Defining the Optimal Cardiac Troponin T Threshold for
Predicting Death Caused by Periprocedural Myocardial
Infarction After Percutaneous Coronary Intervention

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Background—There is controversy about the diagnostic and prognostic significance of percutaneous coronary intervention–related myocardial infarction, especially with the use of cardiac troponin T (cTnT). This analysis was designed to address the question of the presence and the level of a prognostic cTnT threshold.

Methods and Results—We evaluated 5268 consecutive patients who underwent nonemergent percutaneous coronary intervention between 2000 and 2009 with a preprocedural cTnT level below the upper limit of normal (ULN, ≤0.01 ng/mL). Postprocedural cTnT and creatine kinase-MB mass levels (ULN, 6.7 ng/mL in men and 3.8 ng/mL in women) were found to be associated with 3-month mortality in Cox proportional hazard models (hazard ratio per doubling of cTnT, 1.24; 95% confidence interval, 1.08–1.43; \(P=0.003\)) and hazard ratio per doubling of creatine kinase-MB, 1.30; 95% confidence interval, 1.05–1.60; \(P=0.018\)), adjusted for the Mayo Clinic risk scores for in-hospital and postdischarge mortality. The optimal prognostic threshold for 3-month mortality was 25× ULN for cTnT (hazard ratio, 4.53; 99% confidence interval, 1.59–12.9; \(P<0.001\)), which provided similar information as a value of 5× ULN for creatine kinase-MB (hazard ratio, 4.31; 99% confidence interval, 1.27–14.6; \(P=0.002\)). The cumulative mortality rate was 0.6% at 91 days.

Conclusions—A significant association of postpercutaneous coronary intervention cardiac biomarker elevation with a small number of postpercutaneous coronary intervention outcomes was noted for the early (first 91 days) follow-up period with an identifiable optimal threshold of 25× ULN (0.25, ng/mL) for cTnT, which provided similar early outcome information as a cutoff of × ULN for creatine kinase-MB. (Circ Cardiovasc Interv. 2014;7:00-00.)

Key Words: angioplasty ■ biomarkers ■ myocardial infarction ■ prognosis

Myonecrosis occurs in 10% to 40% of patients undergoing percutaneous coronary intervention (PCI), depending on clinical, angiographic, and procedural characteristics of the patients, adjunctive therapy, and biomarker used. However, the diagnostic and prognostic implications of PCI-related myocardial infarction (PMI) and the optimal thresholds for its definition have been questioned for multiple reasons. First, although the majority of studies using creatine kinase (CK) or CK-MB have demonstrated a weak association or no association between PMI and clinical outcome. One reason for this discrepancy is that few of these studies have used the recommended guideline criteria to define a normal baseline (upper limit of normal [ULN]), ie, the 99th percentile cutoff value for the upper reference limit, and therefore have included biomarker negative patients, who, by contemporary definitions, would have been diagnosed with an acute MI prior to the PCI. Second, following the Prequel, the task force for the universal definition of MI has recently raised the cTn cutoff from 3× to 5× ULN for the diagnosis of PMI in conjunction with ≥1 of the following: (1) symptoms of myocardial ischemia, (2) new ischemic ECG changes, (3) angiographic findings consistent with a procedural complication, or (4) imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality. The new diagnostic level is similar to the level of CK-MB elevation that was considered clinically relevant in the 2005 update of the PCI guidelines. The Society of for Cardiovascular Angiography and Interventions has recently proposed yet another definition of clinically relevant PMI, mainly based on CK-MB at a level ≥10× ULN or ≥5× ULN the absence or presence of new Q wave or left new bundle branch block, respectively, but without the caveat of a normal baseline cTnT value as defined above. Third, many studies have not distinguished cardiovascular from noncardiovascular events. Finally, some
WHAT IS KNOWN

- Myocardial infarction related to percutaneous coronary intervention is considered to be a distinct entity in the universal definition of myocardial infarction (type 4a myocardial infarction).
- The diagnostic and prognostic implications of type 4a myocardial infarctions, as well as the optimal threshold criteria for its definition, however, remain in question.

WHAT THE STUDY ADDS

- A prognostically significant level of postprocedural cardiac troponin T elevation can be defined for all-cause and cardiovascular mortality at 3 months after percutaneous coronary intervention.
- Using a contemporary assay for cTnT and the 99th percentile cutoff for upper limit of normal, the prognostic threshold level is 25× upper limit of normal (0.25 ng/mL).
- This level of elevation occurs in only a small number of patients (7%).

Studies have suggested that the clinical implications of PMI might be relevant for short-term but not long-term outcomes.\(^2^\)

To address these clinically important issues, we conducted the current study to examine the relationship between the magnitude of peri-procedural myocardial necrosis, measured simultaneously with cTnT and CK-MB, with postprocedural survival in patients with normal baseline biomarker levels, and to define whether there is a threshold value for cTnT at which prognosis is significantly affected.

Methods

All patients undergoing PCI at the Mayo Clinic in Rochester, MN, are prospectively enrolled in a registry, which includes demographic, clinical, angiographic, and procedural data. Follow-up of all patients is standardized with recording of immediate postprocedural and inhospital events and phone surveys using a standardized questionnaire at 6 months, 1 year, and then annually after the procedure by trained data technicians. Routinely, 10% of all records are randomly audited at 6 months, 1 year, and then annually after the procedure by trained data technicians. Routinely, 10% of all records are randomly audited by the supervisor for data integrity. All adverse events are confirmed by reviewing the medical records of the patients followed up at our institution and by contacting the patients’ physicians and reviewing the hospital records of patients treated elsewhere.

Study Population

The current study includes consecutive patients from the database for the period from November 1, 2000, when routine measurements of cTnT and CK-MB were initiated for all patients with PCI, through October 31, 2009. All patients who underwent nonemergency PCI with normal preprocedural cTnT and CK-MB levels were considered for study inclusion. Patients were excluded if they underwent emergency procedures, defined as those performed within 4 to 6 hours of symptom onset, such as primary PCI, rescue PCI, or PCI for severe refractory ischemia. Furthermore, any patient in whom the diagnosis of any kind of MI was made within 24 hours of PCI was excluded. Also, patients were excluded if paired baseline and postprocedural cTnT and CK-MB values were unavailable. Hospital charts of each patient were reviewed to verify the data, and the study was approved by the institutional review board. There were 10875 nonemergency PCIs performed on 9051 unique patients. Two hundred twenty-eight patients (with 271 PCIs) refused to authorize the use of their records for research, which resulted in a sample size of 10604 PCIs. Of these, 9076 PCIs had both pre- and post-PCI cTnT measures; 3010 were excluded for baseline elevations of either cTnT or CK-MB (isolated cTnT elevation in 1782 patients, isolated CK-MB elevation in 258 patients, and cTnT and CKMB elevation in 970 patients). The initial index PCI was used for the final study population of 5268 unique patients.

Laboratory Tests

The biomarker approach taken was the same as reported before.\(^1^5^\) Blood samples for cardiac biomarkers were collected before the procedure and then 8 and 16 hours after PCI. Ninety percent of postprocedural samples were collected within 2 hours of PCI. Peak postprocedural values were used for the analysis. cTnT was measured using current third- or fourth-generation assay (on Elecsys 2010 or Cobas e 411 analyzer; Roche Diagnostics, Indianapolis, IN). The 99th percentile upper reference limit for the assay is ≤0.01 ng/mL (with a coefficient of variation of 20%), which was used as the ULN in this study (corresponding to 0.03 ng/mL or 30 ng/L with the high-sensitivity-cTnT assay).\(^1^3^\) CK-MB mass levels were likewise measured using a sandwich electrochemiluminescence immunoassay (also Elecsys 2010 or Cobas e 411 analyzer) with the ULN (97.5 percentile value) of 6.7 and 3.8 ng/mL for men and women, respectively.

Definitions

All-cause mortality was defined as death because of any cause. Cardiovascular mortality was defined as death caused by MI, congestive heart failure, arrhythmia, or other cardiovascular reasons, including sudden death within 1 hour of onset of symptoms. All deaths were verified by review of patient charts and death certificates and were marked as unknown in case these documents on the cause of death were not available. All deaths without known cause were considered cardiovascular for purposes of the present analysis. Any elevation in troponin and CK-MB measures was defined as a measurement >1×ULN.

Statistical Analysis

Data are summarized as mean±SD or median (first, third quartile) for continuous variables and as frequency (percentage) for discrete data. The Kaplan–Meier method was used for time-to-event analyses. Three-month survival rates were analyzed by including all events within 91 days after PCI and censoring any survival after 91 days. Long-term analysis refers to analysis of survival after the first 91 days, which excluded those who died or were censored within 91 days. Group comparisons were made using ANOVA. Pearson χ² statistic, and the log-rank test for continuous, nominal, and survival data, respectively. The best prognostic cut point with regards to 3-month mortality for postprocedural peak cTnT and CK-MB was identified using the methodology of Contal and O’Quigley.\(^2^4^\) This method chooses the cut point that maximizes a rank-based statistic, thus resulting in the smallest P value, when comparing survival between 2 groups defined by the cut point, and corrects the P value for multiple tests.\(^2^5^\) Bootstrapping was used to estimate 95% confidence intervals for the cut points by identifying the 2.5th and 97.5th percentiles of cut points from 500 bootstrap samples. In addition, the extent of linearity in the association between troponin values and 3-month mortality was investigated as follows. A model for 3-month mortality without independent variables was fit, and the martingale residuals were calculated. The residuals were then plotted against troponin values, and a scatterplot smoother was used to display the relationship.\(^2^9^\) Cox proportional hazards models were used to estimate unadjusted and adjusted hazard ratios (HRs) for 3-month and long-term events. We tested whether 3-month mortality was different between patients...
divided by high and low values of biomarkers. We investigated various cut points to define high and low for both troponin (≥1 ULN, >5 ULN, ≥5 ULN, >25 ULN, >50 ULN, and >100 ULN) and CK-MB (≥1 ULN, >3 ULN, >5 ULN, >8 ULN). The significance level was set by dividing 0.05 by the number of cut points tested, to retain an overall type I error rate of 0.05. Plots of scaled Schoenfeld residuals were used to assess the proportional hazards assumption. Previously published risk scores for short- and long-term post-PCI mortality were used as covariate adjustments for survival analysis. Because these scores were constructed from our own PCI database, they could be readily calculated for our study sample. This approach allowed us to create composite indices of risk from those variables previously shown to be predictive of mortality after PCI at our institution and thus avoid variable overload of the model. Using time-dependent covariates, the risk score for in-hospital mortality was applied to the predischARGE time period and the risk score for long-term mortality was applied to the postdischarge time period, consistent with the construction of those scores. The risk score for in-hospital mortality included 7 variables (age, MI ≤24 hours, preprocedural shock, serum creatinine level, left ventricular ejection fraction, congestive heart failure, and peripheral artery disease). The risk score for long-term mortality included 13 variables (age, MI ≤24 hours, preprocedural shock, serum creatinine level, left ventricular ejection fraction, congestive heart failure, and peripheral artery disease). The risk score for long-term mortality included 13 variables (age, body mass index, coronary artery disease [CAD] co-morbidity index, history of congestive heart failure, left ventricular ejection fraction <37%, MI 1–7 days before, cTnT ≥0.01, previous smoking history, total cholesterol >240 mg/dL, previous coronary artery bypass graft, ventricular arrhythmia during PCI, glycoprotein IIb/IIIa use, and low medication score). Spearman correlation coefficient was used to summarize the monotonic association between postprocedural peak cTnT and CK-MB. Linear regression without an intercept was used to estimate the typical ratio between cTnT/ULN and CK-MB/ULN. All analyses were conducted using SAS 9.3 software (SAS Institute, Cary, NC).

**Results**

**Clinical Characteristics**

Of the 5268 patients with a normal baseline cTnT value, 2289 (43%) and 1142 (22%) patients developed cTnT or CK-MB elevation (defined as >1x ULN), respectively, after PCI. Post-PCI elevations tended to be small; the peak level was 0.05 ng/mL (median [interquartile range], 0.02 [0.15]) for cTnT and 10.8 ng/mL (median [interquartile range], 7.3 [19.5]) for CK-MB. As summarized in Table 1, patients with postprocedural cTnT elevation had more adverse characteristics, including age, reduced left ventricular ejection fraction, chronic kidney disease, and chronic obstructive pulmonary disease. At baseline, β-blocker (72% versus 75%; P=0.012) and lipid-lowering therapy (45% versus 48%; P=0.038) were less common in patients with elevated cTnT. The use of aspirin and angiotensin-converting enzyme inhibitor therapy was similar in both groups. Similar differences were observed when the data were analyzed by postprocedural peak CK-MB values (Table I in the Data Supplement).

**Angiographic and Procedural Characteristics**

As outlined in Table 2, patients with postprocedural cTnT elevation had more complex disease, both in terms of overall extent (multivessel disease) and lesion type (type C, thrombotic, calcified, moderately to severely angulated lesions with major side branches present). They were also more likely to have multivessel PCI or intervention on a saphenous vein graft. Postprocedural thrombolysis in myocardial infarction grade 3 flow was less common with increasing levels of cTnT elevation (Table 2). Similar trends for more adverse angiographic features and complex intervention were observed for post-PCI CK-MB (Table II in the Data Supplement).

**cTnT Level and Outcomes**

Patients were followed up for a median of 65 months (25th, 75th percentiles, 36, 90 months) during which 824 deaths (15.6%) were observed (32 deaths occurred within the first 91 days). Three-month (91 days) mortality was 0.4% in patients without and 0.9% in those with any level of postprocedural cTnT elevation (P=0.01). The relationship between cTnT levels and unadjusted 3-month mortality is shown in Figure 1. The optimal cTnT cutoff value for 3-month mortality prediction was 0.25 mg/mL (ie, 25× ULN; Figure I in the Data Supplement). The all-cause mortality was 2.8% at 91 days in patients with cTnT values ≥0.25 ng/mL and 0.5% in patients with cTnT values <0.25 ng/mL (Figure 2). This difference remained statistically significant after a propensity score-matched comparison analysis (Figure II in the Data Supplement; group details in Table III in the Data Supplement).

In a multivariable model that adjusted for the Mayo Clinic risk scores for in-hospital and postdischarge mortality, postprocedural cTnT elevation remained associated with 3-month all-cause death (HR per doubling of cTnT, 1.24; 1.08–1.43; P=0.003) and cardiovascular death (HR per doubling of cTnT, 1.26; 1.04–1.54; P=0.02). The 5 different cut points for cTnT were tested for significance (above versus below the threshold) in 5 different models at the 0.01 significance level (Table 3). The strongest association with 3-month all-cause mortality was noted at cTnT level ≥25× ULN (HR, 4.53; 99% CI, 1.59–12.9; P<0.001). This threshold also predicted cardiovascular mortality (HR, 5.20; 99% CI, 1.39–20.1; P<0.001) but not non-cardiovascular mortality (HR, 3.53; 99% CI, 0.64–19.6; P=0.058).

The potential effect of creatinine clearance on cTnT kinetics and outcome was tested by including interaction terms into the multivariable models. For 3-month mortality, there was no significant interaction between creatinine clearance level and the troponin effect (interaction test P=0.99; log-2 troponin HR when CrCl ≤60, 1.24; 95% CI, 1.02–1.51 and log-2 troponin HR when CrCl>60, 1.25; 95% CI, 1.00–1.55).

Similarly, interaction terms were incorporated into the multivariable models to assess whether the cTnT effect might be modified by stable versus unstable CAD presentation. Again, for 3-month all-cause mortality, there was no significant interaction between CAD presentation and troponin effect (interaction test P=0.81; log-2 troponin HR in stable CAD, 1.20; 95% CI, 0.88–1.62 and log-2 troponin HR in unstable CAD, 1.25; 95% CI, 1.07–1.47). The same was observed for 3-month cardiovascular mortality (interaction test P=0.81; log-2 troponin HR in stable CAD, 1.31; 95% CI 0.88, 1.96 and log-2 troponin HR in unstable CAD, 1.24; 95% CI, 0.99–1.56).

Additional analyses demonstrated that the prognostic implication was clearly evident in the unstable CAD group, whereas of smaller magnitude in the stable CAD, in keeping with the HRs outlined above (Figure III in the Data Supplement). The same results were obtained when the analysis was confined to patients with peak cTnT elevations late after PCI (18–20 hours; Figures IV–VI in the Data Supplement).
Among the 5064 patients who survived >91 days, the median follow-up duration was 67 months (25th, 75th percentiles, 42, 91 months). Long-term (>91 days) all-cause mortality was higher in patients with postprocedural cTnT elevation but without any distinct prognostic cut off level (Figure VII in the Data Supplement; Table 3). In a multivariable model that included the Mayo Clinic risk score, as well as several angiographic and procedural variables (Table 4), the risk score was by far the most powerful independent predictor with a C-statistic value of 0.753. Postprocedural cTnT elevation was a weak independent predictor (HR per doubling, 1.05; 1.01–1.09; P=0.011) and added minimal additional prognostic value (increase in C-statistic by <0.001). Data on CK-MB levels and outcomes are provided in the Data Supplement.

### Correlation of Postprocedural cTnT and CK-MB Elevation

For the entire cohort, correlation analysis of peak post-PCI cTnT and CK-MB levels yielded a Spearman correlation coefficient of 0.75 (P<0.001; Figure 3). The regression coefficient between CK-MB and cTnT units of ULN was 8.8 (SE, 0.11).

### Table 1. Clinical Characteristics Stratified by Postprocedural cTnT Level

<table>
<thead>
<tr>
<th>Postprocedural cTnT Level</th>
<th>n (%)</th>
<th>Overall</th>
<th>Normal (n=2979)</th>
<th>&gt;1–5× ULN (n=1042)</th>
<th>&gt;5–25× ULN (n=876)</th>
<th>&gt;25–50× ULN (n=213)</th>
<th>&gt;50–100× ULN (n=95)</th>
<th>&gt;100× ULN (n=63)</th>
<th>PValue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>66.8±11.2</td>
<td>65.5±11.1</td>
<td>68.3±11.3</td>
<td>68.4±11.2</td>
<td>68.0±9.9</td>
<td>69.3±10.6</td>
<td>70.6±11.6</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Male sex</td>
<td>3834 (73%)</td>
<td>2180 (73%)</td>
<td>757 (73%)</td>
<td>631 (72%)</td>
<td>150 (70%)</td>
<td>70 (74%)</td>
<td>46 (73%)</td>
<td>0.95</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1412 (27%)</td>
<td>808 (27%)</td>
<td>281 (27%)</td>
<td>218 (25%)</td>
<td>61 (29%)</td>
<td>31 (33%)</td>
<td>13 (21%)</td>
<td>0.40</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>3993 (79%)</td>
<td>2258 (79%)</td>
<td>777 (78%)</td>
<td>665 (80%)</td>
<td>166 (79%)</td>
<td>75 (83%)</td>
<td>52 (84%)</td>
<td>0.74</td>
<td></td>
</tr>
<tr>
<td>Body mass index</td>
<td>30.1±5.7</td>
<td>30.2±5.7</td>
<td>30.1±5.7</td>
<td>29.9±5.7</td>
<td>30.2±5.7</td>
<td>29.9±5.7</td>
<td>28.8±5.3</td>
<td>0.33</td>
<td></td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>4360 (86%)</td>
<td>2479 (88%)</td>
<td>851 (87%)</td>
<td>725 (89%)</td>
<td>173 (87%)</td>
<td>78 (89%)</td>
<td>54 (89%)</td>
<td>0.97</td>
<td></td>
</tr>
</tbody>
</table>

Smoking status
- Never: 1881 (37%) | 1059 (37%) | 364 (36%) | 322 (38%) | 74 (36%) | 41 (44%) | 21 (35%) | 0.60 |
- Former: 2573 (50%) | 1443 (50%) | 519 (51%) | 428 (50%) | 107 (52%) | 44 (47%) | 32 (53%) | 0.016 |
- Current: 661 (13%) | 393 (13%) | 127 (13%) | 104 (12%) | 25 (12%) | 8 (9%) | 7 (12%) | 0.07 |

Most recent MI
- 1–7 d: 58 (1%) | 21 (1%) | 17 (2%) | 14 (2%) | 5 (2%) | 1 (1%) | 0 (0%) | <0.001 |
- >7 d: 1618 (31%) | 900 (31%) | 332 (33%) | 274 (32%) | 52 (25%) | 29 (31%) | 31 (50%) | 0.40 |
- Never: 3464 (67%) | 1981 (68%) | 666 (66%) | 569 (66%) | 153 (73%) | 64 (68%) | 31 (50%) | 0.005 |

Unstable angina
- 3060 (58%) | 1703 (57%) | 629 (60%) | 526 (60%) | 120 (56%) | 50 (53%) | 32 (51%) | 0.19 |

Current congestive heart failure
- Ejection fraction ≤40%: 441 (8%) | 204 (7%) | 104 (10%) | 85 (10%) | 30 (14%) | 10 (11%) | 8 (13%) | <0.001 |
- Prophylactic IABP: 15 (0%) | 9 (0%) | 2 (0%) | 3 (0%) | 0 (0%) | 1 (2%) | 0 (0%) | 0.40 |
- Preprocedural shock: 19 (0%) | 8 (0%) | 5 (0%) | 3 (0%) | 1 (0%) | 0 (0%) | 2 (3%) | 0.008 |
- Preprocedural cardiac arrest: 2 (0%) | 1 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 1 (2%) | 0 (0%) | <0.001 |
- Previous PCI: 1849 (35%) | 1081 (36%) | 340 (33%) | 312 (36%) | 60 (28%) | 30 (32%) | 26 (41%) | 0.06 |
- Previous CABG: 1273 (24%) | 714 (24%) | 265 (25%) | 196 (22%) | 49 (23%) | 26 (22%) | 23 (37%) | 0.13 |
- Peripheral vascular disease: 512 (10%) | 256 (9%) | 131 (13%) | 90 (11%) | 24 (12%) | 8 (9%) | 3 (5%) | 0.005 |
- Previous stroke or transient ischemic attack: 520 (10%) | 268 (9%) | 120 (12%) | 87 (10%) | 21 (10%) | 15 (16%) | 9 (15%) | 0.040 |
- Moderate or severe renal disease: 92 (2%) | 45 (2%) | 18 (2%) | 15 (2%) | 6 (3%) | 4 (4%) | 4 (7%) | 0.015 |
- Chronic obstructive pulmonary disease: 482 (9%) | 246 (8%) | 111 (11%) | 76 (9%) | 26 (12%) | 15 (16%) | 8 (13%) | 0.011 |
- Malignancy: 727 (14%) | 396 (13%) | 150 (15%) | 130 (15%) | 26 (12%) | 19 (20%) | 6 (10%) | 0.29 |

Values are provided as mean±SD, or n (%). CABG indicates coronary artery bypass graft; cTnT, cardiac troponin T; IABP, intraaortic balloon pump; MI, myocardial infarction; PCI, percutaneous coronary intervention; and ULN, upper limit of normal.
respectively, and related HRs for 25× ULN cTnT and 5× ULN CK-MB were 4.53 (99% CI, 1.59–12.9; P<0.001) and 4.31 (99% CI, 1.27–14.6; P=0.002), respectively.

Causes of Death in the First 91 Days After PCI
Details about early post-PCI mortality are provided in Figure 4 and in the Data Supplement provided. Absolute cardiac mortality was 1.9% in those with postprocedural cTnT levels ≥0.25 ng/mL and 0.2% in those with levels <0.25 ng/mL. Noncardiac mortality was 0.8% and 0.3%, respectively. Six of the 7 cardiac deaths (86%) and 2 of the 3 noncardiac deaths (67%) in the ≥0.25 ng/mL elevation group occurred within 30 days. On the contrary, only 5 of 12 cardiac deaths (42%) and 2 of the 10 noncardiac deaths (20%) in the <0.25 ng/mL elevation group occurred within 30 days. Hence, all-cause mortality in patients with cTnT elevation ≥0.25 ng/mL was based primarily on cardiovascular mortality and occurred early on after PCI.

Discussion
These data from a large cohort of patients with normal baseline cTnT values indicate that a prognostically important level can be defined for post-PCI cTnT elevations. A value >25× ULN (>0.25 ng/mL) identified individuals at increased risk for 3-month all-cause and cardiovascular mortality. This level of elevation, however, was noted only in a small number of patients and related to the presence of high-risk baseline and procedural characteristics. Finally, even though significant interpatient variability was noted, there was a good correlation between the magnitude of increase in cTnT and CK-MB after PCI in the cohort as a whole and cutoff values of 5× ULN for CK-MB and 25× ULN for cTnT provided similar early outcome information.

Our study population is representative of contemporary practice with the majority of patients being treated with stents (92%) and dual antiplatelet therapy. Using the contemporary

### Table 2. Angiographic and Procedural Characteristics by Postprocedural cTnT Level

<table>
<thead>
<tr>
<th>Postprocedural cTnT Level</th>
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<th>&gt;100× ULN (n=63)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multivessel coronary artery disease</td>
<td>3139 (64%)</td>
<td>1683 (60%)</td>
<td>641 (66%)</td>
<td>564 (70%)</td>
<td>140 (71%)</td>
<td>63 (72%)</td>
<td>48 (81%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Type C lesion</td>
<td>2090 (41%)</td>
<td>1046 (36%)</td>
<td>446 (44%)</td>
<td>413 (48%)</td>
<td>100 (49%)</td>
<td>47 (52%)</td>
<td>38 (60%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Thrombotic lesion</td>
<td>395 (8%)</td>
<td>176 (6%)</td>
<td>76 (8%)</td>
<td>82 (10%)</td>
<td>31 (16%)</td>
<td>16 (18%)</td>
<td>14 (25%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Calcified lesion</td>
<td>1913 (42%)</td>
<td>1002 (38%)</td>
<td>417 (46%)</td>
<td>347 (46%)</td>
<td>82 (45%)</td>
<td>33 (44%)</td>
<td>32 (57%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Eccentric lesion</td>
<td>3690 (79%)</td>
<td>2047 (74%)</td>
<td>710 (78%)</td>
<td>644 (83%)</td>
<td>160 (82%)</td>
<td>75 (90%)</td>
<td>54 (92%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Blunt cusp lesion</td>
<td>911 (18%)</td>
<td>463 (16%)</td>
<td>194 (20%)</td>
<td>183 (22%)</td>
<td>47 (24%)</td>
<td>16 (19%)</td>
<td>8 (13%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ulcerated lesion</td>
<td>325 (7%)</td>
<td>172 (6%)</td>
<td>63 (7%)</td>
<td>37 (7%)</td>
<td>8 (11%)</td>
<td>3 (4%)</td>
<td>3 (4%)</td>
<td>0.004</td>
</tr>
<tr>
<td>Moderate or severe angulation</td>
<td>2395 (48%)</td>
<td>776 (28%)</td>
<td>446 (45%)</td>
<td>357 (43%)</td>
<td>72 (36%)</td>
<td>32 (35%)</td>
<td>27 (43%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Minor side branch present</td>
<td>1905 (38%)</td>
<td>1026 (37%)</td>
<td>387 (39%)</td>
<td>330 (40%)</td>
<td>92 (46%)</td>
<td>42 (48%)</td>
<td>28 (44%)</td>
<td>0.13</td>
</tr>
<tr>
<td>Major side branch present</td>
<td>1076 (22%)</td>
<td>551 (20%)</td>
<td>229 (23%)</td>
<td>198 (24%)</td>
<td>58 (29%)</td>
<td>24 (28%)</td>
<td>16 (27%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Preprocedural TIMI 0/1 flow</td>
<td>394 (10%)</td>
<td>209 (9%)</td>
<td>75 (10%)</td>
<td>78 (12%)</td>
<td>16 (10%)</td>
<td>8 (11%)</td>
<td>8 (20%)</td>
<td>0.09</td>
</tr>
<tr>
<td>Urgent PCI</td>
<td>2441 (46%)</td>
<td>1302 (44%)</td>
<td>524 (50%)</td>
<td>439 (50%)</td>
<td>99 (46%)</td>
<td>44 (46%)</td>
<td>33 (52%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No. of vessels treated</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>1</td>
<td>4323 (82%)</td>
<td>2594 (87%)</td>
<td>820 (79%)</td>
<td>658 (75%)</td>
<td>139 (65%)</td>
<td>69 (73%)</td>
<td>43 (88%)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>874 (17%)</td>
<td>362 (12%)</td>
<td>202 (19%)</td>
<td>201 (23%)</td>
<td>68 (32%)</td>
<td>22 (23%)</td>
<td>19 (30%)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>69 (1%)</td>
<td>21 (1%)</td>
<td>20 (2%)</td>
<td>17 (2%)</td>
<td>6 (3%)</td>
<td>4 (4%)</td>
<td>1 (2%)</td>
<td></td>
</tr>
<tr>
<td>No. of stents placed</td>
<td>1.5±1.0</td>
<td>1.3±1.0</td>
<td>1.5 (1.0)</td>
<td>1.7 (1.1)</td>
<td>2.0±1.2</td>
<td>1.9±1.1</td>
<td>2.3±1.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Drug-eluting stents</td>
<td>2896 (55%)</td>
<td>1660 (55%)</td>
<td>557 (53%)</td>
<td>482 (55%)</td>
<td>115 (54%)</td>
<td>51 (54%)</td>
<td>31 (49%)</td>
<td>0.74</td>
</tr>
<tr>
<td>Glycoprotein IIb/IIIa inhibitor use</td>
<td>2356 (48%)</td>
<td>1321 (44%)</td>
<td>514 (49%)</td>
<td>472 (54%)</td>
<td>134 (63%)</td>
<td>60 (63%)</td>
<td>35 (56%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Vein graft intervention</td>
<td>276 (7%)</td>
<td>183 (6%)</td>
<td>77 (7%)</td>
<td>59 (7%)</td>
<td>17 (8%)</td>
<td>11 (12%)</td>
<td>14 (22%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Procedural success</td>
<td>5065 (96%)</td>
<td>2872 (96%)</td>
<td>999 (96%)</td>
<td>842 (96%)</td>
<td>206 (97%)</td>
<td>88 (93%)</td>
<td>58 (92%)</td>
<td>0.22</td>
</tr>
<tr>
<td>Postprocedural TIMI 0/1 flow</td>
<td>4920 (99%)</td>
<td>2775 (97%)</td>
<td>951 (97%)</td>
<td>806 (97%)</td>
<td>191 (95%)</td>
<td>84 (92%)</td>
<td>48 (80%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Post-PCI CK-MB levels, ng/mL</td>
<td>3.1 (2.2, 5.1)</td>
<td>2.4 (1.8, 3.0)</td>
<td>3.6 (2.8, 4.8)</td>
<td>7.4 (5.3, 10.9)</td>
<td>19.3 (14.3, 27.8)</td>
<td>35.8 (26.0, 48.0)</td>
<td>69.9 (41.0, 131.5)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Values are provided as mean±SD, median (quartile 1, quartile 3), or n (%). CK-MB indicates creatine kinase-MB; cTnT, cardiac troponin T; PCI, percutaneous coronary intervention; and ULN, upper limit of normal.
cTnT assay, we detected postprocedural myonecrosis in a large proportion (43%) of patients, but the magnitude of injury was small (median peak value, 0.05 ng/mL). We identified cTnT > 25× ULN, which was observed in 7% of patients, as the cutoff that correlated with an increased mortality at 3 months after PCI, independent of the following variables: age, MI within hours of PCI, preprocedural shock, serum creatinine level, left ventricular ejection fraction, congestive heart failure, and peripheral artery disease. This threshold is much greater than the 3× and 5× ULN threshold recommended for type 4a MI by the second and third Universal Definition of MI, respectively.16–18 However, those guidelines were developed for all cTn assays with some being more and others being less sensitive than the cTnT assay we have used and for which the current findings apply. Nonetheless, the concept seems clear that higher thresholds are needed for cTn than for CK-MB assays to identify those at risk for adverse outcomes after PCI.

The need for a higher cTn threshold for defining prognostically significant PMI is consistent with recent observations. A small study of 32 patients reported that a 40-fold increase in the ULN was the optimal postprocedural cTnI cutoff for identifying a confluent area of PMI by late gadolinium enhancement.24 Second, an analysis from the Evaluation of Drug Eluting Stents and Ischemic Events registry suggested that a cTn threshold of 20× ULN was the best cutoff to match the frequency of PMI diagnosed using the universal definition for CK-MB (3× ULN).25 However, the latter analysis had several limitations that are not present in our study, such as the use of pooled data from multiple centers using different assays for cTn, lack of measurement of pre-PCI cTn values, and absence of long-term follow-up. Third, a post hoc investigation from the Resolute All-Comers stent trial recently reported that the 2007 Universal Definition of PMI did not correlate with 2-year cardiovascular mortality.26 Finally, Cavallini et al.31 found that a rise in CK-MB but not in cTnI elevations 1 to 10× ULN were independently associated with death at 2 years.

Older studies suggested that only more substantial (>5–8× ULN) increases of post-PCI CK-MB would be associated with outcomes.3,4 The most recent and largest pooled analysis indicated that although CK-MB elevations >3× ULN are an independent predictor of all-cause mortality during a follow-up time of 3 years, CK-MB elevations >5× ULN are a stronger predictor still.32 Other reports were more indicative of a graded association between CK-MB levels and outcome.3,4 The most recent and largest pooled analysis indicated that although CK-MB elevations >3× ULN are an independent predictor of all-cause mortality during a follow-up time of 3 years, CK-MB elevations >5× ULN are a stronger predictor still.32 Other reports were more indicative of a graded association between CK-MB levels and outcome.3,4

In our study, we noted that any level of elevation of CK-MB was associated with higher 3-month mortality, independent of the Mayo risk score. There was no significant correlation with cardiovascular mortality, however, and the modest dose–response relationship with overall mortality did not translate into a clear threshold. There was neither a graded nor a threshold-level association with long-term all-cause or cardiac mortality for either biomarker in this study, and, in fact, the association with long-term survival was much weaker and even only of marginal statistical significance for CK-MB. Although a factor of 8 provided the best conversion from CK-MB to cTnT when the magnitude of post-PCI myonecrosis was quantified as multiples of ULN, a value of 5× ULN of CK-MB predicted short-term risk similar to a value of 25× ULN for cTnT. The cTnT level identified in this study is close to the 20× to 44× ULN range identified in recent studies as the cutoff to match sensitivity thresholds for the diagnosis of PMI by MRI and CK-MB elevation >3× ULN.3,4,25 Taken together, the current findings support cTnT as the preferred biomarker of myocardial injury in agreement with the universal definition of MI consensus document but in distinction from it at a higher prognostic threshold level after PCI.17 This threshold level, however, is still lower than the clinically relevant level set by the Society of for Cardiovascular Angiography and Interventions definition of PMI.20

The question how to define clinical relevance is critically important and intertwined with the question whether the myonecrosis is causally related to clinical outcome parameters or
an epiphenomenon. Herein, we focused on 3-month mortality and demonstrated an independent relationship between this outcome parameter and postprocedural cTnT elevation. It should be noted that there were few events in this group. For that reason, the multivariate model we used could adjust only for a few variables (Mayo Risk score), and hence it could not reliably exclude the effect of all confounders. To address this issue, we performed a propensity score–matched analysis, which provided similar results. Moreover, we analyzed the causes of deaths in the 91-day time frame after PCI among those with postprocedural cTnT elevation and noticed a few key points. First, the magnitude of myonecrosis in these patients was small when considered in the context of infarct size generally seen with spontaneous MI in clinical practice. Second, 11 of these 20 patients died of noncardiovascular causes that were unrelated to the PCI. Third, 8 of 9 cardiovascular deaths occurred in patients with high-risk baseline clinical and procedural characteristics. Although these data cannot provide conclusive evidence, they suggest that PMI may not be the cause of death in a significant proportion of patients, but rather an indicator of individual, preprocedurally existing risk. This conclusion is supported by the results of the multivariate Cox model for long-term mortality.

Table 3. Postprocedural Cardiac Troponin T and CK-MB Levels as Predictors of Postprocedural Survival (Adjusted for the Mayo Clinic Risk Score for In-hospital and Postdischarge Mortality)

| Troponin level | Post-PCI to 91-d Survival |  | Post–91-Day Survival |  |
|----------------|--------------------------|--------------------------|--------------------------|
|                | Adjusted HR (95% CI)     |  | Adjusted HR (95% CI)     |  |
| Normal         | 1.00 (reference)         | 0.005*                   | 1.00 (reference)         | 0.010*       |
| 1–5× ULN       | 1.31 (0.48–3.57)         | 0.60                     | 1.30 (1.09–1.56)         | 0.003        |
| 5–25× ULN      | 1.41 (0.49–4.05)         | 0.53                     | 1.33 (1.10–1.62)         | 0.004        |
| 25–50× ULN     | 6.66 (2.43–18.2)         | <0.001                   | 1.13 (0.79–1.63)         | 0.50         |
| 50–100× ULN    | 4.97 (1.10–22.5)         | 0.037                    | 1.05 (0.63–1.73)         | 0.86         |
| >100 ULN       | 2.04 (0.25–16.9)         | 0.51                     | 1.71 (1.02–2.84)         | 0.041        |

Table 4. Multivariable Cox Model for Long-Term Mortality

<table>
<thead>
<tr>
<th>Variable</th>
<th>χ² Test</th>
<th>Hazard Ratio</th>
<th>95% Hazard Ratio Confidence Limits</th>
<th>PValue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mayo long-term mortality risk score*</td>
<td>576.3</td>
<td>1.42</td>
<td>1.38–1.47</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Calcified lesion</td>
<td>8.49</td>
<td>1.24</td>
<td>1.07–1.43</td>
<td>0.004</td>
</tr>
<tr>
<td>Post-PCI cTnT elevation</td>
<td>6.67</td>
<td>1.05</td>
<td>1.012–1.09</td>
<td>0.01</td>
</tr>
<tr>
<td>Vein graft intervention</td>
<td>2.26</td>
<td>1.19</td>
<td>0.95–1.48</td>
<td>0.15</td>
</tr>
<tr>
<td>Type C lesion</td>
<td>2.05</td>
<td>1.11</td>
<td>0.96–1.30</td>
<td>0.15</td>
</tr>
<tr>
<td>Post-PCI TIMI flow 0/I/II</td>
<td>0.60</td>
<td>0.84</td>
<td>0.56–1.29</td>
<td>0.44</td>
</tr>
<tr>
<td>Urgent PCI</td>
<td>0.41</td>
<td>1.05</td>
<td>0.91–1.20</td>
<td>0.52</td>
</tr>
<tr>
<td>Bifurcation lesion</td>
<td>0.15</td>
<td>0.96</td>
<td>0.79–1.17</td>
<td>0.69</td>
</tr>
<tr>
<td>Thrombotic lesion</td>
<td>0.13</td>
<td>0.95</td>
<td>0.73–1.24</td>
<td>0.71</td>
</tr>
<tr>
<td>Branch occlusion</td>
<td>0.02</td>
<td>0.97</td>
<td>0.60–1.57</td>
<td>0.90</td>
</tr>
<tr>
<td>Number of stents placed</td>
<td>0.01</td>
<td>0.99</td>
<td>0.92–1.08</td>
<td>0.93</td>
</tr>
<tr>
<td>Coronary embolus</td>
<td>0.0004</td>
<td>1.01</td>
<td>0.43–2.35</td>
<td>0.98</td>
</tr>
</tbody>
</table>

cTnT indicates cardiac troponin T; PCI, percutaneous coronary intervention; and TIMI, thrombolysis in myocardial infarction.
*Based on age, history of congestive heart failure, body mass index, ejection fraction, MI 1 to 7 days before PCI, pre-PCI troponin elevation (which were absent in our population), former smoker, previous coronary artery bypass graft, history of high cholesterol, glycoprotein IIb/IIIa use, a score based on the use of 4 medications at discharge (aspirin, β-blockers, angiotensin-converting enzyme inhibitors, and lipid-lowering drugs), and a comorbidity index based on 10 risk factors (current smoker, hypertension, history of cerebrovascular/transient ischemic attack, diabetes mellitus, diabetes mellitus with sequelae), chronic obstructive pulmonary disease, peripheral vascular disease, tumor, metastatic cancer, and moderate/severe renal disease.)
from a detailed investigation conducted during the same time period as our study, with a similar cohort size, but among an all-comers PCI population. Although 63% of post-PCI inhospital deaths were because of acute cardiovascular causes, procedural complications accounted for only 8.2% of deaths, and most deaths could be attributed to preexisting or unrelated postprocedural disease processes.33 Similarly, another study noted that only 60% of all deaths in the first 30 days after PCI could be related to cardiovascular causes and only 40% to a PCI-related cause.34 Hence, the definition of clinically relevant PMI is challenging and truly subject to the choice of the outcome parameters.20

Major PMIs (ie, >100 URL), even though infrequent (1.2%), did not confer the worst prognosis. This is in marked contrast to the prognostic significance of spontaneous MI, especially when stratified by infarct size.14,15 In general, spontaneous MIs are associated with greater degrees of myonecrosis when compared with PMI. This may explain the more profound prognostic implications of spontaneous MIs. However, even at similar degrees of CK-MB elevation, the prognosis of PMI is more benign than of spontaneous MI, perhaps, reflecting that the former is a marker of disease complexity although the latter reflects disease acuity.37 Indeed, a combined analysis from the Early Glycoprotein IIb/IIIa Inhibition in Non–ST-Segment–Elevation Acute Coronary Syndrome (EARLY-ACS) and Superior Yield of the New Strategy of Enoxaparin, Revascularization and Glycoprotein IIb/IIIa Inhibitors (SYNERGY) trials, a CK-MB elevation of 28×ULN after PMI was required to have the same prognostic effect as a spontaneous MI.37 Thus, the concept of separating PMI and spontaneous MI into 2 distinct types of events is appropriate in itself, only the definition remains a matter of debate.20,39

There are several limitations related to this investigation. It is a retrospective single-center analysis with inherent limitations; however, the data were collected prospectively in a consecutive series of patients. The multivariable regression models are unable to account for unobserved covariates that may confound the assessment of the independent relationship between cTnT and mortality. We deliberately did not include patients with elevated preprocedural cTnT levels because quantifying PCI-related myonecrosis in this setting is fraught with difficulty, especially in a retrospective study. To address the issue of stable baseline values and the effect of stable versus unstable presentation, as well as renal insufficiency, further,36 we conducted interaction analyses, which demonstrated that the relationship between cTnT and mortality was similar in all groups. An important aspect is that the absolute number of events was low and the study remained underpowered to confirm significant differences in certain patient subpopulations. The prognostic cTnT cutoff identified in this study by the methodology of Contal and Quigley,24 as well as testing of mortality prediction of different cTnT levels, will require further assessment in other and preferably multicenter studies. Another consideration is that the metrics defined in this study cannot be extrapolated to other cardiovascular troponin assays, notably cTnl assays. We cannot exclude the possibility that more sensitive detection of baseline abnormalities might change our conclusions given the greater degree of disease burden found in those with events that might be more sensitively detected with more sensitive cTn assays. With regards to cTnT values after PCI, higher absolute values of cTnT should be the same regardless of the use of the contemporary assays, or the as yet to be Food and Drug Administration–approved high-sensitive cTnT assays because their distinction is at the low and not high cTnT levels. Unavailability of the high sensitivity assay prevented us from performing analyses on the effect of absolute Δ and relative change of cTnT. Finally, whether the defined thresholds apply to those patients who have signs and symptoms related to ischemia and complications after procedure was not specifically addressed by the present study although most of the patients with marked cTnT

**Figure 3.** Scatter plot to illustrate the correlation between peak postprocedural cardiac troponin T and creatine kinase (CK)-MB levels.

**Figure 4.** Illustration of the number and causes of death by follow-up time after percutaneous coronary intervention, cardiac troponin T (cTnT) elevation, and cause. IQR indicates interquartile range.
of isolated troponin I elevation after percutaneous coronary intervention. 


Defining the Optimal Cardiac Troponin T Threshold for Predicting Death Caused by Periprocedural Myocardial Infarction After Percutaneous Coronary Intervention
Joerg Herrmann, Ryan J. Lennon, Allan S. Jaffe, David R. Holmes, Jr, Charanjit S. Rihal and Abhiram Prasad

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