JACC: CARDIOVASCULAR INTERVENTIONS
VOL. 10, NO. 15, 2017

ISSN 1936-8798/$36.00
PUBLISHED BY ELSEVIER
http://dx.doi.org/10.1016/j.jcin.2017.05.051

Differential Rates and Clinical Significance of Periprocedural Myocardial Infarction After Stenting or Bypass Surgery for Multivessel Coronary Disease According to Various Definitions

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ABSTRACT

OBJECTIVES This study sought to estimate the differential incidence and prognostic significance of periprocedural myocardial infarction (MI) according to various definitions.

BACKGROUND In trials comparing percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG), the primary composite endpoint is very sensitive to the definition of MI. Especially, the definition of periprocedural MI has considerably varied, and uniform criteria are still unsettled.

METHODS We evaluated 7,697 patients with multivessel disease who received PCI (n = 4,514) or underwent CABG (n = 3,183) between 2003 and 2013, and for whom serial measurement of creatine kinase-MB was available. According to various MI definitions (second and third universal definitions and the Society for Cardiovascular Angiography and Interventions definition), we assessed the prevalence and prognostic significance of periprocedural MI after both PCI and CABG. Patients were followed for major cardiovascular events (death from cardiovascular causes and spontaneous MI) and death for a median of 4.7 years.

RESULTS According to various definitions of MI, there was a substantial difference in the rates of periprocedural MI after PCI and CABG (18.7% vs. 2.9% by second universal; 3.2% vs. 1.9% by third universal; and 5.5% vs. 18.3% by Society for Cardiovascular Angiography and Interventions definition). The presence of periprocedural MI was associated with increased risks of major cardiovascular events after both PCI and CABG regardless of MI definition. The risk-adjusted 5-year rates of future major cardiovascular events after occurrence of periprocedural MI were similar after PCI and CABG in second and third universal definition. However, using Society for Cardiovascular Angiography and Interventions definition, the rates of major cardiovascular events were significantly higher after PCI than after CABG (24.3% vs. 20.4%; hazard ratio: 1.61; 95% confidence interval: 1.07 to 2.41; p = 0.02).

CONCLUSIONS There were substantial differences in incidence and clinical relevance of periprocedural MI according to various contemporary, widely used definitions of MI. (J Am Coll Cardiol Intv 2017;10:1498–507)

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Manuscript received April 26, 2017; revised manuscript received May 29, 2017, accepted May 30, 2017.

Until recently, several clinical trials comparing percutaneous coronary intervention (PCI) involving drug-eluting stents (DES) and coronary artery bypass grafting (CABG) for complex coronary artery disease (CAD) have adopted a composite of major adverse cardiovascular events (i.e., death, stroke, myocardial infarction [MI], and/or repeat revascularization) as the primary clinical endpoint (1–6). The composite primary endpoint is sensitive to the protocol definition of each component of events. In particular, there has been a substantial interstudy heterogeneity for MI definition.

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Over the last decade, several definitions have been proposed for the diagnosis of MI after coronary revascularization, especially for periprocedural MI (7–9). A nonuniform definition of periprocedural MI can penalize the 1 specific group of revascularization strategies and lead to an imprecise estimate of the relative treatment effects of PCI and CABG. Thus, it might be an important clinical question to determine whether there are differences in incidence and clinical impact of periprocedural MI according to different definitions of MI. To address this issue, using a large cohort of patients with multivessel CAD who received either PCI with DES or CABG, we estimated the differential incidence and prognostic significance of periprocedural MI potentially affected by different criteria of second and third universal definition of MI (7,8) and a clinically relevant MI proposed by the Society for Cardiovascular Angiography and Interventions (SCAI) (9).

METHODS

STUDY POPULATION, PROCEDURES, AND CARDIAC ENZYME MEASUREMENTS. The study population was a part of the ASAN-Multivessel (Asan Medical Center-Multivessel Revascularization) registry, which was a single-center, prospective, observational cohort study designed to evaluate the "real-word" outcomes of patients with multivessel CAD who were treated with PCI, CABG, or medical therapy. The details of the study design and the 3- and 5-year comparative results of PCI and CABG were published previously (10,11). The current study population comprised consecutive patients with multivessel CAD who underwent PCI or CABG and were enrolled between January 1, 2003, and December 31, 2016. To remove potential ascertainment bias, patients who had recent MI with creatine kinase-MB (CK-MB) levels elevated at baseline were excluded. Patients whose both baseline and peak CK-MB levels were not available and those who underwent medical treatment alone were also excluded (Online Figure 1). The study protocol was approved by the institutional review board of Asan Medical Center and written informed consent was acquired from all study participants.

The decision to perform PCI or CABG was dependent on the physician and/or the patient choice. The PCI was performed according to current practice guidelines. The choice of the specific type of DES was left to the operator's discretion. Antiplatelet therapy and periprocedural anticoagulation were provided according to standard regimens. Surgical revascularization was performed using standard bypass techniques. Whenever possible, the internal thoracic artery was used preferentially for revascularization of the left anterior descending artery. On-pump or off-pump surgery was performed at the discretion of the surgeon.

In our center, routine measurements of CK-MB, as measured by mass assay, were performed in all patients who underwent PCI or CABG (12). 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. If clinically needed (i.e., new ischemic symptoms, new electrocardiography [ECG] changes, or complicated PCI or CABG procedures), CK-MB measurement was more frequently performed. For each patient, the CK-MB ratio was calculated as the ratio between the peak CK-MB levels and the upper reference limit. All laboratory testing was performed by personnel unaware of patient information and study objectives. Baseline and follow-up ECG were also performed concomitantly with measurement of cardiac enzyme levels.

EVENT ADJUDICATION AND CLINICAL OUTCOMES. We assessed the occurrence of periprocedural MI after PCI and CABG procedures using the second and third universal definitions of MI and the SCAI definition of a clinically relevant MI (Online Table 1). All cases of periprocedural MI were reviewed independently by 2 experienced interventional cardiologists with comprehensive review of ECG or imaging data at the time of cardiac enzyme elevation. In cases of disagreement, a consensus was established between the 2 reviewers, or a third interventional cardiologist was consulted. The adjudications of the periprocedural MI were performed in parallel of the

ABBREVIATIONS AND ACRONYMS

CABG = coronary artery bypass grafting

CAD = coronary artery disease

CK-MB = creatine kinase-MB

cTn = cardiac troponin

DES = drug-eluting stent(s)

ECG = electrocardiography

MI = myocardial infarction

PCI = percutaneous coronary intervention

SCAI = Society for Cardiovascular Angiography and Interventions

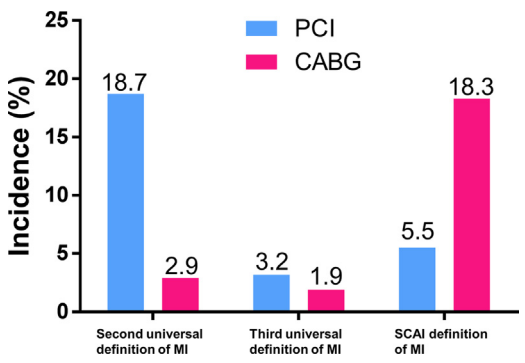
TABLE 1 Baseline Clinical and Angiographic Characteristics

	PCI (n = 4,514)	CABG (n = 3,183)	p Value
Age, yrs	63.0 ± 9.6	63.4 ± 8.9	0.05
Male	3,248 (72.0)	2,336 (73.4)	0.17
Body mass index, kg/m^2	25.0 ± 3.0	24.8 ± 3.0	<0.001
Diabetes	1,597 (35.4)	1,391 (43.7)	<0.001
Hypertension	2,838 (62.9)	2,023 (63.6)	0.56
Hyperlipidemia	1,092 (24.2)	638 (20.0)	<0.001
Current smoker	1,117 (24.7)	750 (23.6)	0.24
Prior MI	299 (6.6)	294 (9.2)	<0.001
Prior PCI	756 (16.7)	502 (15.8)	0.27
Prior CABG	109 (2.4)	21 (0.7)	<0.001
Congestive heart failure	77 (1.7)	109 (3.4)	<0.001
Prior stroke	371 (8.2)	293 (9.2)	0.14
Peripheral vascular disease	118 (2.6)	139 (4.4)	<0.001
Chronic lung disease	65 (1.4)	63 (2.0)	0.08
Renal failure	144 (3.2)	139 (4.4)	0.01
Clinical indication			<0.001
Chronic stable angina	2,961 (65.6)	1,481 (46.5)	
Unstable angina	1,553 (34.4)	1,702 (53.5)	
Diseased vessels			<0.001
2 vessels	2,802 (62.1)	656 (20.6)	
With proximal LAD artery	1,619 (57.8)	323 (49.2)	
Without proximal LAD artery	1,183 (42.2)	333 (50.8)	
3 vessels	1,712 (37.9)	2,527 (79.4)	
With proximal LAD artery	828 (48.4)	867 (34.3)	
Without proximal LAD artery	884 (51.6)	1,660 (65.7)	
Left main disease	696 (15.4)	984 (30.9)	<0.001
Chronic total occlusion	225 (5.0)	316 (9.9)	<0.001
Ejection fraction	58.8 ± 8.2	53.0 ± 11.4	<0.001

Values are mean ± SD or n (%).

CABG = coronary artery bypass graft; LAD = left anterior descending artery; MI = myocardial infarction; PCI = percutaneous coronary intervention.

FIGURE 1 Differential Rates of Periprocedural MI After PCI and CABG, According to Various Definitions



CABG = coronary artery bypass graft surgery; MI = myocardial infarction; PCI = percutaneous coronary intervention; SCAI = Society for Cardiovascular Angiography and Interventions.

3 categories, according to the treatment group (PCI and CABG).

To determine the prognostic significance of periprocedural MI after PCI and CABG, 2 outcomes were assessed for inclusion in the outcome analysis: major cardiovascular events and death from any cause. Major cardiovascular events included death from cardiovascular causes and spontaneous MI during follow-up. All deaths were considered to be from cardiovascular causes unless an unequivocal noncardiovascular cause could be established. Spontaneous MI was defined as an increase in the CK-MB above upper reference limit with ischemic symptoms, ECG changes indicative of ischemia, or new pathological Q-wave. The monitoring process to capture major cardiovascular events and death during follow-up period was described previously (10,11), and all clinical outcomes were carefully verified and adjudicated by independent clinicians.

STATISTICAL ANALYSIS. Categorical variables are presented as numbers (%) and continuous variables are expressed as mean ± SD. Intergroup comparisons of categorical variables were conducted using the chi-square test, whereas those of continuous variables were conducted using Student *t* test or the Wilcoxon rank sum test, as appropriate. Unadjusted event rates were calculated using the Kaplan-Meier method and compared using the log-rank test.

We used multivariable proportional-hazards models to examine the association of the presence of periprocedural MI with the risks of major coronary events and mortality in each stratum of PCI or CABG, according to each definition of MI (13). Then, we determined whether there are differences in prognostic impact of periprocedural MI after PCI and CABG according to various MI definitions on future major cardiovascular events and mortality during follow-up. After unadjusted analyses were initially performed, multivariable Cox regression analyses were performed to adjust potential confounders identified by the investigators using a published data search and based on data available in our previous studies (11,12). These covariates included age, sex, body mass index (calculated as weight in kilograms divided by height in meters squared), diabetes, prior MI, congestive heart failure, peripheral vascular disease, renal failure, clinical indication (stable or unstable angina), number of diseased vessels (2- or 3-vessel disease), proximal LAD disease, left main disease, ejection fraction, and year of the index treatment. The proportional hazards assumption was tested by examination of log-log

TABLE 2 Baseline Characteristics of Patients With Periprocedural MI According to Various Definitions of MI

	PCI Stratum			CABG Stratum		
	Second Universal Definition (n = 842)	Third Universal Definition (n = 145)	SCAI Definition (n = 248)	Second Universal Definition (n = 92)	Third Universal Definition (n = 59)	SCAI Definition (n = 582)
Age, yrs	64.6 ± 9.7	66.6 ± 9.5	63.7 ± 10.0	64.1 ± 9.1	65.3 ± 8.4	64.5 ± 8.7
Male	569 (67.6)	82 (56.6)	167 (67.3)	67 (72.8)	42 (71.2)	443 (76.1)
Body mass index, kg/m^2	24.9 ± 3.0	24.7 ± 3.2	24.8 ± 3.1	24.4 ± 2.9	24.5 ± 2.8	24.8 ± 3.0
Diabetes	277 (32.9)	46 (31.7)	79 (31.9)	23 (25.0)	14 (23.7)	201 (34.5)
Hypertension	563 (66.9)	99 (68.3)	167 (67.3)	53 (57.6)	37 (62.7)	374 (64.3)
Hyperlipidemia	199 (23.6)	33 (22.8)	56 (22.6)	14 (15.2)	10 (16.9)	93 (16.0)
Current smoker	193 (22.9)	32 (22.1)	58 (23.4)	21 (22.8)	12 (20.3)	125 (21.5)
Prior MI	63 (7.5)	11 (7.6)	19 (7.7)	6 (6.5)	4 (6.8)	48 (8.2)
Prior PCI	128 (15.2)	28 (19.3)	43 (17.3)	11 (12.0)	6 (10.2)	73 (12.5)
Prior CABG	22 (2.6)	3 (2.1)	7 (2.8)	0 (0.0)	0 (0.0)	5 (0.9)
Congestive heart failure	16 (1.9)	4 (2.8)	6 (2.4)	3 (3.3)	0 (0.0)	31 (5.3)
Prior stroke	76 (9.0)	13 (9.0)	29 (11.7)	6 (6.5)	4 (6.8)	54 (9.3)
Peripheral vascular disease	23 (2.7)	4 (2.8)	10 (4.0)	3 (3.3)	1 (1.7)	22 (3.8)
Chronic lung disease	10 (1.2)	3 (2.1)	3 (1.2)	1 (1.1)	1 (1.7)	14 (2.4)
Renal failure	33 (3.9)	5 (3.4)	9 (3.6)	3 (3.3)	2 (3.4)	23 (4.0)
Clinical indication						
Chronic stable angina	483 (57.4)	61 (42.1)	138 (55.6)	30 (32.6)	20 (33.9)	224 (38.5)
Unstable angina	359 (42.6)	84 (57.9)	110 (44.4)	62 (67.4)	39 (66.1)	358 (61.5)
Diseased vessels						
2 vessels	456 (54.2)	67 (46.2)	133 (53.6)	16 (17.4)	12 (20.3)	111 (19.1)
With proximal LAD artery	224 (49.1)	41 (61.2)	75 (56.4)	8 (50.0)	7 (58.3)	48 (43.2)
Without proximal LAD artery	232 (50.9)	26 (38.8)	58 (43.6)	8 (50.0)	5 (41.7)	63 (56.8)
3 vessels	386 (45.8)	78 (53.8)	115 (46.4)	76 (82.6)	47 (79.7)	471 (80.9)
With proximal LAD artery	211 (54.7)	46 (59.0)	66 (57.4)	48 (63.2)	26 (55.3)	285 (60.5)
Without proximal LAD artery	175 (45.3)	32 (41.0)	49 (42.6)	28 (36.8)	21 (44.7)	186 (39.5)
Left main disease	150 (17.8)	24 (16.6)	49 (19.8)	63 (68.5)	37 (62.7)	385 (66.2)
Chronic total occlusion	38 (4.5)	9 (6.2)	11 (4.4)	11 (12.0)	4 (6.8)	39 (6.7)
Ejection fraction	58.1 ± 8.9	56.9 ± 8.7	57.1 ± 9.0	46.1 ± 13.2	47.2 ± 12.3	49.7 ± 12.5

Values are mean ± SD or n (%).
SCAI = Society for Cardiovascular Angiography and Interventions; other abbreviations as in Table 1.

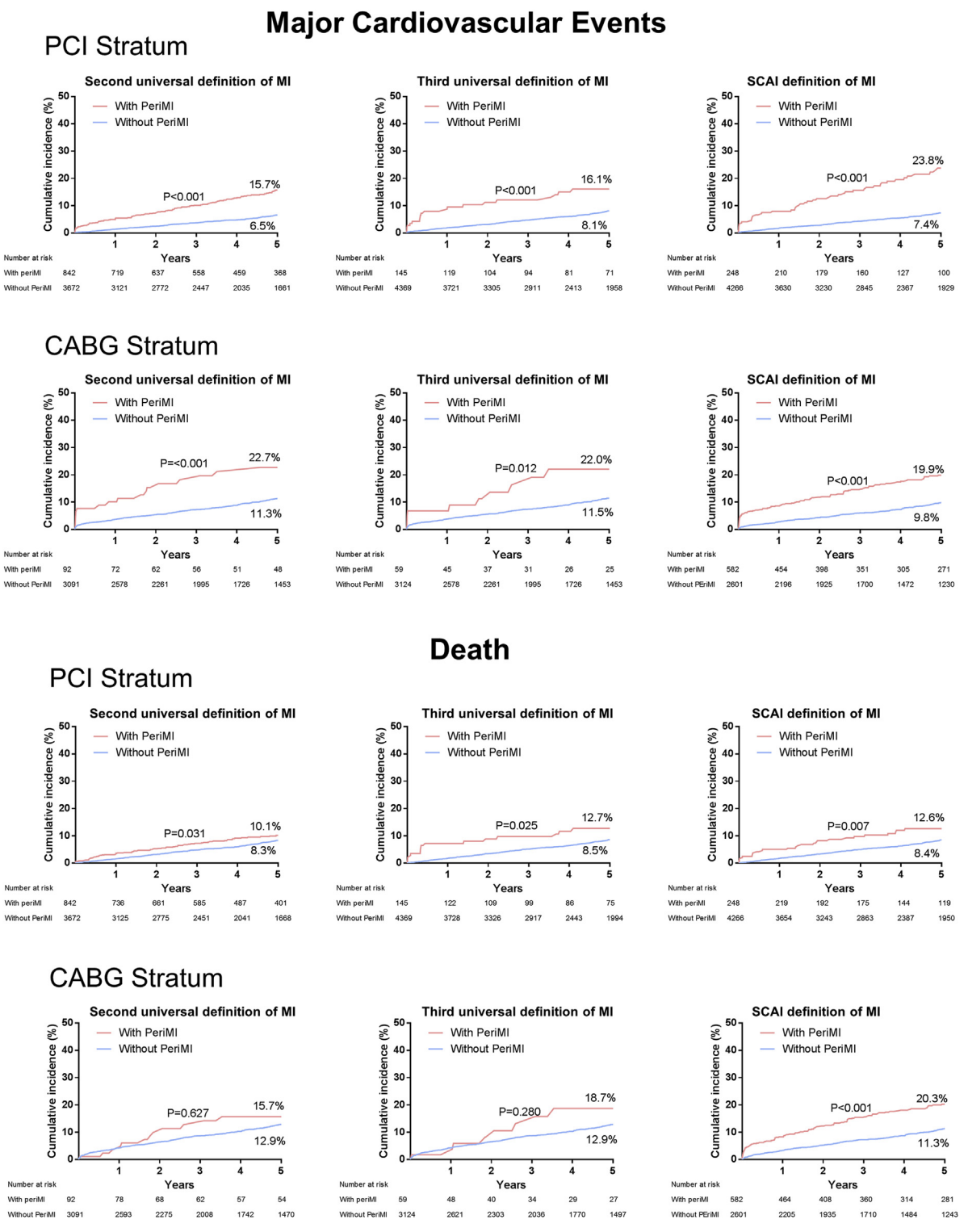
survival curves and partial Schoenfeld residuals, and no significant violations were found. All statistical analyses were performed using R software version 3.3.1 (R Foundation for Statistical Computing, Vienna, Austria). All p values were 2-sided and p values <0.05 were considered statistically significant.

RESULTS

BASELINE CHARACTERISTICS AND INCIDENCE OF PERIPROCEDURAL MI. From January 2003 through December 2013, a total of 11,596 patients with multivessel CAD were enrolled in the ASAN-Multivessel registry. Among them, a total of 7,697 patients (4,514 PCI and 3,183 CABG) met the criteria for inclusion and were included in this analysis (Online Figure 1). The baseline characteristics of the PCI and CABG patients are shown in Table 1. As expected from a real-world registry, the CABG patients had higher clinical and angiographic risk profiles than the PCI patients.

According to various definitions of MI, there was a substantial difference in the incidences of periprocedural MI (Figure 1). Using second universal definition of MI, the incidence of periprocedural MI was significantly higher after PCI than after CABG (18.7% vs. 2.9%). In third universal definition of MI, the overall incidence of periprocedural MI was lowest and the rate of periprocedural MI was slightly higher in the PCI group than in the CABG group (3.2% vs. 1.9%). Using criteria of the SCAI-defined clinically relevant MI, the incidence of periprocedural MI was significantly lower after PCI than after CABG (5.5% vs. 18.3%). Baseline clinical and angiographic characteristics of patients who were adjudicated to have periprocedural MI according to various definitions of MI are summarized in Table 2.

FIGURE 2 Kaplan-Meier Curve for 5-Year Major Cardiovascular Events and Death, According to Presence or Absence of Periprocedural MI in Each Treatment Stratum



Major cardiovascular events included death from cardiovascular causes or spontaneous MI. Abbreviations as in Figure 1.

TABLE 3 5-Year Event Rates and Hazard Ratios for Major Coronary Events and Death, According to Presence or Absence of Periprocedural MI in Each Treatment Stratum

Outcomes	PCI Stratum			CABG Stratum		
	Second Universal Definition	Third Universal Definition	SCAI Definition	Second Universal Definition	Third Universal Definition	SCAI Definition
Major cardiovascular events						
Events/patients, total n						
With periprocedural MI	156/842	28/145	63/248	24/92	14/59	131/582
Without periprocedural MI	298/3,672	426/4,369	391/4,266	421/3,091	431/3,124	314/2,601
Cumulative event rate at 5 yrs*						
With periprocedural MI	15.7	16.1	23.8	22.7	22.0	19.9
Without periprocedural MI	6.5	8.1	7.4	11.3	11.5	9.8
Hazard ratio (95% CI)†						
Unadjusted	2.67 (2.10–3.41)	2.41 (1.53–3.79)	3.75 (2.75–5.12)	2.35 (1.46–3.79)	2.20 (1.17–4.13)	2.36 (1.85–3.02)
Adjusted‡	2.38 (1.86–3.05)	2.07 (1.30–3.30)	3.66 (2.66–5.05)	2.30 (1.41–3.76)	2.12 (1.12–4.03)	2.16 (1.66–2.79)
Death						
Events/patients, total n						
With periprocedural MI	114/842	23/145	39/248	18/92	13/59	142/582
Without periprocedural MI	360/3,672	451/4,369	435/4,266	496/3,091	501/3,124	372/2,601
Cumulative event rate at 5 yrs						
With periprocedural MI	10.1	12.7	12.6	15.7	18.7	20.3
Without periprocedural MI	8.3	8.5	8.4	12.9	12.9	11.3
Hazard ratio (95% CI)						
Unadjusted	1.34 (1.03–1.76)	1.76 (1.07–2.92)	1.72 (1.16–2.56)	1.26 (0.71–2.25)	1.47 (0.73–2.96)	2.04 (1.61–2.58)
Adjusted	1.16 (0.88–1.52)	1.63 (0.97–2.73)	1.58 (1.05–2.37)	1.28 (0.71–2.30)	1.50 (0.74–3.04)	1.87 (1.46–2.40)

Values are n/N or % unless otherwise indicated. Major cardiovascular events were defined as a composite of death from cardiovascular causes or spontaneous MI. *Cumulative rates of events are based on Kaplan-Meier estimates. †Hazard ratios are for patients with periprocedural MI as compared with those without periprocedural MI. ‡Models were adjusted for age, sex, body mass index, diabetes, prior MI, congestive heart failure, peripheral vascular disease, renal failure, clinical indication, number of diseased vessels (2- or 3-vessel disease), proximal LAD disease, left main disease, ejection fraction, and year of the index treatment.

CI = confidence interval; other abbreviations as in Tables 1 and 2.

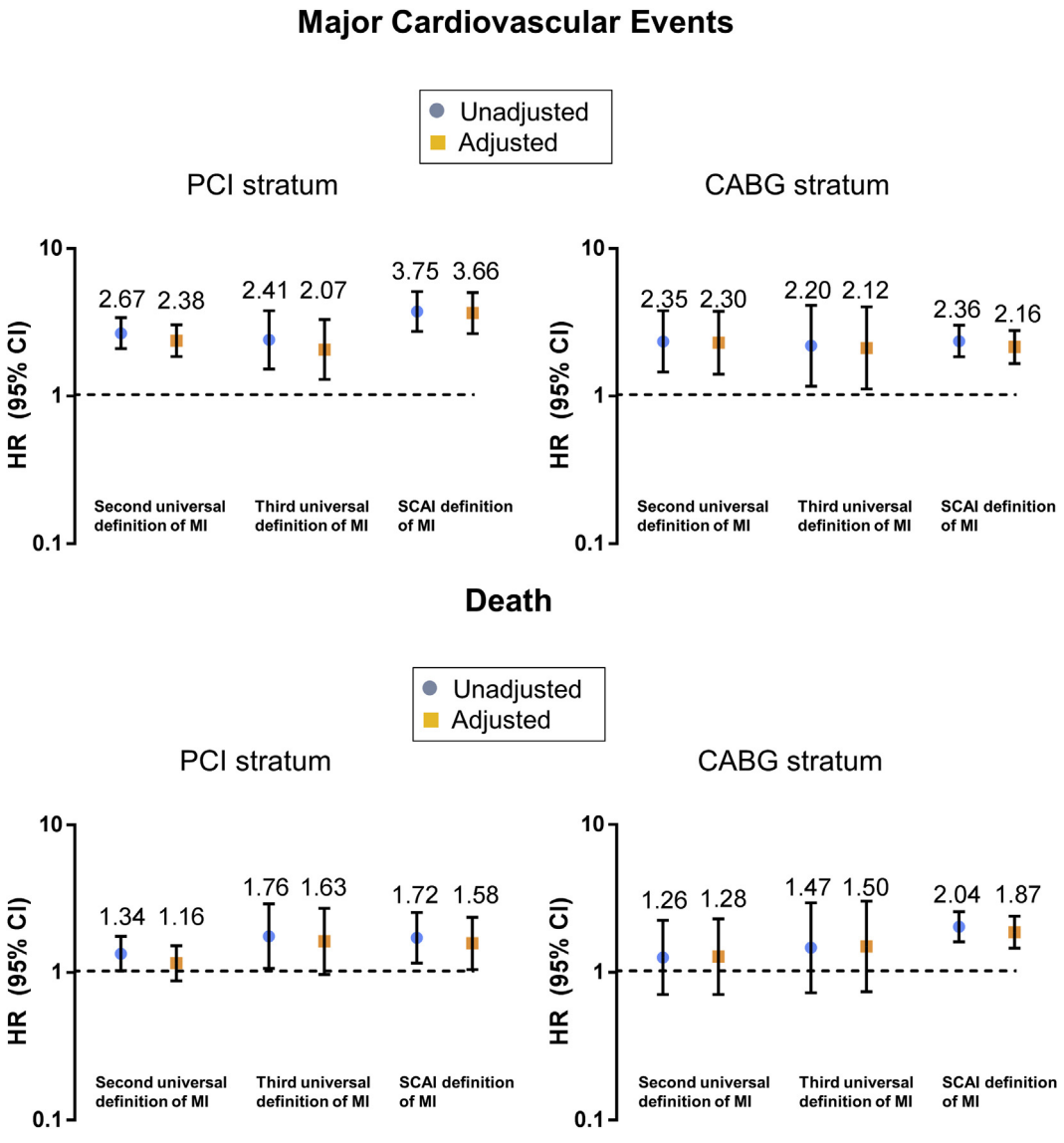
ASSOCIATION OF PERIPROCEDURAL MI WITH CLINICAL EVENTS. The median duration of follow-up was 4.7 years (interquartile range: 2.0 to 7.6 years). During the follow-up period, 988 patients died (779 from cardiovascular causes) and 150 patients had a spontaneous MI. In total, 899 patients had at least 1 major cardiovascular event. The rate of major cardiovascular events during the 5-year follow-up was significantly higher among patients with periprocedural MI than among those without periprocedural MI across various MI definitions in each stratum of PCI and CABG (Figure 2, Table 3). The rate of death at year 5 of follow-up was also higher among patients with periprocedural MI in PCI stratum. However, in CABG stratum, this finding was only maintained by the SCAI definition of MI.

In crude and adjusted analyses using a Cox proportional hazards models, the presence of periprocedural MI was significantly associated with a higher risk of major cardiovascular events in each stratum of PCI and CABG (Figure 3, Table 3). Similar trend was also observed for all-cause mortality (but not always statistically significantly).

DIFFERENTIAL PROGNOSTIC IMPACT OF PERIPROCEDURAL MI AFTER PCI AND CABG. Unadjusted and adjusted rates and risks for future major cardiovascular events and death among patients who had periprocedural MI after PCI and CABG are shown in Table 4. According to various definitions of MI, observed (unadjusted) 5-year rates of future major cardiovascular and mortality during follow-up after periprocedural MI were different; overall, more events occurred after CABG than after PCI.

After adjustment of potentially confounding clinical covariates, the risk-adjusted 5-year rates of future clinical events after periprocedural MI between the PCI and the CABG group are illustrated in Figure 4. Using second and third universal definition of MI, there was no statistically significant between-group (PCI vs. CABG) difference in the future risks of major cardiovascular events and death after periprocedural MI. However, using SCAI definition of MI, the adjusted risk for future major cardiovascular events after periprocedural MI was significantly higher after PCI than after CABG.

FIGURE 3 Hazard Ratio for Major Cardiovascular Events and Death in Patients With Periprocedural MI Relative to Patients Without Periprocedural MI, According to Various Definitions



Major cardiovascular events included death from cardiovascular causes or spontaneous MI. Hazard ratios are for patients with periprocedural MI as compared with those without periprocedural MI. Models were adjusted for age, sex, body mass index, diabetes, prior MI, congestive heart failure, peripheral vascular disease, renal failure, clinical indication, number of diseased vessels (2- or 3-vessel disease), proximal LAD disease, left main disease, ejection fraction, and year of the index treatment. CI = confidence interval; HR = hazard ratio; other abbreviations as in Figure 1.

DISCUSSION

In this large-scale observational study involving patients with multivessel CAD and routine, serial CK-MB measurement, the rates of periprocedural MI were substantially different after PCI and CABG, according to widely used, various definitions of MI. Regardless of any definitions of MI, the presence of periprocedural MI was associated with an increased risk of major cardiovascular events and mortality. The adjusted risks for future cardiovascular events and death after periprocedural MI were similar between

TABLE 4 Unadjusted and Adjusted 5-Year Event Rates for Major Cardiovascular Events and Death in Patients With Periprocedural MI After PCI or CABG

	Unadjusted Event Rates at 5 Years			Adjusted Event Rates at 5 Years*		
Outcome	PCI	CABG	p Value	PCI	CABG	p Value
Second definition of MI						
Major cardiovascular events	15.7	22.7		16.7	20.9	
HR (95% CI)†	0.61 (0.38–1.00)		0.05	0.79 (0.43–1.44)		0.44
Death	10.1	15.7		11.5	14.3	
HR (95% CI)	0.62 (0.34–1.14)		0.12	0.61 (0.29–1.26)		0.18
Third definition of MI						
Major cardiovascular events	16.1	22.0		17.3	20.9	
HR (95% CI)	0.73 (0.34–1.57)		0.43	0.58 (0.22–1.58)		0.29
Death	12.7	18.7		14.8	17.6	
HR (95% CI)	0.75 (0.32–1.75)		0.50	0.51 (0.15–1.75)		0.29
SCAI definition of MI						
Major cardiovascular events	23.8	19.9		24.3	20.4	
HR (95% CI)	1.15 (0.81–1.63)		0.43	1.61 (1.07–2.41)		0.02
Death	12.6	20.3		14.4	20.2	
HR (95% CI)	0.60 (0.39–0.92)		0.02	0.70 (0.44–1.12)		0.13

Values are % unless otherwise indicated. Major cardiovascular events were defined as a composite of death from cardiovascular causes or spontaneous MI. *Models were adjusted for age, sex, body mass index, diabetes, prior MI, congestive heart failure, peripheral vascular disease, renal failure, clinical indication, number of diseased vessels (2- or 3-vessel disease), proximal LAD disease, left main disease, ejection fraction, and year of the index treatment. †Hazard ratios are for patients with periprocedural MI after PCI as compared with those with periprocedural MI after CABG.

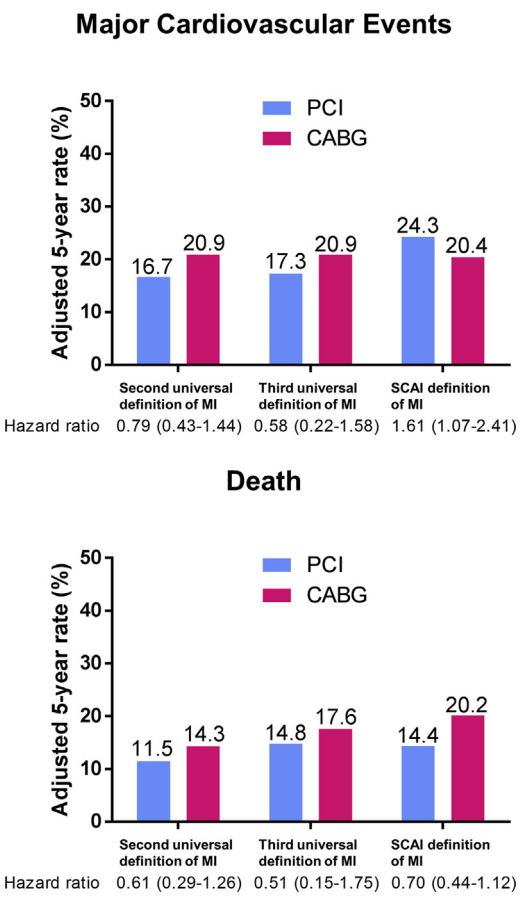
HR = hazard ratio; other abbreviations as in Tables 1 to 3.

PCI and CABG groups with adoption of second and third universal definition of MI; however, using SCAI definition, the future risk of major cardiovascular events after periprocedural MI was more common after PCI than after CABG.

The protocol definition of MI was mostly different in recent landmark clinical trials comparing PCI with DES and CABG (1-6), which could lead to an imprecise estimate of the relative treatment effect. Numerous definitions have been proposed for the diagnosis of MI (especially for periprocedural MI) after coronary revascularization (7-9), but all are arbitrarily defined on the basis of the expert consensus rather than on firm evidence derived from clinical studies. The second and third universal definition of MI applied different diagnostic criteria for PCI- or CABG-related periprocedural MI. By contrast, SCAI-defined clinically relevant MI used the same criteria for both PCI- and CABG-related periprocedural MI. In our study, the incidence of periprocedural MI showed wide variations according to each diagnostic criterion. The rate of periprocedural MI was approximately 6 times higher after PCI than after CABG in second universal definition of MI, but slightly more MI events occurred after PCI than after CABG in third universal definition. By contrast, the rate of periprocedural MI was 3 times higher after CABG than after PCI using SCAI definition of MI.

To minimize ascertainment bias and to use a definition that is clinically relevant, the recent EXCEL (Evaluation of XIENCE versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization) trial used a uniform SCAI definition for PCI and CABG (5). In this trial, an increase of CK-MB >10 times the upper reference limit was also regarded as periprocedural MI regardless of any symptom, sign, or ECG criteria. Post-procedural increases of cardiac enzyme might be more common after CABG than after PCI because of more extensive manipulation and procedural features. Like this, defining of periprocedural MI based on isolated CK-MB elevation without additional electrocardiographic, imaging, or angiographic evidence might induce an unbalanced detection of periprocedural MI after PCI and CABG. More MI occurred after PCI with a lower enzyme threshold (i.e., second universal definition) and more MI occurred after CABG with a higher enzyme threshold (i.e., SCAI definition). Until recently, whether clinically driven MI should be only considered or biomarker-driven MI without clinical symptoms or signs should be also included as a relevant clinical endpoint is not yet clearly determined. Because uniform definition of MI not

FIGURE 4 Adjusted Rate and Risk for Future Major Cardiovascular Events and Mortality After Periprocedural MI Among Patients Who Had Periprocedural MI After PCI or CABG



Major cardiovascular events included death from cardiovascular causes or spontaneous MI. Hazard ratios are for patients with periprocedural MI after PCI as compared with those with periprocedural MI after CABG. Models were adjusted for age, sex, body mass index, diabetes, prior MI, congestive heart failure, peripheral vascular disease, renal failure, clinical indication, number of diseased vessels (2- or 3-vessel disease), proximal LAD disease, left main disease, ejection fraction, and year of the index treatment. Abbreviations as in Figure 1.

penalizing one of revascularization treatment is still lacking, additional studies and efforts by trialists are warranted to improve standardization of MI definition for future clinical trials comparing PCI with CABG.

The prognostic importance of periprocedural MI after PCI and CABG is not yet fully determined. Several previous studies showed that the presence of periprocedural MI was associated with increased risk of major cardiovascular events and mortality, regardless of PCI or CABG (12,14–16). This finding was also consistent in our study. However, the potential mechanisms of myocardial necrosis are many but different in the setting of PCI and CABG (12,16,17). Also, it is still unknown whether the prognostic impact of periprocedural MI defined according to various definitions of MI was equally relevant or not between the PCI and the CABG groups. In our study, the adjusted risks for future major cardiovascular events and mortality after occurrence of periprocedural MI was similar after PCI and CABG with second and third universal definition. However, using SCAI definition, future risk for major cardiovascular events was higher after PCI than after CABG, suggesting prognostic imbalance of criteria for periprocedural MI. Therefore, further research is required to propose a fair definition of PCI- and CABG-related periprocedural MI with a balanced consideration of diagnostic sensitivity and specificity as well as clinical relevance and prognostic value.

It is well known that cardiac troponin (cTn) has higher myocardial tissue specificity and high clinical sensitivity than CK-MB. Unfortunately, because we did not systematically measure cTn, comparison of 2 biomarkers (cTn vs. CK-MB) for detection of periprocedural MI was not possible in the current study. Although cTn was advocated as the primary biomarker by the universal definition group (7,8), the prognostic significance of cTn is less well validated than CK-MB and therefore CK-MB is recommended as the biomarker of choice by the SCAI group (9). Despite this, comparison between SCAI definition (preferably based on CK-MB) and universal definition (preferably based on troponin) using CK-MB as a sole biomarker can be misleading. The current data should be interpreted in this context.

STUDY LIMITATIONS. First, this study has a nonrandomized, observational design; therefore, results should be considered hypothesis-generating and the analysis suffers all limitations of an observational study. In particular, the choice of PCI/CABG was left to the physician and thus was subject to selection bias; a fair comparison of the differential impact of periprocedural MI between PCI and CABG might not be feasible. Second, to reduce ascertainment bias, we excluded patients having recent MI with elevated CK-MB. Thus, the incidence and the prognostic impact of periprocedural MI in patients with acute MI was undetermined. Third, because the study patients were accrued over 10 years, variance in therapy may exist that could have influenced the results. However, even after

adjustment of time factor (fiscal year of cohort entry), overall findings were consistent (data not shown). Finally, the exact mechanism linking post-CABG and post-PCI periprocedural MI with adverse cardiovascular events and mortality is still unknown in our study.

CONCLUSIONS

In this large cohort of patients with multivessel CAD, there were substantial differences in incidence and prognostic impact of periprocedural MI after PCI and CABG, according to contemporary, widely used definitions of MI. To diminish uncertainly of any conclusions regarding the relative treatment effect in future trials comparing PCI with CABG, further research is warranted to implement a more applicable definition of periprocedural MI not penalizing a specific revascularization group.

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PERSPECTIVES

WHAT IS KNOWN? Periprocedural MI is of clinical importance because it has been adopted as 1 component of a primary composite endpoint in several clinical trials comparing PCI with CABG. However, its definition has varied considerably over time and is not yet unified for comparative studies of coronary revascularization.

WHAT IS NEW? Our study showed a significantly different incidence of periprocedural MI according to the various definitions. Although the presence of periprocedural MI was generally associated with a higher risk of major cardiovascular events and mortality after either PCI or CABG, there were some differences between PCI and CABG in the prognostic impact of periprocedural MI.

WHAT IS NEXT? Further research is required to propose a fair, evidence-based definition of PCI- and CABG-related periprocedural MI with a balanced consideration of diagnostic accuracy and clinical relevance. In addition, whether biomarker-driven MI without clinical symptoms or signs should be included in trials as a relevant clinical endpoint or be applied as an independent endpoint (named procedure-related myocardial injury) should be addressed via future studies.

REFERENCES

1. Serruys PW, Morice MC, Kappetein AP, et al. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. N Engl J Med 2009;360:961–72.

2. Farkouh ME, Domanski M, Sleeper LA, et al. Strategies for multivessel revascularization in patients with diabetes. N Engl J Med 2012;367:2375–84.

3. Park SJ, Kim YH, Park DW, et al. Randomized trial of stents versus bypass surgery for left main coronary artery disease. N Engl J Med 2011;364:1718–27.

4. Park SJ, Ahn JM, Kim YH, et al. Trial of everolimus-eluting stents or bypass surgery for coronary disease. N Engl J Med 2015;372:1204–12.

5. Stone GW, Sabik JF, Serruys PW, et al. Everolimus-eluting stents or bypass surgery for left main coronary artery disease. N Engl J Med 2016;375:2223–35.

6. Makikallio T, Holm NR, Lindsay M, et al. Percutaneous coronary angioplasty versus coronary artery bypass grafting in treatment of unprotected left main stenosis (NOBLE): a prospective, randomised, open-label, non-inferiority trial. Lancet 2016;388:2743–52.

7. Thygesen K, Alpert JS, White HD. Universal definition of myocardial infarction. J Am Coll Cardiol 2007;50:2173–95.

8. Thygesen K, Alpert JS, Jaffe AS, et al. Third universal definition of myocardial infarction. J Am Coll Cardiol 2012;60:1581–98.

9. Moussa ID, Klein LW, Shah B, et al. Consideration of a new definition of clinically relevant myocardial infarction after coronary revascularization: an expert consensus document from the Society for Cardiovascular Angiography and Interventions (SCAI). J Am Coll Cardiol 2013;62:1563–70.

10. Park DW, Yun SC, Lee SW, et al. Long-term mortality after percutaneous coronary intervention with drug-eluting stent implantation versus coronary artery bypass surgery for the treatment of multivessel coronary artery disease. Circulation 2008;117:2079–86.

11. Park DW, Kim YH, Song HG, et al. Long-term comparison of drug-eluting stents and coronary artery bypass grafting for multivessel coronary revascularization: 5-year outcomes from the Asan Medical Center-Multivessel Revascularization Registry. J Am Coll Cardiol 2011;57:128–37.

12. Park DW, Kim YH, Yun SC, et al. Frequency, causes, predictors, and clinical significance of periprocedural myocardial infarction following percutaneous coronary intervention. Eur Heart J 2013;34:1662–9.

13. Cox D. Regression models and life tables. J R Stat Soc B 1972;34:187–220.

14. Liou K, Ng B, Isbister J, et al. Peri-procedural myocardial infarction following percutaneous coronary intervention as defined by the Universal Definition predicts increased mortality at 2 years. Int J Cardiol 2015;199:96.

15. Lindsey JB, Kennedy KF, Stolker JM, et al. Prognostic implications of creatine kinase-MB elevation after percutaneous coronary intervention: results from the Evaluation of Drug-Eluting Stents and Ischemic Events (EVENT) registry. Circ Cardiovasc Interv 2011;4:474–80.

16. Domanski MJ, Mahaffey K, Hasselblad V, et al. Association of myocardial enzyme elevation and survival following coronary artery bypass graft surgery. JAMA 2011;305:585–91.

17. Prasad A, Herrmann J. Myocardial infarction due to percutaneous coronary intervention. N Engl J Med 2011;364:453–64.

KEY WORDS bypass surgery, myocardial infarction, percutaneous coronary intervention, prognosis

APPENDIX For a supplemental table and figure, please see the online version of this article.