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Editorial Comment

Pulmonary Embolism Thrombolysis: A Clarion Call for International Collaboration*

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Cardiologists and others have struggled for the past 25 years to find optimal ways of testing thrombolytic therapy for pulmonary embolism. The challenge is daunting because appropriate subjects are difficult to identify and suitable end points for evaluation are not clear-cut. Although venous thromboembolism is the third most common cardiovascular disease (after acute ischemic syndromes and stroke), interest in this condition is diffused among many subspecialties. Therefore, the urge to confront the special problems in pulmonary embolism trial design and execution has been attenuated. This neglect is particularly tragic because the death rate from pulmonary embolism, unlike that from most other cardiovascular diseases, has not declined at all during the past generation (1).

The present study. Despite these obstacles, Professor Marc Verstraete organized 12 centers in five European countries to undertake a randomized, double-blind, double-dummy trial to compare two Food and Drug Administration (FDA)-approved regimens for pulmonary embolism thrombolysis: 100 mg of recombinant tissue-type plasminogen activator (rt-PA) administered as a continuous infusion over 2 h versus 4,400 U/kg of urokinase as a bolus dose, followed by 4,400 U/kg per h for 12 h (2). In the trial reported in this issue of the Journal (2), the investigators took a novel and clever approach. They chose as their principal end point a reduction in total pulmonary resistance, defined as pulmonary artery mean pressure divided by cardiac index, because they believed that this measurement would provide a more sensitive index of pulmonary revascularization than would pulmonary angiography. Nevertheless, they hedged their bets by performing bilateral pulmonary arteriography before and after treatment. This latter strategy, reminiscent of pulmonary embolism thrombolysis trials conducted in the 1970s, was associated with an unacceptably high rate of pericardial perforation and hemorrhage, probably because of protocol violations caused by the use of stiff rather than flexible catheters. By the midpoint of the trial, 5 of 63 patients had pericardial perforation and hemorrhage. Three of these patients developed pericardial tamponade, and two died from this complication. After 27 months of recruitment, the Data Monitoring and Ethical Committee recommended termination of the study because of this grave problem.

Despite the initial sample size calculations, the trial yielded statistically significant results even though it was only half the originally planned size. Recombinant tissue-type plasminogen activator caused a more rapid decrease in total pulmonary resistance than did urokinase during the initial 2 h of therapy. However, by 12 h, the effects of urokinase and rt-PA were equivalent and total pulmonary resistance was reduced to 50% of baseline values in both treatment groups. Angiographic improvement, assessed 12 to 18 h after initiation of therapy, was the same in both groups. All five cases of pericardial perforation occurred in patients treated with rt-PA ($p = 0.17$; two-tailed Fisher's exact test); the rate of all major hemorrhagic complications did not differ between the two groups.

Comparison with multicenter American trial. This European Cooperative Study Group (ECSG) trial provides valuable data on the effect of two FDA-approved regimens for pulmonary embolism thrombolysis. The results agree with and complement our findings (3) in a multicenter American trial reported in 1988. The patients with pulmonary embolism in the European trial were, on average, as ill as the patients in our trial; initial right heart catheterization demonstrated comparable levels of pulmonary hypertension in patients in the two trials. Both trials enrolled a high proportion of patients 11 to 30 days postoperatively, suggesting that efforts to prevent postoperative pulmonary embolism are probably too lax on both sides of the Atlantic. We compared the effects of 2 h of rt-PA with those of 24 h of urokinase. Our principal end points were improvement in clot lysis at 2 h (assessed with unilateral angiography) and pulmonary perfusion at 24 h assessed by perfusion lung scan. In our trial, rt-PA acted more rapidly than urokinase at 2 h, but the effects of the two drugs were similar by 24 h. We also found that rt-PA administered over 2 h caused fewer bleeding complications than did urokinase administered over 24 h. Fortunately, in our trial, no patient died from hemorrhagic problems, and there were no instances of pericardial perforation. In both trials, there was no difference in nadir fibrinogen levels between patients treated with rt-PA or urokinase.

Future strategies. I know that some of the ECSG investigators have become discouraged by stumbling blocks imposed by clinical research in pulmonary embolism thrombolysis; consequently, this prestigious and influential group may consider relinquishing its role in carrying out innovative pulmonary embolism trials. If these investigators choose this course, pulmonary embolism thrombolysis in Europe may revert to orphan status. My hope is that all investigators of

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pulmonary embolism thrombolysis will move forward and focus on three exciting strategies that are just now emerging.

First, we have reached the point where pulmonary angiography is no longer required for every patient enrolled in a pulmonary embolism thrombolysis trial. This concept should be especially familiar and acceptable to cardiologists, who routinely treat patients with myocardial infarction with thrombolytic therapy but without mandatory coronary angiography. In the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) study (4) published last year, patients with a high probability of pulmonary embolism on the basis of ventilation-perfusion lung scans and clinical findings had a 96% positive predictive value for pulmonary embolism at angiography. If pulmonary angiography is undertaken, flexible rather than stiff catheters should be used, especially if patients will receive thrombolytic therapy (5).

Second, recently published experimental (6) and clinical (7) pulmonary embolism studies suggest that more concentrated and shorter thrombolysis regimens may yield improved efficacy and safety. Our collaborative group has just completed a trial comparing 100 mg of rt-PA over 2 h versus urokinase in a novel dosing regimen of 3 million U over 2 h, with the 1st 1 million U administered as a bolus over 10 min. We are now initiating an international trial (USA, Canada, Italy) in which we are comparing the 2-h FDA-approved dose of 100 mg of rt-PA over 2 h with a bolus dose of rt-PA (0.6 mg/kg over 15 min, with a maximal dose of 50 mg). We hypothesize that bolus rt-PA will be safer than rt-PA administered over 2 h and that efficacy will be comparable in both groups.

Third, future trials need to test an optimal thrombolytic regimen followed by anticoagulation versus anticoagulation alone to determine which patients with pulmonary embolism should receive thrombolytic therapy. Such studies will need to focus on relevant clinical end points such as reduction of mortality, recurrent pulmonary embolism and chronic pulmonary hypertension. More emphasis is needed on determining whether differences emerge in the quality of life between patients who receive thrombolytic therapy compared with those who receive anticoagulation alone. Such trials will require sample sizes of many hundreds of patients. To carry out this plan, a clarion call for international collaboration must be answered.

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