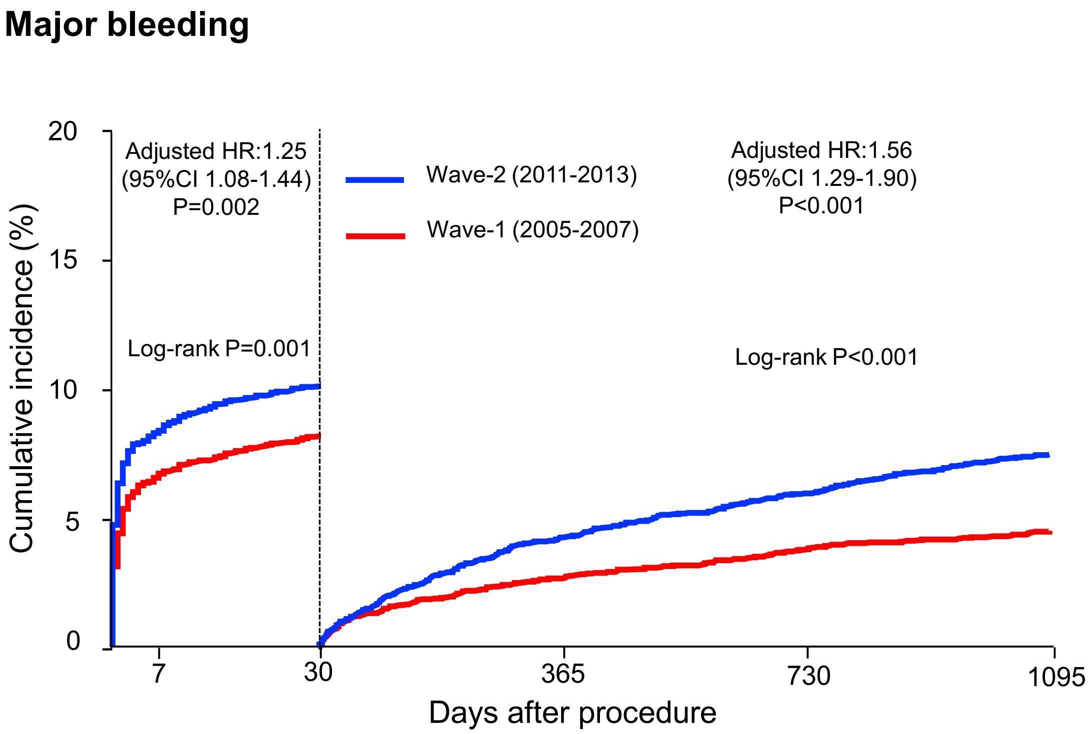
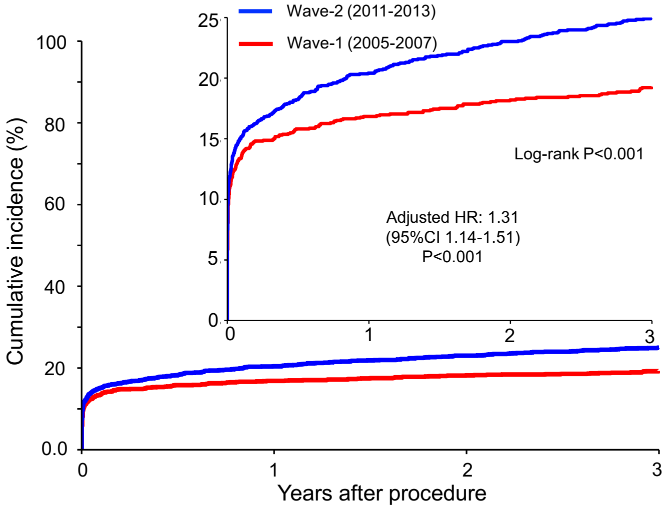
Supplemental Figure II. Landmark analysis within and beyond 30 days for major bleeding comparing between Wave-1 and Wave-2



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%

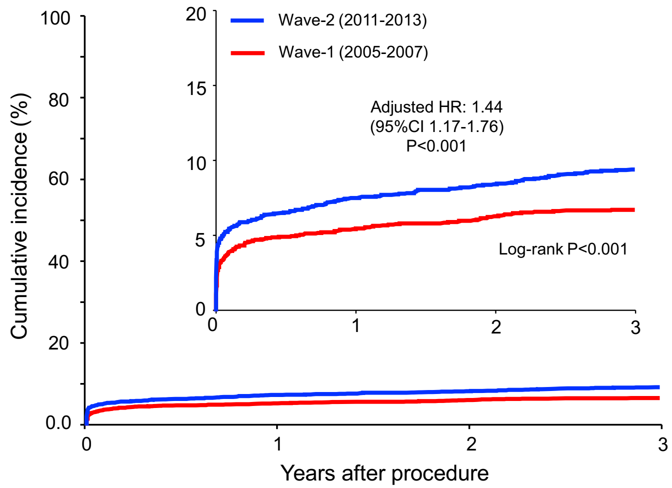
Supplemental Figure III. Kaplan-Meier curves for major bleeding comparing between Wave-1 and Wave-2 for major bleeding (A) in patients with ARC-HBR and (B) in patients without ARC-HBR

(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%

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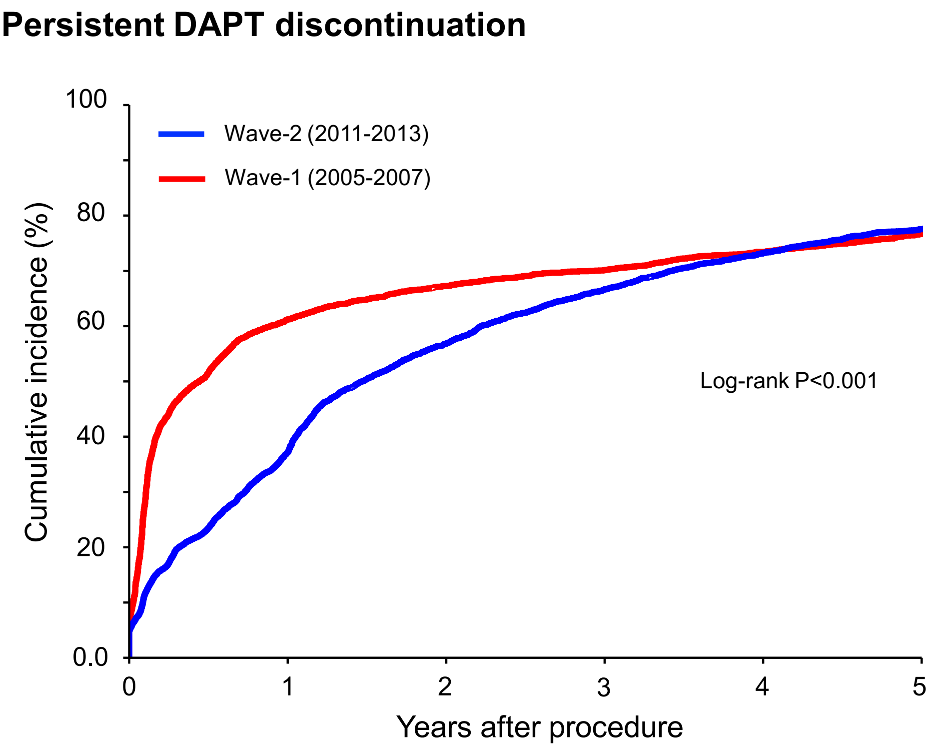
Supplemental Figure IV. Kaplan-Meier curves for persistent DAPT discontinuation comparing between Wave-1 and Wave-2



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%

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