EuroIntervention 2023;18:1272-1283 published online ahead of print January 2023

Impact of periprocedural major adverse events on 10-year mortality after revascularisation

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This paper also includes supplementary data published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-22-00681

KEYWORDS

- clinical research
- drug-eluting stent
- multiple vessel disease

Abstract

Background: The long-term prognostic impact of a composite of periprocedural major adverse events (PMAE) following revascularisation for patients with complex coronary artery disease (CAD) has not yet been established.

Aims: This study aimed to assess the impact on 10-year mortality of non-fatal PMAE following percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG). Other objectives were to evaluate 1) whether PMAE affect mortality predicted by the SYNTAX score II 2020 (SSII-2020) and 2) whether optimal medical therapy (OMT) positively affects the prognosis of patients with non-fatal PMAE.

Methods: The association between 10-year mortality and non-fatal PMAE occurring within 30 days of PCI or CABG in patients with three-vessel disease and/or left main disease enrolled in the SYNTAXES study was investigated.

Results: The main findings are that non-fatal PMAE occurred less frequently following PCI than CABG (11.2% vs 28.2%; p<0.001) and that non-fatal PMAE were an independent predictor of all-cause mortality in the first year post-procedure, but not at 5 or 10 years, in both treatment modalities. PMAE substantially alter the individual predictions of 10-year mortality by the SSII-2020. In patients with non-fatal PMAE, OMT may provide survival benefits during the first year post-procedure as well as in the long term.

Conclusions: In patients with complex CAD, non-fatal PMAE were more common following CABG than PCI, but their prognostic impact was similar, being significant in the first year and then diminishing out to 10 years. Patients with non-fatal PMAE may therefore require more careful follow-up and additional preventive treatment in the first year post-procedure.

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SUBMITTED ON 08/08/2022 - REVISION RECEIVED ON 1st 05/10/2022 / 2nd 13/10/2022 - ACCEPTED ON 18/10/2022

DOI: 10.4244/EIJ-D-22-00681

Abbreviations

3VD	three-vessel disease
CABG	coronary artery bypass grafting
CAD	coronary artery disease
DES	drug-eluting stent
LMCAD	left main coronary artery disease
MI	myocardial infarction
OMT	optimal medical therapy
PCI	percutaneous coronary intervention
PMAE	periprocedural major adverse events
SSII-2020	SYNTAX score II 2020

Introduction

In patients with complex coronary artery disease (CAD), such as left main coronary artery disease (LMCAD) or three-vessel disease (3VD), the decision by the Heart Team between either percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) is aided using an objective risk model such as the SYNTAX score II 2020 (SSII-2020), which facilitates an individual assessment of the short- and long-term risk benefits with each treatment modality[1-7].

Prospective data from a multicentre study showed that postoperative events after major surgery were an important predictor of long-term mortality[8]. A retrospective analysis of data from 833,344 patients in the US Nationwide Database who underwent PCI showed that unplanned readmissions within 30 days of PCI were associated with increased in-hospital mortality and healthcare costs, with more than half of readmissions related to baseline comorbidities or non-cardiac causes[9].

The impact on mortality of a single adverse post-procedural event such as a stroke[10-12], stent thrombosis/graft occlusion[13,14], myocardial infarction (MI)[15,16] or infection[17] is documented in a few studies amongst patients with complex CAD undergoing PCI or CABG. However, the long-term prognostic impact of a composite of periprocedural major adverse events (PMAE) following revascularisation has not yet been established. To investigate this, we assessed the impact of non-fatal PMAE on 10-year mortality amongst patients with complex CAD enrolled in the SYNTAXES study, the long-term extended follow-up study of the SYNergy Between PCI With TAXUS and Cardiac Surgery (SYNTAX) Study (ClinicalTrials.gov: NCT00114972).

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Methods

STUDY DESIGN AND DATA SOURCE

The SYNTAX Study design, protocol and results up to 5 years have been previously reported[18,19]. The design and extended vital status of the SYNTAX Study up to 10 years (SYNTAXES; ClinicalTrials.gov: NCT03417050) have also been reported elsewhere[20]. Briefly, the SYNTAX Study was a multicentre (85 European or American sites), multinational, open-label, randomised controlled trial (N=1,800: PCI: n=903; CABG: n=897) with parallel nested registries (PCI registry: n=198; CABG registry: n=1,077, of which n=644 were followed up for 5 years) designed to assess clinical outcomes following treatment of *de novo* 3VD and/or LMCAD with PCI using the TAXUS Express Stent (Boston Scientific) or CABG.

Information on vital status at 10-year follow-up was complete in 841 (93%) and 848 (95%) of patients in the PCI and CABG groups, respectively. Clinical and angiographic characteristics were well matched between groups as previously reported[20]. The median follow-up time was 11.2 years (interquartile range [IQR] 7.7-12.1) overall and 11.9 years (IQR 11.2-12.3) in survivors[20]. The SYNTAX and SYNTAXES studies were approved by the ethics committees at each investigating centre, and all patients provided their written informed consent prior to participation in the SYNTAX Study.

DEFINITIONS

Non-fatal PMAE were defined as the occurrence of periprocedural or spontaneous MI, ischaemic or haemorrhagic stroke, repeat percutaneous or surgical revascularisation, major infection, stent thrombosis/graft occlusion, bleeding, major arrhythmia, heart failure, acute respiratory failure, acute renal failure, or wound dehiscence within 30 days post-procedure **(Supplementary Appendix 1, Supplementary Table 1)**[21]. Major adverse cardiac or cerebrovascular events (MACCE) were a composite of all-cause death, MI, stroke, and repeat revascularisation, with definitions of these individual components previously reported[17,22], and all events were adjudicated by an independent clinical events committee comprised of cardiologists, cardiac surgeons, and a neurologist[20]. Infection-related events, defined as the occurrence of deep incisional surgical site infection at the primary chest incision or at a secondary incision site (e.g., saphenous harvest and groin cannulation site), mediastinitis, infectious myocarditis or pericarditis, endocarditis, cardiac device infection, pneumonia, empyema, clostridium difficile colitis, or blood-stream infection, were adjudicated *post hoc* by an independent committee according to the Centers for Disease Control and Protection/National Healthcare Safety Network (CDC/NHSN) criteria[23]. For other events, the event terms (e.g., bleeding, major arrhythmia, heart failure, acute respiratory failure, acute renal failure, and wound dehiscence) were searched for in the electronic case report form for serious adverse events **(Supplementary Appendix 1, Supplementary Table 2)** and adjudicated by the consensus of 2 cardiologists (N. Kotoku, K. Ninomiya) and 1 cardiovascular surgeon (A. Soo).

ENDPOINTS AND TIME INTERVALS

To assess the impact of non-fatal PMAE on long-term mortality, the primary endpoint was all-cause mortality between 30 days and 10 years. Secondary endpoints included all-cause mortality between 30 days and 1 year and, separately, between 1 year and 10 years as landmark analyses. An exploratory analysis was also performed to identify the benefit of optimal medical therapy (OMT) on mortality after a non-fatal PMAE. We also investigated whether non-fatal PMAE affect mortality predicted by the SSII-2020.

STATISTICAL ANALYSIS

To assess the impact of a non-fatal PMAE on long-term mortality, patients who died within 30 days of the procedure (fatal periprocedural events) were excluded. After exclusion of the patients with fatal periprocedural events, the timeline was defined as "time since index procedure." Therefore, the main analysis of this study was done according to the per-protocol principle after the exclusion of patients who did not have a procedural date (i.e., patients who did not receive PCI or CABG, including those receiving medical therapy only or who died before the procedure). As a sensitivity analysis, we also performed intention-to-treat (ITT) analyses, including death ≤30 days post-procedure, according to the definition of PMAE.

Patients with missing follow-up data were included in the analysis and censored at the time they were lost to follow-up. Patients were stratified according to the occurrence of ≥1 non-fatal PMAE within 30 days of the procedure. The Kaplan-Meier method was used to estimate cumulative event rates, and the log-rank test was performed to examine the differences between groups. Day 0 was defined as the day of the procedure. Landmark analyses were performed separately from 30 days to 1 year and from 1 year to 10 years. Hazard ratios (HR) with 95% confidence intervals (CI) for all-cause mortality from 30 days to 1 year, at 5 years and at 10 years were determined based on Cox proportional hazards regression. Cox regression analysis was performed to address the difference between patients with and without a non-fatal PMAE by adjusting the baseline variables **(Supplementary Appendix 2)**.

The statistical analysis methods employed to evaluate i) the discriminative ability and calibration of the SSII-2020 for outcome risk, and ii) the agreement between the predicted and observed benefit of treatment with PCI or CABG[5] are described in **Supplementary Appendix 3**. For the SSII-2020, ITT analyses were performed, and death within 30 days post-procedure was included in the definition of PMAE.

Continuous variables were described as mean±standard deviation (SD) and were compared using the Student's t-test or Mann-Whitney U test as appropriate. Categorical variables are expressed as proportions and were compared using the χ^2 test or Fisher's exact test. A 2-sided p-value ≤0.05 was considered statistically significant. All statistical analyses were conducted with SPSS version 27 (IBM) and R version 3.5.1 (R Foundation for Statistical Computing).

Results

PATIENTS AND PMAE

From a total of 1,800 patients randomised in the SYNTAX Study between March 2005 and April 2007, 1,739 patients received their allocated treatment (PCI arm n=885; CABG arm n=854) **(Supplementary Figure 1)**.

Within 30 days of the procedure, there were 20 deaths following PCI and 10 after CABG (2.3% vs 1.2%; HR 1.94, 95% CI: 0.91-4.15; p=0.086), of which 83.3% were cardiovascular deaths (90% following PCI; 70% following CABG). As described in the methods, to assess the impact of a non-fatal PMAE on long-term mortality, the 30 patients who died within 30 days of their procedure (fatal periprocedural events) were excluded.

Non-fatal PMAE within 30 days of PCI and CABG occurred in 97 and 238 patients, respectively (11.2% vs 28.2%; p<0.001) **(Table 1, Supplementary Figure 2)**.

As shown in **Table 1**, within 30 days of the procedure, patients treated with PCI had fewer strokes, major infections, major arrhythmias, acute respiratory failure, and acute renal failure compared to those treated with CABG.

Table 1. Non-fatal periprocedural major adverse events within 30 days after PCI and CABG.

	PCI (n=865)	CABG (n=844)	*p*-value
Non-fatal periprocedural major adverse events	97 (11.2%)	238 (28.2%)	<0.001
MI	22 (2.5%)	16 (1.9%)	0.414
Within 7 days post-procedure	15 (1.7%)	12 (1.4%)	0.699
Between 7 days and 30 days post-procedure	7 (0.8%)	4 (0.5%)	0.548
Stroke	1 (0.1%)	9 (1.1%)	0.011
Repeat revascularisation	20 (2.3%)	11 (1.3%)	0.147
Major infection	15 (1.7%)	127 (15.0%)	<0.001
Stent thrombosis/graft occlusion	17 (2.0%)	7 (0.8%)	0.063
Bleeding	21 (2.4%)	21 (2.5%)	1.000
Major arrhythmia	21 (2.4%)	73 (8.6%)	<0.001
Heart failure	10 (1.2%)	11 (1.3%)	0.829
Acute respiratory failure	0 (0.0%)	12 (1.4%)	<0.001
Acute renal failure	8 (0.9%)	19 (2.3%)	0.032
Wound dehiscence	1 (0.1%)	12 (1.4%)	0.002

CABG: coronary artery bypass grafting; MI: myocardial infarction; PCI: percutaneous coronary intervention

Demographic characteristics and comorbidities of patients with, versus without, a non-fatal PMAE following PCI or CABG are shown in **Table 2**. In both arms, patients with a non-fatal PMAE were older, more frequently had chronic kidney disease (CKD) and had a higher EuroSCORE than those without a PMAE. Ten-year mortality calculated by the SSII-2020 was higher in patients with a non-fatal PMAE irrespective of treatment modality.

IMPACT OF NON-FATAL PMAE ON LONG-TERM MORTALITY

Between 30 days and 10 years, 103 patients with a non-fatal PMAE and 310 patients without a PMAE died (30.7% vs 22.6%; HR 1.46, 95% CI: 1.16-1.82; p<0.001). Kaplan-Meier survival curves from 30 days to 10 years **(Figure 1A)** show higher mortality amongst patients with non-fatal PMAE compared to those without after CABG (29.8% vs 19.3%; log-rank p<0.001) and PCI (33.0% vs 25.1%; log-rank p=0.063). Landmark analyses

Table 2. Baseline characteristics of patients with and without a non-fatal PMAE within 30 days after PCI and CABG.

		After PCI			After CABG		
		With non-fatal PMAE (n=97)	Without non-fatal PMAE (n=768)	*p*-value	With non-fatal PMAE (n=238)	Without non-fatal PMAE (n=606)	*p*-value
Age (years)		68.7±9.3	64.7±9.6	<0.001	66.4±9.8	64.2±9.8	0.004
Male		70 (72.2%)	596 (77.6%)	0.249	187 (78.6%)	486 (80.2%)	0.634
BMI (kg/m^2)		27.6±5.1	28.2±4.7	0.279	28.2±4.5	27.7±4.4	0.113
Dyslipidaemia		73 (76.0%)	604 (79.2%)	0.508	195 (81.9%)	454 (75.9%)	0.066
Hypertension		75 (77.3%)	523 (68.1%)	0.080	146 (61.3%)	386 (63.7%)	0.527
Medically treated diabetes		32 (33.0%)	185 (24.1%)	0.063	62 (26.1%)	134 (22.1%)	0.239
CKD		31 (33.3%)	127 (17.4%)	<0.001	53 (25.4%)	93 (16.8%)	0.010
COPD		9 (9.3%)	59 (7.7%)	0.550	22 (9.2%)	54 (8.9%)	0.894
Current smoking		16 (16.5%)	144 (18.8%)	0.678	49 (20.7%)	138 (22.9%)	0.520
Previous MI		36 (37.5%)	237 (31.2%)	0.245	78 (33.3%)	201 (33.5%)	1.000
Previous stroke or TIA		12 (12.4%)	53 (6.9%)	0.065	22 (9.4%)	54 (9.0%)	0.894
LVEF <30%		2 (3.6%)	4 (0.8%)	0.120	6 (4.3%)	9 (2.3%)	0.244
History of congestive heart failure		4 (4.2%)	28 (3.7%)	0.774	17 (7.4%)	26 (4.3%)	0.083
Peripheral vascular disease		12 (12.4%)	63 (8.2%)	0.179	34 (14.3%)	51 (8.4%)	0.015
History of carotid artery disease		12 (12.4%)	59 (7.7%)	0.117	19 (8.0%)	50 (8.3%)	1.000
Preoperative unstable angina		33 (34.0%)	216 (28.1%)	0.235	71 (29.7%)	167 (27.1%)	0.446
SYNTAX score I		30.0±10.7	28.0±11.3	0.101	30.0±11.5	28.8±11.2	0.169
SYNTAX 2020 score II (%)	Predicted 10 year-mortality with PCI	36.9±20.0	27.3±18.5	<0.001	34.0±22.1	27.5±19.0	<0.001
	Predicted 10 year-mortality with CABG	29.8±16.9	23.0±16.2	<0.001	28.4±19.7	22.9±16.7	<0.001
EuroSCORE		4.7±2.5	3.5±2.5	<0.001	4.1±2.5	3.5±2.6	0.003
Left main lesion		29 (29.9%)	310 (40.4%)	0.048	93 (39.1%)	241 (39.8%)	0.876

Values are mean±SD or % (n/N). BMI: body mass index; CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease; LVEF: left ventricular ejection fraction; PMAE: periprocedural major adverse events; SYNTAX: Synergy Between PCI with Taxus and Cardiac Surgery; TIA: transient ischaemic attack

show that this increased mortality with non-fatal PMAE following PCI and CABG was seen predominantly between 30 days and 1 year (6.2% vs 2.0%; log-rank p=0.010 and 5.5% vs 1.2%; log-rank p<0.001, respectively). This was no longer apparent in the following 6-7 years of follow-up, whilst a resurgence of increased mortality occurred in the final 3 years **(Figure 1B, Figure 1C)**.

In Cox regression analysis, after adjustment for confounders, non-fatal PMAE remained an independent predictor of all-cause mortality between 30 days and 1 year irrespective of treatment modality (PCI 6.2% vs 2.0%, adjusted HR 3.42, 95% CI: 1.03-11.33; p=0.044; CABG 5.5% vs 1.2%, adjusted HR 9.99, 95% CI: 2.10-47.46; p=0.004) **(Figure 2)**. Non-fatal PMAE, however, was not an independent predictor for all-cause mortality between 30 days and 5 years, nor between 30 days and 10 years in either treatment modality **(Figure 2)**.

When we stratify patients according to the number of PMAE 0, 1, or ≥2 (a Kaplan-Meier curve for all-cause mortality is shown in **Supplementary Figure 3**), non-fatal PMAE ≥2 was an independent predictor for all-cause 10-year mortality (42.3% vs 22.5%, adjusted HR 1.78, 95% CI: 1.11-2.86; p=0.016, compared to PMAE =0) **(Supplementary Table 3)**.

The difference and time dependency of the HR for mortality over 1, 5, and 10 years for each individual PMAE component are shown in **Supplementary Table 4** with the event details at 1, 5, and 10 years in **Supplementary Table 5**-**Supplementary Table 7**, respectively.

Sensitivity analyses of the impact of non-fatal PMAE with alternative definitions[15] **(Supplementary Table 8)** of periprocedural MI on all-cause mortality are shown in **Supplementary Figure 4**-**Supplementary Figure 8**. All the results were consistent with the result of the main analysis, with MI within 30 days post-procedure (see definition in **Supplementary Table 1**).

THE BENEFIT OF OMT ON MORTALITY AFTER NON-FATAL PMAE

According to a previously reported substudy of the SYNTAXES trial, OMT was defined as the combination of 4 types of medications with at least 1 antiplatelet drug, statin, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker and a beta

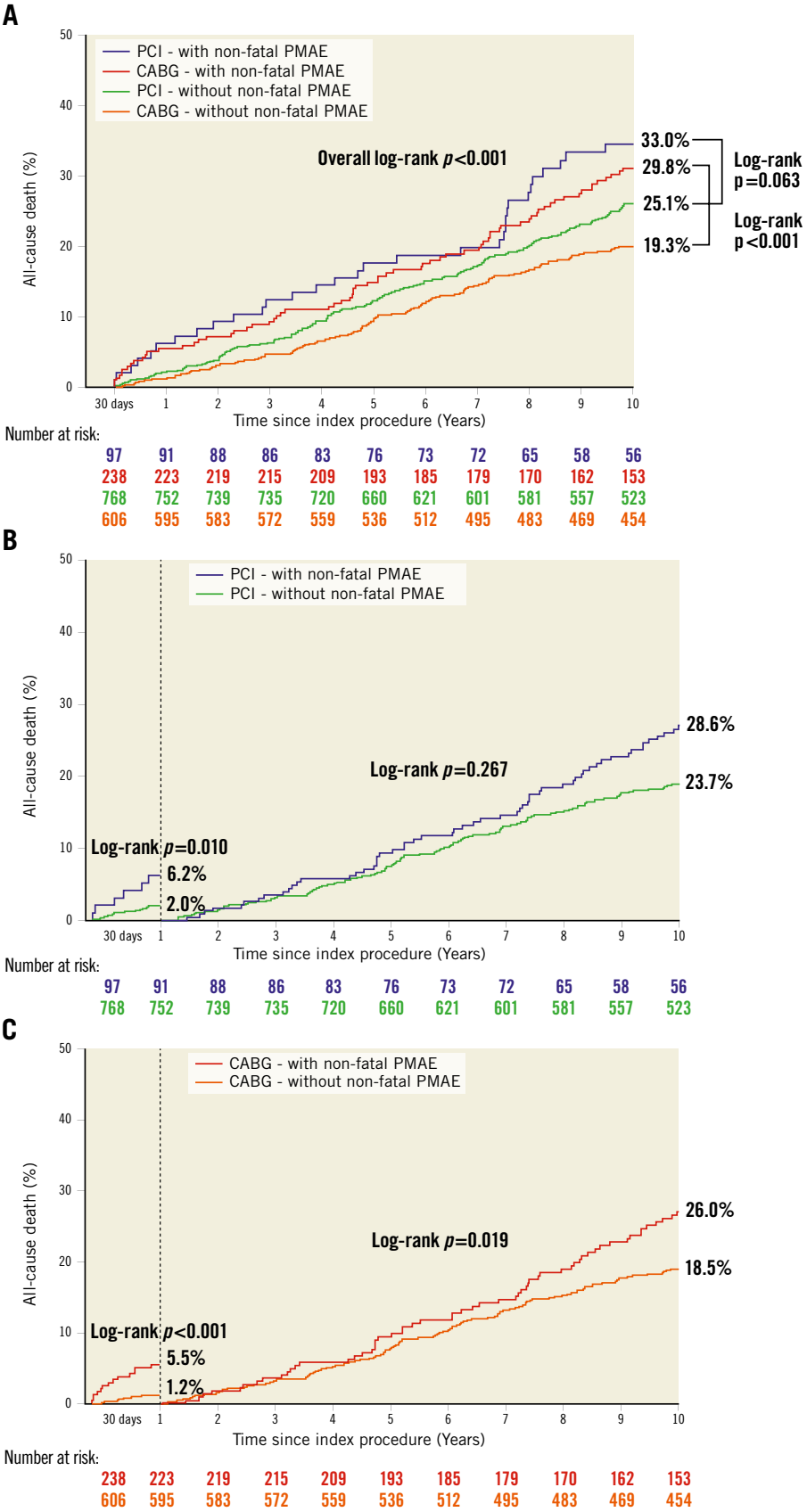

Figure 1. *Kaplan-Meier curve for all-cause mortality with and without non-fatal PMAE. A) In patients after PCI and CABG, B) landmark analysis from 30 days to 1 year and from 1 year to 10 years in PCI, and C) in CABG. CABG: coronary artery bypass grafting; PCI: percutaneous coronary intervention; PMAE: periprocedural major adverse events*

	PMAE (n=335)	Non-PMAE (n=1,374)	Unadjusted HR (95% CI)	*p*-value	Adjusted HR (95% CI)	*p*-value	*p*-value for interaction
At 1 year							
Overall	5.7 (19/335)	1.6 (22/1,374)	3.63 (1.97-6.72)	<0.001	3.59 (1.61-8.01)	0.002	
PCI	6.2 (6/97)	2.0 (15/768)	3.23 (1.25-8.33)	0.015	3.42 (1.03-11.33)	0.044	
CABG	5.5 (13/238)	1.2 (7/606)	4.86 (1.94-12.19)	<0.001	9.99 (2.10-47.46)	0.004	0.511
At 5 years							
Overall	15.5 (52/335)	10.3 (142/1,374)	1.56 (1.14-2.15)	0.006	1.18 (0.76-1.84)	0.455	
PCI	17.5 (17/97)	11.6 (89/768)	1.58 (0.94-2.66)	0.082	1.52 (0.77-2.98)	0.224	
CABG	14.7 (35/238)	8.7 (53/606)	1.76 (1.14-2.69)	0.009	1.21 (0.66-2.24)	0.525	0.481
At 10 years							
Overall	30.7 (103/335)	22.6 (310/1,374)	1.46 (1.16-1.82)	<0.001	1.16 (0.86-1.56)	0.314	
PCI	33.0 (32/97)	25.1 (193/768)	1.42 (0.97-2.06)	0.064	1.17 (0.70-1.96)	0.529	
CABG	29.8 (71/238)	19.3 (117/606)	1.66 (1.24-2.24)	<0.001	1.32 (0.89-1.95)	0.161	0.857

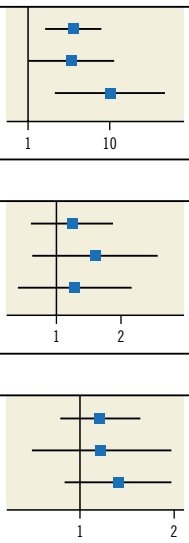

Figure 2. *Impact of non-fatal PMAE on all-cause mortality expressed as hazard ratios. CABG: coronary artery bypass grafting; CI: confidence interval; HR: hazard ratio; PCI: percutaneous coronary intervention; PMAE: periprocedural major adverse events*

blocker included in current practice guidelines for the management of ischaemic heart disease **(Supplementary Appendix 4)**[24]. Kaplan-Meier survival curves between 1 month and 1 year in patients with and without non-fatal PMAE, classified according to the number of individual OMT agents at 1-year follow-up, show significantly lower mortality amongst patients on ≥3 types of medications compared to those on ≤2, irrespective of whether a non-fatal PMAE occurred (3.2% vs 13.1%; log-rank p<0.001) or not (1.2% vs 3.5%; log-rank p=0.006) **(Figure 3A)**. Similarly, mortality between 5 and 10 years tended to be lower in patients on ≥3 types of medications at 5-year follow-up compared to those on ≤2 in patients with (14.3% vs 25.7%; log-rank p=0.060) as well as in those without a non-fatal PMAE (12.2% vs 18.4%; log-rank p=0.017), **(Figure 3B)**. In Cox regression analysis, after adjustment for confounders, ≥3 types of medications at 1-month follow-up reduced all-cause mortality between 1 month and 1 year compared to those on ≤2 types of medications in patients with a non-fatal PMAE (adjusted HR 0.18, 95% CI: 0.05-0.57; p=0.004), with no significant difference in those without (adjusted HR 0.75, 95% CI: 0.18-3.10; p=0.693; p for interaction=0.027) **(Supplementary Figure 9)**. All-cause mortality between 5 and 10 years was reduced by taking ≥3 types of medications at 5-year follow-up, irrespective of whether a non-fatal PMAE occurred (adjusted HR 0.21, 95% CI: 0.07-0.65; p=0.007) or not (adjusted HR 0.56, 95% CI: 0.34-0.91; p=0.019; p for interaction=0.473) **(Supplementary Figure 10)**.

INTENTION-TO-TREAT ANALYSIS

As a sensitivity analysis, we also performed an ITT analysis, including death within 30 days post-procedure, according to the definition of PMAE. Non-fatal and fatal PMAE within 30 days of PCI and CABG occurred in 118 and 248 patients, respectively (13.1% vs 27.6%; p<0.001) **(Supplementary Table 9, Supplementary Figure 11)**. In the ITT analysis, which included fatal PMAE, the occurrence of MI, repeat revascularisation, or stent thrombosis/graft occlusion within 30 days post-procedure was more frequent following PCI than CABG. Demographic characteristics and comorbidities of patients in the ITT analysis are shown in **Supplementary Table 10**. In the ITT analysis, 133 patients with a PMAE and 328 patients without a PMAE died within 10 years of randomisation (36.3% vs 22.9%; HR 1.82, 95% CI: 1.49-2.23; p<0.001). Kaplan-Meier survival curves show that mortality at 10 years was higher among patients with PMAE compared to those without in both arms (PCI arm 44.9% vs 25.0%; log-rank p<0.001; CABG arm 32.3% vs 20.3%; log-rank p=0.001) **(Supplementary Figure 12A)**. Landmark analyses in the ITT analysis showed increased mortality between 1 and 10 years after a PMAE following CABG (25.9% vs 19.3%; log-rank p=0.039) but not PCI (36.8% vs 23.9%; log-rank p=0.200) **(Supplementary Figure 12B, Supplementary Figure 12C)**. In the Cox regression analysis of the ITT, including fatal PMAE and after adjustment of confounders, PMAE remained an independent predictor of all-cause mortality at 10 years in the PCI arm (44.9% vs 25.0%; adjusted HR 1.96, 95% CI: 1.29-2.97; p=0.001), whereas in the CABG arm, PMAE was an independent predictor for 1-year mortality but no longer an independent predictor for 10-year mortality (32.3% vs 20.3%; adjusted HR 1.39, 95% CI: 0.95-2.02; p=0.084) **(Supplementary Figure 13)**. However, a landmark analysis between 1 and 10 years in the Cox regression analysis shows that PMAE was not an independent

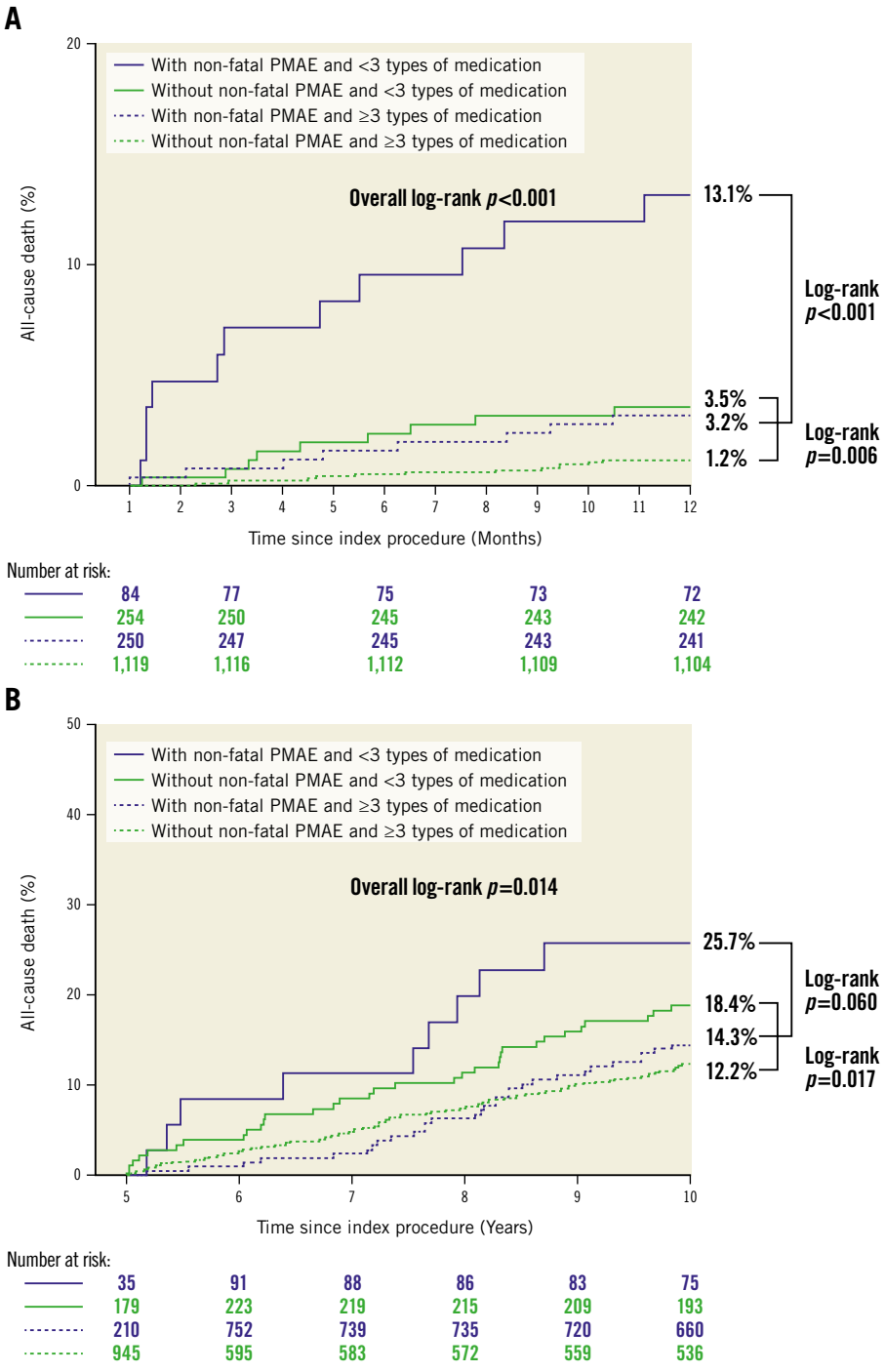

Figure 3. *Kaplan-Meier curve for all-cause mortality in patients with and without non-fatal PMAE, classified according to the number of the individual OMT agents. A) Between 1 month and 1 year, classified according to the number of the individual optimal medical therapy (OMT) agents at 1-month follow-up and (B) between 5 and 10 years, classified according to the number of the individual OMT agents at 5-year follow-up. PMAE: periprocedural major adverse events*

predictor of long-term death in either treatment arm after eliminating the prognostic impact of short-term mortality (PCI arm: 29.3% vs 23.6%, adjusted HR 0.93, 95% CI: 0.52-1.66; p=0.806; CABG arm: 25.9% vs 19.3%, adjusted HR 1.04, 95% CI: 0.68-1.59; p=0.835).

PREDICTED AND OBSERVED INDIVIDUAL TREATMENT BENEFIT IN SURVIVAL BY SSII-2020

Calibration plots for 10-year all-cause mortality **(Figure 4)** suggest that patients with a PMAE had a higher overall predicted mortality by the SSII-2020 than those without a PMAE, whilst also showing

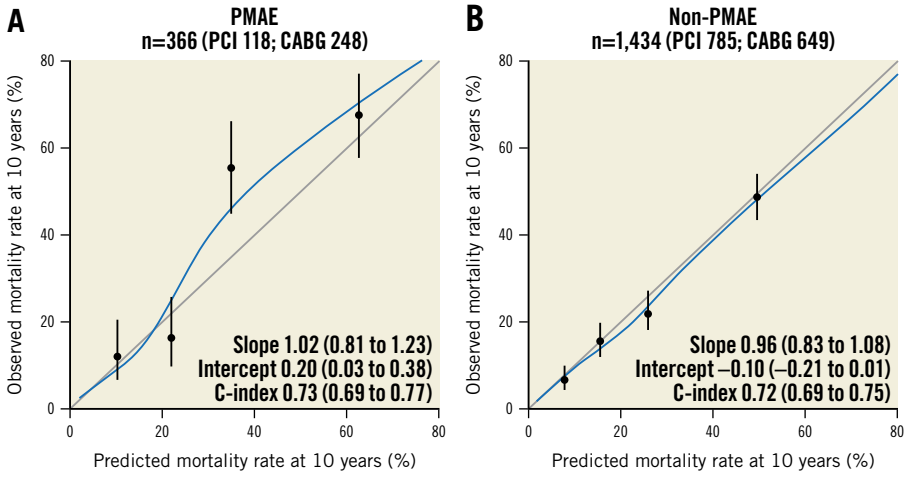

Figure 4. *Calibration plots for 10-year all-cause mortality with and without PMAE. Dots correspond to quartiles of patients with mean predicted probability and mean observed mortality rate with 95% CI. The smooth calibration curves (blue line) to each plot are based on a Cox model that fitted outcomes to a restricted cubic spline of the predictions. CABG: coronary artery bypass grafting; CI: confidence interval; PCI: percutaneous coronary intervention; PMAE: periprocedural major adverse events*

a tendency to underestimate the observed 10-year all-cause mortality, particularly in the third and fourth quartiles.

Absolute risk differences in predicted and observed mortality after PCI or CABG **(Figure 5, Supplementary Figure 14)** show that PMAE substantially alter the individual predictions of 10-year mortality by the SSII-2020.

Discussion

The major findings of this study were 1) non-fatal PMAE occur less frequently following PCI than CABG; 2) after adjusting for confounders, non-fatal PMAE were an independent predictor of all-cause mortality at 1 year, but not at 5 or 10 years, in both treatment modalities. The results of the ITT analysis were consistent with the clinical implications of the impact of non-fatal PMAE on long-term mortality from the per-protocol analysis.

A few studies comparing PCI to CABG in patients with LMCAD or 3VD have reported PMAE **(Supplementary Table 11)**.

In this study, landmark analyses showed that the increased mortality associated with having a PMAE following PCI or CABG was seen predominantly in the first year (6.2% vs 2.0%; log-rank p=0.010 and 5.5% vs 1.2%; log-rank p<0.001, respectively) and was no longer apparent in the following 6-7 years of follow-up, with a resurgence of increased mortality in the final 3 years **(Figure 1B, Figure 1C)**. The mean ages at enrolment of

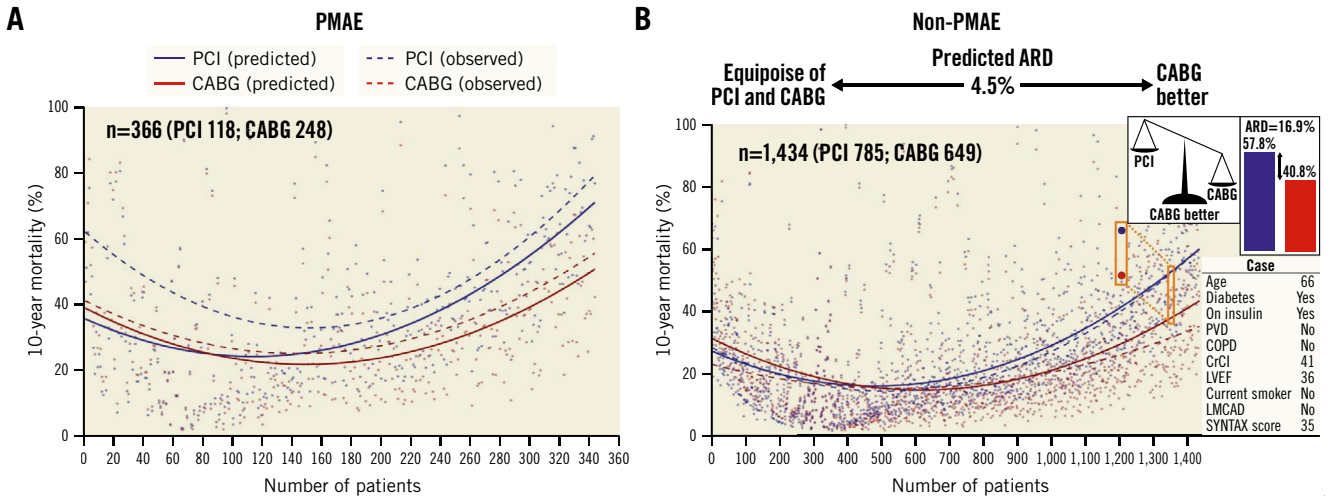

Figure 5. *Absolute risk difference for 10-year all-cause mortality after PCI or CABG with and without PMAE in the intention-to-treat analysis. Individual differences in predicted mortality (individual scatterplot and solid smoothing curve) and observed mortality (dashed smoothing curve) after PCI or CABG are shown. ARD: absolute risk difference; CABG: coronary artery bypass grafting; COPD: chronic obstructive pulmonary disease; CrCl: creatinine clearance; LMCAD: left main coronary artery disease; LVEF: left ventricular ejection fraction; PCI: percutaneous coronary intervention; PMAE: periprocedural major adverse events; PVD: peripheral vascular disease*

patients who died in the final 3 years in the PCI arm who had a non-fatal PMAE compared to those without were 74.3±7.8 vs 68.5±8.9 (p=0.034), whilst in the CABG arm they were 73.3±7.3 vs 69.7±8.9 (p=0.109), respectively. A previous analysis from the SYNTAXES study reported that the mean survival time (within 10 years) after PCI or CABG in the elderly >70 years was 7.7 years (95% CI: 7.4-8.1) and 7.9 years (95% CI: 7.5-8.3), respectively[25]. Therefore, the resurgence of increased mortality in the final 3 years in patients with a PMAE may be due to the difference in age at randomisation, considering the overall difference in life expectancy.

In this study, non-fatal PMAE was an independent predictor of all-cause mortality at 1 year following PCI or CABG; however, it ceased to have any prognostic impact long term, either at 5 or at 10 years **(Figure 2)**. Hence, the prognostic impact of a non-fatal PMAE on short-term mortality appears to subside over long-term follow-up. The impact of preprocedural factors or periprocedural events on clinical outcomes is seemingly time dependent. For example, a substudy of the SYNTAXES trial showed that the association between post-procedural infections and long-term mortality was significant at 5 years but not at 10 years[17], suggesting that these infections could contribute to early- or mid-term mortality. However, once the infection had cleared it no longer affected long-term survival. In another substudy of the SYNTAXES trial, landmark analyses showed that, in diabetic patients with 3VD, all-cause death at 5 years was higher after PCI compared with CABG. Between 5 and 10 years, this risk was reversed such that PCI no longer had a significantly increased risk of all-cause death at 10 years compared with CABG[6]. As a caveat, however, among the small number of insulin-treated patients (n=182), all-cause death at 10 years remained numerically higher with PCI than CABG (47.9% vs 39.6%, difference 8.2%, 95% CI: −6.5 to 22.5%; p=0.227).

In this study, Cox regression analysis showed that non-fatal PMAE were not an independent predictor of long-term death. Despite its potential confounding interaction with other preprocedural and/or procedural risk factors, the presence of PMAE at 1 month may therefore serve as a trigger for physicians to consider more frequent follow-up and aggressive adjunctive pharmacological therapy to amend or prevent the recurrence of adverse events for at least a year. Even though patients enrolled in this trial received follow-up with scheduled visits at 1, 6, and 12 months, non-fatal PMAE still impacted the 1-year mortality. Future studies with protocols mandating specific algorithms for patients with non-fatal PMAE are warranted. Of note, when we stratify patients according to the number of PMAE, non-fatal PMAE ≥2 was an independent predictor for all-cause 10-year mortality.

THE BENEFIT OF OMT ON MORTALITY AFTER NON-FATAL PMAE

A substudy of the SYNTAXES trial previously reported that at 5 years, patients on OMT, defined as the combination of 4 types of medications, had significantly lower mortality at 10 years compared with those on ≤2 types of medications (13.1% vs 19.9%; adjusted HR 0.470, 95% CI: 0.292-0.757; p=0.002), and similar mortality to those on 3 types of medications[24]. Our results suggest that in patients with non-fatal PMAE, OMT with guideline-recommended pharmacological therapy may provide survival benefits during the first year post-procedure as well as in the long term **(Supplementary Figure 9, Supplementary Figure 10)**.

DOES PMAE AFFECT MORTALITY PREDICTED BY SSII-2020?

The SSII-2020, which was derived from cross-correlation and has been externally validated in randomised trials and registries, predicts death and MACCE at 5 and 10 years following PCI and CABG in patients with 3VD and/or LMCAD[4-7,26].

Calibration plots for 10-year all-cause mortality suggest that PMAE synergistically increase the predicted (and observed) rate of all-cause death compared to preprocedural risk assessment **(Figure 4)**.

Although the patients with PMAE had higher SSII-2020 at baseline **(Supplementary Table 10)**, absolute risk differences show that PMAE disrupted the accuracy in predicting their 10-year mortality **(Figure 5)**. Our findings suggest that the parameters predicting mortality after PMAE need to be re-evaluated given that the SSII-2020 no longer accurately predicts all-cause death when a PMAE occurs in the first 30 days.

Limitations

This study reports a *post hoc* analysis of the SYNTAX Study and, hence, is merely hypothesis-generating. Periprocedural events, except for MACCE, were adjudicated *post hoc*. In the SYNTAX Study, PCI was performed with a first-generation drug-eluting stent (DES) (TAXUS; Boston Scientific), and it has been widely demonstrated that novel current-generation DES have the potential to reduce MACCE components of non-fatal PMAE. The SYNTAX II Trial (ClinicalTrials.gov: NCT02015832) demonstrated that contemporary PCI, using current-generation DES, physiology-guided treatment, and intravascular ultrasound optimisation of stent deployment, has improved clinical outcomes including all-cause death, periprocedural MI, subacute stent thrombosis, and repeat revascularisation[27]. Indeed, in comparison with the landmark SYNTAX Study, the SYNTAX II registry, in a prospective propensity analysis based on the SYNTAX score II, demonstrated an absolute reduction in all-cause death of 5.7% at 5 years[28]. While the impact of the suggested combination of OMT agents was found beneficial in reducing mortality post-PMAE, case-specific clinical judgment should prevail, as the current guidelines propose the best management strategies for an individual patient with a given condition[29,30]. Considering the long follow-up in this study and the age of the patients at enrolment, despite Cox regression adjustment, age (i.e., mortality due to age) may have led to an underestimation of the impact of PMAE at long-term follow-up.

Conclusions

In patients with 3VD and/or LMCAD, non-fatal PMAE were more common following CABG than PCI, but their prognostic impact

was similar, being significant in the first year and then diminishing out to 10 years. Patients with non-fatal PMAE may therefore require more careful follow-up and additional preventive treatment in the first-year post-procedure.

Impact on daily practice

The prognostic impact of non-fatal PMAE occurring within 30 days of PCI or CABG in patients with 3VD and/or LMCAD was significant in the first year and then diminished out to 10 years. Patients with non-fatal PMAE may require more careful follow-up and additional preventive treatment in the first year post-procedure. Further studies incorporating contemporary PCI using current-generation DES with physiological and imaging guidance, and contemporary CABG with multiple arterial grafting, fractional flow reserve guidance, and a minimally invasive approach, are needed to address the prognostic impact and management strategy of PMAE for patients with complex CAD.

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Funding

SYNTAXES was supported by the German Foundation of Heart Research. The SYNTAX Study, up to 5-year follow-up, was funded by Boston Scientific. Both sponsors had no role in the study design, data collection, data analyses, or interpretation of the study data and were not involved in the decision to publish the final manuscript. The principal investigators and authors had complete scientific freedom.

Conflict of interest statement

N. Kotoku has received a grant for studying overseas from Fukuda Foundation for Medical Technology. P.W. Serruys has received consultancy fees from Philips/Volcano, SMT, Novartis, Xeltis, and Meril Life, outside of the submitted work. K. Ninomiya has received a grant from Abbott Medical, Japan, outside the submitted work. S. Masuda has received a grant from Terumo, outside the submitted work. M-C. Morice is the CEO and a shareholder of CERC, a contract research organisation based in Paris, which had no role in this trial; and a minor shareholder of Electroducer, which had no role in this trial. A.P. Kappetein has been an employee of Medtronic. The other authors have no conflicts of interest to declare.

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Supplementary data

Supplementary Appendix 1. Methods: definitions of PMAEs.

Supplementary Appendix 2. Adjustment model.

Supplementary Appendix 3. Methods of statistical analysis to evaluate the discriminative ability and treatment benefit of the SYNTAX score II-2020.

Supplementary Appendix 4. Evaluation of the benefit of optimal medical therapy on mortality after non-fatal PMAE.

Supplementary Table 1. Definitions of 30-day PMAE components based on the original protocol of the SYNTAX Trial.

Supplementary Table 2. Adverse event description in the CRF of the SYNTAX Trial.

Supplementary Table 3. Impact of non-fatal PMAE on all-cause mortality of patients stratified according to the number of PMAE.

Supplementary Table 4. Difference and time dependency of the HR for the mortality over 1, 5, and 10 years for each individual PMAE component.

Supplementary Table 5. Different prognostic weights of individual PMAE components at 1 year.

Supplementary Table 6. Different prognostic weights of individual PMAE components at 5 years.

Supplementary Table 7. Different prognostic weights of individual PMAE components at 10 years.

Supplementary Table 8. Alternative definitions of periprocedural MI for sensitivity analyses.

Supplementary Table 9. Non-fatal and fatal PMAE within 30 days after PCI and CABG in the intention-to-treat analysis.

Supplementary Table 10. Baseline characteristics of patients with and without a PMAE within 30 days after PCI and CABG in the intention-to-treat analysis.

Supplementary Table 11. Frequency of periprocedural adverse events in patients with complex CAD in previous studies.

Supplementary Figure 1. Study profile.

Supplementary Figure 2. Non-fatal PMAE within 30 days after PCI and CABG in the per-protocol analysis.

Supplementary Figure 3. Kaplan-Meier curve for all-cause mortality of patients stratified according to the number of PMAE.

Supplementary Figure 4. Sensitivity analysis of the impact of non-fatal PMAE with the SYNTAX definition of periprocedural MI within 48 hours.

Supplementary Figure 5. Sensitivity analysis of the impact of non-fatal PMAE with the 4th UDMI definition of periprocedural MI.

Supplementary Figure 6. Sensitivity analysis of the impact of non-fatal PMAE with the ISCHEMIA definition of periprocedural MI.

Supplementary Figure 7. Sensitivity analysis of the impact of non-fatal PMAE with the SCAI definition of periprocedural MI.

Supplementary Figure 8. Sensitivity analysis of the impact of non-fatal PMAE with the EXCEL definition of periprocedural MI.

Supplementary Figure 9. The benefit of the number of individual OMT agents at 1-month follow-up on all-cause mortality between 1 month and 1 year of patients with and without non-fatal PMAE.

Supplementary Figure 10. The benefit of the number of individual OMT agents at 5-year follow-up on all-cause mortality between 5 and 10 years of patients with and without non-fatal PMAE.

Supplementary Figure 11. Non-fatal and fatal PMAE within 30 days after PCI and CABG in the intention-to-treat analysis.

Supplementary Figure 12. Kaplan-Meier curve for all-cause mortality with and without PMAE in the intention-to-treat analysis.

Supplementary Figure 13. Impact of PMAE on all-cause mortality expressed as hazard ratios in the intention-to-treat analysis.

Supplementary Figure 14. Predicted versus observed treatment benefit for 10-year mortality with and without PMAE in the intention-to-treat analysis.

The supplementary data are published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-22-00681

Supplementary data

Supplementary Appendix 1. Methods: definitions of PMAE

Adverse events were reported from sites in the case report form (CRF) using the classification shown in **Supplementary Table 2.** Components and the period of periprocedural major adverse events (PMAE) were defined based on the previous studies which investigate PMAE following percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG). The availability of event data based on the CRF was also considered. Definitions of each component of PMAE were defined based on the original protocol of the SYNTAX trial (**Supplementary Table 1**).

Supplementary Appendix 2. Adjustment model.

The following baseline variables included in the SYNTAX score II 2020 were applied for adjustment: age, medically treated diabetes mellitus, chronic kidney disease (CKD) [creatinine clearance (CrCl) calculated by using the Cockroft Gault formula <60 ml/min], chronic obstructive pulmonary disease (COPD), current smoking, left ventricular ejection fraction (LVEF) <30%, peripheral vascular disease, anatomical SYNTAX score, and disease type (left-main coronary artery disease [LMCAD] or three-vessel disease [3VD]), using the forced entry method.

Supplementary Appendix 3. Methods of statistical analysis to evaluate the discriminative ability and treatment benefit of the SYNTAX score II-2020.

The SYNTAX score II 2020 was developed using the 10-year mortality data from the SYNTAXES study and the 5-year MACE of the SYNTAX trial.

The discriminative ability was assessed using Harrell's C statistic (C-index). Agreement between observed and predicted mortality rates was assessed by calibration plots in quarters of predicted risk and as a smooth function of predicted risk, using weighted scatterplot

smoothing. Calibration-in-the-large (intercept) and calibration slope were evaluated by fitting the calculated linear predictor in all patients, with all-cause mortality as the outcome in the Cox regression model. An intercept of 0 and a slope of 1 indicate perfect calibration.

The agreement between predicted and observed benefit of treatment with CABG over PCI was assessed by a benefit calibration plot, which displays observed versus predicted treatment benefit in quarters of predicted treatment benefit. The observed benefit of treatment with CABG over PCI (absolute risk difference, ARD) was calculated by the difference in Kaplan-Meier estimates between the CABG and PCI group. A smooth calibration curve was added to each benefit calibration plot based on local polynomial regression between observed and predicted treatment benefit in small group classified by 10% with increasing predicted benefit.

An individual benefit plot was used to visualize the predicted and observed mortality after PCI or CABG. All patients were ranked by ascending order according to their ARDs, and then a patient number was given to each patient. Scatterplots of the predicted mortality after PCI and CABG to the y-axis and case number to the x-axis were drawn, and 2 locally estimated scatterplot smoothing curves were fitted to the dots. The observed mortality after PCI or CABG of each patient was estimated by calculating the mortality in a small group classified by 10%. Other 2 smoothing curves were fitted to the observed mortality after PCI or CABG.

Supplementary Appendix 4. Evaluation of the benefit of optimal medical therapy on mortality after non-fatal PMAE.

Definition of OMT

Optimal medical therapy (OMT) was defined as the combination of four types of medications with at least one antiplatelet drug, statin, angiotensin-converting enzyme (ACE) inhibitor/

angiotensin receptor blocker (ARB), and a beta-blocker.

In the original protocol of the SYNTAX trial, optimal medical therapy including statin, ACE inhibitor/ARB, and beta-blocker was strongly recommended according to the guideline of the time. For patients treated by PCI using TAXUS in this trial, dual antiplatelet therapy (DAPT) by aspirin and clopidogrel or ticlopidine post-procedure and after discharge was mandated. For patients treated by CABG, medication with aspirin post-procedure was recommended.

Statistical analysis

The Kaplan-Meier method was used to estimate cumulative events rates, and the log-rank test was performed to examine the differences between patients with and without non-fatal PMAE i) between 1 month and 1 year classified according to the number of the individual OMT agents at 1-month follow-up, and ii) between 5 and 10 years classified according to the number of the individual OMT at 5-year follow-up. Day 0 was defined as the day of the procedure. Hazard ratios (HRs) with 95% confidence intervals (CIs) for all-cause mortality from 30 days to 1 year, 5 years, and 10 years were determined based on Cox proportional hazards regression. Cox regression analysis was performed to also address the benefit of the number of individual OMT agents i) at 1-month follow-up on all-cause mortality between 1 month and 1 year, and ii) at 5-year follow-up on all-cause mortality between 5 and 10 years of patients with and without the non-fatal PMAE. Cox regression analysis was performed by adjusting the baseline variables as well as the main analysis **(Supplementary Appendix 2)**.

Supplementary Table 1. Definitions of 30-day PMAE components based on the original protocol of the SYNTAX Trial.

Adverse event	Definition
Myocardial Infarction*	**<7 days after intervention:** either a) new Q-waves and one ratio of peak CK-MB/peak total CK >10%; b) new Q-waves and one plasma level of CK-MB 5× ULN. **≥ 7 days after intervention:** either a) new Q-waves; b) enzyme changes defined as more than 10% of the ratio of peak CK-MB/peak total CK; or if no ratio is available: - CK-MB 5× ULN - CK 5× ULN
Stroke	A focal, central neurological deficit lasting >72 hours which results in irreversible brain damage or permanent body impairment, classified as ischemic or hemorrhagic based on imaging studies
Repeat revascularization	Any repeat PCI or CABG Repeat PCI included target lesion revascularization, target vessel revascularization (TVR), revascularization of a de novo lesion in a target vessel (remote TVR), and revascularization of a de novo lesion in a nontarget vessel.
Major infection	Infection requiring antibiotics or surgical intervention Defined as the occurrence of deep incisional surgical site infection at the primary chest incision or at a secondary incision site (e.g., saphenous harvest and groin cannulation site), mediastinitis, infectious myocarditis or pericarditis, endocarditis, cardiac device infection, pneumonia, empyema, clostridium difficile colitis, and blood-stream infection
Stent thrombosis/ graft occlusion	Defined as either a) clinical presentation of ACS with documented of a flow limiting thrombus or occlusion within a bypass graft of adjacent to the anastomosis of a

	previously bypassed coronary artery (for CABG patients) or within or adjacent to a previously successfully treated artery (for PCI patients); b) a Q-wave MI in the territory of ≥1 treated vessels within first 30 days.
Bleeding	Defined as either a) need for transfusion of blood products (no surgical intervention) (not in the first 24 hours after surgical intervention); b) need for surgical intervention to remedy excessive bleeding after initial surgery during the hospital stay.
Major arrhythmia	Any variation from the normal rhythm of the heartbeat, including sinus arrhythmia, atrioventricular block, atrial fibrillation, atrial flutter, and tachycardia
Heart failure	Inadequacy of the heart so that it fails to maintain the circulation of blood, including the CRF report as cardiac shock
Acute respiratory failure	Based on the CRF report as acute respiratory failure
Acute renal failure	Renal failure: 1.0 mg/dL or more rise in serum creatinine level or renal dysfunction requiring new onset hemodialysis.
Wound dehiscence	The splitting or bursting open of a procedural wound.

* Sensitivity analyses with alternative definitions (**Supplementary Table 8**) of periprocedural myocardial infarction on all-cause mortality are shown in **Supplementary Figure 4, 5, 6, 7, and 8**.

ACS = acute coronary syndrome; CABG = coronary artery bypass grafting; ULN = upper limited for normal; MI = Myocardial Infarction; PCI = percutaneous coronary intervention.

Supplementary Table 2. Adverse event description in the CRF of the SYNTAX Trial.

Category	Events
Blood and lymphatic system	Anemia; Leukopenia; Neutropenia; Thrombocytopenia
Cardiac	Angina pectoris (stable, unstable); Arrhythmia (Atrial fibrillation, Atrial flutter, Bradycardia, Tachycardia, Ventricular fibrillation, Ventricular tachycardia); Cardiac arrest; Cardiac perforation; Cardiac tamponade; Cardiogenic shock; Congestive heart failure; Heart failure; Coronary artery aneurysm; Pericardial effusion; Pericarditis; Silent myocardial ischemia
Gastrointestinal	Retroperitoneal hemorrhage; Gastrointestinal Bleed
General disorders and administration site	Catheter site (bleeding, discharge, ecchymosis, hematoma, pain); Peripheral edema
Immune system	Anaphylactic shock
Infections and infestations	Catheter site, infection; Mediastinitis; Pericarditis, Acute infective; Sepsis; Wound infection
Injury, poisoning and procedural	Wound dehiscence; Coronary artery perforation; Hemothorax
Nervous system	Carotid artery stenosis; Pre-Syncope; Syncope; Vasovagal attack
Renal and urinary	Radiocontrast nephropathy; Renal artery stenosis; Renal failure (acute, chronic)
Respiratory, thoracic and mediastinal	Pulmonary edema; Pulmonary hypertension; Respiratory failure, acute; Pneumothorax; Pulmonary embolism; Chronic obstructive pulmonary disease
Skin and subcutaneous tissue	Angioedema; Pruritus; Urticaria
Vascular	Aortic aneurysm; Aortic dissection; Claudication; Deep vein thrombosis; Hypertension, uncomplicated; Hypertensive crisis; Hypotension; Peripheral ischemia; Peripheral vascular disease; Pseudoaneurysm
Other (specify)	

CRF = case report form.

Supplementary Table 3. Impact of non-fatal PMAE on all-cause mortality of patients stratified according to the number of PMAE.

	Event rate % (n)		Unadjusted HR (95% CI)	P value	Adjusted HR (95% CI)	P value
At 1 year						
PMAE 1 vs. 0	3.9 (10/258)	vs. 1.5 (21/1373)	2.58 (1.21-5.49)	0.013	2.60 (1.00-6.78)	0.050
PMAE ≥2 vs. 0	12.8 (10/78)	vs. 1.5 (21/1373)	8.92 (4.20-18.94)	<0.001	6.66 (2.30-19.26)	<0.001
PMAE ≥2 vs. 1	12.8 (10/78)	vs. 3.9 (10/258)	3.43 (1.42-8.24)	0.006	2.38 (0.74-7.60)	0.142
At 5 years						
PMAE 1 vs. 0	12.0 (31/258)	vs. 10.3 (141/1373)	1.19 (0.80-1.75)	0.381	0.93 (0.54-1.60)	0.809
PMAE ≥2 vs. 0	28.2 (22/78)	vs. 10.3 (141/1373)	3.19 (2.03-5.01)	<0.001	1.87 (0.97-3.57)	0.059
PMAE ≥2 vs. 1	28.2 (22/78)	vs. 12.0 (31/258)	2.62 (1.52-4.54)	<0.001	1.87 (0.83-4.20)	0.127
At 10 years						
PMAE 1 vs. 0	27.5 (71/258)	vs. 22.5 (309/1373)	1.25 (0.97-1.63)	0.080	1.00 (0.70-1.42)	0.984
PMAE ≥2 vs. 0	42.3 (33/78)	vs. 22.5 (309/1373)	2.37 (1.65-3.39)	<0.001	1.78 (1.11-2.86)	0.016
PMAE ≥2 vs. 1	42.3 (33/78)	vs. 27.5 (71/258)	1.86 (1.23-2.81)	0.003	1.53 (0.85-2.76)	0.150

See **Supplementary Appendix 2**. CI = confidence interval; HR = hazard ratio; PMAE = peri-procedural major adverse events.

Supplementary Table 4. Difference and time dependency of the HR for the mortality over 1, 5, and 10 years for each individual PMAE component.

Component of PMAE in order of decreasing HR for overall at 1 year	Treatment modality	Adjusted HR (95% CI) at 1 year	P value	Adjusted HR (95% CI) at 5 years	P value	Adjusted HR (95% CI) at 10 years	P value
Non-fatal PMAE	Overall	3.59 (1.61-8.01)	0.002	1.18 (0.76-1.84)	0.455	1.16 (0.86-1.56)	0.314
	PCI	3.42 (1.03-11.33)	0.044	1.52 (0.77-2.98)	0.224	1.17 (0.70-1.96)	0.529
	CABG	9.99 (2.10-47.46)	0.004	1.21 (0.66-2.24)	0.525	1.32 (0.89-1.95)	0.161
MI	Overall	11.30 (4.29-29.72)	<0.001	2.88 (1.25-6.67)	0.013	2.09 (1.13-3.86)	0.019
	PCI	5.99 (1.48-24.16)	0.012	2.35 (0.70-7.91)	0.165	2.23 (0.95-5.25)	0.064
	CABG	34.16 (5.41-215.55)	<0.001	2.93 (0.87-9.83)	0.081	1.88 (0.75-4.73)	0.177
Repeat revascularization	Overall	10.03 (2.85-35.26)	<0.001	2.78 (1.06-7.32)	0.037	1.90 (0.86-4.18)	0.109
	PCI	14.36 (3.12-65.98)	<0.001	3.37 (0.99-11.46)	0.051	2.56 (1.00-6.54)	0.049
	CABG	4.53 (0.41-50.30)	0.218	3.18 (0.71-14.15)	0.128	1.34 (0.31-5.65)	0.688
Stent thrombosis/graft occlusion	Overall	9.08 (1.91-43.12)	0.005	2.19 (0.52-9.10)	0.279	1.78 (0.65-4.85)	0.257
	PCI	14.74 (2.20-98.58)	0.005	3.05 (0.69-13.38)	0.139	2.54 (0.89-7.24)	0.080
	CABG	-	-	-	-	-	-
Wound dehiscence	Overall	6.47 (0.81-51.43)	0.077	2.14 (0.51-8.86)	0.293	2.29 (0.83-6.26)	0.107

	PCI	-	-	-	-	-	-
	CABG	14.99 (1.55-144.37)	0.019	3.26 (0.76-13.95)	0.111	3.21 (1.14-9.06)	0.027
Heart failure	Overall	3.88 (0.82-18.23)	0.085	1.53 (0.47-4.97)	0.478	1.54 (0.67-3.53)	0.303
	PCI	4.74 (0.89-25.16)	0.068	3.38 (0.99-11.51)	0.051	2.25 (0.80-6.29)	0.122
	CABG	-	-	-	-	0.82 (0.19-3.43)	0.788
Stroke	Overall	3.87 (0.45-33.38)	0.217	0.77 (0.10-5.75)	0.801	0.78 (0.18-3.28)	0.740
	PCI	-	-	-	-	-	-
	CABG	6.40 (0.51-78.94)	0.148	0.87 (0.10-7.18)	0.903	0.87 (0.19-3.95)	0.862
Bleeding	Overall	3.32 (0.74-14.87)	0.116	2.26 (0.97-5.26)	0.057	1.49 (0.72-3.07)	0.277
	PCI	-	-	0.96 (0.22-4.08)	0.968	0.93 (0.33-2.61)	0.892
	CABG	106.03 (11.19-1004.70)	<0.001	2.26 (0.97-5.26)	0.057	4.95 (1.77-13.78)	0.002
Major infection	Overall	3.20 (1.20-8.57)	0.020	1.61 (0.89-2.90)	0.111	1.20 (0.77-1.87)	0.413
	PCI	1.53 (0.18-13.03)	0.696	2.26 (0.67-7.57)	0.186	1.63 (0.58-4.56)	0.350
	CABG	9.61 (2.38-38.82)	0.001	2.02 (0.99-4.13)	0.051	1.34 (0.81-2.23)	0.251
Acute renal failure	Overall	1.19 (0.23-6.10)	0.830	1.12 (0.46-2.73)	0.790	1.33 (0.71-2.49)	0.359
	PCI	3.03 (0.29-31.10)	0.350	1.59 (0.40-6.20)	0.505	2.17 (0.77-6.09)	0.141
	CABG	2.15 (0.21-22.05)	0.519	1.14 (0.33-3.99)	0.828	1.11 (0.49-2.52)	0.798
Major arrhythmia	Overall	0.98 (0.23-4.20)	0.981	0.61 (0.24-1.52)	0.294	1.06 (0.64-1.75)	0.808
	PCI	0.76 (0.06-9.06)	0.828	1.00 (0.22-4.52)	0.997	0.41 (0.09-1.77)	0.236

	CABG	0.68 (0.08-5.80)	0.726	0.45 (0.13-1.50)	0.196	1.39 (0.79-2.43)	0.242
Acute respiratory failure	Overall	-	-	-	-	0.22 (0.03-1.64)	0.142
	PCI	-	-	-	-	-	-
	CABG	-	-	-	-	0.29 (0.04-2.13)	0.225

See **Supplementary Appendix 2**. CABG = coronary artery bypass grafting; MI = myocardial infarction; PCI = percutaneous coronary intervention; other abbreviations as in **Supplementary Table 3**.

Supplementary Table 5. Different prognostic weights of individual PMAE components at 1 year.

Component of PMAE in order of decreasing HR for overall	Treatment modality	With	Without	Adjusted HR (95% CI)	P value	P value for interaction
At 1 year						
Non-fatal PMAE	Overall	5.7(19/335)	1.6(22/1374)	3.59 (1.61-8.01)	0.002	
	PCI	6.2(6/97)	2.0(15/768)	3.42 (1.03-11.33)	0.044	0.511
	CABG	5.5(13/238)	1.2(7/606)	9.99 (2.10-47.46)	0.004	
MI	Overall	15.8(6/38)	2.1(35/1671)	11.30 (4.29-29.72)	<0.001	
	PCI	13.6(3/22)	2.1(18/843)	5.99 (1.48-24.16)	0.012	0.398
	CABG	18.8(3/16)	2.1(17/828)	34.16 (5.41-215.55)	<0.001	
Repeat revascularization	Overall	12.9(4/31)	2.2(37/1678)	10.03 (2.85-35.26)	<0.001	
	PCI	15.0(3/20)	2.1(18/845)	14.36 (3.12-65.98)	<0.001	0.493
	CABG	9.1(1/11)	2.3(19/833)	4.53 (0.41-50.30)	0.218	
Stent thrombosis/ graft occlusion	Overall	8.3(2/24)	2.3(39/1685)	9.08 (1.91-43.12)	0.005	
	PCI	11.8(2/17)	2.2(19/848)	14.74 (2.20-98.58)	0.005	0.951
	CABG	0.0(0/7)	2.4(20/837)	-	-	
Wound dehiscence	Overall	7.7(1/13)	2.4(40/1696)	6.47 (0.81-51.43)	0.077	
	PCI	0.0(0/1)	2.4(21/864)	-	-	-
	CABG	8.3(1/12)	2.3(19/832)	14.99 (1.55-144.37)	0.019	
Heart failure	Overall	2.3(39/1688)	9.5(2/21)	3.88 (0.82-18.23)	0.085	
	PCI	20.0(2/10)	2.2(19/855)	4.74 (0.89-25.16)	0.068	-
	CABG	0.0(0/11)	2.4(20/833)	-	-	
Stroke	Overall	10.0(1/10)	2.4(40/1699)	3.87 (0.45-33.38)	0.217	

	PCI	0.0(0/1)	2.4(21/864)	-	-	-
	CABG	11.1(1/9)	2.3(19/835)	6.40 (0.51-78.94)	0.148	
Bleeding	Overall	2.3(39/1667)	4.8(2/42)	3.32 (0.74-14.87)	0.116	
	PCI	0.0(0/21)	2.5(21/844)	-	-	-
	CABG	9.5(2/21)	2.2(18/823)	106.03 (11.19-1004.70)	<0.001	
Major infection	Overall	7.7(11/142)	1.9(30/1567)	3.20 (1.20-8.57)	0.020	
	PCI	6.7(1/15)	2.4(20/850)	1.53 (0.18-13.03)	0.696	0.414
	CABG	7.9(10/127)	1.4(10/717)	9.61 (2.38-38.82)	0.001	
Acute renal failure	Overall	14.8(4/27)	2.2(37/1682)	1.19 (0.23-6.10)	0.830	
	PCI	12.5(1/8)	2.3(20/857)	3.03 (0.29-31.10)	0.350	0.416
	CABG	15.8(3/19)	2.1(17/825)	2.15 (0.21-22.05)	0.519	
Major arrhythmia	Overall	4.3(4/94)	2.3(37/1615)	0.98 (0.23-4.20)	0.981	
	PCI	4.8(2/21)	2.4(20/844)	0.76 (0.06-9.06)	0.828	0.758
	CABG			0.68 (0.08-5.80)	0.726	
Acute respiratory failure	Overall	8.3(1/12)	2.4(40/1697)	-	-	
	PCI	-	2.4(21/865)	-	-	-
	CABG	8.3(1/12)	2.3(19/832)	-	-	

See **Supplementary Appendix 2**. Abbreviations as in **Supplementary Table 4**.

Supplementary Table 6. Different prognostic weights of individual PMAE components at 5 years.

Component of PMAE in order of decreasing HR for overall	Treatment modality	With	Without	Adjusted HR (95% CI)	P value	P value for interaction
At 5 years						
Non-fatal PMAE	Overall	15.5(52/335)	10.3(142/1374)	1.18 (0.76-1.84)	0.455	
	PCI	17.5(17/97)	11.6(89/768)	1.52 (0.77-2.98)	0.224	0.481
	CABG	14.7(35/238)	8.7(53/606)	1.21 (0.66-2.24)	0.525	
MI	Overall	18.4(7/38)	11.2(187/1671)	2.88 (1.25-6.67)	0.013	
	PCI	18.2(4/22)	12.1(102/843)	2.35 (0.70-7.91)	0.165	0.876
	CABG	18.8(3/16)	10.3(85/828)	2.93 (0.87-9.83)	0.081	
Repeat revascularization	Overall	16.1(5/31)	11.3(189/1678)	2.78 (1.06-7.32)	0.037	
	PCI	15.0(3/20)	12.2(103/845)	3.37 (0.99-11.46)	0.051	0.751
	CABG	18.2(2/11)	10.3(86/833)	3.18 (0.71-14.15)	0.128	
Bleeding	Overall	21.4(9/42)	11.1(185/1667)	2.26 (0.97-5.26)	0.057	
	PCI	14.3(3/21)	12.2(103/844)	0.96 (0.22-4.08)	0.968	0.002
	CABG	28.6(6/21)	10.0(82/823)	14.07(4.64-42.63)	<0.001	
Stent thrombosis/ graft occlusion	Overall	8.3(2/24)	11.4(192/1685)	2.19 (0.52-9.10)	0.279	
	PCI	11.8(2/17)	12.3(104/848)	3.05 (0.69-13.38)	0.139	-
	CABG	0.0(0/7)	10.5(88/837)	-	-	
Wound dehiscence	Overall	15.4(2/13)	11.3(192/1696)	2.14 (0.51-8.86)	0.293	
	PCI	0.0(0/1)	12.3(106/864)	-	-	-
	CABG	16.7(2/12)	10.3(86/832)	3.26 (0.76-13.95)	0.111	
Major infection	Overall	17.6(25/142)	10.8(169/1567)	1.61 (0.89-2.90)	0.111	

	PCI	26.7(4/15)	12.0(102/850)	2.26 (0.67-7.57)	0.186	0.858
	CABG	16.5(21/127)	9.3(67/717)	2.02 (0.99-4.13)	0.051	
Heart failure	Overall	28.6(6/21)	11.1(188/1688)	1.53 (0.47-4.97)	0.478	
	PCI	50.0(5/10)	11.8(101/855)	3.38 (0.99-11.51)	0.051	0.936
	CABG	9.1(1/11)	10.4(87/833)	-	-	
Acute renal failure	Overall	37.0(10/27)	10.9(184/1682)	1.12 (0.46-2.73)	0.790	
	PCI	50.0(4/8)	11.9(102/857)	1.59 (0.40-6.20)	0.505	0.308
	CABG	31.6(6/19)	9.9(82/825)	1.14 (0.33-3.99)	0.828	
Stroke	Overall	40.0(4/10)	11.2(190/1699)	0.77 (0.10-5.75)	0.801	
	PCI	100.0(1/1)	12.2(105/864)	-	-	-
	CABG	33.3(3/9)	10.2(85/835)	0.87 (0.10-7.18)	0.903	
Major arrhythmia	Overall	16.0(15/94)	11.1(179/1615)	0.61 (0.24-1.52)	0.294	
	PCI	19.0(4/21)	12.1(102/844)	1.00 (0.22-4.52)	0.997	0.317
	CABG	15.1(11/73)	10.0(77/771)	0.45 (0.13-1.50)	0.196	
Acute respiratory failure	Overall	8.3(1/12)	11.4(193/1697)	-	-	
	PCI	-	12.3(106/865)	-	-	-
	CABG	8.3(1/12)	10.5(87/832)	-	-	

See **Supplementary Appendix 2**. Abbreviations as in **Supplementary Table 4**.

Supplementary Table 7. Different prognostic weights of individual PMAE components at 10 years.

Component of PMAE in order of decreasing HR for overall	Treatment modality	With	Without	Adjusted HR (95% CI)	P value	P value for interaction
At 10 years						
Non-fatal PMAE	overall	30.7 (103/335)	22.6(310/1374)	1.16 (0.86-1.56)	0.314	
	PCI	33.0(32/97)	25.1(193/768)	1.17 (0.70-1.96)	0.529	0.857
	CABG	29.8(71/238)	19.3(117/606)	1.32 (0.89-1.95)	0.161	
Wound dehiscence	overall	30.8(4/13)	24.1(409/1696)	2.29 (0.83-6.26)	0.107	
	PCI	0.0(0/1)	26.0(225/864)	-	-	-
	CABG	33.3(4/12)	22.1(184/832)	3.21 (1.14-9.06)	0.027	
MI	overall	39.5(15/38)	23.8(398/1671)	2.09 (1.13-3.86)	0.019	
	PCI	45.5(10/22)	25.5(215/843)	2.23 (0.95-5.25)	0.064	0.746
	CABG	31.3(5/16)	22.1(183/828)	1.88 (0.75-4.73)	0.177	
Repeat revascularization	overall	25.8(8/31)	24.1(405/1678)	1.90 (0.86-4.18)	0.109	
	PCI	25.0(5/20)	26.0(220/845)	2.56 (1.00-6.54)	0.049	0.256
	CABG	27.3(3/11)	22.2(185/833)	1.34 (0.31-5.65)	0.688	
Stent thrombosis/ graft occlusion	overall	20.8(5/24)	24.2(408/1685)	1.78 (0.65-4.85)	0.257	
	PCI	23.5(4/17)	26.1(221/848)	2.54 (0.89-7.24)	0.080	0.921
	CABG	14.3(1/7)	22.3(187/837)	-	-	
Heart failure	overall	42.9(9/21)	23.9(404/1688)	1.54 (0.67-3.53)	0.303	
	PCI	60.0(6/10)	25.6(219/855)	2.25 (0.80-6.29)	0.122	0.229
	CABG	27.3(3/11)	22.2(185/833)	0.82 (0.19-3.43)	0.788	

Bleeding	overall	35.7(15/42)	23.9(398/1667)	1.49 (0.72-3.07)	0.277	
	PCI	28.6(6/21)	25.9(219/844)	0.93 (0.33-2.61)	0.892	0.018
	CABG	42.9(9/21)	21.7(179/823)	4.95 (1.77-13.78)	0.002	
Acute renal failure	overall	59.3(16/27)	23.6(397/1682)	1.33 (0.71-2.49)	0.359	
	PCI	75.0(6/8)	25.6(219/857)	2.17 (0.77-6.09)	0.141	0.134
	CABG	52.6(10/19)	21.6(178/825)	1.11 (0.49-2.52)	0.798	
Major infection	overall	28.9(41/142)	23.7(372/1567)	1.20 (0.77-1.87)	0.413	
	PCI	46.7(7/15)	25.6(218/850)	1.63 (0.58-4.56)	0.350	0.875
	CABG	26.8(34/127)	21.5(154/717)	1.34 (0.81-2.23)	0.251	
Major arrhythmia	overall	33.0(31/94)	23.7(382/1615)	1.06 (0.64-1.75)	0.808	
	PCI	23.8(5/21)	26.1(220/844)	0.41 (0.09-1.77)	0.236	0.160
	CABG	35.6(26/73)	21.0(162/771)	1.39 (0.79-2.43)	0.242	
Stroke	overall	60.0(6/10)	24.0(407/1699)	0.78 (0.18-3.28)	0.740	
	PCI	100.0(1/1)	25.9(224/864)	-	-	-
	CABG	55.6(5/9)	21.9(183/835)	0.87 (0.19-3.95)	0.862	
Acute respiratory failure	overall	16.7(2/12)	24.2(411/1697)	0.22 (0.03-1.64)	0.142	
	PCI	-	26.0(225/865)	-	-	-
	CABG	52.6(10/19)	21.6(178/825)	0.29 (0.04-2.13)	0.225	

See **Supplementary Appendix 2**. Abbreviations as in **Supplementary Table 4**.

Supplementary Table 8. Alternative definitions of periprocedural MI for sensitivity analyses.

Definitions	Time after procedure	PCI arm	CABG arm
SYNTAX	<7 days Re-evaluated in <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× 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× 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	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

		major vessel/side branch or NHLBI ≥ type C dissection OR 2. CK-MB >10× ULN*	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 <48 h in this analysis	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.

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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; 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.

Supplementary Table 9. Non-fatal and fatal PMAE within 30 days after PCI and CABG in the intention-to-treat analysis.

	PCI (n=903)	CABG (n=897)	P value
Peri-procedural major adverse events	118 (13.1%)	248 (27.6%)	<0.001
Death	20 (2.2%)	10 (1.1%)	0.097
MI	35 (3.9%)	18 (2.0%)	0.025
Within 7 days post-procedure	26 (2.9%)	13 (1.4%)	0.051
Between 7 days and 30 days post-procedure	9 (1.0%)	5 (0.6%)	0.422
Stroke	1 (0.1%)	9 (1.0%)	0.011
Repeat revascularization	28 (3.1%)	12 (1.3%)	0.015
Major infection	17 (1.9%)	129 (14.4%)	<0.001
Stent thrombosis/graft occlusion	25 (2.8%)	7 (0.8%)	0.002
Bleeding	24 (2.7%)	22 (2.5%)	0.882
Major arrhythmia	24 (2.7%)	75 (8.4%)	<0.001
Heart failure	19 (2.1%)	16 (1.8%)	0.733
Acute respiratory failure	2 (0.2%)	13 (1.4%)	0.004
Acute renal failure	10 (1.1%)	22 (2.5%)	0.033
Wound dehiscence	1 (0.1%)	12 (1.3%)	0.002

Abbreviations as in **Supplementary Table 4**.

Supplementary Table 10. Baseline characteristics of patients with and without a PMAE within 30 days after PCI and CABG in the intention-to-treat analysis.

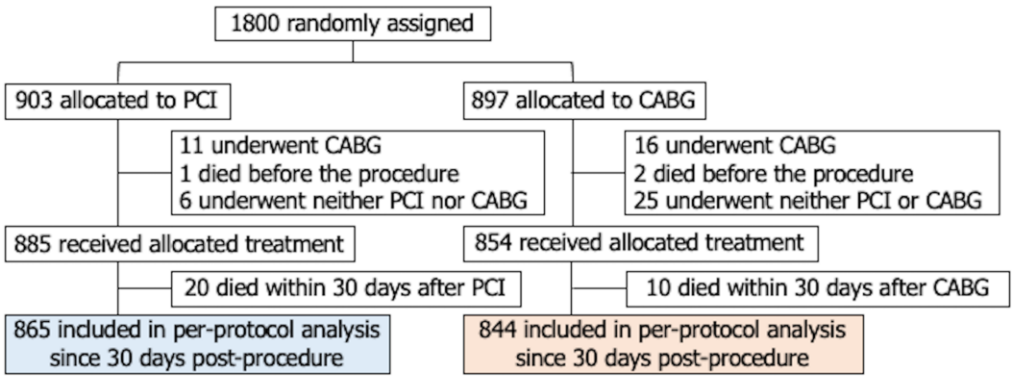
	PMAE after PCI (n=118)	No PMAE after PCI (n=785)	P value	PMAE after CABG (n=248)	No PMAE after CABG (n=649)	P value
Age (years)	69.0 ± 9.0	64.6±9.6	<0.001	66.5 ± 9.7	64.3 ± 9.7	0.002
Male	82 (69.5%)	608 (77.5%)	0.063	193 (77.8%)	515 (79.4%)	0.647
BMI (kg/m^2)	27.5 ± 5.0	28.1±4.7	0.195	28.2 ± 4.5	27.7 ± 4.5	0.175
Dyslipidemia	88 (75.2%)	617 (79.2%)	0.334	202 (81.5%)	484 (75.5%)	0.062
Hypertension	90 (76.3%)	532 (67.8%)	0.070	156 (62.9%)	418 (64.4%)	0.698
Medically treated diabetes	43 (36.4%)	188 (23.9%)	0.005	67 (27.0%)	154 (23.7%)	0.341
CKD	40 (33.9%)	127 (16.2%)	<0.001	55 (25.2%)	94 (16.5%)	0.008
COPD	12 (10.2%)	59 (7.5%)	0.357	24 (9.7%)	59 (9.1%)	0.797
Current smoking	20 (16.9%)	147 (18.7%)	0.704	51 (20.7%)	145 (22.5%)	0.589
Previous MI	45 (38.5%)	240 (30.9%)	0.111	82 (33.6%)	218 (33.9%)	1.000
Previous stroke or TIA	15 (12.7%)	54 (6.9%)	0.039	23 (9.4%)	58 (9.0%)	0.896
LVEF < 30%	2 (2.8%)	4 (0.8%)	0.169	6 (4.1%)	11 (2.6%)	0.404
History of congestive heart failure	7 (6.0%)	29 (3.7%)	0.307	18 (7.5%)	29 (4.5%)	0.092
Peripheral vascular disease	18 (15.3%)	64 (8.2%)	0.024	39 (15.7%)	56 (8.6%)	0.003
History of carotid artery disease	14 (11.9%)	59 (7.5%)	0.144	22 (8.9%)	53 (8.2%)	0.787
Preoperative unstable angina	42 (35.6%)	220 (28.0%)	0.103	76 (30.6%)	175 (27.0%)	0.280
SYNTAX score I	30.9±11.7	28.0±11.3	0.009	29.8 ± 11.5	28.7 ± 11.3	0.233
SYNTAX 2020 score II (%)						
predicted10 year-mortality with PCI	39.5±21.2	27.1±18.5	<0.001	34.5±22.4	27.8±19.4	<0.001
predicted 10 year-mortality with CABG	32.1±18.8	22.8±16.1	<0.001	28.9±20.0	23.1±16.9	<0.001
EuroSCORE	5.0 ± 2.5	3.5 ± 2.5	<0.001	4.2 ± 2.6	3.6 ± 2.6	<0.001
Left main lesion	38 (32.2%)	319 (40.6%)	0.086	96 (38.7%)	252 (38.8%)	1.000

BMI = body mass index; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; LVEF = left ventricular ejection fraction; SYNTAX = Synergy Between PCI with Taxus and Cardiac Surgery; TIA = transient ischemic attack; other abbreviations as in **Supplementary Table 4**.

Supplementary Table 11. Frequency of periprocedural adverse events in patients with complex CAD in previous studies.

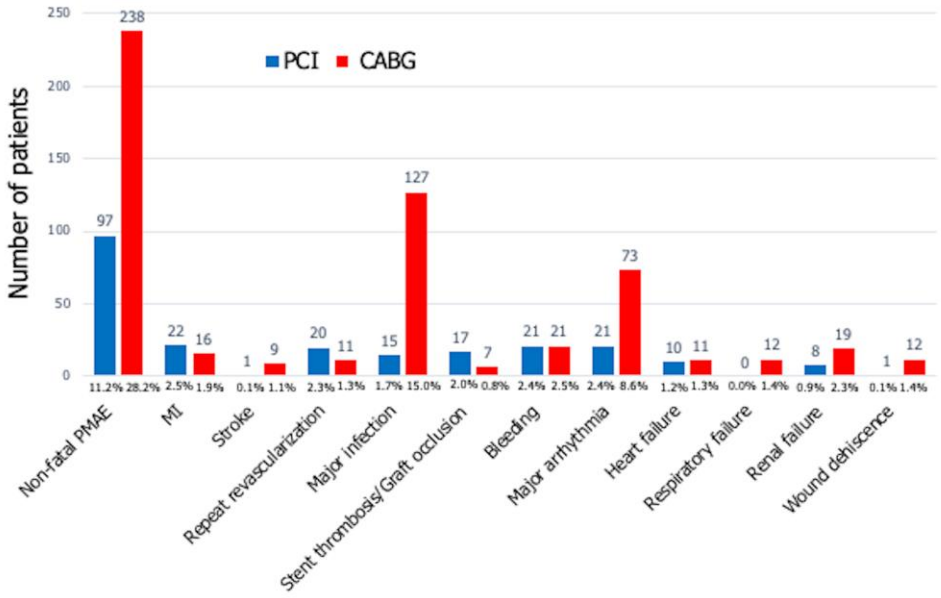
Trial	Population and stent type	Definition of PMAE	Frequency of Periprocedural adverse events			
			Events	PCI	CABG	P Value
EXCEL	Patients with left main coronary artery disease of low or intermediate anatomical complexity randomized between 2010 to 2014 Fluoropolymer-cased cobalt-chromium everolimus-eluting stent (XIENCE)	The composite of the following within 30-days post procedure; Death, stroke, MI, bleeding, arrhythmia, ischemia-driven revascularization, unplanned surgery or radiologic procedure, renal failure, sternal wound dehiscence, infection, prolonged intubation, post-pericardiotomy syndrome	Composite of PMAE	12.4%	44.0%	<0.001
NOBLE	Patients with left main coronary artery disease randomized between 2008 to 2015 Biolimus-eluting stent (NOBORI)	All-cause mortality, cardiac death, vascular death, periprocedural MI, non-procedure-related MI, definite stent thrombosis or symptomatic graft occlusion, stroke, reoperation for bleeding, blood transfusion, surgery for sternum infection, surgery for access site complications, CT-verified pulmonary embolus, and duration of index treatment admission within 30 days post procedure.	Death	0.3%	1.2%	0.09
			Procedural MI	5%	7%	0.52
			Non-procedural-related MI	1%	0%	0.08
			Stent thrombosis/graft occlusion	<1%	<1%	0.56
			Repeat revascularisation	1%	2%	0.46
			Stroke	0%	<1%	0.04
			Reoperation for bleeding	<1%	0%	<0.001
			Blood transfusion	2%	28%	<0.001
BEST	Patients with multivessel disease underwent procedure between 2008 to 2013	Death, stroke, and MI in hospital or 30 days after the procedure	Death	0.6%	1.1%	<0.001
			Stroke	0.2%	1.2%	<0.001

	Everolimus-eluting stent (XIENCE)		MI	3.5%	0.7%	0.004
FREEDOM	Patients with diabetes and multivessel coronary artery disease enrolled from 2005 and 2010 Sirolimus-eluting stents (Cypher) and paclitaxel-eluting stents (Taxus)	MACCE (death, MI, stroke, repeat revascularization) within 30 days after procedure	MACCE	4.8%	5.2%	0.68
			Stroke	0.3%	1.8%	0.002
			Repeat revascularisation	3.3%	1.1%	0.02
PRECOMBAT	Patients with left main coronary disease randomized between 2004 and 2009 Sirolimus-eluting stent (Cypher)	MACCE (death, MI, stroke, TVR) within 30 days after procedure	MACCE	1.3%	3.0%	
ARTS	Patients with multivessel disease randomised between 1997 and 1998 Bare metal stents	Following within 1 year after randomisation; death, cerebrovascular accident, MI, any event, CABG, repeat PCI, any revascularization	Any event within 1 year	26.5%	12.1%	<0.001
			Any repeat revascularization within 1 year	21.0%	3.8%	<0.001
CARDia	Patients with diabetes and multivessel or complex single-vessel disease randomized between 2002 and 2007 Bare-metal stent, switch to sirolimus-eluting stent (Cypher)	Periprocedural MI within 7 days Following within 1year after randomisation; death, MI, stroke, revascularisation, TIMI major bleed	Periprocedural MI within 7 days	4.7%	4.4%	0.088
			MI > 7 days within 1 year	5.5%	1.2%	0.016
			Revascularisation within 1 year	11.8%	2.0%	<0.001
			TIMI major bleed within 1 year	1.2%	6.1%	0.009



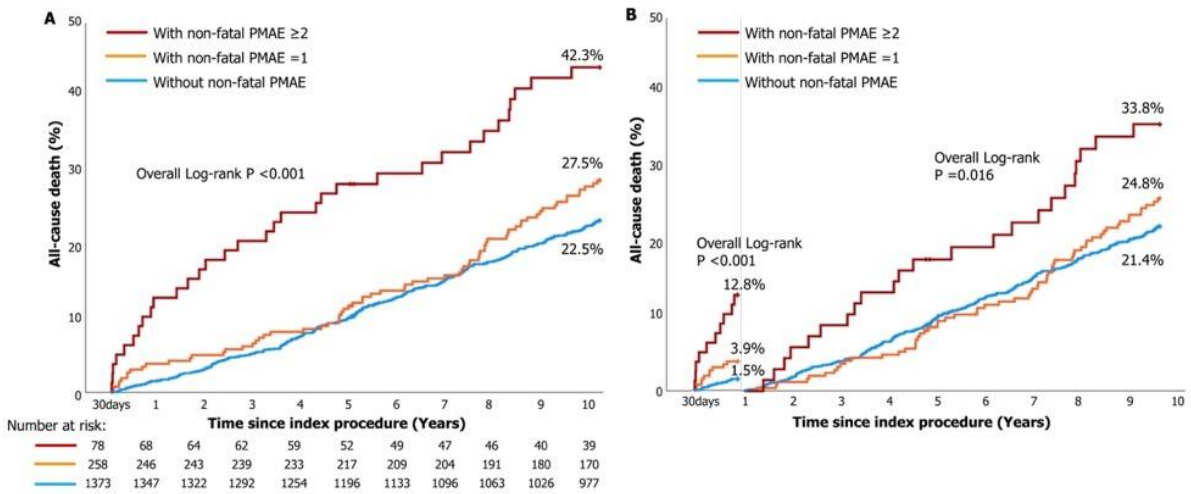
Supplementary Figure 1. Study profile.

The flow chart shows study patients. CABG = coronary artery bypass grafting; PCI = percutaneous coronary intervention.



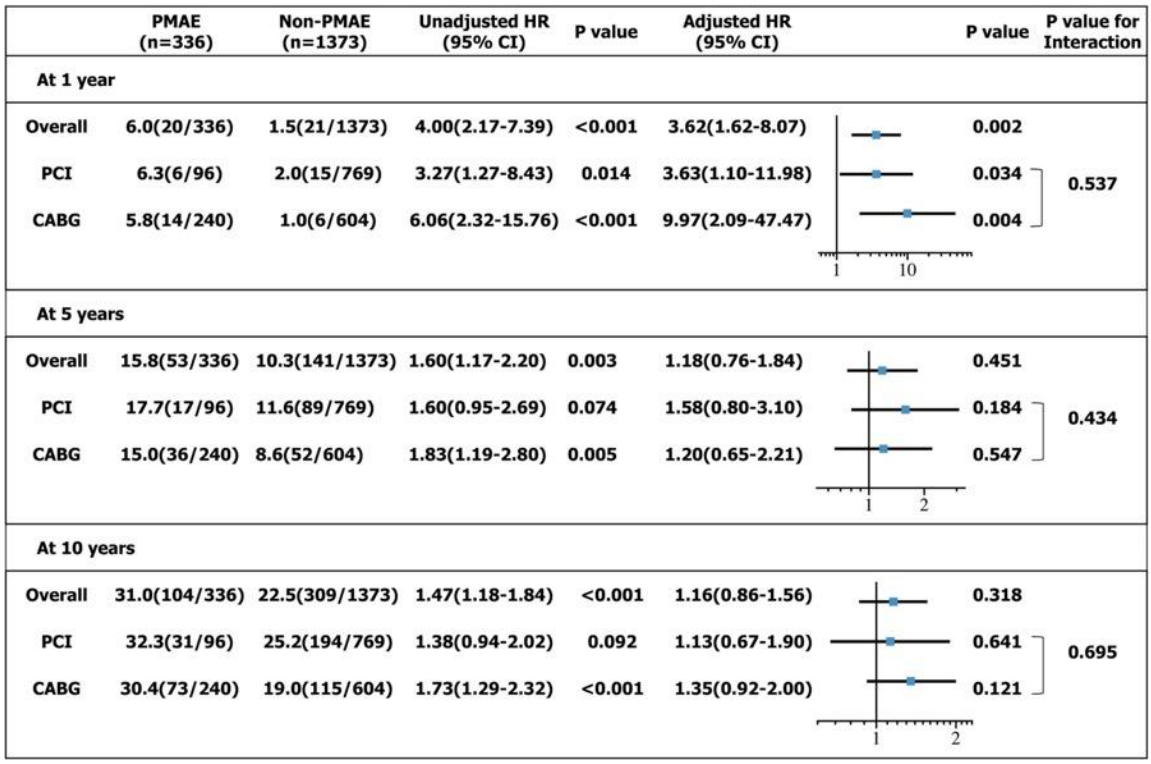
Supplementary Figure 2. Non-fatal PMAE within 30 days after PCI and CABG in the per-protocol analysis.

MI = myocardial infarction; PMAE = peri-procedural major adverse events; other abbreviations as in Supplementary Figure 1.



Supplementary Figure 3. Kaplan-Meier curve for all-cause mortality of patients stratified according to the number of PMAE.

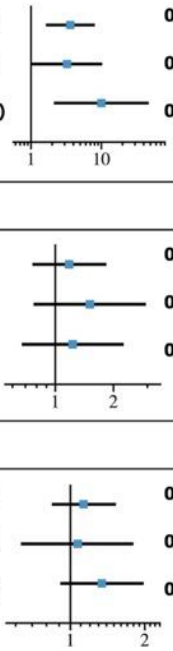
(A) In patients after PCI and CABG, (B) landmark analysis from 30 days to 1 year, and from 1 year to 10 years after PCI and CABG



Supplementary Figure 4. Sensitivity analysis of the impact of non-fatal PMAE with the SYNTAX definition of periprocedural MI within 48 hours.

See the definition in Supplementary Table 8. See Supplementary Appendix 2. CABG = coronary artery bypass grafting; CI = confidence interval; HR = hazard ratio; MI = myocardial infarction; PCI = percutaneous coronary intervention; PMAE = peri-procedural major adverse events.

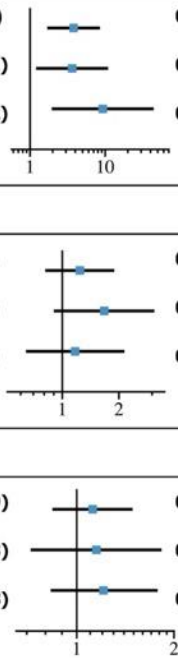
	PMAE (n=337)	Non-PMAE (n=1372)	Unadjusted HR (95% CI)	P value	Adjusted HR (95% CI)	P value	P value for Interaction
At 1 year							
Overall	5.9(20/337)	1.5(21/1372)	3.99(2.16-7.36)	<0.001	3.62(1.62-8.10)	0.002	
PCI	6.1(6/99)	2.0(15/766)	3.15(1.22-8.14)	0.017	3.25(1.02-10.28)	0.045	0.513
CABG	5.9(14/238)	1.0(6/606)	6.13(2.35-15.96)	<0.001	10.01(2.11-47.32)	0.004	
At 5 years							
Overall	15.7(53/337)	10.3(141/1372)	1.60(1.16-2.19)	0.003	1.18(0.76-1.84)	0.451	
PCI	17.2(17/99)	11.6(89/766)	1.54(0.91-2.59)	0.101	1.51(0.77-2.95)	0.230	0.505
CABG	15.1(36/238)	8.6(52/606)	1.85(1.21-2.83)	0.004	1.23(0.67-2.26)	0.495	
At 10 years							
Overall	30.6(103/337)	22.6(310/1372)	1.45(1.16-1.81)	0.001	1.13(0.84-1.53)	0.396	
PCI	31.3(31/99)	25.3(194/766)	1.32(0.90-1.93)	0.145	1.07(0.63-1.80)	0.795	0.618
CABG	30.3(72/238)	19.1(116/606)	1.72(1.28-2.30)	<0.001	1.34(0.91-1.98)	0.135	



Supplementary Figure 5. Sensitivity analysis of the impact of non-fatal PMAE with the 4th UDMI definition of periprocedural MI.

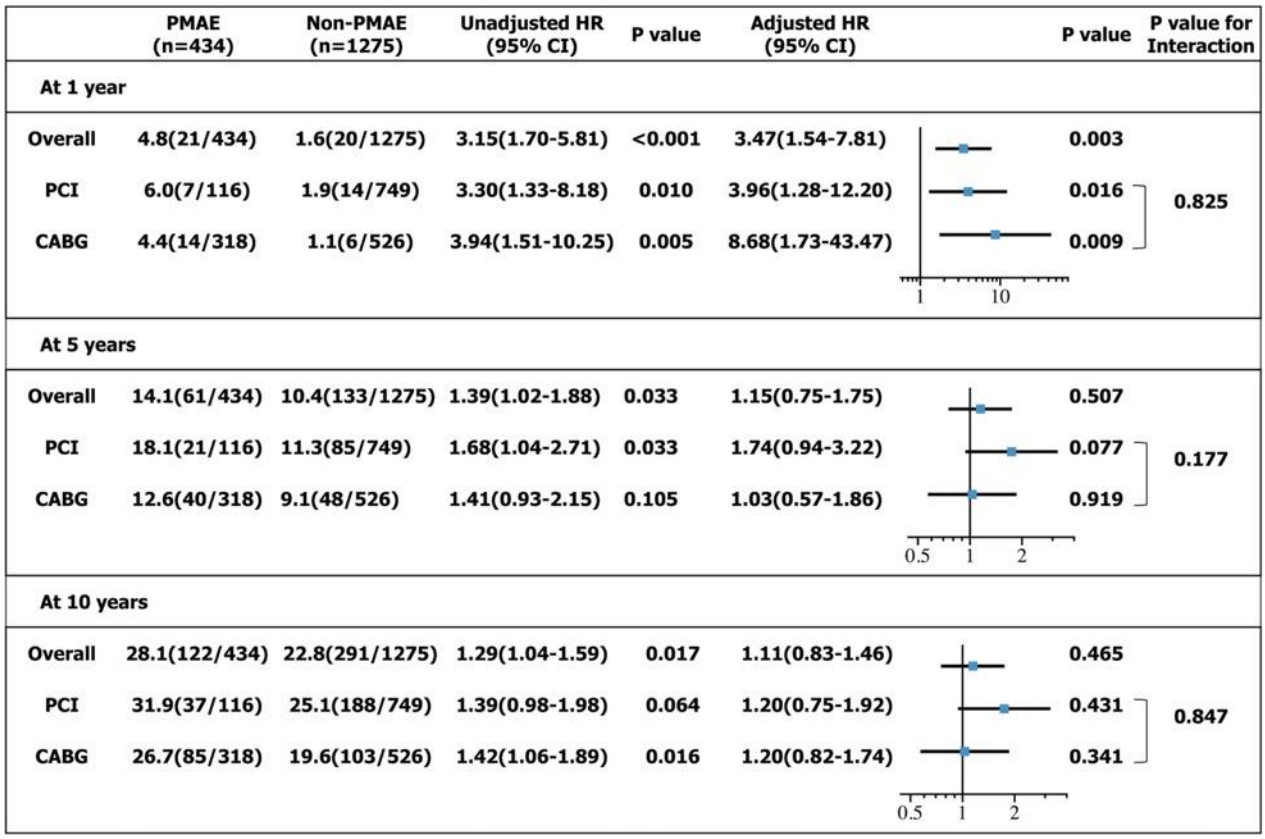
See the definition in Supplementary Table 8. See Supplementary Appendix 2. UDMI = universal definition of myocardial infarction; other abbreviations as in Supplementary Figure 4.

	PMAE (n=388)	Non-PMAE (n=1321)	Unadjusted HR (95% CI)	P value	Adjusted HR (95% CI)	P value	P value for Interaction
At 1 year							
Overall	5.4(21/388)	1.5(20/1321)	3.67(1.98-6.77)	<0.001	3.80(1.69-8.54)	0.001	
PCI	5.9(7/118)	1.9(14/747)	3.23(1.30-8.02)	0.011	3.63(1.20-10.91)	0.022	0.675
CABG	5.2(14/270)	1.0(6/574)	5.09(1.95-13.25)	<0.001	9.26(1.94-44.22)	0.005	
At 5 years							
Overall	15.2(59/388)	10.2(135/1321)	1.55(1.14-2.10)	0.005	1.24(0.81-1.89)	0.316	
PCI	17.8(21/118)	11.4(85/747)	1.64(1.02-2.65)	0.041	1.67(0.90-3.09)	0.098	0.311
CABG	14.1(38/270)	8.7(50/574)	1.68(1.10-2.56)	0.016	1.17(0.64-2.14)	0.589	
At 10 years							
Overall	29.1(113/388)	22.7(300/1321)	1.36(1.10-1.69)	0.005	1.12(0.84-1.49)	0.441	
PCI	31.4(37/118)	25.2(188/747)	1.36(0.95-1.93)	0.087	1.15(0.72-1.83)	0.551	0.983
CABG	28.1(76/270)	19.5(112/574)	1.53(1.14-2.05)	0.004	1.21(0.83-1.78)	0.312	



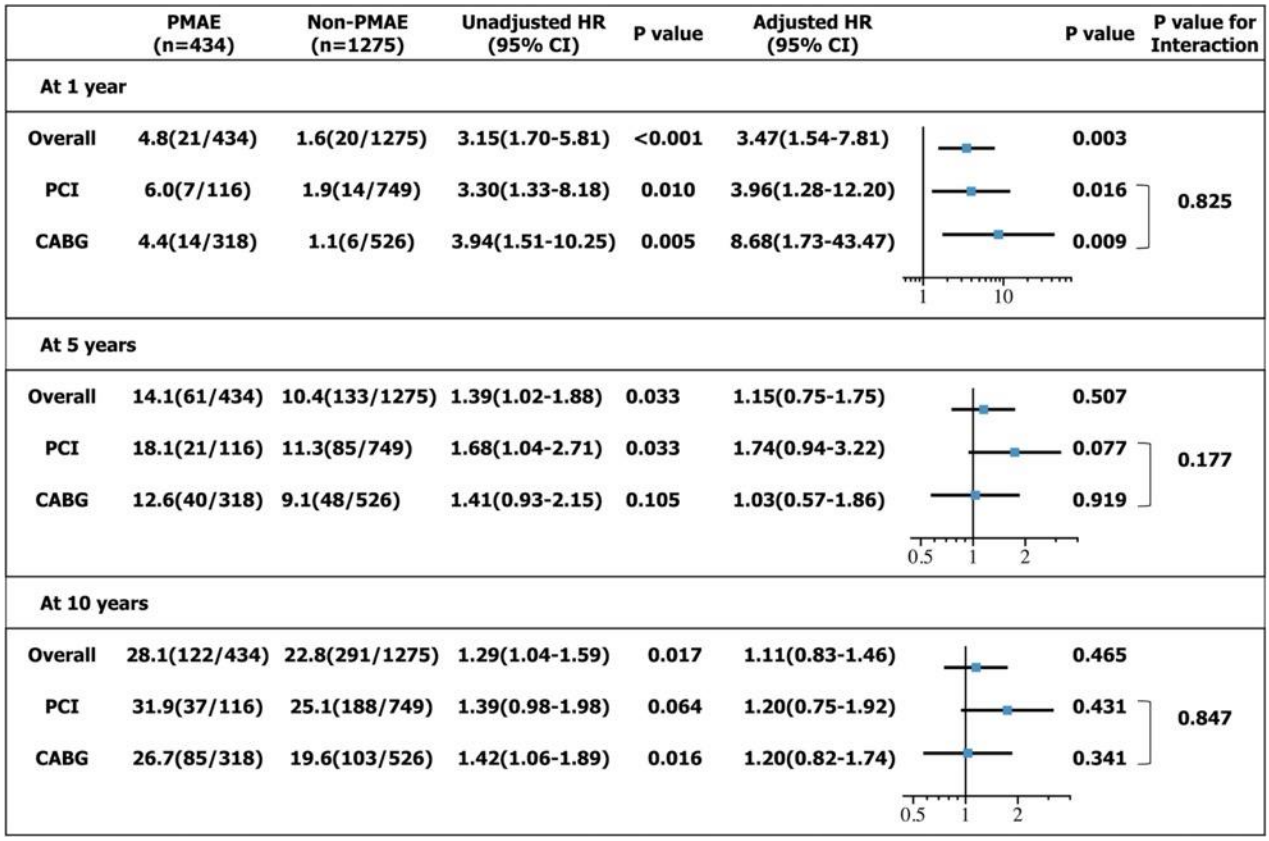
Supplementary Figure 6. Sensitivity analysis of the impact of non-fatal PMAE with the ISCHEMIA definition of periprocedural MI.

See the definition in Supplementary Table 8. See Supplementary Appendix 2. ISCHEMIA = International Study of Comparative Health Effectiveness With Medical and Invasive Approaches; other abbreviations as in Supplementary Figure 4.



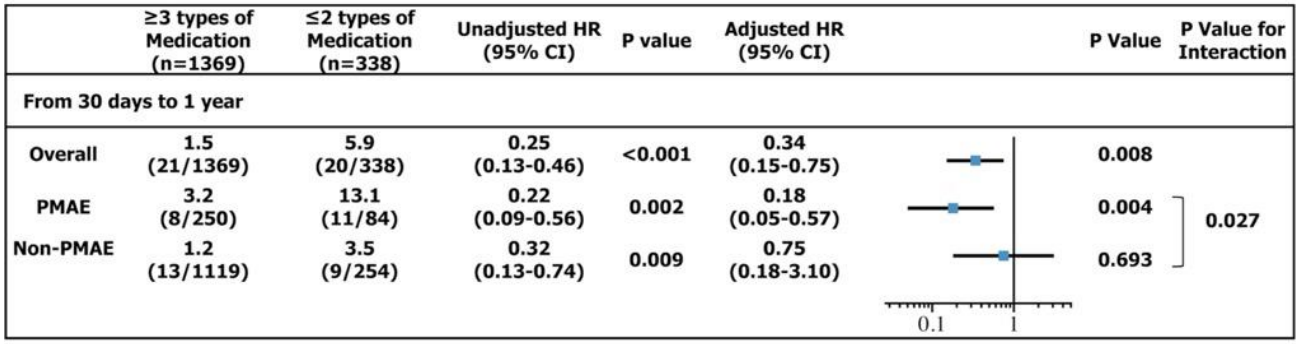
Supplementary Figure 7. Sensitivity analysis of the impact of non-fatal PMAE with the SCAI definition of periprocedural MI.

See the definition in Supplementary Table 8. See Supplementary Appendix 2. SCAI = Society for Cardiovascular Angiography and Interventions; other abbreviations as in Supplementary Figure 4.



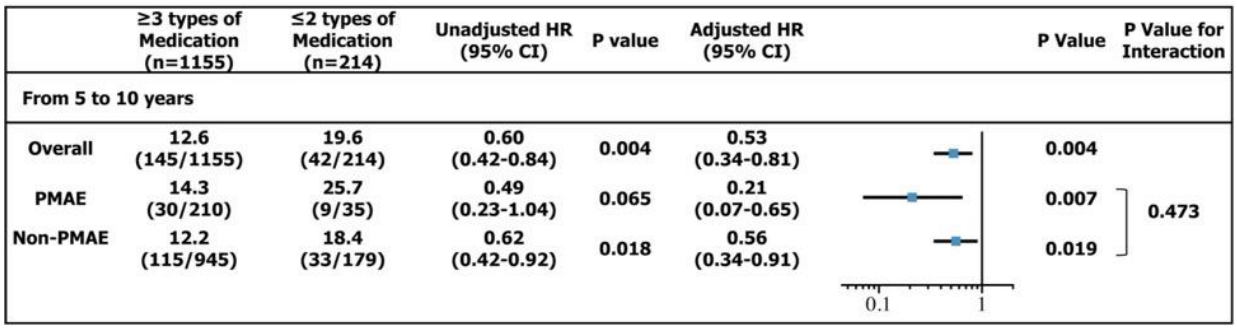
Supplementary Figure 8. Sensitivity analysis of the impact of non-fatal PMAE with the EXCEL definition of periprocedural MI.

See the definition in Supplementary Table 8. See Supplementary Appendix 2. EXCEL = Evaluation of XIENCE versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization; other abbreviations as in Supplementary Figure 4.



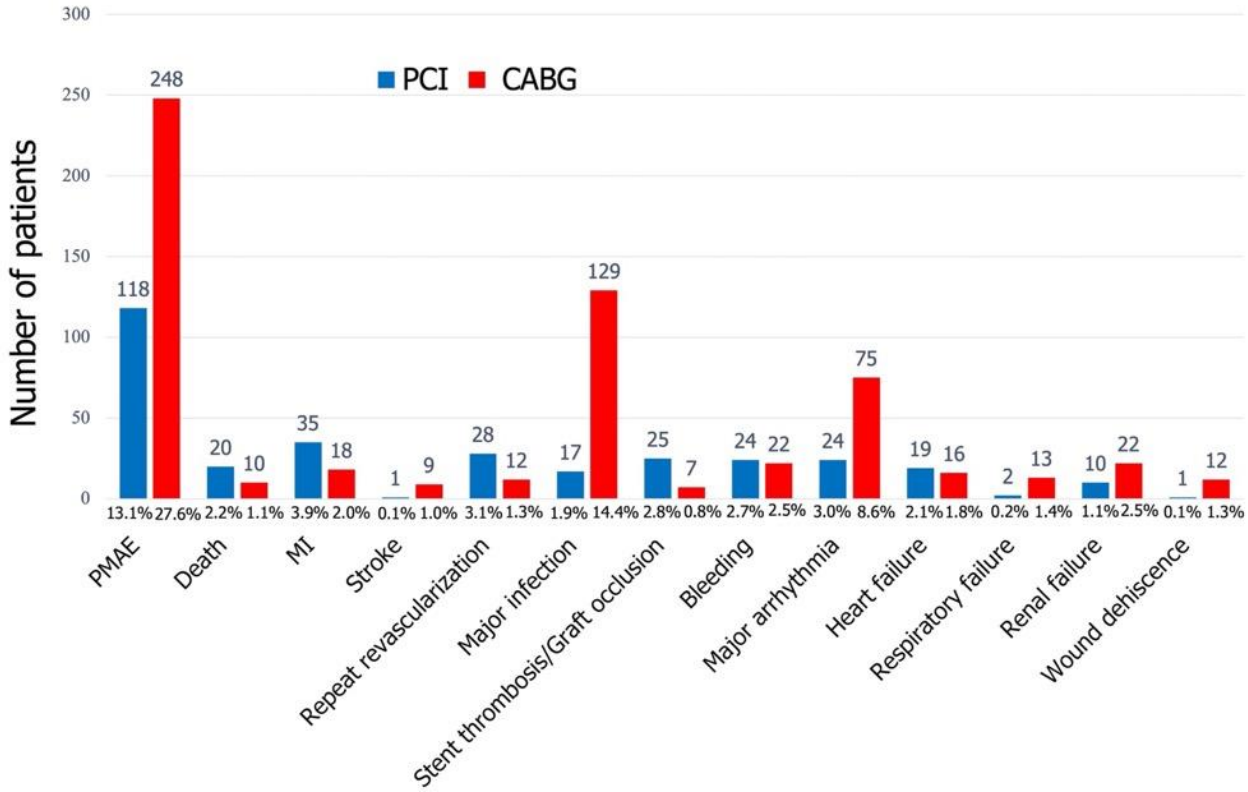
Supplementary Figure 9. The benefit of the number of individual OMT agents at 1-month follow-up on all-cause mortality between 1 month and 1 year of patients with and without non-fatal PMAE.

OMT = optimal medical therapy; other abbreviations as in Supplementary Figure 4.



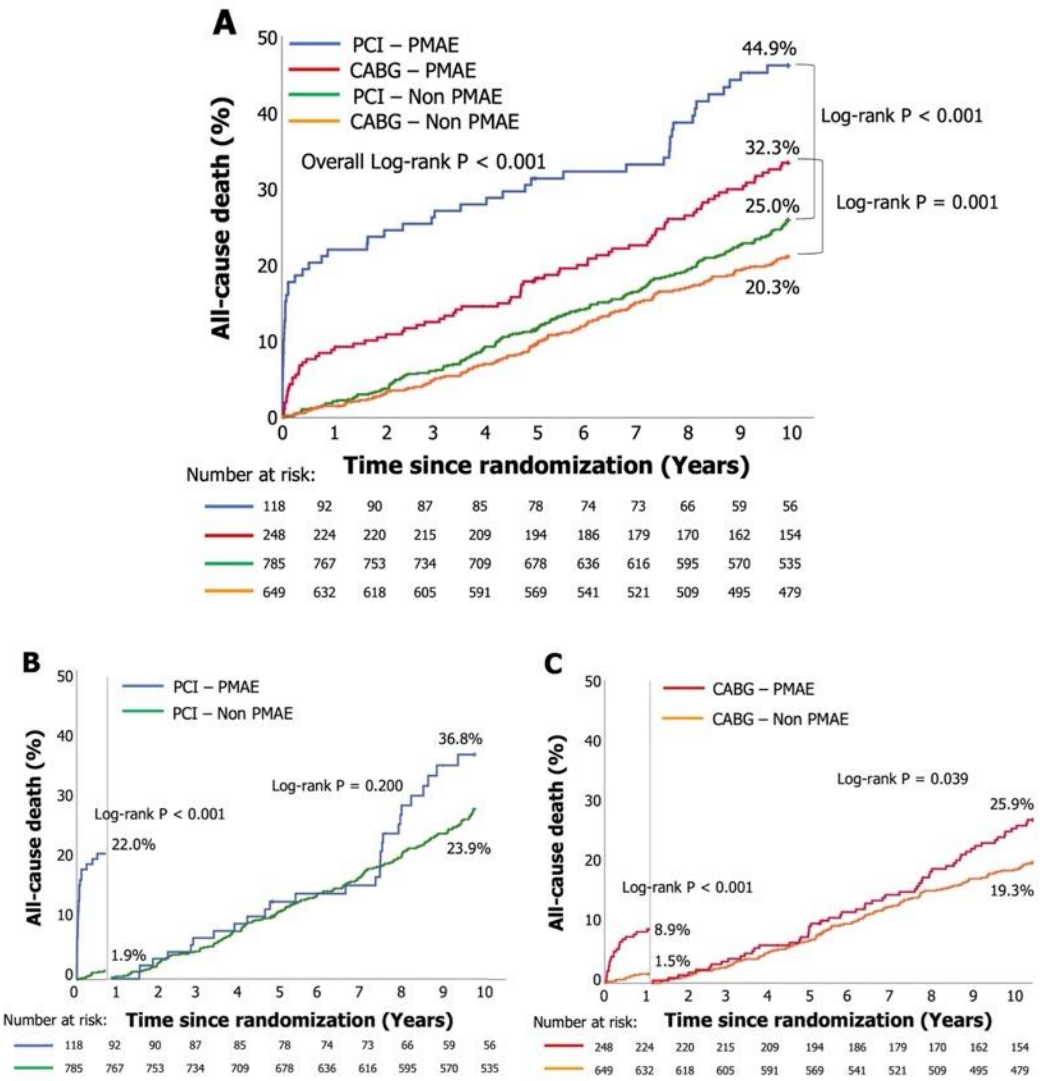
Supplementary Figure 10. The benefit of the number of individual OMT agents at 5-year follow-up on all-cause mortality between 5 and 10 years of patients with and without non-fatal PMAE.

Abbreviations as in Supplementary Figure 9.



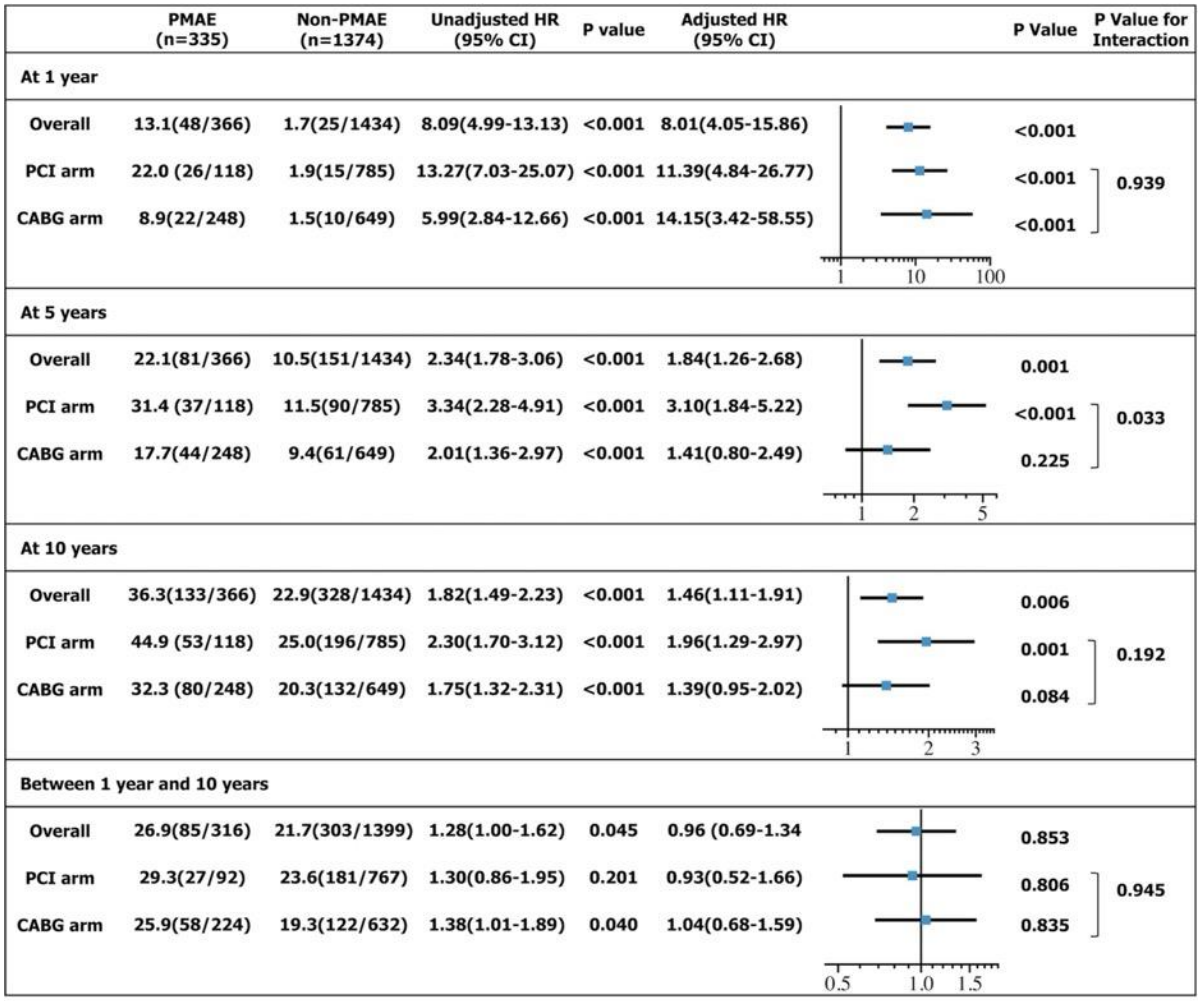
Supplementary Figure 11. Non-fatal and fatal PMAE within 30 days after PCI and CABG in the intention-to-treat analysis.

Abbreviations as in Supplementary Figure 2.



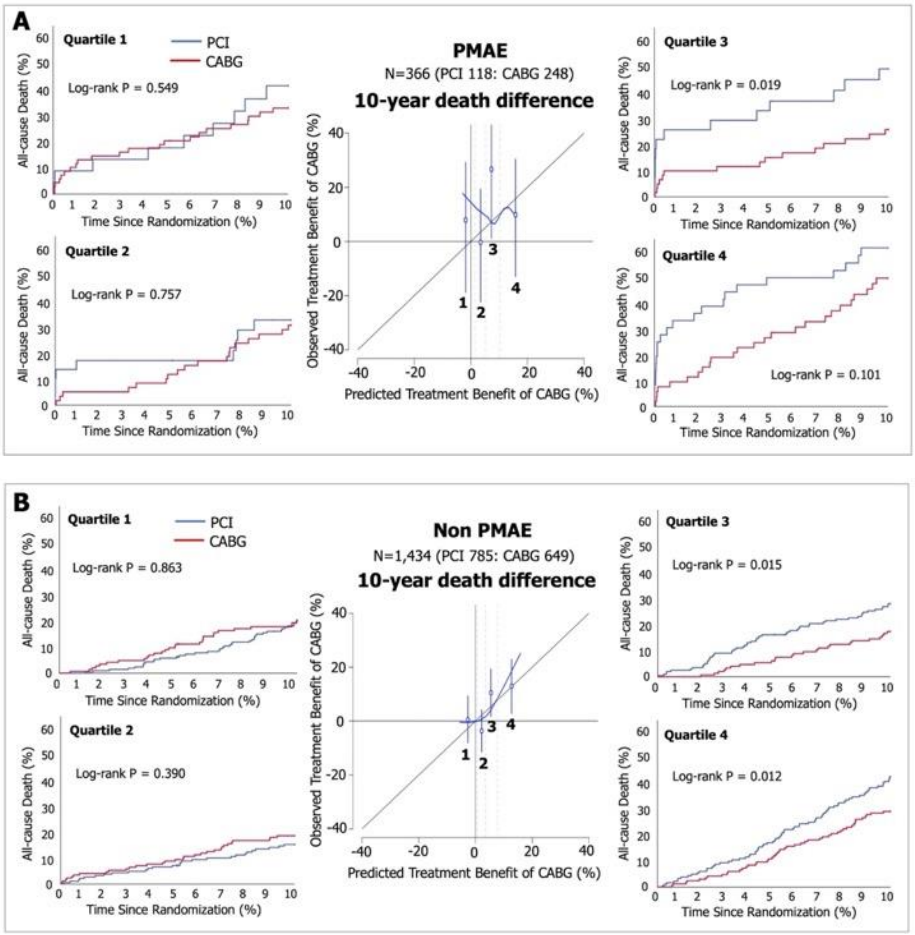
Supplementary Figure 12. Kaplan-Meier curve for all-cause mortality with and without PMAE in the intention-to-treat analysis.

(A) In patients after PCI and CABG, (B) landmark analysis from 30 days to 1 year, and from 1 year to 10 years in PCI, and (C) in CABG. Abbreviations as in Supplementary Figure 4.



Supplementary Figure 13. Impact of PMAE on all-cause mortality expressed as hazard ratios in the intention-to-treat analysis.

See Supplementary Appendix 2. Abbreviations as in Supplementary Figure 4.



Supplementary Figure 14. Predicted versus observed treatment benefit for 10-year mortality with and without PMAE in the intention-to-treat analysis.

Calibration plots present the observed versus predicted treatment benefit of CABG over PCI for 10-year death of quarters. Circles show each group of patients with a mean predicted rate and mean observed mortality rate with 95% CI. The smooth calibration curves (blue line) to each benefit calibration plot are based on local polynomial regression between observed and predicted treatment benefits. Abbreviations as in Supplementary Figure 4.