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Prognostic Significance of Periprocedural Versus Spontaneously Occurring Myocardial Infarction After Percutaneous Coronary Intervention in Patients With Acute Coronary Syndromes

An Analysis From the ACUITY (Acute Catheterization and Urgent Intervention Triage Strategy) Trial

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Objectives The aim of this study was to evaluate the relative impact of spontaneously occurring and periprocedural myocardial infarction (MI) on survival after percutaneous coronary intervention (PCI).

Background The clinical significance of periprocedural MI after PCI remains uncertain.

Methods Outcomes during a 1-year follow-up were evaluated among 7,773 patients enrolled in the ACUITY (Acute Catheterization and Urgent Intervention Triage Strategy) trial with a non–ST-segment elevation acute coronary syndrome in whom PCI was performed.

Results Periprocedural MI developed in 466 patients (6.0%), and spontaneous MI unrelated to PCI subsequently developed in 200 patients (2.6%). Patients developing spontaneous and periprocedural MI compared with those patients without MI had significantly greater unadjusted rates of mortality at 30 days (5.0% vs. 3.2% vs. 0.8%, respectively, $p < 0.0001$) and at 1 year (16.0% vs. 6.0% vs. 2.6%, respectively, $p < 0.0001$). In a time-updated multivariable analysis, after adjusting for differences in baseline and procedural characteristics between the groups, we found that spontaneous MI was a powerful independent predictor of subsequent mortality (hazard ratio: 7.49, 95% confidence interval: 4.95 to 11.33, $p < 0.0001$), whereas periprocedural MI was not a significant predictor of mortality (hazard ratio: 1.30, 95% confidence interval: 0.85 to 1.98, $p = 0.22$).

Conclusions Among patients with acute coronary syndrome undergoing PCI, the spontaneous development of an MI unrelated to PCI is a powerful predictor of subsequent mortality. In contrast, periprocedural MI is a marker of baseline risk, atherosclerosis burden, and procedural complexity but in most cases does not have independent prognostic significance. (Comparison of Angiomax Versus Heparin in Acute Coronary Syndromes [ACS]; NCT00093158) (J Am Coll Cardiol 2009;54:477–86) © 2009 by the American College of Cardiology Foundation

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Abbreviations and Acronyms

ACS = acute coronary syndrome

CK-MB = creatine phosphokinase MB fraction

MI = myocardial infarction

PCI = percutaneous coronary intervention

ULN = upper limit of normal

Myonecrosis is a common sequela of percutaneous coronary intervention (PCI) (1). However, the incidence (3.6% to 48.8%) and magnitude of myocardial damage after PCI is highly variable, depending on the patient's clinical, angiographic, and procedural characteristics; adjunctive pharmacotherapy; and the biomarker and thresholds applied to detect its presence (1). Early studies, in which the investigators predominantly used creatine phosphokinase myocardial band (CK-MB) fraction as a measure of myocardial injury, indicated that periprocedural myocardial infarction (MI), defined as either a peak post-procedural CK-MB of >5 × the upper limits of normal (ULN) (2,3) or >8 × ULN or associated with the development of new pathologic Q waves (4), is associated with an independent risk of in-hospital death (2–5) and reduced long-term survival (2,4–7).

Although the clinical significance of PCI-related myonecrosis remains controversial, particularly when it is relatively minor and occurs in the absence of angiographic complications or clinical evidence of ischemia (8,9), periprocedural MI (which is most commonly due to distal embolization, side-branch occlusion, coronary dissection, and altered collateral flow) (10,11) and spontaneous MI unrelated to PCI (typically due to atherosclerotic plaque rupture) (12,13) are often equated as outcome measures in clinical trials (14,15). Whether this practice is valid has not been examined and is confounded by the variable definitions used for periprocedural MI, making comparisons between studies difficult.

Although large MIs occurring after PCI are undoubtedly prognostically important, small degrees of myonecrosis (e.g., troponin elevations greater than the ULN) have not been correlated with early or late mortality (16). Even when greater thresholds of myonecrosis are used to define periprocedural MI, there is a paucity of data regarding the relative prognostic significance of MI occurring after a PCI procedure compared with a spontaneously occurring event. We therefore sought to compare the prognostic impact of periprocedural and spontaneously occurring MI on subsequent mortality among moderate- and high-risk patients with acute coronary syndrome (ACS) undergoing PCI from the large, multicenter, prospective ACUITY (Acute Catheterization and Urgent Intervention Triage Strategy) trial (17–19).

Methods

Patients. The design of the ACUITY trial has been described previously (17,18). In brief, to enroll a study population with moderate- and high-risk non–ST-segment elevation ACS, patients age 18 years or older with symptoms of myocardial ischemia lasting for 10 min or longer within the preceding 24 h were deemed to be eligible for enrolment if one or more of the following criteria were met: new ST-segment depression or transient elevation of 1 mm or more; increased levels of troponin I, T, or CK-MB; known coronary artery disease; or the presence of all 4 other unstable angina risk criteria as defined by the Thrombolysis In Myocardial Infarction (TIMI) study group (20).

Major exclusion criteria included acute ST-segment elevation MI or shock; bleeding diathesis or major bleeding episode within 2 weeks; thrombocytopenia; calculated creatinine clearance <30 ml/min; recent administration of abciximab, warfarin, fondaparinux, fibrinolytic agents, bivalirudin, or 2 or more doses of low molecular mass heparin; and allergy to study drugs or iodinated contrast that could not be adequately pre-medicated. The study was approved by the institutional review board or ethics committee at each participating center, and all patients gave written, informed consent.

Procedures. Patients were randomly assigned in open-label fashion to heparin (unfractionated or enoxaparin) plus a glycoprotein IIb/IIIa inhibitor, bivalirudin plus a glycoprotein IIb/IIIa inhibitor, or bivalirudin monotherapy (allowing for the use of provisional glycoprotein IIb/IIIa inhibitors). Details of the anticoagulant regimens have been described previously (18,19). Angiography was performed per protocol within 72 h after randomization, after which the decision was declared and recorded for primary treatment either with PCI, coronary artery bypass grafting, or medical management. All patients undergoing PCI received dual antiplatelet therapy for a recommended duration of 1 year.

Of the 13,819 patients enrolled into the ACUITY trial, 7,789 (56%) were managed with an invasive strategy that included PCI. The baseline clinical and angiographic characteristics and outcomes of the PCI population have been previously reported (18,19). We determined CK-MB measurements every 8 h within the first 24 h after PCI. Systematic analysis of CK-MB curves was performed for all patients after PCI to detect unreported MI. The definitions of MI used in the trial are listed in Table 1. The Clinical Events Committee reviewed original source documentation from all patients with suspected MI to ensure consistency of MI determination.

With regards to timing of the event, periprocedural MI was defined as an event occurring on the day of or the day

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Table 1 Definition of MI

Periprocedural MI	Patients presenting with or without NSTEMI in whom elevated CK-MB (or CPK) levels are decreasing from a previous peak or are normal: any CK-MB (or CPK in the absence of CK-MB measurement) >3 × ULN within 24 h after PCI that is also increased at least 50% over the most recent pre-PCI levels or the development of new, significant (≥0.04 s) Q waves in 2 or more contiguous electrocardiographic leads with CK-MB (or CPK) greater than ULN. Patients presenting with NSTEMI in whom the peak CK-MB (or CPK) has not yet been reached before PCI: recurrent chest pain lasting ≥30 min and/or new electrocardiographic changes consistent with a second MI and either the next CK-MB (or CPK) level measured 8 to 12 h after the event is increased by at least 50% greater than the previous level or the development of new, significant (≥0.04 s) Q waves in 2 or more contiguous electrocardiographic leads.
Spontaneous MI	Any elevation of troponin or CPK-MB (or CPK) greater than the ULN.

CK-MB = creatine kinase-myocardial band; CPK = creatine phosphokinase; MI = myocardial infarction; NSTEMI = non–ST-segment myocardial infarction; PCI = percutaneous coronary intervention; ULN = upper limit of normal.

after the procedure, whereas a spontaneous MI was defined as one occurring after this time period. Periprocedural MIs were recorded, whether related to the index procedure performed at the time of enrollment into the trial or a subsequent PCI during follow-up. To minimize the impact of crossover, patients were excluded if they exhibited both types of MI during the study period, that is, periprocedural MI followed by a subsequent spontaneous MI (n = 13, 5 of whom died during 1-year follow-up) or spontaneous MI followed by a MI related to PCI performed after the index revascularization (n = 3, no deaths). Thus, the study cohort for the current analysis consisted of 7,773 (99.8%) of the 7,789 patients undergoing an index PCI.

Statistical analysis. Categorical variables were compared with the chi-square test or Fisher exact test. Continuous variables were compared with the nonparametric Wilcoxon rank-sum test. Comparisons among groups for the 30-day end points were made with the use of the normal approximation test for population proportions. A 2-sided $\alpha = 0.05$ was used for all superiority testing. One-year follow-up analysis on mortality was performed with the use of time-to-event data (for which patients were censored at the time of withdrawal from the study or at last follow-up), are displayed with the use of Kaplan-Meier methodology, and were compared with the log-rank test. The independent impact of the occurrence of MI by type was evaluated by the use of a time-updated Cox proportional hazards regression model. Covariates were selected by the use of a forward stepwise procedure from a large number of candidate variables with $p < 0.20$ as the criterion for entry into the model. Adjusted hazard ratios of the risk for mortality with 95% confidence intervals are presented. All statistical analyses were performed with SAS version 8.2 (SAS Institute, Cary, North Carolina).

Results

Frequency and timing of MI. Of the 7,773 patients with non–ST-segment elevation ACS undergoing PCI, 466 patients (6.0%) and 200 patients (2.6%) developed a periprocedural MI and spontaneous MI, respectively, within the 1-year follow-up duration of the study. Of patients with periprocedural MI, 366 (78.5%) occurred within the index-PCI procedure, and 100 (21.5%) occurred after subsequent PCI procedures at a median time of 68 (interquartile range 7 to 214) days after randomization. Thus, 410 (88.0%) of all the periprocedural MIs occurred within 30 days of randomization. Eighty-seven (18.7%) of all the periprocedural MIs occurred after index-hospital discharge. The spontaneously occurring MI events occurred at a median time of 107.5 (interquartile range 20 to 247) days after randomization; 64 (32.0%) of all the spontaneous MIs occurred within 30 days of randomization. New Q waves, as determined by the clinical events committee, developed in 81 (17.4%) of periprocedural MIs and in 37 (18.5%) of spontaneous MIs ($p = 0.73$).

Stent thrombosis (ST) was classified as either definite or probable. Definite ST was defined as angiographic thrombus or subacute closure within the stented vessel at the time of clinically driven angiography for ischemia. Probable ST was defined as any death not attributed to a noncardiac cause or any Q-wave MI in the absence of documented angiographic stent patency. At 1 year, definite and probable rates of ST in the overall study population were 1.2% and 0.7%, respectively. The respective rates in patients with periprocedural MI were 58 (12.4%) and 10 (2.1%), and for those with spontaneous MI were 21 (10.1%) and 15 (7.5%).

Baseline characteristics. The clinical characteristics of the 3 groups are summarized in Table 2. In general, patients with either periprocedural or spontaneous MI compared with those in whom MI did not develop were more likely to have had a past medical history of MI, previous revascularization, impaired renal function and a greater TIMI risk score. There were no differences in age, sex distribution, history of hyperlipidemia or smoking, and the frequency of non–ST-segment elevation MI at the time of enrollment between the 3 groups of patients. There were no significant baseline differences between the 2 MI groups, except for a greater prevalence of diabetes mellitus in patients with spontaneously occurring MI. Treatment with aspirin, beta-blockers, angiotensin-converting enzyme inhibitors, and statins in the first 30 days after discharge was similar among the 3 groups (Table 2).

Angiographic and procedural characteristics. As shown in Table 3, compared with patients in whom a MI did not develop, patients sustaining a periprocedural MI were more

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Table 2 Baseline Clinical Characteristics

	Periprocedural MI (n = 466)	Spontaneous MI (n = 200)	p Value	PCI Without MI (n = 7,107)
Age (yrs)	64.0 (55, 73)	64.0 (53, 73)	0.87	63.0 (54, 71)
Female	133/466 (28.5)	57/200 (28.5)	0.99	1,896/7,107 (26.7)
Diabetes	123/461 (26.7)	77/200 (38.5)‡	0.002	1,928/7,064 (27.3)
Hypertension	323/464 (69.6)*	137/200 (68.5)	0.78	4,603/7,071 (65.1)
Hyperlipidemia	265/457 (58.0)	119/200 (59.5)	0.72	3,889/6,967 (55.8)
Current cigarette smoker	145/460 (31.5)	60/197 (30.5)	0.79	2,152/6,968 (30.9)
Previous MI	169/451 (37.5)‡	78/195 (40.0)†	0.54	2,064/6,959 (29.7)
Previous PCI	200/463 (43.2)*	97/197 (49.2)†	0.15	2,681/7,050 (38.0)
Previous CABG	118/465 (25.4)‡	55/200 (27.5)‡	0.57	1,182/7,092 (16.7)
Baseline CrCl <60 ml/min	112/443 (25.3)‡	56/190 (29.5)‡	0.27	1,179/6,698 (17.6)
Baseline increased CK-MB/troponin	295/442 (66.7)	129/189 (68.3)	0.71	4,292/6,618 (64.9)
TIMI risk score				
0–2	44/466 (9.4)†	18/200 (9.0)*	0.86	1,047/7,107 (14.7)
3–4	224/446 (48.1)	91/200 (45.5)	0.54	3,380/7,107 (47.6)
5–7	148/466 (31.8)*	71/200 (35.5)†	0.35	1,898/7,107 (26.7)
Post-discharge to 30 days' medications				
Aspirin	431/444 (97.1)	180/186 (96.8)	0.84	6,735/6,947 (96.9)
Clopidogrel	397/444 (89.4)	166/186 (89.2)	0.95	6,240/6,947 (89.8)
Angiotensin-converting enzyme inhibitor	288/444 (64.9)	113/186 (60.8)	0.33	4,319/6,947 (62.2)
Statins	379/444 (85.4)	163/186 (87.6)	0.45	5,912/6,947 (85.1)

Values are median (interquartile range) or n/N (%). The p values are for the comparison of periprocedural MI versus spontaneous MI: *$p < 0.05$ for comparison with patients without MI; †$p < 0.01$ for comparison with patients without MI; ‡$p < 0.001$ for comparison with patients without MI.

CABG = coronary artery bypass grafting; CrCl = creatinine clearance; TIMI = Thrombolysis In Myocardial Infarction; other abbreviations as in Table 1.

likely to undergo multilesion and multivessel PCI and intervention involving the left main coronary artery, left circumflex artery, or a saphenous vein bypass graft. Bypass graft intervention was also more common in patients in whom a spontaneous MI developed, although no other angiographic or procedural predictors were predictive of spontaneous MI.

Clinical outcomes. By univariate analysis, patients with both periprocedural MI and spontaneous MI had greater rates of unplanned revascularization for ischemia, major bleeding, and mortality within 30 days compared with patients without MI (Fig. 1). Compared with patients without MI, mortality rates at 1 year were significantly increased in patients with both periprocedural MI (6.0% vs. 2.6%, $p < 0.0001$) and spontaneous MI (16.0% vs. 2.6%, $p < 0.0001$) (Fig. 2A). The difference in mortality in patients with spontaneously occurring MI versus periprocedural MI was also highly significant ($p < 0.0001$). The findings were similar when the analysis was performed separately for patients with unstable angina or non–ST-segment elevation MI as the index diagnosis (Figs. 2B and 2C). The rate of mortality in patients with ST compared with those without ST was significantly greater for both types of MI ($p < 0.01$) (Fig. 3). Mortality at 1 year in patients with periprocedural Q-wave MI and spontaneous Q-wave MI was 27.0% and 17.3%, $p = 0.22$, respectively.

In the time-updated covariate adjusted multivariate analysis, spontaneously occurring MI was the strongest independent predictor of subsequent mortality within the following year (hazard ratio: 7.49, 95% confidence interval: 4.95 to 11.33, $p < 0.0001$). In contrast, after adjustment for baseline variables, periprocedural MI as a group was not significantly related to subsequent mortality (hazard ratio: 1.30, 95% confidence interval: 0.85 to 1.98, $p = 0.22$) (Fig. 4).

Discussion

The major findings of the present study among patients undergoing PCI for a non–ST-segment elevation ACS are as follows: 1) periprocedural and spontaneously occurring MIs develop in patients with a greater prevalence of adverse clinical and angiographic baseline characteristics; 2) periprocedural and spontaneously occurring MIs are both associated with greater 30-day morbidity and 1-year mortality; and 3) after correction for differences in baseline clinical and angiographic characteristics of the groups, the development of a spontaneous MI, but not a periprocedural MI, independently predicts subsequent mortality within the following year.

Outcomes after spontaneous and procedural MI. The ACUITY trial was designed to be representative of contemporary practice in moderate- and high-risk patients with non–ST-segment elevation ACS; an invasive approach was routinely used (with 93% of PCI patients stented), and adjunctive anticoagulant therapy included either the administration of bivalirudin alone or a glycoprotein IIb/IIIa inhibitor in combination with either unfractionated or low molecular weight heparin, all of which are recommended with Class I level of evidence according to the most recent American College of Cardiology/American Heart Associa-

Table 3 Angiographic and Procedural Characteristics

	Periprocedural MI (n = 466)	Spontaneous MI (n = 200)	p Value	PCI Without MI (n = 7,107)
Baseline ejection fraction (%)	55 (45, 60)	55 (40, 60)	0.54	55 (50, 62)
Number of lesions treated				
1	241/457 (52.7)‡	111/192 (57.8)*	0.24	4,655/7,010 (66.4)
2	142/457 (31.1)‡	55/192 (28.6)	0.54	1,668/7,010 (23.8)
3	49/457 (10.7)†	20/192 (10.4)	0.91	518/7,010 (7.4)
Number of vessels treated				
1	357/465 (76.8)‡	167/200 (83.5)	0.05	5,968/7,104 (84.0)
2	90/465 (19.4)†	30/200 (15.0)	0.18	1,027/7,104 (14.5)
3	14/465 (3.0)†	3/200 (1.5)	0.26	101/7,104 (1.4)
Treated vessel				
Left main	13/462 (2.8)*	2/198 (1.0)	0.15	108/7,061 (1.5)
Left anterior descending	196/462 (42.4)	88/198 (44.4)	0.63	3,031/7,061 (42.9)
Right coronary artery	175/462 (37.9)	71/198 (35.9)	0.62	2,598/7,061 (36.8)
Left circumflex artery	187/462 (40.5)*	73/198 (36.9)	0.38	2,433/7,061 (34.5)
Bypass graft	67/462 (14.5)‡	31/198 (15.7)‡	0.70	458/7,065 (6.5)
Stent implanted	431/459 (93.9)	181/196 (92.3)	0.46	6,535/7,046 (92.7)
Distal protection	17/459 (3.7)‡	4/196 (2.0)	0.27	90/7,046 (1.3)
Atherectomy	3/459 (0.7)	1/196 (0.5)	0.83	44/7,046 (0.6)
Thrombectomy	11/459 (2.4)	4/196 (2.0)	0.78	113/7,046 (1.6)
Anticoagulant therapy				
Heparins and glycoprotein IIb/IIIa	140/466 (30.0)	58/200 (29.0)	—	2,360/7,107 (33.2)
Bivalirudin and glycoprotein IIb/IIIa	162/466 (34.8)	68/200 (34.0)	—	2,372/7,107 (33.4)
Bivalirudin alone	164/466 (35.2)	74/200 (37.0)	—	2,375/7,107 (33.4)

Values are median (interquartile range) or n/N (%). The p values are for the comparison of periprocedural myocardial infarction (MI) versus spontaneous MI: *$p < 0.05$ for comparison with patients without MI; †$p < 0.01$ for comparison with patients without MI; and ‡$p < 0.001$ for comparison with patients without MI.

tion guidelines (21). Although one third of patients in this trial were also treated with bivalirudin plus a glycoprotein IIb/IIIa inhibitor (not a currently recommended regimen), the outcomes in this cohort (including rates of MI, bleeding, and mortality) were comparable with patients receiving heparin plus a glycoprotein IIb/IIIa inhibitor, thus justifying pooling the results from the present analysis.

Among patients with moderate- and high-risk non–ST-segment elevation ACS in ACUITY who did not experience either a periprocedural or subsequent MI within the year after undergoing PCI, the 30-day and 1-year rates of mortality were relatively low (0.8% and 2.6%, respectively). However, the unadjusted rates of mortality at both 30 days and 1 year were significantly greater among the 6.0% and

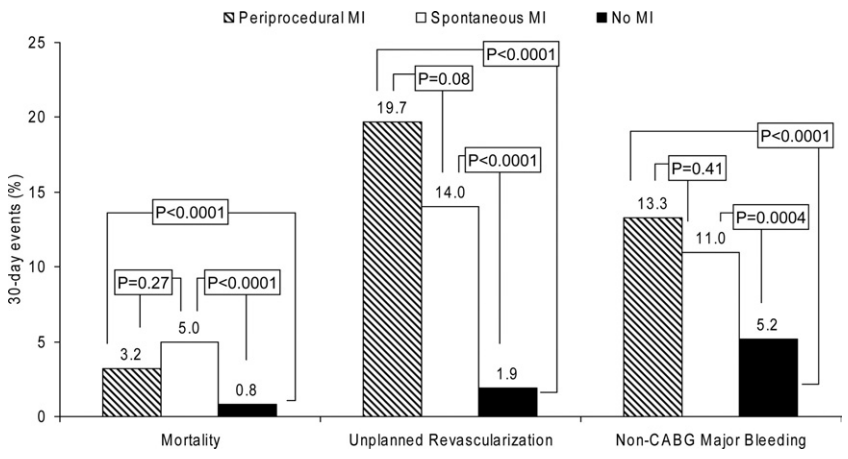

Figure 1 30-Day Rates of Mortality, Unplanned Revascularization, and Major Bleeding Unrelated to CABG

Results are shown for patients with periprocedural myocardial infarction (MI), spontaneous MI, and no MI. CABG = coronary artery bypass grafting.

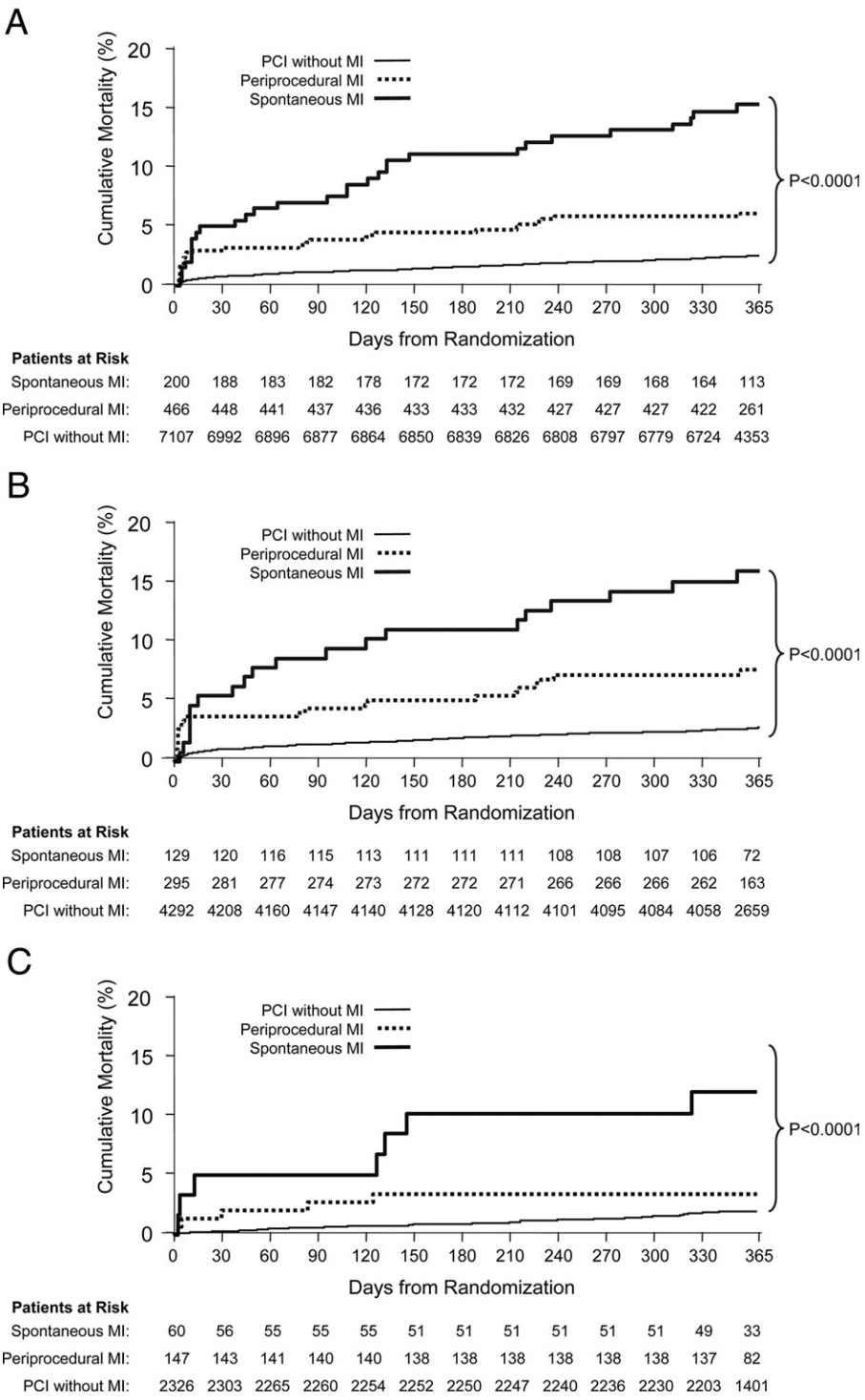

Figure 2 **Time-to-Event Curves for 1-Year Mortality**

(A) Kaplan-Meier estimates of 1-year death among all patients. **(B)** Kaplan-Meier estimates of 1-year death among percutaneous coronary intervention (PCI) patients admitted with a diagnosis of non–ST-segment elevation myocardial infarction (MI). **(C)** Kaplan-Meier estimates of 1-year death among PCI patients admitted with a diagnosis of unstable angina.

2.6% of the study cohort in whom a procedure-related or spontaneously occurring MI did develop. At least part of this risk may be attributed to a greater underlying burden of atherosclerosis in patients in whom an MI developed, as indicated by the greater prevalence of classic risk factors for atherosclerosis, history of previous MI and revascularizа-

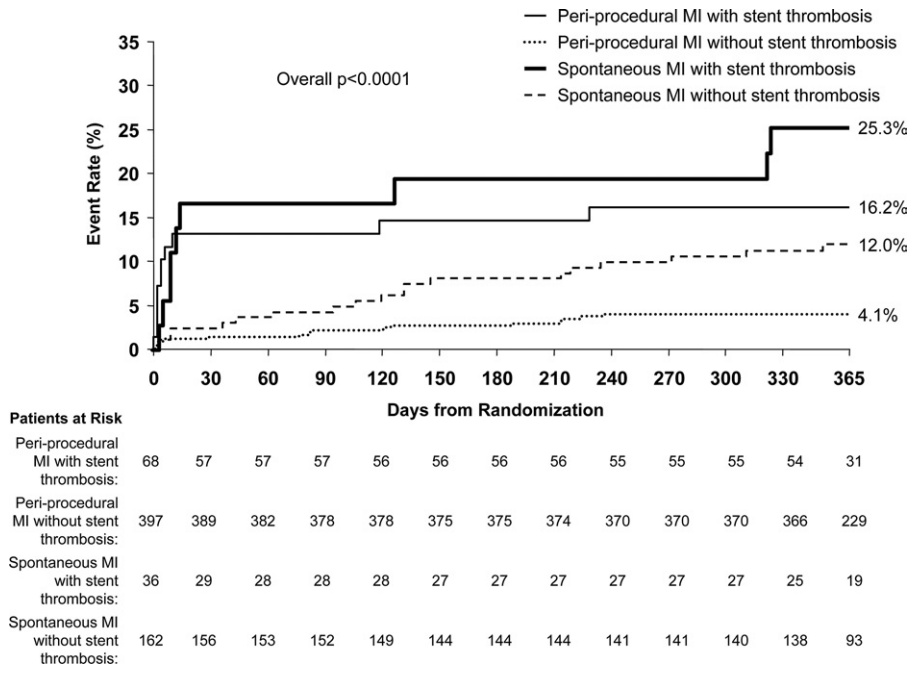

Figure 3 **Time-to-Event Curves for 1-Year Mortality in Patients With and Without Stent Thrombosis**

Mortality in patients with stent thrombosis was greater ($p < 0.01$) compared with those without, for both types of myocardial infarction (MI).

tion, and greater renal impairment and TIMI risk scores among these patients.

The PCI procedure in patients in whom a periprocedural MI developed, in particular, was also more complex; it more frequently involved multilesion and multivessel, left main, and bypass graft intervention. The frequency of definite ST at 1 year was similar in both types of MI ($p = 0.48$), and the rate of mortality in patients with ST was markedly greater compared with those without for both types of MI ($p < 0.01$) (Fig. 3). However, spontaneous MI even without ST was associated with high rates of mortality at 1 year (12.0%), but the rate of mortality in patients with periprocedural MI without ST (4.1%) approximated that of patients without MI.

A time-updated multivariable regression analysis was performed to adjust for the differences in baseline clinical and procedural characteristics and the timing of MI among patients with periprocedural MI, spontaneous MI, and no MI. In this model, the spontaneous development of an MI (unrelated to PCI) was the strongest independent predictor of subsequent mortality within the 1-year follow-up period (hazard ratio: 7.5), whereas periprocedural MI was not an independent predictor of death. Age, diabetes mellitus, previous MI, and renal failure, as well as markers for the severity of the ACS such as preprocedural biomarker elevation and ST-segment shift, were additional independent predictors of long-term mortality. These findings demonstrate that the development of a spontaneously occurring MI is of significantly greater prognostic importance than a periprocedural MI.

Prognostic significance of periprocedural MI. The lack of independent association between PCI-related MI and mortality in the present analysis is contrary to the findings of previous studies (2,4–7), which may in part be attributable to the different thresholds and definitions for MI used. Periprocedural MI in the present trial required a CK-MB elevation of $>3 \times$ ULN, which is significantly below the threshold levels of CK-MB >5 or $>8 \times$ ULN required for prognostic significance in the 2 largest previous studies (2,4). Moreover, we have recently demonstrated that this magnitude of periprocedural CK-MB elevation is infrequent in patients with normal pre-procedural cardiac biomarkers and is mostly observed in patients with increased levels of troponin T (>0.5 ng/ml) (22).

We have also demonstrated in the previous study that among patients with normal pre-procedural CK-MB (approximately one-third of patients in the current study), a post-procedure increase in CK-MB greater than normal does not independently predict mortality when the pre-procedural cardiac troponin T levels are included in the multivariate models (22). Most previous studies correlating periprocedural MI to subsequent mortality have not routinely assessed or adjusted the results for the baseline troponin level (2,4–7), representing an important unmeasured confounder in these studies.

Moreover, in the present and previous studies (1,22), periprocedural myonecrosis has been shown to occur more frequently in patients with multiple cardiac risk factors, including advanced age, diabetes, and hypertension; in

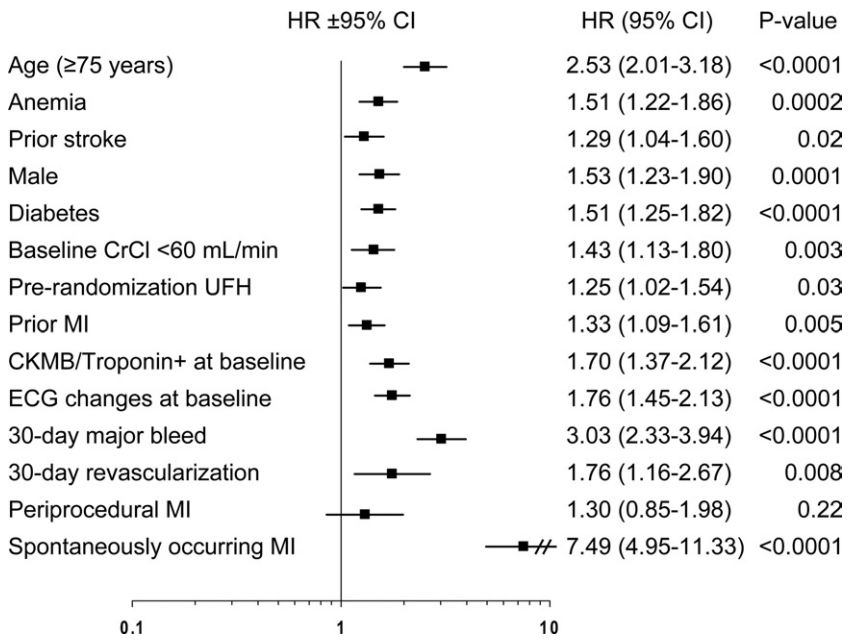

Figure 4 **Independent Predictors of 1-Year Mortality**

Time-updated baseline covariate adjusted multivariate model in which periprocedural MI, spontaneously occurring MI, non-CABG major bleeding, and unplanned revascularization were entered as time-dependent covariates. Additional variables included in the model that were not independent predictors included weight, history of hyperlipidemia, hypertension, current smoking, coronary artery disease, previous PCI or CABG, thienopyridine therapy pre-intervention, heparin use pre-randomization, and treatment assignment in the trial. CK-MB = creatine kinase, myocardial band; CrCl = creatinine clearance; ECG = electrocardiogram; MI = myocardial infarction; UFH = unfractionated heparin; other abbreviations as in Figure 1.

patients with ACS and thrombus; and in those undergoing multilesion and multivessel intervention. The results of intravascular ultrasound studies have shown patients developing periprocedural myonecrosis after PCI have more extensive atherosclerosis (23). Thus, periprocedural MI is a marker of clinical syndrome acuity, atherosclerotic plaque burden, and procedural complexity, and although increases in periprocedural cardiac enzyme do represent myonecrosis (24,25), in most cases the level of myocardial damage is below the threshold to significantly increase short-term or late mortality.

Prognostic significance of spontaneous MI. Our study quantifies the risk associated with a spontaneously occurring MI occurring after an initial invasive strategy for patients with non–ST-segment elevation ACS. Indeed, after adjusting for differences in baseline and procedural characteristics, spontaneous MI was the strongest independent predictor of subsequent mortality. This observation is consistent with studies conducted among patients with ST-segment elevation MI treated with primary PCI. Kernis et al. (26) reported data from the PAMI (Primary Angioplasty in MI) trial and demonstrated that recurrent MI in the first month after primary PCI occurred in 2.1% of patients and was associated with a 7-fold increased risk of death at 6 months. Similar data were reported by de Luca et al. (27). It is noteworthy that, despite the difference in the patient populations and MI definitions and greater use of stents and glycoprotein IIb/IIIa inhibitors in the present study, the incidence of spontaneous MI and the magnitude of impact on mortality were comparable to the previous studies.

Previous studies. Akkerhuis et al. (28) have previously compared the impact of periprocedural CK-MB elevation after PCI with spontaneous, non–PCI-related, CK-MB elevation on 6-month mortality in patients with non–ST-segment elevation ACS. There was a direct correlation between CK-MB levels and mortality in both groups. As in the present study, however, the rate of mortality was significantly greater in patients with spontaneous MI compared with those with periprocedural myonecrosis. The authors concluded that the adverse prognostic implications of periprocedural myocardial necrosis should be considered similar to the adverse consequences of spontaneous myocardial necrosis. Several important differences between our study and that by Akkerhuis et al. (28) may account for the discordant conclusions. First, the previous study was conducted in the balloon angioplasty era and, hence, not representative of contemporary practice. Second, Akkerhuis et al. (28) did not adjust for confounding clinical variables to determine whether the observed relationship was independent of baseline risk. Finally, the previous study consisted of a heterogeneous group of patients from 5 different clinical trial databases.

Study limitations. Although the ACUITY trial was a large, multicenter, prospective trial incorporating currently

recommended class I guideline therapies for ACS, the present analysis was retrospective and post hoc and, hence, subject to bias. Core laboratory angiographic analysis was not available in all patients. There are several limitations with regards to the definition of MI used in the present analysis. First, creatine phosphokinase and CK-MB were used to define periprocedural MI (based on the accepted practice at the time the study was designed), whereas CK-MB and troponins were used for spontaneous MI (reflecting clinical practice). Second, core laboratory analysis of biomarkers was not performed, as recommended in the recently published "universal definition" of MI (28). Third, the determination of PCI-related MI can be difficult among patients presenting with a non–ST-segment elevation MI in whom the pre-procedural cardiac markers have not returned to baseline. Fourth, a dichotomous cut-off of time after PCI was used to define periprocedural versus spontaneous MI, which may have resulted in some late periprocedural events crossing over into the spontaneous category.

The impact of these limitations was minimized by the use of strict definitions formulated a priori to identify the 2 types of MI, and each event was adjudicated by an independent clinical events committee after review of original source documents. Importantly, the results of this study thus apply to patients with unstable angina and non–ST-segment elevation MI and should not be generalized to other clinical scenarios, such as PCI in patients with stable coronary artery disease or evolving ST-segment elevation MI. Data regarding biomarker levels after the MI were not routinely collected and, therefore, the relationship between the magnitude of myocardial injury and outcomes cannot be determined, although Q-wave MI developed in a similar percentage of patients with both periprocedural and spontaneous MI. This is relevant because spontaneous MI were clinical events whereas screening for periprocedural MI was performed systematically using biomarker measurements.

Thus, spontaneous MI that occurred without symptoms or had an atypical presentation may not have been included in the analysis. Even though the threshold for detection of spontaneous MI (any troponin > normal) was lower than that for periprocedural MI (CK-MB >3 × ULN), it is possible that spontaneous MI were larger than periprocedural MI. However, the present study demonstrates that periprocedural MI, as a class, are not of significant independent prognostic importance after PCI in ACS using contemporary management strategies. In contrast, spontaneous MI, as a class, are a powerful predictor of subsequent mortality. Among such patients, it is intuitive that large MI would impact mortality greater than small MI, though the present study is unable to evaluate this possibility.

Conclusions

For the approximately 91% of patients with non–ST-segment elevation ACS undergoing PCI who do not sustain a periprocedural or spontaneous MI, the 1-year prognosis is favorable. Periprocedural MI, defined as a post-procedure CK-MB >3 × ULN, occurs in 6% of patients and correlates with baseline patient comorbidities, underlying atherosclerosis, and procedural complexity. However, after accounting for these covariates, periprocedural MI is not a significant predictor of subsequent mortality in most patients. In contrast, the spontaneous occurrence of MI unrelated to PCI in patients with ACS is a relatively infrequent event, developing in only 2.6% of patients within the first year, but when it occurs is a powerful independent predictor of subsequent mortality. Our findings support the recommendation of the European Society of Cardiology/American College of Cardiology/American Heart Association/World Heart Federation global task force that spontaneous and periprocedural MI should be classified separately (29) and considered discretely for clinical decision making. Furthermore, these findings have important implications for the design of future randomized trials, demonstrating that periprocedural and spontaneous MI should not necessarily be considered equivalent as clinical event end points (30).

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