Prevalence and Prognostic Significance of Preprocedural Cardiac Troponin Elevation Among Patients With Stable Coronary Artery Disease Undergoing Percutaneous Coronary Intervention

Results From the Evaluation of Drug Eluting Stents and Ischemic Events Registry

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Background—Although cardiac troponin (cTn) elevation is associated with periprocedural complications during percutaneous coronary intervention (PCI) in the setting of acute coronary syndromes, the prevalence and prognostic significance of preprocedural cTn elevation among patients with stable coronary artery disease undergoing PCI are unknown.

Methods and Results—Between July 2004 and September 2006, 7592 consecutive patients who underwent attempted stent placement at 47 hospitals throughout the United States were enrolled in a prospective multicenter registry. We analyzed the frequency of an elevated cTn immediately before PCI and its relationship to in-hospital and 1-year outcomes among patients who underwent PCI for either stable angina or a positive stress test. Among the stable coronary artery disease population (n=2382, 31.4%), 142 (6.0%) had a cTn level above the upper limit of normal before the procedure. Compared with patients who had normal baseline cTn, patients with elevated cTn had a higher rate of in-hospital death or myocardial infarction (13.4% versus 5.6%; P<0.001) and a trend toward higher rates of urgent repeat PCI (1.4% versus 0.2%; P=0.06). In multivariable analyses adjusted for demographic, clinical, angiographic, and procedural factors, baseline cTn elevation remained independently associated with the composite of death or myocardial infarction at hospital discharge (odds ratio, 2.1; 95% confidence interval, 1.2 to 3.8; P=0.01) and at the 1-year follow-up (odds ratio, 2.0; 95% confidence interval, 1.2 to 3.3; P=0.005).

Conclusions—Baseline elevation of cTn is relatively common among patients with stable coronary artery disease undergoing PCI and is an independent prognostic indicator of ischemic complications. If these data are confirmed in future studies, consideration should be given to routine testing of cTn before performance of PCI in this patient population. (Circulation. 2008;118:632-638.)

Key Words: catheterization ▪ coronary disease ▪ myocardial infarction ▪ stents ▪ troponin

Cardiac troponin (cTn) T and I are highly sensitive and specific biomarkers for myocardial injury.1 In the setting of unstable angina or non–ST-segment elevation myocardial infarction (MI), their elevation is associated with more complex coronary stenoses, angiographically visible thrombus, and multivessel coronary artery disease (CAD).2-4 Moreover, in the setting of an acute coronary syndrome, patients with baseline elevations of cTn have a higher risk of death or recurrent MI early after presentation,5-8 after percutaneous coronary intervention (PCI),9 and during long-term follow-up.10 In patients with an elevated cTn, aggressive antithrombotic and antplatelet therapy has been shown to confer...
particular benefit in reducing periprocedural ischemic complications.\textsuperscript{9,11,12}

**Editorial p 609**

Clinical Perspective p 638

Although cTn status is thus well established as a predictor of adverse outcomes among patients presenting with unstable coronary syndromes, cTn typically is not evaluated in patients with stable CAD. Nonetheless, cTn elevation has been described in a number of disease states in the absence of acute coronary syndromes and has been shown to be associated with adverse outcomes in various clinical settings.\textsuperscript{13} To date, however, the incidence and prognostic significance of cTn elevation among patients with stable CAD undergoing PCI are unknown. Thus, the aim of the present study was to determine the prevalence of baseline cTn elevation in an unselected population of patients undergoing PCI for stable angina or an abnormal cardiac stress test and to examine the association between elevated cTn and periprocedural ischemic complications.

**Methods**

Data for this study were obtained from the Evaluation of Drug Eluting Stents and Ischemic Events (EVENT) registry. The details of this registry have been described previously.\textsuperscript{14,15} Briefly, EVENT is a collaborative effort to assess the contemporary practice of stenting by prospective evaluation of unselected patients undergoing PCI with stent implantation at 47 centers in the United States. Although enrollment in the registry is limited to prespecified recruitment “waves,” specific efforts are made to enroll patients consecutively during each enrollment period (eg, on predetermined days of the week) to minimize selection bias. The present analysis is based on the first 3 waves of enrollment, which occurred between July 2004 and September 2006.

**Patient Population**

For the present analysis, we stratified the PCI population according to the type of coronary syndrome before revascularization. Patients were excluded if the indication for PCI was reported by the investigators as either ST-elevation MI or an acute coronary syndrome (unstable angina or non–ST-elevation MI). An acute coronary syndrome was considered to be present if the principal indication for PCI was new onset or rest angina, dynamic ST-segment changes on the ECG, or an elevated creatine kinase (CK) or CK-MB immediately before PCI. All other patients were considered to have stable CAD. Patients also were excluded if they had missing baseline cTn data or if a minimum of 2 postprocedure assessments of CK or CK-MB were not available (see flow diagram in Figure 1).

Patients with stable CAD were then stratified on the basis of their baseline cTn status into 2 groups: Patients with any cTn elevation above the upper limit of normal (ULN; as defined by the laboratory reference values at each individual site) made up the cTn-positive group, and the remaining patients were considered cTn negative. Which cTn isoform (troponin T or I) and assay were used was determined by local practices at each study site.

Data on patient characteristics, clinical presentation, and treatment were collected prospectively on standardized case report forms and submitted to the data coordinating center. cTn, CK, and CK-MB levels were assessed at baseline (within 1 hour before the procedure) and every 8 hours for a minimum of 2 samples after the procedure and assayed using the clinical laboratory and reference values for each site. If an MI was suspected clinically at a later point, additional biomarkers were obtained as clinically indicated. The study protocol was approved by ethics review committees at all participating institutions, and all patients provided written informed consent before participation.

**Definitions and Study Outcomes**

The definition of a procedural MI was elevation of CK-MB (or CK in the absence of CK-MB data) of at least 3 times the ULN (as determined by the local reference laboratory) or by new and persistent ST-segment elevation >1 mm in 2 contiguous limb leads or >2 mm in 2 contiguous precordial leads on the ECG. All events were adjudicated by 2 independent observers without knowledge of patient characteristics or procedural details.

The primary study end point was a composite of death or MI during the index hospitalization. Additional end points included angiographically confirmed stent thrombosis and urgent target vessel revascularization by repeat PCI or coronary artery bypass grafting during the index hospitalization, as well as death and MI over the first year of follow-up.

**Statistical Analysis**

Continuous variables are given as mean±SD and were compared by use of unpaired \(t\) tests or the Wilcoxon rank-sum test (for nonnormally distributed variables). Categorical variables are given as counts and percentages and were compared by means of the \(\chi^2\) test or the Fisher exact test. To test the independent association between cTn status and in-hospital clinical outcomes, odds ratios and their 95% confidence intervals (CIs) were calculated from multiple logistic regression. A sequentially saturated model was used with...
Table 1. Baseline Clinical Characteristics

<table>
<thead>
<tr>
<th></th>
<th>cTn Positive (n=142)</th>
<th>cTn Negative (n=2240)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>65.5±10.8</td>
<td>64.5±10.7</td>
<td>0.315</td>
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<tr>
<td>Age ≥80 y, n (%)</td>
<td>14 (9.9)</td>
<td>189 (8.4)</td>
<td>0.556</td>
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<tr>
<td>Male gender, n (%)</td>
<td>107 (75.4)</td>
<td>1556 (69.5)</td>
<td>0.138</td>
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<tr>
<td>Diabetes mellitus, n (%)</td>
<td>53 (37.3)</td>
<td>774 (34.6)</td>
<td>0.514</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>119 (84.4)</td>
<td>1762 (78.7)</td>
<td>0.109</td>
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<tr>
<td>Hyperlipidemia, n (%)</td>
<td>115 (81.6)</td>
<td>1761 (79.0)</td>
<td>0.475</td>
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<tr>
<td>Current smoking, n (%)</td>
<td>29 (20.7)</td>
<td>454 (20.5)</td>
<td>0.944</td>
</tr>
<tr>
<td>eGFR, ml/min/1.73m²</td>
<td>81.6±36.7</td>
<td>89.5±44.1</td>
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<tr>
<td>Renal dialysis, n (%)</td>
<td>5 (3.5)</td>
<td>28 (1.3)</td>
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<tr>
<td>Prior stroke, n (%)</td>
<td>9 (6.3)</td>
<td>188 (8.4)</td>
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<td>Peripheral arterial disease, n (%)</td>
<td>17 (12.0)</td>
<td>205 (9.2)</td>
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<td>Prior MI, n (%)</td>
<td>29 (20.6)</td>
<td>525 (23.7)</td>
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<td>Prior PCI, n (%)</td>
<td>44 (31.0)</td>
<td>812 (36.4)</td>
<td>0.193</td>
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<td>Previous CABG, n (%)</td>
<td>33 (23.2)</td>
<td>523 (23.4)</td>
<td>0.967</td>
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<tr>
<td>Diseased vessels (&gt;/=50%), n</td>
<td>1.8±0.8</td>
<td>1.7±0.8</td>
<td>0.107</td>
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<tr>
<td>Single-vessel disease, n (%)</td>
<td>55 (41.4)</td>
<td>1109 (50.3)</td>
<td>0.078</td>
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<td>Double-vessel disease, n (%)</td>
<td>50 (37.6)</td>
<td>679 (30.8)</td>
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<tr>
<td>Triple-vessel disease, n (%)</td>
<td>28 (21.1)</td>
<td>417 (18.9)</td>
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<tr>
<td>Congestive heart failure, n (%)</td>
<td>12 (8.5)</td>
<td>161 (7.2)</td>
<td>0.585</td>
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<tr>
<td>LV ejection fraction &lt;35%, %</td>
<td>9 (6.3)</td>
<td>130 (5.9)</td>
<td>0.319</td>
</tr>
</tbody>
</table>

CABG indicates coronary artery bypass grafting; LV, left ventricular. Values are mean±SD when appropriate.

*Defined as total cholesterol >200 mg/dL or on lipid-lowering therapy.
†eGFR is based on the Cockcroft-Gault equation.

Results

Baseline Clinical and Angiographic Characteristics

Of the 2382 patients who underwent PCI for stable CAD, 6.0% had a baseline cTn level above the ULN. Among patients with elevated baseline cTn, 69.7% of patients had an elevation of 1 to 3 times the ULN, whereas elevations of 3 to 5, 5 to 10, and >10 times the ULN were present in 8.5%, 14.1%, and 7.7% of the population, respectively.

Patients with baseline cTn elevation had lower eGFRs and were more likely to have complex lesion morphology and to undergo treatment of bifurcation lesions (Tables 1 and 2). No other significant clinical or angiographic differences were found between the 2 groups. Procedural characteristics, including the number of lesions treated, stents implanted, total stent length, and drug-eluting stent use, also were generally similar between the 2 groups (Table 3). Patients with elevated cTn levels were more likely to receive heparin plus a glycoprotein IIb/IIIa inhibitor or heparin monotherapy and less like to receive bivalirudin during the PCI. Patients with elevated cTn also were less likely to have received clopidogrel before PCI.

Table 2. Preprocedural Angiographic Characteristics (Lesion-Based Analysis)

Table 3. Procedural Data
In-Hospital Clinical Outcomes

Clinical outcomes during the index hospitalization are summarized in Table 4. During the index hospitalization, cTn-positive patients had higher rates of the primary end point of death or MI compared with cTn-negative patients (13.4% versus 5.6%; P<0.001). This difference was driven mainly by a 2-fold increase in the incidence of periprocedural MI among cTn-positive patients because only 1 in-hospital death occurred during the index hospitalization in the study cohort. The need for urgent CABG and urgent repeat PCI also tended to be higher among cTn-positive patients, although these differences were not statistically significant.

Among patients who experienced an in-hospital MI, peak CK-MB levels did not differ between cTn-positive and cTn-negative patients (CK-MB 3 to 5 times normal, 47.4% versus 48.4%; CK-MB 5 to 10 times normal, 31.6% versus 27.8%; and CK-MB >10 times normal, 21.1% versus 21.4%; P=0.922). Similarly, no significant difference was found with respect to the timing of CK-MB elevation between the 2 groups. Among cTn-positive patients who developed a postprocedural MI, CK-MB elevation to >3 times the ULN was initially detected in the first postprocedural assessment in 36.8%, the second assessment in 42.1%, and the third measurement or later in 21.1%. Among cTn-negative patients, CK-MB elevation to >3 times the ULN was initially detected in the first postprocedural assessment in 50.4%, the second assessment in 35.8%, and the third measurement or later in 13.8% (P=0.50).

By multivariate analysis with sequential adjustments for demographic, clinical, angiographic, and treatment factors (Figure 2), cTn elevation remained an independent predictor of in-hospital death or MI in this patient population with an overall adjusted odds ratio of 2.1 (95% CI, 1.2 to 3.8; P=0.01).

Impact of Renal Function

Exploratory analyses demonstrated that the association between cTn elevation and in-hospital outcomes was not modified by the presence of baseline renal dysfunction. Among patients with an eGFR <60 mL/min (n=487), baseline cTn elevation was present in 44 (9.0%) and was associated with an approximate 3-fold increase in the incidence of in-hospital death or MI (18.2% versus 5.6%; P=0.006). Among patients with an eGFR ≥60 mL/min (n=1787), baseline troponin elevation was present in 93 (5.2%) and was associated with an approximate 2-fold increase in in-hospital death or MI (11.8% versus 5.7%; P=0.02). In the fully adjusted multivariable analysis, the odds ratio for in-hospital death or MI was 3.35 (95% CI, 1.23 to 9.16; P=0.02) among patients with an eGFR <60 mL/min and 1.76 (95% CI, 0.83 to 3.73; P=0.14) among patients with an eGFR ≥60 mL/min. No significant interaction was found between renal function and the prognostic importance of preprocedural cTn elevation in the multivariable analysis, however (P=0.52).

One-Year Outcomes

In general, the association between baseline cTn elevation and adverse cardiovascular outcomes remained significant at the 1-year follow-up in both univariate and multivariable analyses (Table 5). In particular, 1-year cardiac mortality was significantly higher among cTn-positive patients compared with cTn-negative patients (2.4% versus 0.4%; P=0.002), an association that remained significant in risk-adjusted analyses (adjusted hazard ratio, 4.8; 95% CI, 1.2 to 19.4; P=0.03).

Discussion

This is the first study to examine the prevalence and prognostic significance of preprocedural cTn elevation among a broad population of unselected patients undergoing PCI for stable CAD. The present study indicates that despite their apparent clinical stability, baseline cTn elevation is not uncommon in this population, occurring in approximate 6% of such patients. Moreover, among these patients who were undergoing PCI predominantly because of stable angina or abnormal cardiac functional testing, we found a strong and independent association between elevated baseline cTn and an increased risk of death or periprocedural MI during the index hospitalization. Finally, these findings were consistent across a broad range of ischemic end points, including death, urgent repeat revascularization, and angiographic complications (except stent thrombosis) during the index hospitalization and remained durable to 1 year.
Although the prevalence of baseline cTn elevation was higher among patients with chronic renal insufficiency, pre-procedural cTn elevation was still observed in ≈5% of patients with normal renal function in our stable PCI population. Whereas the effect in patients with chronic renal insufficiency was numerically stronger, the prognostic significance of baseline cTn elevation in terms of in-hospital events was similar among patients with normal and abnormal renal function with no significant interaction noted between renal function and the prognostic importance of pre-procedural cTn elevation.

Comparison With Previous Studies
Numerous studies have established the prognostic significance of baseline cTn elevation in the setting of acute coronary syndromes. In a meta-analysis of clinical trials and cohort studies of patients with suspected non-ST-elevation acute coronary syndromes, patients with an elevated cTn had a 3- to 8-fold-higher short-term risk of death than patients with normal cTn. The prognostic value of elevated cTn appears to be even stronger among patients undergoing PCI in the setting of an acute coronary syndrome. In addition to its documented value in predicting risk among patients with non-ST-elevation MI, elevation of cTn levels has been associated with benefit from aggressive antiplatelet therapy (mainly parenteral glycoprotein IIb/IIIa receptor antagonists) in the acute coronary syndrome setting among patients undergoing medical management and revascularization.

The results of the present study extend these findings (which were derived predominantly from clinical trials) to an unselected population undergoing PCI and, for the first time, specifically to patients with stable CAD. Although the prevalence of pre-procedural cTn elevation among stable patients undergoing PCI was significantly lower than among those with unstable ischemic syndromes (6.0% versus 26.9% in the EVENT population), we found that the presence of an elevated cTn immediately before PCI was nonetheless associated with a ≥2-fold increase (95% CI, 1.2 to 3.8) in the risk of major periprocedural ischemic complications. In fact, both the relative and absolute risks associated with elevated cTn in our study were similar to those observed in previous studies among unstable patients and in the acute coronary syndrome subgroup of EVENT (data not shown). It is important to recognize, however, that the association between baseline cTn elevation and in-hospital mortality was uncertain in our study (because only 1 in-hospital death occurred). Nonetheless, the 1-year analysis provides further confidence in this association, which remained significant in both univariate and risk-adjusted analyses.

Potential Mechanisms
Multiple potential mechanisms may explain the increase in ischemic events among the cTn-positive PCI population. In the setting of unstable angina and acute coronary syndromes, cTn elevation is associated with more complex coronary stenoses and an increased likelihood of multivessel CAD. For example, among the 853 patients in the C7E3 fab Antiplatelet Therapy in Unstable Refractory Angina (CAPTURE) trial with complete cTn data, patients with cTn elevation were found to have significantly higher rates of angiographically visible thrombus, Thrombolysis in Myocardial flow grade <2, and more complex lesion morphology. Another explanation for the higher adverse event rates among cTn-positive acute coronary syndrome patients is the observation that this group has greater impairment of myocardial tissue perfusion compared with cTn-negative patients, possibly because of embolization of platelet aggregates to the microvasculature.

In patients with stable CAD such as those in our study, the adverse prognosis associated with elevated cTn also may reflect differences in the physical constitution of atherosclerotic plaque or unrecognized acute coronary syndromes resulting from either silent ischemia or underreporting of symptoms by patients. Finally, cTn elevation has been observed in patients with chronic congestive heart failure and a range of noncardiac conditions. In these settings, elevation of cTn also has been associated with an adverse prognosis, most likely reflecting a more aggressive underlying disease process or impaired clearance of cTn.

Future Implications
These findings have several implications for both clinical care and future research. Because cTn elevation is relatively common among patients with stable CAD and was a strong, independent predictor of adverse outcomes after PCI in this study, routine measurement of this biomarker among patients referred for elective cardiac catheterization may be useful for the purposes of risk stratification and potentially for the selection of more potent antithrombotic medications. Because our analysis was not prespecified, however, it should be considered hypothesis generating, and validation of our findings in a separate cohort is critical before routine cTn testing before elective PCI can be recommended outside the research setting. Moreover, similar to the acute coronary syndrome setting, the ultimate value of cTn as a routine screening test before cardiac catheterization and PCI in the stable CAD population requires demonstration that this information allows rational modification of the approach to revascularization or the periprocedural antithrombotic regimen. At present, data are insufficient to know whether such an approach should be extrapolated to the population with...
stable CAD undergoing PCI. Nonetheless, this subset of patients may represent a promising subgroup in which to test aggressive antiplatelet and antithrombotic regimens in the future.

**Study Limitations**

The present study has several limitations. First, it is possible that some patients with ongoing acute coronary syndromes may have been classified as having stable CAD in our study. Because our definition of stable CAD was clinical, however, and relied on a general impression based on each patient’s classification of his or her symptoms at the time of PCI, it is likely that similar misclassification would occur in clinical practice. We therefore believe that our findings apply most directly to the “real world” clinical practice setting from which they were derived. Second, cTn thresholds varied at the different participating sites, precluding our ability to define a specific threshold for clinical use that identifies patients at increased risk.

Third, this study does not provide information about therapeutic options to reduce ischemic risk in patients with cTn elevation. Although it might have been theoretically possible to examine whether use of alternative antiocoagulation regimens such as glycoprotein IIb/IIIa inhibitors was associated with a lower risk of ischemic complications among cTn-positive patients, it is likely that use of glycoprotein IIb/IIIa inhibition in our unselected population reflects a complex decision process integrating multiple factors, including the troponin level itself. Consequently, even with careful risk adjustment, such an analysis would be far more likely to identify residual unmeasured confounding than a true treatment effect. Of note, no evidence was found of a differential effect of cTn elevation on the incidence of ischemic complications between patients who were treated with or without glycoprotein IIb/IIIa inhibition at the time of PCI (P for interaction=0.20).

Finally, a relatively large number of eligible patients were excluded from our analysis because either the cTn or the CK-MB level was not assessed within the specified time frame before the procedure. Only minor differences were found in baseline characteristics between included and excluded patients, however, suggesting minimal selection bias in our analytical sample.

**Conclusions**

Among patients undergoing PCI for either chronic stable angina or abnormal functional testing, preprocedural elevation of cTn is relatively common and is associated with a 2-fold-increased risk of death or MI during the associated hospitalization and at a 1-year follow-up. If these findings are confirmed in future studies, consideration should be given to routine testing of cTn in this population before PCI, and future research should be directed at developing and testing strategies to decrease the risk of adverse events in this high-risk group.

**Sources of Funding**

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**Disclosures**

None.

**References**


Baseline cardiac troponin (cTn) elevation is associated with periprocedural complications during percutaneous coronary intervention (PCI) in the setting of acute coronary syndromes. However, the prevalence and prognostic significance of preprocedural cTn elevation among patients with stable coronary artery disease undergoing PCI are unknown. In the multicenter prospective Evaluation of Drug Eluting Stents and Ischemic Events (EVENT) registry, 2382 consecutive patients with stable angina or positive stress test undergoing PCI were analyzed with respect to the frequency of an elevated cTn immediately before PCI and its relationship to in-hospital and 1-year outcomes. A total of 142 (6.0%) had a cTn level above the upper limit of normal before the procedure. Compared with patients who had normal baseline cTn, patients with elevated cTn had a higher rate of in-hospital death or myocardial infarction (13.4% versus 5.6%; \( P<0.001 \)). In multivariable analyses, baseline cTn elevation remained independently associated with the composite of death or myocardial infarction at hospital discharge (odds ratio, 2.1; 95% confidence interval, 1.2 to 3.8; \( P=0.01 \)) and at a 1-year follow-up (odds ratio, 2.0; 95% confidence interval, 1.2 to 3.3; \( P=0.005 \)). Among patients undergoing PCI for chronic stable angina or abnormal functional testing, preprocedural elevation of cTn is relatively uncommon but when present is associated with a 2-fold-increased risk of death or MI during the associated hospitalization and at a 1-year follow-up. If these findings are confirmed in future studies, consideration may be given to routine testing of cTn in patients with stable coronary artery disease before PCI.
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