ORIGINAL ARTICLE
Interventional cardiology

Association between the magnitude of periprocedural myocardial injury and prognosis in patients undergoing elective percutaneous coronary intervention

You Zhou [1,2], Zhangwei Chen[1,2,*], Ao Chen[1,2], Jiaqi Ma[1,2], Chunfeng Dai [1,2], Danbo Lu [1,2], Yuan Wu[1,2], Su Li[1,2], Jinxiang Chen [1,2], Muyin Liu[1,2], ChenGuang Li[1,2], Hao Lu[1,2], Juying Qian[1,2,*] and Junbo Ge [1,2,*]

[1]Department of Cardiology, Zhongshan Hospital, Fudan University, 1609 Xietu Road, Shanghai 200032, P. R. China; and [2]Shanghai Institute of Cardiovascular Diseases, National Clinical Research Center for Interventional Medicine, Shanghai 200032, P. R. China

Aims	This study aimed to investigate the prognostic implications of increased post-procedural cardiac troponin levels in patients undergoing elective percutaneous coronary intervention (PCI) and to define the threshold of prognostically relevant periprocedural myocardial injury (PMI).
Methods and results	A total of 3249 patients with normal baseline troponin levels referred for elective PCI were enrolled and followed up for a median period of 20 months. The primary endpoint was major adverse cardiovascular events (MACEs) comprising all-cause death, myocardial injury (MI), and ischaemic stroke. Post-PCI high-sensitivity cardiac troponin T (hs-cTnT) >99% upper reference limit (URL) occurred in 78.3% of the patients and did not increase the risk of MACEs [adjusted hazard ratio (adHR) 1.00, 95% confidence interval (CI) 0.58–1.74, $P = 0.990$], nor did 'major PMI', defined as post-PCI hs-cTnT >5× URL (adHR 1.30, 95% CI 0.76–2.23, $P = 0.340$). Post-PCI troponin >8× URL, with an incidence of 15.2%, started to show an association with a higher risk of MACEs (adHR 1.89, 95% CI 1.06–3.37, $P = 0.032$), mainly driven by myocardial infarction (adHR 2.38, 95% CI 1.05–5.38, $P = 0.037$) and ischaemic stroke (adHR 3.35, 95% CI 1.17–9.64, $P = 0.025$).
Conclusion	In patients with normal baseline troponin values undergoing elective PCI, PMI defined as hs-cTnT >8× URL after PCI was more appropriate for identifying patients with an increased risk of MACEs, which may help guide clinical practice in this population.

* Corresponding authors. Tel: 86 21 64041990 ext. 2728, 86 21 64041990 ext. 2728, 86 21 64041990 ext. 2745, Fax: 86 21 64223006, Email: qian.juying@zs-hospital.sh.cn, chen.zhangwei@zs-hospital.sh.cn, jbge@zs-hospital.sh.cn

Graphical Abstract   In multivariate regression model, high-sensitivity cardiac troponin T above 8 × URL was associated with increased risk of longterm adverse clinical outcomes.
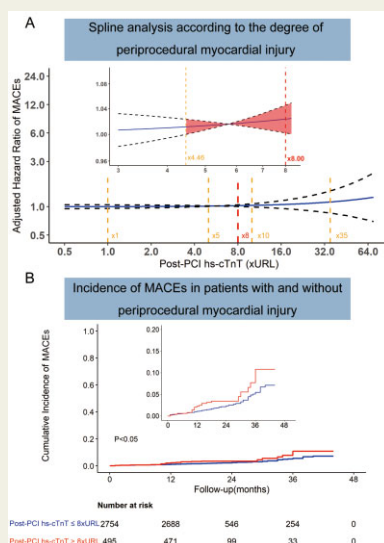
Introduction

With advances in equipment and innovation of techniques, percutaneous coronary intervention (PCI) has become a mainstay of coronary revascularization. Although the incidence rates of serious complications such as perforation and death have dramatically decreased, periprocedural myocardial injury (PMI) remains a common phenomenon after PCI, with a reported frequency of 3–50%,[1–6] depending on variable biomarkers and thresholds. The introduction of highly sensitive and specific cardiac biomarkers, such as cardiac troponin I and troponin T, permits us to detect minor myocardial damage, which goes beyond the traditional definition of myocardial infarction and brings about the concept of myocardial injury.[3,7–10]

Debates over the magnitude of prognostically significant myocardial injury have existed for a long time because of inconsistent definitions and conflicting outcomes.[5,11–15] In 2021, a consensus document from the European Society of Cardiology (ESC) working group and European Association of Percutaneous Cardiovascular Interventions (EAPCI) proposed that post-PCI cardiac troponin >5× the upper reference limit (URL) could be used to define prognostically relevant 'major PMI'.[16] However, considering that most studies used conventional troponins and arbitrary cut-off values of troponins based mainly on expert opinions, more evidence is needed to establish the thresholds of high-sensitivity troponins defining clinically significant PMI.

To minimize the influence of pre-PCI troponins, this study included patients with normal baseline troponin levels scheduled for elective PCI only. We aimed to evaluate the prognostic impact of increases in post-PCI high-sensitivity cardiac troponin T (hs-cTnT) levels and, moreover, to define the threshold at which PMI would implicate adverse cardiovascular events.

Methods

Study population

The present study retrospectively analysed 3249 patients with normal pre-procedural hs-cTnT levels referred for elective PCI at Zhongshan Hospital, Fudan University (between 2016 and 2019). The indication for intervention was significant coronary stenosis found by diagnostic angiography in patients with symptoms or by scheduled angiography after previous stenting. Each patient was included in the analysis only once. Patients with non-ST segment elevation MI (NSTEMI), STEMI, malignancy, infection, or respiratory failure were excluded. The study was approved by the Ethics Committee of Zhongshan Hospital (approval no.: B2016-018, date: 29 February 2016) and conducted in accordance with the guidelines of the Declaration of Helsinki. All patients gave written informed consent.

Laboratory measurements

Venous blood samples for hs-cTnT measurements were obtained at admission (usually 24–48 h before the procedure) and 12–18 h after PCI. In case of elevated hs-cTnT above URL after PCI or indicated by clinical manifestations, serial measures were taken to assess peak troponin values. Troponin T was measured by an automated analyser using a high-sensitivity assay (Roche Diagnostics). The lower limit of hs-cTnT that can be reproducibly measured with a coefficient of variation <10% was 0.003 ng/mL, and the 99th percentile URL was 0.014 ng/mL. Clinical, biochemical, and procedural data were recorded prospectively for all patients.

Patient follow-up and endpoints

The median interval of follow-up was 20 months [interquartile range (IQR) 17–23 months]. Follow-up data were collected through telephone interviews or clinic visits by trained research staff blinded to grouping
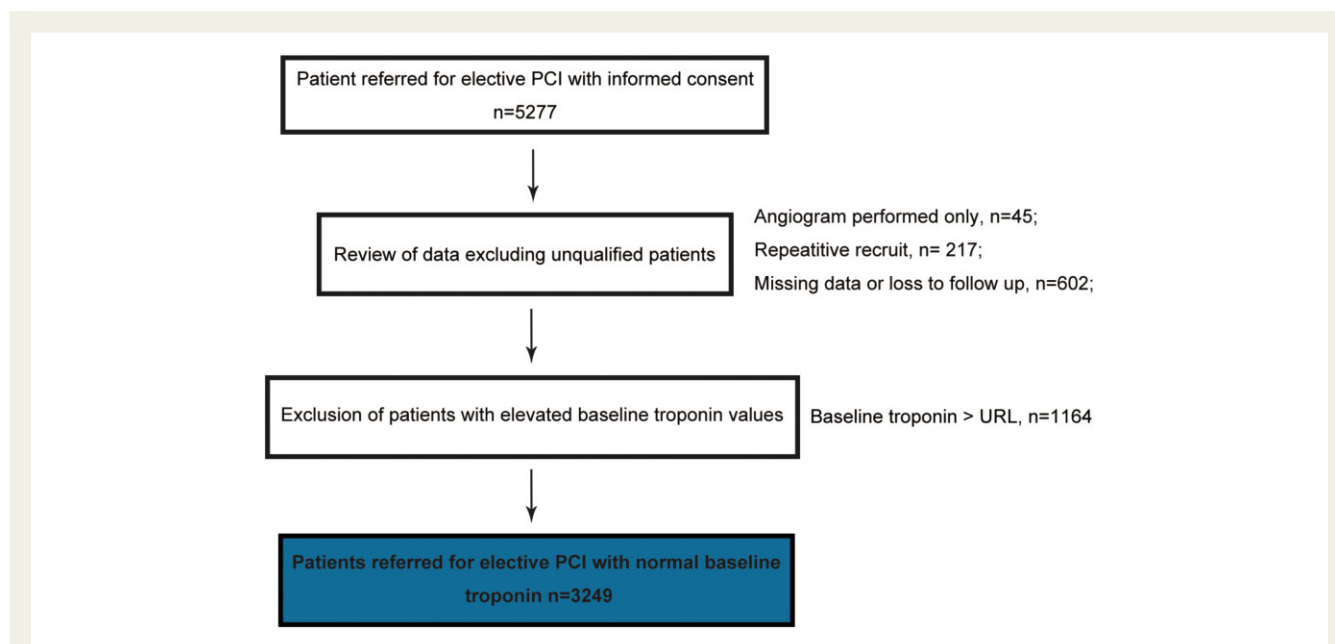
Figure 1 Flowchart of the study.

information. With the evolving understanding of coronary heart disease as a panvascular process involving not only the heart but also the brain, both cardio- and cerebrovascular events were recorded. The primary endpoint was defined as a composite of all-cause death, myocardial infarction (MI), and ischaemic stroke [major adverse cardiovascular events (MACEs)]. The key secondary endpoints were all-cause death, MI, ischaemic stroke, and ischemia-driven coronary revascularization, separately.

Statistical analysis

Statistical analysis was performed using R software (version 4.0.2) and SPSS (version 25.0, IBM, Armonk, NY). Categorical variables are summarized as numbers and percentages per group, and continuous variables as mean $\pm$ standard deviation (SD) or median with IQRs. Categorical data were compared using the χ^2 test or Fisher's exact test. Differences between groups in normally and non-normally distributed variables were assessed by unpaired Student's t-test or the Mann–Whitney U-test, respectively. The odds ratio (OR) was analysed with logistic regression. Correlations between individual serum levels of hs-cTnT and endpoints were evaluated using spline curve analysis. The prognostic impact of PMI was assessed with a Cox regression model or competing risk model, accordingly. A bootstrap resampling procedure (500 repeats, with a P-value of 0.05 for selection) was used to identify variables for the final multivariate analysis (i.e. age per 5 year increase). Additionally, we adjusted for the following clinical confounders: sex, diabetes mellitus, hypertension, smoking history, estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2, prior PCI, old myocardial infarction (OMI), stent length (per 10 mm increase), number of treated vessels, and procedural complications (including side-branch loss, non-flow-limiting dissection, and slow flow/no reflow). Two-tailed $P < 0.05$ was considered indicative of significance. Bonferroni correction was used in multiple comparisons.

Results

Patient demographics

This study enrolled 3249 patients with normal baseline hs-cTnT values who were scheduled for elective PCI (Figure 1). The clinical characteristics of the study population are summarized in Tables 1 and 2. The distribution of post-PCI hs-cTnT values is displayed in Figure 2. The mean age was 63.0 (57.0–69.0) years, and 73.1% were male. A total of 29.5% of the patients had prior PCI, and 0.6% had previously undergone coronary artery bypass graft (CABG). Chronic total occlusion (CTO) was treated in 423 (13.0%) patients. A total of 118 (3.6%) patients underwent percutaneous transluminal coronary angioplasty (PTCA) without stent implantation. Dual antiplatelet therapy comprised aspirin/cilostazol and clopidogrel/ticagrelor, according to bleeding and ischaemic risks. The mean hospitalization stay post PCI was 1.4 $\pm$ 0.9 days.

Defining a threshold of periprocedural myocardial injury

During a median follow-up interval of 20 months (IQR 17–23 months), the primary endpoint was documented in 91 (2.8%) patients. We investigated the association between post-PCI hs-cTnT levels and endpoints using spline curve analysis to define the primary reference values for prognostically relevant PMI (see the Graphical Abstract). Post-PCI hs-cTnT was considered a continuous variable and values >4.46$\times$ URL began to increase the risk of MACEs ($P < 0.05$). In addition, the cut-off thresholds at which hs-cTnT drove MI, ischaemic stroke, and unplanned revascularization were 4.84, 3.96, and 5.00$\times$ URL, respectively (Supplementary material online, Figure S1). However, we could not find a cut off value of hs-cTnT statistically significant enough to increase mortality.

Table I   Baseline demographics and clinical characteristics

	Total (*n* = 3249)	Non-PMI (*n* = 2754)	PMI (*n* = 495)	*P*-value
Age (years)	63.0 (57.0–69.0)	63.0 (56.0–69.0)	65.0 (58.0–71.0)	<0.001
Male	2375 (73.1%)	2017 (73.2%)	358 (72.3%)	0.672
Hypertension	2077 (63.9%)	1743 (63.3%)	334 (67.5%)	0.074
Diabetes mellitus	923 (28.4%)	788 (28.6%)	135 (27.3%)	0.543
Smoking history	1244 (38.3%)	1067 (9.6%)	177 (35.8%)	0.208
OMI	333 (10.2%)	264 (9.6%)	69 (13.9%)	0.003
Prior PCI	957 (29.5%)	810 (29.4%)	147 (29.7%)	0.898
Prior CABG	18 (0.6%)	15 (0.5%)	3 (0.6%)	0.865
Stroke	138 (4.2%)	111 (4.0%)	27 (5.5%)	0.148
Atrial fibrillation	102 (3.1%)	87 (3.2%)	15 (3.0%)	0.880
OAC	112 (3.4%)	95 (3.4%)	17 (3.4%)	0.986
Hospitalization stay after PCI (days)	1.4 ± 0.9	1.3 ± 0.8	1.8 ± 1.2	<0.001
Laboratory and auxiliary examinations				
Creatinine (mg/dl)	76.0 (66.0–87.0)	76.0 (66.0–86.0)	77.0 (59.0 107.0)	<0.001
CK (U/L)	80 (61–109)	92 (61–110)	92 (59–107)	0.357
CK-MB (U/L)	14 (11–17)	14 (11–17)	14 (11–17)	0.133
hs-CRP (mg/L)	1.10 (0.50–2.60)	1.10 (0.50–2.50)	1.10 (0.50–2.60)	0.794
White blood cell count (×10^9/L)	6.22 (5.28–7.32)	6.24 (5.28–7.34)	6.15 (5.23–7.23)	0.379
Platelet (×10^9/L)	202 (169–238)	202 (169–238)	203 (170–203)	0.584
Haemoglobin (g/L)	138 (128–148)	139 (129–148)	136 (125–147)	<0.001
Total cholesterol (mmol/L)	3.54 (3.03–4.28)	3.53 (3.02–4.27)	3.60 (3.09–4.34)	0.112
Low-density lipoprotein (mmol/L)	1.65 (1.22–2.58)	1.64 (1.21–2.24)	1.70 (1.31–2.38)	0.028
Triglyceride (mmol/L)	1.64 (1.16–2.44)	1.65 (1.16–2.47)	1.58 (1.11–2.32)	0.155
High-density lipoprotein (mmol/L)	1.09 (0.89–1.44)	1.09 (0.89–1.42)	1.12 (0.90–1.50)	0.103
Lp(a) (mg/L)	141 (60–348)	139 (59–337)	170 (71–397)	0.003
HbA1c (%)	5.9 (5.5-6.6)	5.90 (5.50–6.60)	5.80 (5.50–6.40)	0.027
Ejection fraction (%)	65(62-68)	65 (62–68)	64 (61–67)	0.005
Antiplatelet therapy at discharge				
Aspirin	2944 (90.6%)	2494 (90.6%)	450 (90.9%)	0.806
Clopidogrel	2836 (87.3%)	2443 (88.7%)	393 (79.4%)	<0.001
Ticagrelor	416 (12.8%)	313 (11.4%)	103 (20.8%)	<0.001
Cilostazol	288 (8.9%)	248 (9.0%)	40 (8.1%)	0.505

Data are shown as median (interquartile range), *n* (%), or mean ± SD.

CABG, coronary artery bypass graft; CK-MB, creatinine kinase myocardial band; hs-CRP, high-sensitivity C-reactive protein; Lp(a), lipoprotein (a); OMI, old myocardial infarction; OAC, oral anticoagulation; PCI, percutaneous coronary intervention; and PMI, periprocedural myocardial injury.

Periprocedural myocardial injury and outcomes

We further assessed the prognostic impact of PMI using univariate and multivariate models considering troponin as a categorical variable. In this study, PMI, defined as post-PCI troponin levels >99% URL, occurred in 78.3% of the patients and did not increase the risk of MACEs [adjusted hazard ratio (adHR) 1.00, 95% confidence interval (CI) 0.58–1.74, *P* = 0.990]. Based on the results derived from spline analysis, we speculated that hs-cTnT >5× URL after PCI, that is, 'major' PMI proposed by EAPCI, may be able to identify patients with poor prognosis. However, increases in hs-cTnT >5× URL following PCI were not prognostically significant in the multivariate analysis (adHR 1.30, 95% CI 0.76–2.23, *P* = 0.340) (*Figure 3*). Then, we explored the correlation between PMI and clinical outcomes by setting higher cut-off values of hs-cTnT. Patients with post-PCI

hs-cTnT >8× URL compared with those without had a higher risk of MACEs (adHR 1.89, 95% CI 1.06–3.37, *P* = 0.032), mainly driven by MI (adHR 2.38, 95% CI 1.05–5.38, *P* = 0.037) and ischaemic stroke (adHR 3.35, 95% CI 1.17–9.64, *P* = 0.025). Predictors of MACEs included in the multivariate analysis are shown in *Table 3*. Kaplan–Meier analysis also demonstrated a significant increase in the incidence of MACEs (log-rank *P* < 0.05) in patients with post-PCI hs-cTnT >8× URL (see the Graphical Abstract). Since there are sex-specific cut-offs for hs-cTnT, we also analysed the impact of PMI using corresponding cut-off values in male and female patients, respectively, which revealed similar findings (Supplementary material online, *Figure S2*). Survival analysis of key secondary endpoints are displayed in *Figure 4*. In addition, the sensitivity and specificity of post-PCI hs-cTnT values to predict MACEs are shown in the Supplementary material online, *Table S1*, which indicate 8× URL had

Table 2 Lesion and procedural features

	Total (*n* = 3249)	Non-PMI (*n* = 2754)	PMI (*n* = 495)	*P*-value
Syntax score	14.0 (8.0–21.5)	13.0 (8.0–21.0)	19.0 (13.0–25.0)	<0.001
Bifurcation lesion	635 (19.5%)	480 (17.4%)	155 (31.3%)	<0.001
Calcification	305 (9.4%)	214 (7.8%)	91 (18.4%)	<0.001
CTO	423 (13.0%)	312 (11.3%)	111 (22.4%)	<0.001
ISR	195 (6.0%)	169 (6.1%)	26 (5.3%)	0.421
DCB	122 (3.8%)	109 (4.0%)	13 (2.6%)	0.112
Rotablator	55 (1.7%)	23 (0.8%)	32 (6.5%)	<0.001
Target vessel number				
1	2391 (73.6%)	2129 (77.3%)	262 (52.9%)	<0.001
2	744 (22.9%)	556 (20.2%)	188 (38.0%)	<0.001
3	114 (3.5%)	69 (2.5%)	45 (9.1%)	<0.001
Left main treated	242 (7.4%)	174 (6.3%)	68 (13.7%)	<0.001
PTCA without stenting	118 (3.6%)	109 (4.0%)	9 (1.8%)	0.044
Stent length (mm)	50.2 ± 33.2	38.0 (23.0–60.0)	70.0 (48.0–96.0)	<0.001
Stent number				
1	1470 (45.2%)	1387 (50.4%)	83 (16.8%)	<0.001
2	1018 (31.3%)	835 (30.3%)	183 (37.0%)	0.084
≥3	643 (19.9%)	423 (15.3%)	220 (44.4%)	<0.001
Slow/no reflow	54 (1.7%)	31 (1.1%)	23 (4.6%)	<0.001
Side-branch loss	13 (0.4%)	5 (0.2%)	8 (1.6%)	<0.001
Non-flow-limiting dissention	11 (0.3%)	8 (0.3%)	3 (0.6%)	0.162
Bailout use of GPI	554 (17.1%)	418 (15.2%)	136 (27.5%)	<0.001

Data are shown as median (interquartile range) or *n* (%).
CTO, chronic total occlusion; DCB, drug-coated balloon; ISR, intrastent restenosis; GPI, glycoprotein IIb/IIIa inhibitor; PMI, periprocedural myocardial injury; and PTCA, percutaneous transluminal coronary angioplasty.

better performance (sensitivity of 23.1% and specificity of 85.1%) to efficiently identify patients at high risk of MACEs. Still, we failed to find a threshold of post-PCI hs-cTnT that would increase the risk of mortality even if hs-cTnT values elevated >10× URL or 35× URL.

Clinical characteristics according to periprocedural myocardial injury

Since hs-cTnT > 8× URL was indicated to be correlated with poor prognosis by spline curve and multivariate analysis, patients were divided into PMI or non-PMI groups based on whether hs-cTnT was >8× URL after PCI. In the present study, 495 (15.2%) patients had PMI. Clinical characteristics are summarized in *Tables 1* and *2*. Patients with PMI were older [65.0 (58.0–71.0) vs. 63.0 (56.0-69.0), *P* < 0.001] and more likely to have a history of myocardial infarction (13.9% vs. 9.6%, *P* < 0.003). Baseline laboratory tests showed that patients in the PMI group tended to have higher creatinine, lower haemoglobin, and a lower ejection fraction (all *P* < 0.01). Compared with patients without PMI, patients with PMI had higher syntax scores [19.0 (13.0–25.0) vs. 13.0 (8.0–21.0), *P* < 0.001], more bifurcation lesions (31.3% vs. 17.4%, *P* < 0.001), more CTO treatments (18.4% vs. 11.3%, *P* < 0.001), more frequent calcifications (18.4% vs. 7.8%, *P* < 0.001), and subsequent rotablator use (6.5% vs. 0.8%, *P* < 0.001). Patients with PMI had more target vessels, more stents implanted, and were more likely to have undergone left main treatment (all *P* < 0.001). Notably, patients with PMI

were more frequently prescribed ticagrelor (22.2% vs. 12.6%, *P* < 0.001), had higher use of bailout therapy with a glycoprotein IIb/IIIa inhibitor (27.5% vs. 15.2%, *P* < 0.001) and longer hospitalization after PCI (1.8 ± 1.2 vs. 1.3 ± 0.8 days, *P* < 0.001). In addition, procedural complications, such as instant slow flow/no reflow (4.6% vs. 1.1%, *P* < 0.001) and side-branch loss (1.6% vs. 0.2%, *P* < 0.001) were more common in patients with PMI. In order to assess whether the higher incidence of complications could be attributed to the increased risk of MACEs, we conducted spine curve analysis as well as survival analysis excluding patients with slow flow/no reflow, side-branch loss, or dissection. Post-PCI hs-cTnT above 8× URL, in accordance with previous results, significantly increased the risk of MACEs, MI, and ischaemic stroke. Detailed findings are shown in the Supplementary material online, *Figures S3–S5*.

Subgroup analysis

The association between PMI and MACEs was further assessed in subgroups (*Figure 5*). Interactions in all subgroups were not significant. After Bonferroni correction in the *post hoc* analysis, PMI predicted a higher risk of MACEs in hypertensive, female patients and those without smoking history, increased high-sensitivity C-reactive protein (hs-CRP), or aortic valve calcification. In patients receiving bailout use of glycoprotein IIb/IIIa inhibitors, PMI was also correlated with increased risk of MACEs.
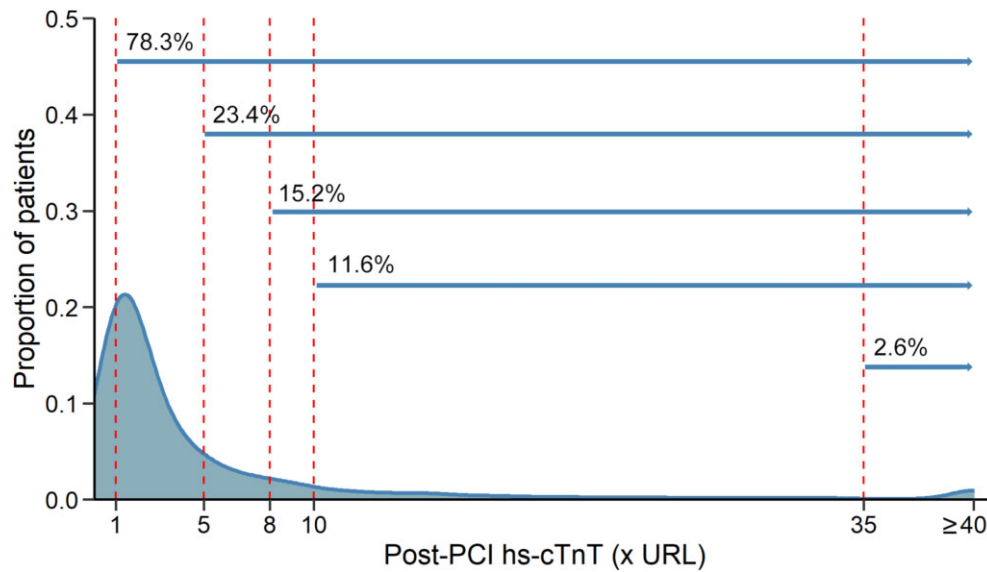
Figure 2 Distribution of post-percutaneous coronary intervention troponins. Distribution of post-percutaneous coronary intervention high-sensitivity cardiac troponin T in all patients. Horizontal lines indicate the incidence of periprocedural myocardial injury according to the cut-off thresholds of high-sensitivity cardiac troponin levels. hs-cTnT, high-sensitivity cardiac troponin T; PCI, percutaneous coronary intervention; PMI, periprocedural myocardial injury; and URL, upper reference limit.
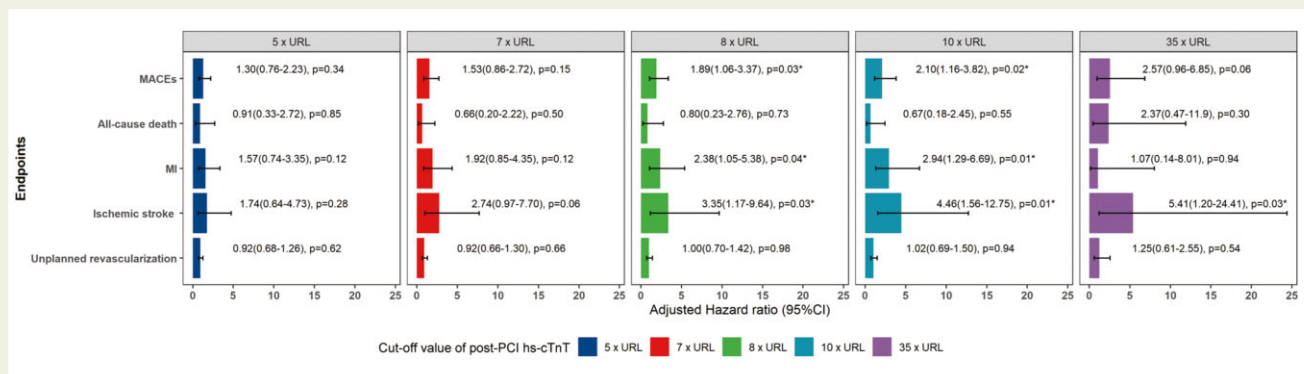

Figure 3 Adjusted hazard ratios of clinical endpoints According to periprocedural myocardial injury, *a significant $P < 0.05$. Different thresholds of post-percutaneous coronary intervention high-sensitivity cardiac troponin are used to define periprocedural myocardial injury. Adjusted hazard ratios of major adverse cardiovascular events, all-cause death, myocardial infarction, ischaemic stroke, and unplanned revascularization according to cut-off values of periprocedural myocardial injury are shown in columns. The variables included in the multivariate model were as follows: age (per 5 years increase), sex, hypertension, diabetes, smoking history, old myocardial infarction, prior percutaneous coronary intervention, eGFR <60 mL/min/1.73 m^2, number of target vessels, stent length (per 10 mm increase), and procedural complications (side-branch loss, dissection, and slow flow/no reflow). MACEs, major adverse cardiovascular events; MI, myocardial infarction; PCI, percutaneous coronary intervention; PMI, periprocedural myocardial injury; and URL, upper reference limit.

Predictors of periprocedural myocardial injury

Risk factors for PMI were evaluated by logistic regression. After adjustment, independent predictors of PMI encompassing age (per 5 years increase), OMI, stent length (per 10 mm increase), syntax score, and multivessel disease (more than one vessel treated) are shown in the Supplementary material online, *Figure S6*.

Discussion

Over the past decades, several definitions of PMI have been put forward as the field of PCI and measurements of myocardial injury have been revolutionized.[6–8,16,17] In 2021, the ESC working group and EAPCI proposed the concept of prognostically relevant 'major PMI' through expert consensus. However, more scientific evidence

Table 3 Predictors of major adverse cardiovascular events in multivariate Cox regression model

	Adjusted hazard ratio (95% CI)	P-value
Periprocedural myocardial injury[a]	1.89 (1.06–3.37)	0.032
Age (per 5 years increase)	1.13 (1.01–1.28)	0.041
Procedural complications[b]	1.29 (0.40–4.14)	0.674
Male	0.88 (0.52–1.48)	0.624
Hypertension	1.41 (0.88–2.29)	0.156
Diabetes Mellitus	1.09 (0.69–1.72)	0.727
Smoking history	0.99 (0.60–1.66)	0.997
OMI	0.98 (0.47–2.06)	0.963
Prior PCI	1.12 (0.69–1.80)	0.655
eGFR<60 ml/min/1.73 m^2	0.95 (0.41-2.22)	0.905
Stent length (per 10 mm increase)	0.95 (0.87–1.03)	0.195
Target vessel number	1.11 (0.72–1.72)	0.630

[a] Defined as post-percutaneous coronary intervention high-sensitivity cardiac troponin T >8× upper reference limit.
[b] Including side-branch loss, non-flow-limiting dissection, and slow flow/no reflow.
CI, confidence interval; OMI, old myocardial infarction; and PCI, percutaneous coronary intervention.

is still needed to confirm the association between PMI and long-term outcomes as well as the thresholds defining clinically significant PMI.

Our findings are summarized as follows: (i) both PMI, defined as post-PCI hs-cTnT >99% URL, and 'major' PMI, defined as post-PCI hs-cTnT >5 × URL, seem to be oversensitive to correlate with MACEs; (ii) hs-cTnT >8× URL post-PCI, with an incidence of 15.2%, started to have a detrimental effect on MACEs, mainly driven by MI and ischaemic stroke, but not mortality; (iii) post-PCI hs-cTnT >8× URL had better diagnostic performance compared with 5× URL to more efficiently identify patients at high risk of MACEs; (iv) patients with hs-cTnT >8× URL after PCI were older, more likely to have OMI, underwent more sophisticated procedures, accepted more competent antiplatelet therapy, and had longer inpatient care than those without; (v) independent predictors of PMI (post-PCI hs-cTnT >8× URL) were age (per 5 years' increase), OMI, stent length (per 10 mm increase), syntax score, and multivessel disease (more than one vessel treated).

In the present large-scale observational study, we enrolled patients with normal pre-PCI troponin values to minimize the influence of baseline troponin levels. Elevated baseline troponin levels implied confounding disease courses and could interfere with the analyses of post-PCI troponins.[18,19] Cardiac troponin T was measured using a high-sensitivity assay for each patient during hospitalization, as recommended by universal definition of myocardial infarction (UDMI).[20] This was virtually a strength of our study, as most research used creatinine kinase-myocardial band (CK-MB) or conventional cTnT, and data concerning hs-cTnT are lacking.[16,21]

Consistent with previous reports, post-PCI hs-cTnT >99% URL did not influence the risk of mortality or MACEs.[5] Silvain et al. reported that post-PCI hs-cTnT >5× URL alone was related with an increased risk of mortality. However, in the present study, we could not find a cut-off value of post-PCI hs-cTnT to significantly influence mortality. In fact, this is not the solitary case concerning PMI and mortality.[3] We went through previous publications reporting association between PMI and mortality, finding out that in our study, incidence of procedural complications was lower, especially

in patients with PMI.[1,19] Although these discrepancies may be confounded by enrolment criteria or definition of PMI, we speculated the lower prevalence of complications could at least partially explain the insignificant relationship between PMI and mortality in the present study. Moreover, it is acknowledged that pre-PCI troponin elevation, even as moderately as 1× URL, posed great impact on the risks of MI and MACEs in CAD patients. On the contrary, when it comes to post-PCI troponin values, there have always been controversies and some argued troponin may need to be over 70 times URL to have clinical significance. In this sense, the poor prognosis of PMI may not be in a linear correlation with post-PCI hs-cTnT values. The true mechanism underlies post-PCI troponin elevation, PMI and prognosis needs to be verified in larger-scale and more comprehensive researches.

Since atherosclerosis as well as endothelial dysfunction underlying ischaemic cardiac events was recognized as a panvascular disease involving both coronary and non-coronary circulation, it has been suggested that this systemic pathological process should be studied and managed across all vascular territories.[22–24] Cerebrovascular events were recorded during follow-up in this study. Therein, we used a composite of death, MI, and ischaemic stroke as the primary endpoint, which not only strengthened the power of this study, but also provided a wider view of the development and prognosis of this disease. Higher incidence of MACEs, MI, and ischemic stroke in patients with elevation of hs-cTnT >8× URL indicated the correlation between PMI and late adverse outcomes, even when signs or symptoms of ischaemia were absent. Besides, post-PCI hs-cTnT >8× URL also had better sensitivity and specificity to appropriately identify patients at high risk of MACEs. In this case, whether prognostically significant 'major PMI' should be defined as 5× URL, as proposed before, requires more evidence.

It has been recommended that patients undergoing PCI should have troponins tested routinely before and after the procedure.[7,16] In our study, each patient had hs-cTnT measured at admission and 12–18 h post-PCI. To date, definitions of PMI have focused on the fold changes of troponins referred to as 99% URL. It was noted
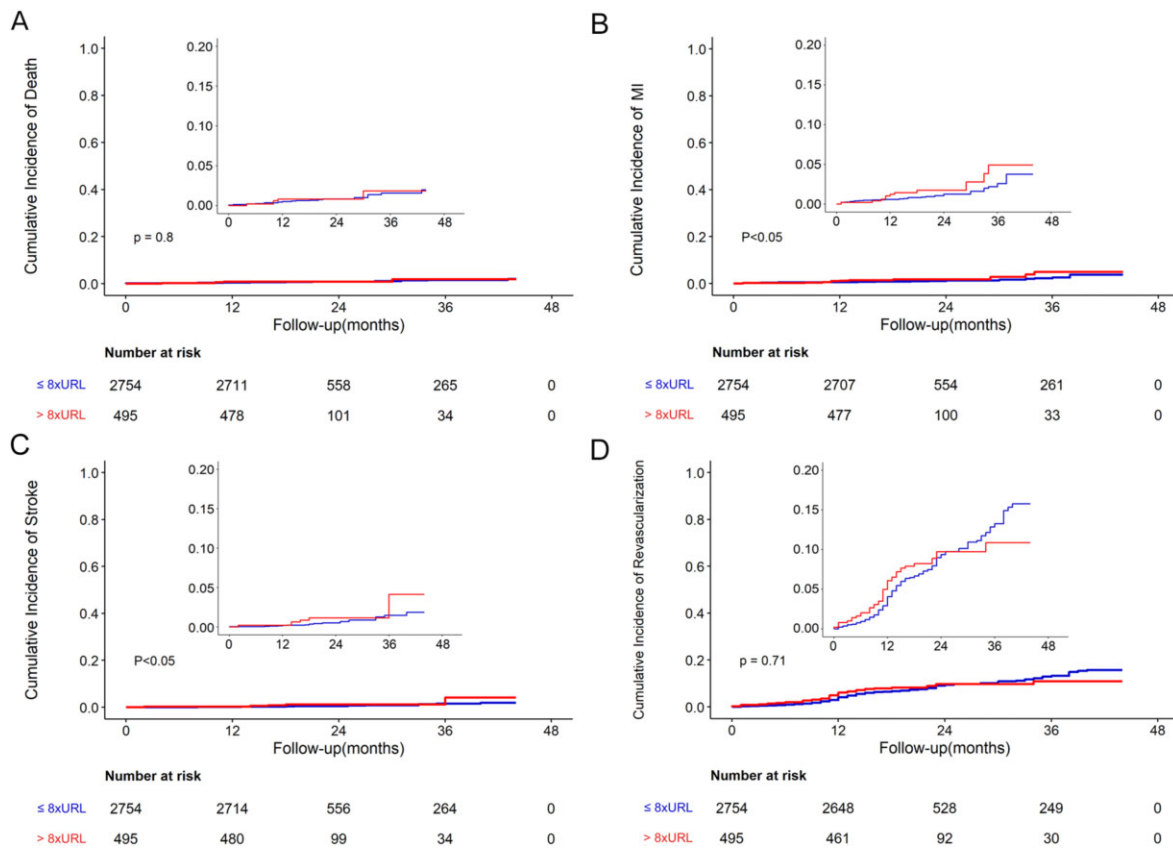
Figure 4 Time-to-event curves for clinical endpoints. (*A*) The cumulative incidence of all-cause death in patients with post-percutaneous coronary intervention high-sensitivity cardiac troponin >8× upper reference limit and those without. (*B*) The cumulative incidence of myocardial infarction. (*C*) The cumulative incidence of ischaemic stroke, and (*D*) the cumulative incidence of unplanned revascularization. In each panel, the inset shows the same data on an enlarged *y*-axis. MI, myocardial infarction; PCI, percutaneous coronary intervention; and URL, upper reference limit.

that some patients had very low levels of hs-cTnT at baseline, and their hs-cTnT values could remain below 99% URL even if they increased several-folds. We wondered whether it would be feasible to take the baseline hs-cTnT values as the reference and whether the ratio of post-PCI hs-cTnT values to pre-PCI values serves as the criterion defining PMI, as has been suggested in other circumstances.[25,26] Much more evidence is needed to draw a clear picture of this issue.

We divided patients into PMI and non-PMI groups based on whether post-PCI hs-cTnT was >8× URL. Patients with PMI tended to be older and suffer from prior MI. Low-density lipoprotein cholesterol was lower in patients without PMI. Although triglyceride and high-density lipoprotein did not significantly differ between groups, lipoprotein (a) was much higher in the PMI group, indicating that remnant cholesterol may be involved in the occurrence of PMI and that therapy to reduce residual cardiovascular risk could be further investigated.[27]

Patients with PMI had higher syntax scores and underwent more complicated procedures. It has been argued that poor prognosis of PMI is a result of high plaque burden and more complex intervention. Nevertheless, in our opinion it would be inappropriate to merely regard PMI as a collateral of severe atherosclerosis. We included

confounders reflecting lesion and procedural complexity in the multivariate models, and PMI proved to be an independent risk factor for adverse events. In addition, in subgroup analysis, non-smoking female patients with lower hs-CRP levels, who were considered a low-risk population, had higher incidence of MACEs if PMI occurred. Although these findings from *post hoc* analysis were more hypothesis generating than definitive, deeper investigation of the mechanism of PMI is inspired. PMI could be caused by microcirculatory dysfunction (MVD), and vice versa.[28] It was acknowledged that structural and functional alterations in endothelium and microcirculation could be a marker of an early event of atherosclerosis in coronary, cerebral, and peripheral artery disease,[29] which would increase the risk of organ damage and ischaemic events.[30] Hence, we speculated that MVD was more prevalent in patients with PMI and could be the reason for the higher incidence of MACEs. This point needs to be confirmed by specific studies.

This study is not without limitations. First, it is a single-centre retrospective study, which limited the study power, even though a relatively large-scale population was enrolled. The incidence of adverse outcomes would decrease as the post-PCI hs-cTnT decreased. This study was designed to draw conclusions of the association between MACEs and PMI on the overall population. When it
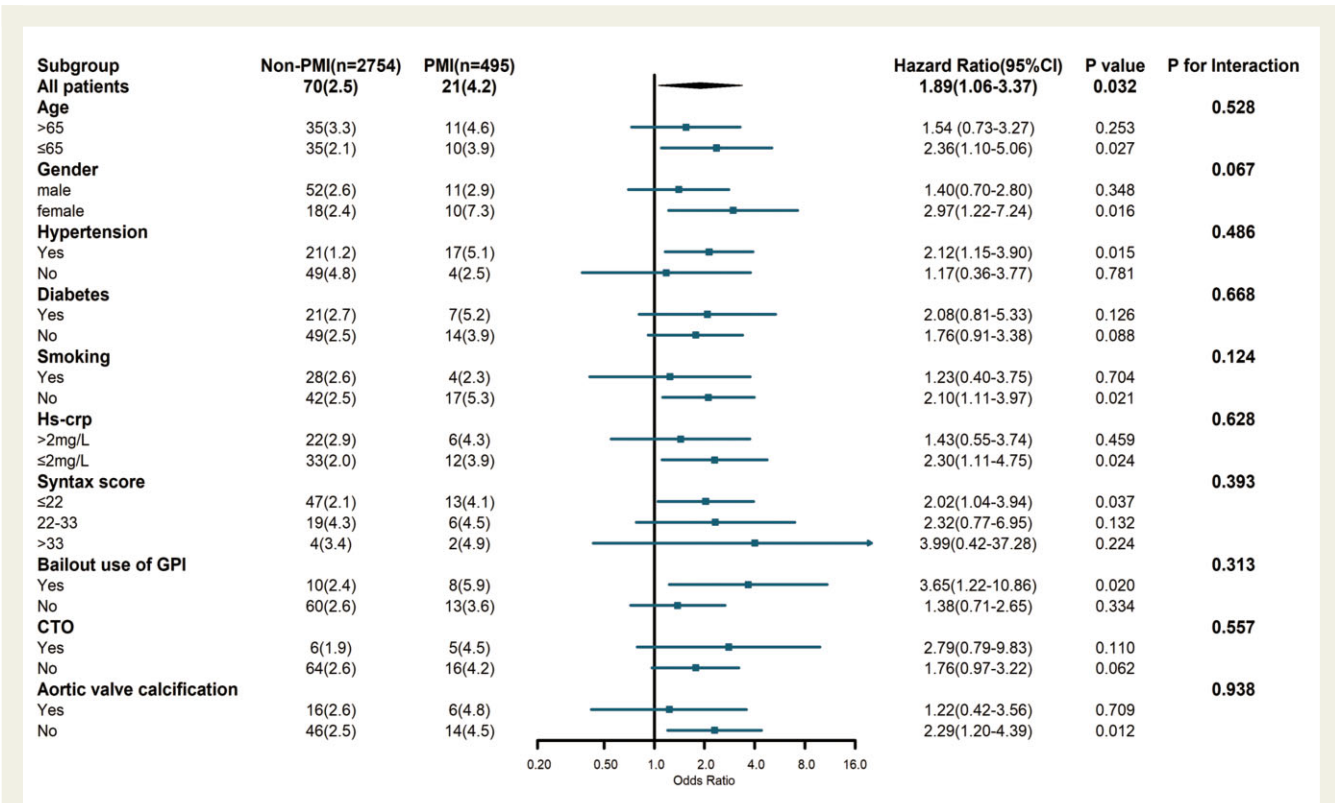
Figure 5 Subgroup analysis for major adverse cardiovascular events. Data are *n/n* assessed (%). The adjusted hazard ratio for major adverse cardiovascular events was calculated in patients who had a post-percutaneous coronary intervention high-sensitivity cardiac troponin >8× URL compared with patients who did not. CI, confidence interval; HR, hazard ratio; PCI, percutaneous coronary intervention; PMI, periprocedural myocardial injury; OMI, old myocardial infarction.

comes to patients with slightly elevated hs-cTnT after PCI, in which the incidence of MACEs was particularly lower, the findings may be underpowered in these subgroups. More research is still needed to accomplish the whole picture of PMI. Second, only patients who had normal baseline troponin levels were included. This was beneficial for us to focus on the impact of post-procedural troponins, but evidence concerning ACS patients is lacking. Third, although we used a multivariate model adjusted for many confounders, unmeasured variables affecting troponins as well as endpoints cannot be completely excluded. Fourth, the event rate of secondary endpoints was relatively low. These findings need to be confirmed by subsequent studies to draw firm conclusions. Fifth, patients with PMI have prolonged hospitalization, which has higher medical costs. Therapy targeting the detection, prevention, and treatment of PMI is needed in future research.

Conclusions

Post-PCI hs-cTnT >8× URL is appropriate to define PMI associated with a higher risk of MACEs in patients with normal baseline troponin values undergoing elective PCI. This may serve as a valuable tool for clinical decision-making.

Supplementary material

Supplementary material is available at *European Heart Journal— Quality of Care and Clinical Outcomes* online.

Conflict of interest: The authors declare that there are no conflicts of interest.

Data availability

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

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