Significance of Periprocedural Myonecrosis on Outcomes After Percutaneous Coronary Intervention
An Analysis of Preintervention and Postintervention Troponin T Levels in 5487 Patients

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Background—Myonecrosis after percutaneous coronary intervention (PCI) has been correlated with a worse prognosis, but controversy exists about the clinical significance and potential mechanisms for the association. The aim of this study was to evaluate the relative impact of preprocedural and postprocedural cardiac troponin T (cTnT) levels on survival rate after PCI.

Methods and Results—We evaluated 5487 patients from the Mayo Clinic registry who required nonemergency PCI, and we examined the relationship between periprocedural cTnT levels, with the 99th percentile cutoff value used for normal (<0.01 ng/mL), and outcomes. The patients were divided into 3 groups: normal preprocedural and postprocedural cTnT levels (no myonecrosis), normal preprocedural but elevated postprocedural cTnT levels (PCI-related myonecrosis), and abnormal preprocedural cTnT. The 30-day death rates were 0.1%, 0.6%, and 2.3%, respectively, in the 3 groups. In a multivariable model, an abnormal pre-PCI cTnT level (hazard ratio 9.66 [2.30–40.57]; P=0.002), and PCI-related myonecrosis (4.71 [1.02–21.83]; P=0.048) were independent predictors of 30-day mortality. Over a median follow-up of 28 months, an abnormal pre-PCI cTnT level (hazard ratio 1.79 [1.35–2.39]; P=0.001) independently predicted death, but the occurrence of PCI-related myonecrosis did not. A postprocedural elevation in creatine kinase MB fraction was not an independent predictor of long-term risk of death (0.912 [0.70–1.19]; P=0.5).

Conclusions—A preprocedural cTnT level >0.01 is a powerful independent predictor of prognosis after PCI and is of greater prognostic significance than the postprocedural biomarker levels. PCI-related myonecrosis occurs frequently and predicts short-term but not long-term risk of death. (Circ Cardiovasc Intervent. 2008;1:10-19.)

Key Words: troponin ▪ angioplasty ▪ coronary disease ▪ outcome

The association between percutaneous coronary intervention (PCI) and subsequent myonecrosis has been recognized for many years.1,2 Its incidence ranges from 10% to 40%, depending on clinical, angiographic, and procedural characteristics; adjunctive therapy; and the biomarker used to detect myocardial injury.3 Postprocedural myonecrosis has been associated with an increased risk of in-hospital adverse cardiac events. It has been suggested that a significant rise in the biomarker (eg, creatine kinase-MB [CK-MB] fraction >3 to 5 times the upper limit of normal) may identify those patients who merit a longer duration of observation in the hospital after elective procedures.4–7 Similarly, myonecrosis has been associated with reduced likelihood of long-term survival, and a direct correlation between the magnitude of myonecrosis and risk of death has been reported.4,5,7–10 Despite the abundance of data on this subject, there is an ongoing debate about the clinical significance of myonecrosis and the mechanisms for its association with adverse clinical events.11,12

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This gap in knowledge is even greater now with the use of cardiac troponins, which are more sensitive cardiac biomarkers than CK-MB fraction. Furthermore, it is clear that the baseline troponin value carries prognostic information, a fact that was not accounted for in prior analyses that used CK-MB fraction. Only 2 studies to date have reported on the relative significance of pre- and post-PCI troponin elevation. One used a cutoff value for normal that was far higher than presently advocated and lacked the power to explore the relationship with outcomes.13 The other study, which used more contemporary cutoff values, suggested that preprocedural cardiac troponin T (cTnT) level was an important
predictor for the occurrence of post-PCI myonecrosis.14 We now examine this hypothesis in a much larger cohort, using the sensitive cutoff values currently advocated by the new European Society of Cardiology/American College of Cardiology/American Heart Association/World Heart Federation (ESC/ACC/AHA/WHF) guidelines.15 Thus, the aim of the present study was to evaluate the relative impact of preprocedural and postprocedural cTnT levels on short- and long-term survival rate after PCI, with the 99th percentile value of <0.01 ng/mL used as the cutoff for normal.

Methods
Since 1979, all patients undergoing percutaneous coronary revascularization at the Mayo Clinic in Rochester, Minn, have been prospectively followed up in a registry. The registry includes demographic, clinical, angiographic, and procedural data. Immediate postprocedural and in-hospital events are recorded, and each patient is surveyed by telephone, with a standardized questionnaire, at 6 months, at 1 year, and then annually after the procedure by trained data technicians. Ten percent 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.

The present study includes all consecutive patients from the database for the period from November 1, 2000, when routine measurements of cTnT were initiated for our PCI patients, through October 31, 2005. The inclusion criterion was that patients required nonemergency procedures. Emergency procedures were defined as those that would need to be performed within hours of symptom onset, such as primary PCI, rescue PCI, or PCI for severe refractory ischemia. Patients were excluded if paired baseline and postprocedural cTnT 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 6884 PCIs performed on 5908 unique patients. One hundred nineteen patients refused to authorize the use of their records for research, which resulted in a sample size of 6744 PCIs. Of these, 6348 had both pre- and post-PCI cTnT measures. The initial index PCI was used for the 5487 unique patients.

Blood samples for cardiac biomarkers were collected before PCI and at 8 and 16 hours after PCI. Ninety percent of preprocedural samples were collected within 2 hours of PCI. Peak postprocedural values were used for the analysis. cTnT was measured with a sensitive and precise third-generation assay (Elecsys; Roche Diagnostics, Indianapolis, Ind). The upper limit of normal for the assay is <0.01 ng/mL (99th percentile value); the value at which the coefficient of variation is <10% is 0.035 ng/mL. Myonecrosis was defined as a cTnT level ≥0.01 ng/mL. Analysis was also conducted to evaluate the prognostic significance of the recently published ESC/ACC/AHA/WHF definition of myocardial infarction (MI), which arbitrarily defines a post-PCI MI, among patients with normal preprocedural values, as an increase in biomarker value that is ≥3 times the upper limit of normal (99th percentile).15

Definitions
The following definitions were used for the database. MI during follow-up was defined by the presence of 2 of 3 criteria: chest pain lasting ≥20 minutes, new ST/T-wave changes or Q waves on the ECG, and increased cardiac biomarker (creatinine kinase or CK-MB fraction) levels at least twice the upper limit of the normal range. The number of diseased coronary arteries was defined by the number of major coronary arteries with luminal diameter stenosis ≥50%, with ≥70% stenosis in at least 1 vessel. Significant disease (≥50%) in the left main was considered 2-vessel disease if there was right dominance and 3-vessel disease if there was left dominance. Angiographic success was defined as PCI with residual stenosis <50% in ≥1 treatment site.

Statistical Analysis
Data are presented as mean±SD for most continuous variables, median (inner quartile range) for skewed variables, or as a frequency (percentage) for discrete data. Kaplan-Meier methods were used to estimate survival curves. Comparisons between groups are made using the Student t test, Pearson’s χ^2 statistic, the Mann-Whitney rank-sum test, and the log-rank test for continuous, nominal, ordinal (specifically, most recent MI, smoking status, ACC/AHA lesion class, degree of angulation at lesion site, number of vessels treated, and length of stay) or skewed data, and survival data, respectively. For baseline clinical, angiographic, and procedural comparisons, P values were adjusted for the number of tests computed. To do so, 2000 permutation datasets were created (preprocedural troponin elevation was randomly permuted among the study subjects), and the P values reported in Tables 1, 2, and 3 were calculated. The minimum P value was recorded for each permuted dataset. The adjusted P value for each variable was calculated as the proportion of minimum P values less than or equal to the variable’s observed P value.

Cox proportional-hazards models were used to estimate partial hazard ratios for 30-day and long-term survival. Efron’s method was used for handling tied survival times. Long-term survival excluded the 30-day post-PCI period. Thus, patients who died or had an MI within 30 days after PCI were excluded from the long-term analysis. For 30-day analyses, the Mayo Clinic Risk Score16 was used to adjust for risks other than biomarker elevation. The score is derived from 8 clinical or angiographic variables that are correlates of procedural complications: cardiogenic shock, left main coronary artery disease, severe renal disease, urgent or emergent procedure, congestive heart failure Class III or higher, thrombus, multivessel disease, and older age. For long-term follow-up, clinically relevant covariates, including a history of MI within 7 days of PCI, were chosen for adjustment, and no variable selection process was used. Splines were used to estimate associations between continuous covariates and long-term events. All analyses presented here were performed with SAS version 9 software (SAS, Inc, Cary, NC).

The authors had full access to the data and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results
Baseline Characteristics
The study included 5487 patients, of whom 3457 (63%) had normal baseline cTnT. The clinical characteristics of patients according to preprocedural cTnT levels are summarized in Table 1. Patients with elevated baseline cTnT values had significantly more adverse clinical characteristics: They were older and more likely to present with congestive heart failure, an ejection fraction ≤40%, MI within 7 days of PCI, cerebrovascular disease, and chronic renal failure. Aspirin (91% versus 86%, P<0.001), β-blocker (84% versus 71%, P<0.001), and angiotensin-converting enzyme inhibitor (49% versus 41%, P<0.001) therapy was more commonly prescribed in patients with elevated cTnT. The use of lipid-lowering therapy was identical in both groups (60%).

Angiographic and Procedural Characteristics
Table 2 summarizes the angiographic characteristics according to preprocedural cTnT levels. Patients with elevated preprocedural cTnT values were more likely to have preprocedural TIMI 0 or 1 flow and had more multivessel coronary artery disease, type C lesions, and lesions associated with thrombus and ulceration. Procedural characteristics are presented in Table 3. In concert with more extensive disease and adverse baseline clinical characteristics, patients with ele-
Elevation occurred frequently (43%), but the magnitude of preprocedural cTnT levels were more likely to have procedural complications such as coronary embolism and in-laboratory persistent coronary vessel occlusion.

**Preprocedural cTnT Level and 30-Day Outcomes**

In patients with normal preprocedural cTnT levels, post-PCI elevation occurred frequently (43%), but the magnitude of rise was minor (interquartile range: <0.01, 0.04). Twenty-one percent of these patients also had a rise in CK-MB fraction above the upper limit of normal after PCI (Table 4), with CK-MB fraction values >5- and >8-fold above the upper limit of normal occurring in 3.5% and 1.6%, respectively. In-hospital death was exceedingly rare (0.1%) among patients with normal preprocedural cTnT levels, regardless of whether cTnT rose after PCI. In-hospital death, any MI, MI ≥24 hours after the procedure, and the composite of death, MI, coronary artery bypass grafting, and target vessel revascularization were more frequent among patients with elevated preprocedural cTnT levels (Table 5). Thirty-day death rates among those with preprocedural cTnT levels <0.01 versus ≥0.01 were 0.3% and 2.3%, respectively.

**Relationship Between Preprocedural and Postprocedural cTnT Levels and 30-Day Outcomes**

To explore the interaction between pre- and post-PCI cTnT levels with regard to outcomes, the patients were divided into 3 groups: normal preprocedural and postprocedural cTnT levels (n=1973), normal preprocedural but elevated postprocedural cTnT levels (n=1484), and abnormal preprocedural cTnT level (n=2030). The 30-day death rates in the 3 groups were 0.1%, 0.6%, and 2.3%, respectively (Figure 1). Compared with those with normal cTnT levels before and after PCI, both an abnormal pre-PCI cTnT level (hazard ratio 22.4 [5.4–92.1]; P<0.001) and a post-PCI cTnT elevation among those with normal pre-PCI cTnT level (hazard ratio 6.00 [1.30–27.8]; P=0.022) were significantly associated with an increased risk of death by 30 days. In a multivariable model that adjusted for the Mayo Clinic Risk score, these biomarker profiles remained independently associated with death by 30 days: hazard ratio 9.66 ([2.30–40.57]; P=0.002) and 4.71 ([1.02–21.83]; P=0.048), respectively. The difference in the 2 hazard ratios showed a trend toward significance.
Multivessel disease              2116 (65)  248 (66)  265 (73)  441 (76)  168 (73)  279 (72)  1401 (72)  <0.001
Worst lesion type

A                               125 (4)  11 (3)  6 (2)  21 (4)  4 (2)  12 (3)  54 (3)   <0.001
B1                              733 (22)  73 (19)  78 (21)  89 (15)  36 (15)  61 (16)  337 (17)
B2                              1254 (37)  147 (38)  119 (33)  206 (35)  94 (40)  141 (37)  707 (36)
C                               1236 (37)  153 (40)  160 (44)  276 (47)  102 (43)  171 (44)  862 (44)
Thrombus                        257 (8)  57 (15)  83 (24)  170 (29)  97 (41)  193 (50)  600 (31)  <0.001
Calcified lesion               1210 (40)  152 (43)  119 (37)  215 (40)  86 (39)  128 (36)  700 (39)  1.00
Eccentric lesion               2543 (84)  302 (85)  299 (90)  460 (86)  191 (89)  289 (87)  1541 (87)  0.040
Bifurcation lesion             500 (15)  49 (13)  38 (11)  71 (12)  34 (15)  50 (13)  242 (13)  0.27
Ulceration                      226 (7)  38 (11)  30 (9)  63 (12)  38 (17)  55 (15)  224 (12)  <0.001
Ostial lesion                  565 (23)  71 (25)  56 (21)  96 (21)  32 (18)  54 (19)  309 (21)  1.00
Worst angulation

None                            660 (20)  82 (22)  64 (18)  113 (19)  51 (21)  92 (23)  402 (20)  1.00
Mild                            1764 (54)  199 (53)  201 (56)  325 (55)  130 (54)  218 (55)  1073 (55)
Moderate                        783 (24)  84 (22)  84 (23)  139 (23)  53 (22)  76 (19)  436 (22)
Severe                          90 (3)  13 (3)  12 (3)  19 (3)  5 (2)  7 (2)  56 (3)
Preprocedural TIMI flow 0/1     242 (10)  25 (8)  38 (14)  60 (13)  39 (21)  80 (26)  242 (16)  <0.001

Values are provided as mean ± SD or n (%). TIMI indicates Thrombolysis in Myocardial Infarction.
*P for comparison between patients with cTnT ≤0.01 vs >0.01.

(P=0.056). There were 5 deaths in the first 7 days among those with an isolated post-PCI elevation in cTnT. Four occurred in hospital, of which 2 were noncardiac (gastrointestinal bleeding in one patient and acute respiratory failure in another patient with severe pulmonary fibrosis) and 2 were cardiac deaths in patients who had preexisting high-risk characteristics (refractory ventricular tachycardia and non-ST-elevation MI 3 weeks before PCI). One patient, who had suffered an abrupt closure of the target vessel during PCI that was successfully treated, died a day after discharge with sudden cardiac death. Thus, early deaths in this group either were noncardiac or were related to very high-risk clinical or procedural characteristics.

cTnT Levels and Long-Term Outcomes
Among those who had 30 days of follow-up without death or MI, the median follow-up duration was 28 months (interquartile range 14 to 49 months) after PCI; 89% had ≥1 year of follow-up. All-cause death and the combined rate of death and MI were lowest among patients with normal pre-PCI cTnT levels (Figures 2A and 3A). This relationship was similar to the association between post-PCI cTnT level and outcomes (Figures 2B and 3B). Estimated 1-year survival rates were 98%, 95%, 94%, 92%, and 91% for those with cTnT levels <0.01, 0.01 to 0.03, >0.03 to 0.1, >0.1 to 0.5, >0.5 to 1, and >1.0 ng/dL, respectively. Patients with normal pre- and post-PCI cTnT levels had the lowest death rates, whereas those with normal pre-PCI but elevated post-PCI cTnT levels had intermediate death rates and those with elevated preprocedural cTnT values had the highest death rates (Figure 4). In a multivariable model, an abnormal pre-PCI cTnT level, age, diabetes, history of congestive heart failure, and cerebrovascular disease were independent predictors of increased long-term risk of death, but an isolated post-PCI cTnT elevation among those with normal preprocedural cTnT values was not (Table 6).

Independent Prognostic Value of Post-PCI CK-MB Fraction Elevation
The multivariable analysis for predictors of long-term risk of death was also performed among a subgroup of 4180 patients with normal preprocedural CK-MB fraction. A postprocedural elevation in CK-MB fraction among these patients was not an independent predictor of death (hazard ratio 0.912 [0.70–1.19]; P=0.5) in a model that included preprocedural cTnT level as a variable.

Analysis Based on the Universal Definition of Post-PCI MI
According to the universal definition of post-PCI MI, 32% of patients with normal preprocedural cTnT levels sustained an MI if cTnT (≥0.03 ng/mL) is used as the criterion, and 6.5% sustained an MI if CK-MB fraction is used as the criterion. The multivariable models for outcomes were repeated with this cTnT cutoff used to define an MI, and the findings were unchanged. A post-PCI elevation in cTnT ≥0.03, among those with a normal pre-PCI cTnT level, remained an independent predictor of 30-day death (4.55 [1.21–17.1]; P=0.02) but not long-term death (1.04 [0.77–1.41]; P=0.8).
Discussion
The present study, which was conducted in a mixed cohort of patients undergoing PCI for either stable coronary artery disease or acute coronary syndromes and used a sensitive contemporary cTnT assay, produced the following major findings: (1) Greater prognostic information is gained from a single preprocedural cTnT value than from the postprocedural biomarker levels; (2) an abnormal cTnT value before PCI is associated with an increased 30-day and long-term risk of death, independent of other adverse characteristics; (3) a preprocedural cTnT value ≥ 0.01 represented a threshold, such that any value above this level correlated with an increased risk for adverse events, which supports the ESC/ACC/AHA/WHF15 and National Academy of Clinical Biochemistry17 recommendations that the cutoff value of the 99th percentile represents the optimal threshold to correlate troponin values with increased risk; but (4) elevation of cTnT after PCI in patients with normal preprocedural levels was a significant predictor of 30-day death but did not independently predict long-term outcomes.

cTnT and Outcomes
The present study provides a detailed analysis of the relationship between pre- and post-PCI cTnT levels and outcomes after nonemergency procedures. The findings are representative of contemporary practice, as the majority of patients were treated with stents (92%), atherectomy devices were used infrequently (<2%), and glycoprotein IIb/IIIa inhibitors were used in 54% of interventions on a background of dual antiplatelet therapy. Among patients with normal preprocedural cTnT levels (stable or unstable angina), the in-hospital (0.1%) and 30-day (0.3%) death rates were very low. The

Table 4. Biomarker Levels

<table>
<thead>
<tr>
<th>Preprocedural cTnT Level</th>
<th>Post-PCI cTnT</th>
<th>Pre-PCI CK-MB</th>
<th>Post-PCI CK-MB</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.01 (n=3457)</td>
<td>&lt;0.01 (&lt;0.01, 0.04)</td>
<td>2.0 (1.5, 2.6)</td>
<td>2.8 (1.9, 5.1)</td>
</tr>
<tr>
<td>≥0.01 to 0.03 (n=389)</td>
<td>0.05 (0.03, 0.11)</td>
<td>2.6 (1.9, 3.6)</td>
<td>3.7 (2.4, 7.1)</td>
</tr>
<tr>
<td>&gt;0.03 to 0.1 (n=378)</td>
<td>0.11 (0.07, 0.22)</td>
<td>2.9 (2.1, 4.7)</td>
<td>4.8 (2.9, 10.7)</td>
</tr>
<tr>
<td>&gt;0.1 to 0.5 (n=613)</td>
<td>0.4 (0.2, 0.6)</td>
<td>4.1 (2.3, 9.0)</td>
<td>6.1 (3.3, 14.1)</td>
</tr>
<tr>
<td>&gt;0.5 to 1.0 (n=247)</td>
<td>0.9 (0.7, 1.2)</td>
<td>6.8 (3.2, 17.9)</td>
<td>10.5 (4.2, 21.7)</td>
</tr>
<tr>
<td>&gt;1.0 (n=403)</td>
<td>2.6 (1.7, 4.2)</td>
<td>21.6 (5.8, 79.8)</td>
<td>19.8 (7.0, 51.8)</td>
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<tr>
<td>≥1.0 (n=2030)</td>
<td>0.4 (0.1, 1.2)</td>
<td>4.0 (2.4, 10.5)</td>
<td>6.3 (3.3, 18.6)</td>
</tr>
</tbody>
</table>

Values are provided as median (quartile 1, quartile 3).

*P for comparison between patients with cTnT <0.01 vs ≥0.01.

Table 3. Procedural Characteristics

<table>
<thead>
<tr>
<th>Preprocedural cTnT Level</th>
<th>No. vessels treated</th>
<th>Vessel treated</th>
<th>Procedural success</th>
<th>Postprocedural TIMI 3 flow</th>
<th>Graft occlusion</th>
<th>Left anterior descending</th>
<th>Circumflex</th>
<th>Right coronary artery</th>
<th>Left main artery</th>
<th>Saphenous vein graft</th>
<th>Superior vena cava</th>
<th>Total grafts</th>
<th>No. stents placed</th>
<th>No. vessels treated</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.01 (n=3457)</td>
<td>1620 (47)</td>
<td>162 (42)</td>
<td>133 (35)</td>
<td>231 (38)</td>
<td>93 (38)</td>
<td>152 (38)</td>
<td>771 (38)</td>
<td>1.00</td>
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<tr>
<td>≥0.01 to 0.03 (n=389)</td>
<td>980 (28)</td>
<td>115 (30)</td>
<td>113 (30)</td>
<td>201 (33)</td>
<td>79 (32)</td>
<td>138 (34)</td>
<td>646 (32)</td>
<td>0.25</td>
<td>1.00</td>
<td>1.00</td>
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</tr>
<tr>
<td>&gt;0.03 to 0.1 (n=378)</td>
<td>1174 (34)</td>
<td>123 (32)</td>
<td>151 (40)</td>
<td>225 (37)</td>
<td>95 (38)</td>
<td>146 (36)</td>
<td>740 (36)</td>
<td>0.90</td>
<td>1.00</td>
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<tr>
<td>&gt;0.1 to 0.5 (n=613)</td>
<td>88 (3)</td>
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<td>13 (2)</td>
<td>1 (0)</td>
<td>7 (2)</td>
<td>43 (2)</td>
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<td>1.00</td>
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</tr>
<tr>
<td>&gt;0.5 to 1.0 (n=247)</td>
<td>241 (7)</td>
<td>45 (12)</td>
<td>42 (11)</td>
<td>56 (9)</td>
<td>18 (7)</td>
<td>28 (7)</td>
<td>189 (9)</td>
<td>0.74</td>
<td>1.00</td>
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<td>1.00</td>
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</tr>
<tr>
<td>&gt;1.0 (n=403)</td>
<td>3395 (98)</td>
<td>381 (98)</td>
<td>365 (97)</td>
<td>591 (96)</td>
<td>242 (98)</td>
<td>378 (94)</td>
<td>1957 (96)</td>
<td>&lt;0.001</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
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<td>1.00</td>
</tr>
<tr>
<td>≥1.0 (n=2030)</td>
<td>3159 (97)</td>
<td>361 (97)</td>
<td>344 (95)</td>
<td>556 (95)</td>
<td>230 (95)</td>
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<td>1860 (95)</td>
<td>0.48</td>
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</table>

Values are provided as mean±SD or n (%).

*P for comparison between patients with cTnT <0.01 vs ≥0.01 (final column).
The annual death rate was 2.5% (Figure 2). Using the 99th percentile value of \(0.01\) ng/mL as normal, we determined that 37% of the cohort had evidence of myonecrosis before PCI. The risk for in-hospital death after PCI rose with increasing levels of preprocedural cTnT. The in-hospital and 30-day death rates for those with elevated pre-PCI cTnT levels were 1.3% and 2.3%, respectively, and the annual death rate during follow-up was approximately 5%.

Patients with an elevated preprocedural cTnT level had greater atherosclerotic burden. This observation is consistent with prior reports that troponin elevation is a marker for lesion complexity,18 even at the low cutoff values used in our study.19 Consequently, procedural success (98% versus 96%) and postprocedural TIMI grade 3 blood flow (97% versus 95%) were marginally lower among those with elevated preprocedural cTnT, and there was a higher incidence of angiographic complications.

The association between pre-PCI cTnT level and long-term outcomes mirrored that seen between post-PCI levels and outcomes (Figures 2A and 3A). This is very likely because most of those with postprocedural cTnT elevations were patients with abnormal pre-PCI cTnT levels. To explore the relationship between preprocedural and postprocedural cTnT levels and outcomes, the cohort was separated into 3 clinically relevant groups: normal cTnT levels before and after PCI (no myonecrosis), normal preprocedural cTnT value but postprocedural cTnT elevation (PCI-related myonecrosis), and elevated baseline cTnT levels (predominantly patients with acute coronary syndromes). Those with no myonecrosis represented an exceedingly low-risk group with a 30-day death rate of 0.1% (Figure 1). Those with post-PCI myonecrosis had a higher, yet relatively low death rate of 0.6%.

Multivariable regression analysis was performed to adjust for the numerous differences in baseline clinical, angiographic, and procedural characteristics among individuals with normal versus elevated cTnT levels. An elevated preprocedural cTnT value was a more powerful independent predictor of 30-day death (10-fold increased risk, \(P=0.002\)) than was post-PCI myonecrosis (5-fold increased risk, \(P=0.048\)). The confidence intervals for these estimates were relatively wide, however, which indicates that these estimates, though statistically significant, are unreliable and may be substantially underestimated or overestimated. Similarly, an elevated preprocedural cTnT level was an independent predictor of long-term risk of death, but a postprocedural cTnT elevation in patients with normal baseline value was not. Of note, the predictive value of cTnT was independent of a history of MI within 7 days of PCI. The conclusions were the same when the universal definition of post-PCI MI was used.15 Markers of atherosclerotic burden such as age and diabetes were additional independent predictors of long-term death. We speculate that like these clinical variables, pre-PCI cTnT level may in part be an indicator of atherosclerotic burden and disease activity, and when included in the multivariable models, diminishes the association between post-PCI biomarker elevation and outcomes.

### Comparison With Previous Studies That Used CK-MB Fraction

Early studies establishing the association between myonecrosis and outcomes after PCI used CK-MB fraction, which is a less sensitive biomarker,1,2,4–10 and were based exclusively on

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**Table 5. In-Hospital Outcomes**

<table>
<thead>
<tr>
<th>Preprocedural cTnT Level</th>
<th>Death</th>
<th>Any MI</th>
<th>MI &gt;24 h after PCI</th>
<th>Q-wave MI</th>
<th>Coronary artery bypass surgery</th>
<th>Death/MI/coronary artery bypass surgery/target vessel revascularization</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.01 (n=3457)</td>
<td>4 (0.1)</td>
<td>2 (0.5)</td>
<td>6 (1.6)</td>
<td>1 (0.0)</td>
<td>3 (0.1)</td>
<td>143 (4.1)</td>
</tr>
<tr>
<td>0.01 to 0.03 (n=389)</td>
<td>2 (0.5)</td>
<td>1 (0.3)</td>
<td>2 (0.5)</td>
<td>0 (0.0)</td>
<td>1 (0.3)</td>
<td>24 (6.2)</td>
</tr>
<tr>
<td>&gt;0.03 to 0.1 (n=378)</td>
<td>6 (1.6)</td>
<td>7 (2.0)</td>
<td>3 (0.5)</td>
<td>6 (1.6)</td>
<td>4 (0.7)</td>
<td>34 (9.0)</td>
</tr>
<tr>
<td>&gt;0.1 to 0.5 (n=613)</td>
<td>5 (0.8)</td>
<td>3 (0.5)</td>
<td>21 (3.4)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>31 (5.1)</td>
</tr>
<tr>
<td>&gt;0.5 to 1.0 (n=247)</td>
<td>3 (1.2)</td>
<td>1 (0.4)</td>
<td>10 (4.1)</td>
<td>1 (0.4)</td>
<td>1 (0.4)</td>
<td>12 (4.9)</td>
</tr>
<tr>
<td>&gt;1.0 (n=403)</td>
<td>11 (2.7)</td>
<td>4 (1.0)</td>
<td>23 (5.7)</td>
<td>5 (1.2)</td>
<td>5 (1.2)</td>
<td>35 (8.7)</td>
</tr>
<tr>
<td>≥0.01 (n=2030)</td>
<td>27 (1.3)</td>
<td>16 (0.8)</td>
<td>108 (5.3)</td>
<td>12 (0.6)</td>
<td>12 (0.6)</td>
<td>136 (6.7)</td>
</tr>
</tbody>
</table>

Values are provided as n (%). *P for comparison between patients with cTnT <0.01 vs ≥0.01.

---

![Figure 1.](http://circinterventions.ahajournals.org/) Kaplan-Meier estimates for death by 30 days according to periprocedural cTnT levels.
postprocedural CK-MB fraction elevation in the face of normal preprocedural CK-MB fraction. In the present study, pre-PCI CK-MB fraction values were in the normal range in the majority of patients with preprocedural cTnT values up to 0.1 ng/mL (Table 4). The 2 largest studies to date by Ellis and colleagues and Stone and colleagues reported an association with outcomes only in the presence of a marked (5 to 8 times the upper limit of normal) post-PCI increase. In the present study, this magnitude of CK-MB fraction elevation after PCI was extremely infrequent in patients with normal preprocedural cTnT and was mostly observed in patients with significantly elevated preprocedural cTnT (>0.5 ng/mL). Thus, it is very likely that a large proportion of patients in the prior studies had non–ST-elevation MI at the time of the PCI according to contemporary definitions. We hypothesize that the strong association between post-PCI elevation in CK-MB fraction and outcomes in the prior studies may have been due to an unmeasured impact of acute coronary syndromes, which are associated with post-PCI myonecrosis and adverse outcomes. This is supported by our observation in the present study that among the patients with normal preprocedural CK-MB fraction, a postprocedural rise in CK-MB fraction above normal did not independently predict risk of death when the preprocedural cTnT level was included in the multivariate model. These data also support the observations of the ESC/ACC/AHA/WHF global task force and the National Academy of Clinical Biochemistry that, in evaluating postprocedural biomarker values, it is extremely difficult to distinguish the effects of the interventional procedure from the ischemic episode that leads to it.

Comparison With Previous Studies That Used Troponins

More recent studies have investigated the association between cardiac troponins and death. These have invariably examined the impact of postprocedural measurements and have not systematically explored the impact of preprocedural levels. The results have been inconsistent, with some reporting that an elevated troponin and others that it is not an independent predictor of survival. The variable findings may relate to heterogeneity in the inclusion criteria, sample size, the sensitivity and specificity of the assay used to measure troponin, and the duration of follow-up. Kizer and colleagues conducted a small study in 212 patients in which preprocedural and postprocedural cTnT values were analyzed. Elevated pre- but not post-PCI values were predictive of long-term adverse events; however, a much less sensitive, 10-fold higher value of ≥0.1 ng/mL was used to diagnose myonecrosis. A recent study from our institution highlighted the significance of pre-PCI cTnT values in understanding the biomarker response to PCI. The study used the 10% coefficient of variation value of 0.035 ng/mL to define a normal level. An important observation from our study is that even a low-level elevation of cTnT before PCI, in the range ≥0.01 to 0.03 ng/mL, is associated with an increased long-
term risk of death and MI (Figures 2 and 3). These data are consistent with the prior reports in patients with acute coronary syndromes, where the use of the 99th percentile optimizes the prognostic effects of cTnT.26

We have previously shown, using a cutoff value of 0.03 ng/mL, that an isolated elevation of cTnT was a predictor of long-term risk of death.27 In the present study, in which we used a lower cutoff of 0.01 ng/mL, an elevation in post-PCI cTnT was an independent predictor of 30-day death but did not determine long-term death. This leads us to speculate that the PCI-related myonecrosis in this subset of patients, and the associated risk, may be a marker for unstable coronary artery disease that might be biochemically detectable before PCI if even lower cutoff values are used in conjunction with more sensitive assays. Indeed, evidence suggests that values <0.01 ng/mL may still provide prognostic information.28 Our study does not entirely exclude the alternative explanation that, in patients with normal preprocedural cTnT, PCI-induced myocardial injury may directly impair left ventricular function and predispose to arrhythmias that would influence survival. However, this seems unlikely given the trivial levels of myonecrosis (75% of patients had post-PCI cTnT value ≤0.04; Table 4), the weak statistical significance for the independent prediction of 30-day death (hazard ratio 4.71 [1.02–21.83]; \(P=0.048\)), and the lack of association with long-term death. Moreover, the absence of a causal association is supported by the observation that the etiology for deaths within 7 days of the PCI was either noncardiac or related to very high-risk clinical or procedural characteristics.

Limitations

Although the data were collected prospectively, this is a retrospective single-center analysis and is subject to the limitations of such analyses. Furthermore, multiple-regression models are unable to account for unobserved covariates that may be confounded with troponin. We intentionally did not try to quantify PCI-related myonecrosis in patients with elevated preprocedural cTnT because this is fraught with difficulty in the setting of non–ST-elevation MI, especially in a retrospective analysis. Moreover, Miller and colleagues14 have reported recently that an increase above

Table 6. Multivariable Cox Model for Long-Term Risk of Death

<table>
<thead>
<tr>
<th>Variable</th>
<th>(\chi^2) test</th>
<th>Hazard Ratio</th>
<th>95% Hazard Ratio Confidence Limits</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-PCI cTnT elevation</td>
<td>15.9</td>
<td>1.79</td>
<td>1.35, 2.39</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Isolated post-PCI cTnT elevation</td>
<td>3.4</td>
<td>1.31</td>
<td>0.98, 1.75</td>
<td>0.065</td>
</tr>
<tr>
<td>Age (3 df spline)</td>
<td>83.0</td>
<td>*</td>
<td>...</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>History of congestive heart failure</td>
<td>42.8</td>
<td>2.11</td>
<td>1.69, 2.65</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body mass index (2 df spline)</td>
<td>25.5</td>
<td>*</td>
<td>...</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Chronic renal failure</td>
<td>22.5</td>
<td>2.256</td>
<td>1.61, 3.16</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes</td>
<td>19.4</td>
<td>1.60</td>
<td>1.30, 1.97</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ejection fraction (3 df spline)</td>
<td>11.3</td>
<td>*</td>
<td>...</td>
<td>0.010</td>
</tr>
<tr>
<td>History of cerebrovascular disease</td>
<td>9.3</td>
<td>1.43</td>
<td>1.14, 1.80</td>
<td>0.002</td>
</tr>
<tr>
<td>History of smoking</td>
<td>5.3</td>
<td>1.28</td>
<td>1.04, 1.60</td>
<td>0.021</td>
</tr>
<tr>
<td>Male</td>
<td>3.4</td>
<td>1.23</td>
<td>0.99, 1.54</td>
<td>0.064</td>
</tr>
<tr>
<td>Triple-vessel disease</td>
<td>2.0</td>
<td>1.18</td>
<td>0.94, 1.49</td>
<td>0.16</td>
</tr>
<tr>
<td>Vein graft intervention</td>
<td>1.4</td>
<td>1.19</td>
<td>0.89, 1.59</td>
<td>0.24</td>
</tr>
<tr>
<td>Left main coronary artery stenosis ≥50%</td>
<td>1.0</td>
<td>1.23</td>
<td>0.83, 1.81</td>
<td>0.31</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.6</td>
<td>1.10</td>
<td>0.86, 1.42</td>
<td>0.44</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>0.3</td>
<td>0.95</td>
<td>0.78, 1.15</td>
<td>0.59</td>
</tr>
<tr>
<td>Procedural success</td>
<td>0.2</td>
<td>0.85</td>
<td>0.42, 1.72</td>
<td>0.65</td>
</tr>
<tr>
<td>MI within 7 days before PCI</td>
<td>0.1</td>
<td>1.06</td>
<td>0.80, 1.40</td>
<td>0.70</td>
</tr>
<tr>
<td>History of MI</td>
<td>0.00</td>
<td>1.00</td>
<td>0.79, 1.26</td>
<td>0.99</td>
</tr>
</tbody>
</table>

*The spline-estimated relationship between age and death demonstrates low risk at <55 years of age, with a roughly linear increase in risk thereafter. The spline for body mass index shows the lowest risk at a body mass index of ~33 kg/m², with risk rising more sharply at the lower values of body mass index. Ejection fraction had a roughly linear association with long-term death, with higher risk at lower values of ejection fraction.
baseline after PCI among those with abnormal levels before PCI is not associated with significant additional risk.

Conclusions and Implications

Preprocedural cTnT is a powerful independent predictor of prognosis after nonemergency PCI. Our data suggest that the observed association between post-PCI myocardial necrosis and outcomes in prior studies is a reflection of the preprocedural risk that may be estimated by using baseline cTnT and clinical characteristics. Moreover, the findings highlight the critical importance of early initiation of therapies proven to improve outcomes, such as glycoprotein IIb/IIIa inhibitors and aggressive secondary prevention measures, in any patient with an elevated preprocedural cTnT.39 PCI in patients with normal preprocedural cTnT (<0.01 ng/mL) is extremely safe. In these patients, an elevation in troponin after PCI is common and predicts short-term but not long-term risk of death. Extending hospitalization solely on the merits of a minor elevation in cTnT, in the absence of a significant procedural complication or clinical indications, is unlikely to be beneficial. Finally, it is unlikely that additional clinically relevant information can be gained from the post-PCI cTnT levels in patients with elevated preprocedural values, independent of baseline clinical risk and any procedural complications that may occur.

Disclosures

Dr Jaffe is a consultant for Beckman-Coulter, Dade-Behring, Ortho Diagnostics, Critical Diagnostics, and Singulex. He is currently consulting or has consulted for almost all of the major diagnostic companies. The other authors report no potential conflicts.

References


CLINICAL PERSPECTIVE

Controversy exists with regard to the clinical significance of postprocedural myonecrosis after percutaneous coronary intervention (PCI). Prior studies have relied on creatine kinase-MB fraction to detect myonecrosis and have largely focused on postprocedural levels. In this study, we evaluated the relative impact of preprocedural and postprocedural cardiac troponin T (cTnT) levels on survival rates after PCI. Our study demonstrates that preprocedural cTnT is a powerful independent predictor of prognosis and suggests that the observed association between post-PCI myonecrosis and outcomes in prior studies is a reflection of the preprocedural risk that may be estimated by using baseline cTnT and clinical characteristics. Moreover, PCI in patients with normal preprocedural cTnT (<0.01 ng/mL) is extremely safe. An elevation in troponin after PCI is common among these patients and predicts short-term but not long-term risk of death. Moreover, the study findings indicate that extending hospitalization in these patients solely on the merits of a minor elevation in cTnT, in the absence of a significant procedural complication or clinical indications, is unlikely to be beneficial.
Significance of Periprocedural Myonecrosis on Outcomes After Percutaneous Coronary Intervention: An Analysis of Preintervention and Postintervention Troponin T Levels in 5487 Patients
Abhiram Prasad, Charanjit S. Rihal, Ryan J. Lennon, Mandeep Singh, Allan S. Jaffe and David R. Holmes, Jr

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