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Prognostic Implications of Evolving Universal Definitions of Periprocedural Myocardial Infarction in Patients With Acute Coronary Syndrome

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BACKGROUND: The universal definition of percutaneous coronary intervention (PCI)–related myocardial infarction (MI) has been substantially updated over the years, including an increase in the biomarker threshold (from 3 to 5 times the upper reference limit) and the introduction of ancillary criteria such as ischemic symptoms and electrocardiographic or angiographic complication. The impact of these changes in patients with acute coronary syndrome (ACS) remains incompletely understood. The objective of this study was to compare prognostic implications of evolving universal definitions of PCI-MI in a large cohort of patients with ACS from the MATRIX trial (Minimizing Adverse Haemorrhagic Events by Transradial Access Site and Systemic Implementation of AngioX).

METHODS: Among 6724 patients undergoing PCI in the MATRIX trial, PCI-MI was prospectively adjudicated by the second, third and fourth universal definition of MI (UDMI). The 2 co-primary end points were all-cause and cardiovascular death (from 24 hours to 1 year after PCI) in patients with non–ST-segment–elevation ACS. Hazard ratios and 95% CIs were generated for primary and secondary end points with the use of Cox proportional hazards time-to-event analyses for each MI definition.

RESULTS: PCI-MI occurred in 590 patients (9%) with the second UDMI, 193 (3%) with the third UDMI, and 182 (3%) with the fourth UDMI applied in the overall ACS population. Among patients with non–ST-segment–elevation ACS, the corresponding figures were 15%, 5%, and 5%. Only PCI-MI defined by the fourth UDMI in patients with non–ST-segment–elevation ACS was associated with increased risks of all-cause (hazard ratio, 2.08 [95% CI, 1.00–4.30]; *P*=0.048) and cardiovascular (hazard ratio, 2.62 [95% CI, 1.03–6.65]; *P*=0.043) death. In patients with ST-segment–elevation myocardial infarction, PCI-MI was uncommon (1% to 4% depending on the working definition) and was not associated with increased mortality. In the absence of objective ancillary criteria (electrocardiographic and angiographic complications), isolated troponin elevations up to 20 times the upper reference limit were not associated with increased mortality risk.

CONCLUSIONS: PCI-MI defined according to the fourth UDMI was associated with increased risks of 1-year mortality only in patients with non–ST-segment–elevation ACS. These data support the evolution of the universal definition of PCI-MI.

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Key Words: acute coronary syndrome ■ myocardial infarction ■ percutaneous coronary intervention

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Clinical Perspective

What Is New?

- In patients with non–ST-segment–elevation acute coronary syndrome undergoing percutaneous coronary intervention (PCI), PCI-related myocardial infarction (MI) defined only by the fourth (but not the second or the third) universal MI definition was associated with increased risk of mortality.
- In patients with ST-segment–elevation MI undergoing PCI, PCI-MI was very rare and was not associated with increased mortality risk.

What Are the Clinical Implications?

- These findings support the evolution of the universal MI definition that recommends a clinical definition of PCI-MI combining a troponin elevation of at least 5 times the upper reference limit with objective evidence of PCI-related ischemic complications across patients with non–ST-segment–elevation acute coronary syndrome.
- Future studies should refine the PCI-MI definition for further use in practice and across trials.

Nonstandard Abbreviations and Acronyms

ACS	acute coronary syndrome
CK-MB	creatine kinase-MB
cTn	cardiac troponin
HR	hazard ratio
MATRIX	Minimizing Adverse Haemorrhagic Events by Transradial Access Site and Systemic Implementation of AngioX
MI	myocardial infarction
NSTE	non–ST-segment–elevation
PCI	percutaneous coronary intervention
STEMI	ST-segment–elevation myocardial infarction
UDMI	Universal Definition of Myocardial Infarction
URL	upper reference limit

Percutaneous coronary intervention (PCI) represents the most frequent revascularization modality in patients with acute coronary syndrome (ACS) undergoing invasive management.[1,2] Improvements in revascularization techniques and devices,[3,4] along with advancements in pharmacological treatments,[5–7] have reduced the risk of periprocedural ischemic complications such as stent thrombosis, side-branch occlusion, and distal embolization of plaque debris in the past decade.[8,9] Nevertheless, post-PCI cardiac biomarker elevation, with or without additional manifestations of myocardial ischemia, is common after successful and apparently uncomplicated coronary interventions.[10]

Despite recent iterations of the Universal Definitions of Myocardial Infarction (UDMI),[11] evidence on the prognostic relevance of PCI-related myocardial infarction (MI) or type 4a MI remains unclear; some studies found an association between PCI-MI and mortality risk,[12–14] whereas others did not.[15,16] These discrepancies might reflect the use of high-sensitivity cardiac troponin (cTn) compared with creatine kinase-MB (CK-MB) as a biomarker, incomplete assessment of ancillary criteria, and inclusion of mixed populations, including patients with ACS and chronic coronary syndromes. Patients with ACS frequently exhibit increased cardiac biomarkers at baseline; therefore PCI-MI, has historically been defined by UDMI as a relative increase in cardiac biomarkers from baseline (≥20%) for patients with stable or falling values.[11,17] However, the later definitions were based mainly on expert consensus, and validation in a contemporary ACS cohort is lacking.

In a recent observational registry encompassing 1412 patients with non–ST-segment–elevation (NSTE) MI undergoing PCI, periprocedural myocardial injury (with and without type 4a MI) was associated with increased risks of adverse clinical events.[14] Type 4a MI showed the highest risk of 1-year all-cause mortality and major adverse cardiovascular events after multivariable adjustment. However, this study investigated retrospectively only the prognostic relevance of the latest iteration of the UDMI (eg, the fourth UDMI) in patients with ST-segment–elevation myocardial infarction non-STEMI (NSTEMI) with stable or falling cTnI levels at baseline.

In this study, we sought to prospectively investigate the prevalence, features, and prognostic relevance of PCI-MI defined by the Second, Third, and Fourth UDMI across the entire spectrum of patients with ACS undergoing PCI from the MATRIX trial (Minimizing Adverse Haemorrhagic Events by Transradial Access Site and Systemic Implementation of AngioX).[18,19]

METHODS

The data that support the findings of this study are available from the corresponding author on reasonable request.

Study Design and Population

This is a prespecified analysis of the MATRIX trial, a program of 3 independent randomized controlled, multicenter, superiority trials (NCT01433627) in patients with ACS undergoing invasive management.[20] In the first trial (MATRIX-Access), 8404 patients with ACS were randomly allocated to radial versus femoral access.[19,21] The MATRIX-Antithrombin and Treatment Duration compared bivalirudin with unfractionated heparin and prolonged post-PCI bivalirudin infusion with short-term bivalirudin administration in patients undergoing PCI.[18] The trial was

approved by the institutional review board at each participating site, and all patients gave written informed consent.

The inclusion and exclusion criteria of the MATRIX trial were previously reported.[20] All patients undergoing PCI enrolled in the MATRIX trial were eligible for this study. This study adhered to the Strengthening the Reporting of Observational Studies in Epidemiology reporting guidelines (Supplemental Material).

PCI-MI Definitions

PCI-MI was prospectively adjudicated according to the second,[22] third,[17] and fourth UDMI,[11] as displayed in Figure 1, by an independent clinical event committee blinded to randomized treatment allocation. The Second UDMI definition required a biomarker elevation of at least 3 times the upper reference limit (URL); the third and fourth UDMI required an elevation of 5 times the URL. It is important to note that the third and fourth UDMI also required ancillary criteria in addition to the post-PCI biomarker elevation. These criteria included new electrocardiographic changes, angiographic complications, or new ischemic symptoms in the third udmi, whereas the fourth UDMI restricted the ancillary evidence to objective criteria (ie, removed the symptoms; Figure 1).

The MATRIX protocol required the collection of cardiac biomarkers (cTnI or cTnT with or without CK-MB) at baseline (before PCI) and at prespecified time points (8, 16, and 24 hours) after PCI. Preprocedural and postprocedural troponin and CK-MB peak values were used for the present analysis. In patients with positive baseline biomarkers of myocardial necrosis, biomarkers trends before PCI were reported by the investigators in the case report form as stable or falling or rising and were verified by the clinical event committee using source documentation to discriminate PCI-MI from the index MI. In patients with STEMI, a re-elevation of cardiac biomarker (ie, a second peak) was necessary to adjudicate PCI-MI. ECG was performed at baseline, immediately after PCI (±30 minutes), at 24±1 hours after PCI, and at day 7 or hospital discharge (whichever came first). In case of PCI-MI, additional serial ECGs were collected, and cardiac biomarkers were systematically obtained at 6 to 8±1, 12±1, 24±1, and 48±1 hours. In case of recurrent ischemic events, echocardiography and angiography were repeated according to investigator discretion.

Follow-Up and Study Outcomes

The primary results of the MATRIX study have been reported previously.[18,19] The 2 co–primary end points of this analysis were all-cause and cardiovascular death (from 24 hours to 1 year after PCI) in patients with non–ST-segment–elevation acute coronary syndrome (NSTE-ACS). We also assessed

A Normal baseline cTn concentrations

	2nd Universal definition of MI	3rd Universal definition of MI	4th Universal definition of MI
Troponin threshold			
> 3x URL	■		
>5x URL		■	■
Ancillary criteria			
New ischemic ECG changes		■	■
New Q waves			■
New LBBB		■	
Imaging findings		■	■
Angiographic findings		■	■
Symptoms		■	

B Baseline cTn values are elevated and are stable or falling

	3rd Universal definition of MI	4th Universal definition of MI
Post-procedural cTn rise >20%	■	■
Ancillary criteria		
New ischemic ECG changes	■	■
New Q waves		■
New LBBB	■	
Imaging findings	■	■
Angiographic findings	■	■
Symptoms	■	

Figure 1. Criteria of periprocedural myocardial infarction according to the Universal definitions.
Criteria for periprocedural myocardial infarction (MI) definitions in patients with normal baseline troponin concentrations (**A**) and elevated and stable or falling baseline troponin values (**B**). *If cardiac troponin (cTn) levels are higher than the upper reference limit (URL) and still in the ascending phase (ie, markers are not stable or decreasing in ≥2 assessments taken before randomization), periprocedural MI is defined in the presence of symptoms (eg, chest pain) and new ST-segment elevation of ≥1 mm in ≥2 contiguous leads or new left bundle-branch block (LBBB; 1) or angiographic evidence of reocclusion of a previously patent coronary artery or bypass graft (2). For patients with elevated and stable or falling troponin values, no specific criteria are provided by the second universal definition of MI.

all-cause and cardiovascular death in the total ACS population, including patients presenting with STEMI. Secondary end points included cardiac death and noncardiovascular death in patients with NSTE-ACS and STEMI. End-point definitions of the MATRIX trial are presented in the Supplemental Material.

Statistical Analysis

All patients who underwent PCI from the MATRIX trial were included in this analysis, and clinical events from 24 hours to 1 year after PCI were considered. Differences across groups were assessed with the Student *t* test in case of continuous variables and the χ^2 or Fisher exact test in case of categorical data. Hazard ratios (HRs) and 95% CIs were generated for primary and secondary end points with the use of Cox proportional hazards time-to-event analyses for each MI definition. The proportional hazards assumption was assessed by visual assessment of log-log plots and with the 2-sided test of the scaled Schoenfeld residuals over time when ≥5 events were observed in each comparison group. Kaplan-Meier event curves were also generated for each definition. We also examined the relationship between mortality and thresholds of cTn elevation (>20% or >5× URL, >100% or >10× URL, and 200% or >20× URL) with or without ancillary criteria in patients with stable or declining troponin values. *P* values were 2 tailed, and values of $P<0.05$ were considered statistically significant in all analyses. The analyses were done with Stata release 17.0 (StataCorp LLC, College Station, TX).

RESULTS

Study Population and Patient Characteristics

Among 8404 patients enrolled in the MATRIX trial from 78 centers in Italy, the Netherlands, Spain, and Sweden between October 2011 and July 2014, 6724 patients (80%) underwent PCI and were included in the present analysis. At 1 year, complete follow-up information was available for 6719 of 6724 patients (99.9%) included in this analysis.

Baseline and procedural characteristics are presented in Table 1 and Tables S1 and S2. Patients with PCI-MI (according to at least one definition) were older and had higher prevalence of risk factors (arterial hypertension, dyslipidemia, smoking, previous MI, or revascularization) and comorbidities (peripheral vascular disease, previous cerebrovascular accident, or anemia) compared with patients without PCI-MI. Patients with PCI-MI more frequently underwent complex PCI and received longer stents, more contrast volume, and longer procedures than patients without PCI-MI (Table S2). Among patients without ST-segment elevation (n=3066), increased cardiac biomarkers at baseline were present in 2758 (89.95%).

A high-sensitivity cTn assay was available in 645 of 6724 patients (9.6%) included in the study.

Incidence of PCI-MI

The incidence of PCI-MI across the investigated definitions is presented in Figure 2. PCI-MI was 3 times more common with the second (n=590, 9.0%) than the third (n=193, 3%) or fourth (n=182, 3%) UDMI. The adjudication of PCI-MI was more common in patients with NSTE-ACS than patients with STEMI (Table S3), in whom the second UDMI remained the most frequent (15%), followed by the third UDMI (5%) and fourth UDMI (5%). Among patients with STEMI, the corresponding figures were 4%, 1% and 1%, respectively. A significant overlap across PCI-MI definitions was observed in both patients with NSTE-ACS and patients with STEMI (Table S3).

Absolute Rise in Cardiac Biomarkers and Frequency of Ancillary Criteria

In the overall cohort (Figure 3), absolute increase (baseline to peak) in troponin values >5× URL was more common when the third (86%) and fourth (91%) UDMI was applied compared with the second UDMI (82%). Patients fulfilling the second UDMI had a lower frequency of ancillary criteria compared with those fulfilling the third or fourth UDMI. Among the 193 patients fulfilling the third UDMI and 182 patients fulfilling the fourth UDMI, angiographic criteria (53% and 54%, respectively) and symptoms (49% and 48%, respectively) were the most frequent ancillary criteria, followed by new electrocardiographic changes (21% with both definitions), whereas imaging evidence of ischemia was rare (2% with both definitions). A consistent pattern distribution of cardiac biomarker elevation and ancillary criteria was observed among patients with NSTE-ACS and patients with STEMI when separately assessed (Table 2). Among patients with NSTE-ACS, cTn peak values were significantly higher in patients with than those without PCI-MI when the third and fourth, but not the second, UDMI was applied (Figure S1). Among patients with STEMI, cTn peak values were not significantly higher in subjects with than those without PCI-MI (Figure S1).

Relationship Between PCI-MI and Mortality

Clinical outcomes at 1 year according to the second, third, and fourth UDMI in the overall study cohort are summarized in Table S4. In the overall cohort, the risk of all-cause or cardiovascular mortality did not differ in patients with and those without PCI-MI, regardless of the working definition.

Among patients with NSTE-ACS, an increased risk of 1-year all-cause (HR, 2.08 [95% CI, 1.00–4.30]; $P=0.048$) and cardiovascular (HR, 2.62 [95% CI, 1.03–6.65]; $P=0.043$) mortality was observed in patients with PCI-MI based on the fourth UDMI (Figures 4 and 5; Table S5). A numerical increase in the risk of all-cause (HR, 1.96 [95% CI, 0.95–4.06]; $P=0.069$) and cardiovascular (HR, 2.47 [95% CI, 0.97–6.27]; $P=0.057$) mortality

Table 1. Baseline and Procedural Characteristics of Patients Fulfilling the Second, Third, and Fourth UDMI

	Second UDMI (n=590)	Third UDMI (n=193)	Fourth UDMI (n=182)
Baseline characteristics			
Mean age, y	67.2±11.3	67.8±11.1	68.1±11.1
Male sex	446 (76)	140 (73)	130 (71)
BMI, kg/m^2	27.0±4.0	27.0±4.2	27.0±4.2
Diabetes	158 (27)	50 (26)	46 (25)
Smoker	301 (51)	85 (44)	77 (42)
Hypercholesterolemia	284 (48)	89 (46)	81 (45)
Hypertension	399 (68)	136 (71)	130 (71)
Family history of CAD	175 (30)	56 (29)	53 (29)
Previous MI	104 (18)	47 (24)	41 (23)
Previous PCI	104 (18)	36 (19)	31 (17)
Previous CABG	27 (5)	13 (7)	12 (7)
Previous CVA	41 (7)	18 (9)	17 (9)
Peripheral vascular disease	64 (11)	23 (12)	22 (12)
COPD	36 (6)	10 (5)	9 (5)
Anemia*	141 (24)	58 (30)	56 (31)
Dialysis	1 (1)	1 (1)	1 (1)
Clinical presentation			
ACS (STEMI)	145 (25)	40 (21)	37 (20)
NSTE-ACS negative	51 (9)	17 (9)	15 (8)
NSTE-ACS positive	394 (67)	136 (71)	130 (71)
NSTE-ACS with ST-segment deviation	196 (33)	62 (32)	58 (32)
NSTE-ACS with T-wave inversion	147 (25)	54 (28)	51 (28)
Cardiac arrest	5 (1)	1 (1)	1 (1)
Killip class III or IV	12 (2)	5 (3)	4 (2)
Procedural characteristics			
Radial access	273 (46)	80 (42)	78 (43)
IABP	3 (1)	2 (1)	2 (1)
Bailout GPI	38 (6)	28 (15)	27 (15)
UFH	310 (53)	112 (58)	109 (60)
Bivalirudin	294 (50)	88 (46)	80 (44)
TIMI flow after procedure			
0 or 1	12 (2)	8 (4)	7 (4)
2	11 (2)	8 (4)	8 (4)
3	553 (96)	175 (92)	165 (92)
Coronary stenosis <30%	557 (94)	174 (90)	166 (91)
Full procedural success	542 (92)	162 (84)	154 (85)
Treated vessels			
Left main coronary art.	25 (4)	12 (6)	11 (6)
Left anterior descending	300 (51)	103 (53)	99 (54)
Left circumflex artery	185 (31)	65 (34)	61 (34)
Right coronary artery	195 (33)	66 (34)	60 (33)
Bypass graft	4 (1)	0 (0)	0 (0)
≥2-vessel PCI	112 (19)	48 (25)	44 (24)
Overall stent length, mm	87.0±53.2	99.4±60.8	99.5±62.0
Fluoroscopy time, min	16.3±10.6	18.6±12.5	18.8±12.7
Total contrast volume, mL	203.1±89.7	225.5±92.7	226.3±94.1
Duration of procedure, min	61.1±28.9	66.2±34.2	66.5±34.7

ACE indicates angiotensin-converting enzyme; BMI, body mass index; CABG, coronary artery bypass grafting; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; GPI, glycoprotein IIb/IIIa inhibitor; IABP, intra-aortic balloon pump; MI, myocardial infarction; NSTE-ACS, non–ST-segment–elevation acute coronary syndrome; PCI, percutaneous coronary intervention; STEMI, ST-segment–elevation myocardial infarction; TIMI, Thrombolysis in Myocardial Infarction; UDMI, universal definition of myocardial infarction; and UFH, unfractionated heparin.

Values are number (percentage), mean±SD, number, or median (interquartile range).

*Less than 12g/dL for women, and <13g/dL for men.

was observed with the third UDMI, whereas the mortality risk was similar based on the presence or absence of the second UDMI (Figures 4 and 5; Table S5). The increase in cardiovascular mortality mainly accrued from cardiac mortality in both patients with NSTE-ACS (Table S5; Figure S2) and patients with STEMI (Table S6; Figure S3).

Among patients with STEMI, the risk of all-cause or cardiovascular mortality did not differ in patients with and those without PCI-MI, regardless of the adopted definition (Figure S4 and S5). No significant heterogeneity of the effect by sex was observed in patients with NSTE-ACS (Table S7) and patients with STEMI (Table S8). The proportional hazards assumption was met for all comparisons (Table S9; Figures S6 and S7).

Prognostic Impact of Different Threshold Values of Troponin and Presence of Ancillary Criteria

The relationship between mortality and various troponin increase thresholds with or without ancillary criteria among patients with NSTE-ACS is illustrated in Figure 6. Isolated increase of cTn (eg, without ancillary criteria) up to 20× URL was not associated with higher all-cause or cardiovascular mortality risks.

A >5× URL/>20% troponin rise was associated with a borderline increase of all-cause or cardiovascular mortality when combined with angiographic criteria (HR, 2.50 [95% CI, 0.96–6.47]; *P*=0.059; HR, 2.97 [95% CI, 0.85–10.34]; *P*=0.087, respectively) and significantly higher mortality when combined with electrocardiographic criteria (HR, 3.57 [95% CI, 1.09–11.68]; *P*=0.036; HR, 4.69 [95% CI, 1.07–20.51]; *P*=0.040, respectively). On the other hand, mortality risk was not increased when a 5× URL/>20% troponin rise

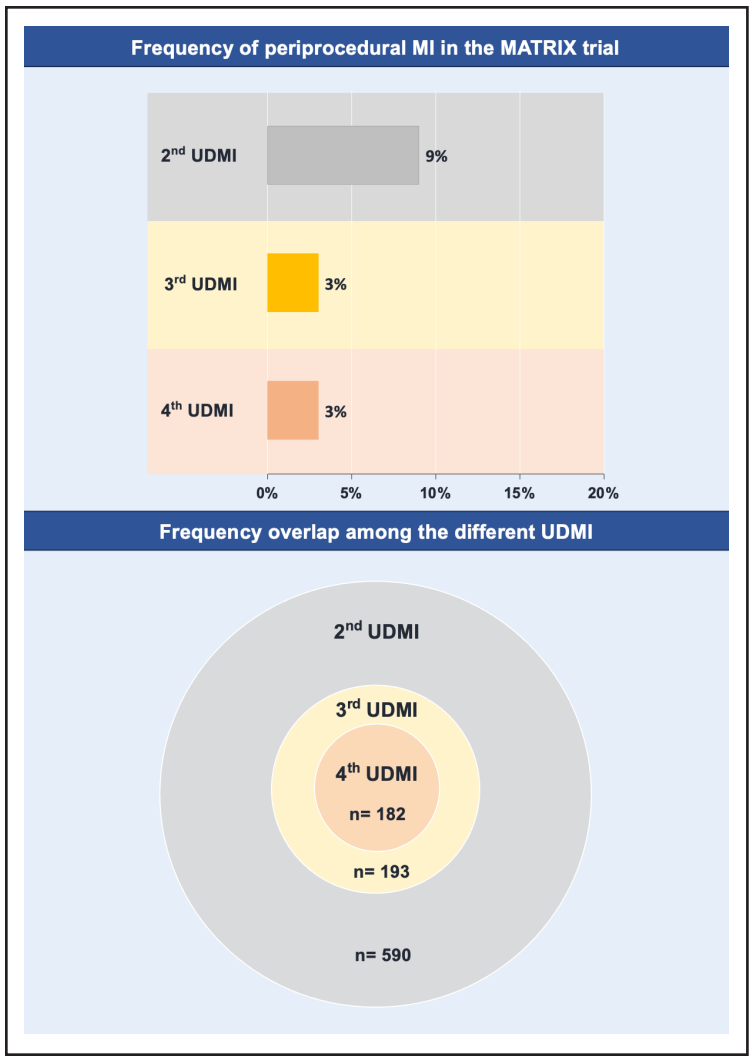

Figure 2. Frequency of periprocedural MI and overlap between the second, third, and fourth UDMI.
MI indicates myocardial infarction; and UDMI, universal definition of myocardial infarction.

was combined with symptoms (HR, 1.49 [95% CI, 0.46–4.89]; *P*=0.510; HR, 0.93 [95% CI, 0.12–6.99]; *P*=0.941, respectively). It is important to note that the directionality of all HRs and 95% CI was consistent across analyses, indicating a uniform pattern of elevated mortality risk regardless of the magnitude of troponin increase or ancillary criteria.

DISCUSSION

In this large, multicenter study we compared the incidence and prognostic relevance of 3 consecutive iterations of the universal definitions of PCI-MI in patients across the entire spectrum of patients with ACS with several important implications that may be summarized as follows:

First, among the primary cohort of patients with NSTE-ACS, the third UDMI (5%) and fourth UDMI (5%) were 3 times less common than the second UDMI (15%), and only the fourth, but not the second or third UDMI, had >2-fold higher risks of all-cause and cardiovascular mortality.

Second, isolated increase of cTns, even when very high thresholds (ie, >20× URL) are used, was not associated with higher mortality risk in absence of ancillary criteria.

Third, angiographic criteria and symptoms were consistently the most common ancillary criteria across the UDMI definitions; however, only electrocardiographic changes and angiographic criteria were associated with a significant and numerical increase, respectively, of mortality at 1 year combined with >20% or >5× URL troponin elevation among patients with NSTE-ACS.

Fourth, the current data do not support the inclusion of PCI-MI as end point in clinical trials of patients presenting with STEMI.

Frequency and Determinants of PCI-MI in ACS

Among patients undergoing PCI, the relationship between PCI-MI and adverse events is still incompletely defined, particularly regarding the magnitude and type (cTn versus CK-MB) of cardiac biomarker elevation with

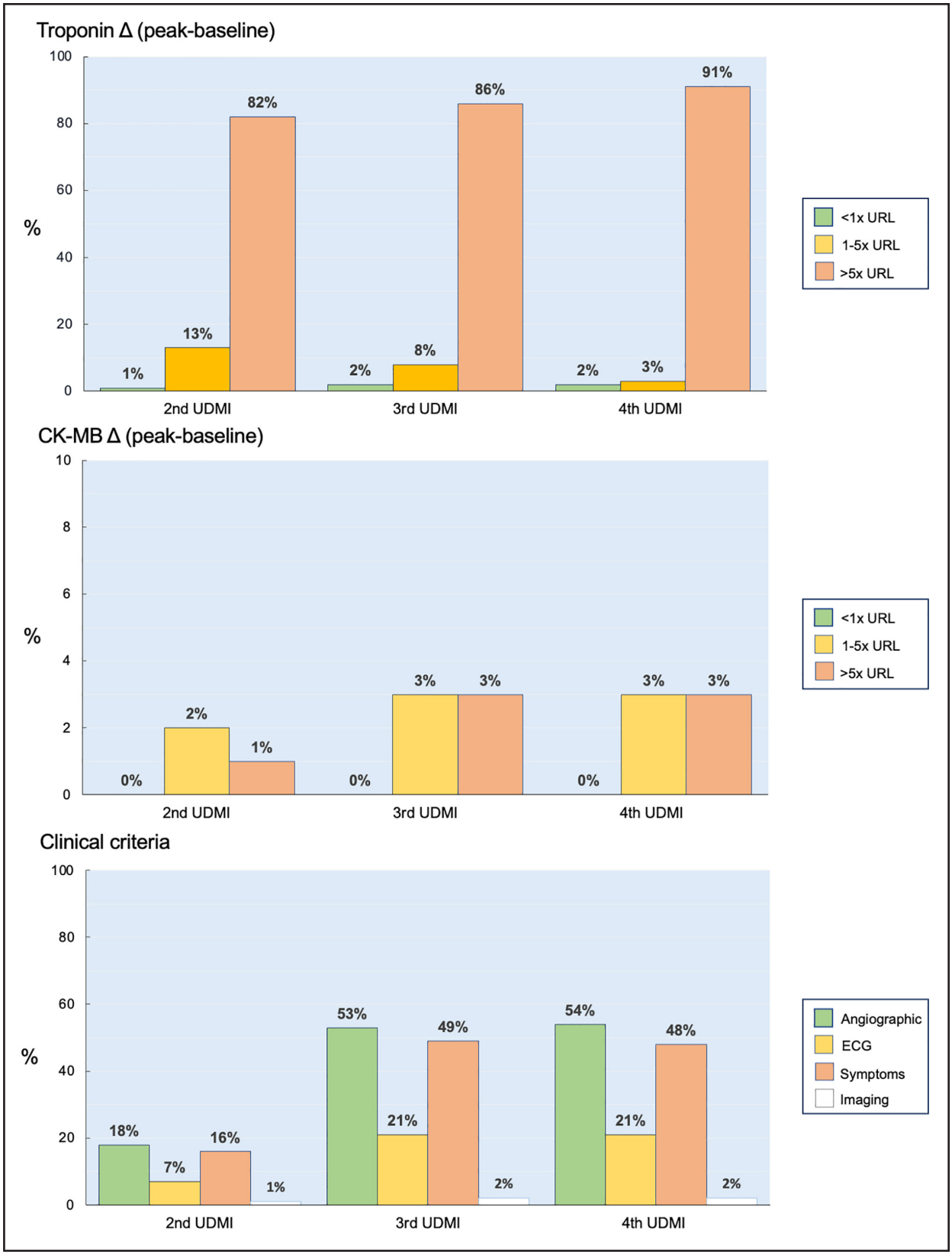

Figure 3. Absolute increase in cardiac biomarkers and frequency of ancillary criteria according to different definitions of periprocedural myocardial infarction.

A and **B**, Absolute rise in troponin or creatine kinase-MB (CK-MB; baseline to peak) values according to different definitions. **C**, Frequency of electrocardiographic, angiographic, clinical, and echocardiographic ancillary criteria. UDMI indicates universal definition of myocardial infarction; and URL, upper reference limit.

Table 2. Absolute Rise in Troponin and CK-MB From Baseline and Ancillary Criteria in Patients With Periprocedural MI According to the Second, Third, and Fourth UDMI Among Patients With NSTE-ACS and STEMI

NSTE-ACS	Second UDMI, n (%)	Third UDMI, n (%)	Fourth UDMI, n (%)
NSTE-ACS, n	445	153	145
Δ Troponin (peak—baseline)			
<1× URL	3 (1)	3 (2)	3 (2)
1–5× URL	63 (14)	13 (8)	5 (3)
>5× URL	366 (82)	135 (88)	135 (93)
Δ CK-MB (peak—baseline)			
<1× URL	0 (0)	0 (0)	0 (0)
1–5× URL	4 (1)	2 (1)	2 (1)
>5× URL	5 (1)	3 (2)	3 (2)
Ancillary criteria			
Angiographic	82 (18)	79 (52)	77 (53)
ECG	35 (8)	34 (22)	32 (22)
Symptoms	80 (18)	78 (51)	72 (50)
Imaging	3 (1)	3 (2)	3 (2)
Unknown	1 (0)	0 (0)	0 (0)
STEMI, n	145	40	37
Δ Troponin (peak—baseline)			
<1× URL	0 (0)	0 (0)	0 (0)
1–5× URL	14 (10)	3 (8)	0 (0)
>5× URL	116 (80)	31 (78)	31 (84)
Δ CK-MB (peak—baseline)			
<1× URL	0 (0)	0 (0)	0 (0)
1–5× URL	8 (6)	3 (8)	3 (8)
>5× URL	2 (1)	2 (5)	2 (5)
Ancillary criteria			
Angiographic	24 (17)	23 (57)	22 (59)
ECG	8 (6)	7 (18)	7 (19)
Symptoms	16 (11)	16 (40)	15 (41)
Imaging	0 (0)	0 (0)	0 (0)
Unknown	0 (0)	0 (0)	0 (0)

CK-MB indicates creatine kinase-MB; MI, myocardial infarction; NSTE-ACS, non–ST-segment–elevation acute coronary syndrome; STEMI, ST-segment–elevation myocardial infarction; UDMI, universal definition of myocardial infarction; and URL, upper reference limit.

respect to clinical, angiographic, electrocardiographic, and imaging criteria of new myocardial ischemia. Small studies using intracoronary Doppler guide wires have demonstrated that distal embolization of thrombus or plaque debris after balloon inflation or stent implantation is not infrequent.[23] However, the impact of post-PCI cardiac biomarkers elevations on hard clinical end points remains controversial in ACS. Mounting evidence suggests that the magnitude of post-PCI cTn elevation is linearly correlated with a greater lipid core burden[24] and a higher frequency of thin-cap fibroatheroma[25] by intravascular imaging. In addition, patients with ACS frequently exhibit large thrombus burden, a more complex and diffuse coronary artery disease, and a widespread activation of the inflammatory and coagulation cascade, which increase the risk of distal embolization, microvascular obstruction, and myocardial injury.[26]

The prevalence of PCI-MI largely varies, depending on the definition used and the patient population. A recent real-world registry of patients with chronic coronary syndrome treated by PCI found that PCI-MI, defined by the third and fourth UDMI, occurred in a significant proportion of patients (18% and 14.9% of patients, respectively).[27] Both definitions were prognostically relevant and were associated with a 76% (third UDMI) and 93% (fourth UDMI) relative risk increase of cardiac mortality at 1 year.[27] In another observational registry including 1412 patients with NSTEMI undergoing PCI, type 4 MI according to the fourth UDMI occurred in 17%, and periprocedural myocardial injury was seen in 20.4%. At variance with this study, we found that PCI-MI occurred at least 3 times less frequently with the third or fourth UDMI (5%) in patients with NSTE-ACS. A possible explanation for this lower prevalence of type 4a MI might lie in the unselected inclusion of patients with NSTEMI regardless of cardiac biomarker trend (eg, including patients with pre-PCI cardiac cTn rise as those with stable or falling values).

Prognostic Relevance of Periprocedural Myocardial Injury and Infarction

To the best of our knowledge, this is the largest study demonstrating that, among patients with NSTE-ACS undergoing PCI, PCI-MI defined by the fourth, but not the second or third, UDMI is associated with a 2-fold higher risk of all-cause and a 3-fold higher risk of cardiovascular mortality at 1 year. Troponin increase in isolation was not associated with greater mortality. In addition, not all ancillary criteria carried incremental mortality risk when assessed in combination with troponin rise, although symptoms and angiographic criteria were the most common ancillary criteria across all definitions and only new electrocardiographic changes or angiographic criteria were associated with higher mortality in combination with troponin rise.

These findings are relevant for the maturation of the definition of myocardial infarction in the setting of PCI and support the distinction between myocardial injury (ie, an isolated troponin elevation) and MI, a clinical diagnosis defined by additional procedural related ischemic complications, especially if they are objective. Symptoms after PCI are by definition subjective, have varying causes that may be potentially unrelated to myocardial ischemia or may be caused by the index MI, and are harder to standardize. It is also possible that a larger degree of troponin elevation or more sophisticated methodologies for the

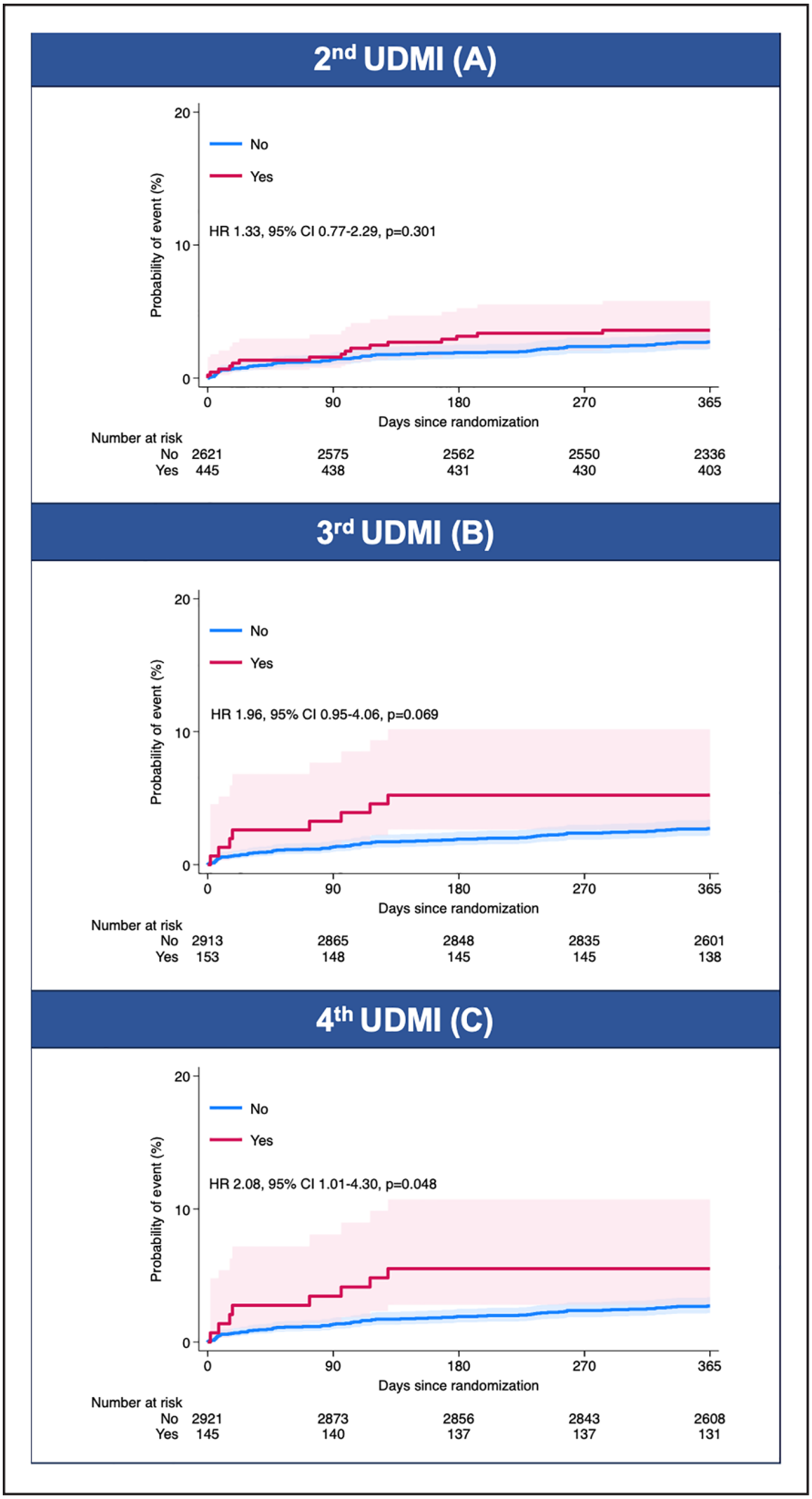

Figure 4. Kaplan-Meier cumulative incidence curves for all-cause death according to different definitions of myocardial infarction in patients presenting with non–ST-segment–elevation acute coronary syndrome. HR indicates hazard ratio; and UDMI, universal definition of myocardial infarction.

assessment of troponin trends are required for these to be prognostically relevant.[28]

Our study confirms and extends previous observations from the CHAMPION (Cangrelor Versus Standard Therapy to Achieve Optimal Management of Platelet Inhibition) PLATFORM and CHAMPION PCI trials,[29] which included 13 968 patients (89% with ACS). PCI-MI was defined in those studies as CK-MB elevation ≥3× URL

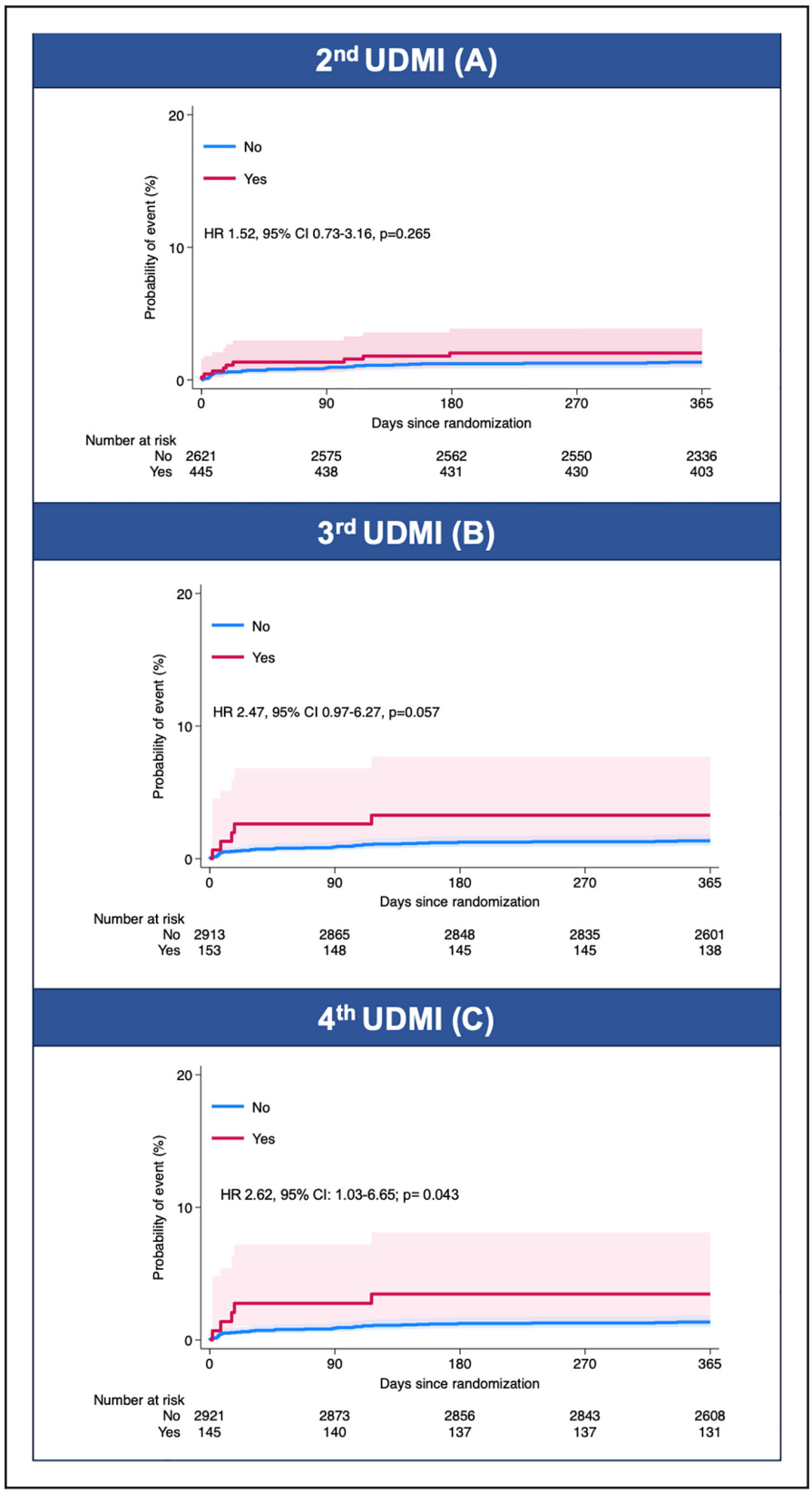

Figure 5. Kaplan-Meier cumulative incidence curves for cardiovascular death according to different definitions of myocardial infarction in patients presenting with non–ST-segment–elevation acute coronary syndrome.
HR indicates hazard ratio; and UDMI, universal definition of myocardial infarction.

and ≥150% of the nadir or prerandomization value (if baseline biomarker values were elevated) or the appearance of new Q-waves; if CK-MB was not available, then CK, cTnI, or cTnT was used to define PCI-MI. PCI-MI occurred in 7.2% and 2.0% of patients with NSTEMI and STEMI, respectively. PCI-MI was associated with a 2-fold higher mortality risk at 1 year (HR, 2.30 [95% CI, 1.76–3.01]; $P<0.001$). CK-MB elevations <10× URL without

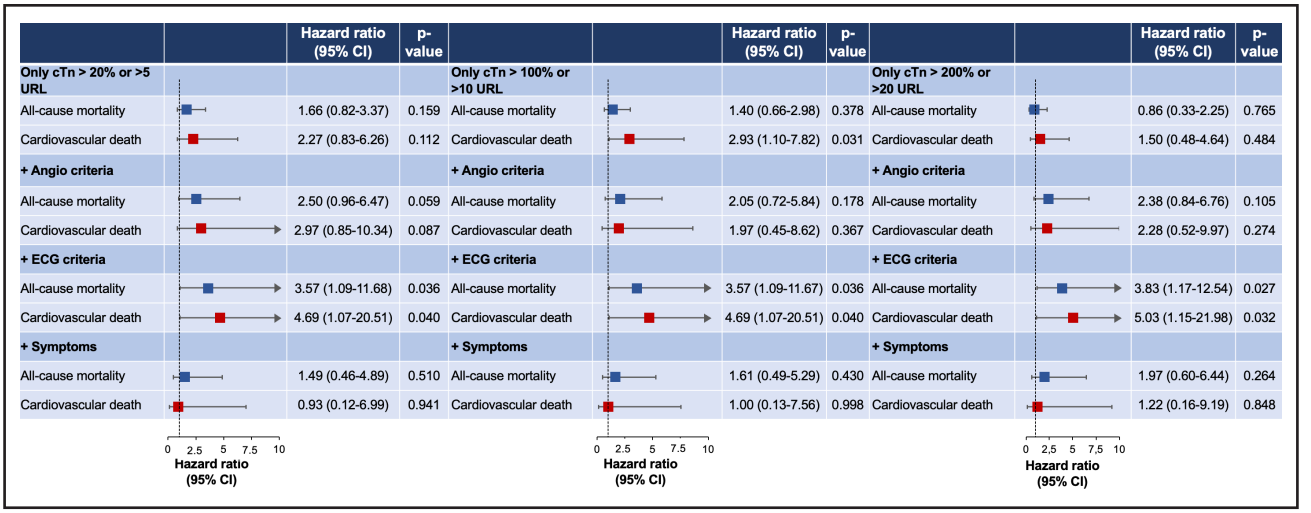

Figure 6. Clinical outcomes among patients with non-ST-segment elevation acute coronary syndrome with stable or declining troponin values.

Periprocedural myocardial injury or infarction was defined with different biochemical criteria (cardiac troponin [cTn] >20% or 5× upper reference limit [URL], >100% or 10× URL, and >200% or >20× URL) with or without ancillary criteria.

additional criteria did not carry considerable prognostic weight.[28]

A recent study by Armillotta et al[14] showed that patients with PCI-MI (defined as post-PCI cTnI increase >20% with an absolute postprocedural value of ≥5× the 99th percentile URL) had a 3-fold higher risk of 1-year mortality compared with those without PCI-MI. At variance with our findings, in this study, post-PCI Δ cTnI increase of >40% was associated with a 4-fold increase in the risk of 1-year all-cause mortality, regardless of the presence of ancillary criteria. Some aspects deserve careful consideration in the interpretation of these apparently discrepant findings. First, the study by Armillotta et al used a registry of 1412 patients with NSTEMI from 2 participating sites in Italy, whereas our study is a randomized trial of 6724 (3066 with NSTEMI) across 79 sites in Europe, thereby providing greater statistical power and broader generalizability. In addition, a retrospective periprocedural myocardial injury adjudication was implemented by Armillotta et al according to a single definition, whereas all end points, including PCI-MI and cause-specific mortality, were prospectively adjudicated by an independent clinical event committee in MATRIX according to prespecified definitions.

Implications for Current and Future Guidelines and Clinical Trials

Our study may have implications for current and future definitions of PCI-MI.

First, our findings suggest that in patients with ACS, a diagnosis of PCI-MI based only on biomarkers may have limited discrimination and clinical significance. The integration of additional criteria for PCI-related ischemic complications may potentially increase operational complexity and costs but could help identify a minority of prognostically relevant events. Overall, this evidence supports the transition from a biomarker-based definition (second UDMI) to a clinical definition including symptoms and objective evidence (third UDMI) and eventually to the fourth UDMI definition in which ancillary criteria were restricted to objective evidence only (ie, symptoms were excluded). Objective ancillary evidence after PCI, typically represented by electrocardiographic and angiographic complications, is therefore diagnostically important and should be systematically acquired in trials of patients with NSTE-ACS.

The accurate definition of PCI-MI may influence the study results and have implications on their interpretation, especially when its incidence is expected to vary across randomized treatments. For example, in the ISCHEMIA trial (International Study of Comparative Health Effectiveness With Medical and Invasive Approaches),[30] the results differed depending on the PCI-MI definition. With the primary MI definition (>5× URL CK-MB elevation within 48 hours with additional criteria), no differences in the primary composite end point between the invasive and conservative strategy groups were observed. Conversely, as a result of the increased rate of PCI-MI with the secondary definition (>5× URL of cTn associated with the additional criteria), a significant difference in the primary composite outcome favoring the conservative strategy was observed.[30] A subanalysis of the CHAMPION program yielded similar considerations.[31]

Last, the STEMI presentation substantially challenged the adjudication of PCI-MI, which was uncommon in this population and had no association with increased mortality. The present analysis therefore indicates that PCI-MI adjudication should be restricted to patients with NSTE-ACS.

Study Limitations

Some limitations of this study should be considered. First, although the MATRIX trial is one of the largest trials enrolling patients with ACS undergoing invasive management, the study was not powered to detect differences in mortality among patients with PCI-MI; our findings are exploratory and therefore not corrected for type I or II errors. In addition, no formal correction for multiple testing was applied; consequently, the additional analyses with higher troponin thresholds with or without ancillary criteria should be interpreted with caution. Second, cardiac markers, cTn type and generation and CK-MB, and their respective upper limit cutoff values were site specific. However, all PCI-MI definitions and clinical events, including cause of mortality, were adjudicated by an independent clinical event committee. Third, only the presence or absence, not the type, of ancillary (eg, side-branch occlusion, embolization, flow impairment, localization of new wall motion abnormalities) criteria was collected in the electronic case report form. Fourth, the follow-up was limited to 1 year; therefore, we could not exclude differences in mortality at longer-term follow-up across the different MI definitions. Fifth, because PCI-MI was defined as a postprocedural troponin rise >20% in patients with stable or falling values, it is possible that some patients with STEMI with rising troponin values were not accurately captured by the current definitions.

Conclusions

Among patients with ACS undergoing PCI, PCI-MI incidence varied by a factor of 3 across definitions, and the fourth (but not the second or the third) UDMI was associated with higher 1-year mortality risk in patients with NSTE-ACS but not patients with STEMI. Troponin elevation was associated with higher mortality risk only when combined with objective ancillary criteria such as electrocardiographic changes or angiographic complications but not symptoms. These data support the evolution of the universal definition of PCI-MI as end points.

ARTICLE INFORMATION

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Supplemental Material

Checklist
Tables S1–S9
Figures S1–S7

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