



Thrombolysis for patients with pulmonary embolism, right ventricular dysfunction or pulmonary hypertension, and normal blood pressure

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Author: Henry Ko and Tari Turner
Requestors: Simon Craig
Emergency physician
Emergency Department, Monash Medical Centre, Clayton

Abstract

- Background:** Pulmonary embolism (PE) is a blockage of the pulmonary artery or one of its branches which can cause death or significant morbidity. Patients with PE usually receive treatment with anticoagulants and may also receive thrombolytics. There is controversy about whether in the sub-group of patients with PE, right ventricular dysfunction (RVD) or pulmonary artery hypertension (PAH), and normal blood pressure, treatment with thrombolytics prior to anticoagulants would be more effective than treatment with anticoagulants alone.
- Clinical Question:** In patients with pulmonary embolism and normal blood pressure, but with right ventricular dysfunction or pulmonary artery hypertension diagnosed via echocardiogram or ECG in the emergency department, does treatment with thrombolysis plus anticoagulation therapy compared to anticoagulation therapy alone reduce the incidence of mortality, pulmonary hypertension and other clinical outcomes?
- Methods:** We included all relevant studies published in English since January 1980. We searched The Cochrane Library, including The Cochrane Database of Systematic Reviews, DARE, CENTRAL and HTA. We also searched Medline, EMBASE, and CINAHL. Searches were conducted in January 2009. Studies were selected by one reviewer in consultation with colleagues, using inclusion and exclusion criteria established *a priori*. Studies were appraised by two reviewers using standard appraisal criteria.
- Results:** Two randomised controlled trials (RCTs) were included in this review, and both had high risk of bias. The risk of bias was primarily due to unclear methods of blinding (of treatment allocation, of patients, outcome assessments, and data analysis), potential conflict of interest from funding sources, small sample sizes and subjective assessments of data. Neither study showed significant differences between treatments in rates of death, recurrent PE, major bleeding or ischaemic stroke, however the small sample sizes mean an effect cannot be ruled out. There was a reduction in the rate of clinical deterioration requiring further patient treatment in the group receiving thrombolytics prior to anticoagulants in one study (12/118 (10%) vs 34/138 (25%); $P=0.004$), but this result should be interpreted with caution due to the high risk of bias of the study.
- Conclusions:** For adult patients with PE, RVD or PAH, and normal blood pressure, studies have not shown a significant benefit of using thrombolytics in addition to anticoagulants compared to anticoagulants alone for rates of death, recurrent PE, major bleeding, and ischaemic stroke. There may be a reduction in the rate of clinical deterioration requiring further patient treatment with the use of thrombolytics in addition to anticoagulants compared to using anticoagulants alone, however this should be interpreted cautiously due to the high risk of bias of the studies.

Background

Pulmonary embolism (PE) is a blockage of the pulmonary artery which can cause death or significant morbidity¹. A subpopulation of patients with PE have normal blood pressure (are normotensive or haemodynamically stable) but have right ventricular dysfunction (RVD) or strain, or pulmonary artery hypertension (PAH). This clinical presentation is also known as submassive PE^{2,3}. There is controversy about whether in this subgroup of patients, treatment with thrombolytics prior to anticoagulants is more effective than treatment with anticoagulants alone^{2,3}.

The purpose of this review is to determine for patients with PE, RVD or PAH, and normal blood pressure, whether treatment with thrombolysis in addition to anticoagulation therapy versus anticoagulation therapy alone produces better clinical outcomes. This is important as clinicians at Southern Health are formulating guidelines for treating such patients in the Southern Health emergency departments.

Clinical Question

In patients with pulmonary embolism and normal blood pressure, but with right ventricular dysfunction or pulmonary artery hypertension diagnosed via echocardiogram or ECG in the emergency department, does treatment with thrombolysis plus anticoagulation therapy compared to anticoagulation therapy alone reduce the incidence of mortality, pulmonary hypertension and other clinical outcomes?

Methods

Study Selection Criteria

Patient	Patients with pulmonary embolism and normal blood pressure [systolic >100mmHg and mean arterial >65mmHg], but with right ventricular dysfunction or pulmonary artery hypertension diagnosed via echocardiogram or ECG.				
Intervention	Thrombolysis in addition to anticoagulation therapy				
Comparison	Anticoagulation therapy alone.				
Outcomes	Clinical outcomes such as: <ul style="list-style-type: none">• Death.• Recurrent pulmonary embolism, secondary thrombosis, major haemorrhage (fatal bleeding, retroperitoneal or intracranial bleeding, haemorrhagic stroke, decrease in haemoglobin by >4 or 2 g/dL, haemorrhage needing a transfusion of ≥2 units of blood and/or haemorrhage leading to discontinuation of anticoagulant therapy), dyspnoea, respiratory failure, persistent or worsening pulmonary hypertension or right ventricular dysfunction.• Exercise tolerance.• Length of hospital stay.				
Study Type	For the specified outcomes, RCTs addressing the outcomes will be sought. If there are outcomes not addressed by RCTs, then evidence from lower quality studies will be sought.	Publication Date	1980 onwards	Language	English

Search Strategy

Evidence Source	Date of Search or Issue searched
All EBM (Ovid)*	29/1/2009 (4 th quarter 2008)
Medline (Ovid)	29/1/2009 (1950 to 28 th January 2009)
CINAHL (Ovid)	29/1/2009 (1982 to December week 2 2008)
EMBASE	29/1/2009 (1980 to 2009)

*(including The Cochrane Database of Systematic Reviews, DARE, CENTRAL, CMR, ACP Journal Club, HTA and

Search Terms in Medline*

Patient	Exp pulmonary embolism/ OR (((exp pulmonary artery/ OR (pulmonary OR lung).mp) AND ((exp thrombosis/ OR exp thromboembolism/) OR (embol\$ OR thromb\$).mp))) AND (Exp ventricular dysfunction, right/) OR ((right AND ventric\$).mp) AND ((dysfunction\$ OR hypokine\$ OR strain\$ OR fail\$).mp) OR (pulmonary AND hypertension).mp
Intervention	(Exp fibrinolysis/ OR exp fibrinolytic agents/ OR exp thrombolytic therapy/) OR (thromboly\$ OR clot-dissolv\$ OR anti-thrombo\$ OR antithrombo\$ OR blood clot lys\$ OR fibrinoly\$).mp OR (streptokinase OR urokinase OR alteplase OR rtPA OR reteplase OR tenecteplase OR tissue plasminogen activator OR tPA OR anistreplase).mp
Comparison	(Exp heparin/ OR exp anticoagulants/) OR (anticoagula\$ OR anti-coagula\$).mp OR (Heparin OR enoxaparin OR dalteparin OR fondaparinux).mp
Outcomes	-

*Syntax adapted as appropriate for other databases

We also searched for evidence-based clinical practice guidelines. The search term used to find guidelines was “pulmonary embolism”.

Guideline websites	URLs – All searched 3/11/2008
Guidelines Advisory Committee	www.gacguidelines.ca/
Guidelines International Network	www.g-i-n.net/
Joanna Briggs Institute database	www.joannabriggs.edu.au/about/home.php
NHMRC Guidelines	www.nhmrc.gov.au
New Zealand Guideline Group	www.nzgg.org.nz
US National Guideline Clearinghouse	www.guidelines.gov
Scottish Intercollegiate Guidelines Network (SIGN)	www.sign.ac.uk/
TRIP	www.tripdatabase.com/index.html

We also searched on the World Health Organisation International Clinical Trials Registry (<http://www.who.int/trialsearch/>) and the USA ClinicalTrials.gov (<http://www.clinicaltrials.gov/>) websites to find relevant randomised controlled clinical trials (RCTs) currently underway, using the keywords “pulmonary embolism” and “thrombolysis”.

Data Collection & Analysis

Studies were selected by one reviewer in consultation with colleagues using study selection and appraisal criteria established *a priori*. These studies were then appraised by two reviewers using standard appraisal criteria.

Relevant guidelines were appraised by two reviewers using the AGREE tool.

The details of the appraisal are in Appendix A.

Results

The search of All EBM, Medline, EMBASE and CINAHL databases returned 336 results. These were reviewed by title and abstract. When a decision could not be made based on abstract alone, full text was retrieved. Fifty-six full text articles were retrieved for review and three articles met all the inclusion and exclusion criteria – two RCTs^{4,5} and one systematic review².

Upon examination of full text, most articles were excluded because they were narrative reviews or commentary, did not compare thrombolysis to anticoagulants, or did not do echocardiographic or ECG diagnosis of RVD or PAH. Only two RCTs found were relevant to our patient population. Other studies were excluded because they were retrospective cohort studies that measured the same outcomes as the RCTs or did not include the specific population characteristics needed (i.e. patients presenting with PE, RVD or PAH, and normal blood pressure).

There were three systematic reviews found relevant to our question, but only one met all the inclusion and exclusion criteria². This review by Worster et al, 2007², was excluded as it reviewed the same two included RCTs we have included in this evidence request, but did not present all relevant clinical outcomes we needed.

There were three guidelines that considered our patient population, but assessment using the AGREE tool found that these were not demonstrably developed in an evidence-based way, so they were excluded from this analysis.

There is one RCT in progress which is relevant to the clinical question. It started recruiting in November 2007 (ID# NCT00639743)⁶. The two relevant studies that were identified and the met study selection criteria were both RCTs – one by Goldhaber et al, 1993⁴, and another by Konstantinides et al, 2002⁵. A critical appraisal of the quality of the two RCTs is presented in Appendix A at the end of this report.

Both studies met the inclusion criteria for this review as they used recombinant tissue-type plasminogen activator (rtPA)/alteplase as the thrombolytic and heparin as the anticoagulant, were conducted in populations who had diagnosed PE with RVD or PAH and were normotensive.

The study by Goldhaber et al, 1993,⁴ was a RCT in 101 adult patients in various hospitals in the USA, however only 46 of these patients had PE with RVD and normal blood pressure. RVD was diagnosed by qualitative assessment of RV wall motion on echocardiograph⁴. Patients in the intervention group received rtPA followed by heparin. Patients in the control group received heparin alone (no placebo was used). Dosing regimens for heparin differed between the intervention and control groups, meaning that these groups may have received different doses of heparin (see appraisal table for details).

The study by Goldhaber et al, 1993,⁴ has a high risk of bias due to:

- (1) Lack of blinding;
- (2) Funding of the study by Genetech Inc, which produces rtPA/alteplase;
- (3) The small number of patients with PE and RVD included in the analysis (n=46 overall, but only 36 patients were comprehensively analysed – 18 from each treatment arm). There were no power calculations reported for the outcomes in this subgroup, so the sample size may not have been adequate to detect an effect;
- (4) Inclusion of at least one patient who did not meet the criteria in the control arm of the study. This patient who subsequently died artificially inflating the mortality rate and rate of recurrent PE in the control group;

This study found no significant difference between the groups receiving thrombolytics prior to anticoagulants versus anticoagulant therapy alone. The results were:

	RR (95% CI)	Raw data
Death:	0.20 (0.01-3.95)	0 in the intervention group (n=23); 2 in the control group (n=23)
Recurrent PE:	0.09 (0.01-1.55)	0 in the intervention group (n=23); 5 in the control group (n=23)
Major bleeding:	0.33 (0.01-7.78)	0 in the intervention group (n=23); 1 in the control group (n=23)

The study by Konstantinides et al, 2002, was an RCT in 256 adult patients in 49 hospitals in Germany⁵.

Eligible patients either had RVD or pulmonary hypertension. RVD was diagnosed by echocardiographically detected RVD (defined as RV enlargement combined with loss of inspiratory collapse of the inferior vena cava, without left ventricular or mitral-valve disease). Pulmonary-artery hypertension was detected either (1) echocardiographically (defined as a tricuspid regurgitant jet velocity greater than 2.8m.s⁻¹); (2) by a diagnosis of precapillary pulmonary hypertension based on catheterisation of the right side of the heart, defined as a mean pulmonary-artery pressure >20mmHg and a pulmonary-capillary wedge pressure <18mmHg, followed by confirmation of PE; or (3) by new

electrocardiographic signs of RV strain (defined as complete or incomplete right bundle-branch block, S waves in lead I combined with Q waves in lead III, or inverted T waves in precordial leads V₁, V₂, and V₃), followed by confirmation of PE.⁵

Patients in both intervention and control groups received an initial dose of heparin given before diagnostic workup and enrolment. Patients in the intervention group then received rtPA followed by heparin. Patients in the control group received a placebo followed by heparin.

The study by Konstantinides et al, 2002,⁵ has a high risk of bias because:

- (1) Boehringer Ingelheim Pharma, the manufacturer of alteplase, funded the study, had one employee as a primary investigator, and two employees as statistical advisors.
- (2) Although this study stated that it was randomised by a randomisation program, it did not state what type of program this was, whether allocation was concealed or who was blinded and by what methods;
- (3) The study did not reach the *a priori* calculated sample size. It terminated recruitment when “statistically significant differences” were found in interim analyses (favouring alteplase) (p1144);

It was noted that 217 patients were required in each study arm to reject the null hypothesis with a power of 80% at $\alpha=5\%$, by the detection of a 33% relative reduction or 13% absolute reduction in the incidence of the primary endpoint (death from all causes or clinical deterioration requiring escalation of treatment). Since the study ended recruitment early, the power calculation is of little value.

The study found that patients receiving thrombolytics in addition to anticoagulant therapy had reduced incidence of clinical deterioration requiring escalation of treatment than those receiving anticoagulants alone (12/118 (10.2%) vs 34/138 (24.6%); P=0.004). There was also a significant reduction in the combined primary endpoint (death from all causes or clinical deterioration requiring escalation of treatment) using thrombolytics in addition to anticoagulants. There were no statistically significant differences between the groups for the other clinical outcomes of recurrent PE, major bleeding, and ischemic stroke.

The results relevant for this evidence request were:

	Heparin + alteplase (n=118)	Heparin + placebo (n=138)	P value
Primary endpoint (death from all causes or escalation of treatment)	13	34	0.006
Death from all causes	4	3	0.71
Escalation of treatment	12	34	0.004
Recurrent PE	4	4	0.89
Major bleeding	1	5	0.29
Ischemic stroke	0	1	1.0

Discussion

There has been much controversy surrounding the use of anti-thrombolytic drugs to treat patients with PE, RVD or PAH, and normal blood pressure. Retrospective cohort studies in the past have added to this debate with their contradictory results^{7, 8, 9, 10}.

In the two included RCTs in patients with PE, RVD or PAH, and normal blood pressure, rtPA/alteplase used in conjunction with heparin was not found to affect rates of death, stroke, major bleeding or recurrent PE, however the small sample sizes mean an effect cannot be ruled out. In one study there was a reduction in the rate of clinical deterioration requiring the escalation of treatment compared with using heparin alone⁵. The systematic review by Worster et al, 2007, also concluded that there was no significant difference between treatments². The results from the RCTs reported have potentially biased methods, so these findings should be read with caution.

While both included RCTs compared the effectiveness of rtPA and heparin to heparin alone, they used quite different regimens. In the Konstantinides study, both groups received an initial dose of heparin, followed by rtPA or placebo, and then more heparin. In the Goldhaber study, the intervention group received an initial dose of rtPA, followed by heparin. The control group received only heparin, no placebo, and the rate of heparin provision was different to that in the

intervention group. These differences in drug regime may have an effect on the results, but we cannot be certain about this. In both RCTs patients were diagnosed with RVD either by echocardiograph or electrocardiograph. For example, Konstantinides et al, 2002, used echocardiography or electrocardiographic signs of RV strain to diagnose RVD.

In the ED setting, it is unclear whether outcomes are different for patients with clinically suspected PE versus echocardiographically or electrocardiographically confirmed PE because there were no studies (RCTs or other designs) that had the relevant populations (i.e. PE, RVD or PAH, and normal blood pressure) in this situation.

Methodologically, we have strong concerns with the RCT by Konstantinides et al, 2002, that the conclusions are not justified. This is due to the fact that recruitment was prematurely stopped before reaching a predefined sample size, for which it was powered, after an interim analysis found "statistically significant differences" (favouring rtPA/alteplase). According to the Cochrane Handbook for Systematic Reviews of Interventions, studies that are "stopped early (whether or not as a result of a formal stopping rule) are more likely to show extreme intervention effects than those that continue to the end"¹¹. This means there is a high risk of bias in trials that stop early. In addition to these general concerns about premature cessation of trials is the specific issue in this study that the reason for stopping is prone to bias in itself. The decision to stop the trial is based on the finding that more patients in the control group had clinical deterioration requiring further treatment. This subjective assessment was undertaken by investigators who were not blinded to the status of the intervention.

We are also concerned that the authors of both articles may have had substantial conflict of interest, given that one of the primary authors on the paper by Konstantinides et al, 2002, was an employee of Boehringer Ingelheim Pharma, and both studies were funded by pharmaceutical companies that produce the thrombolytic drug rtPA/alteplase.

Currently, there is a RCT underway that may provide further information. The prospective Pulmonary Embolism Thrombolysis Study (PEITHO) is targeting a sample size of 1000 and started recruitment in November 2007⁶. This study is using tenecteplase as the thrombolytic. This study will report on outcomes including the incidence of death within 7 days, haemodynamic collapse within 7 days, recurrent PE within 7 days, death within 30 days, total strokes, and major bleeding.

Conclusions

For adult patients with PE, RVD and normal blood pressure, studies have not shown any significant benefit of using thrombolytics in addition to anticoagulants compared to anticoagulants alone for rates of death, recurrent PE, major bleeding, and ischaemic stroke. There may be a reduction in the rate of clinical deterioration requiring further patient treatment with the use of thrombolytics in addition to anticoagulants compared to using anticoagulants alone, however this should be interpreted cautiously due to the high risk of bias of the studies.

References

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Appendix A - Appraisal of included studies:

Study: Goldhaber, S Z, Haire, W D, Feldstein, M L, Miller, M, Toltzis, R, Smith, J L, Taveira da Silva, A M, Come, P C, Lee, R T, Parker, J A, Mogtader, A, McDonough, T J and Braunwald, E (1993). "Alteplase versus heparin in acute pulmonary embolism: Randomised trial assessing right-ventricular function and pulmonary perfusion." *Lancet* **341**(8844): 507-511.

Description of study

Patient/population	Patients ≥ 18 yr with symptoms or signs of PE and within 14 days PE "confirmed by high probability ventilation-perfusion lung scans and/or pulmonary angiograms". RVD was diagnosed by echocardiographic study of right ventricular wall motion.
N	N=101 (Intervention = 46; Control = 55); But for patients with PE+RVD at baseline N = 46 (Intervention = 23; Control = 23)
Setting	Numerous hospitals in the USA (number not stated in the article)
Intervention	Thrombolysis with recombinant tissue-type plasminogen activator (rtPA) + heparin Course: (1) 100mg rtPA infused IV over 2hr (50mg/hr) + (2) Heparin administered IV at 1000units/hr when the thrombin time or partial thromboplastin (PTT) time less than twice the control and subsequent heparin administered to achieve a target PTT of 1.5-2.5 times the upper limit of normal. + (3) Heparin for at least 5 days + oral anticoagulants (dosage adjusted to obtain an international normalised ratio of 2.0-4.0)
Comparison	Anticoagulant only: heparin Course: (1) Initial dose of heparin = 5000units as a bolus + (2) 1000units/hr as a continuous peripheral IV infusion. 4hr after randomisation, a PTT was obtained, and subsequent heparin administered to achieve a target PTT of 1.5-2.5 times the upper limit of normal. + (3) Heparin for at least 5 days + oral anticoagulants (dosage adjusted to obtain an international normalised ratio of 2.0-4.0)
Outcomes	Outcomes published specific to PE+RVD patients: Death; Recurrent PE; Major bleeding Outcomes for combined patient group measured at 3hr and 24hr after randomisation and treatments: Echocardiographic qualitative assessment of RV wall movement / RV hypokinesis (normal, mild, moderate or severely hypokinetic) RV end-diastolic area; Perfusion lung scans Recurrent PE (fatal and non-fatal)

Inclusion Criteria	<p>Patients ≥ 18yr with symptoms or signs of PE within 14 days confirmed by high probability ventilation-perfusion lung scans and/or pulmonary angiograms within 24hr of randomisation. High probability lung scans were defined as having 2 or more segmental or greater perfusion defects in the presence of normal ventilation (i.e. a ventilation-perfusion mismatch). The decision as to whether a scan was high probability was made locally at the participating hospital.</p> <p>Patients with abnormal but not high probability scans were also eligible to be screened for the trial if angiograms demonstrated pulmonary arterial thrombus.</p> <p>All patients had to undergo a baseline echocardiogram that was considered technically adequate at the local participating hospital. (It should be noted that echocardiogram was used to confirm RVD in the patient population, and that not all enrolled patients in this study had RVD at baseline)</p>
Exclusion Criteria	<p>Exclusions were made for:</p> <ol style="list-style-type: none"> (1) Major internal bleeding in the previous 6 months; (2) Intracranial or intraspinal disease; (3) Operation or biopsy in the preceding 10 days (or open heart surgery within 14 days); (4) Occult blood in stool; (5) Haematocrit $< 28\%$ or platelet count $< 100,000/\mu\text{L}$; (6) Blood pressure $> 200\text{mmHg}$ systolic or 110mmHg diastolic; (7) Severe impairment of hepatic function; (8) Pregnancy; (9) Active infective endocarditis; (10) Haemorrhagic retinopathy; or (11) Any concurrent condition considered to limit survival to within 1 month.

Study Validity

Were there any conflicts of interest in the writing or funding of this study?	Yes	The study was supported in part by a grant from Genetech Inc (p510). In the acknowledgements and author information sections, the authors did not make declarations of interests.
Does the study have a clearly focused question?	Partial	The question was adequate. It asked “whether thrombolysis followed by anticoagulation was superior to anticoagulation alone in reversing echocardiographic evidence of right-ventricular dysfunction associated with PE” (p507). It also asked whether thrombolysis improved pulmonary tissue perfusion more rapidly than heparin, and if thrombolysis more effectively lowered the incidence of recurrent PE compared to heparin treatment (p507). However, the mixing of patients with PE+RVD and patients without RVD may have confounded the outcome results particularly to the absence of published baseline characteristics defining the clinical status of the RVD group.
Is a RCT the appropriate method to answer this question?	Yes	
Does the study have specified inclusion/exclusion criteria?	Yes	The PICO were generally well defined. The inclusion and exclusion criteria were well defined (p508).
If there were specified inclusion/exclusion criteria, were these appropriate?	Yes	The inclusion/exclusion criteria were appropriate for finding patients with PE, and for the subpopulation with RVD (see section on “Echocardiograms and lung scans” on p508).

Did the study have an adequate method of randomisation?	Partial	“patients were randomized ... by opening the appropriate consecutively numbered sealed envelope. Separate, non-blinded, open label treatment assignments for each hospital were generated by permuted block random number sequences” (p508). Block randomization should usually lead to equal numbers of patients in each treatment arm. This trial ended up with unequal treatment arm numbers.
Was allocation to intervention group concealed?	Partial	Allocation was done with “consecutively numbered sealed envelope(s)” (p508). There was no mention if they were opaque or not.
Were patients blind to intervention group?	Not reported	
Were investigators and care providers blind to intervention group?	No	It is unlikely that investigators were blind as the article mentions “separate, non-blinded, open label treatment assignments for each hospital” (p508).
Were outcome assessors blind to intervention group?	Partial	Assessment of degree of right ventricular motion was undertaken on scans that “were coded to prevent identification of treatment and timing in relation to therapy” (p508). However blinding of assessment for clinical suspicion of recurrent PE is not reported.
Aside from the experimental intervention, were the groups treated the same?	Yes	This study compares two interventions.
Was there sufficient duration of follow-up?	Yes	Follow-up was performed 3hr and 24hr after the start of therapy. “For adverse outcomes, patients were followed up for 14 days, or longer if they remained in hospital” (p508). However, the situation of patients having the clinically important outcomes after discharge from the hospital was not addressed (e.g. if a patient died the day after discharge from the hospital). Post-discharge follow-up may be relevant for this study.
All outcomes were measured in a standard, valid and reliable way?	Partial	Subjective measures, such as qualitative evaluation of RV wall motion, were judged using a scoring system and a consensus of at least two assessors (p508).
Were outcomes assessed objectively and independently?	Partial	Post-treatment assessment of RVD and lung perfusion was undertaken by independent assessors. These assessments are qualitative and subjective as “judged by consensus of the panellists” (p508). Independence of assessment of other outcomes is not reported.
Was the study sufficiently powered to detect any differences between the groups?	Partial	The trial had 80% power and a two-sided level of significance of 0.05 for all outcomes (p508-509) in the combined patient group (40 per treatment arm), but was not adequately powered to detect differences in the PE+RVD subgroup. There were no power calculations done for the outcomes of death, recurrent PE and major bleeding, so we cannot assume that the sample size was adequate for these measurements. There were no confidence intervals reported.
If statistical analysis was undertaken, was this appropriate?	Partial	Positives: The authors present the statistical results, tables and graphs. The authors used standard statistical tests. Negatives: It is unclear whether the statistical analyses were planned <i>a priori</i> . It is also unclear whether the data was analysed according to protocol/methods defined <i>a priori</i> because there is no published protocol available. No point estimates or measures of variability were given (p509). Intention-to-treat analysis was mentioned (p509), but not done. However, the PE+RVD subgroup was briefly discussed separately in the Results section (p509). As is discussed below a large number of patients with RVD were not included in the analysis.

Were the groups similar at baseline with regards to key prognostic variables?	No	No baseline characteristics were provided for the subgroup with RVD. For the whole population, in the rtPA/alteplase intervention group, there were 16 males and 30 females. There were about equal numbers of males and females in the heparin control group (28 to 27 respectively). There were 8/46 people (17%) in the intervention group that had an operation 11-30 days previously, compared to 4/55 (7%) in the control group. In the whole study, there was a slightly higher proportion of patients in the intervention treatment arm that had RVD (23/46 (50%) compared to the control treatment arm 23/55 (41%)).
What percentage of the individuals recruited into each arm of the study dropped out? What percentage was lost to follow-up?	Varied	Only 1 patient dropped out – “withdrawal from the trial before drug administration” (p508). Of the 46 patients who were recruited at baseline only 36 “had three serial echocardiograms that were technically adequate”. This is a more than 20% loss to follow up due to missing or inadequate data.
Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Partial	ITT was mentioned as being undertaken in the methods section (p509). However as is noted above, a substantial proportion of randomised patients were not included in the analysis due to inadequate data, and it was unclear in the results presented if ITT was actually adhered to because the number of patients used for analysis were less than the 101 patients enrolled.
Is the paper free of selective outcome reporting?	Not reported	We do not have access to a prospectively published trial protocol and therefore cannot confirm if all analyses undertaken have been reported or selectively reported.
Were the outcomes measured appropriate?	Yes	
Other		One patient with RVD, who subsequently died, was erroneously included in the study. This patient should have been excluded due to a head injury at baseline. Given the low number of deaths in the study (n=2), her inclusion in the control group substantially affects the results.
What is the overall risk of bias?	High	The major elements surrounding this study regarding risk of bias were: (1) Lack of blinding; (2) Genetech Inc funded the study, and produces rtPA/alteplase; (3) The population of the PE and RVD sub-population within this trial was very small (n=46 overall, but only 36 patients were comprehensively analysed – 18 from each treatment arm). There were no power calculations done for the outcomes of death, recurrent PE and major bleeding, so we cannot assume that the sample size was adequate to detect an effect. There was a high loss to follow-up; (4) Inclusion of at least one patient who did not meet the criteria, who went into the control arm of the study, and who also contributed to the outcome measures for this group.

Results

For results within the population with PE and RVD (RR analysed in Worster, A, Smith, C, Silver, S and Brown, M D (2007). "Thrombolytic Therapy for Submassive Pulmonary Embolism?" *Annals of Emergency Medicine* **50**(1): 78-84):

	RR (95% CI)	Raw data
Death:	0.20 (0.01-3.95)	0 in the intervention group (n=23); 2 in the control group (n=23)
Recurrent PE:	0.09 (0.01-1.55)	0 in the intervention group (n=23); 5 in the control group (n=23)
Major bleeding:	0.33 (0.01-7.78)	0 in the intervention group (n=23); 1 in the control group (n=23)

There was a results table (Table II) that compared the qualitative assessment of RV wall motion (e.g. improved, same or worse) at 3hr and 34hr versus baseline, but this was not included here because the results were from the whole patient population, which was a mixture of patients with and without RVD at baseline. We could not extract the results for the subpopulation of patients with RVD at baseline.

Other results in this study that are not of importance to the outcomes for investigation in the evidence request included tricuspid regurgitation and RV end-diastolic endocardial area.

Author's Conclusions

The study found that "rapid improvement of right ventricular function and pulmonary perfusion, accomplished with thrombolytic therapy followed by heparin, can lead to a lower rate of death and recurrent PE, especially among patients who present with right ventricular hypokinesis" (p510).

Our comments

This study has some methodological weaknesses and uncertainties, including questions on blinding.

However, the non statistical significance (at 95% CI) of the clinical outcomes for the PE and RVD subgroup in this study does not support the author's conclusions that thrombolytics prior to anticoagulants improve patient clinical outcomes compared to anticoagulant therapy only.

When considering the results of this study, it should be noted that:

- (1) This study may have had a conflict of interest due to Genetech Inc funding the study and being the manufacturers of rtPA/alteplase.
- (2) It also seems the investigators and assessors were not blinded, which could also add bias to the analysis of results.
- (3) In this study there were 23 patients in the PE+RVD subpopulation in each treatment arm of the trial. This is a small sample size. There was no power calculation for this subgroup for any of the results.
- (4) Only 18 patients in each treatment arm of the PE+RVD subpopulation in this study had comprehensive follow-up data recorded. There were no power calculations done for the outcomes of death, recurrent PE and major bleeding, so we cannot assume that the sample size was adequate for these measurements.
- (5) The dose of heparin given may potentially be higher in the control treatment arm due to the different heparin dosing regimes between the intervention and control arms of this study. However, this can not be confirmed because we do not know the exact total volume of heparin given.

Study: Konstantinides, S, Geibel, A, Heusel, G, Heinrich, F and Kasper, W (2002). "Heparin plus alteplase compared with heparin alone in patients with submassive pulmonary embolism." *New England Journal of Medicine* **347**(15): 1143-1150.

Description of study

Patient/population	Patients with acute PE without arterial hypotension or shock and either echocardiographically detected RVD or echocardiographically detected pulmonary-artery hypertension or precapillary hypertension or new electrocardiographic signs of right ventricular strain.
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N	Total = 256 (Intervention = 118; Control = 138).
Setting	49 hospitals in Germany.
Intervention	<p>Thrombolysis with alteplase + heparin.</p> <p>Course:</p> <p>(1) Intravenous bolus of 5000U unfractionated heparin (given before diagnostic workup and enrolment)</p> <p>+</p> <p>(2) Thrombolysis (100mg alteplase as a 10mg bolus, followed by a 90mg IV infusion over a period of 2hr).</p> <p>+</p> <p>(3) IV infusion of unfractionated heparin at a start rate of 1000U/hr and then adjusted to maintain the activated partial-thromboplastin time at 2.0-2.5 times the upper limit of normal and overlapping oral anticoagulant therapy started on day 3 after randomisation, with the dosage adjusted to maintain an international normalised ratio of 2.5-3.5.</p>
Comparison	<p>Placebo + anticoagulant.</p> <p>Course:</p> <p>(1) Intravenous bolus of 5000U unfractionated heparin (given before diagnostic workup and enrolment)</p> <p>+</p> <p>(2) Placebo.</p> <p>+</p> <p>(3) IV infusion of unfractionated heparin at a start rate of 1000U/hr and then adjusted to maintain the activated partial-thromboplastin time at 2.0-2.5 times the upper limit of normal and overlapping oral anticoagulant therapy started on day 3 after randomisation, with the dosage adjusted to maintain an international normalised ratio of 2.5-3.5.</p>
Outcomes	<p>Death from all causes.</p> <p>Clinical deterioration requiring escalation of treatment (i.e. further treatment) (includes catecholamine infusion for persistent hypotension or shock, secondary thrombolysis, endotracheal intubation, cardiopulmonary resuscitation, and embolectomy or thrombus fragmentation).</p> <p>Recurrent PE (confirmed by ventilation-perfusion lung scanning, spiral CT, or pulmonary angiography).</p> <p>Major bleeding (defined as fatal bleeding, hemorrhagic stroke, or a drop in the haemoglobin concentration by $\geq 4\text{g/dL}$, with or without the need for red-cell transfusion).</p> <p>Ischaemic stroke (hemorrhagic or ischemic stroke had to be confirmed by CT or MRI).</p>
Inclusion Criteria	<p>Patients with acute PE plus either:</p> <p>(1) echocardiographically detected RVD (defined as RV enlargement combined with loss of inspiratory collapse of the inferior vena cava, without left ventricular or mitral-valve disease);</p> <p>(2) echocardiographically detected pulmonary-artery hypertension (defined as a tricuspid regurgitant jet velocity greater than $2.8\text{m}\cdot\text{s}^{-1}$);</p> <p>(3) a diagnosis of precapillary pulmonary hypertension based on catheterisation of the right side of the heart, defined as a mean pulmonary-artery pressure $>20\text{mmHg}$ and a pulmonary-capillary wedge pressure $<18\text{mmHg}$, followed by confirmation of PE; or</p> <p>(4) new electrocardiographic signs of RV strain (defined as complete or incomplete right bundle-branch block, S waves in lead I combined with Q waves in lead III, or inverted T waves in precordial leads V₁, V₂, and V₃), followed by confirmation of PE.</p>

Exclusion Criteria	<p>Patients were excluded from the study if they had one or more of the following characteristics:</p> <ol style="list-style-type: none"> (1) age over 80 years; (2) haemodynamic instability, defined as persistent arterial hypotension (i.e., systolic pressure <90mmHg), with or without signs of cardiogenic shock; (3) onset of symptoms more than 96hr before diagnosis; (4) thrombolytic treatment, major surgery, or biopsy within the preceding 7 days; (5) major trauma within the preceding 10 days; (6) stroke, transient ischaemic attack, craniocerebral trauma, or neurologic surgery within the preceding 6 months; (7) gastrointestinal bleeding within the preceding 3 months; (8) uncontrolled hypertension; (9) a known bleeding disorder; (10) known inability to tolerate alteplase; (11) known diabetic retinopathy; (12) current therapy with an oral anticoagulant; (13) current pregnancy or lactation; (14) a life expectancy of <6 months because of underlying disease; or (15) planned use of thrombolytic agents for extensive DVT.
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Study Validity

Were there any conflicts of interest in the writing or funding of this study?	Yes	One of the authors was employed by Boehringer Ingelheim Pharma. (p1143) This study was supported by Boehringer Ingelheim Pharma. (p1149) Boehringer Ingelheim Pharma is the maker of alteplase.
Does the study have a clearly focused question?	Yes	The study wanted to “compare the effects of treatment with heparin plus alteplase with the effects of heparin plus placebo on the outcome of patients with acute submassive pulmonary embolism” (p1143).
Is a RCT the appropriate method to answer this question?	Yes	
Does the study have specified inclusion/exclusion criteria?	Yes	The PICO and inclusion/exclusion criteria were very clearly defined. (p1143-1144)
If there were specified inclusion/exclusion criteria, were these appropriate?	Yes	The inclusion/exclusion criteria were appropriate for finding patients with PE, and for the subpopulation with RVD (p1143-1144).
Did the study have an adequate method of randomisation?	Partial	This study did not specifically state the method to generate randomisation. It only said “Randomization was performed on a 1:1 basis with a fixed block size of 6 patients at each center, according to a standard randomization program” (p1144). It is unclear what type of program this was.
Was allocation to intervention group concealed?	Not reported	
Were patients blind to intervention group?	Not reported	This study only stated that it was “double-blind” without mentioning who was blinded and the exact method (p1144).
Were investigators and care providers blind to intervention group?	Not reported	This study only stated that it was “double-blind” without mentioning who was blinded and the exact method (p1144).

Were outcome assessors blind to intervention group?	Not reported	This study only stated that it was “double-blind” without mentioning who was blinded and the exact method (p1144).
Aside from the experimental intervention, were the groups treated the same?	Partial	This study seems to have treated all patients the same as per the experimental protocol, except if “additional therapy had to be provided on an emergency basis to a patient whose condition was deteriorating” (p1144). Given that blinding was not confirmed, therapy may have been applied differently to different patients.
Was there sufficient duration of follow-up?	Partial	The duration of follow-up seemed clinically relevant. “Patients were evaluated at the end of their hospital stay or on day 30 after randomization, whichever occurred first” (p1144). However, the situation of patients having the clinically important outcomes after discharge from the hospital was not addressed (e.g. if a patient died the day after discharge from the hospital). Post-discharge follow-up may have been relevant for this study, especially for patients who were discharged much earlier than 30 days after treatment. Having all patients followed up for the same amount of time (e.g. 30 days) may have been better.
All outcomes were measured in a standard, valid and reliable way?	Partial	Most outcomes were measured using pre-defined clinically relevant measures and objective instruments and techniques. However, for the determination of “clinical deterioration requiring escalation of treatment” it is not stated if the detection of persistent or worsening RVD via echocardiograph was done by consensus by a group of clinicians or if they used a scoring system (as was done for the study by Goldhaber et al, 1993).
Were outcomes assessed objectively and independently?	Partial	“Clinical deterioration” is based on the treating clinicians’ own qualitative judgement on the condition of the patient. Given that it was unclear whether blinding was used during treatment and outcome assessment, it cannot be assumed that assessments were objective.
Was the study sufficiently powered to detect any differences between the groups?	Partial	An initial power calculation indicated that 217 patients in each treatment arm would be required, however the study was prematurely terminated after interim analysis demonstrated a statistically significant difference in favour of alteplase treatment after enrolment of a total of 256 patients (i.e. 118 in the intervention arm and 138 in the control arm). The study states that “217 patients would be required in each group to reject the null hypothesis with a power of 80% and at an alpha level of 5%, by the detection of a 33% relative reduction (or a 13% absolute reduction, from 39 to 26%) in the incidence of the primary end point. An interim analysis after the enrolment of the first 250 patients was prospectively planned to verify these calculations. The study was terminated after the interim analysis, which demonstrated a statistically significant difference in favour of alteplase treatment at that point.” (p1144) The primary endpoint mentioned in this paragraph is the combined outcomes of death from all causes and escalation of treatment, which includes catecholamine infusion (for persistent hypotension or shock), secondary thrombolysis, endotracheal intubation, cardiopulmonary resuscitation, and embolectomy or thrombus fragmentation. It is noted that power calculations for individual outcomes were not calculated.
If statistical analysis was undertaken, was this appropriate?	Partial	An independent research organisation monitored the study and analysed the data (p1144). The authors also participated in the data analysis. However it was not known whether or not they were blinded to the outcome data categories. According to the authors the data was analysed according to the study protocol, but such a protocol had not been published prospectively. The statistical tests were appropriate for the type of data. Point estimates and measures of variability were not presented for the primary outcome. Only raw data and p-values were presented (Table 2, p1146). It was not known if potential confounders were identified or taken into account in the analysis. The authors analysed statistical data using the intention-to-treat principle.

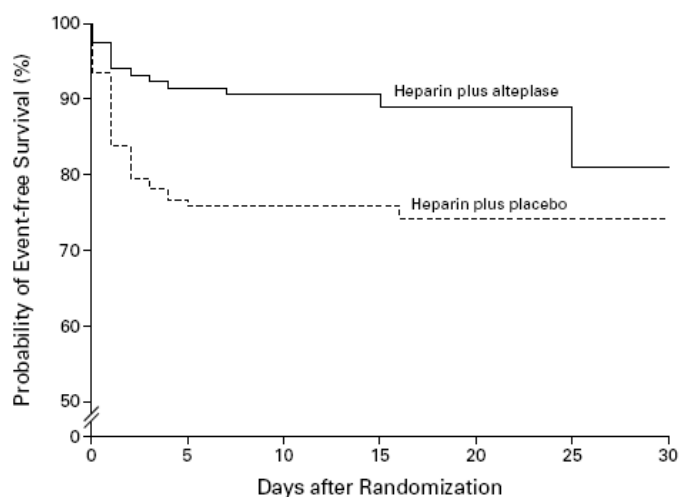
Were the groups similar at baseline with regards to key prognostic variables?	Yes	There were no significant differences between the groups, except for the readings for “S wave in lead I plus Q waves in lead III” (Table 1, p1145).
What percentage of the individuals recruited into each arm of the study dropped out? What percentage was lost to follow-up?	Not reported	
Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Yes	ITT analysis was stated to have been undertaken (p1144)
Is the paper free of selective outcome reporting?	Not reported	We do not have access to a prospectively published trial protocol and therefore cannot confirm if all analyses undertaken have been reported or selectively reported.
Were the outcomes measured appropriate?	Yes	The outcomes measured were appropriate and important.
What is the overall risk of bias?	High	<p>The major opportunities for bias were:</p> <ol style="list-style-type: none"> (1) Boehringer Ingelheim Pharma funded the study, had one employee as a primary investigator, and two employees as statistical advisors, and produces alteplase; (2) Although this study stated that it was randomised by a randomisation program, it did not state what type of program this was, whether allocation was concealed or who was blinded and by what methods. (3) The study did not reach the a priori calculated sample size. It terminated recruitment when “statistically significant differences” were found in interim analyses (favouring alteplase) (p1144). (4) Since it was unclear whether the clinicians were blinded, and that one of the study authors was an employee of the pharmaceutical company making alteplase, there is a possibility that a potentially subjective decision was made to terminate the trial when interim analysis found a “statistically significant difference in favour of alteplase treatment”. The article does not mention if there were any explicit stopping rules agreed upon <i>a priori</i> by the researchers. This raises the possibility for subjective decision for stopping.

Results

Results from the study include:

	Heparin + alteplase (n=118)	Heparin + placebo (n=138)	P value
Primary endpoint (death from all causes and escalation of treatment)	13	34	0.006
Death from all causes	4	3	0.71
Escalation of treatment	12	34	0.004
Recurrent PE	4	4	0.89
Major bleeding	1	5	0.29
Ischemic stroke	0	1	1.0

Also analysed in this study was the Kaplan-Meier estimates of the probability of event-free survival (Figure 1, p1147), as well as analyses of the determinants of the risk of in-hospital death or escalation of treatment (Table 3, p1148), and a graph of the mean activated partial-thromboplasmin time in patients (graph not included here). Figure 1 and Table 3 from the paper are included below.



No. AT Risk							
Heparin plus alteplase	118	107	96	57	26	11	6
Heparin plus placebo	137	105	87	53	24	3	2

Figure 1. Kaplan-Meier Estimates of the Probability of Event-free Survival among Patients with Acute Submassive Pulmonary Embolism, According to Treatment with Heparin plus Alteplase or Heparin plus Placebo.

An event was defined as in-hospital death or clinical deterioration requiring an escalation of treatment after termination of the infusion of the study drug. Escalation of treatment was defined as at least one of the following: infusion of a catecholamine because of arterial hypotension or shock (except for dopamine infused at a rate of no more than 5 µg per kilogram per minute), secondary thrombolysis, endotracheal intubation, cardiopulmonary resuscitation, or emergency surgical embolectomy or thrombus fragmentation by catheter. P=0.005 by the log-rank test for the overall comparison between the groups.

TABLE 3. DETERMINANTS OF THE RISK OF IN-HOSPITAL DEATH OR ESCALATION OF TREATMENT.*

VARIABLE	RELATIVE RISK (95% CI)	P VALUE
Treatment with heparin plus placebo (vs. heparin plus alteplase)	2.63 (1.32–5.26)	0.006
Age >70 yr (vs. ≤70 yr)	2.29 (1.14–4.60)	0.02
Female sex (vs. male)	2.68 (1.34–5.36)	0.005
Presence of previous or concomitant disease (vs. absence)†		
Cardiac disease	1.72 (0.82–3.61)	0.15
Pulmonary disease	1.26 (0.65–2.43)	0.48
Diabetes mellitus	0.70 (0.36–1.37)	0.30
Systolic blood pressure ≤100 mm Hg (vs. >100 mm Hg)‡	1.50 (0.32–7.00)	0.60
Heart rate >100 beats/min (vs. ≤100 beats/min)	1.42 (0.75–2.68)	0.28
Respiratory rate >24 breaths/min (vs. ≤24 breaths/min)	1.50 (0.78–2.85)	0.22
Presence of arterial hypoxemia (vs. absence)§	3.57 (1.55–8.20)	0.003

*Relative risks and P values were calculated with the use of a proportional-hazards model. The relative risk associated with each variable at base line was adjusted for the type of treatment (heparin plus placebo or heparin plus alteplase). CI denotes confidence interval.

†Information on previous or concomitant cardiac disease, pulmonary disease, or diabetes mellitus was provided by the patients' physicians or was obtained from their medical records.

‡Patients who had a systolic blood pressure persistently below 90 mm Hg or who had signs of cardiogenic shock at base line were excluded from the trial.

§Arterial hypoxemia was defined as a partial pressure of arterial oxygen below 70 mm Hg or severe dyspnea requiring the administration of oxygen at a rate greater than 2 liters per minute.

Author's Conclusions

"When given in conjunction with heparin, alteplase can improve the clinical course of stable patients who have acute submassive pulmonary embolism and can prevent clinical deterioration requiring the escalation of treatment during the hospital stay." (p1143)

Our comments

This study has some methodological weaknesses and uncertainties, including questions about the randomisation method, and blinding or concealment of allocation.

The non statistical significance (at 95% CI) of the majority of the clinical outcomes does not support the author's conclusions that thrombolytics improve patient clinical outcomes compared to anti-coagulants only.

When considering the results of this study, it should be noted that:

- (1) The study may have a conflict of interest as the study was funded by and an author employed by, a pharmaceutical company (Boehringer Ingelheim Pharma), which is a manufacturer of alteplase); and
 - (2) The results of the clinical events/outcomes are questionable because recruitment was prematurely stopped before reaching an adequately powered sample size due to a decision to stop recruitment after an interim analysis found "statistically significant differences" (favouring alteplase). The study recruited far less than the 217 patients in each treatment arm that it needed to have 80% power for adequate analysis of its primary endpoint. According to the Cochrane Handbook for Systematic Reviews of Interventions, studies that are "stopped early (whether or not as a result of a formal stopping rule) are more likely to show extreme intervention effects than those that continue to the end".
-