Impact of the Angiographic Mechanisms Underlying Periprocedural Myocardial Infarction After Drug-Eluting Stent Implantation

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Periprocedural myocardial infarction (MI) can be induced by several angiographic mechanisms. However, there are limited data on whether these mechanisms differentially affect clinical outcomes. The purpose of our study was to investigate the impact of periprocedural MI on mortality according to the underlying angiographic mechanisms after drug-eluting stent (DES) implantation. We pooled the databases from 7 coronary stent trials using DES. Periprocedural MI was classified according to its underlying angiographic mechanisms as type 1 (due to side-branch occlusion), type 2 (due to other angiographic complications), or type 3 (without angiographically identifiable causes). Among 10,889 patients treated with DES, 768 (7.1%) experienced periprocedural MI; 463 cases (60.3%) were driven by type 1 cause, 138 (18.0%) by type 2 cause, and 167 (21.7%) by type 3 cause. Mortality rates at 2 years were higher in patients with periprocedural MI than in those without (3.5% vs 2.1%, respectively). Significant differences in mortality were observed according to the angiographic mechanisms of MI (type 1: 2.8% vs type 2: 6.1% vs type 3: 3.1%). After multivariable adjustment, type 2 MI was significantly associated with an increased risk of mortality (hazard ratio 2.65, 95% confidence interval 1.77 to 3.96), whereas type 1 and type 3 MI were not related with increased mortality. In conclusion, among patients receiving DES implantation, periprocedural MI was associated with increased mortality, and there were differential associations with mortality according to the underlying angiographic mechanisms. **(Am J Cardiol 2014;113:1105−1110)**

The purpose of the present study was to investigate the angiographic mechanisms of periprocedural myocardial infarction (MI) using a core laboratory angiographic analysis and to evaluate the different effects of periprocedural MI on mortality according to the mechanisms of procedural infarction among patients who underwent percutaneous coronary intervention (PCI) with drug-eluting stent (DES) implantation. To accomplish this, we pooled and analyzed data from several clinical studies with similar methods, including case report forms, definitions, and adjudication process.

Methods

For the present analysis, databases from 7 independent, prospective clinical studies (6 randomized clinical trials and 1 observational study), in which enrolled patients had undergone PCI with DES for the treatment of stable coronary artery disease or acute coronary syndromes, were pooled to provide a patient-level data analysis. The details of the study designs and primary results have been previously published elsewhere,[1−7] and justification for pooling has been previously reported.[8] These studies contain information on patient demographics, cardiac or coexisting risk factors, clinical manifestations, left ventricular function, angiographic and procedural characteristics, and clinical outcomes. The primary clinical outcome of this study was cumulative all-cause mortality. 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 using a unique personal identification number. All the studies were approved by the local institutional review board, and all patients provided written informed consent.

Routine measurements of creatine kinase-MB (CK-MB) isoenzyme 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 hours for the first 24 hours 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 measurement of cardiac troponin after PCI was not available.[8]

For all studies included in this analysis, all CK-MB elevations were reviewed by an independent clinical events committee, classifying MIs according to the predefined criteria. Periprocedural MI was defined as an elevation of

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Table 1
Summary of clinical studies used in the pooled analysis

Source	No. of Patients Enrolled	Types of Study Design		Type of Patients or Lesions Evaluated	DESs Compared
		Multicenter	Randomized		
ZEST[1]	2,645	O	O	All-comer patients with PCI	Zotarolimus vs sirolimus vs paclitaxel eluting
ZEST-AMI[2]	328	O	O	STEMI	Zotarolimus vs sirolimus vs paclitaxel eluting
LONG-DES II[3]	500	O	O	Long (≥25 mm) native coronary lesions	Sirolimus vs paclitaxel eluting
LONG-DES III[4]	450	O	O	Long (≥25 mm) native coronary lesions	Everolimus vs sirolimus eluting
LONG-DES IV[5]	500	O	O	Long (≥25 mm) native coronary lesions	Zotarolimus vs rolimus eluting
ESSENCE-Diabetes[6]	300	O	O	Patients with diabetes	Everolimus vs sirolimus eluting
IRIS-DES[7]	6,166	O	X	All-comer patients with PCI	Everolimus vs sirolimus eluting

ESSENCE-DM = randomized comparison of everolimus-eluting stent versus sirolimus-eluting stent implantation for de novo coronary artery disease in patients with diabetes mellitus; IRIS-DES = Interventional Cardiology Research In-cooperation Society-Drug-Eluting Stents Registry; LONG-DES = percutaneous treatment of long native coronary lesions with drug-eluting stent; STEMI = ST-segment elevation myocardial infarction; ZEST = comparison of the efficacy and safety of zotarolimus-eluting stent with sirolimus-eluting and paclitaxel-eluting stent for coronary lesions; ZEST-AMI = comparison of the efficacy and safety of zotarolimus-, sirolimus-, and paclitaxel-eluting stents in patients with STEMI.

Table 2
Underlying angiographic causes of periprocedural myocardial infarction

Underlying Causes	
Type 1	
Side-branch occlusion	463 (60.3)
Type 2 (other angiographic complications)	138 (18.0)
Slow flow or no-reflow (abrupt closure)	59 (7.7)
Distal embolization	23 (3.0)
Thrombus	25 (3.3)
Flow-limiting dissection	26 (3.4)
Disruption of collateral flow	1 (0.1)
Others	4 (0.5)
Type 3	
Nonidentifiable mechanical causes	167 (21.7)

Data are presented as n (%).

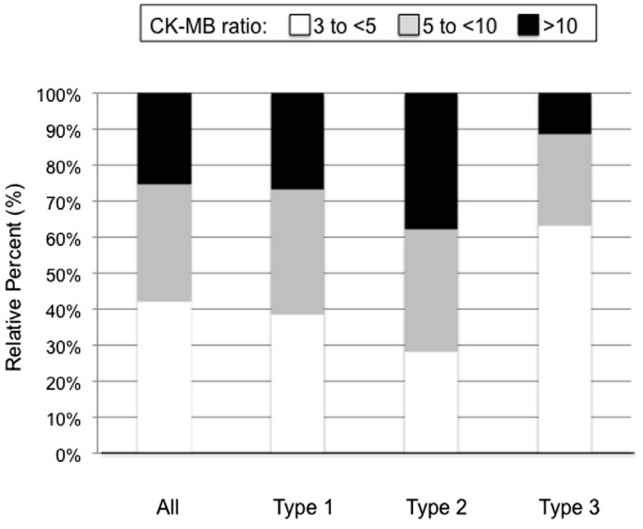

Figure 1. Relative proportions of cardiac enzyme elevation levels according to the types of angiographic mechanisms underlying periprocedural MI. Type 1 denotes MI due to side-branch occlusion, type 2 denotes MI due to other angiographic complications, and type 3 denotes MI without angiographically identifiable causes.

CK-MB >3 times the upper limit of the normal range in at least 2 blood samples with a normal baseline value within 48 hours after the procedure. In patients with pre-PCI values higher than the upper normal limits, a CK-MB re-elevation at least 50% greater than the most recent preprocedure concentration was required with documentation that biomarkers were decreasing or at nadir before PCI. All the studies utilized the same angiographic core laboratory (Asan Medical Center, Seoul, Korea). For periprocedural MI events, angiographic mechanisms of MI were recorded as one of the following (as prespecified in the 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 nonidentifiable mechanical causes. For the current analysis, according to the underlying angiographic mechanisms, MI was classified into 1 of the 3 types: type 1, MI due to side-branch occlusion; type 2, MI due to other angiographic complications (e.g., slow flow or no-reflow, distal embolization, thrombus, flow-limiting dissection, disruption of collateral flow, or others); type 3, MI without angiographically identifiable causes. A similar classification scheme was suggested in previous study.[9]

Continuous variables are described as mean and SD, and categorical variables are described as counts and percentages. Baseline clinical, angiographic, and procedural characteristics were compared among groups without periprocedural MI and with different types of periprocedural MI using the analysis of variance for continuous variables and the chi-square or Fisher's exact test for categorical variables, as appropriate. Cumulative mortality rates and survival curves between groups were constructed from Kaplan-Meier estimates and compared by the use of the log-rank test. Cox proportional hazards regression models were used to

Table 3
Baseline clinical characteristics

Variable	No MI (n = 10,121)	Type 1 (n = 463)	Type 2 (n = 138)	Type 3 (n = 167)	p Value
Age (yrs)	62.7 ± 10.4	64.7 ± 9.4	64.8 ± 9.7	65.6 ± 10.2	<0.001
Men	6,876 (67.9)	275 (59.4)	89 (64.5)	97 (58.1)	<0.001
Body-mass index (kg/m^2)	24.8 ± 3.0	24.9 ± 3.0	24.4 ± 2.9	24.5 ± 3.1	0.20
Diabetes mellitus	3,483 (34.4)	161 (34.8)	45 (32.6)	48 (28.7)	0.46
Hypertension	6,132 (60.6)	322 (69.6)	78 (56.5)	114 (68.3)	<0.001
Current smoker	2,910 (28.8)	108 (23.3)	31 (22.5)	51 (30.5)	0.03
Hypercholesterolemia (total cholesterol >200 mg/dl)	4,342 (42.9)	220 (47.5)	70 (50.7)	69 (41.3)	0.06
Previous MI	509 (5.0)	19 (4.1)	5 (3.6)	8 (4.8)	0.72
Previous PCI	1,331 (13.2)	50 (10.8)	18 (13.0)	18 (10.8)	0.41
Previous coronary artery bypass grafting	186 (1.8)	7 (1.5)	1 (0.7)	0	0.26
Previous congestive heart failure	179 (1.8)	10 (2.2)	2 (1.5)	5 (3.0)	0.52
Previous stroke	690 (6.8)	29 (6.3)	9 (6.5)	14 (8.4)	0.83
Peripheral vascular disease	135 (1.3)	3 (0.7)	3 (2.2)	1 (0.6)	0.39
Chronic lung disease	240 (2.4)	11 (2.4)	7 (5.1)	5 (3.0)	0.21
Renal insufficiency	245 (2.4)	17 (3.7)	3 (2.2)	8 (4.8)	0.08
Acute coronary syndrome	5,705 (56.4)	222 (48.0)	73 (52.9)	96 (57.5)	0.004
Ejection fraction (%)	59.5 ± 9.2	59.7 ± 8.3	57.5 ± 10.8	60.0 ± 9.8	0.06

Data are shown as mean (SD) for continuous variables and absolute numbers (percentage) for dichotomous variables.

Table 4
Lesion and procedural characteristics

Variable	No MI (n = 10,121)	Type 1 (n = 463)	Type 2 (n = 138)	Type 3 (n = 167)	p Value
Multivessel coronary disease	5,095 (50.3)	332 (71.7)	92 (66.7)	108 (64.7)	<0.001
Left anterior descending	6,225 (61.5)	315 (68.0)	90 (65.2)	115 (68.9)	0.007
Left main	389 (3.8)	41 (8.9)	9 (6.5)	13 (7.8)	<0.001
Bifurcation lesion	2,546 (25.2)	195 (42.1)	52 (37.7)	64 (38.3)	<0.001
Long lesion (>20 mm)	7,263 (71.8)	419 (90.5)	120 (87.0)	137 (82.0)	<0.001
Total occlusion	1,364 (13.5)	25 (5.4)	22 (15.9)	18 (10.8)	<0.001
DES subtype					<0.001
Sirolimus	4,596 (45.4)	215 (46.4)	67 (48.6)	72 (43.1)	
Paclitaxel	1,170 (11.6)	48 (10.4)	11 (8.0)	15 (9.0)	
Zotarolimus	952 (9.4)	23 (5.0)	13 (9.4)	3 (1.8)	
Everolimus	3,185 (31.5)	157 (33.9)	44 (31.9)	68 (40.7)	
Resolute zotarolimus	218 (2.2)	20 (4.3)	3 (2.2)	9 (5.4)	
No. of stents					<0.001
1	5,571 (55.0)	95 (20.5)	36 (26.1)	61 (36.5)	
2	2,730 (27.0)	146 (31.5)	46 (33.3)	46 (27.5)	
≥3	1,820 (18.0)	222 (48.0)	56 (40.6)	60 (35.9)	
Mean	1.7 ± 1.0	2.6 ± 1.3	2.5 ± 1.4	2.2 ± 1.2	<0.001
Total stent length (mm)					<0.001
<10	4 (0.1)	0	0	0	
10–19	1,853 (18.3)	31 (6.7)	11 (8.0)	24 (14.4)	
20–29	2,481 (24.5)	61 (13.2)	25 (18.1)	27 (16.2)	
≥30	5,783 (57.1)	371 (80.1)	102 (73.9)	116 (69.5)	
Mean	40.9 ± 25.5	58.5 ± 31.8	57.4 ± 34.2	50.9 ± 31.3	<0.001
Guidance of intravascular ultrasound	5,339 (52.8)	312 (67.4)	88 (63.8)	95 (56.9)	<0.001
Use of glycoprotein IIb/IIIa inhibitor	2,660 (37.2)	92 (24.3)	41 (32.8)	26 (24.1)	<0.001
Use of cilostazol	5,339 (52.8)	312 (67.4)	88 (63.8)	95 (56.9)	<0.001

Data are shown as mean (SD) for continuous variables and absolute numbers (percentage) for dichotomous variables.

estimate the effect of different types of periprocedural MI on mortality with reference to nonperiprocedural MI. To account for between-study heterogeneity and within-study clustering, because patients at the same study may have similar profiles of characteristics, p values and confidence intervals were calculated using robust standard errors based on sandwich estimators.[10] After unadjusted analyses were initially performed, multivariable Cox proportional hazards regression modeling was performed to adjust potentially confounding factors, which were significantly associated with outcomes ($p < 0.05$) or clinically relevant irrespective of their statistical significance. The following variables were entered into the final multivariable models: study, age, sex, body-mass index, diabetes, previous MI, renal insufficiency, acute coronary syndrome, ejection fraction, multivessel disease, left main disease, bifurcation lesion, total occlusion, DES type, total number of stents, and use of glycoprotein IIb/IIIa inhibitor. All reported p values were two sided, and

Table 5
Incidence rates, unadjusted and adjusted hazard ratios for mortality, according to the presence of periprocedural myocardial infarction*

Outcome	Mortality Rate (%)		Unadjusted		Multivariable Adjusted†	
	1 yr	2 yrs	HR (95% CI)	p Value	HR (95% CI)	p Value
No periprocedural MI (n = 10,121)	1.4	2.1	Referent		Referent	
Periprocedural MI						
Any (n = 768)	1.8	3.5	1.52 (1.13−2.05)	0.006	1.24 (1.02−1.50)	0.03
Type 1 (n = 463)	1.1	2.8	1.09 (0.59−2.01)	0.79	0.89 (0.54−1.46)	0.65
Type 2 (n = 138)	4.3	6.1	3.19 (2.15−4.73)	<0.001	2.65 (1.77−3.96)	<0.001
Type 3 (n = 167)	1.8	3.1	1.33 (0.82−2.17)	0.26	1.04 (0.84−1.29)	0.71

CI = confidence interval; HR = hazard ratio.
* HRs are shown for patients with different types of periprocedural MI compared with those without periprocedural MI.
† Adjustments were made for study, age, sex, body-mass index, diabetes, previous MI, renal insufficiency, acute coronary syndrome, ejection fraction, multivessel disease, left main disease, bifurcation lesion, total occlusion, DES type, total number of stents, and use of glycoprotein IIb/IIIa inhibitor.

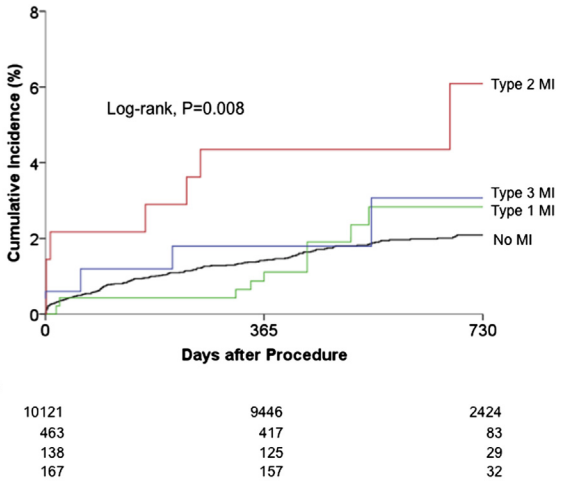

Figure 2. Time-to-event curve for mortality according to the types of the angiographic mechanisms underlying periprocedural MI with reference to non-MI. Kaplan-Meier curves show the cumulative incidence of death, and the log-rank test was used to compare between-group differences. Type 1 denotes MI due to side-branch occlusion, type 2 MI denotes MI due to other angiographic complications, and type 3 denotes MI without angiographically identifiable causes.

p values of <0.05 were considered to indicate statistical significance. SAS software, version 9.1 (SAS Institute, Cary, North Carolina) was used for all statistical analyses.

Results

A total of 10,889 patients from 7 PCI studies using DES were included in this analysis. The number of patients enrolled in each study, the types of study design, the types of patients or lesions evaluated, and the type of DES compared are listed in Table 1. Among them, 768 (7.1%) patients sustained a periprocedural MI. After source documentation of MI with a detailed angiographic review at baseline and postprocedure, the angiographic mechanisms underlying periprocedural MI were listed in Table 2. Of the 768 patients with a periprocedural MI, 463 cases (60.3%) were driven by side-branch occlusion (type 1), 138 (18.0%) by other angiographic complications (type 2), and 167 (21.7%) had no identifiable angiographic causes (type 3). Among 768 patients with a periprocedural MI, 324 (42.2%) had mild CK-MB elevation (3 to <5 ratio), 249 (32.4%) had moderate CK-MB elevation (5 to <10 ratio), and 195 (25.4%) had large CK-MB elevation (>10 ratio). Figure 1 shows the significant differences in the levels of cardiac enzyme elevation according to the type of MI. The proportion of large infarct with a CK-MB ratio >10 was higher in patients with type 2 MI rather than in those with type 1 and type 3 MI (37.7% vs 26.8% and 11.4%, respectively).

Baseline clinical characteristics among patients without periprocedural MI and those with different types of periprocedural MI are listed in Table 3. Compared with patients without periprocedural MI, those with periprocedural MI were older, were more likely to be women, and had lower prevalence of acute coronary syndrome presentations. Detailed data on angiographic and procedural characteristics between groups are listed in Table 4. Overall, patients who sustained a periprocedural MI had higher risk lesion characteristics such as multivessel disease, left main disease, bifurcation lesion, and long lesion. The number of stents used was significantly higher, and the total stent length was longer in patients with periprocedural MI than in those without periprocedural MI.

The median follow-up duration was 517 days (interquartile range 380 to 726 days). During follow-up, 208 deaths occurred. Event rates, unadjusted, and adjusted risks for mortality, according to the types of periprocedural MI with reference to nonperiprocedural MI, are listed in Table 5. At 2 years of follow-up, the unadjusted rate of mortality was higher in patients with periprocedural MI than in those without periprocedural MI (3.5% vs 2.1%, respectively). The mortality rates significantly differed by the angiographic types of periprocedural MI (2.8% in type 1, 6.1% in type 2, and 3.1% in type 3, log-rank p = 0.008; Figure 2). In unadjusted and adjusted analyses using a Cox proportional hazards model, type 2 periprocedural MI was significantly associated with an increased risk of mortality, but type 1 and type 3 MI were not related with increased mortality compared with nonperiprocedural MI.

Discussion

In this large-sized clinical and angiographic data from 7 DES studies, we found that there were substantial differences in mortality depending on the different angiographic

mechanisms; MI due to complicated angiographic causes was significantly associated with an increased risk of mortality, but MI due to side-branch occlusion or without identifiable angiographic causes was not associated with increased mortality.

There is limited support in the literature for determining the relative frequency of plausible angiographic mechanisms. In our study, approximately 80% of patients who sustained periprocedural MI had angiographically visible mechanisms. Among them, side-branch occlusion was the most common cause, accounting for 60% of all procedural infarcts. Approximately 20% of periprocedural MI involved more complicated angiographic mechanisms, most likely associated with microvascular dysfunction. The remaining 20% of periprocedural MI showed no identifiable angiographic mechanisms; this type of MI without angiographically visible mechanisms might be in part due to micro-embolization of thrombotic or atherosclerotic material compromising the microvascular circulation, which could be detected as a focal infarction on cardiac magnetic resonance imaging.[11] Previous studies suggested 2 distinct locations for procedural infarction: "proximal" myonecrosis, mainly due to a side-branch occlusion, and "distal" myonecrosis, mainly due to a structural and functional microvascular obstruction.[11–13] The frequency of the 2 locations was similar. Similarly, in our study, approximately 60% of patients had the proximal type of MI (type 1) and 40% had the distal type of MI (types 2 and 3).

Although several small-sized imaging studies have suggested plausible mechanisms of periprocedural MI, none of the prior studies were powered to examine the clinical impact of MI according to the different angiographic mechanisms. Previous clinical studies have been mostly confined to evaluate the prognostic impact of periprocedural MI according to the magnitude of enzyme elevation.[14–17] In the present study, periprocedural MI with complicated angiographic mechanisms was independently associated with a higher risk of mortality. However, periprocedural MI derived from side-branch occlusion and without identifiable mechanical causes was not significantly associated with increased mortality. Similarly, a previous study suggested that the adverse effect of any MI on mortality was confined to patients with evident angiographic complications and not to those without angiographic complications.[18] Our findings can be in part explained by that in cases of side-branch occlusion and nonidentifiable angiographic causes, periprocedural MI results in less severe myonecrosis and therefore does not influence cardiac function. In contrast, cases with complicated angiographic causes were related to large periprocedural MI, resulting in substantially impaired cardiac function, which is one of the most important determinants of mortality after PCI.

The second universal definition of MI indicated periprocedural MI as an enzyme elevation more than 3 times the upper normal limit without consideration of angiographic causes, signs, or symptoms. Therefore, asymptomatic isolated enzyme elevation can be labeled as PCI-related MI.[19] In contrast, the third universal definition of MI adopted a higher arbitrary threshold of enzyme elevations (5 times the upper normal limit) and considered angiographic evidence of flow-limiting complications (such as loss of patency of a side branch, persistent slow flow or no-reflow, or embolization) as one of the diagnostic criteria.[20] However, the clinical significance of periprocedural MI according to these underlying mechanisms and their management still remains a matter of uncertainty. Our findings might highlight the need for further research to determine the diagnostic and prognostic values of angiographic mechanisms, when defining periprocedural MI, and to inform optimal management of these complications.

Potential limitations of the present study warrant discussion. As a retrospective observational analysis, residual confounding or selection bias cannot be completely excluded. Second, our analysis merged data from several clinical studies. Although adequate statistical techniques were used to account for between-study heterogeneity and within-study clustering, interstudy variability may have influenced results. Third, in the present study, we did not systematically measure cardiac troponin for the detection of periprocedural MI, and therefore, it is still unknown whether the current findings would be same with measurement of troponin. Finally, as this is a secondary data analysis, results should be considered hypothesis-generating only, and we cannot address causal effect of periprocedural MI with mortality.

Disclosures

The authors have no conflicts of interest to disclose.

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