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ORIGINAL ARTICLE

Mortality impact of post-discharge myocardial infarction size after percutaneous coronary intervention: a patient-level pooled analysis from the 4 large-scale Japanese studies

Hirotoshi Watanabe[1] · Takeshi Morimoto[2] · Hiroki Shiomi[1] · Yusuke Yoshikawa[1] · Takao Kato[1] · Naritatsu Saito[1] · Satoshi Shizuta[1] · Koh Ono[1] · Kyohei Yamaji[3] · Kenji Ando[3] · Shuichiro Kaji[4] · Yutaka Furukawa[4] · Masaharu Akao[5] · Tetsuya Ishikawa[6] · Takashi Tamura[7] · Yoshito Yamamoto[8] · Toshiya Muramatsu[9] · Satoru Suwa[10] · Yoshihisa Nakagawa[11] · Kazushige Kadota[12] · Yoshiki Takatsu[13] · Hideo Nishikawa[14] · Yoshikazu Hiasa[15] · Yasuhiko Hayashi[16] · Shunichi Miyazaki[17] · Takeshi Kimura[1]

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Abstract

It is unknown whether there is a threshold of creatine kinase (CK) or CK-MB affecting the subsequent mortality for post-discharge myocardial infarction (PDMI) after percutaneous coronary intervention. Current study sought to evaluate the impact of PDMI. The study population included 30,051 patients with successful coronary stenting and discharged alive in the pooled patient-level database of 4 Japanese studies (j-Cypher registry, CREDO-Kyoto PCI/CABG registry cohort-2, RESET, and NEXT). During 4.4 ± 1.4 year follow-up, 915 patients experienced PDMI (cumulative 5-year incidence of 3.6%). Among 466 patients with available peak CK ratio (peak CK/upper limit of normal), peak CK ratio (< 3) was present in 21% of patients, while peak CK ratios (≥ 3 and < 5), (≥ 5 and < 10), (≥ 10 and < 30), and (≥ 30) were present in 17, 25, 30, and 7.3% of patients, respectively. The excess mortality risk of patients with relative to those without PDMI for subsequent mortality was significant (adjusted HR 5.12, 95% CI 4.52–5.80, $P < 0.001$) by the Cox model with PDMI incorporated as the time-updated covariate. However, the mortality risk of patients in the smallest peak CK ratio category (< 3) was insignificant (HR 0.85, 95% CI 0.43–1.71, $P = 0.65$). In conclusion, despite significant overall mortality risk of PDMI, the mortality risk of small PDMI was similar to that of no PDMI, suggesting the presence of some threshold about infarct size influencing mortality.
Trial registrations The Randomized Evaluation of Sirolimus-Eluting Versus Everolimus-Eluting Stent Trial (RESET); NCT01035450 and NOBORI Biolimus-Eluting Versus XIENCE/PROMUS Everolimus-Eluting Stent Trial (NEXT); NCT01303640. J-Cypher and CREDO-Kyoto PCI/CABG registry cohort 2 were not registered into clinical trial database.

Keywords Percutaneous coronary intervention · Myocardial infarction · Mortality · Prognosis

Introduction

In the clinical studies after percutaneous coronary intervention (PCI), there are two types of myocardial infarction (MI), namely periprocedural MI related to the index PCI procedure and post-discharge myocardial infarction (PDMI). In the case of periprocedural MI, recent studies have suggested that there was a threshold of peak creatine kinase (CK) or CK-MB ratio values (CK: 3 times of normal or CK-MB: 8 times of normal) affecting the subsequent long-term mortality, though some controversies remain [1–3]. In the case of PDMI, the previous studies have suggested nearly two-to-sevenfold increased mortality risk in patients with PDMI than in patients without [4–6]. In the Universal definition of MI, which focuses on high-sensitivity biomarkers, even a minimal elevation of troponin without elevation of CK nor CK-MB is regarded as myonecrosis and thus adjudicated as MI except for that occurring in the periprocedural period [7]. Therefore, there would be a wide variation in the infarct size among the adjudicated PDMI events. A small MI

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✉ Takeshi Kimura
taketaka@kuhp.kyoto-u.ac.jp

Extended author information available on the last page of the article

adjudicated only by elevation of high-sensitivity troponin might have less prognostic importance as compared with a large MI with CK elevation. However, there was no previous study evaluating the relation between the size of PDMI and subsequent mortality. It is currently unknown whether there is a threshold of peak CK or CK-MB ratio values affecting the subsequent long-term mortality for PDMI similar to that for periprocedural MI. Current study sought to evaluate the distribution of the PDMI size and the impact of the PDMI size on subsequent mortality in a large-pooled patient-level database of the 4 large-scale Japanese PCI studies.

Methods

Study population

This study was derived from a pooled analysis of the 4 PCI studies conducted after the introduction of drug-eluting stent (DES) in Japan including J-Cypher registry, The Coronary REvascularization Demonstrating Outcome study in Kyoto (CREDO-Kyoto) PCI/CABG registry cohort-2, the Randomized Evaluation of Sirolimus-Eluting Versus Everolimus-Eluting Stent Trial (RESET), and NOBORI Biolimus-Eluting Versus XIENCE/PROMUS Everolimus-Eluting Stent Trial (NEXT) (Appendix S1) [8–11]. The design and main results of the individual studies were previously published and summarized in Table S1. The study protocols of all four studies were approved in each ethical committee of all the participating centers. Written informed consent was obtained in J-Cypher, RESET, and NEXT, and it was waived in CREDO-Kyoto PCI/CABG registry cohort-2 because of its retrospective enrollment. Among the total 31,352 patients in the pooled database, 30,051 patients with successful coronary stenting and discharged alive constituted the current study population (Fig. 1). Demographic, angiographic, and procedural data were collected from hospital charts or hospital databases according to the pre-specified definitions by the experienced clinical research coordinators from the clinical research organization (Research Institute for Production Development, Kyoto, Japan; Appendix S2), or by the site investigators. Follow-up data were obtained from hospital charts or by the letter from and/or telephone interview with the patients, their family members and/or referring physicians. Clinical follow-up data were available for 5 years in the j-Cypher and CREDO-Kyoto PCI/CABG registry cohort-2, and for 3 years in the RESET and NEXT.

Definitions

MI in follow-up period was defined according to the Arterial Revascularization Therapy Study definition in j-Cypher and CREDO-Kyoto PCI/CABG registry cohort-2 and was defined according to the Academic Research Consortium definition in the RESET and NEXT (Table S2) [12, 13]. In both definitions, spontaneous MI after discharge from the index procedure was defined with any elevation of a cardiac enzyme over upper limit of normal (ULN). In cases of suspected MI without biomarker data, the independent clinical event committee adjudicated the event based on the clinical, electrocardiographic, and/or angiographic information. Periprocedural MI was defined as a new abnormal Q wave in contiguous two leads of electrocardiogram or elevation of CK-MB over 3 times of ULN. Definitions of baseline

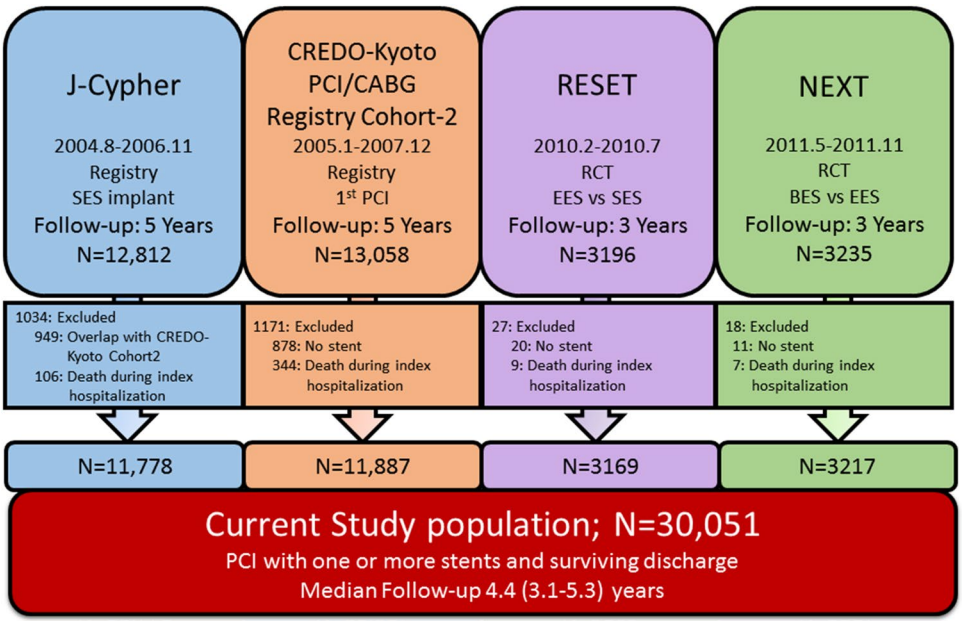


Fig. 1 Study flow chart. The present study included 4 original studies (2 registries and 2 randomized-controlled trials). *BES* biolimus-eluting stent, *CABG* coronary artery bypass grafting, *CREDO-Kyoto* The Coronary REvascularization Demonstrating Outcome study in Kyoto, *EES* everolimus-eluting stent, *NEXT* NOBORI Biolimus-Eluting Versus XIENCE/PROMUS Everolimus-Eluting Stent Trial, *PCI* percutaneous coronary intervention, *RCT* randomized-controlled trial, *RESET* the Randomized Evaluation of Sirolimus-Eluting Versus Everolimus-Eluting Stent Trial, *SES* sirolimus-eluting stent

characteristics, other endpoints, and recommended regimen of dual antiplatelet therapy (DAPT) were consistent across the 4 studies (Appendix S3) [8–11]. The status of antiplatelet therapy was evaluated throughout the follow-up period by the same methodology across all the studies. Discontinuation of DAPT was defined as persistent discontinuation of either aspirin or thienopyridine for 2 months or longer [8]. All the events were adjudicated by the independent clinical event committee.

In patients with PDMI, all the data for serial CK and CK-MB were collected when these data were recorded in the hospital chart. The PDMI events were categorized according to the peak CK ratio or peak CK-MB ratio defined as peak CK or CK-MB value divided by their upper limit of normal (ULN) value in each site. Categorization of the CK or CK-MB ratio was determined based on the previously published reports on periprocedural MI: (<3), (≥ 3 and <5), (≥ 5 and <10), (≥ 10 and <30), and (≥ 30) [1–3]. Besides missing CK/CK-MB or ULN values, peak CK or CK-MB ratio was regarded as non-assessable when obtained CK/CK-MB value was thought not representing the true peak value; typical up and down of CK/CK-MB was not captured; it took >24 h from onset of MI to hospitalization; or death occurred before the true peak value was captured. Fatal MI was defined as MI with subsequent death within 30 days.

Statistical analysis

Categorical variables were expressed as number and percentages. Continuous variables were expressed as mean $\pm$ SD or median and interquartile range (IQR). Categorical variables were compared with the Chi-square test. Continuous variables were compared using Student's *t* test or Wilcoxon rank sum test based on their distributions. The cumulative incidence was estimated by the Kaplan–Meier method. Prognostic impact of PDMI was evaluated by the Cox proportional hazard model for mortality with PDMI or its size categories incorporated as the time-updated covariate [14]. The peak CK ratio category was hierarchically updated only when the patient experienced larger sized MI. As a sensitivity analysis, mortality risk was similarly evaluated according to the peak CK-MB ratio categories. PDMI size and the subsequent mortality risk were also compared among subsets of PDMI, relation with stent thrombosis (ST), spontaneous or periprocedural, lesion locations, and receiving reperfusion therapy or not. In adjusting the mortality hazard ratio (HR), the 27 clinically meaningful covariates listed in Table 1 were selected, which were commonly captured in all the 4 studies. The continuous variables were dichotomized using clinically meaningful reference values or medians. Missing data were imputed as negative value for binary covariates; the numbers of missing cases were negligibly small. The proportional hazard assumption was verified for each variable by the plot of log (time) versus log [− log (survival)]. The study code was incorporated as a stratification variable.

Analyses were performed with SPSS ver. 19 (IBM Corporation, Armonk, NY, USA), and JMP ver. 10.0.2 (SAS institute Inc., Cary, NC, USA). All reported P values were 2-tailed, and P values <0.05 were considered statistically significant.

Results

Baseline characteristics and DAPT discontinuation rate

The baseline patient characteristics included a large proportion of patients with advanced age, diabetes, and multi-vessel disease. The prescription rate at hospital discharge was optimal for antiplatelet agents, but not optimal for statins (Table 1). Among the 4 included studies, age and gender distributions were similar, while there were some differences in the proportion of patients with acute MI presentation, prior PCI, prior MI, and DES use. The prevalence of stain use was higher in the 2 studies conducted in the later period (Table S1).

Patients with PDMI more often had comorbidities such as acute myocardial infarction (AMI) at index, diabetes, current smoking, heart failure, multi-vessel disease, and renal failure than in patients without PDMI. The total stent length was longer, and the minimal stent size was smaller in patients with PDMI, whereas DES use, especially second-generation DES use, use of intravascular ultrasound, and statin use were more prevalent in patients without PDMI (Table 1).

Discontinuation rate of DAPT was 37.8% at 1-year in the overall cohort and was quite different across the 4 studies (Figure S1). The rate was higher in the 2 registries compared with that in the 2 randomized control studies and was also higher in patients with bare-metal stent (BMS) use and AMI presentation, reflecting the lower rate of DES use in AMI as compared with that in non-AMI (53.1 versus 89.8%). Subgroup analyses stratified by stent types and AMI presentation indicated that DAPT duration was primarily influenced not by AMI presentation, but by stent types (Figure S1).

PDMI and other clinical outcomes

Post-discharge myocardial infarction occurred in 915 patients (3.0% of 30,051 patients) during the mean follow-up duration of 4.4 ± 1.4 years (Table 2). The cumulative 5-year incidence of PDMI was only 3.6%, which occurred constantly at the annual incidence of 0.7% (Fig. 2). Among the 4 included studies, the cumulative incidence of PDMI was lower in the NEXT, in which almost all patients had received second-generation DES (Figure S2-A). In the

Table 1 Baseline characteristics and medication at discharge

Characteristics	Total ($N=30,051$)	Post-discharge MI+ ($N=915$)	Post-discharge MI− ($N=29,136$)	P value
Patient characteristics				
Age, mean (SD), years	68 (10)	67 (11)	68 (10)	< 0.001
Age ≥ 75 years[a], *N* (%)	9205 (31)	274 (30)	8931 (31)	0.65
Male[a], *N* (%)	22,444 (75)	691 (76)	21,753 (75)	0.56
BMI, median (IQR), kg/m^2	23.8 (21.7–26.0)	23.9 (21.5–26.0)	23.8 (21.7–26.0)	0.91
BMI < 25[a], *N* (%)	19,679 (66)	599 (66)	19,080 (66)	0.99
AMI at index PCI[a], *N* (%)	5748 (19)	217 (24)	5531 (19)	< 0.001
STEMI, *N* (%)	4784 (16)	185 (20)	4599 (16)	< 0.001
Hypertension[a], *N* (%)	23,788 (79)	729 (80)	23,059 (79)	0.70
DM, *N* (%)	12,277 (41)	433 (47)	11,844 (41)	< 0.001
Insulin therapy[a], *N* (%)	2673 (9)	98 (11)	2575 (9)	0.06
Lipid lowering therapy, *N* (%)	13,168 (44)	379 (41)	12,789 (44)	0.14
Current smoking[a], *N* (%)	7397 (25)	272 (50)	7125 (25)	< 0.001
Heart failure[a], *N* (%)	4554 (15)	180 (20)	4374 (15)	< 0.001
Multi-vessel disease[a], *N* (%)	16,118 (54)	595 (65)	15,523 (53)	< 0.001
Unprotected LMCA disease, *N* (%)	1558 (5)	66 (7)	1492 (5)	0.008
Mitral regurgitation grade 3/4[a], *N* (%)	687 (2)	32 (3)	655 (2)	0.02
Ejection fraction, mean (SD), %	58.6 (12.9)	57.7 (13.0)	58.7 (12.9)	0.04
Ejection fraction ≤ 40%, *N* (%)	2542 (10)	72 (9)	2470 (10)	0.56
Prior PCI, *N* (%)	9089 (30)	267 (29)	8822 (30)	0.48
Prior CABG, *N* (%)	1230 (4)	48 (5)	1182 (4)	0.09
Prior MI[a], *N* (%)	6469 (22)	219 (24)	6250 (22)	0.08
Prior stroke[a], *N* (%)	3011 (10)	95 (10)	2916 (10)	0.71
Peripheral vascular disease[a], *N* (%)	2679 (9)	95 (10)	2584 (9)	0.13
eGFR < 30, not on dialysis[a], *N* (%)	1022 (3)	50 (6)	972 (3)	0.001
Dialysis[a], *N* (%)	1362 (5)	90 (10)	1272 (4)	< 0.001
Lesion characteristics				
Stent use, *N* (%)	30,051 (100)	915 (100)	29,136 (100)	–
DES use[a], *N* (%)	24,868 (83)	713 (78)	24,155 (83)	< 0.001
SES use, *N* (%)	19,592 (65)	622 (68)	18,970 (65)	0.07
PES use, *N* (%)	622 (2)	22 (2)	600 (2)	0.48
EES use, *N* (%)	3215 (11)	56 (6)	3159 (11)	< 0.001
BES use, *N* (%)	1753 (6)	24 (3)	1729 (6)	< 0.001
ZES use, *N* (%)	12 (0.04)	0 (0.0)	12 (0.04)	0.39
BMS use, *N* (%)	7641 (25)	303 (33)	7338 (25)	< 0.001
Number of target vessels, mean(SD)	1.3 (0.5)	1.4 (0.6)	1.3 (0.5)	< 0.001
Number of target lesions, mean(SD)	1.4 (0.7)	1.6 (0.8)	1.4 (0.7)	< 0.001
Target of LAD, *N* (%)	16,707 (56)	522 (57)	16,185 (56)	0.37
Target of proximal LAD[a], *N* (%)	15,903 (53)	500 (55)	15,403 (53)	0.29
Target of RCA, *N* (%)	11,943 (40)	408 (45)	11,535 (40)	0.003
Target of LCX, *N* (%)	8577 (29)	270 (30)	8307 (29)	0.51
Target of unprotected LMCA[a], *N* (%)	1098 (4)	44 (5)	1054 (4)	0.07
Target of SVG, *N* (%)	156 (0.5)	14 (1.5)	142 (0.5)	< 0.001
Target of arterial graft, *N* (%)	37 (0.1)	0 (0.0)	37 (0.1)	0.13
Target of STEMI culprit, *N* (%)	4763 (16)	184 (20)	4579 (16)	< 0.001
Target of CTO[a], *N* (%)	3205 (11)	116 (13)	3089 (11)	0.052
Target of restenotic lesion, *N* (%)	3139 (10)	86 (9)	3053 (10)	0.29
Target of bifurcation[a], *N* (%)	8519 (28)	274 (30)	8245 (28)	0.28
Side-branch stenting[a], *N* (%)	1379 (5)	47 (5)	1332 (5)	0.43

Table 1 (continued)

Characteristics	Total ($N=30,051$)	Post-discharge MI+ ($N=915$)	Post-discharge MI− ($N=29,136$)	P value
Target of aortic ostium, *N* (%)	873 (3)	37 (4)	836 (3)	0.049
Target of ostial LMCA, *N* (%)	202 (0.7)	6 (0.7)	196 (0.7)	0.95
Target of ostial RCA, *N* (%)	674 (2)	31 (3)	643 (2)	0.03
Target of ostial LAD/LCX, *N* (%)	1564 (5)	43 (5)	1521 (5)	0.48
IVUS use, *N* (%)	16,318 (54)	425 (46)	15,893 (55)	< 0.001
Total stent length, mean (SD), mm	39.4 (28.1)	44.1 (32.3)	39.3 (28.0)	< 0.001
Total stent length > 28 mm[a], *N* (%)	14,779 (49)	518 (57)	14,261 (49)	< 0.001
Minimum stent size, mean(SD), mm	2.9 (0.4)	2.8 (0.4)	2.9 (0.4)	< 0.001
Minimum stent size < 3.0 mm[a], *N* (%)	14,057 (47)	479 (52)	13,578 (47)	< 0.001
Medications at discharge				
Aspirin, *N* (%)	29,758 (99)	906 (99)	28,852 (99)	0.98
Thienopyridines, *N* (%)	29,768 (99)	907 (99)	28,861 (99)	0.83
Ticlopidine, *N* (%)	22,884 (76)	775 (85)	22,109 (76)	< 0.001
Clopidogrel, *N* (%)	6820 (22)	131 (14)	6689 (23)	< 0.001
Cilostazol[a], *N* (%)	3073 (10)	102 (11)	2971 (10)	0.36
Statins[a], *N* (%)	16,934 (56)	478 (52)	16,456 (57)	0.01
Beta blockers[a], *N* (%)	9441 (31)	325 (36)	9116 (31)	0.007
ACE-I/ARB[a], *N* (%)	17,284 (58)	513 (56)	16,771 (58)	0.37

ACE-I angiotensin-converting enzyme inhibitors, *ARB* angiotensin-receptor blockers, *AMI* acute myocardial infarction, *BES* biolimus-eluting stent, *BMI* body mass index, *BMS* bare-metal stent, *CABG* coronary artery bypass grafting, *CTO* chronic total occlusion, *DES* drug-eluting stent, *DM* diabetes mellitus, *EES* everolimus-eluting stent, *eGFR* estimated glomerular filtration rate, *IVUS* intravascular ultrasound, *LAD* left anterior descending coronary artery, *LCX* left circumflex coronary artery, *LMCA* left main coronary artery, *MI* myocardial infarction, *PCI* percutaneous coronary intervention, *PES* paclitaxel-eluting stent, *RCA* right coronary artery, *SES* sirolimus-eluting stent, *STEMI* ST-segment elevation myocardial infarction, *SVG* saphenous vein graft, *ZES* zotarolimus-eluting stent

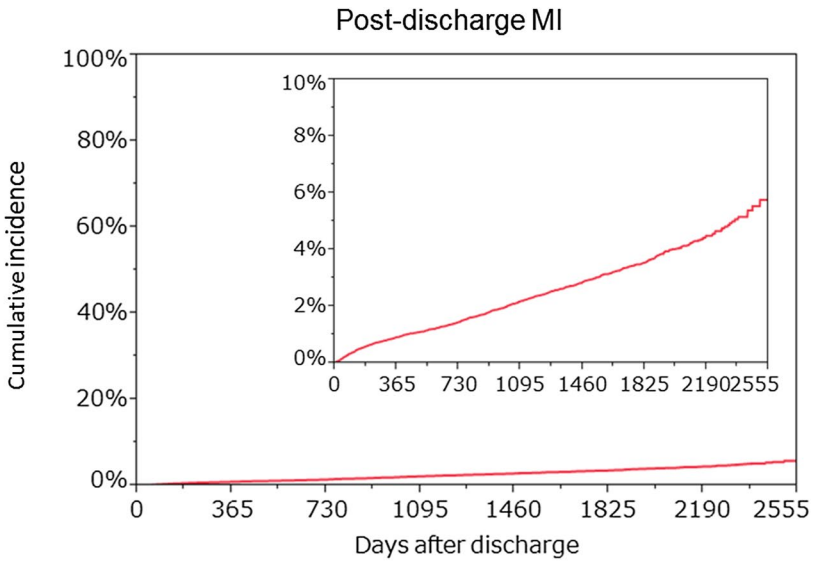
[a]27 risk-adjusting variables used in the multi-variate model evaluating the mortality risk of post-discharge MI

Table 2 Clinical outcomes at 5 years in the entire cohort

Event	Number of patients with at least 1 event during the entire follow-up period (cumulative 5-year incidence, %)
Death	3785 (14.1)
Cardiovascular death	1929 (7.3)
Cardiac death	1478 (5.6)
Sudden cardiac death	558 (2.2)
Non-cardiac death	2307 (8.9)
MI	915 (3.6)
Stroke	1424 (5.5)
Definite stent thrombosis	292 (1.1)
Definite/probable stent thrombosis	375 (1.5)
TLR	4573 (16.8)
Any coronary revascularization	9306 (34.3)
Death/MI/stroke	5318 (19.6)

MI myocardial infarction, *TLR* target-legion revascularization

landmark analysis at 6-month and 1-year after index PCI, incidence of MI beyond each landmark point was similar between patients with on-DAPT and off-DAPT (Figure S2-B, -C). The cumulative 5-year incidences of other clinical events included 14.1% for all-cause death, 5.5% for stroke, 1.5% for definite/probable ST, 16.8% for TLR, and 34.3% for any coronary revascularization (Table 2).



Post-discharge MI	0	365	730	1095	1460	1825	2190	2555
Number of patients with at least 1 event		270	420	612	740	836	898	914
Number of patients at risk	30,051	28,418	26,718	23,966	16,628	10,167	2840	211
Cumulative incidence		0.9%	1.5%	2.2%	2.9%	3.6%	4.5%	5.8%

Fig. 2 Kaplan–Meier curve for post-discharge myocardial infarction. *MI* myocardial infarction

Distribution of peak CK ratios of PDMI

Among the total 915 cases with first PDMI, peak CK ratio was missing in 377 patients and the peak CK values in 72 patients were regarded as not representing the true peak (Appendix S4). Therefore, there were 466 patients (50.9% of 915 cases) with PDMI, in whom the obtained peak CK ratio was adjudicated as capturing the true peak CK ratio.

Median peak CK ratio was 6.6 (IQR 3.3–13.0). Small-sized MI with peak CK ratio (< 3) was present in 21% of patients, while peak CK ratios, (≥ 3 and < 5), (≥ 5 and < 10), (≥ 10 and < 30), and (≥ 30) were present in 17, 25, 30, and 7.3% of patients, respectively (Fig. 3a). Baseline clinical and procedural characteristics as well as medications were generally comparable across the PDMI size categories (Table S3).

Subsequent mortality after PDMI

Overall 160 (17.5%) out of 915 patients with PDMI had fatal MI. The rate of fatal MI was very high among those patients in the largest MI size category and in the unknown MI size category, while it was very low among those

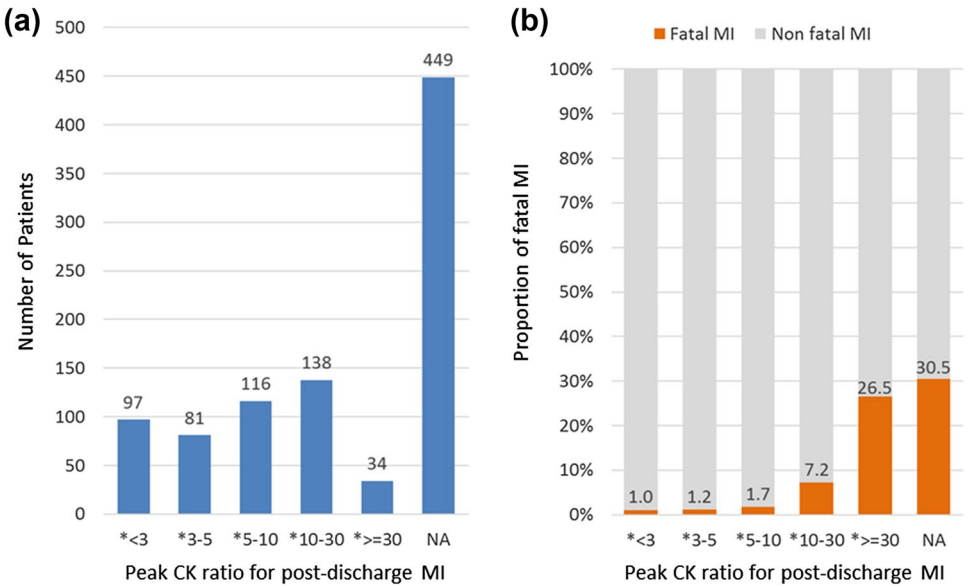


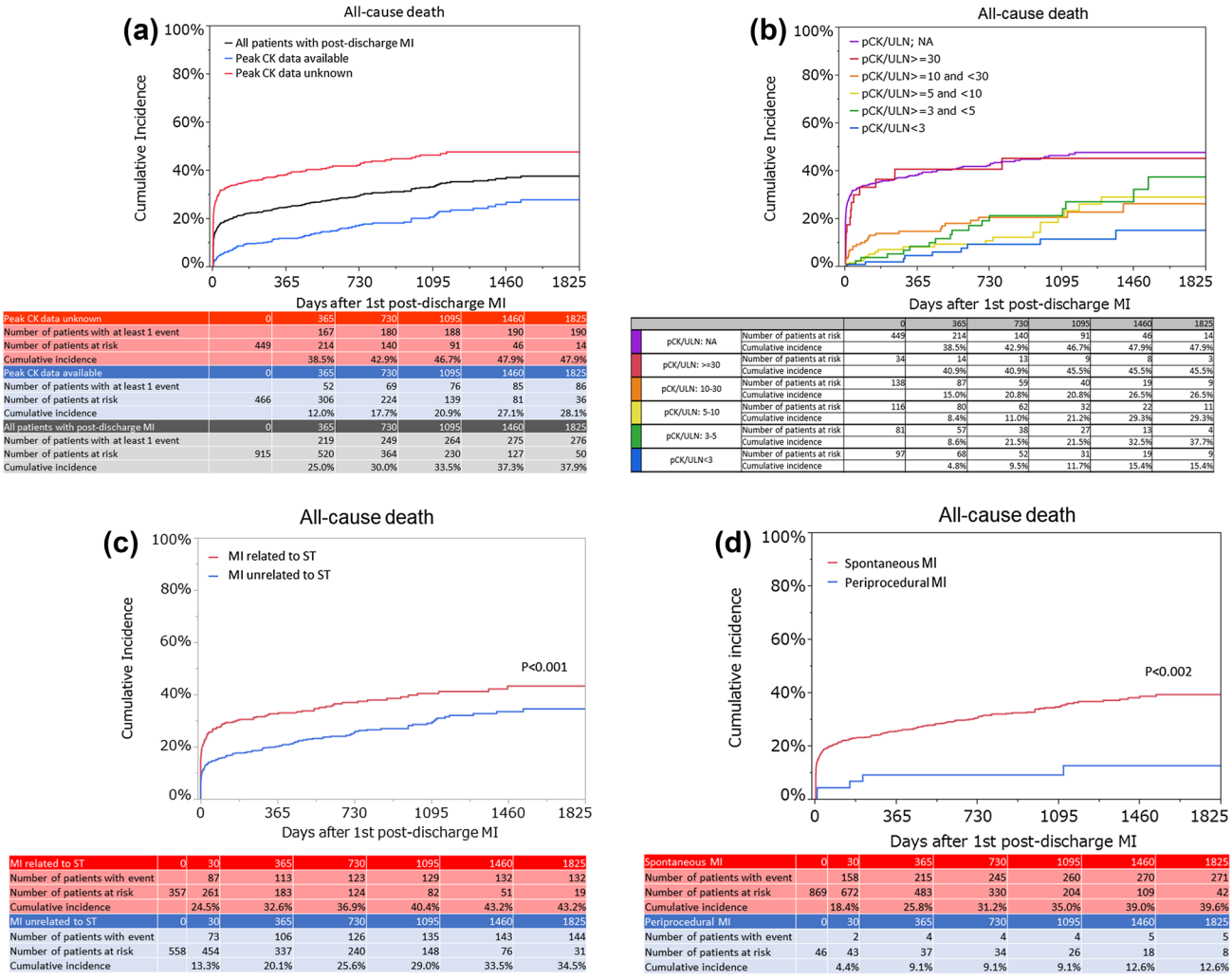
Fig. 3 Distribution of the PDMI size and proportion of fatal MI according to the PDMI size. **a** Number of PDMI cases classified by the peak CK ratio (peak CK divided by upper limit of normal), and **b** proportion of fatal MI according to the PDMI size. Number in **a** indicates the number of patients based on categorization at the first PDMI. NA refers to PDMI with unknown peak CK ratio. Fatal MI refers to fatal cases within 30 days from onset of MI. *CK* creatine kinase, *MI* myocardial infarction, *NA* not assessed

patients in the MI size categories with peak CK ratio < 10 (Fig. 3b). In a sensitivity analysis using the peak CK-MB ratio, the distribution of the PDMI size and the rate of fatal MI classified with MI size categories were consistent with those in the analysis using the peak CK ratio (Figure S3).

Cumulative 5-year incidence of all-cause death after PDMI was 37.9% overall (28.1% for known MI size and 47.9% for unknown MI size) (Fig. 4a). Cumulative 5-year incidence of all-cause death after PDMI varied widely according to the MI size with 15.4% for the smallest MI size category, and 45.5% for the largest MI size category (Fig. 4b). As a reference, the cumulative 5-year incidence of all-cause death after the index PCI procedure was 13.5% in patients without PDMI (Figure S4).

Difference of peak CK ratio and subsequent mortality risk after PDMI among the subsets related to stent thrombosis, spontaneous MI, lesion location, and reperfusion therapy

Among 915 PDMI cases, there were 357 cases related to definite or probable ST (39%), and 558 cases unrelated to ST (61%). Infarct size was significantly larger in ST-related MI than in non-ST-related MI (Table 3). The cumulative incidence of all-cause death after ST-related MI was higher than



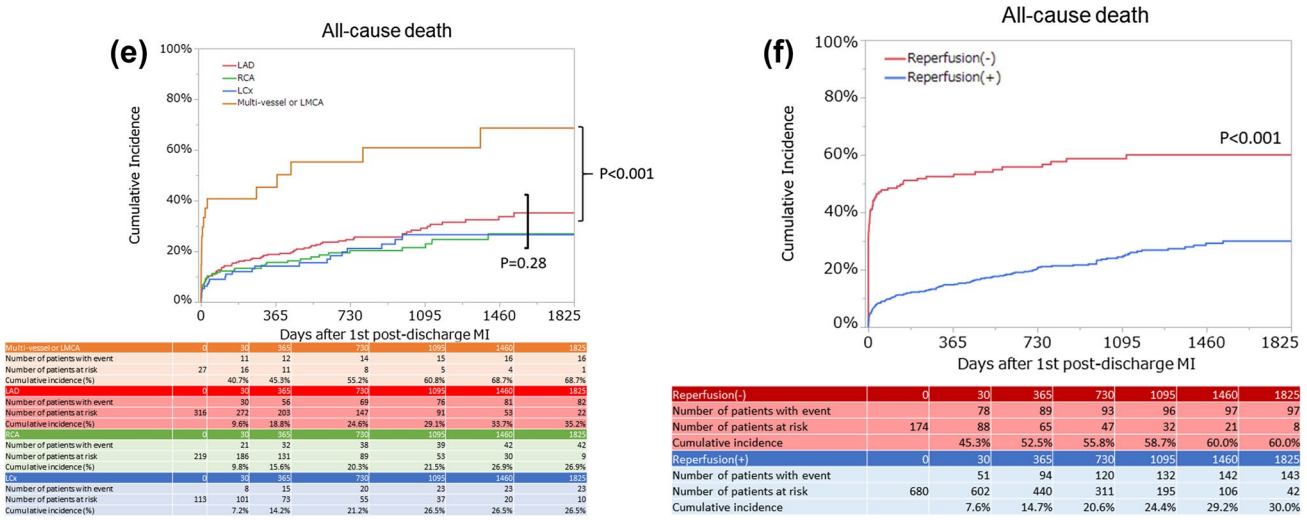
	0	365	730	1095	1460	1825
Peak CK data unknown	0	365	730	1095	1460	1825
Number of patients with at least 1 event		167	180	188	190	190
Number of patients at risk	449	214	140	91	46	14
Cumulative incidence		38.5%	42.9%	46.7%	47.9%	47.9%
Peak CK data available	0	365	730	1095	1460	1825
Number of patients with at least 1 event		52	69	76	85	86
Number of patients at risk	466	306	224	139	81	36
Cumulative incidence		12.0%	17.7%	20.9%	27.1%	28.1%
All patients with post-discharge MI	0	365	730	1095	1460	1825
Number of patients with at least 1 event		219	249	264	275	276
Number of patients at risk	915	520	364	230	127	50
Cumulative incidence		25.0%	30.0%	33.5%	37.3%	37.9%

		0	365	730	1095	1460	1825
pCK/ULN: NA	Number of patients at risk	449	214	140	91	46	14
	Cumulative incidence		38.5%	42.9%	46.7%	47.9%	47.9%
pCK/ULN: >=30	Number of patients at risk	34	14	13	9	8	3
	Cumulative incidence		40.9%	40.9%	45.5%	45.5%	45.5%
pCK/ULN: 10-30	Number of patients at risk	138	87	59	40	19	9
	Cumulative incidence		15.0%	20.8%	20.8%	26.5%	26.5%
pCK/ULN: 5-10	Number of patients at risk	116	80	62	32	22	11
	Cumulative incidence		8.4%	11.0%	21.2%	29.3%	29.3%
pCK/ULN: 3-5	Number of patients at risk	81	57	38	27	13	4
	Cumulative incidence		8.6%	21.5%	21.5%	32.5%	37.7%
pCK/ULN<3	Number of patients at risk	97	68	52	31	19	9
	Cumulative incidence		4.8%	9.5%	11.7%	15.4%	15.4%

		0	30	365	730	1095	1460	1825
MI related to ST		0	30	365	730	1095	1460	1825
Number of patients with event			87	113	123	129	132	132
Number of patients at risk		357	261	183	124	82	51	19
Cumulative incidence			24.5%	32.6%	36.9%	40.4%	43.2%	43.2%
MI unrelated to ST		0	30	365	730	1095	1460	1825
Number of patients with event			73	106	126	135	143	144
Number of patients at risk		558	454	337	240	148	76	31
Cumulative incidence			13.3%	20.1%	25.6%	29.0%	33.5%	34.5%

		0	30	365	730	1095	1460	1825
Spontaneous MI		0	30	365	730	1095	1460	1825
Number of patients with event			158	215	245	260	270	271
Number of patients at risk		869	672	483	330	204	109	42
Cumulative incidence			18.4%	25.8%	31.2%	35.0%	39.0%	39.6%
Periprocedural MI		0	30	365	730	1095	1460	1825
Number of patients with event			2	4	4	4	5	5
Number of patients at risk		46	43	37	34	26	18	8
Cumulative incidence			4.4%	9.1%	9.1%	9.1%	12.6%	12.6%

Fig. 4 Kaplan–Meier curves for all-cause death after PDMI. **a** All patients with PDMI and patients with or without peak CK ratio data, **b** according to the PDMI size categories indicated with pCK/ULN, **c** MI related to ST versus MI unrelated to ST, **d** spontaneous MI versus periprocedural MI related to coronary revascularization procedures during follow-up, **e** classified with culprit lesions, and **f** reperfusion therapy performed or not. Reperfusion therapy refers to either PCI, CABG, or systemic thrombolysis including delayed operation over 24 h from onset. *CABG* coronary artery bypass grafting, *CK* creatine kinase, *LAD* left anterior descending artery, *LCx* left circumflex artery, *LMCA* left main coronary artery, *MI* myocardial infarction, *NA* not assessed, PCI percutaneous coronary intervention, *pCK/ULN* peak creatine kinase divided by upper limit of normal, *ST* stent thrombosis



Multi-vessel or LMCA	0	30	365	730	1095	1460	1825
Number of patients with event		11	12	14	15	16	16
Number of patients at risk	27	16	11	8	5	4	1
Cumulative incidence (%)		40.7%	45.3%	55.2%	60.8%	68.7%	68.7%
LAD	0	30	365	730	1095	1460	1825
Number of patients with event		30	56	69	76	81	82
Number of patients at risk	316	272	203	147	91	53	22
Cumulative incidence (%)		9.6%	18.8%	24.6%	29.1%	33.7%	35.2%
RCA	0	30	365	730	1095	1460	1825
Number of patients with event		21	32	38	39	42	42
Number of patients at risk	219	186	131	89	53	30	9
Cumulative incidence (%)		9.8%	15.6%	20.3%	21.5%	26.9%	26.9%
LCx	0	30	365	730	1095	1460	1825
Number of patients with event		8	15	20	23	23	23
Number of patients at risk	113	101	73	55	37	20	10
Cumulative incidence (%)		7.2%	14.2%	21.2%	26.5%	26.5%	26.5%

Reperfusion(-)	0	30	365	730	1095	1460	1825
Number of patients with event		78	89	93	96	97	97
Number of patients at risk	174	88	65	47	32	21	8
Cumulative incidence		45.3%	52.5%	55.8%	58.7%	60.0%	60.0%
Reperfusion(+)	0	30	365	730	1095	1460	1825
Number of patients with event		51	94	120	132	142	143
Number of patients at risk	680	602	440	311	195	106	42
Cumulative incidence		7.6%	14.7%	20.6%	24.4%	29.2%	30.0%

Fig. 4 (continued)

Table 3 Peak CK ratio and subsequent mortality risk divided by various grouping of post-discharge myocardial infarction

	Number of cases (%)	Peak CK ratio			Mortality risk after first post-discharge MI in each classification[b]		Mortality risk compared with patients without post-discharge MI[c]	
		Number of available cases (%)	Median (IQR)	*P* value[a]	Adjusted HR (95% CI)	*P* value	Adjusted HR (95% CI)	*P* value
Stent thrombosis (ARC definite or probable)								
Unrelated to ST	558 (61.0%)	278 (49.8%)	5.4 (3.0–10.3)	–	1.00 (reference)	–	4.19 (3.54–4.97)	< 0.001
Related to ST	357 (39.0%)	188 (52.7%)	11.2 (4.6–19.2)	< 0.001	1.59 (1.24–2.04)	< 0.001	3.73 (2.92–4.76)	< 0.001
BMS-ST	48 (5.2%)	43 (89.6%)	12.7 (3.7–20.9)	0.002[a]	1.17 (0.65–2.09)	0.61	4.29 (2.61–7.03)	< 0.001
DES-ST	228 (24.9%)	136 (59.6%)	10.7 (4.8–18.6)	< 0.001[a]	0.81 (0.57–1.15)	0.24	3.58 (2.71–4.73)	< 0.001
Periprocedural or spontaneous MI								
Periprocedural MI	46 (5.0%)	32 (70.0%)	5.1 (3.5–7.3)	–	1.00 (reference)	–	1.23 (0.51–2.97)	0.64
Spontaneous MI	869 (95.0%)	434 (50.0%)	6.9 (3.3–14.3)	0.07	3.63 (1.47–8.96)	0.005	4.78 (4.18–5.47)	< 0.001
Involved vessel								
LAD	316 (34.5%)	203 (64.2%)	9.2 (3.7–18.3)	–	1.00 (reference)	–	3.61 (2.89–4.50)	< 0.001
RCA	219 (23.9%)	152 (69.4%)	6.3 (3.3–11.3)	< 0.001[a]	0.69 (0.46–1.03)	0.07	3.22 (2.37–4.37)	< 0.001
LCx	113 (12.3%)	76 (67.3%)	5.1 (3.1–11.3)	0.002[a]	0.69 (0.42–1.13)	0.14	2.84 (1.88–4.29)	< 0.001
Multi-vessel or LMCA	27 (3.0%)	17 (63.0%)	3.7 (1.9–37.0)	0.53	2.82 (1.49–5.33)	0.001	14.61 (8.82–24.19)	< 0.001
Reperfusion therapy								
Yes	680 (74.3%)	420 (61.8%)	6.9 (3.4–14.4)	–	1.00 (reference)	–	3.12 (2.63–3.69)	< 0.001
No	174 (19.0%)	45 (25.9%)	4.8 (3.1–7.6)	0.66	3.94 (2.94–5.29)	< 0.001	13.19 (10.72–16.23)	< 0.001

ARC Academic Research Consortium, *CK* creatine kinase, *ST* stent thrombosis. See also footnote of Table 1

[a]Wilcoxon's *P* value is shown compared with unrelated ST, periprocedural MI, LAD, and reperfusion therapy in each classification. *P* value between the peak CK ratio of BMS-ST and that of DES-ST was 0.67. *P* value between the peak CK ratio of RCA involved MI and LCx involved MI was 0.68

[b]*P* value and adjusted hazard ratio are shown compared with unrelated to ST, periprocedural MI, LAD, and reperfusion therapy, respectively

[c]*P* value and adjusted hazard ratio are shown as a reference for patients without post-discharge MI by Cox's hazard model with time-update covariates

that after non-ST-related MI, with the higher mortality risk mostly seen within 3 months after MI (Fig. 4c). After adjusting confounders, the excess mortality risk of ST-related MI relative to non-ST-related MI remained significant (HR 1.58, 95% CI 1.23–2.03, $P<0.001$, Table 3). There was no significant difference between 48 cases with MI related to BMS-ST and 228 cases with MI related to DES-ST in terms of peak CK ratio and subsequent mortality risk, although the time from index stent implantation to occurrence of stent thrombosis was quite different (Table 3 and Figure S5).

There were 46 periprocedural cases related to coronary revascularization procedures during follow-up, and 869 spontaneous cases among 915 PDMI cases. PDMI size trended to be larger in spontaneous MI than in periprocedural MI (Table 3). The cumulative incidence of all-cause death after PDMI was higher in patients with spontaneous MI than in patients with periprocedural MI (Fig. 4d). After adjusting confounders, the higher mortality risk of spontaneous MI relative to periprocedural MI remained significant (HR 3.63, 95% CI 1.47–8.96, $P=0.005$, Table 3).

MI culprit vessels were left anterior descending (LAD) only in 316 patients (34.5%), right coronary artery (RCA) only in 219 (23.9%), and left circumflex (LCx) only in 113 (12.4%) patients, while 27 (3.0%) patients had multi-vessel or left main coronary artery (LMCA) culprit. The culprit of remaining 240 (26.2%) could not be defined. Infarct size of MI with LAD lesion was higher than RCA or LCx lesion (Table 3). Infarct size of MI with multi-vessel or LMCA lesion had wide variation and was not significantly different from MI with LAD lesion (Table 3), though the subsequent mortality risk after MI was quite higher in MI with multi-vessel or LMCA lesion (Fig. 4e; Table 3). There was no significant difference of mortality risk among the MI culprit vessels involving single vessel only.

Among 915 cases with PDMI, 680 (74.3%) cases received reperfusion therapies including delayed treatment on 2 days or more after onset (642; primary PCI, 15; CABG, 1; systemic thrombolysis, and 22; delayed PCI or CABG). Peak CK ratio was not significantly different between MI with and without reperfusion therapy, while the prognosis of MI without reperfusion therapy was poor (Table 3; Fig. 4f).

Comparison of subsequent mortality risk of patients with PDMI versus patients without PDMI by Cox's hazard model with time-update covariate

Patients with PDMI including and excluding those with unknown peak CK ratio as compared with patients without PDMI had significantly higher risk for subsequent mortality during the entire follow-up period (adjusted HR 5.12, 95% CI 4.52–5.80, $P<0.001$, and adjusted HR 2.90, 95% CI 1.98–3.12, $P<0.001$, respectively). Excess mortality risk of PDMI relative to no PDMI was significant in the peak CK ratio categories except for the smallest MI size category (peak CK ratio < 3), the risk of which was similar to that of patients without PDMI (HR 0.85, 95% CI 0.43–1.71, $P=0.65$) (Fig. 5). In a sensitivity analysis using the peak CK-MB ratio, mortality risk according to the MI size was consistent with that in the analysis using the peak CK ratio (Figure S6).

While subsequent mortality risk of periprocedural MI was not significant, the other subsets of PDMI compared with no PDMI had significantly higher mortality risk (Table 3). The mortality risk of the peak CK ratio < 3 was consistently not significant in all the subsets of MI, except for MI with multi-vessel or left main trunk lesion (Table S4).

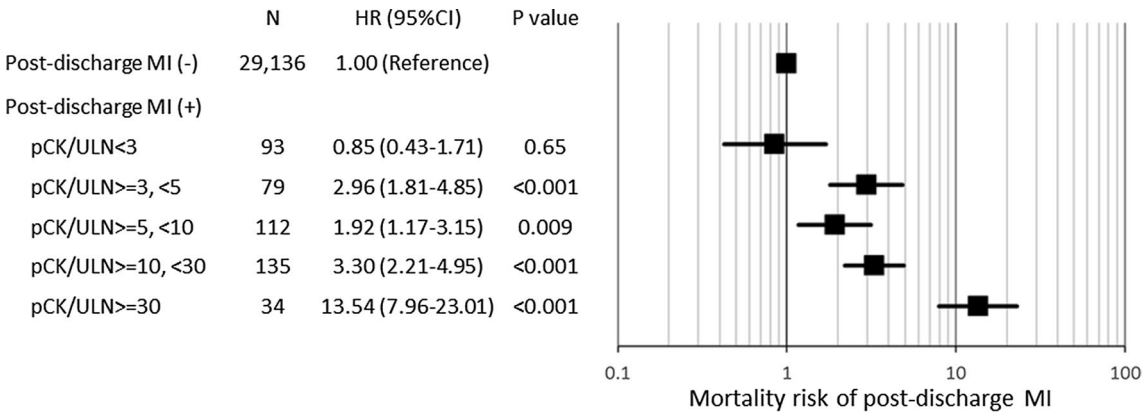


Fig. 5 Long-term mortality risk of PDMI according to the MI size in the time-updated Cox proportional hazard model. *N* indicates the number of patients finally updated into the category through entire follow-up period. *CK* creatine kinase, *MI* myocardial infarction, *pCK/ULN* peak creatine kinase divided by upper limit of normal

Discussion

The main findings of current study were as follows: (1) patients with PDMI were associated with fivefold higher subsequent mortality risk than those without; (2) however, mortality risk of patients with small PDMI with peak CK ratio < 3 was similar to that of patients without PDMI; (3) there was a markedly higher mortality risk in patients with MI related to ST or MI with multi-vessel or LMCA culprit.

MI along with death and stroke is usually included as a component of the primary composite endpoint in many cardiovascular clinical trials. MI has been included in the composite endpoint based on its clinically relevant prognostic impact. In the present study, PDMI was associated with fivefold higher subsequent mortality risk than those without, confirming the finding reported in the previous studies [5, 6]. Therefore, it would be appropriate to include MI along with death and stroke as a component of the primary composite endpoint in the cardiovascular clinical trials. However, in patients with small PDMI with peak CK ratio < 3, who constituted 21% of patients with PDMI with known CK peak ratio, mortality risk was similar to that of patients without PDMI. TRITON-TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis in Myocardial Infarction 38) trial was the only 1 previous study evaluating the impact of the MI size after PCI on subsequent cardiovascular death at 180 days after MI, though the study included periprocedural MI related to the index PCI [15]. Patients with peak biomarker level < 3*ULN trended to have higher cardiovascular mortality risk at 180 days than those without new MI (first MI; $N = 154$, HR 2.3, 95% CI 0.9–5.6, $P = 0.074$, and last MI; $N = 160$, HR 3.6, 95% CI 1.7–7.4, $P = 0.001$). One of the most important differences between the present study and TRITON-TIMI 38 was the duration of follow-up for evaluating subsequent mortality risk of MI. Mortality risk after MI peaks shortly after MI and attenuates thereafter (Fig. 4). Therefore, follow-up duration of 180 days may be too short to evaluate the long-term mortality risk after MI. Another important difference would be the mortality endpoint; all-cause death in the present study, and cardiovascular death in TRITON-TIMI 38. Non-cardiovascular death has been reported to be a frequent cause of death in patients undergoing PCI [16]. All-cause death would be the most robust endpoint to evaluate the mortality risk after MI. If those patients with small PDMI truly do not have excess mortality risk compared with those without PDMI, it may not be appropriate to include small MI as a component of the primary composite endpoint in clinical studies, because we should assume that each component of the primary composite endpoint should be of comparable clinical importance [17].

Further studies would be warranted to draw definitive conclusions on the need for setting a certain threshold CK or CK-MB ratio value for PDMI to be adjudicated as a component of the primary composite endpoint in clinical trials. However, it should be noted that in several recent studies, reduction of MI did not lead to reduction of death. In the DAPT trial, prolonged DAPT was associated with striking reduction of PDMI, but was associated with increase in major bleeding and all-cause death [18]. In the landmark analysis of the current study, prolonged DAPT beyond 6-month or 1-year was not associated with lower rate of MI beyond the landmark point, which was discordant with the result from the DAPT study. In the ADAPT-DES (Assessment of Dual Antiplatelet Therapy With Drug-Eluting Stent) study, post-discharge bleeding after PCI was strongly associated with 2-year mortality (HR 5.03; $P < 0.0001$), with an effect size greater than that of PDMI (HR 1.92; $P = 0.009$) [6]. It could be possible that small MI might be less clinically important than major bleeding. Furthermore, in the recently reported FOURIER (Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk) trial, administration of evolocumab as compared with placebo resulted in significant 27% relative risk reduction of MI (3.4 versus 4.6%) but did not have any impact on mortality (3.2 versus 3.1%) [19]. In the present study, post-discharge ST-related MI was associated with higher mortality risk than non-ST-related MI, while post-discharge periprocedural MI was associated with lower mortality risk than spontaneous MI. The higher mortality risk of ST-related MI versus non-ST-related MI, and spontaneous MI versus periprocedural MI could at least partially be explained by their larger infarct sizes. On the other hand, in patients with MI with multi-vessel or LMCA involvement and MI without reperfusion therapy, the peak CK ratio was not significantly different, but the prognosis was quite poor, though the number of patients was small and peak CK ratio was varied in multi-vessel MI. Left main or multi-vessel disease themselves might be a potent exacerbation factor regardless of infarct size. The previous report suggested that the early reperfusion therapy leads to washout phenomenon, where CK peak was earlier and the peak value tended to be high [20]. This might be a cause of lower peak CK value observed in cases without reperfusion therapy. However, it would be reasonable to focus on patients with reperfusion, because it is rare for patients with MI not receiving reperfusion therapy in contemporary clinical practice.

The present study has several important limitations. First, the incidence of PDMI was lower in the present study than those reported in the global studies such as DAPT trial [18]. The possibility of underreporting of clinical events could not be excluded. However, low rates of MI events have

been consistently reported in the fully monitored company-directed post-market surveillance registries of DES in Japan [21]. Evaluation of troponins might have been performed less widely in real clinical practice than in the clinical trials. Therefore, the proportion of small MI could be greater in the clinical trials than in the present study. Second, MI was adjudicated without biomarker data in a significant proportion of patients. Peak CK ratio was adjudicated as capturing the true peak CK ratio only in half of patients with PDMI. Third, CK is less specific for myocardial necrosis than CK-MB, though availability of CK-MB data is limited and use of CK-MB decrease the power of analysis. Fourth, regarding the peak CK ratio adjudication, it is theoretically undeniable about the potential unmeasured peak value between the 2 adjacent blood samplings. Finally, peak CK ratio categories used in the current analysis are arbitrary, although they were based on the previous reports on periprocedural MI. In addition, the mortality risk analysis in each peak CK ratio category might still be underpowered even in current large-sized pooled database. Therefore, further studies would be warranted to identify the possible threshold MI size influencing the long-term mortality.

Conclusions

Patients with PDMI were associated with fivefold higher subsequent mortality risk than those without. However, mortality risk of patients with small PDMI with peak CK ratio < 3 was similar to that of patients without PDMI, suggesting the presence of some threshold MI size influencing mortality.

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Compliance with ethical standards

Conflict of interest T. Kimura reports position as an advisory board member of Terumo Japan and Abbott Vascular. The other authors report no disclosures with regard to the content of this manuscript.

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Affiliations

Hirotoshi Watanabe[1] · Takeshi Morimoto[2] · Hiroki Shiomi[1] · Yusuke Yoshikawa[1] · Takao Kato[1] · Naritatsu Saito[1] · Satoshi Shizuta[1] · Koh Ono[1] · Kyohei Yamaji[3] · Kenji Ando[3] · Shuichiro Kaji[4] · Yutaka Furukawa[4] · Masaharu Akao[5] · Tetsuya Ishikawa[6] · Takashi Tamura[7] · Yoshito Yamamoto[8] · Toshiya Muramatsu[9] · Satoru Suwa[10] · Yoshihisa Nakagawa[11] · Kazushige Kadota[12] · Yoshiki Takatsu[13] · Hideo Nishikawa[14] · Yoshikazu Hiasa[15] · Yasuhiko Hayashi[16] · Shunichi Miyazaki[17] · Takeshi Kimura[1]

1 Department of Cardiovascular Medicine, Graduate School of Medicine, Kyoto University, 54 Shogoin-Kawahara cho, Sakyo-ku, Kyoto 606-8507, Japan

2 Department of Clinical Epidemiology, Hyogo College of Medicine, Nishinomiya, Japan

3 Division of Cardiology, Kokura Memorial Hospital, Kitakyushu, Japan

4 Department of Cardiovascular Medicine, Kobe City Medical Centre General Hospital, Kobe, Japan

5 Division of Cardiology, National Hospital Organization Kyoto Medical Centre, Kyoto, Japan

6 Division of Cardiology, The Jikei University Kashiwa Hospital, Kashiwa, Japan

7 Division of Cardiology, Japanese Red Cross Wakayama Medical Center, Wakayama, Japan

8 Division of Cardiology, Iwaki Kyoritsu Hospital, Iwaki, Japan

9 Division of Cardiology, Tokyo General Hospital, Tokyo, Japan

10 Division of Cardiology, Juntendo University Shizuoka Hospital, Izunokuni, Japan

11 Division of Cardiology, Tenri Hospital, Tenri, Japan

12 Division of Cardiology, Kurashiki Central Hospital, Kurashiki, Japan

13 Division of Cardiology, Hyogo Prefectural Amagasaki General Medical Centre, Amagasaki, Japan

14 Division of Cardiology, Mie Heart Centre, Mie, Japan

15 Division of Cardiology, Tokushima Red Cross Hospital, Tokushima, Japan

16 Division of Cardiology, Tsuchiya General Hospital, Hiroshima, Japan

17 Division of Cardiology, Department of Medicine, Faculty of Medicine, Kindai University, Osakasayama, Japan