Prognostic Value of Troponins in Acute Pulmonary Embolism

A Meta-Analysis

Cecilia Becattini, MD; Maria Cristina Vedovati, MD; Giancarlo Agnelli, MD

Background—Whether elevated serum troponin levels identify patients with acute pulmonary embolism at high risk of short-term mortality or adverse outcome is undefined.

Methods and Results—We performed a meta-analysis of studies in patients with acute pulmonary embolism to assess the prognostic value of elevated troponin levels for short-term death and adverse outcome events (composite of death and any of the following: shock, need for thrombolysis, endotracheal intubation, catecholamine infusion, cardiopulmonary resuscitation, or recurrent pulmonary embolism). Unrestricted searches of MEDLINE and EMBASE bibliographic databases from January 1998 to November 2006 were performed using the terms “troponin” and “pulmonary embolism.” Additionally, review articles and bibliographies were manually searched. Cohort studies were included if they had used cardiac-specific troponin assays and had reported on short-term death or adverse outcome events. A random-effects model was used to pool study results; funnel-plot inspection was done to evaluate publication bias; and I² testing was used to test for heterogeneity. Data from 20 studies (1985 patients) were included in the analysis. Overall, 122 of 618 patients with elevated troponin levels died (19.7%; 95% confidence interval [CI], 16.6 to 22.8) compared with 51 of 1367 with normal troponin levels (3.7%; 95% CI, 2.7 to 4.7). Elevated troponin levels were significantly associated with short-term mortality (odds ratio [OR], 5.24; 95% CI, 3.28 to 8.38), with death resulting from pulmonary embolism (OR, 9.44; 95% CI, 4.14 to 21.49), and with adverse outcome events (OR, 7.03; 95% CI, 2.42 to 20.43). Elevated troponin levels were associated with a high mortality in the subgroup of hemodynamically stable patients (OR, 5.90; 95% CI, 2.68 to 12.95). Results were consistent for troponin I or T and prospective or retrospective studies.

Conclusions—Elevated troponin levels identify patients with acute pulmonary embolism at high risk of short-term death and adverse outcome events. (Circulation. 2007;116:427-433.)

Key Words: meta-analysis ▪ pulmonary embolism ▪ thromboembolism ▪ thrombosis ▪ troponin

A acute pulmonary embolism has a wide spectrum of clinical presentations. The short-term clinical outcome of patients with pulmonary embolism varies from an early recovery of symptoms to hemodynamic deterioration and death. Prognostic stratification of patients with acute pulmonary embolism is crucial to tailor in-hospital management and to potentially improve clinical outcome.1,2 Currently, prognostic stratification is based primarily on blood pressure at admission. Systemic hypotension is associated with high in-hospital mortality, which increases up to ~50% in patients with shock.3 Among patients with normal blood pressure at admission, right ventricular dysfunction at echocardiography identifies those at high risk for in-hospital mortality.3–6 In these patients, elevated levels of troponin have been shown to be associated with right ventricular dysfunction at echocardiography. The relationship between serum levels of troponin and clinical outcome in patients with pulmonary embolism has been assessed in a number of small studies but remains undefined.

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We performed a meta-analysis aimed at assessing the prognostic value of troponin for both short-term mortality and adverse outcome events in patients with acute pulmonary embolism.

Methods

The methods for this meta-analysis are in accordance with “Meta-Analysis of Observational Studies in Epidemiology: A Proposal for Reporting.”

Study Objectives

The primary objective of this analysis was to assess whether elevated serum troponins are associated with short-term mortality in patients...
with acute pulmonary embolism. The secondary objectives were to assess whether elevated serum troponins are associated with short-term mortality resulting from pulmonary embolism or adverse outcome events.

**Study Outcomes**

Death was adjudicated as the result of pulmonary embolism by the authors of the individual studies. In the large majority of the analyzed studies, death was adjudicated as the result of pulmonary embolism in case of irreversible right ventricular failure or recurrent pulmonary embolism.

For the purpose of this analysis, adverse outcome events were the composite of death and any of the following: shock, need for thrombolysis, endotracheal intubation, catecholamine infusion for sustained hypotension, cardiopulmonary resuscitation, or recurrent pulmonary embolism.

**Study Selection**

Studies were included in this analysis if they had reported on patients with an objective diagnosis of pulmonary embolism, troponin sampling in the initial in-hospital phase, and short-term death or adverse outcome events.

Study authors were contacted when their studies did not report data, allowing the creation of a 2 × 2 table based on troponin levels (normal and elevated) and outcome (death and survival, adverse outcome events, and no adverse outcome events).

**Finding Relevant Studies**

We searched MEDLINE and EMBASE between January 1, 1998, and November 2006. Furthermore, reference lists of retrieved articles and review articles were reviewed manually to implement our search. Search criteria included the terms “pulmonary embolism” and “troponin.” The search was not limited to the English language; only full articles were considered for analysis.

One author (C.B.) performed the electronic search and listed the trials that were eligible for inclusion in the study. Study selection was initially performed by review of title. Candidate abstracts were then reviewed and selected for data retrieval. Two authors (C.B. and C.V.) independently reviewed each study for quality assessment and extracted data on studies and patient characteristics, as well as outcomes, using standardized extraction forms. Because no standardized quality scoring system exists for quality assessment of observational studies, the components of the quality review were derived largely from the Egger’s quality checklist for prognostic studies. Studies were assessed for the presence of 8 features: description of patient sample characteristics, description of inclusion and exclusion criteria, potential selection bias, completeness of follow-up, a priori definition of study outcomes, objectivity of outcomes, and definition and measurement of prognostic variables and treatment. Disagreements were resolved through revision by an additional reviewer (G.A.) and by discussion.

For each study, the following individual data were extracted: general data (study design), patients (number of included patients, mean age, gender, methods for diagnosis of pulmonary embolism, hemodynamic status at inclusion in the study, and treatment for pulmonary embolism), troponin assays (name of the assay, type of examined troponin [I or T], cutoff level, timing of determination, and overall troponin-positive patients), and end points (number of patients who had died or had experienced an adverse outcome event among troponin-positive patients and -negative patients and number of patients with secondary end points among troponin-positive and -negative patients).

**Statistical Analysis**

Meta-analyses of all outcomes are reported using random-effects models because fixed- and random-effects results were similar. Cochran’s $\chi^2$ test and the $I^2$ test for heterogeneity were used to assess between-study heterogeneity. Statistically significant heterogeneity was considered present at $P<0.10$ and $I^2 >50\%$. Pooled odds ratios (ORs) were reported with 95% confidence intervals (CIs). Publication bias was assessed visually by the use of funnel plots.

**Results**

Overall, 96 articles were found searching by “pulmonary embolism” and “troponin” from January 1, 1998, to November 2006. Articles were excluded by review of title if they were review articles (n = 28), editorials or letters (n = 6), or case reports (n = 6) or if they reported on studies on differential diagnosis of elevated troponins (n = 14), comparison of other biomarkers (n = 5), evaluation of troponin assays (n = 3), or animals (n = 1) (Figure 1).

Twenty-four studies were found in which patients with acute pulmonary embolism had blood sampling for troponin at admission. Three studies were excluded because they appeared to report on the same patients included in other analyzed studies. In 6 studies, the numbers of patients who had died or had experienced an adverse outcome event were not reported. For 5 of these studies, the numbers of patients who had died or had experienced an adverse outcome event were obtained by contacting the authors. One of these studies was excluded after the authors were contacted because data were confirmed to be unavailable.

**Selected Studies**

Overall, 20 studies were selected for this analysis, and 4 were retrospective. The main features of the selected studies are reported in Table 1. Demographic features of study populations (age, gender) were similar across the studies, and almost all the included patients had an objective diagnosis of pulmonary embolism. Seven studies included
hemodynamically stable patients only. Overall mortality was reported in all studies, troponin T in 8 studies, and troponin I in 12 studies (Table 2). Two studies reported on the composite end point and not on mortality.

Time to study end point was different among the studies, varying from the in-hospital stay up to 100 days. For the purpose of this analysis, we considered death and adverse outcome events occurring in the short-term follow-up (in-hospital or 30 days). In 2 studies, mortality was available only at 90 days; in a third study, mortality was available only at 100 days.

### Troponin Assays

As reported in Table 2, 3 different assays for troponin T were used throughout the studies, with different cutoff points for abnormal levels. For the troponin I studies, investigators used 5 different manufacturers’ assays and different cutoff points. In most of the studies, the cut points for troponin assays were defined according to standard criteria that were values exceeding the 99% percentile of healthy subjects with a coefficient of variation of 10%.

### Death

Data on death were reported in 20 studies (1985 patients). Four studies were retrospective (all evaluating troponin I). The mean age and the prevalence of heart or respiratory diseases in patients with elevated and normal troponin levels (when these data were available) were similar.

Overall, 122 of 618 patients with elevated troponin levels died (19.7%; 95% CI, 16.6 to 22.8) compared with 51 of 1367 with normal troponin levels (3.7%; 95% CI, 2.7 to 4.7). High levels of troponins, both I and T, were associated with a high risk of short-term death (OR, 5.24; 95% CI, 3.28 to 8.38), with no evidence for overall heterogeneity (Figure 2). The result was consistent for either troponin I (OR, 4.01; 95% CI, 2.23 to 7.23) or troponin T (OR, 7.95; 95% CI, 3.79 to 16.65).

The analysis of the 4 retrospective studies revealed heterogeneity (I², 60.9%). The predictive value of elevated troponin levels with respect to short-term death was confirmed when the analysis was limited to 16 studies (1527 patients) using a prospective design (OR, 6.33; 95% CI, 3.8 to 10.34), with no evidence for heterogeneity. The association between elevated serum troponins and death also was confirmed after substituting 0.5 for 0 in the random-effects calculation (OR, 5.70; 95% CI, 3.62 to 8.95) for prospective studies.

Seven studies (915 patients), all with a prospective design, included only patients with normal blood pressure at hospital admission. The incidence of death was 17.9% (34 of 190; 95% CI, 12.4 to 23.3) in patients with elevated troponin levels and 2.3% (17 of 725; 95% CI, 1.2 to 3.4) in patients with normal troponin levels. The pooled analysis of these studies showed an association between high levels of serum troponins and mortality (OR, 5.90; 95% CI, 2.68 to 12.95), with no evidence for heterogeneity. The results were confirmed after substituting 0.5 for 0 in the random-effects calculation (OR, 4.98; 95% CI, 2.64 to 9.39).
The association between high levels of serum troponins and mortality was found individually for the 3 more commonly used troponin assays (Enhanced Chemiluminescence Immunoassay [ECLIA], Automated Immunoassay System [AxSYM], and Elecroluminescence System [Elecsys]). Among studies using the same troponin assay, ORs for mortality were higher in studies using higher troponin cutoffs (see Figure III of the online Data Supplement). However, meta-regression did not show any significant difference in the risk of death for studies using different cutoffs of the same troponin assay.

Eight prospective studies (645 patients) reported on deaths resulting from pulmonary embolism. Overall, 40 events were observed: 34 in 207 patients with elevated troponin (16.4%; 95% CI, 11.4 to 21.4) and 6 in 438 with normal troponin levels (1.4%; 95% CI, 0.8 to 1.9).10,12,15,18,21,22,24,28 Elevated troponin levels were associated with a high risk of death resulting from pulmonary embolism. Overall, 40 events were observed: 34 in 207 patients with elevated troponin (16.4%; 95% CI, 11.4 to 21.4) and 6 in 438 with normal troponin levels (1.4%; 95% CI, 0.8 to 1.9).10,12,15,18,21,22,24,28 Elevated troponin levels were associated with a high risk of death resulting from pulmonary embolism.

The analysis of 6 studies showed that right ventricular dysfunction is more common in patients with elevated troponin compared with patients with normal troponin levels (P<0.05). Analysis of 3 of these studies10,20,28 showed an independent prognostic value for elevated troponin levels (P=0.01) and right ventricular dysfunction at echocardiography (P=0.005), with no evidence for interaction (P=0.29).

### TABLE 2. Characteristics of Troponin Assays

<table>
<thead>
<tr>
<th>Author</th>
<th>Troponin</th>
<th>Assay</th>
<th>Manufacturer and Location</th>
<th>Kind of Assay</th>
<th>Cutoff, µg/L</th>
<th>Elevated Troponin, %*</th>
<th>Cut Point for Normal, µg/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meyer et al10</td>
<td>I</td>
<td>ACS:180</td>
<td>Bayer</td>
<td>Quantitative</td>
<td>&gt;0.15</td>
<td>39</td>
<td>&lt;0.15</td>
</tr>
<tr>
<td>Douketis et al13</td>
<td>I</td>
<td>AxSYM</td>
<td>Abbott</td>
<td>Quantitative</td>
<td>&gt;0.40</td>
<td>21</td>
<td>&lt;0.40</td>
</tr>
<tr>
<td>Mehta et al14</td>
<td>I</td>
<td>AxSYM</td>
<td>Abbott</td>
<td>Quantitative</td>
<td>&gt;0.40</td>
<td>47</td>
<td>&lt;0.40</td>
</tr>
<tr>
<td>Kucher et al15</td>
<td>I</td>
<td>NA</td>
<td>Abbott</td>
<td>Quantitative</td>
<td>≥0.06</td>
<td>31</td>
<td>&lt;0.40</td>
</tr>
<tr>
<td>La Vecchia et al17</td>
<td>I</td>
<td>RXL</td>
<td>Dade Behring</td>
<td>Quantitative</td>
<td>&gt;0.60</td>
<td>29</td>
<td>&lt;0.07</td>
</tr>
<tr>
<td>Yalamanchili et al19</td>
<td>I</td>
<td>AxSYM</td>
<td>Abbott</td>
<td>Quantitative</td>
<td>≥2.00</td>
<td>16</td>
<td>&lt;2.00</td>
</tr>
<tr>
<td>Scridon et al20</td>
<td>I</td>
<td>NA</td>
<td>Baxter</td>
<td>NA</td>
<td>&gt;0.10</td>
<td>52</td>
<td>&lt;0.10</td>
</tr>
<tr>
<td>Enea et al21</td>
<td>I</td>
<td>Opus</td>
<td>Dade Behring</td>
<td>Quantitative</td>
<td>≥0.10</td>
<td>77</td>
<td>&lt;0.10</td>
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<tr>
<td>Binder et al22</td>
<td>I</td>
<td>ADVIA</td>
<td>Bayer</td>
<td>Quantitative</td>
<td>≥0.07</td>
<td>46</td>
<td>&lt;0.07</td>
</tr>
<tr>
<td>Douketis et al24</td>
<td>I</td>
<td>AxSYM</td>
<td>Abbott</td>
<td>Quantitative</td>
<td>&gt;0.50</td>
<td>14</td>
<td>&lt;0.50</td>
</tr>
<tr>
<td>Amorim et al26</td>
<td>I</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>≥0.10</td>
<td>70</td>
<td>&lt;0.10</td>
</tr>
<tr>
<td>Hsu et al28</td>
<td>I</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
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<td>56</td>
<td>NA</td>
</tr>
<tr>
<td>Pruszczyk et al29</td>
<td>T</td>
<td>ECLIA</td>
<td>Roche</td>
<td>Quantitative</td>
<td>≥0.01</td>
<td>50</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Giannitsis et al31</td>
<td>T</td>
<td>TropT or ES 300</td>
<td>Roche</td>
<td>Qualitative, quantitative</td>
<td>≥0.10</td>
<td>32</td>
<td>&lt;0.10</td>
</tr>
<tr>
<td>Janata et al32</td>
<td>T</td>
<td>Elecsys</td>
<td>Roche</td>
<td>Quantitative</td>
<td>≥0.09</td>
<td>39</td>
<td>&lt;0.10</td>
</tr>
<tr>
<td>Bova et al33</td>
<td>T</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>&gt;0.01</td>
<td>43</td>
<td>NA</td>
</tr>
<tr>
<td>Kostrubiec et al34</td>
<td>T</td>
<td>ECLIA</td>
<td>Roche</td>
<td>Quantitative</td>
<td>≥0.01</td>
<td>39</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Binder et al35</td>
<td>T</td>
<td>Elecsys</td>
<td>Roche</td>
<td>Quantitative</td>
<td>≥0.04</td>
<td>33</td>
<td>&lt;0.04</td>
</tr>
<tr>
<td>Kaczynska et al36</td>
<td>T</td>
<td>ECLIA</td>
<td>Roche</td>
<td>Quantitative</td>
<td>≥0.03</td>
<td>32</td>
<td>&lt;0.03</td>
</tr>
<tr>
<td>Tulevski et al37</td>
<td>T</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>≥0.01</td>
<td>21</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Kline et al38</td>
<td>T</td>
<td>Elecsys</td>
<td>Roche</td>
<td>Quantitative</td>
<td>≥0.10</td>
<td>10</td>
<td>&lt;0.08</td>
</tr>
</tbody>
</table>

ACS:10 indicates Automated Chemiluminescence System; AxSym, Automated Immunoassay Instrument System; ADVIA, Advanced Immunoassay; ECLIA, Enhanced Chemiluminescence Immunoassay; Elecsys, Electroluminescence System; and NA, not applicable.

### Adverse Outcome Events

Nine studies (530 patients), all with a prospective design, evaluated the occurrence of short-term adverse outcome events.10,12,14,15,21,22,24,25 The incidence of adverse outcome was 43.6% (92 of 211 patients; 95% CI, 36.9 to 50.3) and 14.7% (47 of 319 patients; 95% CI, 10.8 to 18.6) in patients with and without elevated troponin levels, respectively. To minimize the effect of heterogeneity among studies (OR, 7.03; 95% CI, 2.42 to 20.43) (Figure 4). Heterogeneity was due mainly to the 5 studies evaluating troponin T (OR, 3.46; 95% CI, 0.92 to 12.80; P=0.0066; I2, 47.3%). A random-effects model was used for analysis. Elevated troponin levels were associated with a high risk of adverse events during the in-hospital phase (OR, 2.00; 95% CI, 1.52 to 2.62) (Figure 3) (ACS:10 indicates Automated Chemiluminescence System; AxSym, Automated Immunoassay Instrument System; ADVIA, Advanced Immunoassay; ECLIA, Enhanced Chemiluminescence Immunoassay; Elecsys, Electroluminescence System; and NA, not applicable.).
Discussion

This meta-analysis shows that elevated serum troponins are associated with short-term death and adverse outcome events in patients with acute pulmonary embolism. Elevated troponin levels also are associated with death related to pulmonary embolism.

In patients with pulmonary embolism, shock or sustained hypotension is associated with increased short-term mortality. In patients with acute pulmonary embolism and normal blood pressure, prognostic stratification remains an unsolved clinical issue. Short-term mortality in these patients has been shown to range from 0% to 10%. Grifoni et al\(^6\) have shown
that acute right ventricular overload, as assessed by echocardiography, can be used to stratify patients with normal blood pressure for the risk of death. However, echocardiography requires around-the-clock dedicated personnel and suffers from some disagreement about criteria for right ventricular dysfunction.

Serum troponins are currently used widely for the diagnosis of acute coronary syndromes and are rapidly available in the urgent setting. We showed that elevated levels of troponin were predictors of short-term death in the overall population of patients with acute pulmonary embolism and in patients with acute pulmonary embolism and normal blood pressure. According to our analysis, troponin and echocardiography are independent prognostic factors with additive prognostic value in risk stratification.

In addition to death, we showed the prognostic value of troponin on adverse outcome events. This cumulative end point was defined differently in the individual studies. However, our results should be of clinical value because all the definitions of adverse outcome events were aimed at identifying those patients who experienced in-hospital clinical deterioration.

The prognostic value of troponin was consistent among the studies, regardless of the specific assay and the relative cutoff point. The results were consistent for both troponin I and T. The association between high levels of serum troponins and mortality is confirmed individually for the 3 more commonly used troponin assays. Thus, it is conceivable that whatever the assay, troponin levels can be used to stratify patients with acute pulmonary embolism.

Individual studies reported a correlation between different levels of elevated troponins and clinical outcome in patients with pulmonary embolism.15,17 Our analysis does not allow the conclusion of such a correlation.

We included retrospective studies in this meta-analysis. However, the results of the analysis are consistent after these studies are excluded.

It is unclear whether thrombolysis has a role in the treatment of hemodynamically stable patients, and if so, it is unclear which among these patients should receive this treatment. The results of this meta-analysis suggest a role for troponin in the selection of hemodynamically stable patients with a worse outcome who could potentially benefit from a more aggressive treatment.

Conclusions

Elevated serum troponins identify a subgroup of patients with acute pulmonary embolism at high risk of in-hospital death and adverse outcome events. These findings identify troponin as a promising tool for rapid risk stratification of patients with pulmonary embolism. Prospective randomized studies are needed to evaluate the clinical benefits of more aggressive treatments in patients with pulmonary embolisms and elevated troponin levels.

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Disclosures

None.

References


Figure 4. OR for short-term adverse outcome events based on elevated or normal serum troponin I and T.


**CLINICAL PERSPECTIVE**

In-hospital mortality associated with pulmonary embolism ranges as widely as from 0% to 30%, depending on clinical features at admission. Hence, prognostic stratification of patients with acute pulmonary embolism is crucial to tailor in-hospital management and to improve patients’ outcome. In patients presenting with shock or hypotension, early pulmonary reperfusion is required to reduce mortality. Prognostic stratification in patients with pulmonary embolism and normal blood pressure is particularly complex. We performed a meta-analysis of studies aimed at assessing the prognostic value of troponin in patients with acute pulmonary embolism. This meta-analysis shows that elevated serum troponins are associated with short-term death, death related to pulmonary embolism, and increased rate of adverse outcome events. Of note, elevated levels of troponin are predictors of short-term death in the overall population of patients with acute pulmonary embolism and in patients with acute pulmonary embolism and normal blood pressure. Troponin and echocardiography appear to be independent prognostic factors with additive prognostic value. The advantages of troponin assay over other prognostic features are related to its ease of use and its wide and rapid availability. Prospective randomized studies are needed to evaluate the clinical benefits of more aggressive treatments in patients with pulmonary embolisms and elevated troponin levels. On the other hand, the benefit of simplified management strategies, including home treatment, for patients with normal blood pressure, normal troponin levels, and normal echocardiography deserves to be further evaluated.
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