Prognostic Value of Troponins in Acute Pulmonary Embolism

A Meta-Analysis

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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 I^2 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

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.[2] 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."[7]

Study Objectives

The primary objective of this analysis was to assess whether elevated serum troponins are associated with short-term mortality in patients

Received December 13, 2006; accepted May 11, 2007.

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The online-only Data Supplement, consisting of a table and figures, is available with this article at http://circ.ahajournals.org/cgi/content/full/CIRCULATIONAHA.106.680421/DC1.

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Circulation **is available at http://www.circulationaha.org** **DOI: 10.1161/CIRCULATIONAHA.106.680421**

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.[8] 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 with the primary end point among troponin-positive or -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 χ^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 $I^2>50\%$.[8] Pooled odds ratios (ORs) were reported with 95% confidence intervals (CIs). Publication bias was assessed visually by the use of funnel plots.[9]

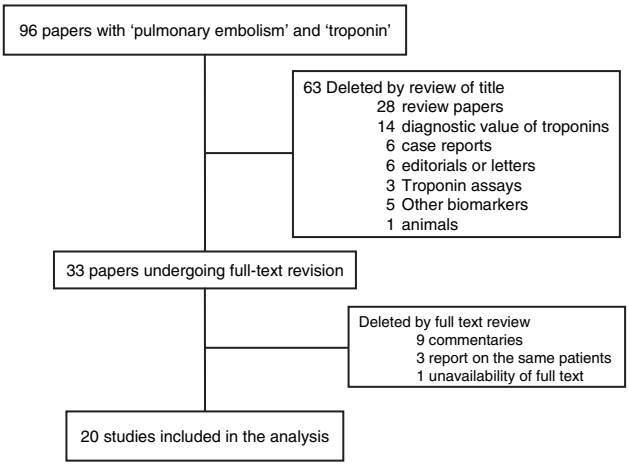

Figure 1. Flow diagram for study selection.

For studies evaluating >1 troponin assay, data on troponin I were considered for the pooled analysis. Separate analyses were performed on retrospective and prospective studies, studies including hemodynamically unstable or hemodynamically stable patients only, and studies assessing troponin I or T. Meta-regression was used to assess the relationship between death and different cutoff levels separately for the 3 troponin assays. Analyses were performed with Review Manager 4.2.8 (The Cochrane Collaboration, Oxford, England).

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

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.[10–33] Three studies were excluded[30–32] because they appeared to report on the same patients included in other analyzed studies.[16–23] In 6 studies,[16,18,23,24,29,33] 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.[16,18,23,24,29] One of these studies was excluded after the authors were contacted because data were confirmed to be unavailable.[33]

Selected Studies

Overall, 20 studies were selected for this analysis,[10–29] and 4 were retrospective.[19,20,27,28] 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

TABLE 1. Characteristics of Selected Studies

Author	Year	Study Design	Patients, n	Confirmed Diagnosis, n	Hemodynamic Instability*	Timing of Troponin Sampling	Study Outcome		Thrombolysis, n	Age	Male, %	Follow-Up
							Primary	Secondary				
Meyer et al[10]	2000	Prosp	36	36	Yes	Admission	B	NA	NA	63±16	36	In hosp
Giannitsis et al[11]	2000	Prosp	56	40	Yes	Admission, 12 h	Death	NA	16	69±2	50	In hosp
Pruszczyk et al[12]	2003	Prosp	64	64	No	Admission, 6, 12, 18 h	Death	G	8	61±17	53	In hosp
Douketis et al[13]	2002	Prosp	24	22	No	8, 12 h	NA	NA	2	NA	NA	In hosp
Mehta et al[14]	2003	Prosp	38	38	Yes	NA	Death	C	Na	64±17	34	In hosp
Kucher et al[15]	2003	Prosp	91	91	Yes	NA	A	Death	13	61±17	45	In hosp
Janata et al[16]	2003	Prosp	106	106	Yes	NA	Death	NA	Na	60	50	In hosp
La Vecchia et al[17]	2004	Prosp	48	46	Yes	Admission, 8 h	Death	NA	32	64±15	48	In hosp
Enea et al[18]	2004	Prosp	26	26	Yes	Admission, 24 h	Tn, BNP, eco	NA	17	68±14	31	In hosp
Bova et al[21]	2005	Prosp	60	60	No	NA	F	Death	0	65	35	In hosp
Kostrubiec et al[22]	2005	Prosp	100	100	No	Admission	PE death	Death, G	7	62±18	35	40 d
Binder et al[23]	2005	Prosp	124	120	Yes	Admission, 4, 8 and 24 h	F	Death	12	60±18	40	In hosp
Douketis et al[24]	2005	Prosp	458	458	No	24 h	Death	E	0	62.2	43	3 mo
Kaczynska et al[25]	2006	Prosp	77	77	Yes	Admission	Death	G	6	65±16	20	30 d
Tulevski et al[26]	2006	Prosp	28	28	No	Admission	Death	D	NA	53±18	43	3 mo
Kline et al[29]	2006	Prosp	193	193	No	NA	A	Death	NA	53±17	41	In hosp
Yalamanchili et al[19]	2004	Retro	147	147	Na	Admission	Death	NA	NA	58±16	50	In hosp
Scridon et al[20]	2005	Retro	141	89	Yes	72 h	Death	NA	14	61±16	45	30 d
Amorim et al[27]	2006	Retro	60	36	Yes	Admission	Death	NA	19	60±15	47	In hosp
Hsu et al[28]	2006	Retro	110	110	Yes	Admission, 24 h	Death	NA	7	66±14	50	100 d

Prosp indicates prospective; hosp, hospital; PE, pulmonary embolism; BNP, brain natriuretic peptide; Tn, troponin; A, in-hospital death, need for cardiopulmonary resuscitation, mechanical ventilation, pressors, thrombolysis, catheter fragmentation, or surgical embolectomy; B, in-hospital death, cardiogenic shock; C, in-hospital death, cardiogenic shock and respiratory failure; D, in-hospital death, right ventricle chronic hypertension; E, recurrent venous thromboembolism; F, in-hospital death, need for thrombolytic treatment, catecholamine administration, endotracheal intubation, or cardiopulmonary resuscitation; and G, in-hospital death, need for thrombolytic treatment, catecholamine administration, or cardiopulmonary resuscitation. Values are mean±SD when appropriate.

*Hemodynamic instability eligible for the study.

hemodynamically stable patients only.[12,13,21,22,24,26,29] One study reported data on both troponin T and I.[23]

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.[23,29]

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[24,26]; in a third study, mortality was available only at 100 days.[28]

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 (I^2, 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, 3.38 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).

TABLE 2. Characteristics of Troponin Assays

Author	Troponin	Assay	Manufacturer and Location	Kind of Assay	Cutoff, μg/L	Elevated Troponin, %*	Cut Point for Normal, μg/L
Meyer et al[10]	I	ACS:180	Bayer	Quantitative	>0.15	39	<0.15
Douketis et al[13]	I	AxSYM	Abbott	Quantitative	>0.40	21	<0.40
Mehta et al[14]	I	AxSYM	Abbott	Quantitative	>0.40	47	<0.40
Kucher et al[15]	I	NA	Abbott	NA	≥0.06	31	<0.40
La Vecchia et al[17]	I	RXL	Dade Behring	Quantitative	>0.60	29	<0.07
Yalamanchili et al[19]	I	AxSYM	Abbott	Quantitative	≥2.00	16	<2.00
Scridon et al[20]	I	NA	Baxter	NA	>0.10	52	<0.10
Enea et al[18]	I	Opus	Dade Behring	Quantitative	≥0.10	77	<0.10
Binder et al[23]	I	ADVIA	Bayer	Quantitative	≥0.07	46	<0.07
Douketis et al[24]	I	AxSYM	Abbott	Quantitative	>0.50	14	<0.50
Amorim et al[27]	I	NA	NA	NA	≥0.10	70	<0.10
Hsu et al[28]	I	NA	NA	NA	≥0.40	56	NA
Pruszczyk et al[12]	T	ECLIA	Roche	Quantitative	>0.01	50	<0.01
Giannitsis et al[11]	T	TropT or ES 300	Roche	Qualitative, quantitative	≥0.10	32	<0.10
Janata et al[16]	T	Elecsys	Roche	Quantitative	>0.09	39	<0.10
Bova et al[21]	T	NA	NA	NA	>0.01	43	NA
Kostrubiec et al[22]	T	ECLIA	Roche	Quantitative	>0.01	39	<0.01
Binder et al[23]	T	Elecsys	Roche	Quantitative	≥0.04	33	<0.04
Kaczynska et al[25]	T	ECLIA	Roche	Quantitative	>0.03	32	<0.03
Tulevski et al[26]	T	NA	NA	Qualitative	>0.01	21	<0.01
Kline et al[29]	T	Elecsys	Roche	Quantitative	>0.10	10	<0.08

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.

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 Instrument System [AxSYM], and Electroluminescence 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 (OR, 9.44; 95% CI, 4.14 to 21.49) (Figure 3).

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 studies[10,20,28] 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 ($P=0.29$).

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 (χ^2, 31.14; $P=0.0001$; I^2, 74.3%), 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, 7.03; 95% CI, 2.42 to 20.43) (Figure 4). Heterogeneity was due mainly to the 5 studies evaluating troponin T (χ^2, 19.58; $P=0.0006$; I^2, 79.6%) compared with studies on troponin I (χ^2, 3.46; $P=0.33$; I^2, 13.2%).

Four studies (252 patients) reported the incidence of adverse outcome events in patients with normal blood pressure at hospital admission.[12,21,22,25] Adverse outcome events were seen in 38 of 103 patients with elevated troponin levels (36.9%) compared with 32 of 149 patients with normal troponin levels (21.5%). Analysis of these studies showed an association between elevated serum troponins and adverse outcome events in hemodynamically stable patients (OR, 4.12; 95% CI, 0.71 to 23.86).

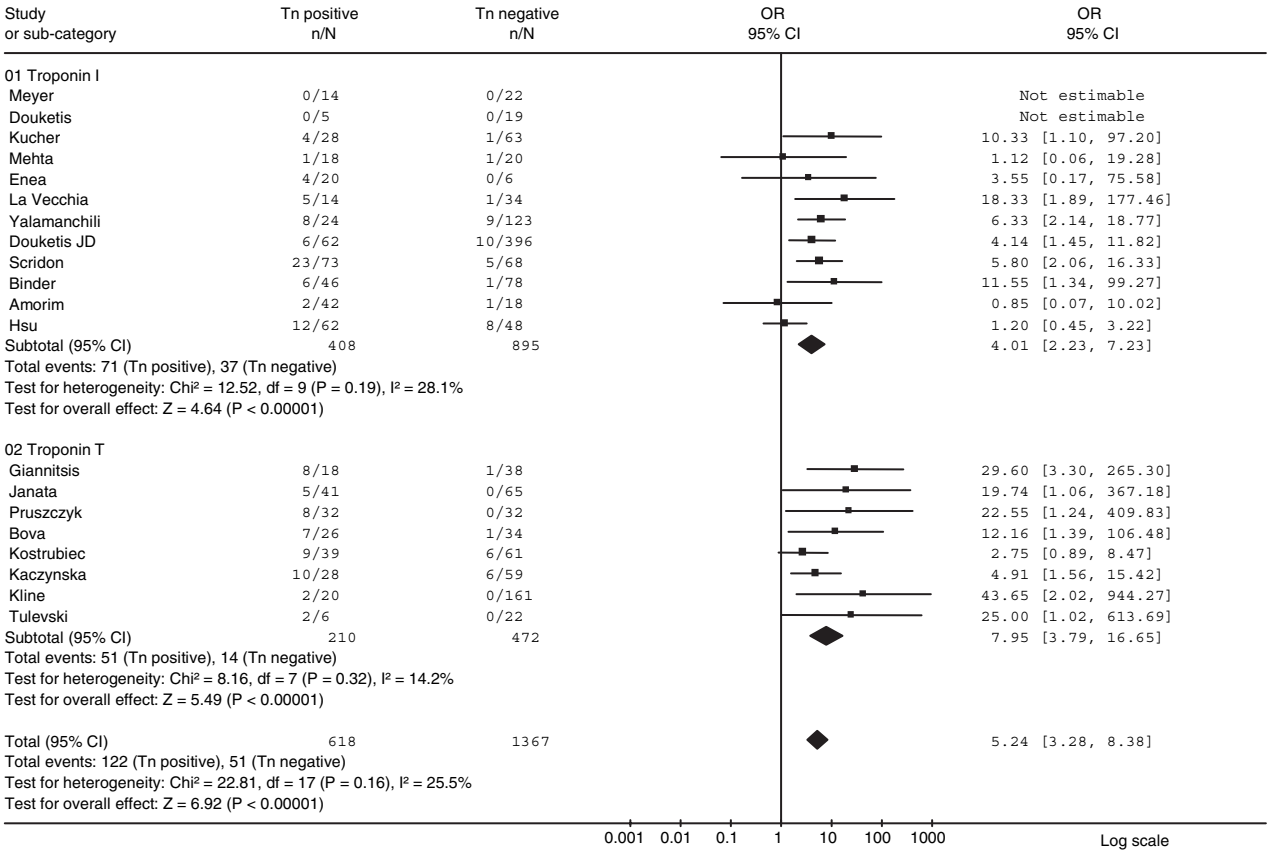

Figure 2. OR for death based on elevated or normal serum troponin I and T.

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[5] have shown

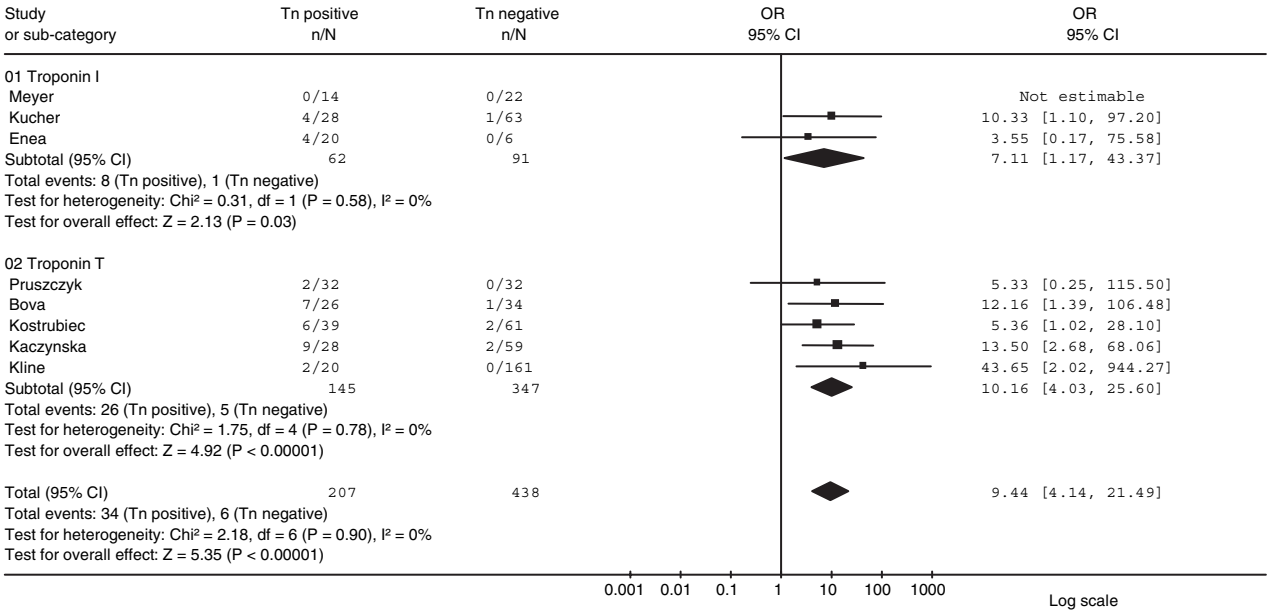

Figure 3. OR for death resulting from pulmonary embolism based on elevated or normal serum troponin I and T.

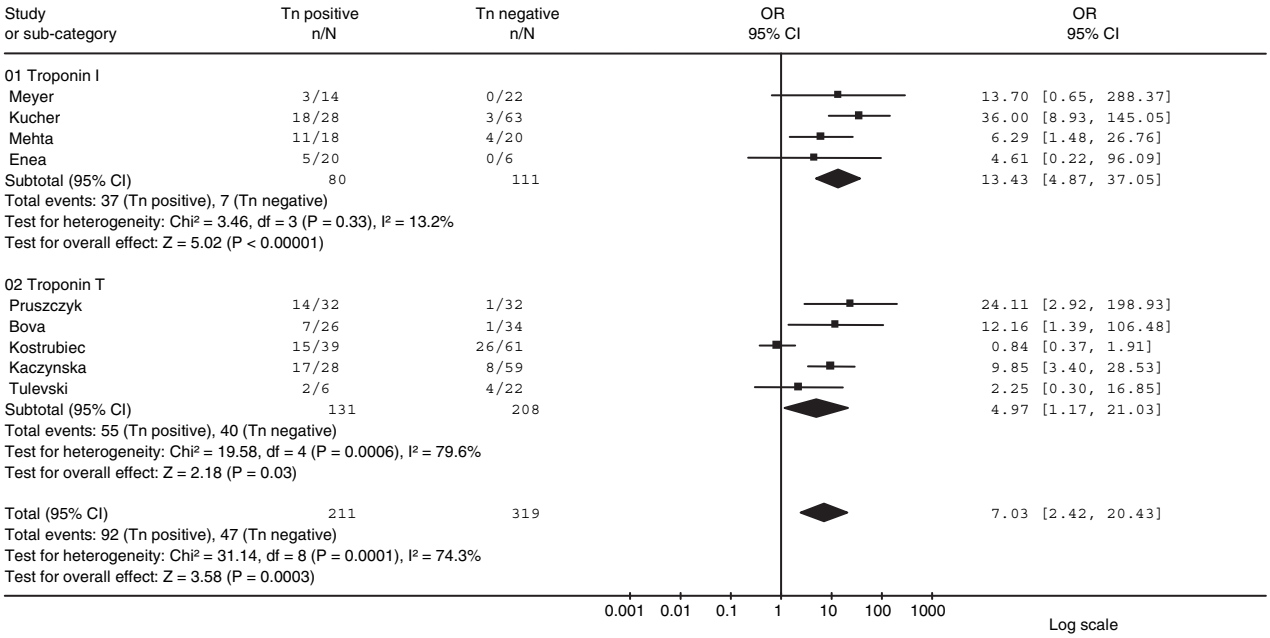

Figure 4. OR for short-term adverse outcome events based on elevated or normal serum troponin I and T.

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 addictive 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.

Acknowledgments

We thank Karin Janata, Iolanda Enea, Jeffrey Kline, James Douketis, and Stavros Konstantinides for their unpublished data that were included in this analysis. We also thank Sandra Maria Amorim for providing her article.

Disclosures

None.

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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 addictive 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.

Prognostic Value of Troponins in Acute Pulmonary Embolism: A Meta-Analysis

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Circulation. 2007;116:427-433; originally published online July 2, 2007;
doi: 10.1161/CIRCULATIONAHA.106.680421
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0009-7322. Online ISSN: 1524-4539