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ORIGINAL ARTICLE

Prognostic Impact of Periprocedural Myocardial Infarction in Patients Undergoing Elective Percutaneous Coronary Interventions

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BACKGROUND: The magnitude of prognostically relevant myocardial injury after percutaneous coronary interventions remains poorly defined. The Society for Cardiovascular Angiography and Interventions (SCAI) proposed marked biomarker elevations to define periprocedural myocardial infarction (PMI). These consensus-based thresholds have not been validated in the era of high-sensitivity cardiac troponins. We sought to assess the prognostic impact of SCAI-defined PMI and explore optimal prognostic thresholds of high-sensitivity cardiac troponin T (hs-cTnT) after elective percutaneous coronary interventions.

METHODS AND RESULTS: We evaluated patients who underwent elective percutaneous coronary interventions at 2 tertiary care centers with serial hs-cTnT measurements. PMI was defined as peak postprocedural hs-cTnT >70× upper reference limit (URL) in patients with nonelevated (≤1× URL) baseline levels; or incremental increase >70× URL in patients with elevated baseline levels. The primary outcome was 1-year all-cause mortality. Of 8140 patients, 220 (2.7%) died within 1 year. In multivariable analyses, patients with SCAI-defined PMI (n=140; 1.7%) had a higher risk of 1-year mortality (12.9% versus 2.5%, adjusted hazard ratio 4.10, 95% CI 2.51–6.68; *P*<0.001) as well as cardiac mortality (11.4% versus 2.1%, adjusted hazard ratio 4.21, 95% CI 2.50–7.11; *P*<0.001). Based on receiver operating characteristics analysis, the optimal prognostic threshold of hs-cTnT was >10×URL, observed in 14.6% of patients. This threshold showed lower specificity (85.7% versus 98.4%) but higher sensitivity (25.4% versus 8.2%) and better overall performance for prediction of 1-year mortality compared with the SCAI-defined cutoff value of troponin.

CONCLUSIONS: In patients undergoing elective percutaneous coronary interventions, SCAI-defined PMI emerged as an independent, highly specific, but insensitive predictor of 1-year mortality. Optimal trade-off between sensitivity and specificity was observed at a lower threshold of hs-cTnT (10× URL) in this cohort.

Key Words: coronary artery disease ■ myocardial infarction ■ prognosis ■ troponin

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WHAT IS KNOWN

- Myocardial injury occurs frequently after percutaneous coronary interventions, but the magnitude of prognostically relevant biomarker elevation (particularly in the era of high-sensitivity troponin assays) is not well established.
- The Society for Cardiovascular Angiography and Interventions proposed marked biomarker elevations to define periprocedural myocardial infarction; the consensus-based threshold for troponin elevation has not been validated.

WHAT THE STUDY ADDS

- In a large, contemporary population of patients undergoing elective percutaneous coronary intervention, periprocedural myocardial infarction defined by the Society for Cardiovascular Angiography and Interventions criteria (troponin elevation >70× upper reference limit) was an independent, highly specific, but insensitive predictor of mortality within 1 year.
- Using a highly sensitive cardiac troponin T assay, a substantially lower threshold (10× upper reference limit) emerged as the optimal prognostic cutoff value and led to a better combination of sensitivity and specificity compared with the cutoff value proposed by the Society for Cardiovascular Angiography and Interventions criteria.

Cardiac troponins (cTn) are the gold-standard biomarkers for the diagnosis of acute coronary syndromes. In clinical settings characterized by less extensive myocardial injury, cTn elevations have been associated with adverse clinical prognosis in apparently healthy individuals[1]; patients with chronic stable coronary artery disease (CAD)[2]; and patients undergoing coronary revascularization procedures.[3] In the context of percutaneous coronary interventions (PCI), the magnitude of postprocedural biomarker elevation reflecting clinically relevant myocardial damage remains controversial.[4] The Society for Cardiovascular Angiography and Interventions (SCAI) proposed a definition of periprocedural myocardial infarction (PMI)[5] which, compared with previous definitions,[6] entails substantially higher creatine kinase-myocardial band fraction (CK-MB) or cTn levels—presumably corresponding to myocardial injury large enough to have clinical consequences. The SCAI threshold of CK-MB elevation was based on previous evidence linking these levels to adverse post-PCI outcomes,[7] and the prognostic impact of this CK-MB-based definition was prospectively validated in subsequent investigations.[8,9] In contrast, because of scarce outcomes data with cTn, the cutoff value for cTn proposed by SCAI was consensus-based and driven by assumptions about bioequivalence between the 2 biomarkers.[5] Although cTn—in particular high-sensitivity cardiac troponin T (hs-cTnT)—has progressively replaced CK-MB in clinical practice, the prognostic value of the troponin-based definition of PMI according to SCAI remains poorly defined.

This study sought to assess the prognostic implications of the SCAI definition of PMI using hs-cTnT, and to explore optimal cutoff values of hs-cTnT for prediction of 1-year mortality in a large population of patients undergoing elective PCI. A secondary objective compared the prognostic performance of the SCAI definition of PMI based on hs-cTnT versus CK-MB.

METHODS

The data, analytic methods, and study materials cannot be made available to other researchers for purposes of reproducing the results or replicating the procedure, given constraints in broader sharing of the data.

Patient Population

This study included patients who underwent elective PCI at 2 institutions: Deutsches Herzzentrum München, Munich, Germany (between October 2009 and January 2015) and Bern University Hospital, Bern, Switzerland[10] (between September 2010 and June 2014). The indication for PCI, performed in de novo lesions or in-stent restenosis within native vessels or bypass grafts, was symptomatic stable CAD or silent ischemia on functional testing. We excluded patients with acute coronary syndromes (STEMI or nonST-elevation acute coronary syndromes); undetermined clinical diagnosis; and those in whom serial (preprocedural and postprocedural) hs-cTnT measurements were not available. Demographic and clinical characteristics, procedural information, in-hospital outcomes and 1-year follow-up data were systematically and prospectively collected. The study was approved by the institutional ethics committees and all patients provided written informed consent for prospective follow-up.

Procedures

PCI was performed in accordance with current practice guidelines.[11] Unfractionated heparin or bivalirudin was administered during the procedure. The periprocedural use of glycoprotein IIb/IIIa inhibitors was left to the discretion of the operator. Dual antiplatelet therapy consisting of aspirin and a $P2Y_{12}$ inhibitor (typically clopidogrel) was initiated before, at the time, or immediately after the procedure. Aspirin was continued indefinitely, and dual antiplatelet therapy duration was typically 12 months (at least 1 month after bare-metal stent implantation and at least 6 months after drug-eluting stent implantation). Other cardiac medications were left at the discretion of treating physicians.

Biochemical Analyses

Levels of hs-cTnT were determined at baseline (usually up to 6 hours before the index procedure), in at least 1 sample within 6 hours after PCI, and on a daily basis thereafter during the hospital stay (usually 48 hours). In case of an increase

in postprocedural hs-cTnT or if clinically indicated (eg, in the presence of new ischemic symptoms or ECG changes), repetitive measurements were obtained to assess peak post-PCI levels. At both institutions, hs-cTnT was measured using the same automated analyzer (cobas e 411 immunoanalyzer using fourth-generation Elecsys troponin T assay; Roche Diagnostics, Mannheim, Germany). This highly sensitive assay has a lower limit of detection of 3 ng/L and a 99th percentile reference limit of 14 ng/L in apparently healthy individuals.[12] Preprocedural and peak postprocedural hs-cTnT values were used for this analysis.

Patient Follow-Up

Patients were prospectively followed throughout 1 year. Follow-up was performed by telephone interview at 1 and 12 months after PCI. Survival data were obtained from hospital records, telephone contact with relatives, general practitioners, referring cardiologists, municipal civil registries, insurance companies, or the registration of address office as necessary. For patients who underwent subsequent treatment at other institutions, external medical records, discharge letters, and coronary angiography documentation were systematically collected and reviewed. Adjudication of events using original source documents was performed by medical personnel blinded to patient clinical or laboratory data.

Clinical End Points and Study Assessments

The primary outcome of this analysis was all-cause death within 1 year in patients with versus without PMI, defined according to the SCAI criteria of troponin elevation (ie, without accounting for ancillary criteria of myocardial ischemia). Cardiac mortality was defined according to Academic Research Consortium criteria as any death because of an immediate cardiac cause, procedure-related mortality, or death of unknown cause.[13] Major adverse cardiac events were defined as the composite of cardiac death or MI. PMI was defined according to cTn criteria (accounting for preprocedural as well as postprocedural levels)[5] as follows: (1) peak post-PCI hs-cTnT >70× URL in patients with nonelevated pre-PCI levels (≤1× URL); or (2) incremental increase in hs-cTnT >70× URL in patients with elevated pre-PCI levels (>1× URL). To explore whether a different threshold for hs-cTnT might perform better compared with the SCAI threshold for prediction of mortality, we assessed baseline-adjusted postprocedural levels of hs-cTnT for all patients in accordance with the SCAI algorithm, ie, peak post-PCI levels in patients with nonelevated pre-PCI levels or incremental increase of hs-cTnT in patients with elevated pre-PCI levels. To directly compare the prognostic performance of hs-cTnT versus CK-MB, a secondary analysis assessed the primary outcome in relation to SCAI-defined PMI based on hs-cTnT levels (≥70× URL) versus CK-MB levels (≥10× URL).[5]

Statistical Analyses

Statistical analyses were performed with Stata version 14.2 (Stata Corp, College Station, TX). Continuous variables are summarized as mean±SD or median with interquartile ranges, and categorical variables as actual numbers and percentages. Baseline and procedural characteristics were compared with *t* test, Kruskal-Wallis and Fisher exact test. Lesion-level variables were compared with mixed effects regression models adjusting for multiple lesions per patient. Predictors of SCAI-defined PMI were assessed using univariable and multivariable models including candidate predictors that were selected based on clinical importance. One-year clinical outcomes were analyzed with Cox proportional hazard models and Kaplan-Meier curves were constructed. We applied Cox regressions to mortality and cardiac mortality using baseline characteristics as predictors. Covariates showing significant ($P<0.05$) bivariate association with 1-year mortality were used in multivariate models. Adjustment was made for the following variables: preprocedural hs-cTnT; age; sex; diabetes mellitus; hypertension; body mass index; multivessel disease; glomerular filtration rate; left ventricular ejection fraction; balloon diameter; restenotic lesion; and pre-PCI TIMI flow. To define a prognostically optimal cutoff of hs-cTnT, the discriminating capacity of different levels of baseline-adjusted post-PCI hs-cTnT with respect to 1-year mortality was assessed by receiver operating characteristic curves (ROC) and quantified by areas under the curve. In an ancillary approach, the optimal prognostic cutoff value was identified applying the methodology of Contal and O'Quigley[14] implemented in R (R Foundation for Statistical Computing, Vienna, Austria) and the package survMisc. The latter method chooses the cut point that maximizes a rank-based statistic, thus resulting in the smallest *P* value, when comparing survival between 2 groups defined by the cut point, and corrects the *P* value for multiple tests.[13] For comparison of the predictive value of the hs-cTnT-based versus CK-MB-based SCAI cutoff of PMI, respective Cox models were compared using Harrell's c statistic.[15] A 2-sided $P<0.05$ was considered statistically significant.

RESULTS

Of 8729 consecutive patients who underwent elective PCI in the 2 institutions during the respective study periods, 8140 patients with available serial hs-cTnT measurements were included in this analysis (Figure I in the Data Supplement). Postprocedural levels of hs-cTnT are shown in Figure 1A and 1B. SCAI-defined PMI was observed in 140 patients (1.7%). Baseline (pre-PCI) levels of hs-cTnT were elevated (>1× URL) in 39.5% (n=3217) of all patients and in 49.3% (n=69) of patients with PMI (Figure 1C).

Baseline Characteristics

Baseline clinical characteristics for the main study population are summarized in Table 1, and are shown for patients with versus without serial hs-cTnT measurements in Table I in the Data Supplement. Patients with versus those without PMI had lower body mass index, lower left ventricular ejection fraction, more frequently had renal dysfunction, tended to be older and more commonly women, and had higher levels

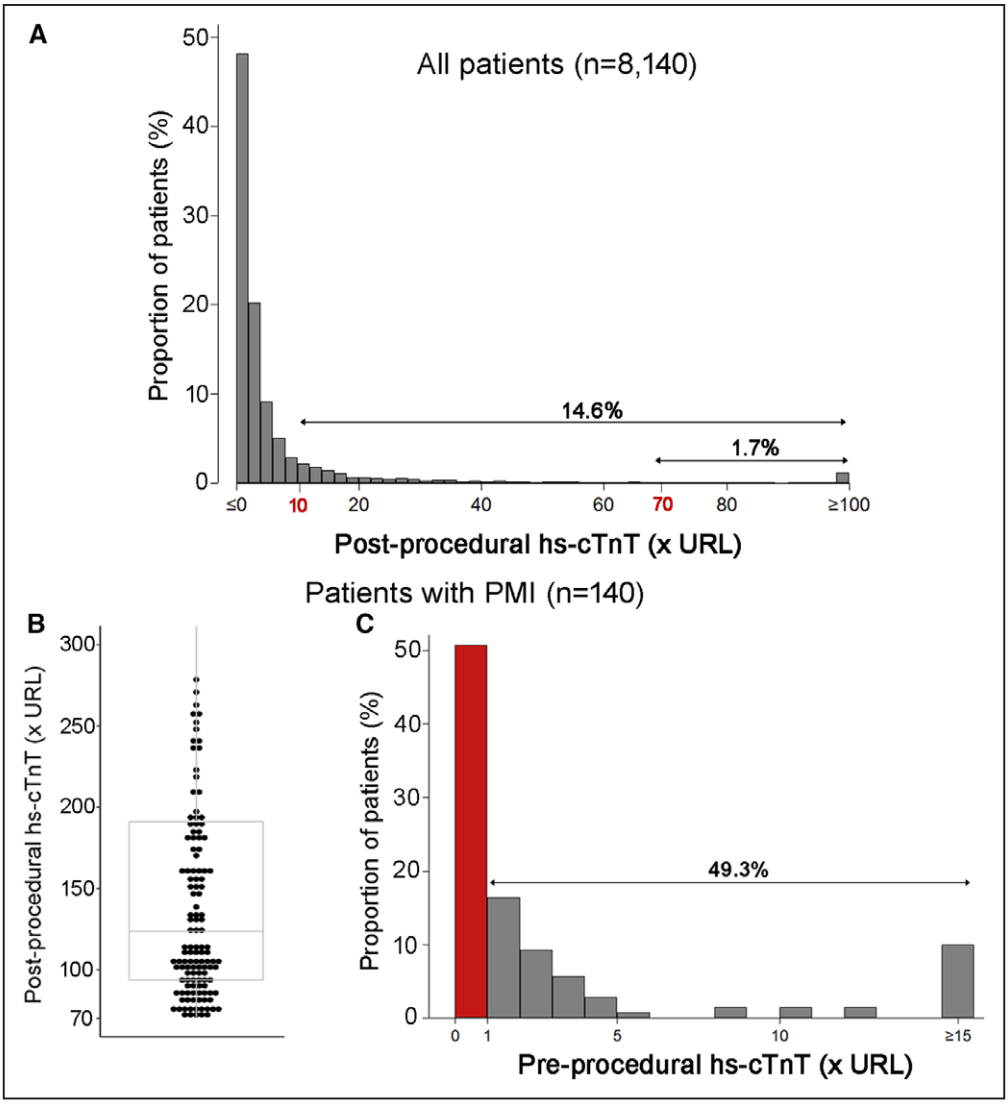

Figure 1. Distribution of preprocedural and postprocedural troponin.
A, Distribution of postprocedural high-sensitivity cardiac troponin T (hs-cTnT) in all patients (n=8 140). Postprocedural values shown are baseline-adjusted according to the Society for Cardiovascular Angiography and Interventions (SCAI) algorithm, ie, peak postprocedural in patients with nonelevated preprocedural levels (≤1× upper reference limit [URL]) and difference (peak postprocedural minus preprocedural hs-cTnT) in patients with elevated (>1× URL) preprocedural levels. **B**, Dot plot of postprocedural hs-cTnT levels in patients with SCAI-defined periprocedural myocardial infarction (PMI; n=140). Bars indicate median level with interquartile range. **C**, Distribution of preprocedural hs-cTnT in patients with SCAI-defined PMI (n=140).

of preprocedural hs-cTnT. Patients with PMI more frequently underwent treatment of multiple lesions, bifurcation or restenotic lesions, received longer stents, and had lower post-PCI TIMI flow (Table 2). Multivariable predictors of PMI included treatment of bifurcation lesion, higher baseline hs-cTnT, lower glomerular filtration rate, and greater total stented length (Table 3) (univariable predictors are detailed in Table II in the Data Supplement).

PMI and 1-Year Mortality

A total of 220 patients (2.7%) died within 1 year, including 182 (2.2%) cardiac deaths. The rate of major adverse cardiac events was 4.29%. Mortality was higher (6.4%) in patients without serial hs-cTnT measurements (*P*<0.001). Patients with compared with those without PMI had a higher risk of all-cause death (HR 5.68, 95% CI 3.51–9.20) and cardiac death (HR 6.12, 95% CI 3.67–10.23), also in landmark analyses between 7 days and 1 year (Table 4). In multivariable analyses, PMI remained a significant predictor of 1-year mortality (adjusted HR 4.10, 95% CI 2.51–6.68 for death; adjusted HR 4.21, 95% CI 2.50–7.11 for cardiac death; *P*<0.001 for both; Table 5; Table III in the Data Supplement). These results held true in a multivariable model that did not include baseline hs-cTnT (Table IV in the Data Supplement). Cumulative event curves in patients with or without PMI are shown in Figure 2; results including also patients without serial hs-cTnT measurements are summarized in Figure II in the Data Supplement. Kaplan-Meier curves for patients stratified by increments of postprocedural

Table 1. Baseline Patient Characteristics

Patient Characteristic	No PMI (n=8000)	PMI (n=140)	*P* Value
Age, y	70.5 (62.9; 76.7)	71.6 (64.2; 79.9)	0.09
Women	1880 (23.5)	42 (30.0)	0.09
BMI, kg/m^2	27.2 (24.7; 30.1)	25.6 (23.5; 29.4)	0.001
Diabetes mellitus	2406 (30.1)	35 (25.0)	0.23
Insulin-dependent diabetes	789 (9.9)	13 (9.3)	0.59
Arterial hypertension	6042 (75.6)	103 (73.6)	0.55
Smoking	1247 (15.6)	25 (17.9)	0.48
Hypercholesterolemia	6279 (78.6)	100 (71.4)	0.048
GFR, mL/min	83.7±34.4	71.7±33.9	<0.001
Renal dysfunction (GFR<60 mL/min)	2024 (25.6)	58 (41.7)	<0.001
LVEF (%)*	55.7±11.6	53.0±14.0	0.02
History of myocardial infarction	2281 (28.5)	39 (27.9)	0.92
History of CABG	1083 (13.54)	19 (13.6)	1.00
Preprocedural hs-cTnT, ng/L	10 (10; 20)	12 (10; 41)	0.004
Preprocedural hs-cTnT >1× URL, n (%)	3148 (39.35)	69 (49.29)	0.02

Values are mean±SD, median (25th to 75th percentile), or n (%). BMI indicates body mass index; CABG, coronary artery bypass graft; GFR, glomerular filtration rate; hs-cTnT, high-sensitivity cardiac troponin T; LVEF, left ventricular ejection fraction; PMI, periprocedural myocardial infarction (according to the troponin-based Society for Cardiovascular Angiography and Interventions [SCAI] definition); and URL, upper reference limit.

*Information available in 5979 patients without PMI and 99 patients with PMI.

Table 2. Procedural Characteristics

Variable	No PMI (n=8000)	PMI (n=140)	*P* Value
Patient-level characteristics			
Multivessel disease	5523 (69.0)	98 (70.0)	0.85
No. of lesions per patient	1.00 (1.00; 2.00)	2.00 (1.00; 3.00)	<0.001
>1 lesions treated	3526 (44.1)	83 (59.3)	<0.001
Bifurcation treatment (at least 1 lesion)	2441 (30.6)	59 (42.1)	0.004
No. of vessels treated			
1	6247 (78.1)	92 (65.7)	0.001
2	1555 (19.4)	37 (26.4)	0.04
≥3	198 (2.5)	11 (7.9)	0.001
Restenotic lesion treatment (at least 1 lesion)	1004 (12.5)	9 (6.4)	0.03
Balloon diameter (mm, max over lesions)	3.32±0.62	3.39±0.68	0.2
Lesion-level characteristics			
Number of lesions	13 132	283	
Intervened vessel			<0.001
Left main coronary artery	459 (3.5)	17 (6.0)	
Left anterior descending	5529 (42.1)	128 (45.2)	
Left circumflex	3090 (23.5)	71 (25.1)	
Right coronary artery	3742 (28.5)	56 (19.8)	
Bypass graft	311 (2.4)	11 (3.9)	
Stent type per lesion			0.49
Balloon angioplasty	334 (2.5)	9 (3.2)	
BMS	277 (2.1)	5 (1.8)	
BVS	405 (3.1)	4 (1.4)	
DES	12 110 (92.2)	265 (93.6)	
Chronic total occlusion	693 (5.3)	10 (3.5)	0.19
TIMI flow post-PCI			<0.001
0	24 (0.2)	5 (1.8)	
1	21 (0.2)	3 (1.1)	
2	163 (1.2)	13 (4.6)	
3	12 794 (98.4)	260 (92.5)	
Lesion length, mm	16.93±10.53	19.36±11.09	0.02
Total stented length, mm	26.25±13.80	30.83±15.02	<0.001

Values are mean±SD, median (25th to 75th percentile), or n (%). BMS indicates bare-metal stent; BVS, bioresorbable vascular scaffold; DES, drug-eluting stent; and PCI, percutaneous coronary intervention.

hs-cTnT are shown in Figure 3, indicating a marked increase in the risk of mortality at levels above the SCAI cutoff value (>70× URL).

One-year mortality was higher in patients with elevated (>1× URL) versus those with nonelevated (≤1× URL) baseline troponin (5.47% versus 0.89%, respectively; *P*<0.001). In a sensitivity analysis including only patients with nonelevated baseline troponin (n=4923), PMI was associated with a significantly higher rate of cardiac, but not all-cause mortality (Tables V and VI in the Data Supplement).

Optimal Predictive Threshold of Troponin

According to ROC analysis, a baseline-adjusted postprocedural hs-cTnT >10× URL was identified as the cutoff value with the best combination of sensitivity and specificity for prediction of all-cause death within 1 year. The optimal (10× URL) threshold, compared with the SCAI threshold (70× URL), had lower specificity (85.7% versus 98.4%) but higher sensitivity (25.4% versus 8.2%; Figure 4), and greater areas under the curve in ROC analysis (0.60 versus 0.56; *P*=0.04) for prediction of 1-year mortality. The positive predictive value for the optimal threshold versus the SCAI threshold was 4.7% versus 12.9%, and the negative predictive value was 9.8% versus 9.7%, respectively. Patients with hs-TnT >10× URL (n=1185; 14.6%) had a higher risk of 1-year mortality (adjusted HR 1.74, 95% CI 1.28–2.36) and cardiac mortality (adjusted HR 1.87, 95% CI 1.34–2.61) in multivariable analyses (Figure III in the Data Supplement). Compared with patients with postprocedural hs-cTnT <10× URL (ie, without PMI according to the optimal cut

Table 3. Multivariable Predictors of SCAI-Defined Periprocedural Myocardial Infarction

Variable	Odds Ratio (95% CI)	*P* Value
Treatment of bifurcation lesion	1.49 (1.06, 2.11)	0.02
Preprocedural hs-cTnT, ng/L	1.43 (1.16, 1.78)	0.001
Total stented length, per 10 mm	1.32 (1.22, 1.44)	<0.001
Glomerular filtration rate, per 20 mL/min	0.81 (0.72, 0.92)	0.001

SCAI indicates Society for Cardiovascular Angiography and Interventions.

point), the risk of 1-year mortality was higher in those with postprocedural hs-cTnT between 10× and 70× URL (HR 1.58, 95% CI 1.11–2.25; *P*=0.011) or >70× (HR 6.10, 95% CI 3.75–9.93; *P*<0.001; Figure IV in the Data Supplement). An ancillary analysis based on the methodology described by Contal and O'Quigley[14] identified a similar hs-cTnT level (8× URL) as the optimal cutoff value for prediction of 1-year mortality.

Sensitivity Analysis: PMI and Mortality in Patients Treated for Chronic Total Occlusions

A total of 639 patients were treated for at least 1 chronic total occlusion (CTO). The incidence of PMI was 1.56% (n=10) according to the SCAI cutoff of hs-cTnT versus 17.37% (n=111) according to the optimal cutoff (>10× URL). There were 9 fatal events in this subgroup; 1-year mortality was higher in patients with versus without PMI according to the SCAI definition (10% versus 1.27%, respectively; *P*=0.04) but not according to the optimal cutoff of hs-cTnT (2.70% versus 1.15% respectively; *P*=0.21; Tables VII and VIII in the Data Supplement).

Troponin Versus CK-MB for Prediction of Mortality

CK-MB measurements were available in 7732 patients (95% of all patients). Elevation of CK-MB above the respective SCAI sthreshold (>10× URL) was observed in 96 patients (1.24%). Patients with versus without CK-MB-defined PMI had a higher risk of mortality (adjusted HR 3.30, 95% CI 1.69–6.46) and cardiac mortality (adjusted HR 3.06, 95% CI 1.43–6.54). The c statistic from the models including the hs-cTnT-based SCAI definition (>70× URL) versus the CK-MB-based SCAI definition of PMI (>10× URL) did not differ significantly (*P*=0.28).

DISCUSSION

The main findings of this study can be summarized as follows. First, in a large, contemporary cohort of patients undergoing elective PCI by current standards, a small proportion (1.7%) of patients fulfilled the SCAI definition of PMI based on hs-cTnT. Second, SCAI-defined PMI emerged as an independent predictor of 1-year mortality, associated with 4-fold higher risk in multivariable analyses. Third, when accounting for the combination of sensitivity and specificity, a substantially lower cutoff value of hs-cTnT (10× URL) performed better than the SCAI threshold; this was because of relatively higher sensitivity that outweighed the lower specificity of the 10× URL threshold compared with the SCAI-defined (70× URL) troponin cutoff. Overall, PMI defined by either of these 2 troponin cutoffs (without ancillary clinical criteria) was a weak predictor of 1-year mortality because of a high rate of false-negative results. Fourth, the troponin-based and CK-MB-based definitions of PMI according to SCAI had comparable value for prediction of 1-year mortality.

PMI according to the troponin cutoff proposed by SCAI was observed in 1.7% patients in this analysis. Previous studies found a higher incidence of PMI, up to 5.5% using the CK-MB-based SCAI definition[8,9] or up to 13.3% using the second and third Universal Definition of MI (ie, based on lower biomarker thresholds and ancillary criteria of myocardial ischemia).[16,17] These findings indicate marked heterogeneity in the diagnosis of PCI-related MI, depending on the biomarker used and

Table 4. Clinical Outcomes Within 1 Year in Patients With Versus Without SCAI-Defined PMI

Outcome	All patients n=8140	No PMI n=8000	PMI n=140	HR (95% CI)	*P* Value
Up to 1 y					
Death	220 (2.70%)	202 (2.53%)	18 (12.86%)	5.68 (3.51–9.20)	<0.001
Cardiac death	182 (2.24%)	166 (2.08%)	16 (11.43%)	6.12 (3.67–10.23)	<0.001
MACE	349 (4.29%)	(3.26%)	(62.86%)	39.24 (30.70–50.15)	<0.001
7 days to 1 y					
Death	191/7580 (2.52%)	181/7454 (2.43%)	10/126 (7.94%)	3.58 (1.90–6.77)	<0.001
Cardiac death	155/7580 (2.04%)	147/7454 (1.97%)	8/126 (6.35%)	3.53 (1.73–7.19)	0.001
MACE	204/7467 (2.73%)	194/7409 (2.62%)	10/58 (17.24%)	8.23 (4.36–15.53)	<0.001

Depicted are first events (% from Kaplan-Meier estimate), hazard ratios (HRs; with 95% CI) from Cox's regression. MACE indicates major adverse cardiac events (defined as the composite of cardiac death or myocardial infarction); PMI, periprocedural myocardial infarction; and SCAI, Society for Cardiovascular Angiography and Interventions.

Table 5. Multivariable Predictors of 1-Year Mortality

Variable	Hazard Ratio (95% CI)	*P* Value
Mortality		
SCAI-defined PMI (based on hs-cTnT)	4.10 (2.51, 6.68)	<0.001
Preprocedural hs-cTnT	1.33 (1.15, 1.54)	<0.001
Age	1.05 (1.04, 1.08)	<0.001
Diabetes mellitus	1.49 (1.12, 1.99)	0.006
Arterial hypertension	0.50 (0.37, 0.66)	<0.001
Glomerular filtration rate	0.98 (0.97, 0.98)	<0.001
Cardiac mortality		
SCAI-defined PMI (based on hs-cTnT)	4.21 (2.50, 7.11)	<0.001
Preprocedural hs-cTnT	1.33 (1.15, 1.55)	<0.001
Age	1.05 (1.03, 1.07)	<0.001
Diabetes mellitus	1.42 (1.03, 1.95)	0.033
Arterial hypertension	0.41 (0.30, 0.56)	<0.001
Glomerular filtration rate	0.98 (0.97, 0.98)	<0.001

hs-cTnT indicates high-sensitivity cardiac troponin T; PMI, periprocedural myocardial infarction; and SCAI, Society for Cardiovascular Angiography and Interventions.

cutoff values applied, as well as the presence or absence of clinical signs or symptoms across various definitions.

The magnitude of clinically relevant myocardial injury after PCI has remained controversial. It has been postulated that over-diagnosis of PMI (on the basis of minor biomarker elevations) may lead to needless additional testing, prolongation of hospitalization, and increased treatment cost, whereas identification of a PMI large enough to affect prognosis might benefit these patients by prompting closer postprocedural surveillance or more intensive secondary-prevention treatment.[18] The SCAI expert consensus document advocated CK-MB as the preferred biomarker for diagnosis of PMI; the respective threshold was based on studies linking marked CK-MB elevation to subsequent adverse events.[7,19] This CK-MB threshold has been validated in subsequent investigations as a predictor of post-PCI outcomes.[8,9] In contrast, the cTn cutoff for diagnosis of PMI in the SCAI document was largely derived from indirect evidence of bioequivalence of the 2 biomarkers, based on magnetic resonance imaging studies.[20] Against this background, the present study focused on troponin—a biomarker that has progressively replaced CK-MB as the gold-standard biomarker of myocardial injury. Our observations are substantiated further by using a highly sensitive troponin assay that is capable of detecting with high precision minor cTn elevations.[21]

This study confirms that PMI based on the SCAI troponin cutoff independently predicted 1-year mortality. However, the SCAI threshold of clinically relevant

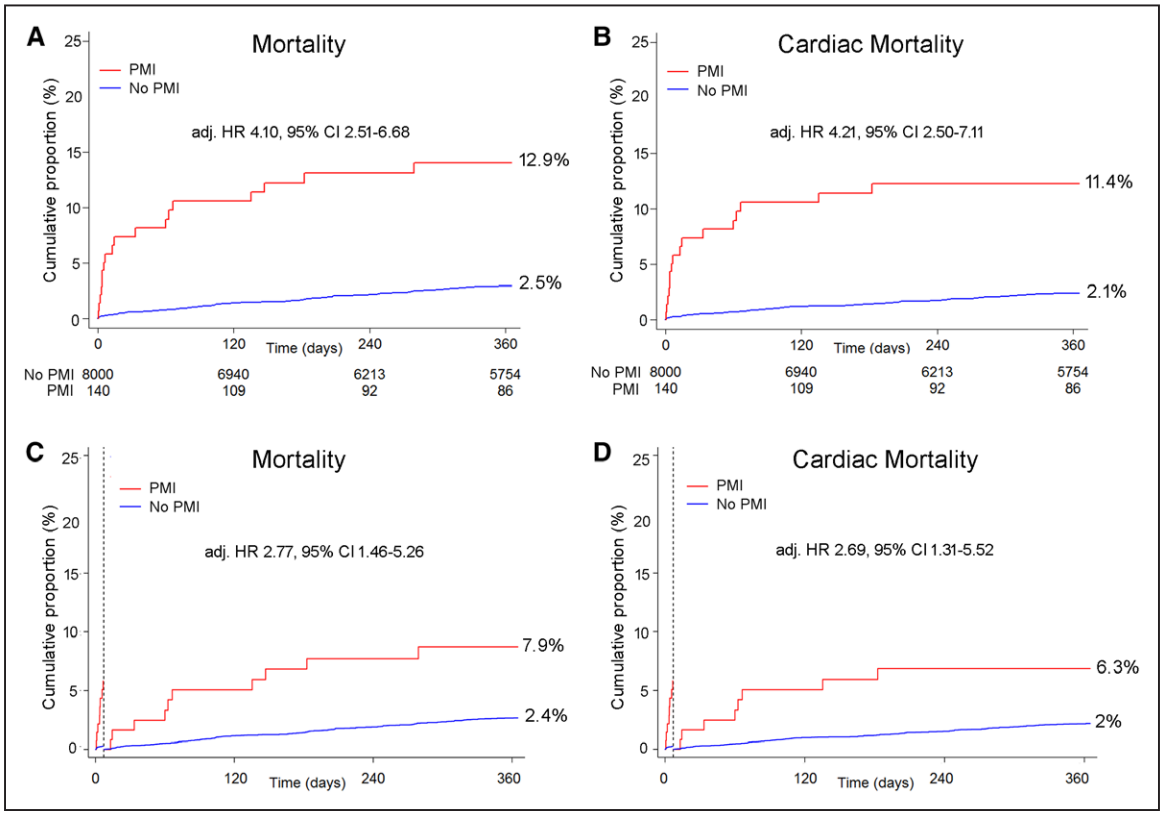

Figure 2. Kaplan-Meier curves for all-cause mortality and cardiac mortality in patients with or without Society for Cardiovascular Angiography and Interventions (SCAI)-defined periprocedural myocardial infarction.
A and **B**, Analyses up to 1 y. **C** and **D**, Respective landmark analyses at 7 d.

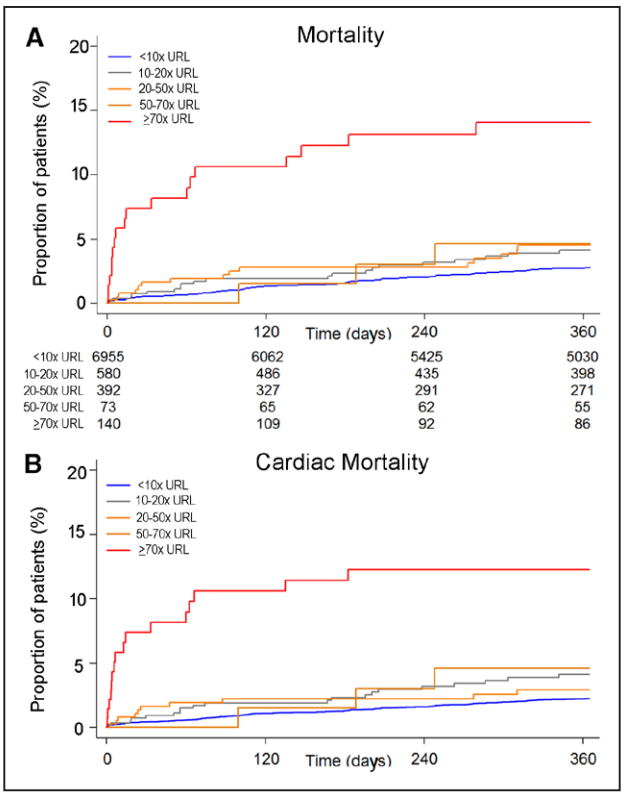

Figure 3. Kaplan-Meier curves for 1-y all-cause mortality and cardiac mortality in patients stratified by increments of postprocedural hs-cTnT levels (multiples of the upper reference limit [URL]).
A and **B**, Postprocedural values shown are baseline-adjusted according to the Society for Cardiovascular Angiography and Interventions (SCAI) algorithm, ie, peak postprocedural in patients with nonelevated preprocedural levels (≤1× URL) and difference (peak postprocedural minus preprocedural hs-cTnT) in patients with elevated (>1× URL) preprocedural levels.

troponin elevation did not emerge as the optimal threshold in our analysis addressing 2 partly competing measures of the biomarker's discriminating ability, that is, sensitivity (the probability of detecting at-risk patients, thus minimizing false negative results) and specificity (minimizing false positive outcomes). As with all biomarkers, the high troponin cutoff proposed by SCAI was highly specific (higher positive predictive value) but had low sensitivity in this study and identified only 8% of patients who died within 1 year. Accordingly, the presence, rather than absence of SCAI-defined PMI appears to be prognostically more relevant, as patients with PMI had 4-fold higher likelihood to die within 1 year. Based on ROC analysis (notably, also supported by an ancillary statistical approach[14]), optimal combination of sensitivity and specificity was observed at a lower hs-cTnT cutoff (>10× URL)—a criterion met 9× more commonly than the SCAI cutoff. This finding is more along the lines of an earlier investigation by Herrmann et al,[22] which identified a prognostically optimal threshold of 25× URL for post-PCI cTn rise (ie, a value in between the Universal Definition of MI[6] and SCAI[5] criteria). The latter study was limited by a small number of events (n=20) confined to a 3-month follow-up period; it included patients with stable CAD as well as recent acute coronary syndromes; and used earlier, less sensitive troponin assays.[22] A recent study by Zeitouni et al[17] in 1390 elective PCI patients found a higher rate of 1-year cardiovascular events in patients with PMI according to the Universal Definition of MI criteria, that is, hs-cTnT rise above 5× URL and additional clinical evidence of myocardial ischemia.

Taken together, while post-PCI troponin elevation above the SCAI threshold of cTn was associated with adverse prognosis, a lower magnitude of hs-cTnT elevation (10× URL) emerged as an overall more accurate prognostic marker that led to a better trade-off in terms of ruling-in versus ruling-out of patients who subsequently died. In view of highly heterogeneous existing definitions of PMI,[5,6] a widely accepted definition would facilitate identification of patients with clinically significant myocardial damage and enable consistency across clinical studies. Against this background, our findings indicate that coupling diagnosis of PMI with subsequent prognosis[18] (a concept introduced in the SCAI document[5]) may be achieved at a lower magnitude of postprocedural troponin elevation than proposed in the SCAI definition. Collectively, it should be noted that, according to ROC analysis: (1) the optimal cutoff only marginally outperformed the SCAI cutoff value of troponin; and (2) cTnT elevation as a standalone criterion of PMI (ie, without ancillary signs of ischemia) emerged as a particularly weak predictor of 1-year mortality at any cutoff level, as suggested by the low area under the curve values.

Myocardial injury occurs frequently in the complex setting of PCI in CTO lesions. We found that troponin elevation above the SCAI cutoff, but not above the cutoff >10× URL, was associated with higher 1-year mortality. These observations require cautious interpretation, considering the small numbers of events in this subgroups analysis. Our findings are along the lines of a dedicated analysis by Lee et al[8] showing that only marked elevation of CK-MB (as in the SCAI definition) predicted mortality in 1058 patients with CTO. Our results also align with a study by Dautov et al[23] indicating that modest troponin elevation (>5× URL) did not predict major adverse cardiac events within a 1.2-year follow-up in 469 patients treated for CTO.

Previous studies have indicated greater prognostic value of preprocedural compared with postprocedural biomarker elevation.[24] In this analysis, we found that SCAI-defined PMI was not associated with significant increase in all-cause mortality in the context of nonelevated preprocedural troponin levels. Ndrepepa et al[25] recently showed that hs-cTnT measured post-PCI does not offer incremental prognostic information beyond that provided by the baseline level for prediction of 3-year mortality. Against this background, it is important to note that that (1) the SCAI definition of PMI,

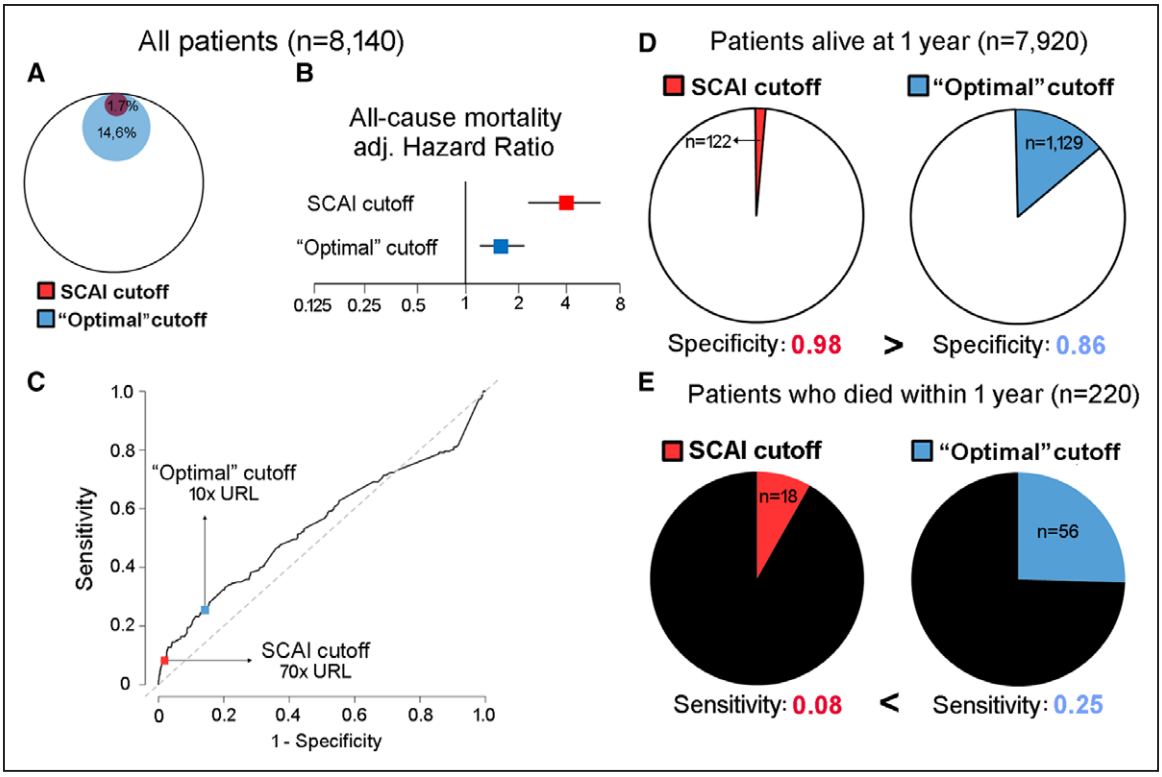

Figure 4. Incidence and prognostic relevance of periprocedural myocardial infarction (PMI) according to the Society for Cardiovascular Angiography and Interventions (SCAI) versus the optimal prognostic threshold.

A, Venn diagram showing the incidence of periprocedural myocardial infarction (PMI) according to the Society for Cardiovascular Angiography and Interventions (SCAI) threshold (hs-cTnT >70× upper reference limit [URL]; 1.7%) versus the optimal prognostic threshold (>10× URL; 14.6%). **B**, Adjusted hazard ratio for all-cause mortality in patients with PMI according to the SCAI threshold vs the optimal threshold. **C**, ROC analysis of hs-cTnT elevation for prediction of 1-y mortality; the SCAI threshold (red) and the optimal threshold (blue) are indicated on the curve. Specificity is higher for the SCAI threshold (**D**), whereas sensitivity is higher for the optimal threshold of hs-cTnT (**E**).

applied in the present study, accounts for both pre- and postprocedural cTn levels[5]; and (2) baseline levels were elevated in 40% of all patients and in half of patients with PMI. Collectively, because of conclusive previous evidence,[25] the primary aim of this analysis was not to compare the relative prognostic impact of baseline versus post-PCI troponin levels; rather, we tested the prognostic performance of a PMI definition[5] incorporating both pre- and post-PCI measurements.

This study is the first to directly compare the hs-troponin-based versus CK-MB-based definitions of PMI with respect to subsequent outcomes. We found that the 2 biomarkers, at the cutoff values proposed by SCAI, confer comparable prognostic information about 1-year mortality. In view of the prevailing use of troponins over CK-MB in clinical practice,[21] this finding supports the bioequivalence assumptions in the SCAI consensus document.[5] While the CK-MB-based PMI definition has been assessed after PCI for CTOs[8] or multivessel CAD[9] (ie, clinical conditions which per se may affect the magnitude and clinical sequelae of biomarker release), the present study analyzed a broadly inclusive population undergoing interventions across a wide spectrum of CAD, ranging from simple, single lesions to complex, multivessel treatment.

This observational study has several limitations. First, while clinical outcomes were collected prospectively, this is a retrospective analysis reflecting the experience of 2 large-volume centers. Second, clinical or ECG signs of myocardial ischemia were not consistently available in this pooled dataset; therefore, similar to previous studies assessing the prognostic relevance of cardiac biomarker elevation,[9,19,22] we explored the SCAI definition of PMI that only considers biomarker elevations without ancillary criteria. Third, this study cannot elucidate mechanisms responsible for cTn elevation and for its association with subsequent outcomes, in particular delayed mortality (ie, beyond the first days following the procedure). Fourth, although we performed extensive adjustments, unmeasured confounders affecting cTn elevation as well as clinical outcomes cannot be excluded. The optimal prognostic cut point for troponin identified in this analysis should be further validated in future studies. Measurements of cTn were performed in accordance with common clinical practice in our centers and the exact timing of blood sampling following PCI was not recorded; similar to previous reports,[8,9,25] we cannot exclude the possibility that peak postprocedural values may have been missed in a number of patients. Finally, because this cohort included only few

patients without serial troponin measurements who had a less favorable risk-factor profile (Table I in the Data Supplement) and higher 1-year mortality, this study cannot address the question whether measuring myocardial biomarkers routinely offers incremental prognostic value compared with a more conservative approach of assessing PMI only if deemed clinically indicated.

CONCLUSIONS

In a large, contemporary population of patients undergoing elective PCI, SCAI-defined PMI was an independent predictor of 1-year mortality. The SCAI cutoff value of hs-cTnT (>70× URL) was associated with 4-fold increase in mortality risk and emerged as a highly specific but insensitive prognostic marker. If optimal trade-off between sensitivity and specificity for prediction of mid-term survival is sought, then a substantially lower, less restrictive threshold of hs-cTnT (10× URL) should be considered.

ARTICLE INFORMATION

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REFERENCES

1. Everett BM, Zeller T, Glynn RJ, Ridker PM, Blankenberg S. High-sensitivity cardiac troponin I and B-type natriuretic peptide as predictors of vascular events in primary prevention: impact of statin therapy. *Circulation*. 2015;131:1851–1860. doi: 10.1161/CIRCULATIONAHA.114.014522
2. Omland T, de Lemos JA, Sabatine MS, Christophi CA, Rice MM, Jablonski KA, Tjora S, Domanski MJ, Gersh BJ, Rouleau JL, Pfeffer MA, Braunwald E; Prevention of Events with Angiotensin Converting Enzyme Inhibition (PEACE) Trial Investigators. A sensitive cardiac troponin T assay in stable coronary artery disease. *N Engl J Med*. 2009;361:2538–2547. doi: 10.1056/NEJMoa0805299
3. Prasad A, Singh M, Lerman A, Lennon RJ, Holmes DR Jr, Rihal CS. Isolated elevation in troponin T after percutaneous coronary intervention is associated with higher long-term mortality. *J Am Coll Cardiol*. 2006;48:1765–1770. doi: 10.1016/j.jacc.2006.04.102
4. White HD. Torrent of troponin. *Circ Cardiovasc Interv*. 2014;7:435–438. doi: 10.1161/CIRCINTERVENTIONS.114.001751
5. Moussa ID, Klein LW, Shah B, Mehran R, Mack MJ, Brilakis ES, Reilly JP, Zoghbi G, Holper E, Stone GW. Consideration of a new definition of clinically relevant myocardial infarction after coronary revascularization: an expert consensus document from the Society for Cardiovascular Angiography and Interventions (SCAI). *J Am Coll Cardiol*. 2013;62:1563–1570. doi: 10.1016/j.jacc.2013.08.720
6. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, Thygesen K, Alpert JS, White HD, Jaffe AS, Katus HA, Apple FS, Lindahl B, Morrow DA, Chaitman BR, Clemmensen PM, Johanson P, Hod H, Underwood R, Bax JJ, Bonow JJ, Pinto F, Gibbons RJ, Fox KA, Atar D, Newby LK, Galvani M, Hamm CW, Uretsky BF, Steg PG, Wijns W, Bassand JP, Menasche P, Ravkilde J, Ohman EM, Antman EM, Wallentin LC, Armstrong PW, Simoons ML, Januzzi JL, Nieminen MS, Gheorghiade M, Filippatos G, Luepker RV, Fortmann SP, Rosamond WD, Levy D, Wood D, Smith SC, Hu D, Lopez-Sendon JL, Robertson RM, Weaver D, Tendera M, Bove AA, Parkhomenko AN, Vasilieva EJ, Mendis S, Bax JJ, Baumgartner H, Ceconi C, Dean V, Deaton C, Fagard R, Funck-Brentano C, Hasdai D, Hoes A, Kirchhof P, Knuuti J, Kolh P, McDonagh T, Moulin C, Popescu BA, Reiner Z, Sechtem U, Sirnes PA, Tendera M, Torbicki A, Vahanian A, Windecker S, Morais J, Aguiar C, Almahmeed W, Arnar DO, Barili F, Bloch KD, Bolger AF, Botker HE, Bozkurt B, Bugiardini R, Cannon C, de Lemos J, Eberli FR, Escobar E, Hlatky M, James S, Kern KB, Moliterno DJ, Mueller C, Neskovic AN, Pieske BM, Schulman SP, Storey RF, Taubert KA, Vranckx P, Wagner DR; Joint ESC/ACCF/AHA/WHF Task Force for Universal Definition of Myocardial Infarction; Authors/Task Force Members Chairpersons; Biomarker Subcommittee; ECG Subcommittee; Imaging Subcommittee; Classification Subcommittee; Intervention Subcommittee; Trials & Registries Subcommittee; Trials & Registries Subcommittee; Trials & Registries Subcommittee; Trials & Registries Subcommittee; ESC Committee for Practice Guidelines (CPG); Document Reviewers. Third universal definition of myocardial infarction. *J Am Coll Cardiol*. 2012;60:1581–1598. doi: 10.1016/j.jacc.2012.08.001
7. Ioannidis JP, Karvouni E, Katritsis DG. Mortality risk conferred by small elevations of creatine kinase-MB isoenzyme after percutaneous coronary intervention. *J Am Coll Cardiol*. 2003;42:1406–1411.
8. Lee SW, Lee PH, Kang SH, Choi H, Chang M, Roh JH, Yoon SH, Ahn JM, Park DW, Kang SJ, Kim YH, Lee CW, Park SW, Park SJ. Determinants and prognostic significance of periprocedural myocardial injury in patients with successful percutaneous chronic total occlusion interventions. *JACC Cardiovasc Interv*. 2016;9:2220–2228. doi: 10.1016/j.jcin.2016.08.005
9. Cho MS, Ahn J-M, Lee C-H, Kang DY, Lee JB, Lee PH, Kang SJ, Lee SW, Kim YH, Lee CW, Park SW, Park DW, Park SJ. Differential rates and clinical significance of periprocedural myocardial infarction after stenting or bypass surgery for multivessel coronary disease according to various definitions. *JACC Cardiovasc Interv*. 2017;10:1498–1507. doi: 10.1016/j.jcin.2017.05.051
10. Koskinas KC, Räber L, Zanchin T, Wenaweser P, Stortecky S, Moschovitis A, Khattab AA, Pilgrim T, Blöchlinger S, Moro C, Jüni P, Meier B, Heg D, Windecker S. Clinical impact of gastrointestinal bleeding in patients undergoing percutaneous coronary interventions. *Circ Cardiovasc Interv*. 2015;8:e002053. doi: 10.1161/CIRCINTERVENTIONS.114.002053
11. Windecker S, Kolh P, Alfonso F, Collet JP, Cremer J, Falk V, Filippatos G, Hamm C, Head SJ, Jüni P, Kappetein AP, Kastrati A, Knuuti J, Landmesser U, Laufer G, Neumann FJ, Richter DJ, Schauerte P, Sousa Uva M, Stefanini GG, Taggart DP, Torracca L, Valgimigli M, Wijns W, Witkowski A. 2014 ESC/EACTS guidelines on myocardial revascularization: the task force on myocardial revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J*. 2014;35:2541–2619.
12. Giannitsis E, Kurz K, Hallermayer K, Jarausch J, Jaffe AS, Katus HA. Analytical validation of a high-sensitivity cardiac troponin T assay. *Clin Chem*. 2010;56:254–261. doi: 10.1373/clinchem.2009.132654
13. Cutlip DE, Windecker S, Mehran R, Boam A, Cohen DJ, van Es GA, Steg PG, Morel MA, Mauri L, Vranckx P, McFadden E, Lansky A, Hamon M, Krucoff MW, Serruys PW; Academic Research Consortium. Clinical end points in coronary stent trials: a case for standardized definitions. *Circulation*. 2007;115:2344–2351. doi: 10.1161/CIRCULATIONAHA.106.685313
14. Contal C, O'Quigley J. An application of changepoint methods in studying the effect of age on survival in breast cancer. *Comput Stat Data Anal*. 1999;30:253–270.
15. Harrell FE, Jr, Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. *Stat Med*. 1996;15:361–387. doi: 10.1002/(SICI)1097-0258(19960229)15:4<361::AID-SIM168>3.0.CO;2-4

16. Idris H, Lo S, Shugman IM, Saad Y, Hopkins AP, Mussap C, Leung D, Thomas L, Juergens CP, French JK. Varying definitions for periprocedural myocardial infarction alter event rates and prognostic implications. *J Am Heart Assoc*. 2014;3:e001086. doi: 10.1161/JAHA.114.001086
17. Zeitouni M, Silvain J, Guedeney P, Kerneis M, Yan Y, Overtchouk P, Barthelemy O, Hauguel-Moreau M, Choussat R, Helft G, Le Feuvre C, Collet JP, Montalescot G; ACTION Study Group. Periprocedural myocardial infarction and injury in elective coronary stenting. *Eur Heart J*. 2018;39:1100–1109. doi: 10.1093/eurheartj/ehx799
18. Stone GW. Periprocedural myocardial infarction: the "SCAI" is the limit. *JACC Cardiovasc Interv*. 2016;9:2229–2231. doi: 10.1016/j.jcin.2016.09.015
19. Lindsey JB, Kennedy KF, Stolker JM, Gilchrist IC, Mukherjee D, Marso SP, Pencina MJ, Kleiman NS, Cohen DJ. Prognostic implications of creatine kinase-MB elevation after percutaneous coronary intervention: results from the Evaluation of Drug-Eluting Stents and Ischemic Events (EVENT) registry. *Circ Cardiovasc Interv*. 2011;4:474–480. doi: 10.1161/CIRCINTERVENTIONS.111.962233
20. Lim CC, van Gaal WJ, Testa L, Cuculi F, Arnold JR, Karamitsos T, Francis JM, Petersen SE, Digby JE, Westaby S, Antoniades C, Kharbanda RK, Burrell LM, Neubauer S, Banning AP. With the "universal definition," measurement of creatine kinase-myocardial band rather than troponin allows more accurate diagnosis of periprocedural necrosis and infarction after coronary intervention. *J Am Coll Cardiol*. 2011;57:653–661. doi: 10.1016/j.jacc.2010.07.058
21. de Lemos JA. Increasingly sensitive assays for cardiac troponins: a review. *JAMA*. 2013;309:2262–2269. doi: 10.1001/jama.2013.5809
22. Herrmann J, Lennon RJ, Jaffe AS, Holmes DR Jr, Rihal CS, Prasad A. Defining the optimal cardiac troponin T threshold for predicting death caused by periprocedural myocardial infarction after percutaneous coronary intervention. *Circ Cardiovasc Interv*. 2014;7:533–542. doi: 10.1161/CIRCINTERVENTIONS.113.000544
23. Dautov R, Ybarra LF, Nguyen CM, Gibrat C, Joyal D, Rinfret S. Incidence, predictors and longer-term impact of troponin elevation following hybrid chronic total occlusion percutaneous coronary intervention. *Catheter Cardiovasc Interv*. 2018;92:E308–E316. doi: 10.1002/ccd.27545
24. Prasad A, Rihal CS, Lennon RJ, Singh M, Jaffe AS, Holmes DR Jr. Significance of periprocedural myonecrosis on outcomes after percutaneous coronary intervention: an analysis of preintervention and postintervention troponin T levels in 5487 patients. *Circ Cardiovasc Interv*. 2008;1:10–19. doi: 10.1161/CIRCINTERVENTIONS.108.765610
25. Ndrepepa G, Colleran R, Braun S, Cassese S, Hieber J, Fusaro M, Kufner S, Ott I, Byrne RA, Husser O, Hengstenberg C, Laugwitz KL, Schunkert H, Kastrati A. High-sensitivity troponin T and mortality after elective percutaneous coronary intervention. *J Am Coll Cardiol*. 2016;68:2259–2268. doi: 10.1016/j.jacc.2016.08.059