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Frequency, causes, predictors, and clinical significance of peri-procedural myocardial infarction following percutaneous coronary intervention

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Aims Peri-procedural myocardial infarction (MI) is a not infrequent complication of percutaneous coronary intervention (PCI), but conflicting information exists regarding incidence and prognostic impact of this event. We investigated frequency, causes, predictors, and clinical relevance of peri-procedural MI, using a large database.

Methods and results We pooled individual patient-level data from 11 PCI studies in which peri-procedural creatine kinase-MB mass was routinely measured and mortality data were prospectively collected. Among 23 604 patients from 11 studies, 1677 {7.1% [95% confidence interval (CI) 6.8–7.5%]} had peri-procedural MI. The most common mechanism of peri-procedural MI was side-branch occlusion. Independent predictors of peri-procedural MI were older age, female gender, diabetes, hypertension, renal dysfunction, multivessel disease, left anterior descending artery disease, left main disease, bifurcation lesion, long lesion, drug-eluting stents, and number of stents. Follow-up varied from 1 year to 5 years. In a crude analysis, patients with peri-procedural MI had significantly a higher risk of mortality than those without peri-procedural MI [hazard ratio (HR) 1.47; 95% CI 1.24–1.74]. After adjustment for baseline covariates, peri-procedural MI was associated with an increased risk of mortality (HR 1.20; 95% CI 1.04–1.39).

Conclusion Among patients undergoing PCI, the occurrence of peri-procedural MI measured by CK-MB mass assay was ~7%, and more than half of cases were associated with side-branch occlusion. Several higher risk patients, lesions, and procedural characteristics were independent predictors of peri-procedural MI. Peri-procedural MI was associated with an increase in mortality.

Keywords Percutaneous coronary intervention • Myocardial infarction • Mortality

Introduction

Percutaneous coronary intervention (PCI) has been one of standard revascularization procedures for patients with significant coronary artery disease and the operators are now performing PCI for a wide variety of clinical and anatomic situations, giving public health significance to factors that affect the outcome of these procedures. Percutaneous coronary intervention can be associated with a small but significant incidence of several peri-procedural complications such as myocardial infarction (MI), thrombosis, stroke, major bleeding, or death. Among these events, peri-procedural MI, which can range from a minor elevation of cardiac enzymes to a large-sized infarct, is the most common complication.

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Previous several studies reported that the incidence of peri-procedural MI varies from 5 to 30% according to the diagnostic criteria and the local practices.[1,2] There have been several investigations regarding criteria, risk factors, and impact of peri-procedural MI on outcome.[3–6] However, the clinical relevance and long-term prognostic value still remain a matter of considerable debate. By this reasoning, there is no clarity adopting peri-procedural MI as a major outcome measure in clinical trials of PCI or pharmacological therapies.

The purpose of the present study was to determine the frequency, causes, and risk factors of peri-procedural MI and to assess the relationship between peri-procedural MI and mortality. To accomplish this, we pooled and analysed data from available randomized clinical trials and registries with similar methods, including case report forms, definitions, and adjudication procedures.

Methods

Study population, procedures, and enzyme measurements

For the present analysis, databases from 11 prospective PCI studies (8 randomized clinical trials and 3 registries) were pooled to provide a patient-level data analysis. Study designs and results have been previously published.[7–17] Among all studies included, peri-procedural enzyme creatine kinase-MB (CK-MB) mass data and mortality data were prospectively collected. These studies contain information on patient demographics, cardiac or coexisting risk factors, clinical manifestations, left ventricular function, angiographic and procedural characteristics, and in-hospital and follow-up outcomes. Relevant data were prospectively collected using a dedicated, electronic case report form by specialized personnel at each centre, and the Internet-based system provides each centre with immediate and continuous feedback on processes and quality-of-care measures. All databases are maintained at the Clinical Research Center of Asan Medical Center, Seoul, Korea, and therefore a convenience sample of 11 clinical studies was available in existing merged data sets. All of these studies were approved by the local institutional review board, and all patients provided written informed consent.

Among studies, PCI was performed according to current standard guidelines. Antiplatelet therapy and peri-procedural anticoagulation were administered according to standard regimens. All patients were prescribed aspirin (loading dose, 200 mg) plus clopidogrel (loading dose, 300 or 600 mg) before or during PCI. After the procedure, aspirin (100–200 mg per day) was continued indefinitely. Patients treated with drug-eluting stents were prescribed clopidogrel (75 mg per day) for at least 12 months and patients treated with bare-metal stents were prescribed clopidogrel for at least 1 month.

Routine measurements of CK-MB, as measured by mass assay, were performed in all patients according to each study protocol. Blood samples were routinely collected for the measurement of CK-MB levels at baseline, every 8 h for the first 24 h after the procedure, and daily thereafter during hospitalization. For each patient, the CK-MB ratio was calculated as the ratio between the peak CK-MB level and the upper limit of normal for the participating laboratory of each study. Among these studies, routine measurements of cardiac troponin after PCI were not performed in each centre due to no reimbursement by the government for this test in such situation. All laboratory testing was performed by personnel unaware of patient information and study objectives.

Event adjudication, definitions, and follow-up

For each study, an independent clinical events committee adjudicated all clinical endpoints of the study, and all outcomes of interest were confirmed by source documentation collected at each hospital. In cases adjudicated to be peri-procedural MI events, after thorough evaluations of baseline and post-procedural coronary angiograms by experienced and independent personnel, causes or mechanisms of MI were recorded as one of the following (as pre-specified in event adjudication form): side-branch occlusion, slow flow or no-reflow (abrupt closure), distal embolization, thrombus, flow-limiting dissection, disruption of collateral flow, others, or non-identifiable mechanical causes. All of the studies utilized the same angiographic core laboratory (Asan Medical Center, Seoul, Korea).

For all studies included in this analysis, peri-procedural MI was defined as an elevation of CK-MB >3 times the upper limit of the normal range in at least two blood samples with a normal range of baseline value within 48 h of the procedure. If the pre-PCI CK-MB values are elevated more than the upper normal limits, such as patients initially presented with acute MI, CK-MB re-elevation at least 50% greater than the most recent pre-procedure concentration with documentation that the values were stable or falling before PCI was required for the diagnosis of peri-procedural MI in this setting. Secondarily, an alternative criteria of MI (an elevation of CK-MB >5 times the upper limit of the normal range), defined post hoc, was also examined on the basis of recent arbitrary criteria of peri-procedural MI.[18] Death was defined as death resulting from any cause.

Among studies, clinical follow-up was performed via office visit or telephone contact at 1, 6, and 12 months and then every 6 or 12 months thereafter according to the study protocol. At each time of follow-up contact, data pertaining to patients' clinical status and interim occurrence of adverse events were collected. All other possible information derived from outpatient visits and hospital readmission or by the referring physician, patients, or relatives were entered into the dedicated database. For validation of complete follow-up data on mortality, information on deaths from the hospital was matched with the records from the National Population Registry of the Korea National Statistical Office by using a unique personal identification number.

Statistical analysis

Continuous variables are described as mean and SD, and dichotomous variables are described as counts and percentages. Baseline clinical, angiographic, and procedural characteristics were compared among patients with and without peri-procedural MI, using Student's *t*-tests or Mann–Whitney *U* tests for continuous variables and the χ^2 test or Fisher's exact test for categorical variables as appropriate.

Multivariable logistic regression analysis was performed to identify independent predictors associated with peri-procedural MI. Generalized estimating equations were used to account for between-study heterogeneity and within-study clustering.[19]

To examine the clinical impact of peri-procedural MI on mortality, we used a Cox proportional hazards model to compare the cumulative mortality rates between patients with peri-procedural MI and those without peri-procedural MI. To account for between-study heterogeneity and within-study clustering, since patients at the same study may have similar profiles of characteristics, the robust standard errors on the basis of sandwich estimators were used.[20] Then, to examine the time-dependent relationship of the presence of peri-procedural MI to mortality, we fitted a Cox proportional hazards model for mortality from 0 to 30 days (short term), 30 days to 1 year (intermediate term), and from 1 to 3 years (long term). This was done both with and

without the baseline covariates, which were clinically relevant or were significantly associated with mortality ($P < 0.05$) (study, age, sex, diabetes, history of MI, peripheral vascular disease, renal dysfunction, acute coronary syndrome, ejection fraction, multivessel disease, left main disease, bifurcation disease, stent type, and number of stents). The assumptions of the proportional hazards were statistically assessed on the basis of Schoenfeld residuals and graphically using log–log plots. No significant deviations from the assumption were noted. Unadjusted survival curves for between-groups were created using the Kaplan–Meier method and compared by the log-rank test.

All reported *P*-values were two-sided, and *P*-values <0.05 were considered to indicate statistical significance. The SAS software, version 9.1 (SAS Institute, Cary, NC, USA) was used for statistical analysis.

Results

Baseline characteristics and incidence of peri-procedural myocardial infarction

A total of 23 604 patients from 11 studies (8 randomized trials and 3 observational studies) were included in this analysis. Major clinical and demographic features of the patients of the included studies are shown in Supplementary material online, Appendix *Table SA1*. All the study populations had a mean age of 62 years, 70% of patients were men, 30% had diabetes, and 58% presented with acute coronary syndromes. For the devices of PCI, 82% patients received implantation of drug-eluting stents. Follow-up varied from 1 to 5 years.

Among 23 604 patients, 1677 {7.1% [95% confidence interval (CI) 6.8–7.4)} had peri-procedural MI; by ratio of CK-MB elevations, 713 (42.5%) had CK-MB ratio of 3 to <5, 567 (33.8%) had CK-MB ratio of 5 to <10, and 397 (23.7%) had CK-MB ratio of >10. The incidence of peri-procedural MI was 6.4% (1059 of 16 424) in men and 8.6% (619 of 7180) in women ($P < 0.001$). And, the incidence of peri-procedural MI was 8.2% (819 of 9948) in patients with stable angina and 6.3% (858 of 13 656) in patients with acute coronary syndromes ($P < 0.001$). By the alternative definition of MI, 964 patients had peri-procedural MI [4.1% (95% CI 3.8–4.3)].

Baseline, angiographic, and procedural characteristics according to the presence or absence of peri-procedural MI are shown in *Table 1*. Compared with patients without peri-procedural MI, those with peri-procedural MI had higher risk profiles of patient-, lesion-, and procedure-related characteristics.

Mechanisms and predictors of peri-procedural myocardial infarction

After source documentation of MI with a detailed review of baseline and procedural coronary angiogram, plausible causes underlying peri-procedural MI are shown in *Table 2*. Among them, side-branch occlusion was the most common cause of peri-procedural MI. In 21% of patients with peri-procedural MI, possible mechanical causes were not identifiable.

In a multivariable logistic generalized estimated equation regression model, older age, female gender, diabetes, hypertension, renal dysfunction, multivessel disease, left anterior descending artery disease, left main disease, bifurcation lesion, long lesion (>20 mm), drug-eluting stents, and number of stents were independent predictors of peri-procedural MI (*Table 3*). When this model was performed for alternative definition of peri-procedural MI, the key predictors were similar.

Association of peri-procedural myocardial infarction with mortality

During a mean follow-up period of 2.9 years, 1023 total deaths occurred. The unadjusted all-cause mortality rate was 5.7% (95% CI 4.6–6.9) in patients with peri-procedural MI and 4.2% (95% CI 3.9–4.5) in those without peri-procedural MI (*Figure 1*). In crude analyses using a Cox proportional hazards model, patients with peri-procedural MI were significantly associated with an increased risk of mortality compared with those without peri-procedural MI (*Table 4*). When a crude Cox model was fitted to the 30-day, 1-year, and 3-year mortality data, the presence of peri-procedural MI was associated with intermediate- and long-term risk of mortality, but not with short-term mortality. These findings were also consistent using the alternative definition of peri-procedural MI (*Figure 2*, *Table 4*).

After baseline risk adjustment, patients with peri-procedural MI had a higher risk of mortality than did patients without peri-procedural MI (adjusted hazard ratio 1.20; 95% CI 1.04–1.39) (*Table 4*). These findings did not differ according to gender and clinical presentation; there was no interactions between subgroup features and the effect of peri-procedural MI on mortality (interaction *P*-value for gender = 0.38, and interaction *P*-value for clinical presentation = 0.52). However, in a landmark analysis according to time interval, none of the interval measures were statistically significant. Analysis of the alternative definition of peri-procedural MI yielded similar results (*Table 4*).

Discussion

This is the largest study, in which CK-MB mass assay was routinely performed in all patients, to systematically evaluate the frequency, causes, predictors, and clinical relevance of peri-procedural MI using patient-level data from several PCI trials. The major findings are (i) the overall incidence of peri-procedural MI was ~7%; (ii) side-branch occlusion is the most common cause, and there was no identifiable mechanical cause in one-fifth; (iii) several higher risk clinical, angiographic, and procedural features were identified as independent predictors; (iv) peri-procedural MI was associated with an increased risk of mortality.

In our study, the overall incidence of peri-procedural MI was 7.1%, which was within the expected range of previous PCI studies using the same CK-MB criteria.[21,22] Recent consensus documents support that the preferred biomarker for myocardial necrosis is cardiac troponin (I or T), which has high myocardial tissue specificity as well as high clinical sensitivity.[18,23] With its increased sensitivity, compared with CK-MB measurement, the use of cardiac troponin might significantly increase the prevalence of peri-procedural MI. Several studies showed that measurement of troponin indeed resulted in a doubling or tripling of the rate of diagnosis of MI.[5,21,24] However, until now, there is less experience using this biomarker and it may be overly sensitive for

Table 1 Baseline characteristics of patients according to peri-procedural myocardial infarction

Variable	Overall population (n = 23 604)	Peri-procedural MI		P-value
		No (n = 21 927)	Yes (n = 1677)	
Demographics				
Age (years)	61.7 ± 10.3	61.5 ± 10.3	64.0 ± 9.6	<0.001
Sex				<0.001
Men	16 424 (69.6)	15 365 (70.1)	1059 (63.1)	
Women	7180 (30.4)	6562 (29.9)	618 (36.9)	
Clinical characteristics or coexisting conditions, n (%)				
Diabetes	6995 (29.6)	6492 (29.6)	503 (30.0)	0.74
Hypertension	13 101 (55.5)	12 054 (55.0)	1047 (62.4)	<0.001
Current smoker	7211 (30.5)	6764 (30.8)	447 (26.7)	<0.001
Hyperlipidaemia	9752 (41.3)	9013 (41.1)	739 (44.1)	0.02
Previous MI	2249 (9.5)	2083 (9.5)	166 (9.9)	0.59
Previous PCI	2898 (12.3)	2710 (12.4)	188 (11.2)	0.17
Previous bypass surgery	419 (1.8)	397 (1.8)	22 (1.3)	0.14
Previous congestive heart failure	315 (1.3)	290 (1.3)	25 (1.5)	0.56
Previous stroke	1327 (5.6)	1206 (5.5)	121 (7.2)	0.003
Peripheral vascular disease	390 (1.7)	353 (1.6)	37 (2.2)	0.07
Renal dysfunction	513 (2.2)	460 (2.1)	53 (3.2)	0.004
Acute coronary syndrome	13 656 (57.9)	12 798 (58.4)	858 (51.2)	<0.001
Ejection fraction (%)				0.54
<40%	852 (3.6)	789 (3.6)	63 (3.8)	
40–50%	2668 (11.3)	2492 (11.4)	176 (10.5)	
>50	20 084 (85.1)	18 646 (85.0)	1438 (85.7)	
Mean	59.1 ± 8.9	59.1 ± 9.0	59.1 ± 8.8	0.89
Lesion and procedural characteristics, n (%)				
Multivessel disease	12 004 (50.9)	10 857 (49.5)	1147 (68.4)	<0.001
Left anterior descending artery disease	14 206 (60.2)	13 085 (59.7)	1121 (66.8)	<0.001
Left main disease	1441 (6.1)	1272 (5.8)	169 (10.1)	<0.001
Bifurcation lesion	5393 (22.8)	4822 (22.0)	571 (34.0)	<0.001
Long lesion (>20 mm)	16 207 (68.7)	14 753 (67.3)	1454 (86.7)	<0.001
Total occlusion	27.0 (11.4)	2544 (11.6)	157 (9.4)	0.005
Use of glycoprotein IIb/IIIa inhibitor	3823 (16.2)	3574 (16.3)	249 (14.8)	0.12
Stent type				0.002
Bare-metal stents	4260 (18.0)	4005 (18.3)	255 (15.2)	
Drug-eluting stents	19 344 (82.0)	17 922 (81.7)	1422 (84.8)	
Number of stents				<0.001
1	12 561 (53.4)	12 114 (55.5)	447 (26.7)	
2	6482 (27.6)	5952 (27.3)	530 (31.6)	
≥3	4465 (19.0)	3766 (17.2)	699 (41.7)	
Mean	1.7 ± 1.0	1.7 ± 1.0	2.4 ± 1.3	<0.001
Total stent length (mm)	41.3 ± 27.3	40.0 ± 26.3	58.4 ± 33.9	<0.001

Data are shown as mean (SD) for continuous variables and absolute numbers (percentage) for dichotomous variables.
MI, myocardial infarction; PCI, percutaneous coronary intervention.

discriminating prognostic impact.[25] In the upcoming year, the specificity for PCI-related coronary events and prognostic relevance of troponin should be confirmed through large clinical trials, and also its increased sensitivity has to be carefully weighed against the reduced specificity for device-specific outcomes.[26]

There is limited support in the literature for determining the relative frequency of plausible mechanisms based on large data sets with solid angiographic documentations. In the current study, peri-procedural MI was most commonly due to side-branch occlusion. The current available evidence and the usual approach

Table 2 Causes underlying peri-procedural myocardial infarction

Underlying causes	Percentage (number of patients)
Side-branch occlusion	57.3 (961)
Slow flow or no reflow (abrupt closure)	9.3 (156)
Distal embolization	3.3 (55)
Thrombus	4.1 (69)
Flow-limiting dissection	4.0 (67)
Disruption of collateral flow	0.1 (2)
Others	0.9 (15)
Non-identifiable mechanical causes	21.0 (352)

Data are shown as percentage (absolute number).

Table 3 Independent predictors of peri-procedural myocardial infarction

Variables	OR (95% CI)	Wald χ^2	*P*-value
Peri-procedural MI, pre-specified definition (CK-MB ratio >3)			
Age, per 1-year increase	1.02 (1.01–1.03)	5.71	0.02
Female gender	1.31 (1.20–1.42)	41.02	<0.001
Diabetes	1.21 (1.15–1.29)	44.01	<0.001
Hypertension	1.15 (1.05–1.27)	9.15	0.003
Renal dysfunction	1.39 (1.19–1.63)	16.55	<0.001
Multivessel disease	1.25 (1.11–1.42)	12.48	<0.001
Left anterior descending artery disease	1.24 (1.12–1.38)	15.78	<0.001
Left main disease	1.25 (1.08–1.46)	8.76	0.003
Bifurcation lesion	1.25 (1.03–1.53)	5.03	0.02
Long lesion (>20 mm)	1.96 (1.63–2.36)	51.61	<0.001
Drug-eluting stents	1.38 (1.08–1.76)	6.86	0.009
Number of stents	1.51 (1.41–1.62)	135.41	<0.001
Peri-procedural MI, alternatively defined (CK-MB ratio >5)			
Age, per 1-year increase	1.02 (1.01–1.03)	4.70	0.03
Female gender	1.44 (1.27–1.63)	31.90	<0.001
Diabetes	1.26 (1.14–1.40)	18.85	<0.001
Current smoking	1.15 (1.05–1.25)	9.86	0.002
Hyperlipidaemia	1.18 (1.00–1.40)	3.90	0.048
Peripheral vascular disease	1.57 (1.10–2.25)	6.16	0.01
Renal dysfunction	1.65 (1.32–2.06)	19.15	<0.001
Multivessel disease	1.35 (1.11–1.63)	9.34	0.002
Left anterior descending artery disease	1.16 (1.02–1.33)	4.94	0.03
Bifurcation lesion	1.33 (1.13–1.56)	11.72	<0.001
Long lesion (>20 mm)	1.97 (1.60–2.42)	40.97	<0.001
Number of stents	1.51 (1.38–1.64)	87.40	<0.001

CI, confidence interval; CK-MB, creatine kinase MB; MI, myocardial infarction; OR, odds ratio. Wald χ^2 and C-statistic for the first model was 917.38 and 0.72, respectively. Wald χ^2 and C-statistic for the second model was 630.75 and 0.73, respectively.

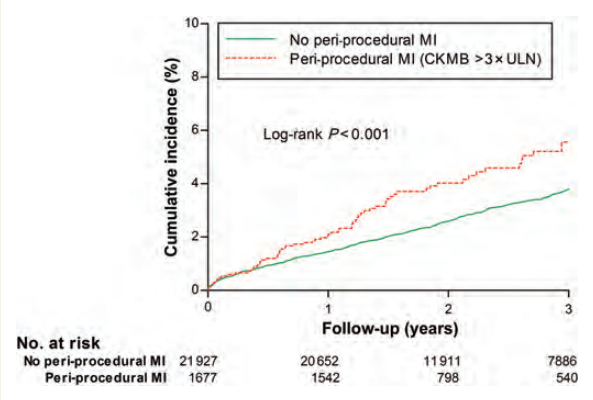

Figure 1 Mortality in patients with and without peri-procedural myocardial infarction using pre-specified definition. Kaplan–Meier survival curves show observed mortality rates for patients with and without peri-procedural myocardial infarction (MI) using original definition of myocardial infarction (CK-MB >3× UNL), which was pre-specified in each study protocol. *P*-value was calculated by the log-rank test. CK-MB, creatine kinase-MB; ULN, upper limit of normal.

support a strategy of main vessel only stenting with provisional stenting of the side branch.[27] Our findings may additionally emphasize that careful review of side-branch anatomy and optimal side-branch protection during extensive PCI is required to minimize procedural necrosis. In 20% of peri-procedural MI events, no mechanical causes were identified. This may be partly attributable to micro-embolization of thrombotic or atherosclerotic material, which can be undetectable in coronary angiogram, as suggested in imaging study using cardiac magnetic resonance.[28] Previous study suggested that the adverse effect of any MI on mortality was confined to patients with evident angiographic complications, not those without angiographic complications.[29] Therefore, it warrants further studies to determine whether additional monitoring or management is indicated for isolated CK-MB elevation without obvious angiographic complications.

There are conflicting data regarding the prognostic relevance of peri-procedural MI.[1,2,22] In our study, peri-procedural MI was associated with an increased risk of morality. However, we cannot address whether peri-procedural MI has direct causality for mortality or it functions as a marker of more severe coronary atherosclerosis and procedural complexity that is responsible for higher mortality after PCI.[2] In addition, our study does not delineate the mechanism linking peri-procedural MI and mortality. Meanwhile, in clinical viewpoint, the presence of peri-procedural MI would be used to be an important biomarker descriptor identifying high-risk patients for future clinical events.

In our study, the incidence of peri-procedural MI was significantly lower in patients with acute coronary syndrome than in those with stable angina (6.3 vs. 8.2%, $P < 0.001$). The current MI definition could have penalized the acute coronary syndrome population, especially in patients with elevated baseline enzyme (i.e. NSTEMI or STEMI), because a second MI could be adjudicated with documentation of falling or nadir levels of enzyme.[2] Since

Table 4 Unadjusted and adjusted hazard ratios for mortality, according to the presence of peri-procedural myocardial infarction[a]

Outcome	Total number of events/patients	Unadjusted		Multivariable adjusted[b]	
		Hazard ratio (95% CI)	*P*-value	Hazard ratio (95% CI)	*P*-value
Peri-procedural MI, pre-specified definition					
No peri-procedural MI (CK-MB ratio 0 to 3)	928/21 927	Referent	Referent	Referent	Referent
Peri-procedural MI (CK-MB ratio >3)					
Overall 3-year mortality	95/1677	1.47 (1.24–1.74)	<0.001	1.20 (1.04–1.39)	0.01
Landmark analysis by time interval					
30-day mortality	8/1677	1.09 (0.48–2.47)	0.84	1.03 (0.42–2.54)	0.95
30-day to 1-year mortality	28/1669	1.57 (1.03–2.41)	0.04	1.34 (0.88–2.03)	0.17
1-year to 3-year mortality	59/1641	1.49 (1.17–1.90)	0.001	1.17 (0.91–1.50)	0.22
Peri-procedural MI, alternatively defined					
No peri-procedural MI (CK-MB ratio 0 to 5)	965/22 640	Referent	Referent	Referent	Referent
Peri-procedural MI (CK-MB ratio >5)					
Overall 3-year mortality	58/964	1.61 (1.25–2.08)	<0.001	1.33 (1.03–1.71)	0.03
Landmark analysis by time interval					
30-day mortality	5/964	1.19 (0.32–4.45)	0.80	1.20 (0.32–4.43)	0.79
30-day to 1-year mortality	17/959	1.64 (1.02–2.64)	0.04	1.39 (0.87–2.23)	0.17
1-year to 3-year mortality	36/942	1.68 (1.18–2.39)	0.004	1.32 (0.90–1.93)	0.16

CK-MB, creatine kinase MB; MI, myocardial infarction.
[a]Hazard ratios are shown for patients with peri-procedural MI compared with those without peri-procedural MI.
[b]Adjustments were made for study, age, sex, diabetes, history of MI, peripheral vascular disease, renal dysfunction, acute coronary syndrome, ejection fraction, multivessel disease, left main disease, bifurcation disease, stent type, and number of stents.

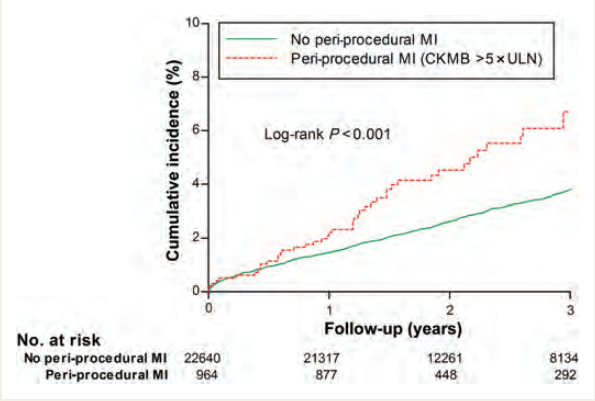

Figure 2 Mortality in patients with and without peri-procedural myocardial infarction using alternative definition. Kaplan–Meier survival curves show observed mortality rates for patients with and without peri-procedural myocardial infarction (MI) using alternative definition (CK-MB >5× UNL), which was defined *post hoc*. *P*-value was calculated using the log-rank test. CK-MB, creatine kinase-MB; ULN, upper limit of normal.

most cases of NSTEMI or STEMI involve PCI during a period when biomarkers are increasing, a reliable distinction between subsequent MI and index MI event is very difficult in clinical practice. Therefore, to define a second MI for such individuals, clearer guidelines and diagnostic criteria remain to be established.

By arbitrary convention of third universal definition of MI,[18] the incidence of peri-procedural MI was significantly lower than the rate of MI, using pre-specified definition (4.1 vs. 7.1%). However, there were no significant differences of important predictors for peri-procedural MI and its prognostic impact among two different criteria. If other mandatory criteria of ischaemic, angiographic, or imaging findings of third definition of MI, which are not currently available in our data sets, are simultaneously applied, the prevalence of MI would be further decreased, but the prognostic influence would be more intensified. Further studies are needed to verify the clinical utility and prognostic value of newer definition of MI among diverse PCI settings.

Potential limitations of our study warrant discussion. As a retrospective observational analysis, residual confounding or selection bias cannot be completely excluded. And, since this is a secondary data analysis, results should be considered hypothesis-generating only and need to be confirmed in an additional dedicated study. Second, the database merged several clinical studies, and inter-study variability may exist that could have influenced results. In addition, our analysis merged data from randomized trials and observational registries, which are different in terms of the nature of study designs. However, to account for between-study heterogeneity and within-study clustering, adequate statistical techniques were used, and major findings were overall consistent in a cohort of randomized trials and a cohort of observation studies.

Third, since we did not systematically measure cardiac troponin, comparison of two biomarkers for the detection of peri-procedural are not feasible. Fourth, a majority of patients did not have a complete follow-up of 3 years; there would be a potential for ascertainment bias to assess late mortality impact beyond 1 year. And, although the study was adequately powered to test the difference in mortality among the overall population, it might be underpowered to detect differences in each landmark analysis. Finally, it should be also recognized that there are differences in the PCI practice and monitoring of cardiac biomarkers at the time of PCI between our and other institutions.[30]

Conclusions

Among patients undergoing PCI in contemporary practice, the occurrence of peri-procedural MI as measured by CK-MB mass assay was 7.1%. More than half of peri-procedural MI was associated with side-branch occlusion, and several higher risk patient-, lesion-, and procedure-related characteristics were identified as major predictors. Peri-procedural MI was associated with an increased risk of mortality. This finding may have important clinical implications for practice and inform the valuable insights for using peri-procedural MI as a major outcome measure in future PCI trials.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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