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CME

Cardiac Troponin After Percutaneous Coronary Intervention and 1-Year Mortality in Non–ST-Segment Elevation Acute Coronary Syndrome Using Systematic Evaluation of Biomarker Trends

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CME Objective for This Article: At the end of this activity, the learner should be able to review cardiac troponin (cTn) trends during non–ST-segment elevation acute coronary syndrome (NSTE ACS) in patients undergoing percutaneous coronary intervention (PCI) in EARLY ACS and SYNERGY and the relationship between post-PCI cTn and mortality.

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Cardiac Troponin After Percutaneous Coronary Intervention and 1-Year Mortality in Non–ST-Segment Elevation Acute Coronary Syndrome Using Systematic Evaluation of Biomarker Trends

Objectives This study sought to review cardiac troponin (cTn) trends during non–ST-segment elevation acute coronary syndrome (NSTE ACS) in patients undergoing percutaneous coronary intervention (PCI) in the EARLY ACS (Early Glycoprotein IIb/IIIa Inhibition in Non–ST-Segment Elevation Acute Coronary Syndromes) and SYNERGY (Superior Yield of the New Strategy of Enoxaparin, Revascularization and Glycoprotein IIb/IIIa Inhibitors) studies and to study the relationship between post-PCI cTn and mortality.

Background The prognostic value of cTn post-PCI is controversial. In patients with NSTE ACS, it is especially difficult to distinguish between cTn elevations due to PCI or index myocardial infarction (MI).

Methods Time and cTn (indexed by upper limit of normal [ULN]) data pairs were plotted for 10,199 patients and independently reviewed by 2 physicians to identify patients in whom post-PCI cTn elevation could be distinguished from that of index MI. Post-PCI cTn peak was identified for each plot, and its relationship with 1-year mortality was evaluated using Cox modeling, correcting for 15 clinical variables from the EARLY ACS 1-year mortality model (including baseline cTn). We used an identical methodology to assess the association between creatine kinase-myocardial band and 1-year mortality.

Results Patients with cTn (re-)elevation post-PCI not evaluable were identified and excluded from further analysis (4,198 [41%] with cTn rising prior to PCI; 229 [2%] with missing cTn). Among the remainder ($n = 5,772$ [57%]), in the multivariable model, peak cTn post-PCI was associated with a 7% increase in mortality (hazard ratio [HR] for 10× ULN increase: 1.07, 95% confidence interval [CI]: 1.02 to 1.11; $p = 0.0038$). Peak post-PCI creatine kinase-myocardial band was significantly associated with 1-year mortality (HR for 1× ULN increase: 1.13, 95% CI: 1.05 to 1.21; $p = 0.0013$).

Conclusions We used a methodology that differentiated post-PCI cTn (re-)elevation from that of presenting MI in more than one-half of patients with NSTE ACS undergoing PCI. This identified a highly significant relationship between post-PCI cTn and 1-year mortality, with implications for both incorporating a cTn post-PCI MI definition and preventing PCI-related myonecrosis. (J Am Coll Cardiol 2013;62:242–51) © 2013 by the American College of Cardiology Foundation

Myocardial infarction (MI) associated with percutaneous coronary intervention (PCI), type 4a MI, represents 25% to 50% of recurrent MIs in patients presenting with acute coronary syndromes (ACS) (1,2). Current diagnostic criteria for PCI-related MI include an elevation of creatine kinase-myocardial band (CK-MB) fraction >3× the upper limit of normal (ULN), which is supported by studies correlating CK-MB increase after PCI with subsequent risk for ischemic events (3–6). As a marker of myocardial necrosis, cardiac troponin (cTn) is more sensitive and more specific than CK-MB is; thus, cTn may enhance detection of myonecrosis associated with PCI (7). The universal definition of MI endorsed the use of cTn in diagnosing peri-PCI MI (3); however, many question whether cTn release following PCI carries any prognostic relevance (8). In addition, the universal definition of MI did not distinguish between diagnostic thresholds for cTn and CK-MB, despite the differences in sensitivity for myonecrosis (3).

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The clinical significance and interpretation of cTn elevation following PCI is even more controversial for patients presenting with MI. Differentiating post-PCI cTn increase from that of the natural evolution of the presenting MI is challenging but essential to properly interpret the clinical relevance of revascularization-related necrosis. In addition, because of the well-known prognostic role of cTn elevation in ACS, it is unclear whether a new cTn release at the time of PCI provides additional prognostic significance (9).

Using a large cohort of patients with non–ST-segment elevation (NSTE) ACS from the combined EARLY ACS (Early Glycoprotein IIb/IIIa Inhibition in Non–ST-Segment Elevation Acute Coronary Syndrome) and SYNERGY (Superior Yield of the New Strategy of Enoxaparin, Revascularization and Glycoprotein IIb/IIIa Inhibitors) trials' datasets, we identified patients in whom cardiac biomarker elevation associated with PCI could be distinguished from elevation associated with the presenting MI. In that cohort, we assessed the association between cTn and CK-MB elevation after PCI and 1-year mortality.

Abbreviations and Acronyms

ACS = acute coronary syndromes(s)
CI = confidence interval
CK-MB = creatine kinase-myocardial band
cTn = cardiac troponin
HR = hazard ratio
IQR = interquartile range
MI = myocardial infarction
NSTE = non–ST-segment elevation
PCI = percutaneous coronary intervention
ULN = upper limit of normal

Methods

Dataset. Analyses were conducted using datasets from the EARLY ACS and SYNERGY trials, which have been published (10,11). These trials enrolled patients with NSTE ACS (N = 9,406, EARLY ACS; N = 10,027, SYNERGY) with at least 2 of the following criteria: age ≥60 years; cardiac biomarkers (cTn or CK-MB) above the local ULN; or ST-segment depression (or transient elevation) ≥1 mm. In addition, the EARLY ACS trial enrolled patients with all 3 of the following criteria: age 50 to 59 years; positive cardiac biomarkers; and history of coronary artery disease. In both trials, patients were planned to undergo an early invasive management strategy. In EARLY ACS and SYNERGY, 84% of patients had elevated cardiac biomarkers at baseline. For this analysis, we included all patients who underwent PCI during the index hospitalization (N = 10,199).

The EARLY ACS and SYNERGY trials were approved by the institutional review board or ethics committee of each participating site, and all patients gave written informed consent. The current analyses were approved by the institutional review board of Duke University Medical Center.

Assessment of cardiac biomarker trends. The SYNERGY and EARLY ACS trials mandated the collection of cardiac biomarkers every 8 h during the first 24 h after randomization, and then daily throughout the hospitalization. Among patients undergoing PCI, cardiac biomarker collection was required before the procedure and every 8 h for 24 h

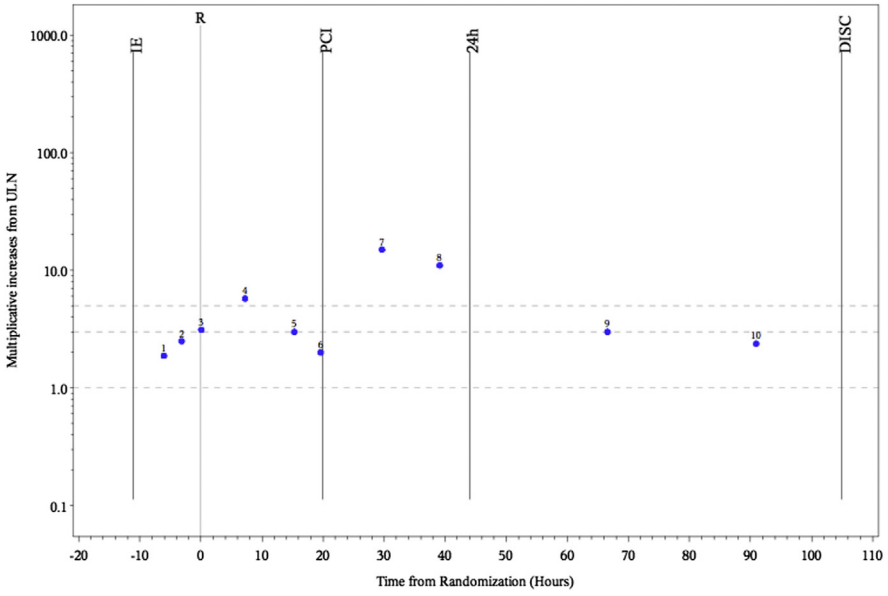

Figure 1 Representative Example of a Patient Plot of cTn and CK-MB Temporal Trends During Index Hospitalization

cTn = cardiac troponin; CK-MB = creatine kinase-myocardial band; DISC = discharge; IE = index event; PCI = percutaneous coronary intervention; R = randomization; ULN = upper limit of normal.

following the procedure. In addition, cardiac biomarker measurements not mandated by protocol but performed as part of the standard of care from hospital presentation to discharge were recorded in the trial databases.

Troponin and CK-MB time-trends plots. We created plots representing temporal trends of cTn and CK-MB values during the index hospitalization. A plot was generated for each patient undergoing PCI. Because values of cardiac biomarkers were analyzed in local laboratories of participating sites, values were indexed by the local ULN. Each graph listed troponin and CK-MB values on the y-axis and time on the x-axis. Key benchmarks included time of index event, randomization, PCI, PCI + 24 h, and discharge. A representative example of the plots is provided in Figure 1.

Two independent reviewers (P.T. and S.L.) visually reviewed each plot. Disagreements were resolved by rereview and consensus. For cases that could not be solved by visual interpretation only, reviewers accessed the actual values. The major goal was to identify patients in whom biomarkers were decreasing or stable before PCI and to separate them from patients in whom biomarkers were increasing before PCI. Decreasing trends were defined by values that were lower than prior values, and stable trends were defined by identical values. For patients with increasing values before PCI, post-PCI biomarkers were considered to be not interpretable, as those elevations could not be separated from natural evolution of the presenting MI. These patients were excluded from subsequent analyses. The initial agreement between the 2 independent reviews in the application of these criteria was overall 94.3% for cTn and 94.2% for CK-MB.

The trends for troponin and CK-MB were read independently, and the results were applied to the respective biomarker analyses. Through the plot review process, patients were classified into the following groups: 1) decreasing or stable biomarker levels before PCI; or 2) increasing biomarker levels before PCI. Patients with decreasing or stable biomarker levels before PCI were further grouped into: 1) patients with new cardiac biomarker increase after PCI (in the 24 h following PCI); or 2) patients without new cardiac biomarker increase after PCI. In patients with new post-PCI increases in biomarker levels, reviewers identified the last value preceding the (re-)elevation and the peak value associated with the elevation.

Statistical analysis. We performed 2 sets of analyses, 1 each with the following variables of interest: 1) post-PCI cTn elevation; and 2) post-PCI CK-MB elevation. We aimed to evaluate the prognostic value of post-PCI cTn elevation for subsequent mortality. Although the primary focus of the analysis was cTn, because CK-MB is a more-established marker for post-PCI myocardial necrosis, the CK-MB analysis was also performed to help interpret the findings of the cTn analyses.

The main outcome for the analysis was 1-year all-cause mortality. For the analysis of post-PCI cTn, we used Cox proportional hazards models to examine the association of the following values with 1-year mortality: 1) peak cTn after PCI; and 2) absolute post-PCI cTn increase (the difference between peak cTn after PCI and the last value preceding the [re-]elevation). Separate models were created for peak cTn and the absolute post-PCI increase. Models were stratified by trial and adjusted for covariates of interest derived from the 1-year mortality model generated from the EARLY ACS trial database (age, ST-segment changes, baseline Killip class, peripheral artery disease history, estimated creatinine clearance, weight, previous MI, heart rate, previous PCI or coronary artery bypass graft surgery, systolic blood pressure, female sex, current smoker, diabetes, and heart failure history). In addition, the pre-PCI cTn peak was included in the model to adjust for risk of death related to the baseline cTn elevation.

Because the relationship between peri-PCI cTn values and 1-year mortality was nonlinear, spline transformation was implemented before modeling. The assumption of proportional hazards was tested and confirmed. The relationship of peri-PCI cTn elevation with 1-year mortality is presented as hazard ratio (HR) per 10-fold increase (95% confidence interval [CI]).

Analyses to determine the association of post-PCI CK-MB with 1-year mortality were performed using an identical methodology but with post-PCI CK-MB peak as the variable of interest.

Using the models described, we generated adjusted survival predictions with 95% CIs to calculate predicted survival at pre-specified thresholds of post-PCI cTn and CK-MB peak levels. We used bootstrapping to calculate the 95% CIs. Survival was then transformed to mortality (1-year survival).

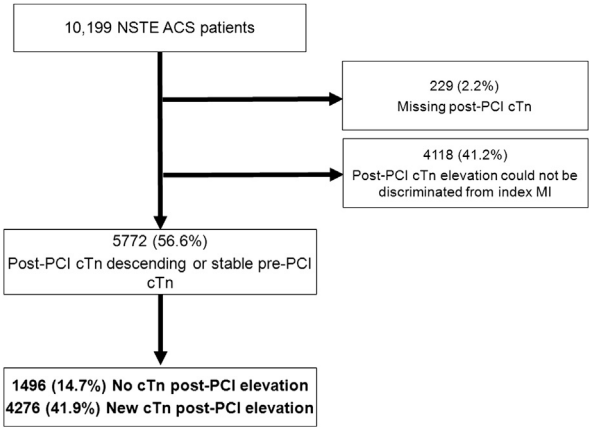

Figure 2 Patients Flow Following cTn Graphic Trend Interpretation

MI = myocardial infarction; NSTE ACS = non–ST-segment elevation acute coronary syndrome; other abbreviations as in Figure 1.

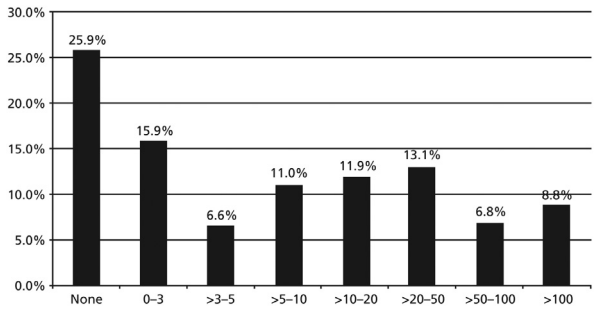

Figure 3 Distribution of Degrees of Elevation of cTn After PCI

Abbreviations as in Figure 1.

Results

Post-PCI cardiac biomarker elevation. Of 10,199 patients who underwent PCI during the index hospitalization in EARLY ACS and SYNERGY, 4,198 (41.2%) patients had increasing cTn levels before PCI and 229 (2.2%) had missing post-PCI values and were excluded from the analyses (Fig. 2). The remaining 5,772 (56.6%) had descending or stable cTn levels before PCI: 4,276 (41.9%) had a new increase in cTn level in the 24 h following PCI, and 1,496 (14.7%) had no new increase in post-PCI cTn level. Among patients included in the analysis, the median number of cTn samples obtained locally prior to PCI was 4 (interquartile range [IQR]: 3 to 6). In the 24 h after PCI, the median was 3 (IQR: 2 to 4).

Figure 3 shows the distribution of degrees of elevation of post-PCI cTn above the local ULN. Baseline demographics, cardiovascular history, and presenting characteristics by degree of post-PCI cTn peak level are shown in Table 1.

In the CK-MB analysis of 10,197 patients, 2,946 (28.9%) had increasing values prior to PCI, 820 (8.0%) had missing post-PCI values, and 6,431 (63.1%) had decreasing or stable values pre-PCI. Among those with decreasing or stable levels prior to PCI, 4,174 had a new increase in CK-MB values following the PCI, and 2,257 had no increase. Most patients (n = 3,243, 77.7%) with increased CK-MB values after PCI had peak values of ≤3× ULN; 402 (9.6%) had peak values of CK-MB >3× to ≤5× ULN, 298 (7.1%) had peak values of >5× to ≤10× ULN, and 231 (5.5%) had peak values of >10× ULN.

There were 4,395 (43.1%) patients in whom both cTn and CK-MB levels were evaluable after PCI; cTn was the only evaluable marker for 1,376 of 10,199 (13.5%) patients, and CK-MB was the only evaluable post-PCI marker for 2,036 of 10,197 (20.0%) patients. Neither cTn nor CK-MB could be evaluated after PCI for 2,390 (23.4%) patients.

Troponin, CK-MB, and 1-year mortality. The relationships between: 1) peak cTn after PCI and absolute increase in cTn after PCI; and 2) 1-year mortality were nonlinear with major inflections at 100× ULN (Fig. 4), and these variables were spline-transformed for modeling. In the adjusted model, peak cTn after PCI was significantly associated with 1-year mortality: for each 10× ULN increase in cTn, there was a 7% relative increase in the hazard of 1-year mortality (HR: 1.07, 95% CI: 1.02 to 1.11; p = 0.0038). The association with 1-year mortality was significant also above 100× ULN (HR: 1.02, 95% CI: 1.00 to 1.03; p = 0.007).The absolute post-PCI cTn increase was significantly associated with 1-year death: for each 10× ULN increase above the pre-elevation value, there was a 6% relative increase in the hazard of mortality (HR: 1.06, 95% CI: 1.01 to 1.11; p = 0.0275). A significant association with 1-year death was also observed above 100× ULN (HR: 1.02, 95% CI: 1.01 to 1.04; p = 0.0027).

The relationships of peak CK-MB after PCI and absolute increase in CK-MB after PCI were nonlinear with respect to 1-year mortality (Fig. 5), with major inflections at 5× ULN, and these variables were spline-transformed for modeling. In the adjusted model, peak post-PCI CK-MB was significantly associated with 1-year mortality: for each 1× ULN increase in CK-MB peak, there was a 13% increase in the hazard of 1-year death (HR: 1.13, 95% CI: 1.05 to 1.21; p = 0.0013). The association was maintained above 5× ULN (HR: 1.03, 95% CI: 1.02 to 1.04; p < 0.0001). The absolute post-PCI CK-MB increase above the pre-elevation value was also significantly associated with 1-year mortality (per 1× ULN increase up to 5× ULN [HR: 1.12, 95% CI: 1.03 to 1.21; p = 0.0057]; above 5× ULN [HR: 1.03, 95% CI: 1.02 to 1.04; p < 0.0001]).

As a sensitivity analysis, we also assessed the predictive value of post-PCI cTn peak in the group of patients in whom both cTn and CK-MB could be assessed after PCI, and the results were not substantively different from the results just reported: for each 10× ULN increase in cTn there was a 9% relative increase in the hazard of 1-year mortality (HR: 1.09, 95% CI: 1.03 to 1.14; p = 0.0009).

Adjusted estimated risk of death at different thresholds of biomarker elevation. Using the models generated for the associations of post-PCI peak cTn and peak CK-MB with 1-year mortality, we determined adjusted estimated risks of death at different threshold levels of biomarker elevation (Table 2). The adjusted estimated risk of 1-year mortality for a CK-MB peak >3× ULN was 5.1% (95% CI: 4.2% to 5.9%), whereas for cTn peak >3× ULN, it was 3.5% (95% CI: 2.9% to 4.1%). A cTn threshold >60× ULN provided a 4.9% (95% CI: 3.9% to 6.0%) estimated risk of death, comparable to CK-MB >3× ULN. A cTn threshold >100× ULN provided a 6.2% (95% CI: 4.5% to 8.4%) estimated risk of death, similar to a CK-MB threshold of >5× ULN.

Of note, the proportion of patients with cTn elevation >60× ULN was 13.5%, which is similar to the proportion

Table 1 Baseline Characteristics According to Extent of Troponin Elevation Above ULN

	No Elevation (n = 1,496)	0–3× ULN (n = 918)	>3–5× ULN (n = 381)	>5–10× ULN (n = 635)	>10–20× ULN (n = 689)	>20–50× ULN (n = 754)	>50× ULN (n = 898)	Not Evaluable (n = 4,427)
Trial								
EARLY ACS	914 (61.1)	450 (49.0)	200 (52.5)	331 (52.1)	385 (55.9)	412 (54.5)	535 (56.9)	2,325 (52.5)
SYNERGY	582 (38.9)	468 (51)	181 (47.5)	304 (47.9)	304 (44.1)	342 (45.4)	363 (40.4)	2,102 (47.5)
Demographics								
Age, yrs	66.2 (59.2–73.6)	67.8 (61.0–74.1)	67.6 (60.0–75.0)	67.9 (60.1–74.3)	67.0 (60.4–74.0)	67.0 (60.0–75.0)	68.0 (60.0–75.1)	66.0 (58.0–74.0)
Female	440 (29.4)	320 (34.9)	121 (31.8)	185 (29.1)	220 (31.9)	209 (27.7)	245 (27.3)	1,304 (29.5)
Weight, kg	80.8 (70.0–92.0)	79.0 (70.0–90.0)	81.0 (70.0–91.0)	80.0 (71.0–91.0)	80.0 (70.0–90.3)	80.0 (70.9–90.0)	80.0 (70.0–90.0)	80.0 (70.0–91.0)
CV history								
Diabetes	432 (28.9)	258 (28.1)	112 (29.4)	171 (26.9)	184 (26.7)	196 (26.0)	237 (26.4)	1,235 (27.9)
Hypertension	981 (65.6)	647 (70.5)	283 (74.3)	436 (68.7)	478 (69.4)	489 (64.9)	581 (64.7)	2,947 (66.6)
CHF	137 (9.2)	88 (9.6)	40 (10.5)	56 (8.8)	49 (7.1)	45 (6.0)	59 (6.6)	414 (9.4)
MI	354 (23.7)	266 (29.0)	105 (27.6)	176 (27.8)	172 (25.0)	204 (27.1)	232 (25.8)	1,158 (26.2)
PAD	135 (9.0)	95 (10.3)	28 (7.3)	63 (9.9)	80 (11.6)	65 (8.6)	93 (10.4)	360 (8.1)
PCI	346 (23.1)	282 (30.7)	99 (26.0)	165 (26.0)	166 (24.1)	152 (20.2)	179 (19.9)	1,006 (22.7)
CABG	214 (14.3)	163 (17.8)	50 (13.1)	101 (15.9)	101 (14.7)	116 (15.4)	124 (13.8)	638 (14.4)
Current smoker	451 (30.1)	237 (25.8)	111 (29.1)	164 (25.8)	178 (25.8)	202 (26.8)	261 (29.1)	1,286 (29.0)
Presentation								
Heart rate, beats/min	72 (64–84)	72 (62–82)	74 (64–85)	72 (63–83)	73 (64–84)	73 (64–84)	74 (64–85)	73 (64–84)
SBP, mm Hg	140 (123–154)	140 (122–145)	140 (124–160)	140 (122–158)	140 (123–158)	139 (121–156)	139 (121–154)	138 (120–155)
Creatinine clearance, ml/min	79.0 (60.3–101.3)	73.7 (55.6–95.9)	76.5 (57.7–102.0)	75.9 (57.7–97.8)	77.5 (58.9 –99.1)	77.0 (59.2–99.8)	76.5 (56.9–97.6)	78.5 (59.7–101.1)
Killip class								
1	1,351 (91.3)	827 (91.4)	343 (92.5)	576 (91.6)	640 (93.8)	673 (90.2)	796 (89.2)	3,934 (90.5)
2	101 (6.8)	65 (7.2)	25 (6.7)	44 (7.0)	32 (4.7)	57 (7.6)	80 (9.0)	327 (7.5)
3	20 (1.4)	11 (1.2)	3 (0.8)	6 (1.0)	7 (1.0)	11 (1.5)	13 (1.5)	72 (1.7)
4	7 (0.5)	2 (0.2)	0 (0.0)	3 (0.5)	3 (0.4)	5 (0.7)	3 (0.3)	13 (0.3)
ST changes	813 (54.4)	543 (59.2)	186 (58.8)	312 (49.3)	355 (51.5)	384 (51.1)	514 (57.2)	2,531 (88.6)
Positive markers	1,285 (85.9)	653 (71.1)	341 (89.5)	589 (92.8)	642 (93.2)	698 (92.6)	858 (95.5)	3,921 (88.6)
Arrival to randomization, h	6.3 (3.4–11.3)	6.5 (3.5–11.7)	6.9 (3.4–11.7)	6.8 (3.6–11.3)	6.0 (3.4–10.9)	6.4 (3.6–10.8)	5.5 (3.0–9.4)	5.4 (2.9–9.8)
Randomization to PCI, h	23.9 (18.5–46.5)	24.1 (18.0–47.2)	22.8 (17.1–44.2)	22.5 (16.7–41.3)	23.1 (17.6–44.3)	23.4 (17.4–42.9)	22.1 (16.4–38.6)	20.5 (12.0–40.4)
CAD extent								
0 vessels	15 (1.0)	8 (0.9)	1 (0.3)	6 (1.0)	6 (0.9)	10 (1.3)	10 (1.1)	41 (0.9)
1 vessel	676 (45.5)	425 (46.7)	157 (42.0)	239 (37.9)	274 (40.2)	280 (37.3)	315 (35.3)	1,800 (41.1)
2 vessels	433 (29.1)	262 (28.8)	102 (27.3)	211 (33.5)	228 (33.4)	258 (34.4)	307 (34.4)	1,360 (31)
3 vessels	363 (24.4)	216 (23.7)	114 (30.5)	174 (27.6)	174 (25.5)	202 (26.9)	261 (29.2)	1,180 (26.9)
Left main	63 (4.2)	38 (4.2)	14 (3.7)	22 (3.5)	32 (4.7)	39 (5.2)	48 (5.4)	200 (4.6)

Values are n (%) or median (interquartile range).

CABG = coronary artery bypass graft; CAD = coronary artery disease; CHF = congestive heart failure; CV = cardiovascular; EARLY ACS = Early Glycoprotein IIb/IIIa Inhibition in Non–ST-Segment Elevation Acute Coronary Syndromes; MI = myocardial infarction; PAD = peripheral artery disease; PCI = percutaneous coronary intervention; SBP = systolic blood pressure; SYNERGY = Superior Yield of the New Strategy of Enoxaparin, Revascularization and Glycoprotein IIb/IIIa Inhibitors; ULN = upper limit of normal.

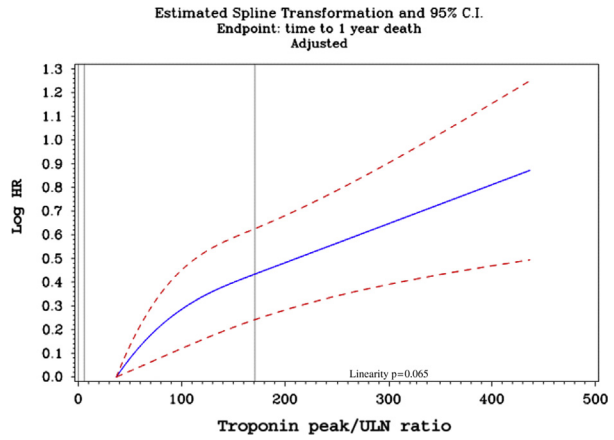

Figure 4 Adjusted Relationship Between Post-PCI Troponin Peak and 1-Year Mortality

Please see text for estimate adjustments. CI = confidence interval; HR = hazard ratio; PCI = percutaneous coronary intervention.

of patients with CK-MB elevation >3× ULN (14.5%). Also, the proportion of patients with cTn elevation >100× ULN was 8.8%, which is comparable to the proportion of patients with CK-MB elevation >5× ULN (8.2%).

Discussion

A graphic-based methodology to review biomarkers trends over time allows identification of patients with NSTE ACS in whom a rise in post-PCI cardiac biomarkers can be distinguished from a rise in cardiac biomarkers due to the presenting MI. In those patients, we observed a statistically significant association between post-PCI cTn peak level and 1-year mortality. A statistically significant association was also observed between post-PCI peak CK-MB and 1-year mortality. Higher cTn elevation thresholds provided estimated mortality risks that were similar to the currently adopted CK-MB thresholds.

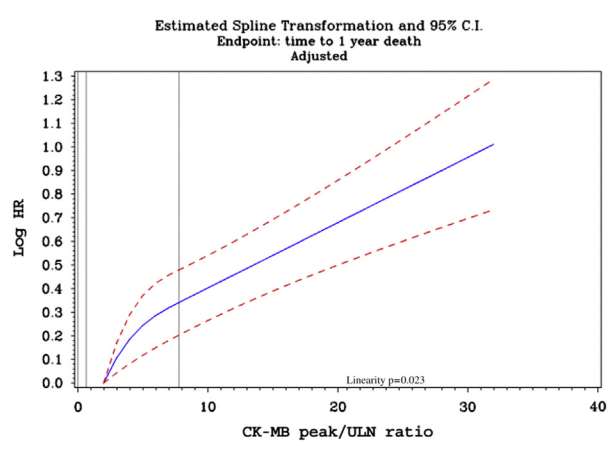

Figure 5 Adjusted Relationship Between Post-PCI CK-MB Peak and 1-Year Mortality

Please see text for estimate adjustments. Abbreviations as in Figures 1 and 4.

Post-PCI biomarker and the diagnosis of MI. Cardiac troponin assays can detect small amounts of myocardial necrosis; therefore, the clinical relevance of increased cTn levels following PCI has been questioned, particularly in the absence of observed procedural complications and clinically apparent consequences of myonecrosis (8). Similar arguments have been made regarding CK-MB elevation after PCI, but available evidence overall supports a correlation between CK-MB elevation after PCI and in-hospital adverse events and long-term mortality (4–6,12). Proposed CK-MB thresholds to diagnose procedure-related MI have historically been 3× or 5× ULN (3,8,13).

Cardiac troponin elevation after PCI correlates with the presence of late enhancement on cardiac magnetic resonance imaging, an indicator of myocardial scarring (14). Nonetheless, the results of studies correlating post-PCI cTn elevation with long-term outcomes have conflicted (6,15–19). Studies assessing the prognostic value of post-PCI cTn levels in patients with ACS have included patients with and without elevated pre-PCI cardiac biomarkers but have not specifically addressed whether elevated post-PCI cTn values were part of the expected rise related to an initial MI or if they represented new cTn release related to the PCI. This difference is key to understanding the prognostic implications of post-PCI cTn increases (20). The current universal definition of MI document recommends that trends in biomarker levels before PCI should be evaluated in order to implement a biomarker-based definition of MI (3).

In the present study of a large, multicenter cohort of patients with ACS, in whom serial collection of cardiac biomarkers was mandated by protocol, we reviewed trends in cardiac biomarkers of each patient undergoing PCI during the index hospitalization to identify those in whom cTn was decreasing or stable prior to PCI. In those patients, post-PCI elevations could be clearly distinguished from those

Table 2 Adjusted Probability of 1-Year Mortality by Thresholds of Biomarker Elevation After PCI

Cutoff, × ULN	Patients Above Cutoff, %		Adjusted Predicted Mortality With 95% CI	
	Troponin	CK-MB	Troponin	CK-MB
>3	58.2	14.5	3.5 (2.9–4.1)	5.1 (4.2–5.9)
>5	51.6	8.2	3.5 (2.9–4.2)	6.3 (4.7–7.8)
>10	40.6	3.6	3.6 (3.1–4.3)	7.2 (5.3–8.7)
>20	28.6	1.3	3.9 (3.3–4.5)	9.1 (7.1–11.3)
>50	15.6	—	4.6 (3.8–5.6)	—
>60	13.5	—	4.9 (3.9–6.0)	—
>80	10.7	—	5.5 (4.2–7.1)	—
>100	8.8	—	6.2 (4.5–8.4)	—
>200	4.2	—	7.2 (5.3–9.3)	—

CI = confidence interval; CK-MB = creatine kinase-MB; ULN = upper limit of normal; — = data not available.

due to the presenting MI. The cTn curves were screened using simple visual interpretation of biomarker trends, which is particularly appealing during the acute event when cardiac biomarker values may change continuously in relation to the initial MI, procedures, or spontaneous recurrent events. A similar approach was adopted by our group to identify patients with suspected recurrent MI during the acute hospitalization in recent large ACS trials (2,21). Using this method, we found that in nearly 60% of patients, post-PCI cTn values could be differentiated from those due to the presenting MI and could be assessed for new PCI-related myocardial necrosis.

After those patients were identified, we showed that increased post-PCI cTn levels were highly significantly associated with 1-year mortality. There was a continuous relationship between increasing post-PCI cTn peak and the risk of 1-year death, although the hazard associated with each unit of cTn increase was relatively small (7% increase in 1-year mortality for every 10× ULN increase), reflecting the sensitivity of cTn in detecting small amounts of myocardial necrosis. In fact, current assays with 10× ULN represent a rather small increase in ng/ml. For example, a cTnT assay with a ULN of 0.1 ng/ml (a 10× ULN increase) would be seen with a value of 1.0 ng/ml, an increase of only 0.09 ng/ml. Therefore, considering the risk per absolute amount of myonecrosis detected, these hazards are quite substantial. The hazard associated with each per-unit increase in CK-MB, a less sensitive marker, is higher because the relative changes in level represent much larger infarcts. Together, we confirm that new, detectable post-PCI myocardial necrosis, using either cTn or CK-MB, is prognostically relevant in an NSTE ACS population, and the greater the degree of myonecrosis, the greater the risk of subsequent mortality. Our results also confirm that the prognostic value of post-PCI peak cTn elevation is incremental to that of pre-PCI cTn elevation, which reflects the size of the index MI. Overall, the data from this study indicate that it is possible to use cardiac biomarkers to diagnose post-PCI MI in a large number of patients with ACS presenting with elevated necrosis biomarkers if trends before PCI are analyzed, adopting the principles established by the universal definition of MI. There is currently no accepted methodology for use of cardiac biomarkers to diagnosis PCI-related MI in patients with ACS when necrosis biomarkers are still increasing before the procedure.

Because of cTn's sensitivity to detect small areas of necrosis, thresholds associated with a clinically relevant risk of adverse events need to be identified and incorporated into definitions of MI. However, this will require the clinical community and patients to define "clinically relevant" risk for death or change in risk from baseline MI. After that, the thresholds for both spontaneous and PCI-related MI using either cTn or CK-MB can be determined relative to that benchmark and then standardized. The revised universal definition of MI indicates an identical threshold (>5× ULN) for the diagnosis of peri-PCI MI for cTn and CK-MB, in addition to clinical and angiographic complications. Yet, because of different sensitivities and, consequently, different hazards of death associated with increased values of cTn and CK-MB, the threshold for cTn should be higher than the threshold for CK-MB, if equivalence in risk-per-unit-increase in level is desired (22). In particular, we observed that an elevation of cTn >60× ULN carries an adjusted estimated risk of death similar to a >3× ULN CK-MB elevation, and an elevation of cTn >100× ULN carries an adjusted estimated risk of death similar to a >5× ULN CK-MB. This suggests that increase of cTn and CK-MB at those thresholds may indicate similar degrees of myocardial necrosis. Supporting this concept, we observed that the frequency of CK-MB >3× ULN was similar to the frequency of cTn >60× ULN, and that the frequency of CK-MB >5× ULN was similar to the frequency of cTn >100× ULN.

Study limitations. This study is a post hoc analysis from 2 clinical trial databases, although the data were prospectively collected. Although we adjusted for important clinical characteristics associated with outcome in our populations, residual confounding by other factors associated with both cTn elevation and mortality but not measured or not included in the model is possible. In particular, the 2 trials assessed a medical intervention in a general NSTE ACS population, and the collection of angiographic and procedural details was limited. Although causality between cTn elevation and mortality is biologically plausible, our study supports association but does not prove causality, nor does it address the mechanism through which myonecrosis occurred and the role it may play in defining the association with mortality. Our study was based on cTn values obtained locally, and ratios were based on ULN provided by local hospitals. We could not account for limitations in assays used or for appropriateness of ULN chosen at each site, and we could not consider absolute amounts of myonecrosis. The results of this study do not imply that cTn elevation after PCI should be considered equivalent to a recurrent MI; rather, we aimed to provide data on the correlation between post-PCI cTn and subsequent mortality. Finally, our results are not applicable to a large group of patients (more than 40%) who had increasing biomarkers up to the time of PCI.

Conclusions

In a large NSTE ACS population undergoing PCI, a patient-level assessment of cTn trends allowed for identification of approximately 60% of patients in whom new cardiac biomarker elevation following PCI could be distinguished from expected elevation due to a presenting MI. In this group, peak post-PCI cTn was significantly associated with 1-year mortality and added prognostic value to cTn elevation associated with a presenting MI. These results support the use of cTn, along with CK-MB, for the diagnosis of PCI-related MI, but they also indicate that thresholds for cTn and CK-MB will be different for similar risks of

mortality. The selection of a threshold for cTn-based diagnosis of PCI-related MI should consider both the sensitivity of the assay (thus, the amount of myonecrosis per unit increase) and an estimate of what defines clinically relevant increases in the rates of complications associated with myonecrosis, whether defined by cTn or CK-MB.

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