

# Thrombolytic Therapy for Submassive Pulmonary Embolism?

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**Study objective:** The purpose of this review was to determine the effectiveness of adding thrombolytics to standard heparin therapy for treatment of submassive pulmonary embolism. Patients with submassive pulmonary embolism were considered to be those with evidence of right ventricular dysfunction but without hemodynamic instability.

**Methods:** We searched for trials comparing thrombolytics to heparin in the Cochrane Central Register of Controlled Trials, MEDLINE, and EMBASE. We included only studies assessing the effectiveness of thrombolytic therapy for submassive pulmonary embolism and reported the patient-important outcomes of mortality, recurrent pulmonary embolism, and major hemorrhage.

**Results:** Two randomized trials met the inclusion criteria; one with a total of 256 patients presenting with submassive pulmonary embolism and the other trial including a subgroup of 46 patients with submassive pulmonary embolism. In the larger study, the relative risk (RR) for mortality, recurrent pulmonary embolism, and major hemorrhage was 1.56 (95% confidence interval [CI] 0.36 to 6.83), 1.17 (95% CI 0.30 to 4.57), and 0.23 (95% CI 0.03 to 1.97), respectively. Our post hoc subgroup analysis of the smaller trial identified 2 deaths and 5 patients with recurrent pulmonary embolism among 23 controls, whereas none of the 23 patients randomized to thrombolytics died or had recurrent pulmonary embolism. None of these findings were statistically significant.

**Conclusion:** Results of randomized trials comparing the addition of thrombolytic therapy to standard heparin therapy for treatment of submassive pulmonary embolism fail to show any significant differences in clinically important outcomes. [Ann Emerg Med. 2007;50:78-84.]

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## CLINICAL SCENARIO

You are working in a small rural emergency department (ED) when a patient arrives just after midnight. The patient is a 68-year-old woman who arrives acutely short of breath after returning from her annual trip to visit family 1 week ago. The review of systems was positive for body aches, lack of appetite, and dyspnea on exertion. She appears to be in moderate distress, with slightly labored respirations, a pulse rate 105 beats/min, and a blood pressure of 110/70 mm Hg. The ECG reveals a right ventricular strain (S1Q3T3) pattern suggestive of pulmonary embolism. Suspecting pulmonary embolism, you order computed tomography angiogram of the thorax, which reveals diffuse bilateral pulmonary emboli.

It is now 2 AM and you call for a helicopter to have the patient transported to a tertiary care facility. The physician on duty at the receiving hospital asks why you have not given thrombolytics yet; he refers to a recent article in a prominent

journal that recommends administration of alteplase to patients with submassive pulmonary embolism. You have started heparin but not thrombolytics. You return to the patient and ask about contraindications to thrombolysis, and there are none. She is still slightly short of breath, and her vital signs have not changed. In the past, you have used thrombolytics for acute myocardial infarction, occasionally for stroke, and only once for a hypotensive patient with massive pulmonary embolism. You are uncomfortable giving thrombolytics to your patient, yet wonder if you are denying her appropriate therapy. The following evidence-based emergency medicine review seeks an answer to the question posed by this clinical scenario.

## FORMULATING THE QUESTION

The thrombotic origin of pulmonary embolism has been known for almost 2 centuries.<sup>1</sup> The high mortality associated with this disease has been reduced by heparin therapy, but there have been minimal treatment advances since its introduction 40

years ago.<sup>2,3</sup> Thrombolysis has been shown to provide improvements in hemodynamic status and pulmonary imaging results compared to heparin.<sup>4-8</sup> However, it is uncertain whether improvements in these surrogate outcomes have translated into improved patient-important outcomes.

Patients with submassive pulmonary embolism, defined as pulmonary embolism occurring in hemodynamically stable patients with evidence of right ventricular heart strain, as seen on ECG or echocardiography, are at increased risk for morbidity and mortality and, according to some, should be considered for thrombolytic therapy.<sup>7,8</sup> Others argue that there is inadequate evidence to recommend routine administration of thrombolytic therapy to patients presenting with submassive pulmonary embolism.<sup>9</sup> These contradictory positions demonstrate clinical equipoise within the medical community and indicate the need for a search to answer this question.

Because there is no evidence of efficacy differences between thrombolytic agents for pulmonary embolism, all thrombolytics should be considered in any search of trials evaluating the effectiveness in this population.<sup>1</sup> Similarly, trials with either unfractionated or low-molecular-weight heparin comparison groups should be included. We selected death, recurrent pulmonary embolism, and major hemorrhage as the outcomes of interest because these are the outcomes to which patients would likely attach the most value. Using the above criteria, we sought to answer this specific clinical question: In patients presenting with evidence of submassive pulmonary embolism (ECG or echocardiographic evidence of right heart strain), does the addition of thrombolytic therapy to standard treatment with heparin reduce mortality or recurrence of pulmonary embolism without increasing major hemorrhagic complications?

## SEARCHING FOR AND SELECTING THE BEST EVIDENCE

A Cochrane systematic review of analyzed data from 8 randomized controlled trials (6 multicenter trials and 2 single-center studies), with a total of 679 unselected patients with pulmonary embolism, demonstrated no difference in all-cause mortality (odds ratio [OR]=0.89; 95% CI 0.45 to 1.78), a trend toward a decrease in the recurrence of pulmonary embolism (OR=0.63; 95% CI 0.33 to 1.2), and a trend toward an increase in major hemorrhagic events (OR=1.61; 95% CI 0.91 to 2.86) among those receiving thrombolytic therapy and heparin compared to heparin alone, but none of these trends reached statistical significance.<sup>1</sup>

A systematic review by Wan et al<sup>10</sup> that pooled data from 11 trials involving 748 patients found similar overall results: thrombolytic therapy compared to heparin therapy alone did not significantly reduce death (OR=0.70, 95% CI 0.37 to 1.30) or recurrent pulmonary embolism (OR=0.67, 95% CI 0.33 to 1.37), nor did it significantly increase major bleeding (OR=1.42; 95% CI 0.81 to 2.46). These authors also conducted a subgroup analysis based on trials that included patients with massive pulmonary embolism who were hemodynamically unstable, which revealed a significant

**Table 1.** Search results of MEDLINE.

No.	Search History	Results
1	exp Pulmonary Embolism/	21,433
2	(pulmon\$ embol\$ or pulmon\$ thromboembol\$ or pe).mp.	37,128
3	(sub\$ adj massive) or submassive or submassive).mp.	313
4	exp Thrombolytic Therapy/	12,475
5	exp Streptokinase/	7,944
6	exp Tissue Plasminogen Activator/	10,442
7	exp Fibrinolytic Agents/	109,231
8	exp Urinary Plasminogen Activator/	8,657
9	(Thromboly\$ or fibrinoly\$).mp.	52,261
10	(streptokinase or alteplase or urokinase or tenecteplase or tpa or rtpa).mp.	31,733
11	or/1-3	37,334
12	or/4-10	150,717
13	11 and 12	5,887
14	Limit 13 to randomized controlled trial	459

reduction in the composite outcome of recurrent pulmonary embolism or death (OR=0.45; 95% CI 0.22 to 0.92); however, the 5 trials included in this subgroup analysis were of lower quality, and none reported blinding of both patients and investigators.<sup>10</sup>

According to these systematic reviews, there is no evidence to support the routine administration of thrombolytic therapy for all patients presenting with acute pulmonary embolism; indirect evidence based on subgroup analysis indicates that thrombolysis may be useful in patients with massive pulmonary embolism. Because neither of these systematic reviews directly addressed the issue of submassive pulmonary embolism, we conducted a separate search of the literature. We searched for randomized controlled trials comparing thrombolytic therapy to heparin in patients with submassive pulmonary embolism, using the Ovid interface from the earliest records of each of the Cochrane Central Register of Controlled Trials, MEDLINE, and EMBASE until February 2006. We used multiple search terms, including “pulmonary embolus” and “thrombolytic therapy” and their root terms and drug-class-specific terms in various combinations (Table 1). When the limit of “randomized controlled trial” was applied, 459 studies were identified. After limiting our search to trials conducted on humans and published in English, 387 studies remained. We eliminated an additional 301 studies for not covering relevant subject or topic by title and if published before 1990 (Figure). A further 71 randomized controlled trials were eliminated for not comparing thrombolytic therapy with heparin or not using heparin as a control. Abstracts were reviewed and studies were eliminated if they did not report on clinically important outcomes such as mortality, recurrent pulmonary embolism, or major bleeding or if the publication was a review. We also scanned the references of 4 systematic reviews to identify any studies that may have been missed with our search strategy<sup>1,10-12</sup>; no other relevant studies were identified. Five studies required full article review and 3 were excluded for not including either ECG results or

**Table 2.** Study characteristics.

Characteristic	Konstantinides et al, <sup>13</sup> 2002	Goldhaber et al, <sup>14</sup> 1993
Population	256 Patients <80 (mean ~60) y old (~48% male) in Germany with submassive pulmonary embolism diagnosed within 96 h by echocardiography or electrocardiography and subsequent pulmonary imaging or cardiac catheterization. Those with hemodynamic instability or contraindications to thrombolytic therapy were excluded.	101 Patients >18 (mean ~58) y old (~44% male) in United States with pulmonary embolism within 24 h by pulmonary imaging and submassive pulmonary embolism (n=46) by echocardiography. Those with severe hypertension or a recent (6 mo) history of internal bleeding were excluded.
Intervention	Alteplase 10 mg single dose IV then 90 mg during 2 h	Recombinant tissue plasminogen activator (rt-PA) 100 mg IV during 2 h
Cointerventions	Unfractionated heparin 1,000 units/h IV and titrated to 2–2.5 times normal for 3 days. Then, oral anticoagulants to INR 2.0–3.5	Unfractionated heparin 1,000 units/h IV and titrated to 2–2.5 times normal PTT for >4 days. Then oral anticoagulants to INR 2.0–4.0
Comparison	Unfractionated heparin 1,000 units/h IV and titrated to 2–2.5 times normal for 3 days. Then, oral anticoagulants to INR 2.0–3.5	Unfractionated heparin 5,000 units IV then 1,000 units/h IV and titrated to 2–2.5 times normal PTT for >4 days. Then oral anticoagulants to INR 2.0–4.0
Outcome	Composite of in-hospital death or clinical deterioration requiring escalation of treatment by day 30 or hospital discharge; secondarily recurrent pulmonary embolism, major bleeding, or stroke	Improvement in physiologic characteristics assessed by echocardiography and pulmonary imaging at 24 h; recurrent pulmonary embolism or death at 14 days; major bleeding at 72 h

*INR*, International normalized ratio; *IV*, intravenously; *PE*, pulmonary embolism; *PTT*, partial thromboplastin time.

**Table 3.** Study validity criteria.

Criterion	Konstantinides et al, <sup>13</sup> 2002	Goldhaber et al, <sup>14</sup> 1993
Randomization	Multicenter randomized trial using blocks of 6 at each site, 1:1 ratio	Multicenter randomized trial using permuted block random number sequences
Concealment	Adequate	Adequate
Intention to treat	Yes	Yes
Baseline comparisons	Baseline characteristics similar	Baseline characteristics similar
Blinding	Described as double-blinded but became open label if patient had clinical deterioration requiring escalation of therapy	Open label
Cointerventions	Both groups received unfractionated heparin at 1,000 units/h; then adjusted according to the activated partial-thromboplastin time and oral anticoagulant therapy adjusted according to the international normalized ratio	Both groups received unfractionated heparin at 1,000 units/h; then adjusted according to the activated partial-thromboplastin time and oral anticoagulant therapy adjusted according to the international normalized ratio
Follow-up	Complete	Complete

echocardiography to identify patients with submassive pulmonary embolism.<sup>4-6</sup> Only 2 studies met our final inclusion criteria: Konstantinides et al<sup>13</sup> and Goldhaber et al.<sup>14</sup>

## ANALYZING THE EVIDENCE

### Description of the Trials

Table 2 summarizes the key characteristics of the 2 clinical trials included in this review. The larger study by Konstantinides et al<sup>13</sup> included only patients with submassive pulmonary embolism diagnosed by echocardiogram or cardiac catheterization demonstrating right ventricular enlargement or pulmonary artery hypertension, or by ECG signs of right heart strain. The primary outcome was a composite endpoint of

in-hospital death or clinical deterioration requiring an escalation of treatment, which was defined as catecholamine infusion, rescue thrombolysis, endotracheal intubation, cardiopulmonary resuscitation, emergency surgical embolectomy, or thrombus fragmentation by catheter. The indications for rescue thrombolysis included worsening clinical symptoms such as dyspnea, respiratory failure caused by pulmonary embolism, hypotension or shock, and persistent or worsening pulmonary hypertension or right ventricular dysfunction. When the clinician decided that escalation of therapy was warranted, the trial protocol permitted breaking the randomization code. Secondary outcomes included recurrent pulmonary embolism and major bleeding; recurrent pulmonary embolism was

confirmed by an imaging study, and major hemorrhage was defined as fatal bleeding, hemorrhagic stroke, or decrease in hemoglobin by at least 4 g/dL. All outcomes were assessed at the end of hospitalization or after 30 days, whichever came first. Although the initial sample size calculations required that 434 subjects be enrolled, a preplanned interim analysis demonstrated a statistically significant difference in favor of thrombolysis, so the study was stopped early after enrollment of 254 subjects.

A summary of the validity assessment of the 2 trials is provided in Table 3. When performing the critical appraisal of the study by Konstantinides et al,<sup>13</sup> we elected not to focus on the composite endpoint as reported by the authors. The limitations of composite endpoints have been well described, and it is difficult to justify combining “escalation of treatment” with “death” because patients may view the importance of adding a catecholamine infusion much differently than death.<sup>15</sup> In addition, the individual components of the composite endpoint should have similar RRs<sup>15</sup>; this was not the case in the Konstantinides et al<sup>13</sup> study, in which the outcomes of “secondary thrombolysis” and “catecholamine infusion” far outweighed any other component of the composite. At a point when clinical deterioration required an escalation of therapy, the study became open label, with 32 control patients (23.2%) receiving delayed thrombolytic therapy compared to 9 patients in the active treatment group (7.6%). The authors reported no significant differences between the study groups in any outcome other than the rate of administration of delayed thrombolytic therapy to these patients. Because unblinding of the study for patients who deteriorated was an explicit part of the protocol, it is hard to avoid the inference that previous administration of lytics was an important factor influencing decisions about who received secondary thrombolytics, particularly in the case of patients whose deterioration was confined to subjective symptoms such as dyspnea. Of the 24 control patients for whom dyspnea constituted the sole rationale for secondary thrombolysis, only 3 required mechanical ventilation, further highlighting the potentially subjective nature of this criterion. As a result of this aspect of the protocol, clinically important differences in outcome in the direction of both harm and benefit may have been masked; it could not be determined how many of the 32 control group subjects that received secondary thrombolysis had a major hemorrhage or the number of deaths in the control group that were averted by providing rescue thrombolysis.

The study by Goldhaber et al<sup>14</sup> randomized 101 patients with symptoms or signs of pulmonary embolism within 14 days before enrollment, confirmed by high-probability ventilation perfusion scan or pulmonary angiogram. The study was designed and powered to measure changes in echocardiographic findings from baseline to 24 hours. The patient-important outcomes of death or recurrent pulmonary embolism were assessed at the end of hospitalization or at 14 days; recurrent pulmonary embolism was based on clinical suspicion and not confirmed by imaging. Major hemorrhage was assessed at 72

**Table 4.** Study outcomes.

Outcome	Konstantinides et al, <sup>13</sup> 2002, RR (95% CI) <sup>†</sup>	Goldhaber et al, <sup>14</sup> 1993,* RR (95% CI) <sup>†</sup>
Death	1.56 (0.36–6.83)	0.20 (0.01–3.95)
Recurrent pulmonary embolism	1.17 (0.30–4.57)	0.09 (0.01–1.55)
Major bleeding	0.23 (0.03–1.97)	0.33 (0.01–7.78)

\*0.5 Added to each cell of 2×2 table; note that the reduced risk of hemorrhage in the treatment group is a result of a single hemorrhage occurring in a head-trauma patient erroneously entered into the control group.  
<sup>†</sup>RevMan version 4.2, Copenhagen: Nordic Cochrane Centre, Cochrane Collaboration, 2003.

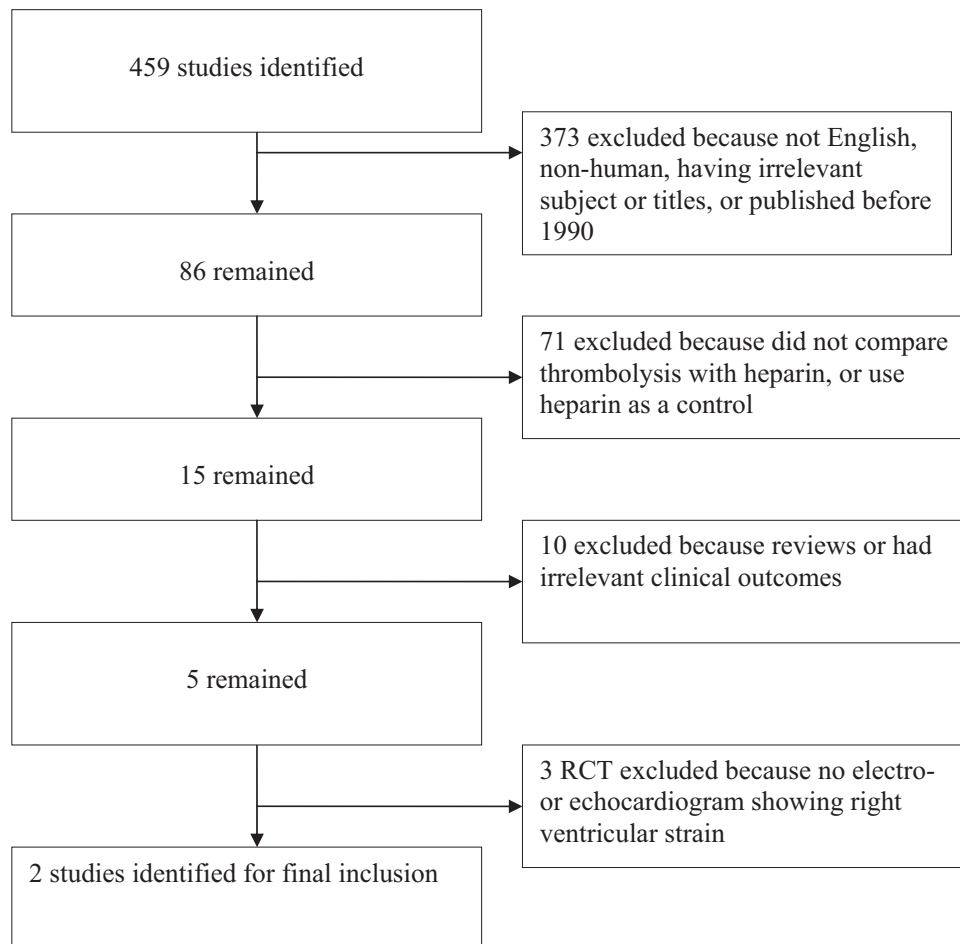
hours and defined as intracranial hemorrhage or bleeding that required surgery. Randomization was concealed, but the patients and clinicians were not blinded to treatment; only those assessing the echocardiograms were blinded. A subgroup of 46 patients was identified as having submassive pulmonary embolism, with echocardiographic evidence of right ventricular impairment; half received thrombolytic treatment and half were in the control arm.

### Primary Results

We report the primary outcome measures of death, recurrent pulmonary embolism, and major hemorrhage for 302 participants from 2 trials (Table 4). Among the 256 patients enrolled in the Konstantinides et al<sup>13</sup> study, 80 patients had evidence of right ventricular hypokinesis or dilatation on echocardiogram; the others appear to have been identified as having submassive pulmonary embolism by right ventricular strain on ECG. According to the publication by Goldhaber et al,<sup>14</sup> we performed a post hoc subgroup analysis of the 23 patients in each study arm that showed echocardiographic evidence of submassive pulmonary embolism. Considering the limitations of retrospective subgroup analyses, the estimates for effect size and precision must be interpreted with caution.<sup>16</sup>

**Death.** In the study by Konstantinides et al,<sup>13</sup> 4 of 118 patients in the thrombolytic group and 3 of 138 in the control group died, yielding an RR of 1.56 (95% CI 0.36 to 6.83). In the subgroup with submassive pulmonary embolism in the Goldhaber et al<sup>14</sup> study, 0 of 23 patients in the thrombolytic group and 2 of 23 in the control group died, with an RR=0.20 (95% CI 0.01 to 3.95). One of the deaths in the control group had been inappropriately enrolled after head trauma and subsequently had an intracranial hemorrhage and was then given rt-PA off protocol for suspected recurrent pulmonary embolism. Although this patient should have been excluded from enrollment because of contraindications to anticoagulation, this subject was randomized to the control group and counted as an outcome in each of the major categories listed below.

**Recurrence of pulmonary embolism.** In the study by Konstantinides et al,<sup>13</sup> 4 of 118 patients in the thrombolytic



**Figure.** Search, inclusion, and exclusion flow diagram.

group and 4 of 138 in the control group had recurrent pulmonary embolism, yielding an RR of 1.17 (95% CI 0.30 to 4.57). In the Goldhaber et al<sup>14</sup> study, 0 of 23 patients in the thrombolytic group and 5 of 23 in the control group had recurrent pulmonary embolism according to clinical criteria, yielding an RR of 0.09 (95% CI 0.01 to 1.55); both patients who died in the control group were also included as having recurrent pulmonary embolism.

**Major hemorrhage.** In the study by Goldhaber et al,<sup>14</sup> the patient with the head injury in the control group described above had the only major hemorrhage identified. In the study by Konstantinides et al,<sup>13</sup> 1 of 118 patients in the thrombolytic group and 5 of 138 in the control group had a major hemorrhage, yielding an RR of 0.23 (95% CI 0.03 to 1.97).

## APPLYING THE EVIDENCE

Returning to our hemodynamically stable, 68-year-old woman with submassive pulmonary embolism, would the addition of thrombolytic therapy to heparin likely provide more benefit than harm?

Several studies have demonstrated an increased risk of death with submassive pulmonary embolism when compared to hemodynamically stable patients devoid of right ventricular dilatation.<sup>17</sup> Although right ventricular impairment might identify a patient population with a poor prognosis, the use of thrombolytic therapy to decrease mortality and the incidence of recurrent pulmonary embolism has not been established. We were able to identify only 2 randomized controlled trials published in the literature that addressed the clinical question, neither of which established clear benefit or harm. Our subgroup analysis based on the publication by Goldhaber et al<sup>14</sup> demonstrated a nonstatistically significant trend in improved outcomes in the thrombolytic group, but this was based on scant data and has all the limitations associated with subgroup analysis.<sup>16,18</sup> The RRs of death or recurrent pulmonary embolism in the study by Konstantinides et al<sup>13</sup> were near unity, indicating no obvious benefit. In addition, given the mechanism of action for thrombolysis and findings opposite to those found in the Cochrane Review,<sup>1</sup> the trend toward protection from major hemorrhage with thrombolysis is counterintuitive and might have ensued

as a result of administration of thrombolytic therapy to patients randomized to the control group in the unblinded phase of the trial.

The discomfort experienced as the ED physician considering thrombolytic therapy for our patient with stable vital signs and evidence of right ventricular strain on ECG is justified because there is no conclusive evidence demonstrating a decrease in the risk of death or recurrent pulmonary embolism with thrombolysis. According to indirect evidence for potential benefit in massive pulmonary embolism and lack of conclusive evidence demonstrating an increased risk of harm because of bleeding, thrombolysis could be considered if she becomes hypotensive or develops other signs of clinical deterioration. If deterioration were to occur at some point in her hospital course, there is certainly no evidence to warrant criticism on the part of consultants for withholding thrombolysis at her initial presentation.

### PATIENT COMMUNICATION

Patients are becoming more informed about medical interventions and frequently ask about issues of safety and benefit. The following is an example of how an emergency physician might convey what is known about the risks and benefits of thrombolytic therapy in patients with submassive pulmonary embolism. The details will, of course, be characteristically modified to reflect the actual clinical circumstances.

"We have determined that you have blood clots in your lung, which are called pulmonary embolisms. The standard treatment includes heparin, which thins your blood so that no further clots form. This gives your body time to start dissolving the clots, which may take weeks. There is an alternative therapy called thrombolysis that actually dissolves the blood clot more rapidly and may restore blood flow to portions of the lung more quickly. However, as with most treatments, there are risks that include the potential for increased gastrointestinal bleeding or, on rare occasion, stroke. It has been determined that thrombolysis is not beneficial for all patients with a pulmonary embolism, but as the number and size of the blood clots increase and start to compromise your cardiovascular system, the risk of serious events, including death, goes up. At some point between these extremes, the benefits of therapy may start to outweigh the risks of bleeding." (Table 5).

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**Critically Appraised Topic (CAT): Thrombolytic Therapy for Submassive Pulmonary Embolism?**

<b>Question</b>	In patients with submassive pulmonary embolism (PE), does thrombolytic therapy reduce mortality or recurrent pulmonary embolism in comparison to anticoagulation with heparin without increased bleeding?
<b>Review by</b>	Worster A, Smith C, Silver S, Brown M
<b>Date</b>	August 30, 2006
<b>Expiration date</b>	August 30, 2008
<b>Clinical bottom line</b>	Current available data provide no conclusive evidence for benefit or harm using thrombolytic therapy with heparin compared to heparin alone for the initial treatment of patients with submassive pulmonary embolism. The number of patients enrolled in randomized trials specifically examining individuals with submassive pulmonary embolism is limited.
<b>Search strategy</b>	The search for randomized trials assessing thrombolytic therapy for submassive pulmonary embolism included MEDLINE, EMBASE, and Cochrane Central Register of Controlled Trials and was searched using the Ovid search engine and limited to English and human. Studies were excluded if they did not use ECG or echocardiography to identify patients with submassive pulmonary embolism. Studies were also excluded if they did not report mortality, recurrent pulmonary embolism, or major hemorrhage.
<b>Citations</b>	(G) Goldhaber SZ, Haire WD, Feldstein ML, et al. Alteplase versus heparin in acute pulmonary embolism: randomized trial assessing right-ventricular function and pulmonary perfusion. <i>Lancet</i> . 1993;341:507-511.  (K) Konstantinides S, Geibel A, Heusel G, et al. Heparin plus alteplase compared with heparin alone in patients with submassive pulmonary embolism. <i>N Engl J Med</i> . 2002;347:1143-1150.
<b>Primary study characteristics</b>	<p><b>Study population</b></p> <p>Adult patients presenting with submassive pulmonary embolism; 256 in Europe (K) were identified by echocardiography or ECG and 46 patients in the United States (G) by echocardiography. Patients with hemodynamic instability on presentation or contraindications to thrombolytic therapy were not included.</p> <p><b>Interventions</b></p> <p>rt-PA IV 50 mg/hour for 2 hours (G) or alteplase 10 mg IV bolus followed by 90-mg drip during 2 hours (K). Cointerventions included unfractionated heparin and oral anticoagulants.</p> <p><b>Outcome Measures</b></p> <p>Death or recurrent pulmonary embolism was assessed at the end of hospitalization or at 14 days (G) and 30 days (K). Secondary endpoint of major hemorrhage was assessed at 72 hours (G) and at 30 days (K).</p>
<b>Critical appraisal</b>	Both trials were randomized and included an adequate description of allocation concealment. The study by Konstantinides et al was blinded unless there was clinical deterioration requiring an escalation of therapy, at which point it became open label; 32 in the control arm and 9 in the treatment arm received open-label thrombolysis. As a result of this unblinding, clinically important differences in outcome in the direction of both harm and benefit may have been masked. The study by Goldhaber et al was open label; the results of our post hoc subgroup analysis must be interpreted with caution. The trend toward reduced risk of hemorrhage in the treatment group in the Goldhaber et al study is a result of a single hemorrhage occurring in a head-trauma patient erroneously entered into the control group.

**Results**

<b>Study Outcomes</b>		
<b>Outcome</b>	<b>Konstantinides et al,<sup>13</sup> 2002, RR (95% CI)<sup>†</sup></b>	<b>Goldhaber et al,<sup>14</sup> 1993,* RR (95% CI)<sup>†</sup></b>
Death	1.56 (0.36–6.83)	0.20 (0.01–3.95)
Recurrent pulmonary embolism	1.17 (0.30–4.57)	0.09 (0.01–1.55)
Major Bleeding	0.23 (0.03–1.97)	0.33 (0.01–7.78)

\*0.5 Added to each cell of 2×2 table.  
<sup>†</sup>RevMan version 4.2, Copenhagen: Nordic Cochrane Centre, Cochrane Collaboration, 2003.