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Impact of Peri-Procedural Myocardial Infarction on Outcomes After Revascularization

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ABSTRACT

BACKGROUND Numerous definitions for peri-procedural myocardial infarction (PMI) following percutaneous coronary intervention (PCI) and coronary bypass grafting (CABG) surgery exist.

OBJECTIVES The purpose of this study was to investigate the PMI rates according to various definitions, their clinically relevant association with all-cause mortality at 10 years, and their impact on composite endpoints at 5 years in the SYNTAXES (Synergy between PCI with Taxus and Cardiac Surgery Extended Survival) trial.

METHODS PMI was classified as a myocardial infarction occurring within 48 h of the procedure according to definitions of the SYNTAX (TAXUS Drug-Eluting Stent Versus Coronary Artery Bypass Surgery for the Treatment of Narrowed Arteries), ISCHEMIA (International Study Of Comparative Health Effectiveness With Medical And Invasive Approaches), and EXCEL (Evaluation of XIENCE versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization) trials; the Fourth Universal Definition of MI; and the Society for Cardiovascular Angiography and Interventions (SCAI). Of the 1,800 patients enrolled, 1,652 with creatine kinase and/or creatine kinase-myocardial band (CK-MB) post-procedure were included. The association between PMI and mortality was analyzed by Cox regression.

RESULTS PMI rates according to the SYNTAX and Fourth Universal Definition of MI, both of which required CK-MB elevation and electrocardiographic evidence of permanent myocardial damage, were 2.7% and 3.0%, respectively, in the PCI arm versus 2.4% and 2.1%, respectively, in the CABG arm. PMI rates according to the SCAI or EXCEL definition were higher in the PCI (5.7%) and CABG (16.5%) arms. PMIs according to the SYNTAX and Fourth Universal Definition of MI were more strongly associated with mortality than EXCEL and SCAI PMIs defined by isolated enzyme elevation when CK-MB was more than 10 times ULN. The impact of these "enzyme-driven events" on time-to-event curves and the composite endpoints was greater in the surgical cohort. PMIs after PCI were associated with 10-year mortality regardless of definition, whereas their impact on mortality after CABG was limited to 1 year.

CONCLUSIONS The rates of PMI are highly dependent on their definition, which affects time-to-event curves, composite endpoints, and their lethal prognostic relevance. (Synergy Between PCI With TAXUS and Cardiac Surgery: SYNTAX Extended Survival [SYNTAXES]; NCT03417050; SYNTAX Study: TAXUS Drug-Eluting Stent Versus Coronary Artery Bypass Surgery for the Treatment of Narrowed Arteries [SYNTAX]; NCT00114972) (J Am Coll Cardiol 2020;76:1622–39)

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The ultimate goal of novel treatments—pharmacological, device, percutaneous, or surgical intervention—is to prolong life (added gained years) and to ensure that patients enjoy a satisfying quality of life. This goal needs, on one hand, the assessment of long-term survival in a quite large group of patients and, on the other hand, repeated interviews and surveys of their quality of life. This combined assessment is expressed in quality-adjusted life years (1).

Short-, medium-, or long-term assessment of a novel treatment in a limited number of patients mandates the multiplication of dated endpoints (death, stroke, spontaneous myocardial infarction [MI], unplanned repeat procedure, hospitalization for heart failure) to ascertain in a meaningful statistically way the benefit of a novel treatment (2).

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In the field of cardiovascular revascularization, peri-procedural myocardial infarction (PMI) as a "dated event" has been integrated as a critical item in composite endpoints, but its definitions encompass a variety of combined or isolated phenomena, such as enzyme elevation, permanent electrocardiographic change, anatomic occlusion of vessels, and loss of viable myocardium.

Conversely, the clinical relevance of a PMI—to be considered as a "dated event"—should be defined as a PMI leading, at short- or long-term, to death, reintervention, or hospitalization for heart failure. Therefore, isolated cardiac biomarker release, even major, without consequential late clinical events may be perceived as clinically irrelevant and artificial in the assessment of otherwise robust composite endpoints. Early isolated enzymatic "PMI events" are frequently incorporated into time-to-event composite endpoints to satisfy trial designers in search of a powered sample size, but they may artificially influence the interpretation of the real benefit of a novel treatment. Although the universal definition of myocardial infarction (UDMI) has been widely accepted as the definition of spontaneous MI, other definitions of PMI exist (**Table 1**), and their potential impact on trial outcomes remains intensely debated (3,4).

In the SYNTAXES (Synergy between PCI with Taxus and Cardiac Surgery Extended Survival) trial (NCT03417050), patients with 3-vessel disease and/or left main coronary artery disease (LMCAD) were randomized to undergo either percutaneous coronary intervention (PCI) or coronary bypass grafting (CABG) surgery, and vital status was evaluated up to 10 years (5). At 10 years, no significant difference existed in all-cause death between PCI and CABG (27% vs. 24%; $p = 0.092$) (5).

In the present study, the statistical association of PMIs, according to various definitions, with all-cause mortality at 1 and 10 years was evaluated in the SYNTAXES trial. We also sought to assess the theoretical impact of these various definitions of PMI on the 5-year composite outcome in the SYNTAX trial (TAXUS Drug-Eluting Stent Versus Coronary Artery Bypass Surgery for the Treatment of Narrowed Arteries) (NCT00114972).

ABBREVIATIONS AND ACRONYMS

CABG = coronary artery bypass grafting

LMCAD = left main coronary artery disease

MI = myocardial infarction

PCI = percutaneous coronary intervention

PMI = peri-procedural myocardial infarction

METHODS

STUDY DESIGN AND PARTICIPANTS. The design and result up to 5 years of the SYNTAX trial have been reported previously (6,7). The vital status up to 10 years has been recently reported in the SYNTAXES study (5). Patients with de novo 3-vessel disease and/or LMCAD, who were eligible for both PCI and CABG based on clinical assessment and the consensus of a heart team, were randomized in a 1:1 fashion either to receive PCI ($n = 903$) with TAXUS Express paclitaxel-drug eluting stents (Boston Scientific Corporation, Marlborough, Massachusetts) or CABG ($n = 897$). The ethics committee at each investigating center approved the trial, and all participants provided their written informed consent prior to

Both sponsors had no role in the study design, data collection, data analyses, and interpretation of the study data, nor were they involved in the decision to publish the final paper. The principal investigators and authors had complete scientific freedom. Dr. Hara has received a grant for studying overseas from the Japanese Circulation Society and a grant from Fukuda Foundation for Medical Technology. Dr. Serruys has received personal fees from Biosensors, Micel Technologies, Sinomedical Sciences Technology, Philips/Volcano, Xeltis, and HeartFlow, outside of the submitted work. Drs. Head and Kappetein have worked as employees of Medtronic, outside of the submitted work. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. Donald E. Cutlip, MD, served as Guest Associate Editor for this paper. Deepak L. Bhatt, MD, MPH, served as Guest Editor-in-Chief for this paper.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC* author instructions page.

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TABLE 1 Definitions of PMI

Definitions	Time After Procedure	PCI Arm	CABG Arm
SYNTAX	<7 days Re-evaluated in the first 48 h	1. Peak CK-MB/peak total CK >10% AND ECG criteria: new Q waves in ≥2 leads OR 2. CK-MB ≥5× ULN AND ECG criteria: new Q waves in ≥2 leads	
4th UDMI	<48 h	1. CK-MB >5× 99th percentile ULN* AND additional criteria: 1) new ischemic ECG changes or new Q waves; 2) angiographic findings consistent with a procedural flow-limiting complication; or 3) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality	1. CK-MB>10× 99th percentile ULN* AND additional criteria: 1) new Q waves; 2) angiographically documented graft or native coronary artery occlusion; or 3) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality
ISCHEMIA	<48 h	1. CK-MB >5× ULN* AND additional criteria: 1) ST-segment elevation or depression in ≥2 contiguous leads, new Q waves, or new persistent LBBB; or 2) angiographically documented new TIMI 0/1 flow in major vessel/side branch or NHLBI ≥ type C dissection OR 2. CK-MB>10× ULN*	1. CK-MB >10× ULN* AND additional criteria: 1) new Q waves or new persistent LBBB; or 2) imaging evidence of new substantial wall motion abnormality OR 2. CK-MB>15× ULN*
SCAI	<48 h	1. CK-MB ≥5× ULN† AND ECG criteria: new Q waves or new persistent LBBB OR 2. CK-MB ≥10× ULN†	
EXCEL	<72 h Evaluated in the first 48 h in the present study	1. CK-MB>5× ULN† AND additional criteria: 1) new Q waves or new persistent LBBB; 2) angiographically documented graft or native coronary artery occlusion or new severe stenosis with thrombosis and/or diminished epicardial flow; or 3) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality OR 2. CK-MB >10× ULN†	

*In patients with normal CK-MB values at baseline. For PCI patients with elevated but stable or falling baseline levels, the peak CK-MB was required to rise by >20% to the values above. †In patients with normal CK-MB values at baseline. For patients with elevated baseline CK-MB at baseline, the peak CK-MB was required to rise from the baseline value by an increment equal to the values above.

CABG = coronary artery bypass grafting surgery; CK = creatine kinase; CK-MB = creatine kinase-myocardial band; ECG = electrocardiogram; EXCEL = Evaluation of XIENCE versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization; ISCHEMIA = International Study of Comparative Health Effectiveness With Medical and Invasive Approaches; LBBB = left bundle branch block; PCI = percutaneous coronary intervention; SCAI = Society for Cardiovascular Angiography and Interventions; SYNTAX = TAXUS Drug-Eluting Stent Versus Coronary Artery Bypass Surgery for the Treatment of Narrowed Arteries; UDMI = universal definition of myocardial infarction; ULN = upper limit of normal.

enrollment. Follow-up complied with local law, regulations of each institution, and the Declaration of Helsinki.

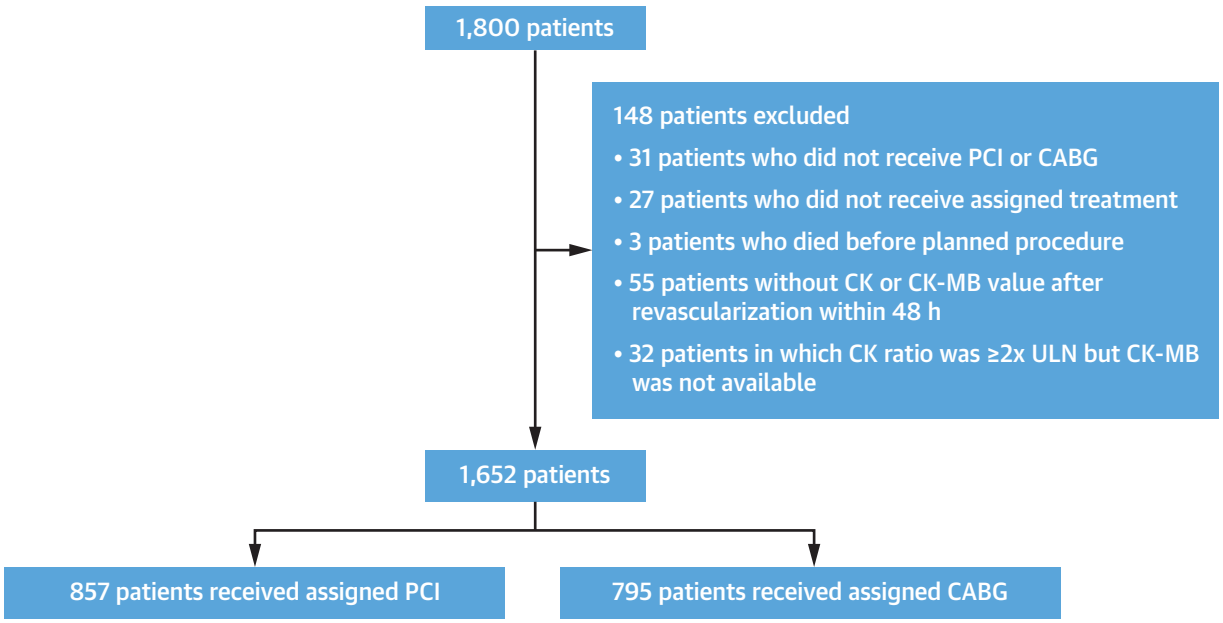
ENDPOINTS AND DEFINITIONS. In the SYNTAX trial, the primary endpoint was the composite rate of major adverse cardiac or cerebrovascular events (MACCE) at 1 year, defined as all-cause mortality, stroke, MI, and repeat revascularization, and the secondary endpoints included MACCE rates at 5 years.

In the protocol of the SYNTAX trial, PMI was defined as either new Q waves in ≥2 leads and peak CK-MB/peak total CK >10%, or new Q waves in ≥2 leads and CK-MB ≥5 times ULN. The definition of PMI according to the Fourth UDMI (3), ICHEMIA (International Study of Comparative Health Effectiveness With Medical And Invasive Approaches) (8), Society for Cardiovascular Angiography and Interventions (SCAI) (4), and EXCEL (Evaluation of XIENCE versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization) (9) are summarized in **Table 1**.

Blood samples for assessment of creatine kinase (CK) pre- and post-revascularization were analyzed on site and by an independent central chemistry laboratory (Covance, Geneva, Switzerland, and Indianapolis, Indiana) (Supplemental Methods). If the CK ratio was <2 times the upper limit of normal (ULN), creatine kinase-myocardial band (CK-MB) assessment was not mandated by the protocol and was not routinely measured by the independent central chemistry laboratory (10). If the CK ratio was ≥2 times ULN, determination of CK-MB was mandated. Patients with a CK ratio ≥2 times ULN but without assessment of CK-MB were excluded from the analysis. To compare PMI rates using the definition of PMI in the SYNTAX trial with more contemporary definitions, the time window for PMI documentation was restricted to the first 48 h post-procedure, which is at variance with the original time window of 7 days (**Table 1**). The peak value of CK-MB within 48 h was used for the assessment of PMI. Patients who did not have a sample taken for CK or CK-MB within the first 48 h post-procedure were excluded from the current analysis. In the Fourth UDMI, CK-MB is recommended as "the best alternative if cardiac troponin assay is not available" (3). Therefore, CK-MB was used instead of cardiac troponin, which was not collected in the SYNTAX trial.

Of 1,800 patients, the following patients were excluded: 31 patients who did not receive PCI or

FIGURE 1 Study Population Flow Chart



CABG = coronary artery bypass grafting surgery; CK = creatine kinase; CK-MB = creatine kinase-myocardial band; PCI = percutaneous coronary intervention; ULN = upper limit of normal.

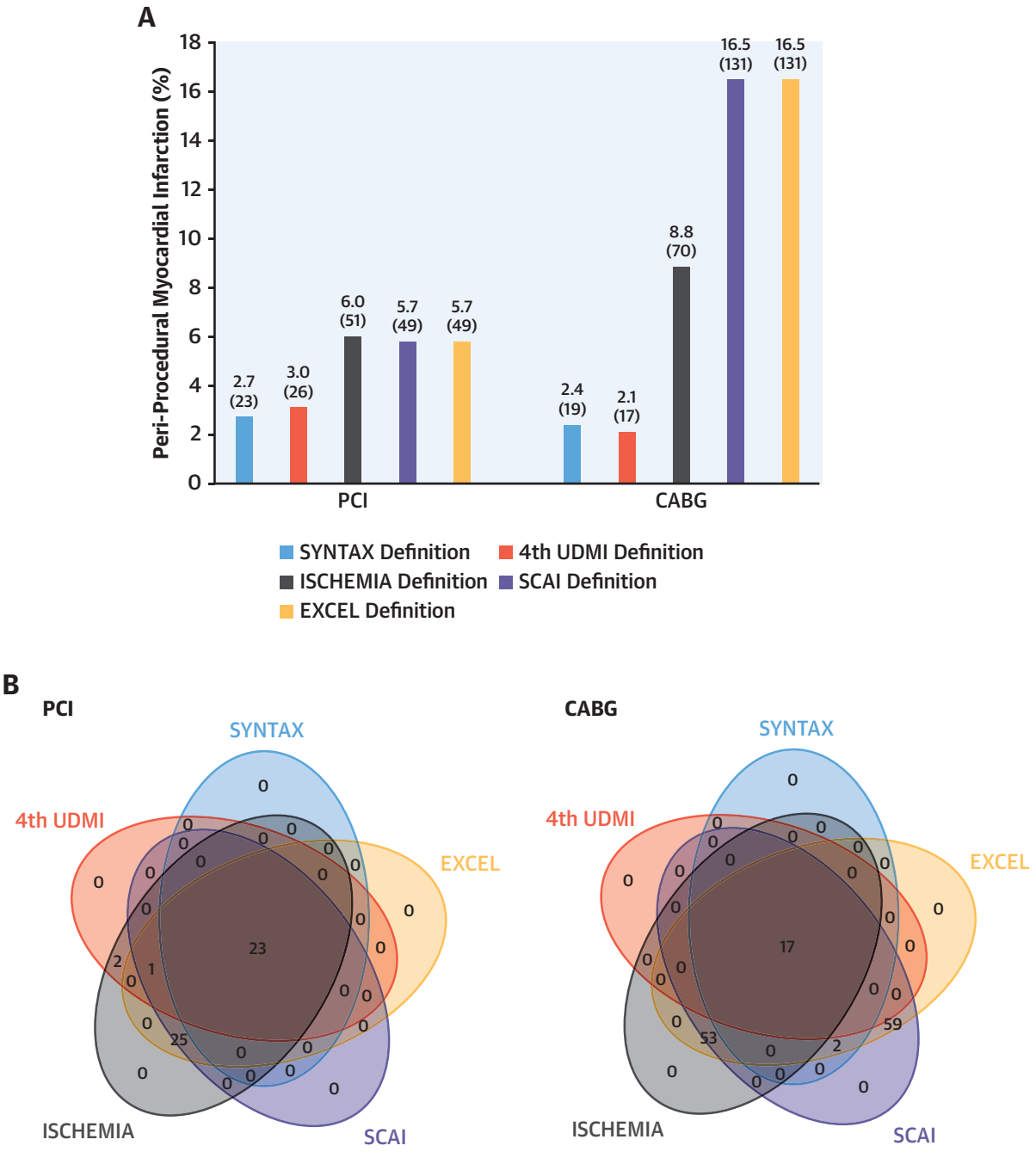
CABG, 27 patients who did not receive assigned treatment, 3 patients who died before planned PCI or CABG, 55 patients without CK or CK-MB values within 48 h of revascularization, and 32 patients in which CK ratio was ≥2 times ULN but CK-MB was not available; of these 32 patients, 2 had new Q waves. Ultimately, 1,652 (91.8%) patients were included in this analysis, with 857 and 795 in the PCI and CABG arm, respectively (Figure 1).

Details of the method of assessment of electrocardiograms (ECG) by independent core laboratories according to the Minnesota code (Cardialysis, Rotterdam, the Netherlands) and the MI adjudication process by the Clinical Events Committee (CEC) are described in the Supplemental Methods. Angiographic findings of flow-limiting peri-procedural complications such as coronary dissection or occlusion were site-reported, as was imaging evidence of the new loss of viable myocardium or new regional wall motion abnormality.

Adverse events, such as stent thrombosis or graft/native coronary artery occlusion, were adjudicated by a central and independent CEC and collected up to 5 years. The causes of death (cardiovascular or noncardiovascular) were adjudicated by a CEC according to the protocol definitions. Rates of PMI and MACCE up to 5 years were re-evaluated applying the SYNTAX, Fourth UDMI, ISCHEMIA, SCAI, and EXCEL definitions. Vital status was confirmed by contact with medical care personnel or using electronic health care record review and national death registries. Patients with missing vital status were included in the analysis and censored at the time they were lost to follow-up. Five patients in 2 investigating centers that did not participate in the SYNTAXES study were censored at 5 years.

STATISTICAL ANALYSIS. The analysis population for the present study was a modified intention-to-treat cohort consisting of patients in whom revascularization was performed according to the assigned procedure, and patients who did not receive the assigned procedure were excluded (9). The rates of PMI were the percentages of patients with a PMI. The cumulative incidences of death and MACCE were calculated using the Kaplan-Meier method. Kaplan-Meier survival curves were analyzed using the log-rank test. Hazard ratios (HRs) with 95% confidence intervals (CIs) for all-cause mortality was determined on the basis of Cox proportional hazards regression, and baseline variables used for adjustment are shown in the Supplemental Methods. Continuous variables

FIGURE 2 The Rates of PMI According to Definitions



(A) Peri-procedural myocardial infarction (PMI) rates according to the definitions. The rates of PMI were the percentages of patients with a PMI. Data are presented as percentage (number). **(B)** The Venn diagram shows the numbers of patients with a PMI according to the definitions. EXCEL = Evaluation of XIENCE versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization; ISCHEMIA = International Study Of Comparative Health Effectiveness With Medical And Invasive Approaches; SCAI = Society for Cardiovascular Angiography and Interventions; SYNTAX = TAXUS Drug-Eluting Stent Versus Coronary Artery Bypass Surgery for the Treatment of Narrowed Arteries; UDMI = universal definition of myocardial infarction; other abbreviations as in Figure 1.

were expressed as mean ± SD, and were compared using Student's *t*-test or Mann-Whitney *U* test. Categorical variables were reported as numbers and percentages, and were compared using chi-square or Fisher exact test as appropriate. A 2-sided p value <0.05 was considered statistically significant. Analyses were performed using JMP Pro14 (SAS Institute Inc., Cary, North Carolina) and R version 3.6.0 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

STUDY POPULATION AND RATES OF PMI ACCORDING TO THE DEFINITIONS. Baseline characteristics in the PCI and CABG arm were similar, although patients treated with PCI had a higher prevalence of hypertension (Supplemental Table 1).

According to the SYNTAX trial definition, PMI occurred within 48 h in 23 patients (2.7%) in the PCI arm and 19 patients (2.4%) in the CABG arm (p = 0.756) (**Figure 2**). Patients with a PMI presented more frequently with unstable angina, compared with those without a PMI (Supplemental Table 2). The numbers of patients with a PMI according to the Fourth UDMI were similar to those identified according to the SYNTAX definition: 26 patients (3.0%) in the PCI arm and 17 patients (2.1%) in the CABG arm (p = 0.281) (**Figure 2**). Using the ISCHEMIA definition, 51 patients (6.0%) and 70 patients (8.8%) experienced PMI in the PCI and CABG arms, respectively (p = 0.030). When applying the SCAI and EXCEL definitions, PMI rates were the same: 49 patients (5.7%) experienced a PMI in the PCI arm, while 131 (16.5%) experienced a PMI in the CABG arm (p < 0.001). Most of the PMI events according to the ISCHEMIA, SCAI, and EXCEL definitions were solely driven by enzyme criteria (CK-MB >10 or >15 times ULN) (Supplemental Figure 1). The presence of supporting evidence of infarction in patients with CK-MB ≥5 times ULN is shown in Supplemental Figure 2.

ASSOCIATION OF PMI WITH ALL-CAUSE MORTALITY AT 1 AND 10 YEARS. The median (quartile 1, quartile 3) durations of follow-up were 11.2 years (8.1, 12.0 years) overall, 11.1 years (7.5, 12.0 years) in the PCI arm, and 11.2 years (8.7, 12.1 years) in the CABG arm (Supplemental Figure 3). In the PCI and CABG arms, PMI according to the SYNTAX definition was associated with higher all-cause mortality at 10 years, mainly driven by a higher mortality rate within the first 30 days and the first year (**Figure 3A**). The impact of PMI on cardiovascular and noncardiovascular deaths was similar (Supplemental Table 3, Supplemental Figures 4 and 5). After adjustment for baseline characteristics, according to the SYNTAX definition, PMI after PCI remained an independent predictor for all-cause mortality at 1 and 10 years. In contrast, PMI after CABG was only an independent predictor for all-cause mortality at 1 year, and not at 10 years (**Figure 4A**). The similar statistical results were observed with the Fourth UDMI and ISCHEMIA definition (**Figures 3B, 3C, 4B, and 4C**). When applying the SCAI or EXCEL definition, PMI was associated with higher all-cause mortality at 1 and 10 years in the PCI arm, whereas it did not have a significant mortality impact in the CABG arm (**Figures 3D and 4D**). Moreover, in the combined cohort of PCI and CABG patients, PMIs according to the SYNTAX or Fourth UDMI definition were significantly associated with all-cause mortality at 1 year (31.0% and 30.2%) and at 10 years (53.4% and 49.6%), whereas the association failed to be significant with the SCAI and EXCEL definitions at 10 years (31.1%) and was low at 1 year (10.6%) (**Figure 4**, Supplemental Table 4).

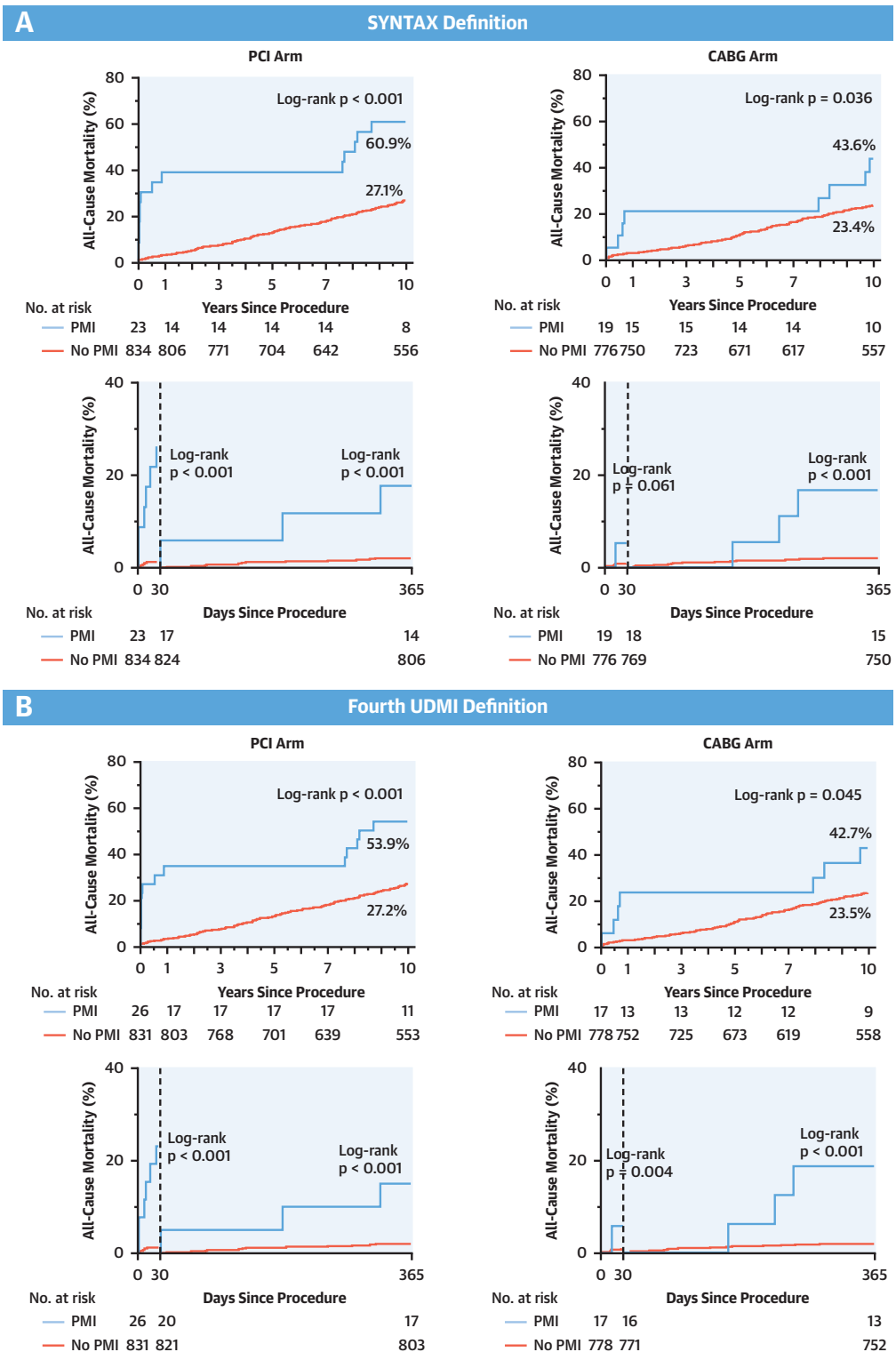
THRESHOLDS FOR ENZYME RELEASE, ADDITIONAL NONENZYMATIC CRITERIA OF INFARCTION, AND ALL-CAUSE MORTALITY. The peak values of CK-MB categorized into 4 subsets: 1) CK <2× ULN or CK-MB <3× ULN; 2) CK-MB ≥3× to <5× ULN; 3) CK-MB ≥5× to <10× ULN; and 4) CK-MB ≥10× ULN—are shown in **Figure 5A**. Overall enzyme values were higher in the CABG arm than in the PCI arm. An isolated enzyme elevation of CK-MB post-PCI had a significant prognostic impact on mortality at 1 and 10 years, and this lethal impact was mainly observed in the first 30 days for a rise in CK-MB of more than 10× ULN (**Figures 5B, 6A, and 6B**).

After CABG, such isolated enzyme elevation in the absence of ECG changes (new Q waves or new persistent left bundle branch block [LBBB]) was not associated with increased 1- or 10-year mortality; however, in contrast elevations of CK-MB accompanied by ECG changes post-surgery were associated with early (1 year) and late (7 to 10 years) all-cause death (**Figures 5C to 5D**).

In the presence of ECG changes, a PMI with a CK-MB elevation of ≥5× or ≥10× ULN resulted in a significantly higher 1-year mortality irrespective of the mode of revascularization (p values for interaction: 0.217 and 0.419) (**Figures 6C and 6D**).

At 10 years, the adjusted HRs for mortality post-PCI in patients with a PMI combining peak CK-MB ≥5× or ≥10× ULN and ECG changes were significant (HRs: 7.01 and 5.69, respectively), whereas the adjusted HRs for mortality post-CABG were not significant (p = 0.292 and p = 0.103, respectively) (**Figures 6C and 6D**).

FIGURE 3 Kaplan-Meier Curves for All-Cause Mortality According to PMI



Kaplan-Meier curves up to 10 years **(top)**, and in the landmark period of 0 to 30 days and 31 to 365 days **(bottom)** in patients with/without PMI in the PCI and CABG arms. **(A)** The SYNTAX definition, **(B)** the Fourth UDMI definition, **(C)** the ISCHEMIA definition, and **(D)** the SCAI/EXCEL definition. The rates were calculated using the Kaplan-Meier method. Abbreviations as in Figures 1 and 2.

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FIGURE 3 Continued

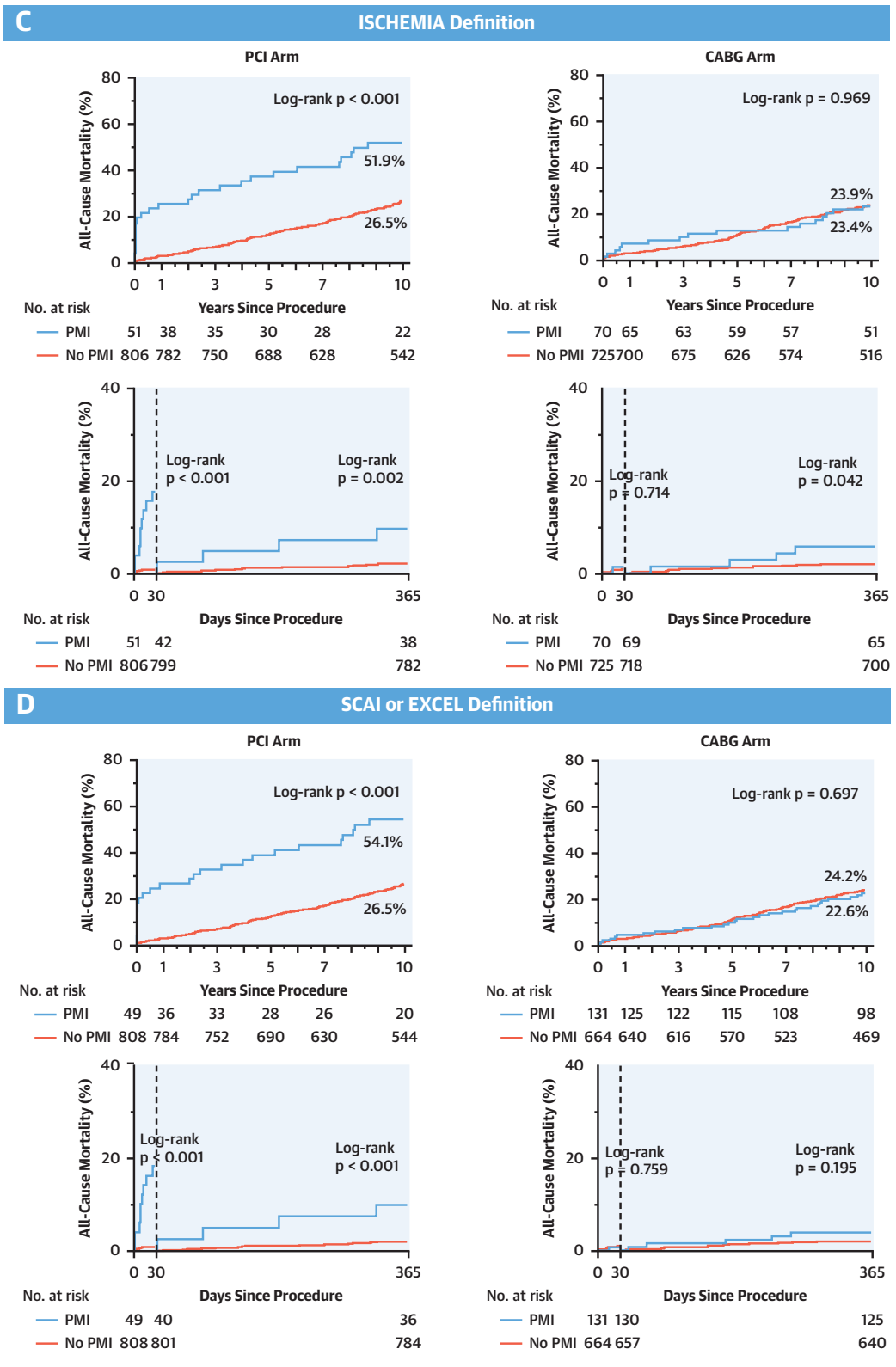
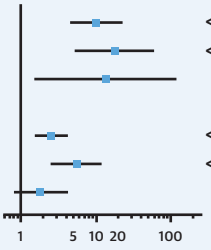


FIGURE 4 Impact of PMI on All-Cause Mortality Expressed as Hazard Ratios

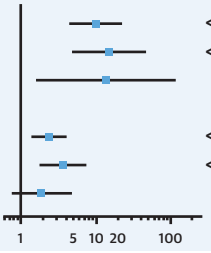
A

SYNTAX Definition	PMI (n = 42)	Non-PMI (n = 1,610)	Unadjusted HR (95% CI)	p Value	Adjusted HR (95% CI)	p Value	p Value for Interaction
At 1 year							
Overall	31.0 (13/42)	3.0 (49/1,610)	11.94 (6.48-22.02)	< 0.001	12.92 (5.73-29.17)	< 0.001	
PCI arm	39.1 (9/23)	3.2 (27/834)	15.38 (7.22-32.75)	< 0.001	22.57 (6.71-75.91)	< 0.001	0.280
CABG arm	21.1 (4/19)	2.8 (22/776)	7.82 (2.69-22.68)	< 0.001	17.15 (1.94-151.88)	0.011	
At 10 years							
Overall	53.4 (22/42)	25.3 (394/1,610)	2.75 (1.79-4.23)	< 0.001	3.26 (1.92-5.51)	< 0.001	
PCI arm	60.9 (14/23)	27.1 (218/834)	3.39 (1.97-5.81)	< 0.001	7.01 (3.23-15.17)	< 0.001	0.117
CABG arm	43.6 (8/19)	23.4 (176/776)	2.10 (1.03-4.27)	0.04	2.31 (0.96-5.56)	0.062	



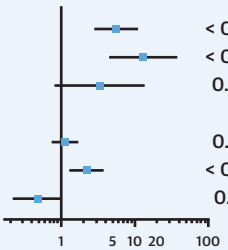
B

4th UDMI Definition	PMI (n = 43)	Non-PMI (n = 1,609)	Unadjusted HR (95% CI)	p Value	Adjusted HR (95% CI)	p Value	p Value for Interaction
At 1 year							
Overall	30.2 (13/43)	3.0 (49/1,609)	11.61 (6.29-21.40)	< 0.001	12.90 (5.70-29.19)	< 0.001	
PCI arm	34.6 (9/26)	3.3 (27/831)	13.10 (6.16-27.89)	< 0.001	19.33 (6.04-61.80)	< 0.001	0.393
CABG arm	23.5 (4/17)	2.8 (22/778)	8.83 (3.04-25.64)	< 0.001	17.38 (1.96-153.99)	0.010	
At 10 years							
Overall	49.6 (21/43)	25.4 (395/1,609)	2.53 (1.63-3.92)	< 0.001	3.00 (1.74-5.16)	< 0.001	
PCI arm	53.9 (14/26)	27.2 (218/831)	2.74 (1.60-4.71)	< 0.001	4.63 (2.25-9.53)	< 0.001	0.333
CABG arm	42.7 (7/17)	23.5 (177/778)	2.13 (1.00-4.53)	0.050	2.35 (0.91-6.06)	0.077	



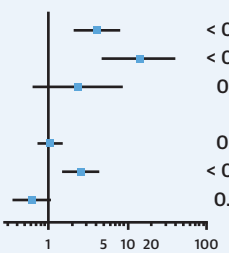
C

ISCHEMIA Definition	PMI (n = 121)	Non-PMI (n = 1,531)	Unadjusted HR (95% CI)	p Value	Adjusted HR (95% CI)	p Value	p Value for Interaction
At 1 year							
Overall	14.9 (18/121)	2.9 (44/1,531)	5.56 (3.21-9.62)	< 0.001	7.19 (3.65-14.17)	< 0.001	
PCI arm	25.5 (13/51)	2.9 (23/806)	10.39 (5.26-20.52)	< 0.001	16.74 (5.76-48.70)	< 0.001	0.150
CABG arm	7.1 (5/70)	2.9 (21/725)	2.49 (0.94-6.60)	0.067	4.33 (1.06-17.70)	0.042	
At 10 years							
Overall	35.4 (42/121)	25.3 (374/1,531)	1.61 (1.17-2.21)	0.003	1.43 (0.94-2.18)	0.097	
PCI arm	51.9 (26/51)	26.5 (206/806)	2.75 (1.83-4.14)	< 0.001	2.85 (1.66-4.88)	< 0.001	0.002
CABG arm	23.4 (16/70)	23.9 (168/725)	0.99 (0.59-1.65)	0.969	0.62 (0.29-1.33)	0.218	



D

SCAI or EXCEL Definition	PMI (n = 180)	Non-PMI (n = 1,472)	Unadjusted HR (95% CI)	p Value	Adjusted HR (95% CI)	p Value	p Value for Interaction
At 1 year							
Overall	10.6 (19/180)	2.9 (43/1,472)	3.78 (2.20-6.49)	< 0.001	5.28 (2.67-10.41)	< 0.001	
PCI arm	26.5 (13/49)	2.9 (23/808)	10.92 (5.53-21.58)	< 0.001	17.63 (6.02-51.61)	< 0.001	0.026
CABG arm	4.6 (6/131)	3.0 (20/664)	1.52 (0.61-3.79)	0.368	2.95 (0.76-11.48)	0.119	
At 10 years							
Overall	31.1 (55/180)	25.4 (361/1,472)	1.32 (1.00-1.76)	0.052	1.32 (0.90-1.92)	0.153	
PCI arm	54.1 (26/49)	26.5 (206/808)	2.95 (1.96-4.44)	< 0.001	3.21 (1.86-5.53)	< 0.001	< 0.001
CABG arm	22.6 (29/131)	24.2 (155/664)	0.92 (0.62-1.37)	0.697	0.78 (0.44-1.38)	0.392	



(A) The SYNTAX definition, **(B)** the Fourth UDMI definition, **(C)** the ISCHEMIA definition, and **(D)** the SCAI/EXCEL definition. The rates of all-cause mortality were calculated using the Kaplan-Meier method. CI = confidence interval; HR = hazard ratio; other abbreviations as in Figures 1 and 2.

IMPACT OF PMI DEFINITION ON TIME-TO-EVENT CURVE AND COMPOSITE ENDPOINT AT 5 YEARS. The MACCE rates at 1 and 5 years were higher in the PCI compared with the CABG arm, when using the SYNTAX, Fourth UDMI, or ISCHEMIA definition of PMI, although the rate of all-cause mortality was not significantly different in the PCI and CABG arms (**Figure 7**). In contrast, with the SCAI or EXCEL definition, MACCE rates were higher with CABG at 1 year, and they were similar between PCI and CABG at 5 years (**Figure 7**).

DISCUSSION

The 5 different definitions of PMI were applied to the SYNTAXES study. Two of them (the SYNTAX and Fourth UDMI) combine elevation of cardiac biomarkers (CK-MB) with other evidence of myocardial damage (e.g., new Q waves on ECG) irrespective of the level of enzyme release, whereas the ISCHEMIA, SCAI, and EXCEL definitions define PMI solely on the basis (sufficient criteria) of biomarker elevation when CK-MB is more than 10× or 15× ULN. Furthermore, the Fourth UDMI and ISCHEMIA definitions have different thresholds of enzyme elevation according to the mode of revascularization: surgical (>10× or >15× ULN) or percutaneous (>5× or >10× ULN) (**Table 1**).

The main findings of the present study are as follows:

1. The rates of PMI are highly dependent on their definitions, which in turn influence the time-to-event curve as well as the composite endpoint of the SYNTAX trial (**Figures 2 and 7**).
2. PMIs following PCI are associated with an increase in all-cause mortality at 1 and 10 years regardless of the definition (**Figure 4**).
3. In patients undergoing CABG, definitions of PMI that in addition to enzyme rises require ECG or other evidence of infarction are associated with all-cause mortality; however, this is limited to the first year post-procedure. Definitions based mostly on isolated (even marked) enzyme elevations have no significant correlation with all-cause mortality after CABG at 1 and 10 years (**Figure 4**).
4. In the combined cohort of PCI and CABG patients, PMIs according to the SYNTAX or Fourth UDMI definition are significantly associated with all-cause mortality and are therefore "clinically relevant," whereas the association at 10 years fails to be significant with the SCAI and EXCEL definitions when PMI is defined solely by enzyme elevation of CK-MB more than 10× ULN. This "enzymatic PMI event" more selectively affects the time-to-event curve and the composite endpoint of the surgical cohort.

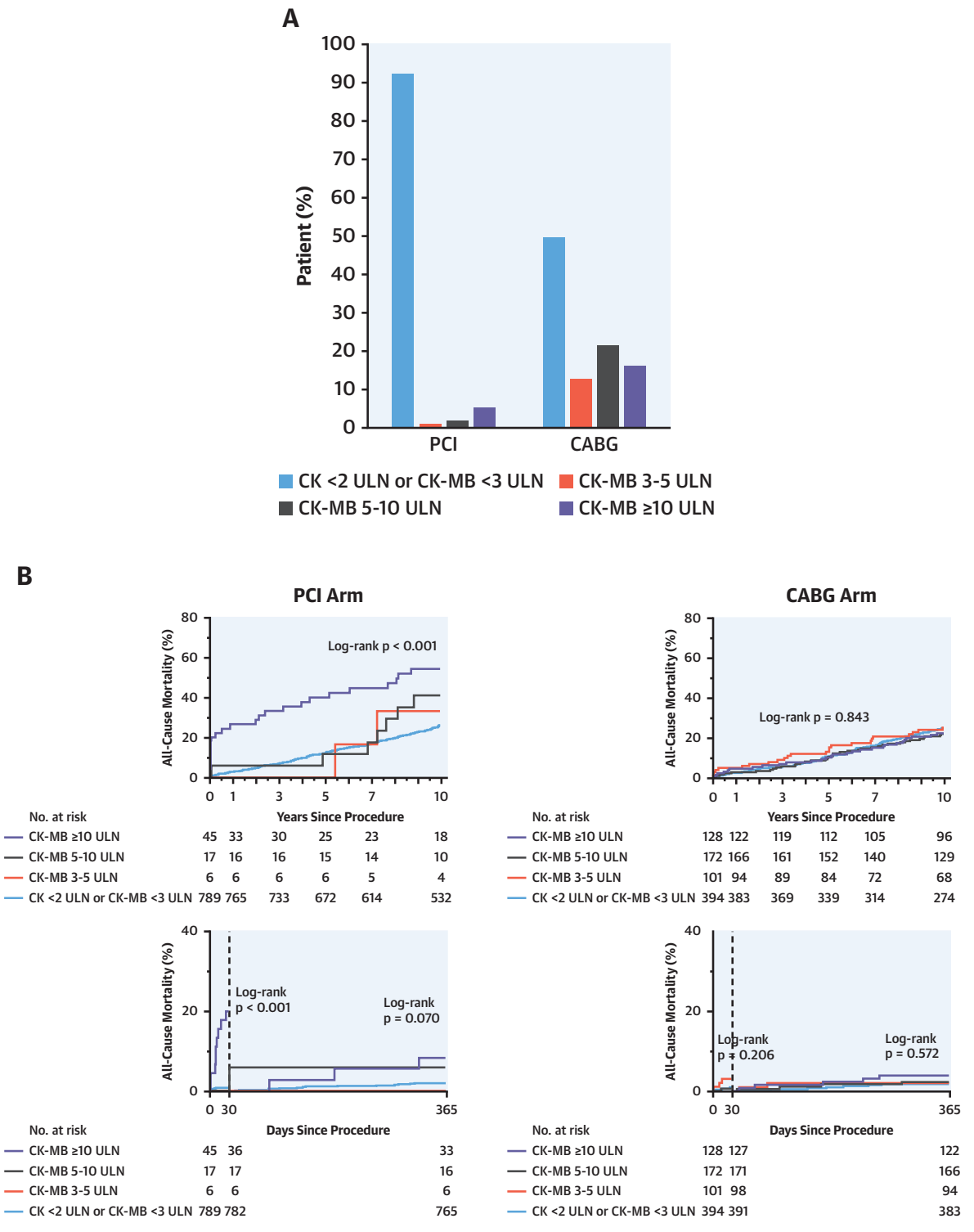
THE RATES OF PMI ACCORDING TO THE DEFINITIONS. The 2 latest randomized trials of PCI versus CABG in patients with LMCAD, EXCEL and NOBLE (Nordic-Baltic-British Left Main Revascularization Study), took diametrically different methodological approaches with respect to PMI (11,12). The EXCEL trial used a definition similar to the SCAI definition (4), whereas the NOBLE trial did not include PMI in the primary endpoint (11). This difference in methodological approach is an extreme case; however, rates of PMI can still vary dramatically between trials using differing definitions, and this can considerably affect time-to-event curves and composite endpoints (**Figure 7**).

We investigated the rates of PMI according to 5 different definitions in the SYNTAX trial. The rates of PMI with the SYNTAX definition were 2.7% and 2.4% in the PCI and CABG arms, respectively (**Figure 2, Central Illustration**), with similar rates (3.0% and 2.1%) observed using the Fourth UDMI definition. Both definitions require supporting evidence of infarction regardless of peak cardiac enzyme values, and patients with PMIs according to these definitions were largely overlapped (**Figure 2B**). On the other hand, the ISCHEMIA, SCAI, and EXCEL definitions do not mandate supporting evidence of infarction if the peak CK-MB is more than 10× or 15× ULN, and the rates of PMIs using these definitions were higher than those adjudicated with the SYNTAX or Fourth UDMI definition. Of note, in the SYNTAX trial, the rate of PMI with the SCAI or EXCEL definition was much higher in patients treated with CABG versus PCI (16.5% vs. 5.7%; $p < 0.001$). In the EXCEL trial, PMI was also observed more frequently in the CABG arm, compared with the PCI arm (6.1% [56 patients] vs. 3.6% [34 patients]; $p = 0.017$) (9). Although the ISCHEMIA definition requires a higher cut-off value of CK-MB in the CABG arm compared with the PCI arm (**Table 1**), the rate of PMI was higher in patients treated with CABG (8.8% vs. 6.0%; $p = 0.030$).

SURVIVAL AFTER PMI ACCORDING TO THE DEFINITIONS. When PMIs are defined according to the SYNTAX and Fourth UDMI definitions, a striking and intriguing observation in the SYNTAX trial is the apparent plateau for approximately 7 years in the survival curve occurring between 2 clusters of mortality observed in the first year and the last 3 years of follow-up.

In the SIRTAX (Sirolimus-Eluting vs. Paclitaxel-Eluting Stents for Coronary Revascularization) trial ($n = 1,012$), using the same TAXUS stent as in the SYNTAX trial, 78 cardiac deaths (63.9% in 122 patients) and 44 noncardiac deaths (36.1% in

FIGURE 5 Kaplan-Meier Curves for All-Cause Mortality According To Peak CK-MB Values With/Without ECG Changes



(A) Percentage of patients (PCI vs. CABG) with their peak values of CK-MB (within 48 h post-revascularization) categorized in 4 subgroups: 1) CK <2× ULN or CK-MB <3× ULN; 2) CK-MB ≥3× to <5× ULN; 3) CK-MB ≥5× to <10× ULN; and 4) CK-MB ≥10× ULN. **(B to D)** Kaplan-Meier curves up to 10 years **(top)**, and in the landmark period of 0 to 30 days and 31 to 365 days **(bottom)** according to **(B)** peak values of CK-MB, **(C and D)** the criteria with peak CK-MB values (cut-off of ≥5× ULN or ≥10× ULN), and ECG changes (new Q waves or new persistent left bundle branch block). The rates were calculated using the Kaplan-Meier method. Abbreviations as in Figure 1.

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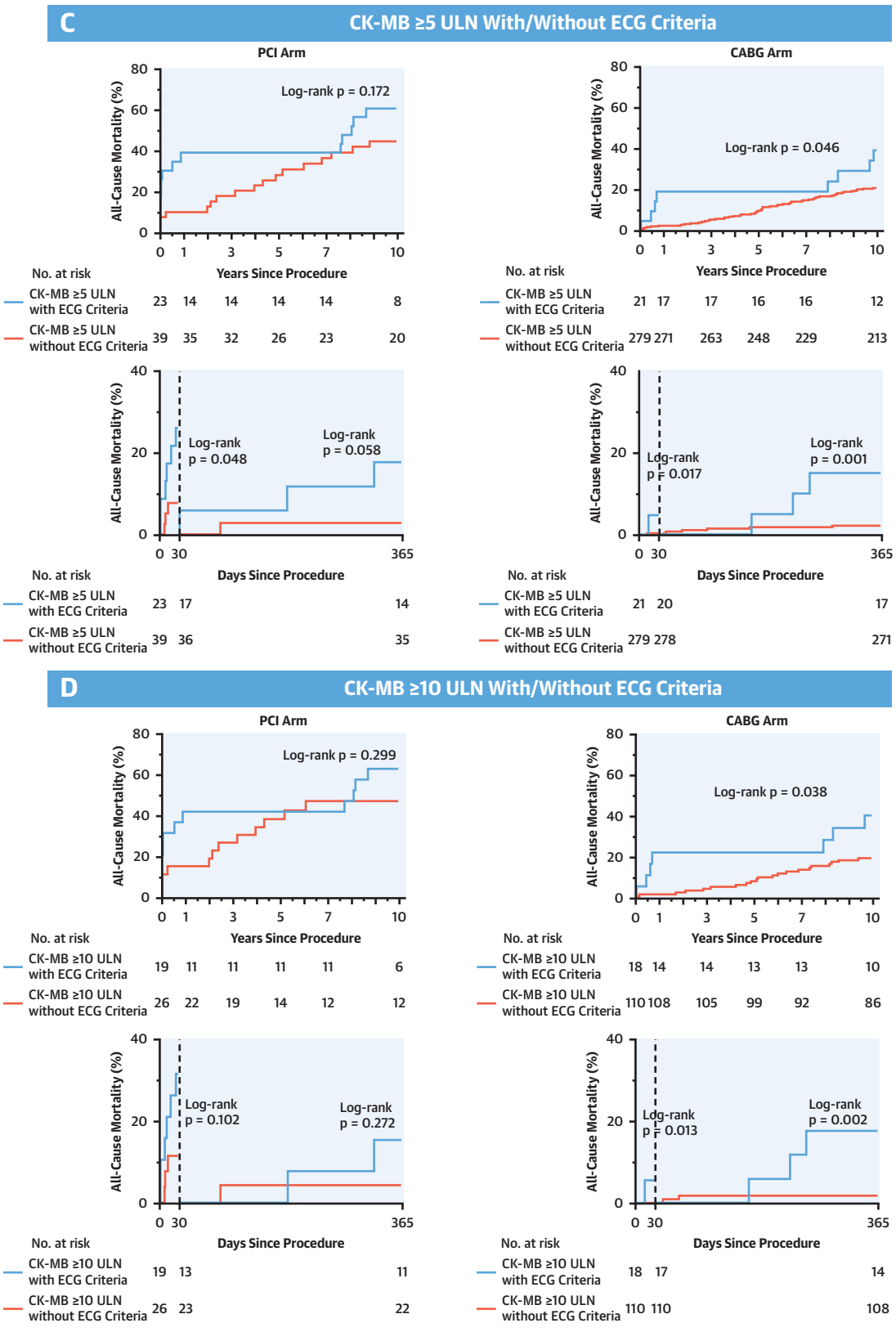
FIGURE 5 Continued



122 patients) occurred between 5 and 10 years (13). However, among the 78 cardiac deaths, 36 deaths were regarded as undetermined and thus categorized as cardiac as a worst-case scenario. The incidence of cardiac death may therefore be overestimated between 5 to 10 years. Further evidence of this comes from a nonrandomized study of PCI in patients with multivessel disease treated between 2003 and 2008, in which cardiac deaths (approximately 40%) were less frequent than noncardiac deaths at 5 years (14).

In the SYNTAXES study, the absence of death between 1 and 7 years in patients with a PMI according to the SYNTAX or Fourth UDMI definitions may be a play of chance in a small sample size of patients at risk of death. Plausible chronological and/or biological explanations for this observation and the second wave of deaths between 7 and 10 years may be that secondary prevention becomes progressively more effective over time (15), whereas the increase in noncardiovascular deaths after 7 years may simply be related to the ongoing aging process. Of the patients who died between 7 and 10 years, the mean ages at the time of procedure of the 9 patients who experienced a PMI according to the SYNTAX definition and 8 patients who experienced a PMI according to the Fourth UDMI were 70.3 and 69.1 years, respectively. It is therefore plausible that these patients, who were already elderly at the time of their procedure, died 7 to 10 years later of unrelated noncardiovascular causes.

In the 10-year follow-up of the PRECOMBAT (Premier of Randomized Comparison of Bypass Surgery versus Angioplasty Using Sirolimus-Eluting Stent in Patients with Left Main Coronary Artery Disease) trial, cardiovascular, noncardiovascular, or undetermined deaths were observed in 22, 11, and 9 patients in the PCI arm (n = 300) and 25, 8, and 7 patients in the CABG arm (n = 300) (16). Thus, cardiovascular death was also the main cause of death at 10 years in this trial with long-term follow-up among patients with extensive and complex coronary artery disease. With respect to very long-term cardiovascular events, very late stent thrombosis occurred in 1.4% of patients in the SIRTAX trial between 5 and 10 years with the first-generation TAXUS DES. After CABG, 10% to 25% of saphenous vein grafts occlude from thrombosis within 1 year, and an additional 1% to 2% occlude each year from 1 to 5 years. Of note, 4% to 5% occlude each year from 6 to 10 years, due to accelerated atherosclerosis (17). In the SYNTAX trial, vein graft conduits were used in 645 patients (81.1%). Thus, very late stent thrombosis or vein graft occlusion might also be plausibly associated with late cardiovascular deaths (between 7 and 10 years).

In contrast, in patients with PMI as per the ISCHEMIA, SCAI, and EXCEL definitions, there was a gradual and almost linear increase in mortality, supposedly more compatible with a biological phenomenon, but definitely less statistically related to PMI at least in the surgical patients (**Figures 3 and 4**).

IMPACT OF PMI ON ALL-CAUSE MORTALITY IN PATIENTS WITH PCI OR CABG. In the present study, PMI after PCI had a significant influence on all-cause mortality regardless of its definition (**Figure 4, Central Illustration**). This observation is mainly derived from the fact that CK-MB elevation ≥5× ULN after PCI was associated with 10-year all-cause death even after adjustment. The impact of CK-MB elevation after elective PCI on mortality within 5 years has been demonstrated in a meta-analysis (18), but it is noteworthy that the significant impact of CK-MB elevation on mortality persisted over 10 years in the present study.

When treated with CABG, a pooled analysis of 18,908 patients showed that CK-MB elevation within 24 h of the procedure was associated with 1-year mortality (19). In the present study, isolated CK-MB elevation after CABG was not associated with subsequent mortality even if a relatively high cut-off threshold of CK-MB ≥10× ULN was applied (**Figure 6B**). However, adding supporting ECG evidence of infarction to enzyme release did affect subsequent mortality after CABG (**Figures 5 and 6**).

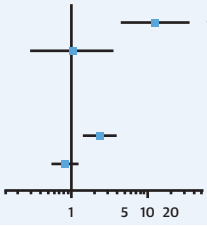
The lethal prognostic impact of PMI after CABG when defined by the EXCEL definition was less severe in the SYNTAXES study than in the EXCEL trial (9). In the SYNTAXES study, of the 131 patients with a PMI post CABG according to the EXCEL definition, 109 had a CK-MB more than 10× ULN, but no other additional evidence of infarction. In other words, 109 PMIs (83.2%) after CABG with the EXCEL definition were purely based on enzymes and, therefore, could not be linked to a specific injured myocardial zone subtended by a specific epicardial coronary artery; these were possibly caused by global myocardium injury, which might be specifically associated with surgical revascularization (cardiac arrest and cardioplegia, transient vessel occlusion during off-pump surgery, and so on) In the CABG arm of the EXCEL trial (n = 923 patients), 56 (6.1%) PMIs were diagnosed using the EXCEL criteria, of which 36 (64.3%) were purely based on a CK-MB more than 10× ULN without any other additional evidence of infarction (9).

In the CABG arm of the SYNTAXES study, ECG evidence of infarction in combination with a CK-MB >10× ULN was associated with a significantly higher 10-year all-cause mortality (40.2%) compared with

FIGURE 6 Impact of the Peak CK-MB Values With or Without ECG Changes on All-Cause Mortality

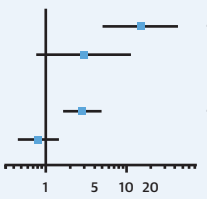
A

	CK-MB ≥5 ULN (n = 362)	CK-MB <5 ULN (n = 1,290)	Unadjusted HR (95% CI)	p Value	Adjusted HR (95% CI)	p Value	p Value for Interaction
At 1 year							0.015
PCI arm	21.0 (13/62)	2.9 (23/795)	8.17 (4.13-16.13)	< 0.001	12.47 (4.44-35.02)	< 0.001	
CABG arm	3.7 (11/300)	3.0 (15/495)	1.21 (0.56-2.63)	0.633	1.03 (0.29-3.61)	0.964	
At 10 years							0.002
PCI arm	50.9 (31/62)	26.2 (201/795)	2.55 (1.75-3.72)	< 0.001	2.37 (1.41-3.99)	0.0012	
CABG arm	22.1 (65/300)	25.0 (119/495)	0.87 (0.65-1.18)	0.382	0.83 (0.55-1.25)	0.377	



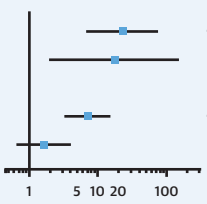
B

	CK-MB ≥10 ULN (n = 173)	CK-MB <10 ULN (n = 1,479)	Unadjusted HR (95% CI)	p Value	Adjusted HR (95% CI)	p Value	p Value for Interaction
At 1 year							0.055
PCI arm	26.7 (12/45)	3.0 (24/812)	10.59 (5.29-21.19)	< 0.001	15.03 (5.12-44.14)	< 0.001	
CABG arm	4.7 (6/128)	3.0 (20/667)	1.56 (0.63-3.90)	0.337	2.96 (0.76-11.50)	0.117	
At 10 years							0.002
PCI arm	54.4 (24/45)	26.6 (208/812)	3.00 (1.96-4.57)	< 0.001	2.84 (1.60-5.04)	< 0.001	
CABG arm	22.3 (28/128)	24.2 (156/667)	0.92 (0.61-1.37)	0.667	0.80 (0.45-1.45)	0.464	



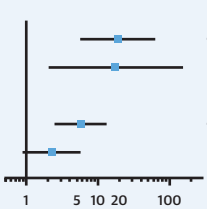
C

	CK-MB ≥5 ULN with ECG (n = 44)	Others (n = 1,608)	Unadjusted HR (95% CI)	p Value	Adjusted HR (95% CI)	p Value	p Value for Interaction
At 1 year							0.217
PCI arm	39.1 (9/23)	3.2 (27/834)	15.38 (7.22-32.75)	< 0.001	22.57 (6.71-75.91)	< 0.001	
CABG arm	19.1 (4/21)	2.9 (22/774)	7.00 (2.41-20.33)	< 0.001	17.17 (1.93-152.88)	0.011	
At 10 years							0.014
PCI arm	60.9 (14/23)	27.1 (218/834)	3.39 (1.97-5.81)	< 0.001	7.01 (3.23-15.17)	< 0.001	
CABG arm	39.3 (8/21)	23.5 (176/774)	1.84 (0.90-3.73)	0.092	1.63 (0.66-4.02)	0.292	



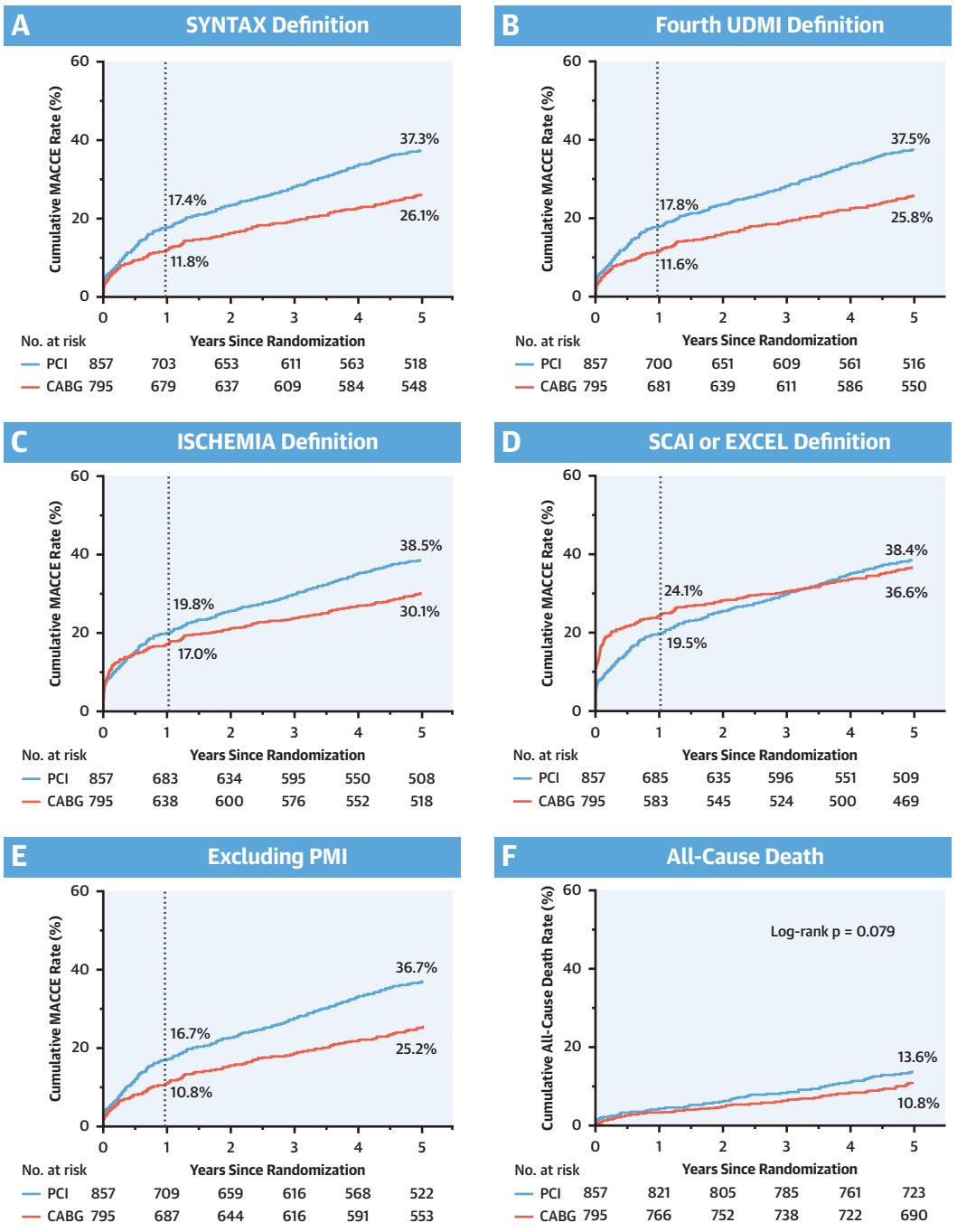
D

	CK-MB ≥10 ULN with ECG (n = 37)	Others (n = 1,615)	Unadjusted HR (95% CI)	p Value	Adjusted HR (95% CI)	p Value	p Value for Interaction
At 1 year							0.419
PCI arm	42.1 (8/19)	3.3 (28/838)	16.42 (7.47-36.08)	< 0.001	18.82 (5.56-63.78)	< 0.001	
CABG arm	22.2 (4/18)	2.8 (22/777)	8.29 (2.86-24.07)	< 0.001	17.35 (1.96-153.79)	0.010	
At 10 years							0.169
PCI arm	63.2 (12/19)	27.2 (220/838)	3.65 (2.04-6.53)	< 0.001	5.69 (2.46-13.18)	< 0.001	
CABG arm	40.2 (7/18)	23.5 (177/777)	1.97 (0.92-4.19)	0.079	2.20 (0.85-5.69)	0.103	



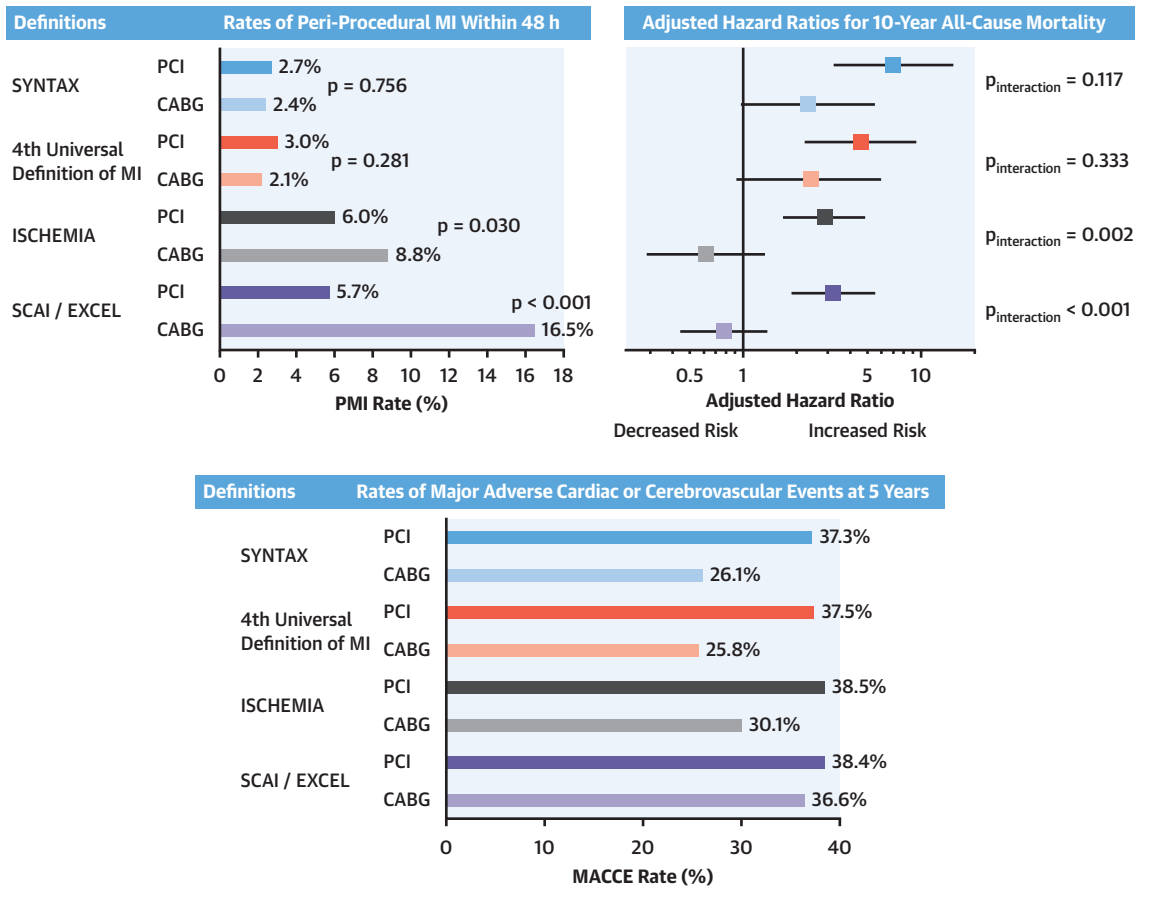
(A) CK-MB ≥5× ULN, **(B)** CK-MB ≥10× ULN, **(C)** CK-MB ≥5× ULN with ECG changes, and **(D)** CK-MB ≥10× ULN with ECG changes. The rates of all-cause mortality were calculated using the Kaplan-Meier method. Abbreviations as in Figures 1 and 4.

FIGURE 7 MACCE Rates According to Definitions



(A to E) Major adverse cardiac or cerebrovascular event (MACCE) rates in the present study population (n = 1,652) according to the **(A)** SYNTAX, **(B)** Fourth UDMI, **(C)** ISCHEMIA, and **(D)** SCAI or EXCEL definitions. The rates of MACCE were calculated using the Kaplan-Meier method. **(E)** MACCE rates excluding PMI. **(F)** Rates of all-cause death. The rates of all-cause death were calculated using the Kaplan-Meier method. Abbreviations as in Figures 1 and 2.

CENTRAL ILLUSTRATION **Rates of Peri-Procedural Myocardial Infarction According to Various Definitions and Their Impact on 5-Year Major Adverse Cardiac or Cerebrovascular Event and 10-Year All-Cause Mortality**



Hara, H. et al. J Am Coll Cardiol. 2020;76(14):1622-39.

(Top left) Rates of peri-procedural myocardial infarction (MI) according to various definitions. The rates of PMI were the percentages of patients with a PMI. **(Top right)** Impact of PMI on 10-year all-cause mortality. **(Bottom)** Rates or major adverse cardiac or cerebrovascular event (MACCE) at 5 years according to various definitions. The rates of MACCE were calculated using the Kaplan-Meier method. CABG = coronary artery bypass grafting; EXCEL = Evaluation of XIENCE versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization; ISCHEMIA = International Study Of Comparative Health Effectiveness With Medical And Invasive Approaches; PCI = percutaneous coronary intervention; SCAI = Society for Cardiovascular Angiography and Interventions; SYNTAX = TAXUS Drug-Eluting Stent Versus Coronary Artery Bypass Surgery for the Treatment of Narrowed Arteries.

the absence of ECG changes (19.4%; log-rank p = 0.038) (Figure 5D). Therefore, the discrepancy in the impact of PMI after CABG on mortality in the SYNTAXES and EXCEL trials may all be due to the different rate of PMIs defined purely by raised cardiac biomarkers.

IMPACT OF PMI DEFINITION ON TIME-TO-EVENT CURVE AND COMPOSITE ENDPOINT AT 5 YEARS. The different rates of PMI greatly affected the rates of MACCE. In the SYNTAX trial using the pre-specified definition of PMI, the rate of MACCE was higher in the PCI arm compared with the CABG arm at 1 and 5 years (6,7). This composite outcome was also observed when PMI was defined using the Fourth UDMI. In contrast, when applying the EXCEL definition, the MACCE rate in the CABG arm was higher than in the PCI arm at 1 year before becoming similar at 5 years. This profile of event rates is consistent with observations from the EXCEL trial (20). The medical community uses the "average treatment effect" of a trial as a summary of outcome—categorized as better, worse, or similar—and that categorical trial evaluation is frequently adopted in guidelines and embraced by physicians in their daily decision

making. Therefore, trialists and practitioners need to be aware of the tremendous impact of the actual definition of PMI on global outcome.

Large patient-level data will be required to definitely ascertain the impact of PMI on mortality, and concomitant use of the Fourth UDMI, SCAI, and Academic Research Consortium-2 definitions may be a solution worth promulgating.

STUDY LIMITATIONS. First, this is a post hoc analysis, and all of the presented findings must be interpreted as hypothesis-generating due to the inherent limitations of post hoc analysis analyses including multiple testing (21).

Second, the data of CK-MB ratios was incomplete because sampling of CK-MB was not mandatory if the CK ratio was <2× ULN. In addition, the values of cardiac troponin were not collected because the SYNTAX trial was initiated prior to the ARC publication of standardized definitions and clinical outcomes (22). Therefore, CK-MB ratios were used as a substitute to troponin in the application of the Fourth UDMI in the SYNTAXES study (3).

Third, the endpoint in the SYNTAXES study was all-cause death only, and although the specific cause of death after 5 years was not available, the actual impact of PMI on all-cause and cardiovascular death at 5 years was similar (Supplemental Figures 4 and 5). All-cause death remains the most robust and unbiased clinical outcome.

Fourth, the rate of death within 30 days post-PCI in patients with PMI was higher than recent trials (9). These deaths were caused by cardiovascular events, and the high mortality rate may be related to the use of the first-generation TAXUS DES and an outdated PCI strategy. The TAXUS stent is no longer commercially available, and the SYNTAX II trial (using the same clinical definition as in the SYNTAX I trial) demonstrated that contemporary, "best practice" PCI, including use of current-generation DES, physiology-guided treatment, and IVUS optimization of stent deployment, has definitely improved clinical outcomes (23).

Fifth, the assessment of the new loss of viable myocardium or new regional wall motion abnormality within 48 h of the procedure was not mandated; it was left to the discretion of the investigators and may have been challenging in patients, especially those treated with CABG, due, for example, to chest bandaging (e.g., echocardiography). Therefore, ascertainment bias is likely.

CONCLUSIONS

The rates of PMI are highly dependent on their definition. PMIs following PCI are associated with 10-year all-cause mortality, regardless of the definition. In patients undergoing CABG, PMI with definitions that require ECG or other evidence of infarction are also associated with all-cause mortality; however, this is only statistically significant in the first year post-procedure. Finally, in the SYNTAX trial, the definition of PMI had a major theoretical impact on time-to-event curves and composite endpoints at 5 years.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: The rates of PMI greatly depend on their definitions. PMIs following PCI are associated with 1- and 10-year all-cause mortality regardless of definitions currently used, whereas in patients with CABG, only definitions that require ECG or other evidence of infarction are associated with mortality, but the association is limited to the first year.

TRANSLATIONAL OUTLOOK: The specific definitions and diagnostic criteria for peri-procedural MI should be considered when interpreting time-to-event and composite outcomes of myocardial revascularization.

REFERENCES

1. Abdallah MS, Wang K, Magnuson EA, et al. Quality of life after surgery or DES in patients with 3-vessel or left main disease. J Am Coll Cardiol 2017;69:2039–50.

2. Pocock SJ, McMurray JJ, Collier TJ. Making sense of statistics in clinical trial reports: part 1 of a 4-part series on statistics for clinical trials. J Am Coll Cardiol 2015;66:2536–49.

3. Thygesen K, Alpert JS, Jaffe AS, et al. Fourth universal definition of myocardial infarction (2018). J Am Coll Cardiol 2018;72:2231–64.

4. 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.

5. Thuijs D, Kappetein AP, Serruys PW, et al. Percutaneous coronary intervention versus coronary artery bypass grafting in patients with three-vessel or left main coronary artery disease: 10-year follow-up of the multicentre randomised controlled SYNTAX trial. Lancet 2019;394:1325–34.

6. 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.

7. Mohr FW, Morice MC, Kappetein AP, et al. Coronary artery bypass graft surgery versus percutaneous coronary intervention in patients with three-vessel disease and left main coronary disease: 5-year follow-up of the randomised, clinical SYNTAX trial. Lancet 2013;381:629–38.

8. Maron DJ, Hochman JS, Reynolds HR, et al. Initial invasive or conservative strategy for stable coronary disease. N Engl J Med 2020;382:1395–407.

9. Ben-Yehuda O, Chen S, Redfors B, et al. Impact of large periprocedural myocardial infarction on mortality after percutaneous coronary intervention and coronary artery bypass grafting for left main disease: an analysis from the EXCEL trial. Eur Heart J 2019;40:1930–41.

10. Farooq V, Serruys PW, Vranckx P, et al. Incidence, correlates, and significance of abnormal cardiac enzyme rises in patients treated with surgical or percutaneous based revascularisation: a substudy from the Synergy between Percutaneous Coronary Interventions with Taxus and Cardiac Surgery (SYNTAX) Trial. Int J Cardiol 2013;168:5287–92.

11. 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.

12. 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.

13. Yamaji K, Räber L, Zanchin T, et al. Ten-year clinical outcomes of first-generation drug-eluting stents: the Sirolimus-Eluting vs. Paclitaxel-Eluting Stents for Coronary Revascularization (SIRTAX) VERY LATE trial. Eur Heart J 2016;37:3386–95.

14. Spoon DB, Psaltis PJ, Singh M, et al. Trends in cause of death after percutaneous coronary intervention. Circulation 2014;129:1286–94.

15. Iqbal J, Zhang YJ, Holmes DR, et al. Optimal medical therapy improves clinical outcomes in patients undergoing revascularization with percutaneous coronary intervention or coronary artery bypass grafting: insights from the Synergy Between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery (SYNTAX) trial at the 5-year follow-up. Circulation 2015;131:1269–77.

16. Park DW, Ahn JM, Park H, et al. Ten-year outcomes after drug-eluting stents versus coronary artery bypass grafting for left main coronary disease: extended follow-up of the PRECOMBAT Trial. Circulation 2020;141:1437–46.

17. Yahagi K, Kolodgie FD, Otsuka F, et al. Pathophysiology of native coronary, vein graft, and in-stent atherosclerosis. Nat Rev Cardiol 2016;13:79–98.

18. Li Y, Pei H, Bulluck H, Zhou C, Hausenloy DJ. Periprocedural elevated myocardial biomarkers and clinical outcomes following elective percutaneous coronary intervention: a comprehensive dose-response meta-analysis of 44,972 patients from 24 prospective studies. EuroIntervention 2020;15:1444–50.

19. 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.

20. Stone GW, Kappetein AP, Sabik JF, et al. Five-year outcomes after PCI or CABG for left main coronary disease. N Engl J Med 2019;381:1820–30.

21. Li G, Taljaard M, Van den Heuvel ER, et al. An introduction to multiplicity issues in clinical trials: the what, why, when and how. Int J Epidemiol 2017;46:746–55.

22. Cutlip DE, Windecker S, Mehran R, et al. Clinical end points in coronary stent trials: a case for standardized definitions. Circulation 2007;115:2344–51.

23. Serruys PW, Kogame N, Katagiri Y, et al. Clinical outcomes of state-of-the-art percutaneous coronary revascularisation in patients with three-vessel disease: two-year follow-up of the SYNTAX II study. EuroIntervention 2019;15:e244–52.

KEY WORDS CABG, PCI, peri-procedural myocardial infarction, SYNTAX

APPENDIX For an expanded Methods section as well as supplemental tables and figures, please see the online version of this paper.