

# Rebuttal

Samuel Z. Goldhaber, MD

**T**HE OPPOSITION TO thrombolysis by Thabut and Logeart is based on their fundamental miscalculation that the mortality from acute PE is only 1.5%. The death rate from acute PE is actually 10-fold higher (15%) when consecutive patients with PE are tracked.<sup>1</sup> Thabut and Logeart were also misled by reading only sanitized clinical trials with dozens of exclusion criteria. These trials skim off the healthiest segment of the PE population. Physicians who evaluate patients in the emergency department or intensive care unit recognize that PE is more deadly than acute myocardial infarction.

Meta-analyses of patients with PE show a 33% reduction of death and recurrent PE with thrombolysis.<sup>2</sup> The same overviews demonstrate an increase in bleeding complications. But the meta-analyses cannot place a value on benefit vs risk. This is our task as treating physicians.

As Thabut and Logeart state, RV dysfunction may reflect an ill population of patients regardless of cause. They might have PE plus congestive heart failure or PE plus chronic obstructive pulmonary disease. Regardless, the added burden of PE places them at increased

or major in-hospital complications because of their comorbid conditions. They will be more susceptible to clinical deterioration with an anatomically small PE than their counterparts who have normal RV function. Therefore, anatomic size of the PE is not the principal criterion used to triage patients for thrombolysis. The decision should be based primarily on overall clinical condition, history of prior cardiopulmonary disease, elevation of cardiac biomarkers, and presence of RV enlargement or dysfunction.

We need to undertake a randomized trial of thrombolysis in patients with PE with RV dysfunction.<sup>3</sup> Such a trial will begin in 2006. It will not be solely European; in fact, it will be a cooperative trial with a North American component. We have been planning this trial for about 3 years, with countless drafts of the protocol and fine tuning of logistics. The trial will enroll hemodynamically stable patients with PE at greatest risk of deterioration, those with a combination of RV dysfunction plus elevation of troponin (a marker of RV microinfarction due to PE). The thrombolytic agent will be tenecteplase, which offers the convenience of administration as a 5-second bolus infusion.

In the meantime, patients with PE will continue to require our clinical decision making. The key step is timely and accurate risk stratification. For patients with moderate or severe RV dysfunction and no contraindication to thrombolysis, we should encourage enrollment in the multinational clinical trial. If this is not feasible, we should discuss with the patient and family that overviews of thrombolytic therapy indicate a one-third decrease in recurrent PE and death compared with anticoagulation alone. We need to explain the risk of bleeding and collaboratively decide on the optimal therapeutic strategy. The estimated 40% surge in the use of thrombolysis for PE this past year in the United States indicates that patients and their physicians are opting for definitive treatment when risk stratification indicates a poor prognosis with anticoagulation alone.

## REFERENCES

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2. Wan S, Quinlan DJ, Agnelli G, Eikelboom JW. Thrombolysis compared with heparin for the initial treatment of pulmonary embolism: a meta-analysis of the randomized controlled trials. *Circulation*. 2004;110:744-749.
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# Rebuttal

Gabriel Thabut, MD; Damien Logeart, MD

**T**HE PROPONENTS OF thrombolysis for patients with PE and RV dysfunction stress the high mortality rates of such patients without treatment and the well-proven hemody-

namic benefit of thrombolysis in this setting. Conversely, the opponents emphasize the doubtful prognostic significance of RV dysfunction and the lack of evidence of clinical benefit and potentially life-threatening adverse effects of thrombolysis.

To move forward the debate, Goldhaber has long championed the implementation of a large international trial comparing thrombolysis and heparin in patients with acute PE and RV dysfunction.<sup>1,2</sup> At the same time, the proponents of this

treatment stress the difficulties in launching such a large-scale trial; the largest randomized controlled trial with published results to date included only 256 patients. Funding support and recruitment difficulties are the 2 arguments commonly used against launching a large-scale trial.<sup>3</sup>

French investigators plan to launch a multicenter trial comparing thrombolysis and heparin in patients with acute PE and echocardiographically proven RV dysfunction, with mortality as an end point. The sample size of this trial has been estimated at 1400 patients, for approximately US \$500 000. Although pharmaceutical firms were reluctant to support this project, governmental support was obtained, and the trial is likely to begin next year. More costly trials have been completed with governmental support: the US national lung screening trial was sponsored by the National Cancer Institute for more than \$200 million.

The second argument against a large-scale trial relates to recruitment difficulties. According to most textbooks, PE occurs in approximately 600 000 patients in the United States yearly, and RV dysfunction is said to affect 40% of those patients.<sup>4</sup> If this hypothesis holds true, the recruitment of such patients should not be difficult.

Perhaps the proponents of thrombolysis do not hasten to launch a trial because they are afraid of the results. The rationale for thrombolysis in PE with RV dysfunction rests on the supposed poor outcome of patients with RV dysfunction without treatment. However, this statement remains debatable and does not match our clinical experience. We have just completed an analysis of 60 patients with hemodynamically stable, acute PE, without left ventricular dysfunction, admitted to our center during an 18-month period, and 55% showed some form of RV dysfunction.<sup>5</sup> Of these patients, only 1 died. Has the paucity of clinical evidence led some investigators to build artificial combined end points to create events, which may explain the low use of thrombolysis in such patients? For instance, less than 25% of patients with RV dysfunction received thrombolysis in the MAPPET registry.<sup>6</sup>

We agree with Goldhaber that a large-scale clinical trial is overdue. But currently, evidence-based medicine does not support the use of thrombolysis in patients without hemodynamic collapse.

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2. Goldhaber SZ. Thrombolysis in pulmonary embolism: a large-scale clinical trial is overdue. *Circulation*. 2001;104:2876-2878.
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#### Submissions

Readers are invited to submit their ideas about a controversial area in internal medicine. The submission should consist of a 250-word abstract clearly outlining the position you take on the controversial issue (either "pro" or "con") and the reasons for your position. If the abstract is selected for a full submission, you will be invited to write a feature article that expands on your arguments, and it will be peer reviewed. Abstracts (no longer than 250 words) and inquiries can be directed to the online submission system at <http://manuscripts.archinternmed.com>.