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CLINICAL RESEARCH
Cardiac and vascular surgery

Impact of myocardial injury after coronary artery bypass grafting on long-term prognosis

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See the editorial comment for this article 'Revisiting the definition of perioperative myocardial infarction after coronary artery bypass grafting', by Kristian Thygesen and Allan S. Jaffe, https://doi.org/10.1093/eurheartj/ehac147.

Aims The most appropriate definition of perioperative myocardial infarction (pMI) after coronary artery bypass grafting (CABG) and its impact on clinically relevant long-term events is controversial. We aimed to (i) analyse the incidence of pMI depending on various current definitions in a 'real-life' setting of CABG surgery and (ii) determine the long-term prognosis of patients with pMI depending on current definitions.

Methods and results A consecutive cohort of 2829 coronary artery disease patients undergoing CABG from two tertiary university centres with the presence of serial perioperative cardiac biomarker measurements (cardiac troponin and creatine kinase-myocardial band) were retrospectively analysed. The incidence and prognostic impact of pMI were assessed according to (i) the 4th Universal Definition of Myocardial Infarction (4UD), (ii) the definition of the Society for Cardiovascular Angiography and Interventions (SCAI), and (iii) the Academic Research Consortium (ARC). The primary endpoint of this study was a composite of myocardial infarction, all-cause death, and repeat revascularization; secondary endpoints were mortality at 30 days and during 5-year follow-up. There was a significant difference in the occurrence of pMI (49.5% SCAI vs. 2.9% 4UD vs. 2.6% ARC). The 4th Universal Definition of Myocardial Infarction and ARC criteria remained strong independent predictors of all-cause mortality at 30 days [4UD: odds ratio (OR) 12.18; 95% confidence interval (CI) 5.00–29.67; $P < 0.001$; ARC: OR 13.16; 95% CI 5.41–32.00; $P < 0.001$] and 5 years [4UD: hazard ratio (HR) 2.13; 95% CI 1.19–3.81; $P = 0.011$; ARC: HR 2.23; 95% CI 1.21–4.09; $P = 0.010$]. Moreover, the occurrence of new perioperative electrocardiographic changes was prognostic of both primary and secondary endpoints.

Conclusion Incidence and prognosis of pMI differ markedly depending on the underlying definition of myocardial infarction for patients undergoing CABG. Isolated biomarker release-based definitions (such as troponin) were not associated with pMI relevant to prognosis. Additional signs of ischaemia detected by new electrocardiographic abnormalities, regional wall motion abnormalities, or coronary angiography should result in rapid action in everyday clinical practice.

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Key question

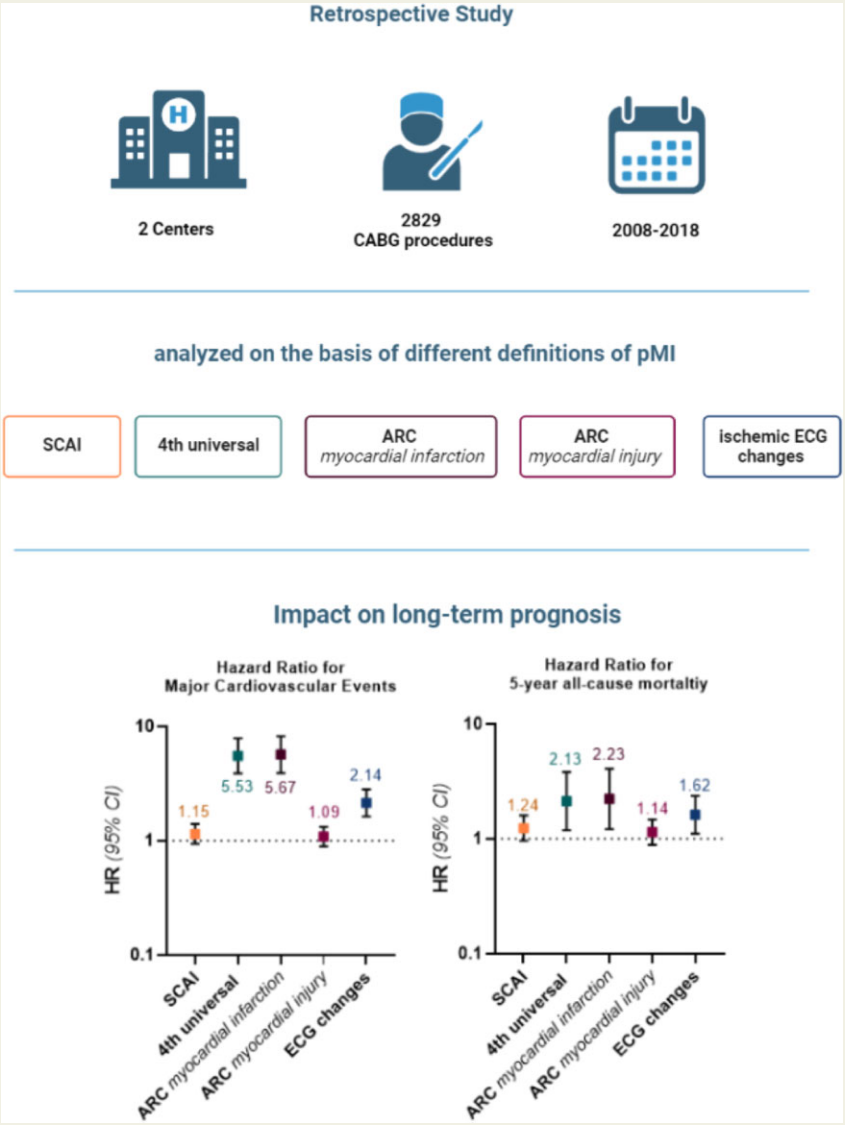
We aimed to (i) analyse the incidence of perioperative myocardial infarction (pMI) depending on different current definitions in a 'real-life' setting of coronary artery bypass graft surgery and (ii) determine the long-term prognosis of patients with pMI according to current definitions.

Key finding

There was a significant difference in the occurrence of pMI. The 4th Universal Definition of Myocardial Infarction and Academic Research Consortium criteria remained strong independent predictors for all-cause mortality at 30 days and during 5-year follow-up.

Take-home message

Isolated biomarker release-based definitions were not associated with pMI relevant to prognosis. Additional signs of ischaemia detected by new electrocardiogram abnormalities, regional wall motion abnormalities, or coronary angiography should result in rapid action in clinical practice.



Structured Graphical Abstract The definition of perioperative myocardial infarction used has a major impact on incidence and prognosis. Created with BioRender.com. Hazard ratios are given for patients with perioperative myocardial infarction (MI) according to various definitions or electrocardiogram (ECG) changes relative to those without perioperative MI or ECG changes after coronary artery bypass grafting. ARC, Academic Research Consortium; CABG, coronary artery bypass grafting; CI, confidence interval; ECG, electrocardiogram; HR, hazard ratio; SCAI, Society for Cardiovascular Angiography and Interventions.

Keywords CABG • Cardiac surgery • Type 5 myocardial infarction • Coronary revascularization • Myocardial injury

Introduction

Coronary artery bypass graft (CABG) surgery remains the treatment of choice for multivessel coronary artery disease (CAD), especially in patients with diabetes or ischaemic heart failure.[1] During CABG surgery, perioperative myocardial ischaemia may occur due to technical shortcomings, insufficient cardioprotection, or other ischaemic events. Perioperative myocardial infarction (pMI) after CABG has been termed 'Type 5 myocardial infarction',[2] the definition of which remains a matter of intense debate. Cardiac biomarkers are usually elevated following cardiac surgery, as myocardial ischaemia with cardioplegic arrest and reperfusion as well as the surgical procedure itself are associated with myocardial injury.[3] As the incidence of pMI was mostly included in the composite endpoint of several large and important clinical trials comparing the outcomes of CABG vs. percutaneous coronary intervention (PCI), this debate has become highly relevant when interpreting the results, as recently revealed by the controversial results of the EXCEL trial.[4,5]

In recent years, several definitions of periprocedural and pMI have been proposed, including the 4th Universal Definition of Myocardial Infarction (4UD), the definition of the Society for Cardiovascular Angiography and Interventions (SCAI definition, used in the EXCEL trial), and the definition of the Academic Research Consortium (ARC). These definitions differ in their enzyme cut-off values and time points, and the inclusion or exclusion of additional markers for diagnosis, including new electrocardiographic (ECG) abnormalities, imaging evidence of ischaemia, or angiographic confirmation of bypass graft or native vessel occlusion.[6]

Recent studies have revealed that the prognosis of patients with periprocedural myocardial infarction differs markedly depending on the definition used after PCI.[7] An ongoing subgroup analysis of the EXCEL trial has revealed clear differences in the outcomes of patients with periprocedural myocardial infarction depending on the definition used.[8]

This study aims (i) to analyse the incidence of pMI depending on the definition in a 'real-life' setting and (ii) to determine the long-term prognosis of patients with pMI depending on the definition. We hypothesized that definitions based on isolated biomarker increases are not associated with mortality and major adverse cardiac events (MACE) following surgery.

Methods

Study population and data collection

The study population was gathered to evaluate outcomes of 'real-world' patients with multivessel CAD who underwent CABG surgery. Patients from two centres (Innsbruck, Austria: $n = 1885$; Essen, Germany: $n = 944$) were retrospectively studied between January 2008 and December 2018. The indication for CABG surgery was discussed in a heart team approach, with cooperation between cardiologists and cardiac surgeons, in accordance with current guidelines. The surgical strategy, including the choice and number of grafts used, was decided by the surgeon performing the operation. General anaesthesia was induced with midazolam, esketamine, propofol, fentanyl, and rocuronium after peripheral vein and radial arterial cannulation. Inhalation anaesthesia (sevoflurane) was used in all patients (2–2.5%, target MAC 0.8–1). St Thomas II or Bretschneider cardioplegic solutions were used in all patients. All but one of the patients underwent on-pump surgery. Levels of cardiac enzymes [creatine kinase (CK), CK-myocardial band, and cardiac troponin (I or T)] were routinely measured before surgery and 4, 12, 24, 48, and 72 h after surgery in Innsbruck and 1, 6, 12, 24, 48, and 72 h after surgery in Essen (see Supplementary material online, *Figure S1A*). In Innsbruck, the Elecsys® Troponin T-high sensitive assay (Roche Diagnostics, Mannheim, Germany) was used for cTnT and the Cobas® assay (Roche Diagnostics, Mannheim, Germany) was used for CK-MB. In Essen, the ENZYMUN® assay (Roche Diagnostics, Mannheim, Germany) was used for cTnT, the Dimension® Xpand assay (Siemens Healthcare Diagnostics Inc., Newark, DE, USA) was used for cTnI and the CK-MB FS assay (Diasys Systems GmbH, Holzheim, Germany) was used for CK-MB (see Supplementary material online, *Figure S1B* and *C*). The same assays were used throughout the entire observation period.

Both CK-MB and cTn were sampled in all patients. Troponin levels were available in 2774 (98.06%) patients before surgery and in 2827 (99.93%) after surgery. Creatine kinase-myocardial band (CK-MB) measurements were available in 278 (9.83%) patients before surgery and in 2705 (95.62%) after surgery. After the CABG procedure, angiography was performed if myocardial ischaemia was clinically suspected. This study was performed in accordance with the Declaration of Helsinki and permission to use anonymized data without patient consent for this study was obtained from the Innsbruck Medical University (UN4232 297/4.3) and the University of Duisburg-Essen Institutional Review Boards (BO-08-3683).

Definitions of perioperative myocardial infarction and data collection

Definitions of pMI according to the SCAI criteria, the 4UD, and the ARC criteria were used (*Table 1*). According to the SCAI criteria, pMI is defined as an increase in CK-MB levels within 48 h after the procedure up to 10 times the local laboratory upper limit of normal (ULN) or to five times the ULN with newly occurring Q-waves in two contiguous leads or a new persistent left bundle branch block (LBBB), or, in the absence of CK-MB determinations, an increase in cTn (T or I) levels up to 70 times the local laboratory ULN, or 35 times the ULN with new pathological Q-waves in two contiguous leads or a new persistent LBBB. In the 4UD, a pMI upon CABG is defined as an increase in cTn levels by 10 times the 99th percentile of upper reference limit (URL) and new Q-waves, angiographic findings, or new regional wall motion abnormalities (RWMA). The consensus ARC criteria distinguish between myocardial injury and myocardial infarction upon CABG. Myocardial infarction is defined as an increase in cTn levels by 10 times the URL and new Q-waves, angiographic findings, or new RWMA. Myocardial injury is defined in the consensus statement as an increase in cTn (T or I) to 70 times the local laboratory URL. A more detailed list of definition characteristics is provided in Supplementary material online, *Table S1*. Electrocardiograms were analysed for ischaemic changes, including Q or R waves, ST-segment elevation or depression, and LBBB, as previously described.[2] Details are provided in Supplementary material online, *Figure S1D*. Post-operative echocardiography or angiography was performed if pMI was clinically suspected.

Patient and operative data were collected retrospectively. Mortality data were updated annually, by connecting the social insurance number of each patient to the corresponding vital status (alive/dead) data, for both centres. Major adverse cardiac events were routinely monitored

over a 4–5-year period. Follow-up was limited to a maximum of 5 years, with routine data collection via interviews and chart reviews (latest available). Follow-up was available for 100% of the patient population (see Supplementary material online, *Figure S2*).

Trial endpoints

The primary endpoint was time to occurrence of a MACE, defined as the composite of myocardial infarction, all-cause mortality, and repeat revascularization. The secondary endpoints were mortality at 30 days and during 5-year follow-up. Myocardial infarction was defined according to the European Society of Cardiology/American College of Cardiology/American Heart Association committee criteria as symptoms of ischaemia and/or new significant ST-segment changes with a rise and fall of high-sensitivity cTnT with at least one value above the 99th percentile URL in patients with normalized values or a 50% increase in the setting of non-normalized troponin values.[2] Repeat revascularization was defined as any PCI or re-CABG after surgery.[9]

Statistical analysis

Continuous variables are presented as mean ± standard deviation, whereas categorical variables are presented as frequencies and proportions. Kolmogorov–Smirnov tests were performed to determine whether continuous variables followed a normal distribution. Non-normally distributed continuous variables are presented as medians and interquartile ranges. Survival and MACE outcomes for the different pMI definitions were subjected to logistic regression analysis for the 30-day results and the Cox proportional hazards model analysis for the 5-year results. The authors checked a possible violation of the proportional hazards assumption in the Cox regression by plotting log–log graphs for the significant results. As there were no deviations from parallelism and/or crossing of the curves visible, we concluded that the proportional hazards assumption was not violated. Kaplan–Meier estimates were used to plot survival curves, which were compared in log-rank tests. Follow-up was censored at 5 years for analysis. Time zero corresponded to the time of the surgical procedure, at which conformity to the various definitions of pMI was assessed. Regression analyses were adjusted for the age and sex of the patient. Hazard ratios (HR) are reported with 95% confidence intervals (CI). *P*-values of <0.05 were considered to indicate statistical significance. All statistical analyses were performed with SPSS Version 24 (IBM Corporation, Armonk, NY, USA).

Results

Patients suffering from perioperative myocardial infarction upon coronary artery bypass grafting

The SCAI definition, the 4UD, and the ARC criteria were applied to our study cohort and differences in the occurrence of pMI according to the definition used were assessed (*Table 1*). For this purpose, cardiac enzymes and ECGs of 2829 'real-world' CABG patients obtained in the first 48 h post-procedure were analysed. The data for 90.9% of the patients could be analysed with the 4UD, 97.7% with the SCAI definition, and 91.4% with the ARC criteria (see Supplementary material online, *Figure S3*). Eighty-two patients (2.9%) experienced pMI according to a clinical diagnosis, 1368 (49.5%) patients according to the SCAI definition, whereas only 75 (2.9%) had pMI according to the 4UD; 67 (2.6%) of the patients had pMI according to the ARC criteria, whereas 1432 (51.5%) suffered from myocardial injury. There were no differences in patient characteristics, pre-existing comorbidities, or perioperative characteristics between the different definition-based groups (*Table 2*).

Impact of perioperative myocardial infarction definitions on major adverse cardiac events

We then aimed to determine the impact of the various definitions on MACE-free survival. Mid-term results after CABG were obtained by including data for a median follow-up of 3.8 years (interquartile range: 2.1–5.7 years). Patients with pMI according to 4UD or ARC had significantly higher rates of MACE during the 5-year follow-up (median follow-up 3.8 years) than patients without pMI (log-rank both $P < 0.001$) (*Figure 1*). In contrast, pMI according to SCAI had no significant impact on 5-year MACE rates (log-rank $P = 0.185$). The same was true for the ARC definition of myocardial injury (log-rank $P = 0.426$).

Table 1 Definitions of perioperative myocardial infarction

	Cardiac biomarker	Additional characteristic indispensable (ECG, RWMA, angiographic findings)	Definition
SCAI	CK-MB/cTn	–	Any of: CK-MB ≥10× ULN; CK-MB ≥5× ULN and new Q-waves or LBBB; cTn ≥70× ULN; cTn ≥35× ULN and evidence of new Q-waves or LBBB
4th universal	cTn	+	>10× 99th percentile URL and new Q-waves, angiographic findings, or new RWMA
ARC myocardial infarction	cTn	+	>35× URL and new Q-waves, angiographic findings, or new RWMA
ARC myocardial injury	cTn	–	>70× URL

ARC, Academic Research Consortium; CK-MB, creatine kinase-myocardial band; cTn, cardiac troponin; ECG, electrocardiogram; LBBB, left bundle branch block; RWMA, regional wall motion abnormalities; SCAI, Society for Cardiovascular Angiography and Interventions; URL, upper reference limit; ULN, upper limit of normal.

Table 2 **Perioperative characteristics**

	All CABG patients $n = 2829$	SCAI 1368/2763 (49.5%)	4th universal 75/2572 (2.9%)	ARC myocardial infarction 67/2586 (2.6%)	ARC myocardial injury 1432/2780 (51.5%)	ECG changes 262/2635 (9.9%)
Demographic characteristics						
Male gender	2316 (81.9%)	1136 (83.0%)	65 (86.7%)	57 (85.1%)	1191 (83.2%)	212 (80.9%)
Age at surgery	67.0 ± 9.6	67.1 ± 9.5	66.3 ± 9.1	66.1 ± 9.2	67.1 ± 9.5	66.9 ± 10.2
BMI	27.0 (25.0–30.0)	27.1 (25.0–30.0)	27.0 (24.8–29.1)	27.3 (25.0–29.0)	27.1 (25.0–30.0)	27.0 (24.8–29.3)
Pre-existing condition						
DM	843 (29.9%)	365 (26.8%)	26 (35.1%)	22 (33.3%)	382 (26.6%)	86 (33.3%)
Insulin-treated DM	274 (9.7%)	113 (8.3%)	10 (13.5%)	8 (12.1%)	122 (8.5%)	30 (11.6%)
Hypertension	2529 (89.9%)	1199 (88.0%)	66 (93.2%)	61 (92.4%)	1254 (87.9%)	239 (92.6%)
Hyperlipidaemia	2098 (74.6%)	997 (73.1%)	59 (79.7%)	53 (80.3%)	1046 (73.3%)	230 (89.1%)
Prior PCI	430 (28.3%)	213 (31.4%)	18 (40.9%)	16 (39.0%)	219 (30.4%)	55 (28.8%)
Prior stroke	53 (2.3%)	34 (3.1%)	2 (3.2%)	2 (3.4%)	33 (2.9%)	3 (1.4%)
Prior MCI	931 (37.2%)	432 (35.5%)	30 (44.8%)	26 (41.9%)	464 (36.2%)	87 (38.5%)
Smoker	1066 (41.6%)	473 (41.4%)	32 (50.0%)	28 (50.0%)	492 (40.9%)	114 (46.2%)
COPD	302 (10.7%)	136 (10.0%)	7 (9.5%)	7 (10.6%)	142 (10.0%)	25 (9.7%)
Creatinine	0.97 (0.7–1.1)	1.00 (0.7–1.2)	0.92 (0.0–1.2)	0.91 (0.0–1.1)	1.00 (0.7–1.2)	0.90 (0.0–1.1)
Surgical procedure						
LVEF	55 (48–79)	55 (49–60)	51 (45–60)	51 (45–60)	55 (49–60)	59 (50–62)
Nb. Grafts	3.0 (3.0–4.0)	3.0 (3.0–4.0)	3.0 (3.0–4.0)	3.5 (3.0–4.0)	3.0 (3.0–4.0)	3.0 (3.0–4.0)
X-clamp time	63 (48–79)	70 (56–85)	70 (55–86)	70 (59–88)	69 (56–85)	66 (50–78)
Log. EURO score II	1.46 (0.9–2.7)	1.40 (0.9–2.5)	1.43 (0.9–3.3)	1.34 (0.8–2.8)	1.40 (0.9–2.5)	1.39 (0.9–2.6)
Follow-up						
MACE within 5 years	420 (14.8%)	222 (16.2%)	34 (45.3%)	31 (46.3%)	226 (15.8%)	62 (23.7%)
PeriOP MACE	82 (2.9%)	52 (3.8%)	23 (30.7%)	21 (31.3%)	52 (3.6%)	27 (10.3%)
Dead within 5 years	258 (9.1%)	141 (10.3%)	12 (16.0%)	11 (16.4%)	141 (9.8%)	29 (11.9%)
PeriOP dead	51 (1.8%)	32 (2.3%)	7 (9.3%)	7 (10.4%)	31 (2.2%)	10 (3.8%)

Values are mean ± SD, median (interquartile range), or *n* (%).
Age at surgery is expressed in years. LVEF is shown in %. X-clamp time is expressed in minutes. Creatinine concentration is expressed in mg/dL. Cardiac enzyme levels are presented as xURL. BMI, body mass index; DM, diabetes mellitus; PCI, percutaneous coronary intervention; MCI, myocardial infarction; COPD, chronic obstructive pulmonary disease; LVEF, left ventricular ejection fraction; MACE, major adverse cardiac events; other abbreviations as in *Table 1*.

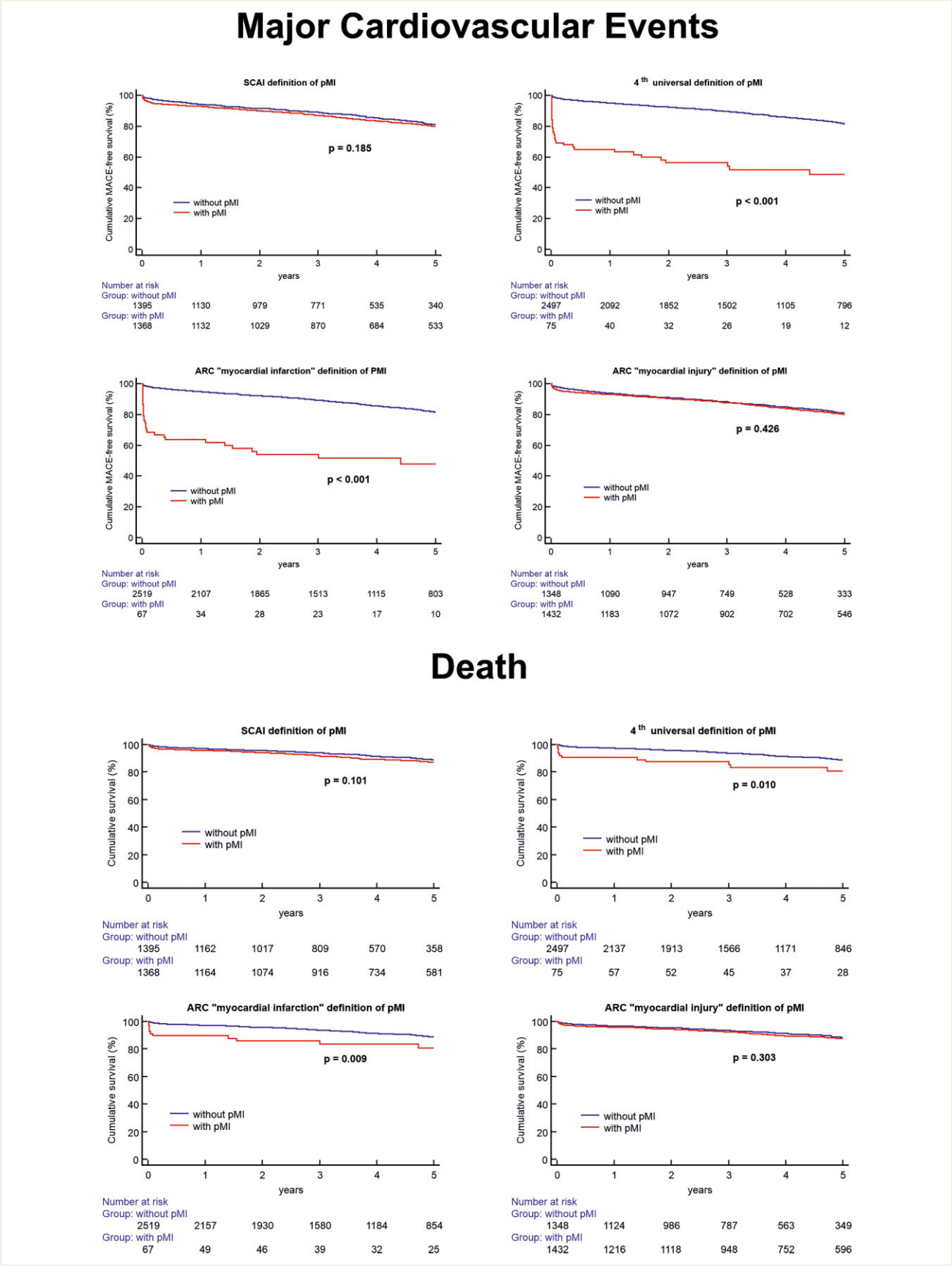
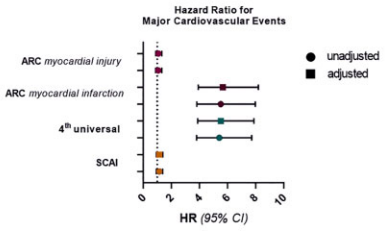


Figure 1 Kaplan–Meier curves for major adverse cardiac events and death according to various perioperative myocardial infarction definitions. Major adverse cardiac events include all-cause death, spontaneous myocardial infarction, or repeat revascularization. ARC, Academic Research Consortium; MACE, major adverse cardiac events; MI, myocardial infarction; SCAI, Society for Cardiovascular Angiography and Interventions.

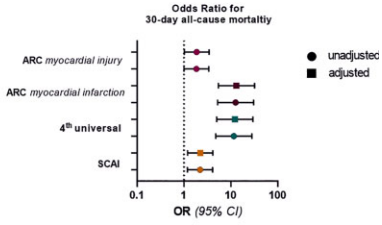
MACE

	SCAI	4th universal	ARC *myocardial infarction*	ARC *myocardial injury*
n	1368/2763 (49.5%)	75/2572 (2,9%)	67/2586 (2.6%)	1432/2780 (51.5%)
MACE within 5 years	222 (16.2%)	34 (45.3%)	31 (46.3%)	226 (15.8%)
Hazard ratio (95% CI)				
unadjusted	1.142 (0.938-1.390)	5.421 (3.807-7.720)	5.518 (3.818-7.976)	1.083 (0.890-1.317)
p-value	0.186	< 0.001	< 0.001	0.426
adjusted	1.148 (0.943-1.397)	5.528 (3.880-7.877)	5.669 (3.920-8.199)	1.088 (0.894-1.323)
p-value	0.170	< 0.001	< 0.001	0.399



30-day all-cause mortality

	SCAI	4th universal	ARC *myocardial infarction*	ARC *myocardial injury*
n	1368/2763 (49.5%)	75/2572 (2,9%)	67/2586 (2.6%)	1432/2780 (51.5%)
Patients died within 30 days	32 (2.3%)	7 (9.3%)	7 (10.4%)	31 (2.2%)
Odds ratio (95% CI)				
unadjusted	2.204 (1.188-4.088)	11.581 (4.784-28.032)	12.661 (5.231-30.645)	1.842 (1.003-3.383)
p-value	0.012	< 0.001	< 0.001	0.049
adjusted	2.226 (1.198-4.138)	12.183 (5.002-29.673)	13.159 (5.410-32.007)	1.869 (1.016-3.438)
p-value	0.011	< 0.001	< 0.001	0.045



5-year all-cause mortality

	SCAI	4th universal	ARC *myocardial infarction*	ARC *myocardial injury*
n	1368/2763 (49.5%)	75/2572 (2,9%)	67/2586 (2.6%)	1432/2780 (51.5%)
Patients died within 5 years	141 (10.3%)	12 (16.0%)	11 (16.4%)	141 (9.8%)
Hazard ratio (95% CI)				
unadjusted	1.235 (0.959-1.591)	2.123 (1.185-3.802)	2.212 (1.205-4.059)	1.142 (0.887-1.470)
p-value	0.102	0.011	0.010	0.303
adjusted	1.236 (0.960-1.592)	2.127 (1.187-3.811)	2.228 (1.214-4.089)	1.143 (0.888-1.471)
p-value	0.101	0.011	0.010	0.303

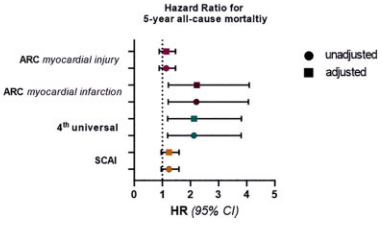


Figure 2 Impact of various perioperative myocardial infarction definitions on major adverse cardiac events and death expressed as hazard ratios. Hazard ratios and odds ratios for patients with perioperative myocardial infarction vs. those without perioperative myocardial infarction after coronary artery bypass grafting according to various definitions. Major adverse cardiac events include all-cause death, spontaneous myocardial infarction, or repeat revascularization. Hazard ratios and odds ratios were adjusted for the sex and age of patients. HR, hazard ratio; CI, confidence interval; OR, odds ratio; ARC, Academic Research Consortium; MACE, major adverse cardiac events; MI, myocardial infarction; SCAI, Society for Cardiovascular Angiography and Interventions; other abbreviations as in *Figure 1*.

The prognostic relevance for MACE of the 4UD (adjusted HR 5.53, 95% CI 3.88–7.88; $P < 0.001$) and the ARC definition (adjusted HR 5.67, 95% CI 3.92–8.20; $P < 0.001$) remained significant after adjustment for age and sex (*Figure 2*). Again, patients suffering from pMI according to the SCAI definition (adjusted HR 1.15, 95% CI 0.94–1.40; $P = 0.170$), or myocardial injury according to the ARC definition had no increased risk of MACE during follow-up (*Figure 2*). We further explored the effect of perioperative MACE on MACE during follow-up by performing an additional landmark analysis in which we truncated all MACE before Day 30, thereby excluding perioperative MACE. Similar results were obtained, consistent with the 4UD, and ARC definitions being of prognostic relevance for the prediction of future MACE (log-rank $P = 0.012$ and $P = 0.012$, respectively) (see Supplementary material online, *Figure S4*). Subsequently, recurrence of MACE events after having experienced a Type 5 myocardial infarction within 30 days after CABG was analysed. Eighty-two (2.9%) patients experienced perioperative MACE, 50 patients died perioperatively (64.1% of all perioperative MACE). Among the 32 MACE survivors, 8 patients had a recurrent MACE (25%).

Impact of perioperative myocardial infarction definitions on 30-day all-cause mortality and during the 5-year follow-up

Perioperative myocardial infarction according to the 4UD and ARC definitions of myocardial infarction was associated with higher all-cause mortality at 5 years (log-rank: 4UD: $P = 0.010$; ARC: $P = 0.009$) (*Figure 1*). No significant association was observed between pMI according to the SCAI definition and all-cause mortality. After adjustment for age and sex, the 4UD and ARC criteria remained strong independent predictors for all-cause mortality at 30 days [4UD: odds ratio (OR) 12.18; 95% CI 5.00–29.67; $P < 0.001$; ARC: OR 13.16; 95% CI 5.41–32.00; $P < 0.001$] and 5 years (4UD: HR 2.13; 95% CI 1.19–3.81; $P = 0.011$; ARC: HR 2.23; 95% CI 1.21–4.09; $P = 0.010$) (*Figure 2*).

Impact of electrocardiogram changes on 30-day all-cause mortality and during the 5-year follow-up

We investigated the possible reasons for the observed differences in outcomes depending on the definition used. In contrast to the

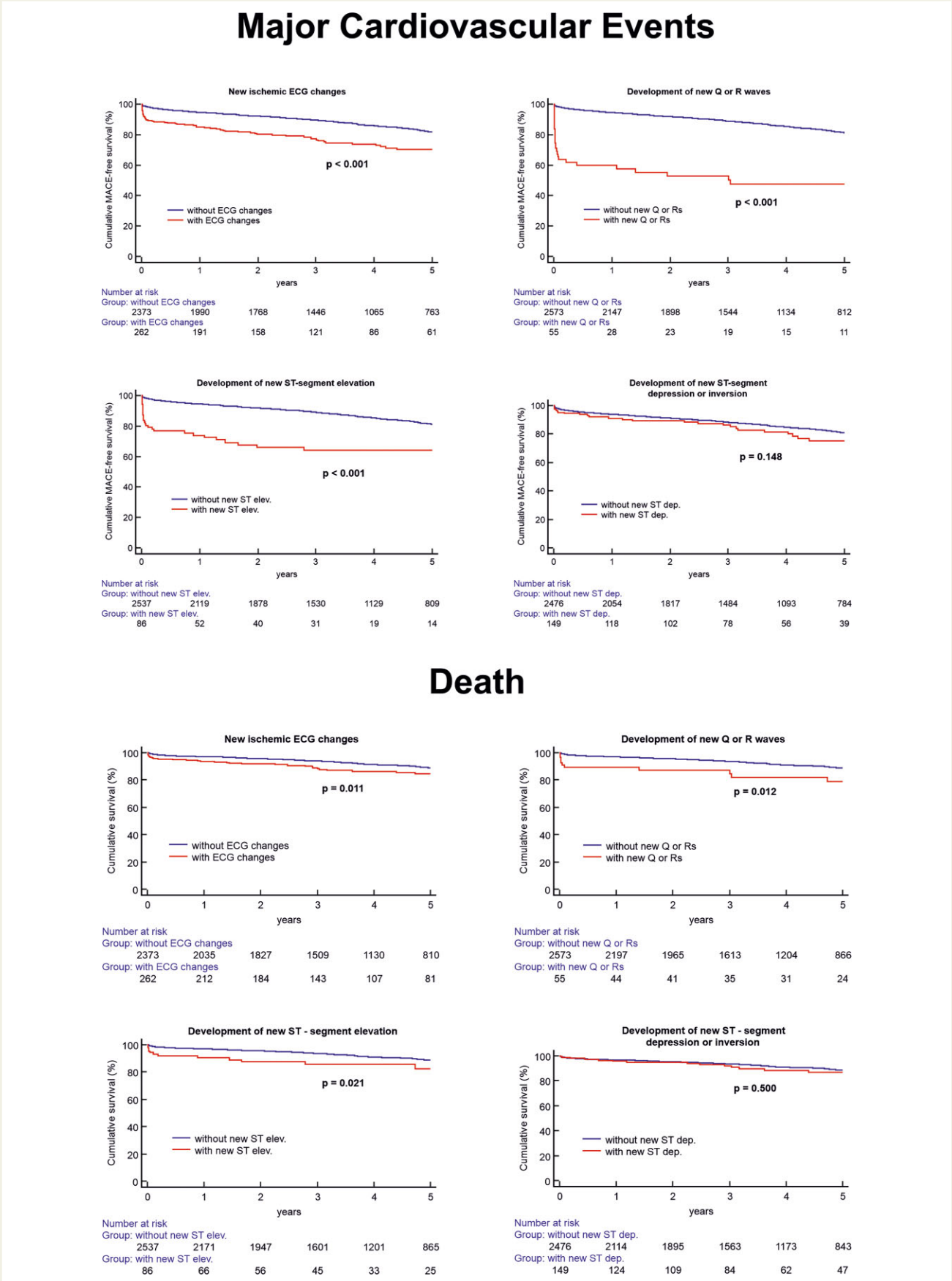
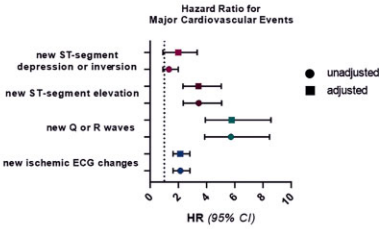


Figure 3 Kaplan–Meier curves for major adverse cardiac events and death according to perioperative electrocardiogram changes. Major adverse cardiac events include all-cause death, spontaneous myocardial infarction, or repeat revascularization. ECG, electrocardiogram; other abbreviations as in *Figure 1*.

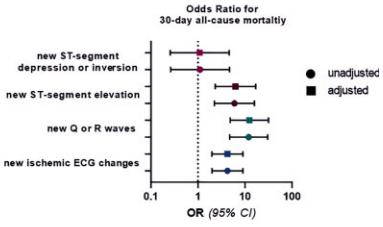
MACE

	new ischemic ECG changes	new Q or R waves	new ST-segment elevation	new ST-segment depression or inversion
n	262/2635 (9,9%)	55/2628 (2,1%)	86/2623 (3,3%)	149/2625 (5,7%)
MACE within 5 years	62 (23.7%)	27 (49.1%)	28 (32.6%)	26 (17.4%)
Hazard ratio (95% CI)				
unadjusted	2.145 (1.633-2.817)	5.726 (3.870-8.472)	3.448 (2.345-5.070)	1.340 (0.900-1.996)
p-value	< 0.001	< 0.001	< 0.001	0.150
adjusted	2.140 (1.630-2.810)	5.789 (3.911-8.569)	3.429 (2.329-5.047)	1.341 (0.900-1.997)
p-value	< 0.001	< 0.001	< 0.001	0.149



30-day all-cause mortality

	new ischemic ECG changes	new Q or R waves	new ST-segment elevation	new ST-segment depression or inversion
n	262/2635 (9,9%)	55/2628 (2,1%)	86/2623 (3,3%)	149/2625 (5,7%)
Patients died within 30 days	10 (3.8%)	6 (10.9%)	5 (5.8%)	2 (1.3%)
Odds ratio (95% CI)				
unadjusted	4.241 (1.986-9.056)	11.995 (4.725-30.451)	5.962 (2.232-15.921)	1.109 (0.263-4.687)
p-value	< 0.001	< 0.001	< 0.001	0.888
adjusted	4.222 (1.976-9.025)	12.416 (4.863-31.701)	6.280 (2.327-16.948)	1.088 (0.257-4.605)
p-value	< 0.001	< 0.001	< 0.001	0.909



5-year all-cause mortality

	new ischemic ECG changes	new Q or R waves	new ST-segment elevation	new ST-segment depression or inversion
n	262/2635 (9,9%)	55/2628 (2,1%)	86/2623 (3,3%)	149/2625 (5,7%)
Patients died within 5 years	29 (11.9%)	10 (18.2%)	12 (14.0%)	14 (9.4%)
Hazard ratio (95% CI)				
unadjusted	1.633 (1.117-2.387)	2.217 (1.176-4.183)	1.956 (1.093-3.500)	1.205 (0.701-2.070)
p-value	0.011	0.014	0.024	0.500
adjusted	1.620 (1.108-2.368)	2.116 (1.121-3.995)	1.858 (1.037-3.328)	1.222 (0.711-2.100)
p-value	0.013	0.021	0.037	0.468

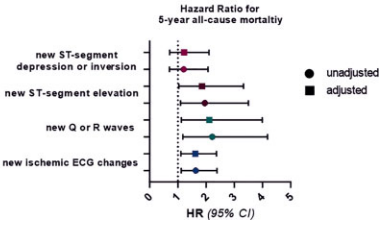


Figure 4 Impact of perioperative electrocardiogram changes on major adverse cardiac events and death expressed as hazard ratios/odds ratios. Hazard ratios and odds ratios for patients with electrocardiogram changes relative to those without electrocardiogram changes after coronary artery bypass grafting. Major adverse cardiac events include all-cause death, spontaneous myocardial infarction, or repeat revascularization. Hazard ratios and odds ratios were adjusted for the sex and age of patients. Abbreviations as in *Figures 2 and 3*.

enzyme-based SCAI and ARC definitions of myocardial injury, the 4UD and the ARC definitions of myocardial infarction include additional criteria, such as ischaemic ECG abnormalities, angiographic findings, or new RWMA for the diagnosis of pMI. However, our data revealed newly occurring RWMA in 30 (1.1%) patients and angiographic findings of native coronary or bypass graft obstruction in only nine (0.3%) patients. In 262 (9.9%) patients, we observed newly occurring ECG changes characteristic of ischaemia, including new Q-waves, missing R-wave progression, or ST-segment depression or inversion within the first 48 h after surgery. We, therefore, hypothesized that the ischaemic ECG changes may be the decisive factor. We observed an increase in the frequency of MACE in patients with one of the above-mentioned signs of ischaemia on ECG (all $P < 0.001$) (*Figure 3*). After adjustment for age and sex, ST-segment elevation remained an independent predictor for MACE (HR 3.43; 95% CI 2.33–5.05; $P < 0.001$). Similar results were obtained for patients with new Q or R waves with a HR of 5.79 (95% CI 3.91–8.57; $P < 0.001$) (*Figure 4*).

Impact of electrocardiogram changes on 30-day and 5-year all-cause mortality

New occurrences of Q or R waves or ST-segment elevations were associated with higher all-cause mortality 5 years after CABG (log-rank: Q or R: $P = 0.012$; ST-segment elevation: $P = 0.021$) (*Figure 3*). Moreover, the presence of any ischaemic ECG change was also associated with an increase in mortality at 5 years (log-rank: $P = 0.011$). Similarly, there was a higher risk of death at 30 days (new Q or R waves: OR 12.42; 95% CI 4.86–31.70; $P < 0.001$; ST-segment elevation: OR 6.28; 95% CI 2.33–16.95; $P < 0.001$) and 5 years (new Q or R waves: HR 2.12; 95% CI 1.12–4.00; $P = 0.021$; ST-segment elevation: HR 1.86; 95% CI 1.04–3.33; $P = 0.037$) (*Figure 4*).

Confirmation of results in a common patient population excluding all missing patient data

Perioperative myocardial infarction definitions were applicable for a different number of patients depending on the underlying

definition. To exclude the risk of confounding, we defined a common patient population ($n = 2572$) excluding all missing data in which all definitions were applicable. Our results were consistent in this population. Patients with a pMI according to the 4UD or ARC myocardial infarction had a higher incidence of MACE within 5 years (both log-rank: $P < 0.001$), whereas this was not the case for patients with pMI according to SCAI or ARC myocardial injury ($P = 0.463$ and 0.850) (see Supplementary material online, *Figure S5*). We observed higher HR for MACE after adjustment for sex and age in patients with a pMI according to the 4UD (adjusted HR 5.53, 95% CI 3.88–7.88; $P < 0.001$) or ARC myocardial infarction (adjusted HR 5.55, 95% CI 3.82–8.07; $P < 0.001$), whereas HR was not increased for patients with pMI according to SCAI or ARC myocardial injury ($P = 0.442$ and 0.813) (see Supplementary material online, *Figure S6*). Perioperative myocardial infarction according to the 4UD and ARC definitions of myocardial infarction was associated with higher all-cause mortality at 5 years (log-rank: 4UD: $P = 0.010$; ARC: $P = 0.007$) (see Supplementary material online, *Figure S5*). No significant association was observed between pMI according to the SCAI definition and all-cause mortality (see Supplementary material online, *Figure S5*). After adjustment for age and sex, the 4UD and ARC criteria remained strong independent predictors for all-cause mortality at 30 days (4UD: OR 12.18; 95% CI 5.00–29.67; $P < 0.001$; ARC: OR 13.98; 95% CI 5.72–34.21; $P < 0.001$) and 5 years (4UD: HR 2.13; 95% CI 1.19–3.81; $P = 0.011$; ARC: HR 2.29; 95% CI 1.25–4.20; $P = 0.008$) (see Supplementary material online, *Figure S6*).

Discussion

The present study investigated the impact of pMI after CABG using different available pMI definitions on long-term MACE occurrence and survival in a 'real-world' patient population. The key findings of this study were that (i) there was a significant difference in the occurrence of pMI depending on the underlying definition; (ii) pMI according to SCAI had no impact on the occurrence of MACE, whereas pMI according to 4UD or ARC was associated with a higher incidence of MACE within 5 years; (iii) pMI according to SCAI had no impact on survival, whereas pMI according to 4UD or ARC was associated with impaired survival; (iv) the occurrence of pMI according to 4UD or ARC increased the probability for MACE or death; and (v) the occurrence of signs of ischaemia on ECG was predictive of MACE and death (*Structured Graphical Abstract*).

These data indicate that the definition of pMI after CABG has a major impact on its incidence and patient prognosis. Isolated biomarker release might not be feasible to detect prognostically relevant pMI after surgery.

There is evidence for an effect of pMI after PCI (Type 4), but long-term results for Type 5 myocardial infarction (after CABG) remain scarce.[7] The true frequency of pMI remains unknown. Perioperative imaging studies have revealed late gadolinium enhancement indicating myocardial injury in 36% of patients undergoing on-pump CABG surgery and 44% of those undergoing off-pump CABG surgery.[10] A similar study found magnetic resonance imaging evidence for procedure-related ischaemia after CABG in 32% of patients.[11] Moreover, these changes were associated with adverse clinical outcomes.

The definition of Type 5 myocardial infarction remains a matter of debate. Myocardial injury during surgery due to surgical manipulation or cardioplegia causes a release of cardiac enzymes; it, therefore, remains challenging to diagnose pMI.[12] However, the correct detection of pMI is of considerable importance, given its major impact on the prognosis of affected patients. Moreover, pMI is part of the combined endpoint of most studies comparing PCI with CABG, including the EXCEL, FREEDOM, and SYNTAX studies.[5,9,13] The definition used affects the interpretation of these large trials, shaping the future of coronary revascularization. The EXCEL trial showed no difference between CABG and PCI for patients with left main coronary disease. However, this study was heavily criticized for its enzyme-based definition of pMI, as it penalizes surgery and accounts for the non-inferiority of PCI in the composite endpoint.[14] The authors published a correction using different definitions in the EXCEL trial. They found that pMI rates differed significantly according to the definition used.[15] The universal definition was associated with mortality after CABG but not after PCI, whereas HRs were similar between the two modalities according to the EXCEL definition.[8] This and other *post hoc* analyses of the EXCEL and SYNTAX trials have demonstrated that the frequency of pMI recorded depends on the definition used for this condition.[16] Our results further support these findings and additionally emphasize the importance of ischaemia correlates on ECG or echocardiography. Those two factors should be taken into consideration in designing and interpreting future randomized clinical trials comparing PCI vs. CABG.

It remains unclear why patients with pMI as defined by the ARC or 4UD criteria have a higher frequency of MACE and higher mortality. It is possible that patients with pMI undergo incomplete revascularization—a known risk factor for death after CABG—and therefore have a poorer prognosis.[17] Alternatively, heart failure may develop after pMI, thereby impairing prognosis. Another possibility is that patients with pMI may simply have a more malignant form of CAD and, therefore, poorer survival. However, this question needs to be addressed in future trials to elucidate the underlying mechanism of the observed phenomenon.

In contrast to the enzyme-based SCAI and ARC definitions of myocardial injury, the 4UD and ARC definitions of myocardial infarction include additional criteria, such as ischaemic ECG changes, angiographic findings, or new RWMA for the diagnosis of pMI. Thus, the specificity of an enzyme-based diagnostic scheme may be sufficient to detect pMI after CABG if used with appropriate cut-off values.[18] However, the optimal cut-off values remain a matter of debate, as the values currently used may be too low.[19,20] The use of higher cut-off values with higher ULNs changes the recorded incidence and prognosis of pMI markedly, as shown in a recent study.[21]

The ARC and 4UD definitions are, thus, similar, as reflected by our results, showing that both definitions are of prognostic significance, unlike definitions based on biomarkers alone. In everyday clinical practice, surgeons and cardiologists need to be aware of clinical criteria after CABG rather than relying exclusively on biomarkers. However, the specificity and prognostic relevance of the ARC and 4UD definitions might come at the expense of

sensitivity, which is clearly higher for biomarker-only definitions. The ideal definition, providing optimal sensitivity, and specificity and with prognostic relevance for pMI has probably yet to be found.

The data for 90.9% of the patients could be analysed with the 4UD, 97.7% with the SCAI definition, and 91.4% with the ARC criteria. Thus, applicability of the definitions differs markedly in a real-world setting.

A recent ESC position paper proposed differentiation between 'minor' and 'major' pMI after PCI. If cTn levels increase above a cut-off of >5× the 99th percentile of the URL with additional angiographic, imaging, or ECG evidence of ischaemia, the injury is considered 'major', whereas isolated biomarker release is considered a 'minor' injury. The presence of a 'major' injury is associated with a higher mortality, whereas 'minor' injuries have a good prognosis.[22]

This phenomenon may even be more pronounced after CABG surgery. Isolated biomarker increases may be related to the procedure or a 'minor' myocardial injury with no impact on patient prognosis. However, additional evidence of ischaemia, including signs of ischaemia on ECG or other types of imaging, might indicate a 'major' and prognostically relevant injury potentially requiring rapid action to solve the underlying problem. According to our data, myocardial injury has no impact on MACE or survival after CABG within our observation period. Myocardial injury occurring during CABG may be masked, and it remains unclear whether such injury can be reliably detected after CABG.

We found newly occurring ECG changes characteristic of ischaemia in 9.9% of patients, including new Q or R waves, and ST-segment depression or inversion within the first 48 h after surgery. Signs of ischaemia on ECG were associated with increases in event rates and survival. Electrocardiogram changes are sometimes seen as 'old-fashioned' and are not always popular among surgeons, but they remain a very valuable tool for identifying prognostically relevant perioperative ischaemia. This finding is consistent with the observation that newly occurring Q-waves coupled with the release of cardiac enzymes are predictive of a complicated post-operative clinical course.[23]

Our findings have various clinical implications. First, patients should undergo close monitoring after CABG, including regular determinations of the biomarkers troponin and CK-MB. Moreover, 'old-fashioned' ECG should be performed routinely after CABG to ensure the detection of ischaemic changes sufficiently early for their effective management. Evidence of ischaemia on ECG or of other clinical signs of ischaemia may require rapid action and the initiation of angiography, with potential consequences for patient prognosis.

Limitations

This is a retrospective observational study with all limitations that are associated with it including confounding and bias. The release of cardiac enzymes is different in patients undergoing on-pump and off-pump surgery. Only one of our patients underwent off-pump surgery. Therefore, our study results are applicable for on-pump surgery and not generalizable to off-pump patients. Further studies are needed to address this specific bypass surgery population in detail. The pMI definitions were intended to provide estimates of patient prognosis. We, therefore, interpret these definitions as a composite parameter including several variables. The intention was simply to validate these definitions. We therefore deliberately refrained from adjusting HR, except for the unavoidable covariables (age and sex). Angiography and echocardiography were performed post-operatively only in cases of clinical suspicion. We report these ratios as a percentage of the total cohort. The alternative would have been to report the ratio of pathologic findings for patients upon clinical suspicion, which we believe would have been misleading. The pMI incidence values obtained are not directly comparable, as they were calculated for different subgroups, and formal comparisons are therefore not possible.

We provide evidence in a 'real-world' setting that the definition of pMI after CABG has a major impact on the calculated incidence and prognosis of patients. Isolated biomarker release is not a feasible means of detecting prognostically relevant pMI after surgery. The combined occurrence of increasing biomarker levels and additional signs of ischaemia, including changes in angiography, echocardiography, or ECG, should result in rapid action in daily clinical practice in the hope of improving the prognosis of affected patients.

Supplementary material

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

Conflict of interest: none declared.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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