Single-bolus tenecteplase plus heparin compared with heparin alone for normotensive patients with acute pulmonary embolism who have evidence of right ventricular dysfunction and myocardial injury: Rationale and design of the Pulmonary Embolism Thrombolysis (PEITHO) trial

The Steering Committee

Background In acute pulmonary embolism (PE), overt right ventricular (RV) failure with cardiogenic shock indicates a poor prognosis. However, normotensive patients with acute RV dysfunction on echocardiography or computed tomography and with myocardial troponin elevation may also have an adverse outcome. Thrombolysis rapidly reverses RV pressure overload in PE, but it remains unclear whether it may improve the early and long-term clinical outcome of selected normotensive patients.

Design The Pulmonary Embolism Thrombolysis (PEITHO) trial is a prospective, multicenter, international, randomized (1:1), double-blind comparison of thrombolysis with tenecteplase vs placebo in normotensive patients with confirmed PE, an abnormal right ventricle on echocardiography or computed tomography, and a positive troponin I or T test result. Both treatment groups receive standard anticoagulation. The primary efficacy outcome is the composite of death from any cause or hemodynamic collapse within 7 days of randomization. Safety outcomes include ischemic/hemorrhagic strokes and other major bleeding episodes. In addition, 180-day clinical and echocardiographic follow-up will be performed. The study is expected to enroll approximately 1,000 patients.

Conclusions By determining the benefits vs risks of thrombolysis in submassive or intermediate-risk PE, this trial is expected to answer a long-standing query on the management of this patient population. (Am Heart J 2012;163:33-38.e1.)
thought to have a much more favorable outcome if anticoagulation is promptly instituted. However, further risk stratification of these patients appears necessary because early detection of (subclinical) RV dysfunction or injury may identify a patient group with an elevated risk of an adverse early outcome. No consensus on the exact definition of “submassive” (as named by the American Heart Association14) or “intermediate-risk” (as named by the European Society of Cardiology15) PE exists to date; however, data accumulating from a growing number of cohort studies suggest that imaging modalities such as echocardiography and computed tomography of the chest, which detect RV enlargement and/or hypokinesis, may need to be combined with laboratory biomarkers of myocardial injury or necrosis such as cardiac troponin levels in the circulation, to identify the appropriate candidates for prompt recanalization.18,19

Thrombolytic agents have been administered to patients with acute PE for almost 40 years.20 Pooled data from (mostly small) randomized trials indicated that, in hemodynamically unstable patients, thrombolysis results in a significant reduction of death rates or symptomatic recurrence of PE.21 Accordingly, it is widely accepted that thrombolysis is indicated in massive, high-risk PE.14,15,22 On the other hand, it remains controversial whether the early angiographic and hemodynamic improvement after thrombolytic treatment may favorably affect the clinical outcome of normotensive patients. Clearly, most thrombolysis trials in PE conducted thus far were too small to address clinical end points; however, even the largest of these trials did not show a survival benefit23,24 possibly because they lacked (in the 1990s) the tools to correctly diagnose submassive/intermediate-risk PE and, thus, identify those patients who might truly benefit from immediate recanalization. Refined diagnostic tools and strategies are now available to detect RV dysfunction and injury, and new agents such as tenecteplase have recently simplified thrombolytic regimens.25 In light of these advances, investigators from Europe and North America joined forces to design and perform an adequately powered multicenter, multinational thrombolysis trial, the largest ever performed in acute PE. The Pulmonary Embolism THROMbolysis (PEITHO; the name of the goddess of persuasion in ancient Greek mythology) trial hopes to terminate a growing number of cohort studies suggesting that imaging modalities such as echocardiography and computed tomography of the chest, which detect RV enlargement and/or hypokinesis, may be required to identify the appropriate candidates for prompt recanalization.18,19

Objectives of the trial
The primary objective of the PEITHO trial is to demonstrate the superiority (i.e., the clinical benefit) of thrombolysis with tenecteplase as opposed to placebo in normotensive patients with acute PE, if they have evidence of RV dysfunction on echocardiography or computed tomography of the chest and, in addition, evidence of myocardial injury/necrosis as indicated by a positive cardiac troponin I or T test result. All patients receive standard anticoagulation as indicated.15,22

The secondary objective is to assess the safety of tenecteplase. Moreover, the long-term (180 days) clinical outcome will be determined, and echocardiographic follow-up studies will be performed to monitor the effects of thrombolysis on the progression to chronic thromboembolic pulmonary hypertension in this largest ever population of patients with submassive/intermediate-risk PE.

Patient population and study design
The inclusion and exclusion criteria of the PEITHO trial (ClinicalTrials.gov identifier NCT00639743) are listed in Table I; the flow diagram is displayed in Figure 1. In a patient with confirmed acute PE, randomization should occur no later than 2 hours after the diagnosis of RV dysfunction and myocardial injury. A single intravenous bolus of tenecteplase (fibrinolytic treatment arm; group A) or placebo (reference treatment arm; group B), adapted for known or estimated body weight, is administered within 30 minutes of randomization during a period of 5 to 10 seconds. The feasibility and safety of tenecteplase in normotensive patients with acute PE was recently demonstrated.25 The dosing regimen is shown in Table II. Unfractionated heparin (UFH) is given as an intravenous bolus immediately after randomization; this step is omitted in patients who have already received an intravenous bolus or infusion of UFH before randomization.

Patients receiving low-molecular-weight heparin (LMWH) or fondaparinux at a therapeutic dose at the time of PE diagnosis can be randomized. In this case, the initial bolus of UFH upon randomization is omitted, and the start of the infusion of UFH is delayed until 12 hours after the last LMWH injection, or until 24 hours after the last fondaparinux injection.

The heparin infusion rate is adjusted to achieve and maintain an activated partial thromboplastin time (aPTT) 2.0 to 2.5 times the upper limit of the control, corresponding to therapeutic heparin levels (equivalent to 0.3-0.7 IU/mL by factor Xa inhibition). The aPTT is measured before study drug administration and subsequently 3, 6, and 12 hours after the start of heparin infusion, followed by measurements at least once daily as long as the patient receives UFH. The aPTT is also determined 3 hours after each adjustment of the infusion rate, which should be based on standardized nomograms.26 Treatment with UFH overlaps with the administration of vitamin K antagonists until therapeutic values of international normalized ratio (2.0-3.0) have
been reached for 2 consecutive days; alternatively, it is possible to switch patients from intravenous UFH infusion to subcutaneous injections of LMWH or fondaparinux at a weight-adjusted dosage 48 hours or later after randomization.

**Outcomes**

The primary efficacy outcome is the composite of death from any cause or hemodynamic collapse within 7 days of randomization. Hemodynamic collapse is defined as at least 1 of the following: (i) the need for cardiopulmonary resuscitation; (ii) systolic blood pressure <90 mm Hg for at least 15 minutes, or a drop of systolic blood pressure by at least 40 mm Hg for at least 15 minutes, with signs of end-organ hypoperfusion (cold extremities, urinary output <30 mL/h, or mental confusion); and (iii) the need for catecholamines (except for dopamine at a rate of ≤5 μg kg⁻¹ min⁻¹) to maintain adequate organ perfusion and a systolic blood pressure of >90 mm Hg. The primary efficacy outcome of PEITHO is, thus, different from that of a previous large thrombolysis trial (death or escalation of treatment, mainly consisting of secondary thrombolysis). The secondary outcomes are as follows: (1) death from any cause within 7 days, (2) hemodynamic collapse (as defined above) within 7 days, (3) imaging-confirmed symptomatic recurrence of PE within 7 days, and (4) death within 30 days. Confirmation of recurrent PE requires a new filling defect demonstrated by pulmonary angiography or spiral computed tomography, or a new perfusion defect by lung scan indicating high probability of PE. There is no routine surveillance for asymptomatic recurrent venous thromboembolism.

Safety outcomes include the following: (1) ischemic or hemorrhagic stroke within 7 days, (2) other major (ie, moderate or severe) bleeding within 7 days, and (3) serious adverse events (SAEs) within 30 days. Moderate bleeding is defined as a bleeding episode requiring blood transfusion(s) but one that is not considered life threatening and does not lead to hemodynamic compromise requiring emergency fluid replacement, inotropic support, or interventional/surgical treatment. Severe bleeding is defined as an episode that leads to hemodynamic compromise requiring emergency intervention (as administration of fluids and/or blood products, inotropic support, or surgical treatment), or is life-threatening, or fatal.

**Long-term follow-up**

The patient's vital status will be recorded 6 months after randomization. This may be done by an appointment at the clinic or, in case of death, by contact (via telephone or mail) with the patient's family or physician. The follow-up can be done between days 180 and 210, but the status must be given for day 180 after randomization. If follow-up is done earlier, a repeated
The PEITHO trial is a prospective, multicenter, international, randomized (1:1), double-blind, parallel group comparison. The aim is to demonstrate the superiority of tenecteplase over placebo with regard to the primary composite end point, that is, death or hemodynamic collapse at 7 days. Null and alternative hypotheses are as follows: $H_0$: 7-day-death-hemcol_{tenect} = 7-day-death-hemcol_{placebo}$ vs $H_1$: 7-day-death-hemcol_{tenect} $\neq$ 7-day-death-hemcol_{placebo} (where hemcol stands for hemodynamic collapse, and tenect for tenecteplase). The main analysis will be based on the intention-to-treat (ITT) population. In addition, an explanatory analysis (per protocol) of all patients randomized and treated without major protocol violations/deviations will be carried out. Analysis on the primary and secondary end point(s) will be carried out using a 2-sided $\chi^2$ test on proportions. The 95% CI on the odds ratio will be presented. Survival status during the 30-day follow-up will be analyzed showing Kaplan-Meier curves, and treatment differences will be compared by means of log-rank test. Subgroup analysis will be carried out for sex, age, and country. Potentially important prognostic factors for efficacy and safety will be explored and used as covariates in relative risk analysis by logistic regression or the Cox model. Serious adverse events will be tabulated per treatment group and analyzed using the $\chi^2$ test. Continuous safety monitoring (blinded) will also be done by the Data and Safety Monitoring Board (DSMB), as explained below.

Interim analyses are planned after recruitment of 25%, 50%, and 75% of the total number of patients. These analyses are made to allow sample size reassessment or early discontinuation of the trial because of efficacy or futility. For these reasons, the $\alpha$-spending functions
determining the boundary limits for the interim analysis are chosen to require an adjustment of the total \( P \) value by less than .003 (\( P = .047 \) for final analysis). Calculations for boundary limits and for sample size reassessments are made using East Software (Cytel, Cambridge, MA) or equivalent validated software.

The adjudication process and cleaning of the database postponed the second planned interim analysis, which was rescheduled to be performed on 625 (instead of 500) recruited patients. An approved amendment to the study protocol determined that if the second interim analysis on the first 625 patients does not indicate futility as a reason to stop enrollment, the third interim analysis, originally planned on 750 included patients, will not be performed and enrollment will proceed to the target study population of approximately 1,000 patients.

### Measures against bias

A computer-generated randomization scheme is used. Randomization is stratified by center and, within the centers, performed in blocks of 4 to ensure balanced distribution of the treatment groups. Randomization is performed centrally via the Internet, and treatment allocation is concealed from all investigators. In the ITT analysis, missing data for the primary outcome will be imputed according to the worst-case principle (end point reached). In case of large differences between per-protocol and ITT populations, an analysis of sensitivity using different methods for missing data replacement, including multiple imputation techniques, will be carried out. The reason for any code break is being documented at the site along with the date and the initials of the person breaking the code.

### Sample size/power calculations

Based on a meta-analysis of previous thrombolysis trials and on the largest randomized PE trial to date, it is estimated that the primary end point (death or hemodynamic collapse within 7 days) in the control group will be approximately 7%. A 2-group \( \chi^2 \) test (not continuity recorded) with a .047 2-sided significance level will have 80% power to detect the difference between a group placebo proportion, \( \pi_1 \), of 0.070 and a group tenecteplase proportion, \( \pi_2 \), of 0.030 (odds ratio of 0.411) when the sample size in each group is 474. Because the allocation ratio in the 2 groups will be equal to 1, the total number of patients in the study will need to be \( n = 948 \). Accordingly, the study plans to randomize approximately 1,000 patients.

### Administrative organization

The PEITHO is an independent, investigator-initiated trial with an academic sponsor (Département de la Recherche Clinique, Assistance Publique-Hôpitaux de Paris, France). The Steering Committee (listed in the online Appendix) consists of the study chairperson, the co-chairperson, and the principal investigators who act as national coordinators for each of the participating countries. Furthermore, nonvoting members include a representative of the Sponsor and representatives of the market authorization holder (MAH) of tenecteplase, Boehringer Ingelheim. The Steering Committee meets periodically to assess the progress, provide scientific input, and address policy issues and operational aspects of the protocol and recommendations of the DSMB. At the end of the trial, the Steering Committee will meet in a closed session (under the exclusion of the MAH and the Sponsor) to discuss the trial results. The results will then be presented to the Sponsor in a meeting immediately after the closed session.

To ensure data quality, an independent Critical Event Committee (CEC; online Appendix) is responsible for centralized and blinded adjudication of critical events (death, hemodynamic collapse, recurrent PE, major bleeding, and stroke). The adjudicated outcomes will be used in the interim and final statistical analysis. The internal rules of the CEC are described in a standardized CEC charter.

The independent DSMB (online Appendix) reviews safety data at regular intervals. Data are provided to the DSMB by a suitably qualified central safety processing group that assesses the category classification and seriousness of reported adverse events and their possible relation to the study drug. Serious adverse events are also transmitted to the study investigators, institutional ethics committees, and/or review boards as per local regulations. Safety analysis by the DSMB is planned after recruitment of 25%, 50%, and 75% of the total number of patients; the DSMB reports to the chairperson of the Steering Committee. The internal rules are described in a DSMB charter.

### Sources of funding

The study is being supported by public funding, specifically by grants from the French Government (Ministry of Health) and the German Government (Federal Ministry of Education and Research). In addition, the Sponsor has obtained the study drug (tenecteplase and placebo) and a grant from the MAH. The MAH is also involved in safety reporting to local authorities as per regulations (except for France, where this is entirely the responsibility of the Sponsor). According to the study protocol and as mentioned previously, representatives of the MAH may be present at the sessions of the Steering Committee as nonvoting members. Neither the MAH nor any other part of the industry is involved at any stage of data management and data analysis or may exert any influence on decisions to discontinue the trial due to futility or safety concerns.
Conclusions

With an expected enrollment of approximately 1,000 patients, PEITHO will be the largest thrombolysis trial ever performed in patients with acute PE. As of September 30, 2011, 793 patients have been enrolled in the study. A confirmation of the study hypothesis will help to expand the use of thrombolysis to normotensive patients who present with findings of acute RV dysfunction and myocardial injury. This increased use of thrombolysis may reduce the number of deaths or complications from PE. In addition, the trial will provide long-term follow-up data in this large patient population and determine whether thrombolytic treatment may prevent the development of chronic thromboembolic pulmonary hypertension. If, on the other hand, the hypothesis of PEITHO is rejected, normotensive patients with PE will no longer need to be exposed to the costly and potentially disabling or even life-threatening bleeding complications of thrombolytic treatment. In any case, we expect that PEITHO will help to resolve a 40-year-old debate on the management of acute PE and permit clear, evidence-based recommendations in favor of (or against) thrombolysis in submassive PE.

Disclosures

The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the manuscript, and its final contents.

References

Appendix

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