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## Fibrinolysis for Intermediate-Risk Pulmonary Embolism

**TO THE EDITOR:** In the Pulmonary Embolism Thrombolysis (PEITHO) study (April 10 issue),<sup>1</sup> a bolus of unfractionated heparin was withheld from 303 patients because they had just received subcutaneous low-molecular-weight heparin or fondaparinux. Low-molecular-weight heparin in particular has a slow onset of action, taking 4 to 6 hours to reach full effect.<sup>2</sup> This delay in the effect of treatment may have been unfavorable to patients not receiving tenecteplase, among whom the incidence of hemodynamic decompensation (often within the first day after randomization) was higher than that among patients receiving tenecteplase.

Guidelines support the safety of low-molecular-weight heparin in patients with pulmonary embolism. Caution is warranted, however, because the majority of relevant trials (10 of 12 trials in a key meta-analysis<sup>3</sup>) used low-molecular-weight heparin after an initial bolus of unfractionated heparin. Omitting this bolus may be unsafe, particularly in high-risk patients such as those involved in the PEITHO study. Previous guidelines have recommended a bolus of unfractionated heparin before the administration of low-molecular-weight heparin.<sup>4</sup> Later, for some reason, this recommendation disappeared.

We would like to know outcome details of the subgroup of patients who did not receive an initial bolus of unfractionated heparin. If hemodynamic decompensation in the placebo group occurred primarily in this subgroup, the explanation may be a delayed onset of anticoagulant activity.

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**TO THE EDITOR:** Meyer et al. reported important results of a large, multicenter trial evaluating the effect of fibrinolysis in patients with intermediate-risk pulmonary embolism. The authors evaluated interactions (i.e., different treatment effects in subgroups of the population) on a relative scale using logistic regression and found a trend toward a greater risk of major extracranial bleeding among patients older than 75 years of age (odds ratio, 20.38, vs. 2.80 among patients 75 years of age or younger;  $P=0.09$ ).

If the interaction had been assessed on an absolute scale, very different conclusions regarding treatment safety in elderly patients would have been drawn. Indeed, among patients 75 years of age or younger, 14 of 344 patients in the fibrinolysis group (4.1%) and 5 of 335 patients in the placebo group (1.5%) had major bleeding, resulting in an absolute risk difference of 2.6 percentage points (95% confidence interval [CI], 0.1 to 5.0). In contrast, among patients older than 75 years of age, 18 of 162 patients in the fibrinolysis group (11.1%) and 1 of 164 patients in the placebo group (0.6%) had major bleeding, resulting in an absolute risk difference of 10.5 percentage points (95% CI, 5.5 to 15.5). The absence of overlap in the confidence intervals indicates that fibrinolysis was associated with a significantly increased absolute risk of major extracranial bleeding among older patients.

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**TO THE EDITOR:** The PEITHO investigators found a significant reduction in death or hemodynamic

decompensation with the use of fibrinolytic therapy in patients with intermediate-risk pulmonary embolism, yet with an increase in hemorrhagic events. Significant variability among study participants in response to plasminogen activators has been reported in healthy volunteers.<sup>1</sup> Furthermore, this variability can be more pronounced in older patients<sup>2</sup> and those with inflammatory conditions, given variations in levels of endogenous inhibitors of fibrinolysis — such as plasminogen activator inhibitor type 1 (PAI-1), thrombin-activatable fibrinolysis inhibitor, antiplasmin, and  $\alpha_2$ -macroglobulin — as well as diurnal fluctuation of PAI-1.<sup>3</sup> We have recently found profound differences in ex vivo tissue plasminogen activator–induced fibrinolysis among severely injured patients, ranging from hypersensitivity (hyperfibrinolysis) to complete resistance (fibrinolysis shutdown).<sup>4</sup> Thromboelastography, which measures changes in the viscoelasticity of whole blood, has been validated clinically as a tool to quantify hyperfibrinolysis in trauma patients and to guide antifibrinolytic therapy.<sup>5</sup> Conversely, a role could exist for viscoelastic assays to guide fibrinolytic therapy by permitting the adjustment of the drug dose on the basis of the patient's fibrinolytic response ex vivo. Such goal-directed therapies with the use of plasminogen activators have yet to emerge and could reduce hemorrhagic complications while ensuring effectiveness, thus allowing for safe implementation of emerging thrombolytic therapies.

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No potential conflict of interest relevant to this letter was reported.

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**TO THE EDITOR:** Although we laud the publication of the results of the PEITHO trial, in which the investigators conclude that prompt fibrinolysis can reduce the risk of hemodynamic decompensation or death among normotensive patients who have pulmonary embolism with right ventricular dysfunction or myocardial injury, we wish to raise the following concerns. The absence of a core laboratory for assessment of imaging of right ventricular dysfunction raises the possibility of a wide variability in the interpretation of images of a cardiac structure that is particularly difficult to evaluate by means of transthoracic echocardiography. On multidetector computed tomographic (CT) pulmonary angiography, the exact image to be chosen for the right ventricular:left ventricular diameter ratio can be quite subjective. Reconstructed CT four-chamber views are also superior to those from axial views.<sup>1</sup>

Because thrombolysis is associated with hemorrhagic complications, the use of the simplified Pulmonary Embolism Severity Index (PESI) score can identify patients at very low risk.<sup>2</sup> It would be interesting to know how many patients in the study who were classified as having intermediate risk according to the European Society of Cardiology criteria would be labeled as having low risk according to the simplified PESI score. Thrombolysis might not be indicated in this subgroup.

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No potential conflict of interest relevant to this letter was reported.

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**TO THE EDITOR:** With regard to the article by Meyer et al.: we would like to share some thoughts

regarding the development of chronic thromboembolic pulmonary hypertension after submassive pulmonary embolism. The overall incidence of chronic thromboembolic pulmonary hypertension after pulmonary embolism is 2 to 4%<sup>1</sup>; however, no one has rigorously studied its incidence after submassive pulmonary embolism. Kline et al.<sup>2</sup> and Fasullo et al.<sup>3</sup> found that patients who received up-front thrombolysis (as the initial therapeutic approach) had reduced right ventricular systolic pressures (<40 mm Hg) and improved function. We believe that uncertainties still exist regarding the potential benefit of thrombolysis in this particular subgroup of patients with objective quantitative echocardiographic evidence of persistent pulmonary hypertension. It would be helpful for clinicians if the authors would consider analyzing the subgroup of patients with persistent pulmonary hypertension, addressing the associated end point of chronic thromboembolic pulmonary hypertension, which confers higher mortality among survivors. We believe that by addressing the echocardiographic predictors of chronic thromboembolic pulmonary hypertension and by characterizing more accurately this controversial but intriguing phenotype of patients, clinicians may better understand who will benefit most from thrombolysis.

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**TO THE EDITOR:** In his editorial about the PEITHO trial, Elliott<sup>1</sup> notes that half-dose fibrinolysis has been studied in the management of myocardial infarction but not pulmonary embolism.<sup>2</sup> We would like to bring the Moderate Pulmonary Em-

bolism Treated with Thrombolysis (MOPETT) trial<sup>3</sup> to the attention of *Journal* readers.

The MOPETT trial used a definition of moderate-risk pulmonary embolism that was similar to that used in the PEITHO study and randomly assigned patients to alteplase infusion or placebo, in addition to fractionated heparin or subcutaneous enoxaparin. However, unlike the PEITHO trial, the MOPETT trial halved the conventional weight-based dosing for the treatment of massive pulmonary embolism. Among the 121 patients who underwent randomization, mortality at index hospitalization was similar in the thrombolysis and control groups (1.6% and 5.0%, respectively), and no bleeding complications were observed in either group. This trial was also positive for its primary outcome of decreased cardiovascular morbidity from pulmonary hypertension at long-term follow-up. Despite a small sample and the need for further validation, the MOPETT trial suggests that half-dose thrombolysis may indeed be a promising, lower-risk therapy for patients with intermediate-risk moderate pulmonary embolism.

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No potential conflict of interest relevant to this letter was reported.

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**THE AUTHORS REPLY:** Smulders and Kramers suggest that withholding the bolus of unfractionated heparin in patients receiving low-molecular-weight heparin may have adversely affected outcomes, particularly among patients in the placebo group. We do not believe that this was the case. First, the median interval between injection

of low-molecular-weight heparin and randomization was 6.5 hours in the patients assigned to placebo. Second, hemodynamic decompensation or death occurred among 5.3% of patients in the placebo group who were receiving low-molecular-weight heparin or fondaparinux before randomization, as compared with 5.5% of those receiving unfractionated heparin from the beginning.

According to Girerd et al., if the interaction between the primary outcome and age had been assessed on an absolute scale, the interpretation of the subgroup analysis would have been different. In randomized trials with binary data, the most frequently used measures of treatment effect are odds ratios, relative risks, and hazard ratios. It is generally best to avoid testing interaction with the use of a different type of scale than the one used for the primary outcome. For this reason, interaction tests based on the logistic model were used in both the main and the subgroup analyses. Our results generate the hypothesis that fibrinolysis may be associated with a lower bleeding risk among younger patients than among those older than 75 years of age.

Gonzalez et al. suggest that variability among study participants in the response to plasminogen activators may account for a reduced efficacy of tenecteplase in older patients. Although we did not perform thromboelastography in the PEITHO trial, the main concern arising from the results in patients older than 75 years of age was the bleeding risk rather than a lack of efficacy.

We agree with Nobre and Thomas that the interpretation of echocardiographic or CT findings may have varied among study sites. Because the PEITHO study protocol permitted only a short delay between confirmation of right ventricular dysfunction and randomization, sending the results to a core laboratory would have been highly impractical. Other possible determinants of outcome such as the PESI score will be analyzed in a future report.

We agree with Porres-Aguilar and Mukherjee that the development of chronic thromboembolic pulmonary hypertension is a concern in patients with intermediate-risk pulmonary embolism. Indeed, the PEITHO study may offer a good opportunity to address the potential role of thrombolytic therapy in the prevention of this complication. Patient follow-up over a period of at least 2 years is being performed in the PEITHO population to address these issues.

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**THE EDITORIALIST REPLIES:** Intracranial hemorrhage is a major risk of fibrinolysis. In my editorial, I pointed out that half-dose tenecteplase was given to patients with myocardial infarction who were 75 years of age or older, but this reduced-dose strategy for older patients has not been studied for acute pulmonary embolism. In the study of fibrinolysis for acute myocardial infarction, half-dose tenecteplase reduced the rate of intracranial hemorrhage dramatically among patients 75 years of age or older.<sup>1</sup> The PEITHO investigators observed a higher rate of intracranial hemorrhage among patients given full-dose tenecteplase who were older than 75 years of age than among younger patients.

Spiegel et al. call attention to a study of half-dose fibrinolysis to treat adults of all ages with “moderate” pulmonary embolism.<sup>2</sup> The patients were younger and probably had a lower risk of intracranial hemorrhage than the patients in the PEITHO trial. As Spiegel et al. note, the MOPETT trial does not provide compelling evidence for the efficacy or safety of half-dose fibrinolysis. I agree with their cautious statement that half-dose thrombolysis may be a promising, lower-risk therapy for patients at intermediate risk of death from acute pulmonary embolism, but one that requires further study.

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