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Long-term prognostic significance of periprocedural myonecrosis in patients with stable coronary artery disease undergoing elective percutaneous coronary intervention

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KEYWORDS

- biochemical markers
- death
- myocardial infarction
- stable angina

Abstract

Aims: The aim of this study was to ascertain the relationship between periprocedural myonecrosis (PPMN) and long-term mortality in patients with stable coronary artery disease (CAD) undergoing elective percutaneous coronary intervention (PCI).

Methods and results: A retrospective cohort study of consecutive patients undergoing elective PCI for stable CAD at a major Australian tertiary centre was undertaken. Cardiac troponin I levels were measured 12-24 hours post procedure in all patients. Those with a troponin I elevation >5x upper reference limit (URL) were diagnosed with PPMN as per the Third Universal Definition of Myocardial Infarction. The primary endpoint was long-term all-cause mortality. Of the 682 patients included in our study, 233 (34%) were diagnosed with PPMN. At a mean follow-up of 5.3±1.3 years, there were 34 (14.6%) deaths in patients with PPMN and 43 (9.6%) deaths in those without PPMN (p=0.04). PPMN was not an independent predictor of long-term mortality (OR 1.52, 95% CI: 0.95-2.43, p=0.08).

Conclusions: Periprocedural myonecrosis, defined by the Third Universal Definition of Myocardial Infarction, does not appear to have prognostic implications for patients with stable CAD undergoing elective PCI.

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Abbreviations

CAD	coronary artery disease
CK	creatine kinase
NDI	National Death Index
PCI	percutaneous coronary intervention
PPMI	periprocedural myocardial infarction
PPMN	periprocedural myonecrosis
SCAI	Society of Cardiovascular Angiography and Interventions
ULN	upper limit of normal
URL	upper reference limit

Introduction

The clinical significance of myonecrosis, measured by cardiac troponin, in the context of percutaneous coronary intervention (PCI) is a matter of ongoing debate. The lack of substantial scientific evidence in this domain is apparent from the ever-changing definitions of periprocedural myocardial infarction and the uncertainty regarding its prognostic relevance[1-4].

Myonecrosis due to PCI is common and occurs in up to 40% of cases, depending on the definition and biomarker used[5]. In the Third Universal Definition of Myocardial Infarction (MI), the cut-off cardiac troponin level to diagnose myonecrosis increased from 3 to 5 times the upper reference limit (URL)[3,4]. In contrast to previous definitions, troponin elevation needs to be associated with clinical, electrocardiographic, angiographic or cardiac imaging-related evidence of ischaemia to be classified as a periprocedural MI, or type 4a MI. However, the occurrence of post-PCI chest pain without troponin elevation and troponin elevation without chest pain, angiographic complications or other signs of ischaemia is well documented[6-9]. The Society of Cardiovascular Angiography and Interventions (SCAI) has proposed an alternative definition of "clinically significant myocardial infarction" requiring troponin levels of ≥70x upper limit of normal (ULN) or ≥35x ULN with electrocardiographic evidence of infarction.

The association between adverse prognosis and periprocedural biomarker elevation has been established when creatine kinase (CK) or its MB fraction is used[10-13]. The Universal Definition of MI preferentially advocates the use of troponin though the arbitrarily chosen threshold has uncertain prognostic significance. Consequently, a range of post-PCI troponin elevation cut-offs has been postulated[14-16].

The aim of our study was to evaluate the effect of periprocedural myonecrosis (PPMN), defined by the Third Universal Definition of MI as cardiac troponin elevation >5x URL, on long-term mortality in patients with stable coronary artery disease (CAD) undergoing elective PCI.

Methods

Consecutive patients who underwent elective PCI for stable CAD at Austin Health, Melbourne, Australia, between May 2007 and January 2011 were included in our study. Austin Health is a large tertiary teaching hospital located in Melbourne, Australia, which services a population of approximately 1.25 million people.

Patients who underwent PCI for acute coronary syndrome were excluded. All patients had cardiac troponin I levels measured 12-24 hours post PCI. The troponin I assay used was the Access AccuTnI (Beckman Coulter, Chaska, MN, USA), with an URL value of 0.04 µg/L. This URL is equivalent to our laboratory's ULN level. Patients with a troponin level >0.2 µg/L (>5x URL) were classified as having PPMN in accordance with the Third Universal Definition of MI troponin threshold. Patients with a troponin level >0.2 µg/L and either clinical, angiographic, electrocardiographic or imaging-related evidence of ischaemia were diagnosed with a periprocedural MI. The treating interventional cardiologist was responsible for adjudicating whether a patient suffered a periprocedural MI after analysing the available evidence.

Baseline demographics, and clinical, angiographic, and procedural characteristics of consecutive patients undergoing PCI were prospectively recorded on case report forms using standardised definitions for all fields[17]. The study protocol was approved by the Human Ethics Committee at Austin Health[18].

In-hospital outcomes and complications were recorded at the time of discharge. Follow-up was conducted at 30 days and 12 months by telephone, using a standardised questionnaire[18]. All adverse events were verified by reviewing the patients' medical records. Long-term mortality data, including date of death, were obtained by linkage to the Australian National Death Index (NDI). The Australian NDI is a database housed at the Australian Institute of Health and Welfare, Canberra, which contains records of all deaths occurring in Australia since 1980.

The primary endpoint was all-cause long-term mortality. Other clinical outcomes assessed included 30-day and 12-month mortality and spontaneous MI. Spontaneous MI was defined as: cardiac troponin elevation; and/or a significant ST-segment change, development of new Q-waves in ≥2 contiguous electrocardiographic leads, or new left bundle branch block pattern in the context of new clinical symptoms. Additionally, we analysed in-hospital mortality and bleeding. In-hospital bleeding was defined as bleeding requiring a transfusion and/or prolonged hospital stay due to bleeding and/or a drop in haemoglobin >3g/dL[17].

Statistical analysis

Continuous variables were expressed as mean±standard deviation (SD), and categorical data expressed as counts and percentages. Continuous variables were compared using Student's t-tests or ANOVA, and categorical variables using Fisher's exact or Pearson's chi-square tests. All calculated p-values were two-sided and p-values <0.05 were considered statistically significant. Cumulative incidence of mortality was estimated by the Kaplan-Meier method and the log-rank test was used to evaluate differences between groups with and without PPMN. Logistic regression modelling was used to identify univariate and multivariate predictors of PPMN. Twelve univariate variables with a p-value ≤0.10 were included in multivariate backward regression models. Cox proportional hazard modelling was used to identify univariate and multivariate predictors of long-term mortality. Fourteen univariate

variables with a p-value ≤0.10 were included in multivariate models. All statistical analysis was performed using SPSS, Version 21 (IBM Corp., Armonk, NY, USA).

Results

Of 682 consecutive patients with stable CAD who underwent elective PCI in our study, 233 (34%) experienced PPMN but only 14 (2%) sustained a periprocedural MI according to the Third Universal Definition of MI. For comparison, if the Second Universal (>3x URL) or SCAI (≥70x ULN or ≥35x with new clinical or electrocardiographic evidence of ischaemia) definitions had been used, 302 (44%) and 25 (4%) patients, respectively, would have received a diagnosis of periprocedural MI.

Baseline clinical characteristics **(Table 1)** reveal that patients with PPMN had higher post-procedural troponin levels (1.59±5.18 vs. 0.07±0.05 µg/L, p<0.01). Furthermore, they were more likely to have a history of congestive heart failure (7.7% vs. 3.1%, p<0.01) and be undergoing staged PCI (18.1% vs. 11.1%, p=0.01). Patients with PPMN had higher rates of multi-lesion PCI (25.8% vs. 13.6%, p<0.01), required longer stent lengths (23.2±15.7 mm vs. 19.0±13.1 mm, p<0.01) and had lesions with greater angiographic complexity as suggested by higher rates of type B2/C lesions (48.3% vs. 39.1%, p=0.02) **(Table 2)**. Glycoprotein IIb/IIIa use was more common in patients with PPMN, most likely due to its use as a bail-out strategy (9.0% vs. 4.5%, p=0.02).

Table 1. Clinical characteristics.

	No PPMN (n=449)	PPMN (n=233)	*p*-value
Troponin level (µg/L)	0.07±0.05	1.59±5.18	<0.01
Age (years)	64.8±10.8	65.6±11.0	0.37
Height (cm)	170.5±9.9	169.2±10.5	0.13
Weight (kg)	83.1±17.6	82.4±15.2	0.74
Gender (female), n (%)	94 (20.9)	61 (26.1)	0.13
Current smoker, n (%)	43 (9.6)	24 (10.3)	0.76
Chronic lung disease, n (%)	29 (6.5)	24 (10.3)	0.08
Diabetes mellitus, n (%)	120 (26.7)	73 (31.3)	0.21
Hypertension, n (%)	370 (82.4)	193 (82.8)	0.89
Hypercholesterolaemia, n (%)	419 (93.3)	212 (91.0)	0.27
Previous MI, n (%)	188 (41.9)	109 (46.8)	0.22
Family history of CAD, n (%)	188 (41.9)	104 (44.6)	0.49
Congestive heart failure, n (%)	14 (3.1)	18 (7.7)	<0.01
PVD, n (%)	31 (6.9)	18 (7.7)	0.70
CVA, n (%)	21 (4.7)	17 (7.3)	0.17
Previous PCI, n (%)	173 (38.5)	100 (42.9)	0.27
Previous CABG, n (%)	63 (14.0)	21 (9.0)	0.06
Recent CHF (<2 weeks), n (%)	7 (1.6)	3 (1.3)	0.78
Atrial fibrillation, n (%)	22 (4.9)	9 (3.9)	0.67
Positive stress test, n (%)	194 (43.2)	99 (42.5)	0.38
Staged PCI, n (%)	50 (11.1)	42 (18.1)	0.01
eGFR <60 ml/min/1.73 m^2	82 (18.3)	46 (19.7)	0.64
Fasting glucose (mmol/L)	6.1±1.6	6.0±2.0	0.82
Total cholesterol (mmol/L)	3.7±1.0	3.7±1.0	0.99
LDL-cholesterol (mmol/L)	2.1±0.9	2.2±0.9	0.81
HDL-cholesterol (mmol/L)	0.9±0.3	0.9±0.3	0.69
Triglycerides (mmol/L)	1.4±0.8	1.3±0.8	0.27

CABG: coronary artery bypass graft surgery; CAD: coronary artery disease; CHF: congestive heart failure; CVA: cerebrovascular accident; eGFR: estimated glomerular filtration rate; HDL: high-density lipoprotein; LDL: low-density lipoprotein; MI: myocardial infarction; PCI: percutaneous coronary intervention; PPMN: post-procedural myonecrosis; PVD: peripheral vascular disease

Table 2. Angiographic and procedural characteristics.

	No PPMN (n=449)	PPMN (n=233)	*p*-value
Multivessel CAD, n (%)	279 (62.3)	162 (69.5)	0.06
Multi-lesion PCI, n (%)	61 (13.6)	60 (25.8)	<0.01
Left main PCI, n (%)	12 (2.7)	2 (0.9)	0.11
Ostial lesion, n (%)	37 (8.3)	11 (4.7)	0.09
Bifurcation lesion, n (%)	67 (14.9)	44 (18.8)	0.19
Chronic total occlusion, n (%)	46 (10.2)	19 (8.2)	0.38
Type B2/C lesion, n (%)	175 (39.1)	112 (48.3)	0.02
PCI to *de novo* lesion, n (%)	398 (88.6)	211 (90.6)	0.67
GP IIb/IIIa use, n (%)	20 (4.5)	21 (9.0)	0.02
Total stent length (mm)	19.0±13.1	23.2±15.7	<0.01

CAD: coronary artery disease; GP IIb/IIIa: glycoprotein IIb/IIIa inhibitor; PCI: percutaneous coronary intervention; PPMN: post-procedural myonecrosis

PCI angiographic success rates were equivalent between groups (97.0% vs. 97.1%, p=0.94). Patients with PPMN had higher rates of acute closure, coronary dissection and no reflow but the differences were not statistically significant as the numbers were small **(Table 3)**. **Table 4** shows medical therapy at 30 days and 12 months.

Table 3. Acute procedural outcomes.

	No PPMN (n=449)	PPMN (n=233)	*p*-value
Successful PCI, n (%)	436 (97.1)	226 (97.0)	0.94
Acute closure, n (%)	0 (0)	2 (0.9)	0.05
Coronary dissection, n (%)	22 (4.9)	17 (7.3)	0.21
Coronary perforation, n (%)	2 (0.4)	1 (0.4)	0.97
No reflow, n (%)	4 (0.9)	7 (3.0)	0.05
Emergency PCI, n (%)	0 (0)	2 (0.9)	0.05
Stent thrombosis, n (%)	0 (0)	1 (0.4)	0.17
Unplanned CABG, n (%)	0 (0)	0 (0)	–
Post-PCI arrhythmia, n (%)	8 (1.8)	4 (1.7)	0.95
Post-PCI stroke, n (%)	0 (0)	0 (0)	–
Post-PCI CHF, n (%)	1 (0.2)	1 (0.4)	0.64
In-hospital bleeding, n (%)	1 (0.2)	0 (0.0)	0.47

CABG: coronary artery bypass graft surgery; CHF: congestive heart failure; PCI: percutaneous coronary intervention; PPMN: post-procedural myonecrosis

Table 4. Medication history at 30 days and 12 months.

		No PPMN (n=449)	PPMN (n=233)	*p*-value
30 days	Aspirin,%	98.8	99.0	0.81
	Clopidogrel,%	96.7	95.7	0.53
	Prasugrel,%	1.20	4.20	0.2
	Statin,%	93.5	94.6	0.61
	Beta-blocker,%	68.1	70.2	0.61
	ACE inhibitor,%	47.9	52.3	0.32
	ARB,%	24.2	26.6	0.52
	Warfarin,%	5.01	3.90	0.55
12 months	Aspirin,%	93.6	93.7	0.98
	Clopidogrel,%	73.1	77.3	0.28
	Prasugrel,%	1.80	2.90	0.44
	Statin,%	93.6	93.7	0.98
	Beta-blocker,%	60.5	62.3	0.70
	ACE inhibitor,%	45.7	48.9	0.49
	ARB,%	28.1	25.0	0.45
	Warfarin,%	6.30	5.60	0.74

ACE: angiotensin-converting enzyme; ARB: angiotensin receptor blocker; PPMN: post-procedural myonecrosis

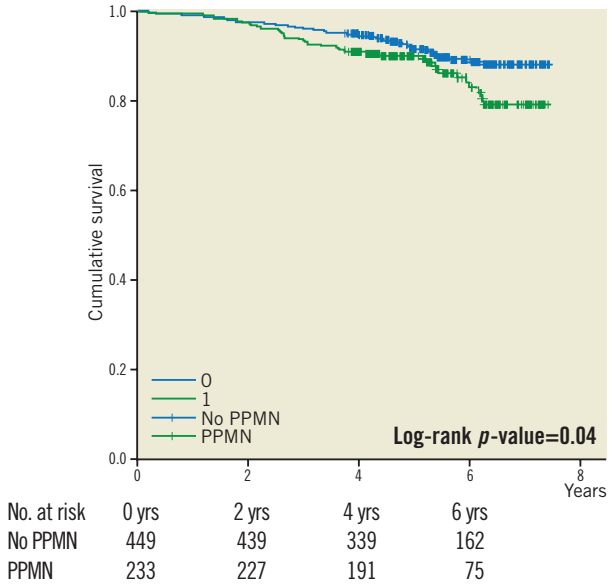

Figure 1. *Kaplan-Meier survival curve for periprocedural myonecrosis (PPMN), defined by the Third Universal Definition of MI (troponin level >5x URL).*

Multivariate logistic regression showed stent length (hazard ratio [HR] 1.02, 95% confidence interval [CI]: 1.01-1.03), congestive heart failure (HR 2.58, 95% CI: 1.22-5.47), multivessel CAD (HR 1.47, 95% CI: 1.02-2.10), transient no-reflow (HR 4.76, 95% CI: 1.16-2.10), and glycoprotein IIb/IIIa inhibitor use (HR 2.01, 95% CI: 1.03-3.92) to be independent predictors of PPMN.

Table 5 shows short, medium, and long-term outcomes. At 30 days, there were no deaths and only two patients experienced spontaneous myocardial infarctions, both in the PPMN group. At 12 months, there were four (0.9%) deaths in the no PPMN group and one (0.4%) in the PPMN group (p=0.5) with equivalent rates of MI (1.6% vs. 1.7%, p=0.88). At a mean follow-up of 5.3±1.3 years, mortality was higher in the PPMN group with 34 (14.6%) deaths compared to 43 (9.6%) deaths in those without PPMN (p=0.04). The Kaplan-Meier survival curve in **Figure 1** shows that patients with PPMN had worse long-term outcomes.

Multivariate analysis using a Cox proportional hazards model showed PPMN was not an independent predictor of long-term mortality (odds ratio [OR] 1.52, 95% CI: 0.95-2.43, p=0.08) **(Table 6)**. Periprocedural MI defined by SCAI (troponin rise ≥70x ULN or ≥35x ULN with new clinical or electrocardiographic evidence of ischaemia) or the Second Universal Definition of MI (troponin rise >3x URL) was also not associated with worse prognosis by Kaplan-Meier analysis **(Figure 2, Figure 3)**.

Table 5. Short, medium-term and long-term clinical outcomes.

		No PPMN (n=449)	PPMN (n=233)	*p*-value
Long-term mortality*, n (%)		43 (9.6)	34 (14.6)	0.04
30 days	Mortality, n (%)	0 (0)	0 (0)	–
	MI, n (%)	0 (0)	2 (0.9)	0.15
12 months	Mortality, n (%)	4 (0.9)	9 (3.9)	0.20
	MI, n (%)	7 (1.6)	4 (1.7)	0.88

*Mean (±standard deviation) follow-up times for the No PPMN and the PPMN groups were 5.4±1.3 and 5.2±1.4 years, respectively ($p=0.11$). MI: myocardial infarction; PPMN: post-procedural myocardial necrosis

Discussion

In this single-centre observational study, we assessed the long-term prognostic implication of periprocedural myonecrosis defined by troponin I elevation in patients with stable coronary

Table 6. Cox proportional hazards model for long-term mortality.

	No PPMN (n=449)	PPMN (n=233)	*p*-value
PPMN	1.52	0.95 - 2.43	0.08
Age (per year)	1.08	1.05 - 1.11	<0.01
Staged PCI	1.82	1.03 - 3.21	0.04
Previous CABG	2.05	1.18 - 3.58	0.01
Chronic lung disease	2.21	1.13 - 4.30	0.02
Peripheral vascular disease	2.91	1.58 - 5.38	<0.01
eGFR <60 ml/min/1.73 m^2	1.64	0.99 - 2.70	0.05
Congestive heart failure	2.10	0.96 - 4.59	0.06
Diabetes mellitus	1.33	0.81 - 2.02	0.26
Single-vessel CAD	0.73	0.38 - 1.40	0.34
Previous MI	1.20	0.70 - 1.90	0.59
Previous stroke	1.13	0.53 - 2.42	0.76

CAD: coronary artery disease; CABG: coronary artery bypass graft surgery; eGFR: estimated glomerular filtration rate; MI: myocardial infarction; PCI: percutaneous coronary intervention; PPMN: post-procedural myonecrosis

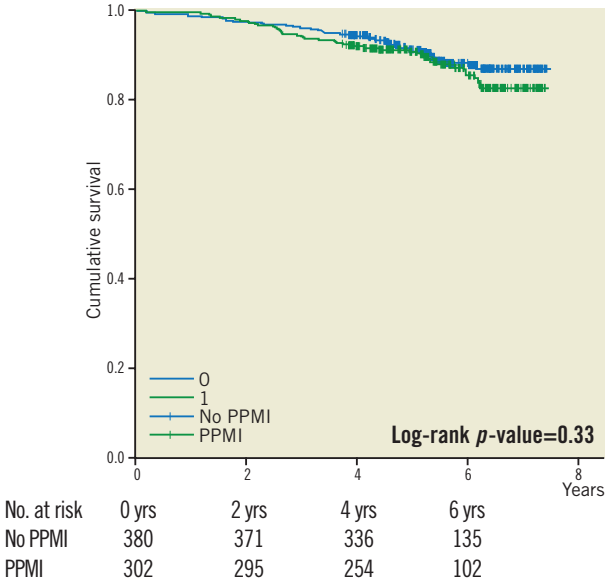

Figure 2. *Kaplan-Meier survival curve for periprocedural MI, defined by the Second Universal Definition of MI (troponin level >3x URL).*

artery disease undergoing elective PCI. Several findings have particular clinical importance. Firstly, the rate of periprocedural myonecrosis and MI varies widely depending on the definition used. Secondly, independent predictors of PPMN include a combination of patient-specific characteristics (congestive heart failure, multivessel CAD, chronic lung disease) and procedural factors (length of stent required, use of GP IIb/IIIa inhibitors, presence of transient no-reflow). Finally, PPMN was not an independent predictor of long-term mortality.

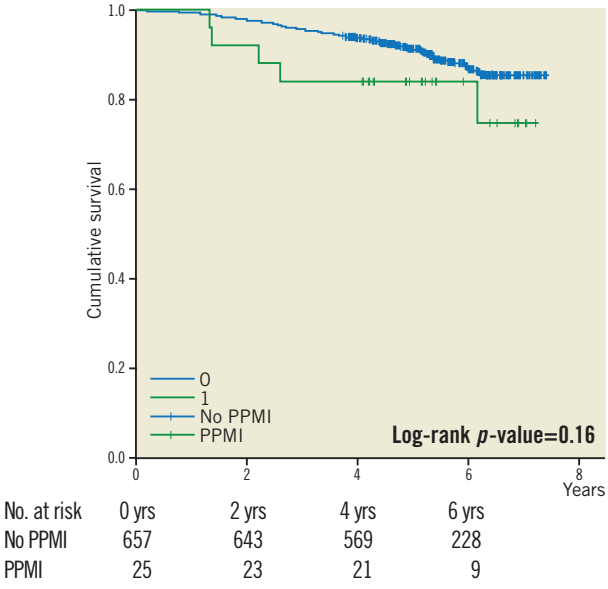

Figure 3. *Kaplan-Meier survival curve for periprocedural MI, defined by the SCAI (troponin level ≥70x ULN or ≥35x ULN with new clinical or electrocardiographic evidence of ischaemia).*

Diagnosing a periprocedural MI in clinical practice is complicated by the varying definitions proposed in international guidelines over the past decade[1-4]. Previously, cardiac biomarker elevation alone was required to diagnose a periprocedural MI[2,4]. However, in the widely used Third Universal Definition of MI, a significant biomarker elevation alone post PCI is no longer an "infarction" but merely myonecrosis[3]. In an attempt to link diagnosis to prognosis, the SCAI proposed a "new definition of a clinically relevant MI after revascularisation"[1]. In this latest attempt to define a periprocedural MI, a considerably higher troponin cut-off has been postulated (≥70x ULN alone or ≥35x ULN with new clinical or electrocardiographic evidence of ischaemia). Our study highlights the clinical difficulties associated with interpreting cardiac biomarkers after elective PCI in the context of differing definitions – periprocedural MI could have been diagnosed in 2% or 44% of our patients. Given the significant implications for the patient, the interventional cardiologist and the healthcare system, the pursuit of a uniform definition for periprocedural MI that has prognostic relevance should continue.

The association between periprocedural MI and mortality, defined by creatine kinase (CK) or CK-MB alone is robust[10-13,19-22]. When defined by cardiac troponin, this association is less certain[1]. Given the greater sensitivity of cardiac troponin, the rate of periprocedural MI diagnosed has increased[16,23]. The diagnostic criteria, however, may be too sensitive to have prognostic implication[5,15]. Aside from SCAI, a number of research groups have proposed differing cut-offs for prognostically significant post-PCI troponin elevations[14-16]. In our study a troponin elevation >5x URL was associated with an unadjusted higher mortality rate while elevations >3x URL or ≥70x ULN were not. However, when adjusting for other confounding variables, PPMN defined by the Third Universal Definition of MI was not an independent predictor of long-term mortality.

The main strength of our study is its long-term mean follow-up of 5.3±1.3 years. To our knowledge, this is the longest study assessing the prognostic value of PPMN diagnosed with cardiac troponin by the Third Universal Definition of MI in patients undergoing elective PCI. Previous studies with shorter follow-up have also failed to find an association between periprocedural myocardial myonecrosis, defined by varying criteria, and mortality[16,20,23,24]. These negative findings have not been unanimous. Prasad et al showed that any troponin elevation post PCI, in the context of normal baseline levels, was associated with increased mortality at two years[25].

It is plausible that PPMN is an epiphenomenon in patients with stable CAD undergoing elective PCI. The extent of atherosclerotic burden has been associated with PPMN and is also an independent predictor of mortality[26-31]. Thus, PPMN may be a marker of advanced atherosclerosis rather than a prognostic factor in its own right. Our findings support this proposition, as longer stent length and multivessel CAD, both variables that suggest advanced atherosclerosis, were independent predictors of PPMN but PPMN itself did not predict long-term mortality. However, distal

microembolisation is also important in the aetiology of PPMN: this is more likely to occur in patients with advanced atherosclerosis who require multi-lesion PCI and longer stent lengths.

As previously stated, the Third Universal Definition of MI requires clinical, angiographic, electrocardiographic or imaging-related evidence of ischaemia along with a troponin elevation >5x URL. However, angiographic complications are not always associated with significant biomarker elevations and biomarker elevations can occur without angiographic complications[6-9]. In our study, only 2% of patients experienced an MI by this definition although a higher number had troponin elevations ≥70x ULN, consistent with a periprocedural MI by the SCAI definition[1]. It is possible that subtle angiographic complications, such as loss of very small side branches, were not recognised. Furthermore, microinfarcts are known to be difficult to identify even with cardiac magnetic resonance imaging[15]. This may account for our relatively low rate of "myocardial infarction" but our high rate of "myonecrosis". An advantage of our study is the inclusion of consecutive patients who had post-PCI troponin measured. Other studies only analysed selected patients who had biomarkers assessed as a result of clinical suspicion of periprocedural complications[24]. This allowed us to undertake an unbiased analysis of the link between PPMN and long-term mortality.

Limitations

A significant limitation of our study is the absence of pre-procedural cardiac troponin levels. Jeremias et al have shown that up to 6% of patients with stable CAD undergoing elective PCI have elevated pre-PCI troponin levels[32]. Furthermore, pre-intervention rather than post-intervention troponin elevation may have greater prognostic significance[23,32]. In our study, patients with PPMN had higher rates of congestive heart failure and were more likely to be undergoing staged PCI. It is conceivable that these patients could have had elevated troponin levels at baseline. In attempting to correct for confounding factors, we found congestive heart failure was an independent predictor of PPMN while staged PCI was not. This highlights the importance of pre-procedural troponin levels in the diagnosis of periprocedural MI[3,33-35]. A further limitation of our study is the potential underestimation of patients classified as having a periprocedural MI by the SCAI criteria as we may not have captured true peak troponin levels. Lastly, our study's single-centre retrospective design has inherent drawbacks. Although we have attempted to account for confounding variables in our multivariate analyses, unmeasured and unaccounted factors may exist. Thus, these results should be considered as hypothesis-generating rather than conclusive.

Conclusion

The incidence of periprocedural myonecrosis and/or MI varies widely depending on the definition utilised. Periprocedural myonecrosis, defined by the Third Universal Definition of MI, does not appear to have prognostic implications for patients with stable CAD undergoing elective PCI.

Impact on daily practice

Periprocedural troponin elevations are common in patients undergoing elective PCI for stable CAD. Our study, which has the longest reported follow-up, suggests that periprocedural myonecrosis may not have prognostic implication in patients with stable CAD. Given the prognostic uncertainty of isolated post-PCI troponin elevation, at present it should only be interpreted in the context of ischaemia, as per the Third Universal Definition of MI.

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Conflict of interest statement

The authors have no conflicts of interest to declare.

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