Prognostic Value of Isolated Troponin I Elevation After Percutaneous Coronary Intervention

Claudio Cavallini, MD; Paolo Verdecchia, MD; Stefano Savonitto, MD; Gustavo Arraiz, BSc, PhD; Roberto Violini, MD; Zoran Olivari, MD; Paolo Rubartelli, MD; Stefano De Servi, MD; Mario Plebani, MD; Giuseppe Steffenino, MD; Paolo Sbarzaglia, MD; Diego Ardissino, MD; on behalf of the Italian “Atherosclerosis, Thrombosis and Vascular Biology” and “Society for Invasive Cardiology–GISE” Investigators

Background—Mild elevations of cardiac troponin are frequent after percutaneous coronary intervention (PCI). Their prognostic value is uncertain in the absence of changes in creatinine kinase-MB (CK-MB).

Methods and Results—We evaluated the relation between isolated elevations of cardiac troponin I (cTnI) and all-cause mortality. We studied 3494 consecutive patients who underwent PCI in 16 Italian tertiary cardiology centers. CK-MB and cTnI were analyzed in a central laboratory. Duration of follow-up was 2 years. The present analysis was restricted to 2362 patients with normal CK-MB and cTnI values at baseline and no CK-MB elevation after PCI. A rise in cTnI after PCI >0.15 ng/mL, the upper reference limit, was found in 932 patients (39.4%). A rise >0.45 ng/mL (>3× upper reference limit) was found in 467 patients (19.7%). Compared with patients with normal cTnI, those with cTnI elevation >0.15 ng/mL showed a slightly increased mortality (3.8% versus 2.6%; hazard ratio, 1.53; 95% confidence interval, 0.97 to 2.42; P=0.069). A cTnI elevation >0.45 ng/mL was associated with a higher risk of mortality (4.5% versus 2.7%; hazard ratio, 1.68; 95% confidence interval, 1.01 to 2.80; P=0.044), which, however, did not remain significant after adjustment for concomitant risk factors (hazard ratio, 1.45; 95% confidence interval, 0.86 to 2.46; P=0.162).

Postprocedural cTnI elevation was associated with coronary and clinical features consistent with a worse risk profile.

Conclusions—In the absence of a rise in CK-MB, elevated cTnI levels after PCI are associated with a modest increased risk of death. However, this is not independent of the concomitant adverse baseline clinical characteristics of these patients. (Circ Cardiovasc Interv. 2010;3:431-435.)

Key Words: cardiac troponin • myonecrosis • angioplasty • stents • complications • prognosis

Postprocedural elevations of creatine kinase-MB (CK-MB) or cardiac troponin levels occur in 5% to 50% of patients undergoing percutaneous coronary interventions (PCI).1 Whereas the adverse prognostic association of CK-MB elevations is well established,2–7 the impact on long-term outcome of isolated elevations in cardiac troponin, not associated with a concomitant rise in CK-MB, is less well defined. This issue has become of particular interest after the recent release of the Universal Definition of Myocardial Infarction8 that states that a rise in cardiac troponin exceeding 3 times the 99th percentile of a normal reference population (upper reference limit, URL) should be labeled as PCI-related myocardial infarction.

The aim of the present study was to determine whether “isolated” (ie, not associated with a concomitant elevation in CK-MB levels) cardiac troponin I (cTnI) elevations after PCI are predictive of all-cause mortality at 2 years. This hypothesis was tested in a large population of patients enrolled in the CK-MB and PCI study.7

Clinical Perspective on p 435

Methods

Our investigation was designed as an ancillary analysis of the CK-MB and PCI study,7 a prospective, multicenter, cohort study enrolling consecutive patients undergoing PCI in 16 Italian hospitals. Briefly, the CK-MB and PCI study evaluated the influence of postprocedural CK-MB elevations on 2-year all-cause mortality in a consecutive population of 3494 patients undergoing PCI. Patients with ST-segment elevation–myocardial infarction and those who refused to provide written informed consent were excluded from the study. Blood samples were to be drawn in each patient immediately before the intervention and each time cardiac enzyme markers were measured, including CK-MB and cTnI. CK-MB and cTnI were measured in a central laboratory.

Received May 5, 2010; accepted August 4, 2010.

From the Division of Cardiology (C.C., P.V., P.S.), S Maria della Misericordia Hospital, Perugia, Italy; the Department of Cardiology (S.S., G.A.), Niguarda Hospital, Milan, Italy; the Department of Interventional Cardiology (R.V.), San Camillo Hospital, Rome, Italy; Ca’ Foscari Hospital (Z.O.), Treviso, Italy; the Division of Cardiology (P.R.), San Martino Hospital, Genoa, Italy; the Department of Cardiovascular Diseases (S.D.S.), Civil Hospital, Legnano, Italy; Laboratory of Clinical Chemistry (M.P.), University Hospital, Padova, Italy; the Division of Cardiology (G.S.), Santa Croce Hospital, Cuneo, Italy; and the Division of Cardiology (D.A.), Maggiore Hospital, Parma, Italy.

Correspondence to Claudio Cavallini, MD, Division of Cardiology, Ospedale S Maria della Misericordia, Piazzale Meneghini 1, 06100 Perugia, Italy. E-mail claudio.cavallini@ospedale.perugia.it

© 2010 American Heart Association, Inc.

Circ Cardiovasc Inter is available at http://circinterventions.ahajournals.org DOI: 10.1161/CIRCINTERVENTIONS.110.957712
before PCI (baseline) and at 12 and 24 hours after the procedure. Serum was stored at −70°C and subsequently shipped to the core biochemistry laboratory, where the biochemical markers of myocardial damage were measured. The patients’ vital conditions were assessed at 6, 12, and 24 months by means of hospital visits or phone interviews.

Biochemical Analyses
Mass CK-MB and cTnI levels were measured using a Dimension RxL/HM analyzer (Dade Behring, Glasgow, Del). The URL for CK-MB was 5.0 ng/mL; the URL for cTnI was 0.15 ng/mL, which represented the 99th percentile of the distribution of a reference control group with an analytic imprecision of no more than 10%.

Study End Point
The outcome of interest was 2-year all-cause mortality, defined as the number of deaths that occurred from the time of the second blood sample up to 24 months thereafter. Mortality coding by specific cause was not available.

Patient Selection
The present study focused on the long-term prognostic implications of isolated elevations of cTnI levels. Therefore, this analysis was restricted to patients with (1) normal baseline values (<URL) of both cTnI and CK-MB; and (2) normal (<URL) post-PCI values of CK-MB. Thus, the selected population included patients with normal preprocedural and postprocedural cTnI values and patients with “isolated” (ie, not associated with concurrent CK-MB elevation) post-PCI cTnI elevation.

Statistical Analysis
We used SAS 9.2 release (SAS Institute, Cary, NC). We expressed the continuous variables as mean value (with interquartile range) and the categorical variables as proportions. The highest postprocedural cTnI value was used for analysis. We compared the characteristics of patients with and without cTnI >3×URL at entry by Student t test for continuous variables and the χ2 test for proportions. Survival curves were estimated using the Kaplan–Meier product-limit method and compared by the Mantel (log-rank) test. We used the Cox proportional hazards model, counting the date of death or censoring, to assess the impact of prognostic factors on survival. In addition to a univariate analysis, we adjusted the relation between postprocedural cTnI and mortality for several other variables known to influence mortality in this population. These were age (years), sex (men vs women), diabetes (yes, no), peripheral arterial disease (yes, no), multivessel disease (yes, no), left ventricular ejection fraction (%). All these variables were included in the multivariate model. Postprocedural cTnI was included in the model as a dichotomous variable (>0.15 [URL] or >0.45 [3×URL] ng/mL).

The degree of cTnI elevation was also estimated in terms of cTnI peak ratio, calculated by dividing the observed postprocedural level by 0.15 ng/mL (upper reference limit). The adjusted probability of death in relation to the cTnI peak ratio expressed as a continuous variable was estimated by a cubic spline function resulting from a multivariate logistic model. Probability values <0.05 were considered statistically significant.

Results
Of 3494 patients included in the CK-MB and PCI population,2 2362 patients were selected for the present analysis. We excluded 669 patients with cTnI and/or CK-MB baseline levels >URL, and 463 patients with postprocedural CK-MB elevation. Follow-up data, including the survival status, were available for all patients (100%). The diagram for selection of patients is shown in Figure 1. During the 2-year follow-up period, 73 patients (3.1%) died.

The main features of patients are shown in the Table. cTnI elevation >0.45 ng/mL (>3×URL) was associated with a worse risk profile at baseline. These patients were older (P=0.0002) and more frequently affected by unstable angina (P=0.02), chronic renal insufficiency (P=0.02), multivessel disease (P=0.01) and procedure (P=0.0001), length of stenosis >20 mm (P=0.04), and coronary thrombosis (P=0.004). These patients also showed a longer fluoroscopy time (P<0.0001) and a higher rate of procedural complications (P=0.02).

cTnI Elevation and Mortality
An isolated postprocedural cTnI elevation >0.15 ng/mL was observed in 932 patients (39.4%). Such elevation exceeded 0.45 ng/mL (>3×URL) in 467 patients (19.8%), being consistent with the diagnosis of periprocedural myocardial infarction.10

Compared with patients with normal cTnI levels, those with cTnI elevation >0.15 ng/mL had a slightly higher, although not statistically significant, 2-year mortality (36/392, or 9.2% versus 37/1430, or 2.6%; univariate hazard ratio [HR], 1.53; 95% confidence interval [CI], 0.97 to 2.42; P=0.069). A cTnI elevation >0.45 ng/mL was associated with a more distinct rise in 2-year mortality (21/467, or 4.5% versus 52/1895, or 2.7%; univariate HR, 1.68; 95% CI, 1.01 to 2.80; P=0.044), which, however, did not remain significant after controlling for concomitant risk factors (HR, 1.45; 95% CI, 0.86 to 2.46; P=0.162) in the Cox analysis.

Results did not change when the analysis was restricted to the subgroup of patients (n=2176) who did not have any angiographic complications (side branch closure, transient abrupt vessel closure, distal thromboembolism, and transient slow flow); adjusted HR for cTnI elevation >3×URL 1.31 (95% CI, 0.75 to 2.29).

The event-free survival curves in patients with and without cTnI elevation >3×URL (0.45 ng/mL) are shown in Figure 2. The cubic spline function reporting the relation between all-cause mortality and the cTnI peak ratio (ratio between the maximal observed cTnI value and the URL [0.15 ng/mL]) is reported in Figure 3.

Discussion
The present study provides 2 novel findings. First, a definite rise of cTnI occurred after PCI in approximately 40% of
patients with normal CK-MB values. These elevations were associated with features of high cardiovascular risk (more advanced age, unfavorable coronary anatomy, and concomitant renal failure). Second, a slightly increased risk of mortality was found in patients with cTnI elevation >0.45 ng/mL (>3×URL), and the survival curves appeared to progressively diverge over time, although the absolute levels of risk were relatively modest in the 2 groups. Such an increase, however, did not remain significant in the multivariate analysis after adjustment for associated baseline adverse risk factors.

**Table. Distribution of Clinical, Angiographic, and Procedural Characteristics in Patients With and Without Troponin I Elevation**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All Patients (n=2362)</th>
<th>Troponin I &gt;3×URL (n=467)</th>
<th>Troponin I ≤3×URL (n=1895)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>62.5±15</td>
<td>64.1±15</td>
<td>62.1±15</td>
<td>0.0002</td>
</tr>
<tr>
<td>Female sex, %</td>
<td>478 (20.3)</td>
<td>97 (20.8%)</td>
<td>380 (20.1%)</td>
<td>0.72</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>430 (18.2)</td>
<td>82 (17.6%)</td>
<td>348 (18.4%)</td>
<td>0.7</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>1441 (61.0)</td>
<td>281 (60.1%)</td>
<td>1159 (61.2%)</td>
<td>0.7</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>234 (9.9)</td>
<td>53 (11.3%)</td>
<td>181 (9.6%)</td>
<td>0.2</td>
</tr>
<tr>
<td>Chronic renal insufficiency</td>
<td>91 (3.9)</td>
<td>27 (5.8%)</td>
<td>64 (3.4%)</td>
<td>0.02</td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>1176 (49.8)</td>
<td>235 (50.3%)</td>
<td>941 (49.7%)</td>
<td>0.7</td>
</tr>
<tr>
<td>Previous CABG</td>
<td>248 (10.5)</td>
<td>59 (12.6%)</td>
<td>189 (9.9%)</td>
<td>0.09</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>1057 (45.1)</td>
<td>233 (49.9%)</td>
<td>823 (43.4%)</td>
<td>0.02</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>110 (4.7)</td>
<td>27 (5.8%)</td>
<td>83 (4.4%)</td>
<td>0.2</td>
</tr>
<tr>
<td>2- or 3-Vessel disease</td>
<td>886 (37.9)</td>
<td>198 (42.4%)</td>
<td>687 (36.3%)</td>
<td>0.01</td>
</tr>
<tr>
<td>B2/C coronary lesion type*</td>
<td>1204 (51.2)</td>
<td>265 (56.7%)</td>
<td>939 (49.6%)</td>
<td>0.06</td>
</tr>
<tr>
<td>Left ventricular ejection fraction, %</td>
<td>57.7±15</td>
<td>57.9±15</td>
<td>57.7±15</td>
<td>0.7</td>
</tr>
<tr>
<td>Multivessel procedure</td>
<td>644 (27.3)</td>
<td>190 (40.7%)</td>
<td>454 (23.9%)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Saphenous vein graft intervention</td>
<td>63 (2.7)</td>
<td>13 (2.8%)</td>
<td>50 (2.6%)</td>
<td>0.7</td>
</tr>
<tr>
<td>Lesion length &gt;20 mm</td>
<td>316 (13.4)</td>
<td>80 (17.1%)</td>
<td>236 (12.4%)</td>
<td>0.04</td>
</tr>
<tr>
<td>Coronary thrombosis</td>
<td>208 (8.8)</td>
<td>57 (12.2%)</td>
<td>151 (7.9%)</td>
<td>0.004</td>
</tr>
<tr>
<td>Stent use</td>
<td>1812 (76.7)</td>
<td>384 (82.2%)</td>
<td>1428 (75.4%)</td>
<td>0.002</td>
</tr>
<tr>
<td>Fluoroscopy time, min</td>
<td>11.8±8</td>
<td>13.9±10</td>
<td>11.2±8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Procedural complications†</td>
<td>187 (7.9)</td>
<td>49 (10.5%)</td>
<td>137 (7.2%)</td>
<td>0.02</td>
</tr>
<tr>
<td>Unsuccessful procedure‡</td>
<td>107 (4.5)</td>
<td>19 (4.1%)</td>
<td>88 (4.6%)</td>
<td>0.6</td>
</tr>
<tr>
<td>Troponin value</td>
<td>0.49±0.32</td>
<td>2.05±0.77</td>
<td>0.10±0.14</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Plus-minus values are means±interquartile range.
*According to American College of Cardiology/American Heart Association Classification.
†The occurrence of 1 or more of the following periprocedural events: side branch closure, transient abrupt vessel closure, distal thromboembolism, and transient slow flow.
‡A residual coronary lumen narrowing of >50% or a Thrombolysis in Myocardial Infarction grade flow of less than III in 1 attempted coronary lesion.

**Figure 2.** Event-free survival in patients with normal creatine kinase-MB levels and troponin elevation more than or =0.45 ng/mL (≥3×URL) after angioplasty.

**Figure 3.** Cubic spline function reporting the relation between the adjusted probability of death and the cTnI peak ratio (ratio between the maximal observed cTnI value and the URL [0.15 ng/mL]). See text for details.
Previous Studies
An association between postprocedural CK-MB elevation and the subsequent risk for cardiac complications, mainly mortality, has been found in several studies.1–7 Such evidence, however, is still lacking for isolated elevations in cTnl, whose prognostic significance after PCI is controversial.11 In a few studies, cTnl elevations occurring after PCI predicted an adverse outcome.12,13 However, these “positive” studies selected cTnl thresholds that were several times higher (×10 and ×15) the URL of the analytic method used.12,13 Increasing the cTnl thresholds value to considerably above the URL led this cTnl elevation to be associated with a concomitant increase in CK-MB, thus leaving the issue of the prognostic significance of milder isolated cTnl elevations unaddressed.

A few other studies addressed the issue of the prognostic value of isolated cTn elevation. A study by Prasad et al14 showed that elevated cTnT after PCI was associated with an increased risk of mortality at 3 years in 1949 patients. The main differences between the Prasad study and the present one include (1) the diverse design (retrospective analysis of a single-center database versus post hoc analysis of a multicenter prospective study specifically designed to focus the relationship between elevation of biochemical marker of myocardial damage and mortality); (2) the exclusion criteria (none of our patients was excluded from analysis because of missing laboratory values and all of them had complete follow-up data); (3) the type of selected troponin (TnT versus the more widely used TnI); and (4) the cutoff value of the marker. In the study of Prasad et al,15 the cutoff value for cTnT was 0.03 ng/mL, which is higher than the 99th percentile for their assay (Elecsys; Roche Diagnostics, Indianapolis, Ind). As a result, a consistent proportion of high-risk patients may have been included in that analysis, thus potentially conditioning the positive independent association with outcome. In a subsequent study,15 the same group used a lower TnT cutoff (<0.01 ng/mL; 99th percentile) to define patients with isolated cTnI elevations. As a result, no significant excess risk of events emerged in these patients.15 Finally, in a study by Natarajan et al,16 isolated post-PCI cTn I release did not predict mortality at 1 year in 1128 patients.

Impact of Associated Clinical Features
In the present study, patients with cTnl elevation after PCI showed a higher frequency of clinical (advanced age, unstable angina, chronic renal insufficiency, and multivessel disease) and angiographic (complex coronary anatomy, long coronary lesions, and coronary thrombosis) adverse prognostic features. Because the HR for mortality slightly decreased from univariate to multivariate analysis, these data suggest that the slightly higher risk of mortality associated with higher cTnl levels might have been captured, at least in part, by the above high-risk clinical features. Another clue of the modest, if any, independent relation of cTnl with mortality came from the multivariate spline function (Figure 3), which did not support a progressively rising risk of death with the peak-cTnl ratio in this population. Therefore, these data confirm the concept previously reported2 of the modest utility of measuring postprocedural troponin I levels in patients undergoing PCI.

Our findings are also consistent with a recent report from the Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) trial, a study conducted in patients with acute coronary syndrome, some of whom with elevated biomarkers at baseline.17 In ACUITY, the association between periprocedural myocardial infarction and 1-year mortality was not significant after adjustment for age, diabetes mellitus, previous myocardial infarction, renal failure, ST-segment shift, and other cardiovascular risk factors.17

Major strengths of our study are its prospective design and the large population of patients with “isolated” troponin elevation, to our knowledge the largest examined so far.

Limitations of the Study
Our analysis was restricted to a relatively “low-risk” subset of patients, with consequent potential attenuation of the power of our study to detect a significant relation between minor changes in cTnl levels and mortality. In addition, although the 2-year duration of follow-up allowed a reasonable estimate of the relation between cTnl and prognosis over a middle or long term, extrapolation of results to longer periods requires caution.

Applicability of Results
Because there are no established criteria for the diagnosis of postprocedural myonecrosis when cardiac cTnl levels are elevated before PCI,10 we focused our analysis on a specific subset of patients with normal cTnl level at baseline. Our conclusions are thus applicable to a well-defined patient population.

Conclusion
The present study suggests that isolated post-PCI elevations of cTnl, even when consistent with the Universal Definition of Myocardial Infarction,18 has no independent impact on mortality at 2-year follow-up and therefore do not add relevant prognostic information beyond that offered by CK-MB. Overall, these data suggest that the treatment of these patients, including the policy for discharge from hospital after PCI, should not be solely guided by cardiac cTnl levels when CKMB is normal, but rather by an overall assessment of cardiovascular risk factors potentially conditioning outcome.

Disclosures
None.

References


### CLINICAL PERSPECTIVE

Although mild elevations of cardiac troponin I (cTnI) or T are frequent after percutaneous coronary intervention (PCI), their prognostic value is uncertain in patients with normal creatine kinase-MB (CK-MB) after PCI. We studied 2362 patients with normal CK-MB and cTnI values at baseline and no CK-MB elevation after PCI. We found a rise in cTnI after PCI >1× upper reference limit (URL) in 932 patients (39.4%) and a rise >3×URL in 467 patients (19.7%). When compared with patients with normal cTnI, those with cTnI elevation >1×URL showed a slightly and not significantly increased risk of mortality (hazard ratio, 1.53; 95% confidence interval, 0.97 to 2.42; P = 0.069). A cTnI elevation >3×URL was associated with a higher risk of mortality (hazard ratio, 1.68; 95% confidence interval, 1.01 to 2.80; P = 0.044), which, however, did not remain significant after adjustment for concomitant risk factors (hazard ratio, 1.45; 95% confidence interval, 0.86 to 2.46; P = 0.162). Patients with cTnI elevation after PCI showed coronary and clinical features consistent with a definitely worse risk profile. Overall, these data suggest that elevated cTnI levels after PCI in the absence of a concomitant rise in CK-MB are associated with only a slightly increased risk of mortality, which is accounted for by the concomitant risk factors. Consequently, the policy for hospital discharge after PCI should not be guided by cardiac cTnI levels when CK-MB is normal but rather by an overall assessment of cardiovascular risk factors.
Prognostic Value of Isolated Troponin I Elevation After Percutaneous Coronary Intervention

Claudio Cavallini, Paolo Verdecchia, Stefano Savonitto, Gustavo Arraiz, Roberto Violini, Zoran Olivari, Paolo Rubartelli, Stefano De Servi, Mario Plebani, Giuseppe Steffenino, Paolo Sbarzaglia, Diego Ardissino and on behalf of the Italian "Atherosclerosis, Thrombosis and Vascular Biology" and "Society for Invasive Cardiology-GISE" Investigators

*Circ Cardiovasc Interv*. 2010;3:431-435; originally published online October 5, 2010; doi: 10.1161/CIRCINTERVENTIONS.110.957712

*Circulation: Cardiovascular Interventions* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Copyright © 2010 American Heart Association, Inc. All rights reserved.

Print ISSN: 1941-7640. Online ISSN: 1941-7632

The online version of this article, along with updated information and services, is located on the World Wide Web at:

http://circinterventions.ahajournals.org/content/3/5/431

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Circulation: Cardiovascular Interventions* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:

http://www.lww.com/reprints

Subscriptions: Information about subscribing to *Circulation: Cardiovascular Interventions* is online at:

http://circinterventions.ahajournals.org//subscriptions/