

## ORIGINAL ARTICLE

# Fibrinolysis for Patients with Intermediate-Risk Pulmonary Embolism

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## ABSTRACT

**BACKGROUND**

The role of fibrinolytic therapy in patients with intermediate-risk pulmonary embolism is controversial.

**METHODS**

In a randomized, double-blind trial, we compared tenecteplase plus heparin with placebo plus heparin in normotensive patients with intermediate-risk pulmonary embolism. Eligible patients had right ventricular dysfunction on echocardiography or computed tomography, as well as myocardial injury as indicated by a positive test for cardiac troponin I or troponin T. The primary outcome was death or hemodynamic decompensation (or collapse) within 7 days after randomization. The main safety outcomes were major extracranial bleeding and ischemic or hemorrhagic stroke within 7 days after randomization.

**RESULTS**

Of 1006 patients who underwent randomization, 1005 were included in the intention-to-treat analysis. Death or hemodynamic decompensation occurred in 13 of 506 patients (2.6%) in the tenecteplase group as compared with 28 of 499 (5.6%) in the placebo group (odds ratio, 0.44; 95% confidence interval, 0.23 to 0.87;  $P=0.02$ ). Between randomization and day 7, a total of 6 patients (1.2%) in the tenecteplase group and 9 (1.8%) in the placebo group died ( $P=0.42$ ). Extracranial bleeding occurred in 32 patients (6.3%) in the tenecteplase group and 6 patients (1.2%) in the placebo group ( $P<0.001$ ). Stroke occurred in 12 patients (2.4%) in the tenecteplase group and was hemorrhagic in 10 patients; 1 patient (0.2%) in the placebo group had a stroke, which was hemorrhagic ( $P=0.003$ ). By day 30, a total of 12 patients (2.4%) in the tenecteplase group and 16 patients (3.2%) in the placebo group had died ( $P=0.42$ ).

**CONCLUSIONS**

In patients with intermediate-risk pulmonary embolism, fibrinolytic therapy prevented hemodynamic decompensation but increased the risk of major hemorrhage and stroke. (Funded by the Programme Hospitalier de Recherche Clinique in France and others; PEITHO EudraCT number, 2006-005328-18; ClinicalTrials.gov number, NCT00639743.)

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\*A complete list of the Pulmonary Embolism Thrombolysis (PEITHO) trial investigators is provided in the Supplementary Appendix, available at NEJM.org.

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**A**CUTE PULMONARY EMBOLISM OCCURS frequently and may cause death or serious disability.<sup>1</sup> Case fatality rates vary widely,<sup>2,3</sup> but approximately 10% of all patients with acute pulmonary embolism die within 3 months after the diagnosis.<sup>4,5</sup>

Acute right ventricular pressure overload at diagnosis is an important determinant of the severity and early clinical outcome of pulmonary embolism.<sup>6</sup> High-risk pulmonary embolism<sup>7</sup> is characterized by overt hemodynamic instability and warrants immediate advanced therapy, including consideration of fibrinolysis. In contrast, for patients presenting without systemic hypotension or hemodynamic compromise, standard anticoagulation is generally considered adequate treatment.<sup>8</sup> However, patients who have acute right ventricular dysfunction and myocardial injury without overt hemodynamic compromise may be at intermediate risk for an adverse early outcome.<sup>7,9</sup> These patients (referred to henceforth as patients with intermediate-risk pulmonary embolism) may also be candidates for early reperfusion therapy.<sup>10</sup>

Randomized clinical trials that test fibrinolytic agents versus heparin alone in patients with acute pulmonary embolism have enrolled, in total, fewer than 1000 patients over the past 40 years.<sup>11</sup> Although these drugs have been shown to rapidly improve hemodynamic variables,<sup>12</sup> their effects on the clinical outcome, particularly in patients without hemodynamic instability at presentation, have not been determined. The Pulmonary Embolism Thrombolysis (PEITHO) trial was designed to investigate the clinical efficacy and safety of fibrinolytic therapy with a single-bolus injection of tenecteplase, in addition to standard anticoagulation therapy with heparin, in normotensive patients with acute pulmonary embolism and an intermediate risk of an adverse outcome.

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## METHODS

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### STUDY DESIGN

We performed a multicenter, double-blind, placebo-controlled randomized trial.<sup>13</sup> The trial was initiated by the investigators and sponsored by Direction de la Recherche Clinique at Assistance Publique-Hôpitaux de Paris, a consortium of university hospitals in Paris. Trial funding was pro-

vided by Programme Hospitalier de Recherche Clinique in France, by the Federal Ministry of Education and Research in Germany, and by a grant from Boehringer Ingelheim. None of the trial funders had any role in the design or conduct of the trial, the analysis of the data, or the preparation of the manuscript.

The trial protocol was written by three of the academic principal investigators and reviewed, modified, and approved by the trial steering committee (see the Supplementary Appendix, available with the full text of this article at NEJM.org). The final protocol was approved by the ethics review board of each study site. An independent data and safety monitoring board periodically reviewed the study outcomes. A clinical research organization appointed by the sponsor was responsible for data collection and monitoring at the participating sites. Data were gathered with the use of electronic case report forms and kept at Unité de Recherche Clinique (Lariboisière Hospital, Université Paris 7) under the supervision of the trial statistician, who independently performed all statistical analyses before the code for concealing the study assignments was broken.

The principal investigators had unrestricted access to the data after the database was locked. The two coauthors of the steering committee and the trial statistician wrote the first draft of the manuscript. The members of the steering committee were involved in the analysis of the data; reviewed, amended, and approved the early version of the manuscript; and made the decision to submit the manuscript for publication. All members of the steering committee vouch for the integrity and completeness of the data and for the fidelity of this report to the trial protocol, available at NEJM.org. Assistance Publique-Hôpitaux de Paris and Boehringer Ingelheim signed a mutual confidentiality agreement on initiation of the study, and an early version of the manuscript was sent to a representative of Boehringer Ingelheim before submission.

### PATIENTS

Patients were eligible for the study if they met all the following criteria: an age of 18 years or older, objectively confirmed acute pulmonary embolism with an onset of symptoms 15 days or less before randomization, right ventricular dysfunction con-

firmed by echocardiography or spiral computed tomography (CT) of the chest, and myocardial injury confirmed by a positive test for troponin I or troponin T.<sup>13</sup> The full inclusion and exclusion criteria for the study, including the criteria for right ventricular dysfunction, are listed in the Supplementary Appendix. Written informed consent was obtained from all patients before randomization.

#### RANDOMIZATION AND TREATMENT

Eligible patients underwent central randomization with the use of a computerized Internet-based system. Randomization was stratified by center and, within centers, was performed in blocks to ensure balanced distribution of the treatment groups. We required that randomization be performed within 2 hours after the investigator became aware of the presence of both right ventricular dysfunction (by receiving the echocardiography or CT report) and myocardial injury (by receiving a report of a positive cardiac troponin test).

Patients who were assigned to undergo fibrinolysis received a single weight-based intravenous bolus (given over a period of 5 to 10 seconds) of the fibrinolytic agent tenecteplase. The dose ranged from 30 mg to 50 mg, depending on body weight (Table S1 in the Supplementary Appendix).<sup>13</sup> Patients assigned to placebo were given a single intravenous bolus of the same volume and appearance as the bolus of tenecteplase.

The administration of unfractionated heparin was started as an intravenous bolus immediately after randomization in both groups; the bolus was not administered to patients who had already received an intravenous bolus or infusion of unfractionated heparin. The initial bolus of unfractionated heparin was also omitted in patients receiving a therapeutic dose of low-molecular-weight heparin or fondaparinux, and the start of the infusion was delayed until 12 hours after the last injection of low-molecular-weight heparin or until 24 hours after the last injection of fondaparinux. The heparin infusion rate was adjusted to achieve and maintain an activated partial-thromboplastin time that was 2.0 to 2.5 times the upper limit of the normal range, corresponding to therapeutic heparin levels (equivalent to factor Xa inhibition of 0.3 to 0.7 IU per milliliter). The use of anticoagulant agents other than un-

fractionated heparin was not allowed until 48 hours after randomization.

#### FOLLOW-UP AND OUTCOME ASSESSMENT

All patients were followed for 30 days and were evaluated for death, hemodynamic decompensation (or collapse), bleeding, stroke, recurrent pulmonary embolism, and serious adverse events. All efficacy and safety outcomes were adjudicated by an independent clinical-events committee whose members were unaware of the treatment-group assignments.

The primary efficacy outcome was the clinical composite of death from any cause or hemodynamic decompensation (or collapse) within 7 days after randomization. The secondary outcomes included death within 7 days after randomization, hemodynamic decompensation within 7 days, confirmed symptomatic recurrence of pulmonary embolism within 7 days, death within 30 days, and major adverse events within 30 days.<sup>13</sup> Safety outcomes were defined as ischemic or hemorrhagic stroke (including hemorrhagic conversion of ischemic stroke) within 7 days after randomization, extracranial major (moderate or severe) bleeding within 7 days, and serious adverse events within 30 days. The definitions of hemodynamic decompensation and bleeding events are provided in the Supplementary Appendix.

#### STATISTICAL ANALYSIS

The main efficacy and safety analyses were based on all events that occurred in the intention-to-treat population, defined as all patients who underwent randomization and who signed the informed consent form. In addition, analysis of safety outcomes was performed in the safety population, which was defined as all patients who received the study drug. The primary efficacy outcome was analyzed by means of a two-sided chi-square test of proportions. A similar analysis was performed for each of the secondary outcomes; all results were for the intention-to-treat population. All tests were performed with the use of SAS software, version 9.2 (SAS Institute). Prespecified subgroup analyses included age ( $\leq 75$  years vs.  $> 75$  years), sex, and country of recruitment. Details of the sample-size estimation and the interim analyses are given in the Supplementary Appendix.

## RESULTS

## PATIENTS

From November 2007 through July 2012, a total of 1006 patients were enrolled at 76 sites in 13 countries. Of these patients, 506 were randomly assigned to treatment with tenecteplase plus unfractionated heparin, and 500 were randomly assigned to placebo plus unfractionated heparin (Fig. S1 in the Supplementary Appendix). The

signed informed consent form of 1 patient in the placebo group could not be found, and this patient was therefore excluded from all data analyses; thus, the intention-to-treat population consisted of 1005 patients. All but 5 patients received the assigned study drug.

The demographic data, clinical status at baseline, and medical history of the patients were well matched between the two treatment groups (Table 1). The median age in the study popula-

**Table 1. Characteristics of the Patients at Baseline.\***

Characteristic	Tenecteplase (N = 506)	Placebo (N = 499)
<b>Demographic data</b>		
Age — yr		
Mean	66.5±14.7	65.8±15.9
Median (interquartile range)	70.0 (59.0–77.0)	70.0 (57.0–78.0)
Male sex — no. (%)	242 (47.8)	231 (46.3)
Mean weight — kg	82.5±17.9	82.6±18.2
<b>Clinical status</b>		
Systolic blood pressure — mm Hg		
Mean	130.8±18.3	131.3±18.5
Missing data — no. (%)	3 (0.6)	4 (0.8)
Heart rate — beats per min		
Mean	94.5±17.1	92.3±16.7
Missing data — no. (%)	6 (1.2)	7 (1.4)
Respiratory rate — breaths per min		
Mean	21.8±5.8	21.6±5.7
Missing data — no. (%)	95 (18.8)	107 (21.4)
Oxygen treatment — no. (%)	436 (86.2)	421 (84.4)
<b>Medical history</b>		
Chronic pulmonary disease — no. (%)		
No	26 (5.1)	34 (6.8)
Missing data	6 (1.2)	6 (1.2)
Chronic heart failure — no. (%)		
No	21 (4.2)	26 (5.2)
Missing data	5 (1.0)	7 (1.4)
Previous venous thromboembolism — no. (%)		
No	126 (24.9)	147 (29.5)
Missing data	2 (0.4)	9 (1.8)
Active cancer — no. (%)		
No	41 (8.1)	32 (6.4)
Missing data	20 (4.0)	20 (4.0)
Surgery or major trauma in previous month — no. (%)		
No	31 (6.1)	27 (5.4)
Missing data	1 (0.2)	4 (0.8)
Immobilization — no. (%)		
No	55 (10.9)	56 (11.2)
Missing data	5 (1.0)	9 (1.8)
Estrogen use — no. (%)		
No	30 (5.9)	33 (6.6)
Missing data	7 (1.4)	5 (1.0)

\* Plus-minus values are means ±SD. Between-group differences in the characteristics listed here were not significant; for heart rate, P=0.05.

**Table 2. Diagnostic Evaluation and Initial Management.\***

Characteristic	Tenecteplase (N = 506) no. (%)	Placebo (N = 499) no. (%)
Confirmation of pulmonary embolism		
CT	480 (94.9)	472 (94.6)
Ventilation–perfusion lung scanning	31 (6.1)	35 (7.0)
Pulmonary angiography	6 (1.2)	8 (1.6)
Confirmation of right ventricular dysfunction		
Echocardiography	278 (54.9)	255 (51.1)
CT	74 (14.6)	72 (14.4)
Both echocardiography and CT	154 (30.4)	172 (34.5)
Confirmation of myocardial injury		
Elevated cardiac troponin I	364 (71.9)	361 (72.3)
Elevated cardiac troponin T	164 (32.4)	164 (32.9)
Either troponin I or troponin T elevation	502 (99.2)	494 (99.0)
Low-molecular-weight heparin or fondaparinux given before randomization	170 (33.6)	133 (26.6)

\* Between-group differences in the characteristics listed here were not significant except for low-molecular-weight heparin or fondaparinux given before randomization ( $P=0.02$ ).

tion was 70 years. All patients were normotensive at randomization. In the vast majority of cases, the diagnosis of pulmonary embolism was confirmed by CT pulmonary angiography (Table 2). Right ventricular dysfunction was diagnosed by echocardiography or CT in all cases, and myocardial injury was confirmed with a test for cardiac troponin I or troponin T in all but 9 patients. Low-molecular-weight heparin or fondaparinux was administered before randomization in 303 patients (30.1%), and the remaining patients received unfractionated heparin before randomization or at the time of randomization. The proportions of patients in whom the activated partial-thromboplastin time was within, above, and below the target range initially and within the first 24 hours after the administration of the study drug are shown in Table S2 in the Supplementary Appendix.

#### EFFICACY OUTCOMES

Between randomization and day 7, the primary efficacy outcome occurred in 13 patients (2.6%)

in the tenecteplase group as compared with 28 patients (5.6%) in the placebo group (odds ratio, 0.44; 95% confidence interval [CI], 0.23 to 0.87;  $P=0.02$ ) (Table 3). Six patients (1.2%) in the tenecteplase group and 9 patients (1.8%) in the placebo group died between randomization and day 7 ( $P=0.42$ ), and hemodynamic decompensation or collapse occurred in 8 patients (1.6%) in the tenecteplase group and 25 patients (5.0%) in the placebo group ( $P=0.002$ ). Persistent hypotension or a drop in blood pressure was recorded in 8 patients in the tenecteplase group and 18 patients in the placebo group, catecholamines were administered to 3 patients in the tenecteplase group and 14 patients in the placebo group, and 1 patient in the tenecteplase group and 5 patients in the placebo group required cardiopulmonary resuscitation. The causes of death at day 7 are shown in Table S3 in the Supplementary Appendix.

Eight patients in the tenecteplase group required mechanical ventilation, as compared with 15 patients in the placebo group. More patients in the placebo group than in the tenecteplase group underwent open-label rescue fibrinolysis (Table 3); in accordance with the protocol, this treatment was administered only after the primary outcome had occurred, with the exception of nine patients. The age, treatment assignment (tenecteplase or placebo), and outcomes for all patients who underwent rescue fibrinolysis are shown in Table S4 in the Supplementary Appendix.

By day 30 after randomization, 12 patients (2.4%) in the tenecteplase group had died, as compared with 16 patients (3.2%) in the placebo group ( $P=0.42$ ) (Table 3). The causes of death at day 30 are shown in Table S3 in the Supplementary Appendix.

#### SAFETY OUTCOMES

Major bleeding, as defined according to the criteria of the International Society on Thrombosis and Haemostasis,<sup>14</sup> occurred between randomization and day 7 in 58 patients (11.5%) in the tenecteplase group and 12 patients (2.4%) in the placebo group (Table 4). Major extracranial bleeding occurred in 32 patients (6.3%) in the tenecteplase group and 6 patients (1.2%) in the placebo group ( $P<0.001$ ). (Data for the safety population are provided in Table S5 in the Supplementary Appendix.)

Overall, 12 patients (2.4%) in the tenecteplase

**Table 3. Efficacy Outcomes.\***

Outcome	Tenecteplase (N = 506)	Placebo (N = 499)	Odds Ratio (95% CI)	P Value
Primary outcome — no. (%)	13 (2.6)	28 (5.6)	0.44 (0.23–0.87)	0.02
Death from any cause	6 (1.2)	9 (1.8)	0.65 (0.23–1.85)	0.42
Hemodynamic decompensation	8 (1.6)	25 (5.0)	0.30 (0.14–0.68)	0.002
Time between randomization and primary efficacy outcome — days	1.54±1.71	1.79±1.60		
Recurrent pulmonary embolism between randomization and day 7 — no. (%)	1 (0.2)	5 (1.0)	0.20 (0.02–1.68)	0.12
Fatal	0	3 (0.6)		
Nonfatal	1 (0.2)	2 (0.4)		
Other in-hospital complications and procedures — no. (%)				
Mechanical ventilation	8 (1.6)	15 (3.0)		
Surgical embolectomy	1 (0.2)	2 (0.4)		
Catheter thrombus fragmentation	1 (0.2)	0 (0.0)		
Vena cava interruption	5 (1.0)	1 (0.2)		
Thrombolytic treatment other than study medication	4 (0.8)	23 (4.6)		
Death from any cause between randomization and day 30 — no. (%)	12 (2.4)	16 (3.2)	0.73 (0.34–1.57)	0.42
Patient still hospitalized at day 30 — no. (%)	59 (11.7)	50 (10.0)		
Rehospitalization between randomization and day 30 — no. (%)	22 (4.4)	15 (3.0)		

\* Plus–minus values are means ±SD. Odds ratios and P values are provided for efficacy outcomes that were prespecified in the trial protocol.

**Table 4. Safety Outcomes in the Intention-to-Treat Population.\***

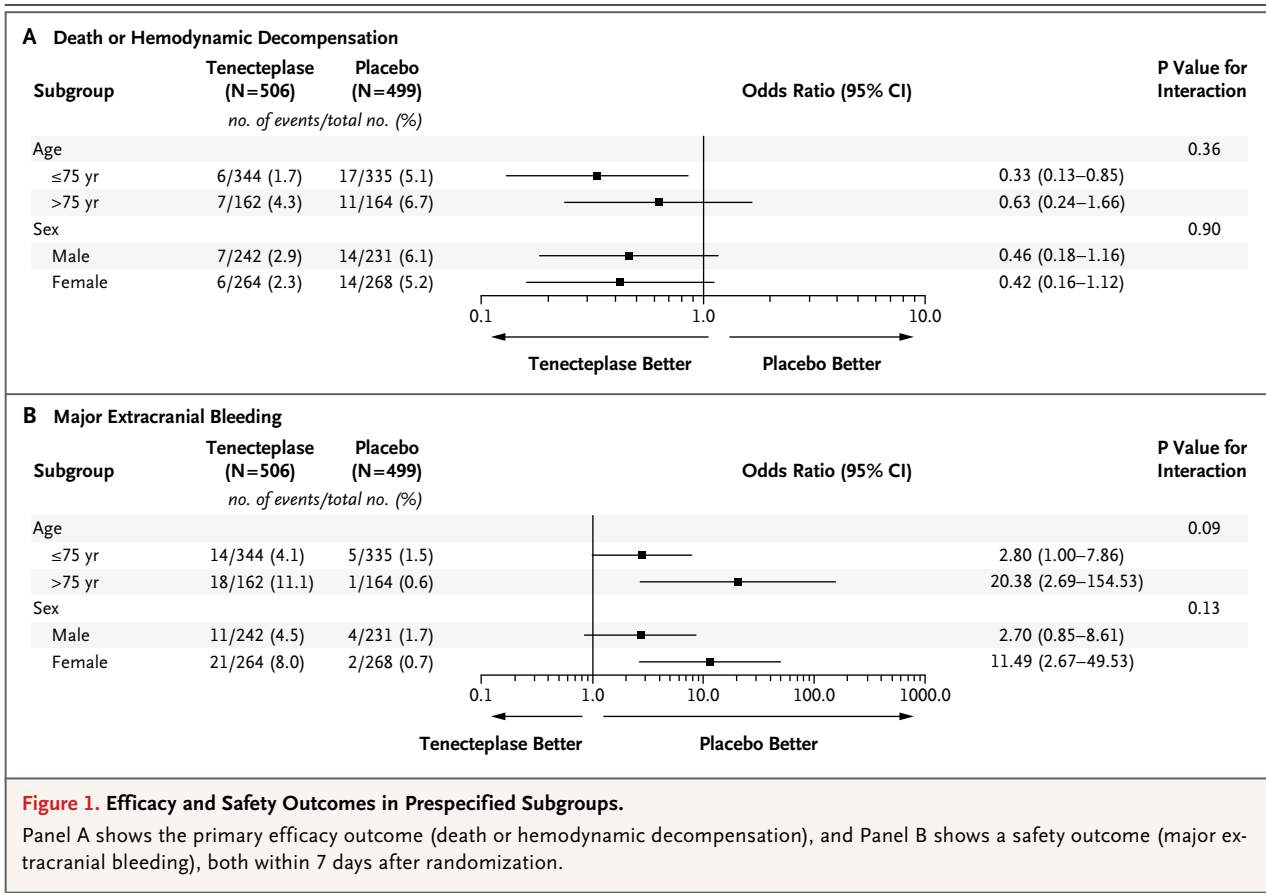
Outcome	Tenecteplase (N = 506)	Placebo (N = 499)	Odds Ratio (95% CI)	P Value
	<i>no. (%)</i>			
Bleeding between randomization and day 7				
Major extracranial bleeding	32 (6.3)	6 (1.2)	5.55 (2.3–13.39)	<0.001
Minor bleeding	165 (32.6)	43 (8.6)		
Major bleeding†	58 (11.5)	12 (2.4)		
Stroke between randomization and day 7	12 (2.4)	1 (0.2)	12.10 (1.57–93.39)	0.003
Ischemic stroke	2 (0.4)	0		
Hemorrhagic stroke‡	10 (2.0)	1 (0.2)		
Serious adverse events between randomization and day 30	55 (10.9)	59 (11.8)	0.91 (0.62–1.34)	0.63

\* Odds ratios and P values are provided for efficacy and safety outcomes that were prespecified in the trial protocol.

† Major bleeding was defined according to the criteria of the International Society on Thrombosis and Haemostasis.

‡ Hemorrhagic stroke included hemorrhagic conversion of ischemic stroke.





group had a stroke within 7 days after randomization; in 10 of these patients, the stroke was hemorrhagic. By comparison, only 1 patient in the placebo group had a stroke ( $P=0.003$ ), and it was a hemorrhagic stroke (Table 4). The characteristics and 30-day outcomes of all patients who had a stroke are shown in Table S6 in the Supplementary Appendix. Six of the 10 patients in the tenecteplase group who had a hemorrhagic stroke were alive 30 days after randomization, corresponding to a case fatality rate of 40%; mild or moderate disability persisted in most of the survivors.

#### PATIENT SUBGROUPS

Prespecified subgroups were defined by age ( $\leq 75$  years vs.  $>75$  years), sex, and country of recruitment. The last subgroup analysis was not performed because some countries had only a small number of patients who would have been included.

The primary efficacy outcome and the rate of extracranial major bleeding in the prespecified subgroups of age and sex are shown in Figure 1. Among patients who were 75 years of age or younger, the primary efficacy outcome occurred in 1.7% of the patients assigned to tenecteplase and 5.1% of those assigned to placebo, corresponding to an odds ratio of 0.33 (95% CI, 0.13 to 0.85) in favor of tenecteplase; by comparison, the odds ratio was 0.63 (95% CI, 0.24 to 1.66) among patients older than 75 years of age. However, on the basis of interaction testing, this difference was not significant ( $P=0.36$ ) (Fig. 1A). Among the patients treated with tenecteplase, older patients had a higher rate of major extracranial bleeding than did younger patients; the difference was not significant ( $P=0.09$ ). The rates of these efficacy and safety outcomes also did not differ significantly between men and women. The results of additional subgroup analyses of the primary

efficacy outcome, which were not prespecified, are shown in Figure S2 in the Supplementary Appendix.

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## DISCUSSION

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In the PEITHO trial, patients with intermediate-risk pulmonary embolism who were treated with standard anticoagulation had a 5.6% incidence of death or hemodynamic decompensation (the primary efficacy outcome) within the first 7 days after randomization. A single-bolus injection of the fibrinolytic agent tenecteplase, in a weight-based dose, resulted in a significantly lower risk of the primary outcome (2.6%). Fibrinolytic treatment was associated with a 2.0% rate of hemorrhagic stroke and a 6.3% rate of major extracranial hemorrhage.

Normotensive patients with pulmonary embolism may have an elevated risk of early death or major complications if they present with right ventricular dysfunction or injury to the myocardium as a result of acute pressure overload.<sup>6,15-20</sup> Fibrinolytic treatment promptly reduces pulmonary-artery resistance and pressure,<sup>21</sup> and trials that included patients with hemodynamic compromise,<sup>11</sup> as well as recently published epidemiologic data,<sup>22</sup> support its use in patients with massive or high-risk pulmonary embolism. In contrast, the efficacy of fibrinolytic agents in improving the outcome for patients with intermediate-risk pulmonary embolism has remained controversial because of the lack of trials of adequate size with a focus on this patient population. Our results indicate that prompt fibrinolysis can reduce the risk of hemodynamic decompensation or death in normotensive patients who have acute pulmonary embolism with right ventricular dysfunction, as indicated by echocardiography or CT, and myocardial injury, as indicated by a positive cardiac troponin test.

In the present trial, the efficacy of thrombolysis was mainly driven by the prevention of hemodynamic decompensation; the study was not powered to detect differences in rates of death, which occurred relatively infrequently in the two treatment groups. Moreover, our definition of hemodynamic decompensation or collapse included a persistent, isolated drop in systolic blood pressure, which could be of questionable clinical significance. Nevertheless, 14 patients with

hemodynamic decompensation in the placebo group needed inotropic support and 5 underwent cardiopulmonary resuscitation. It is possible that the prognosis for some of these patients would have been worse if they had not been closely monitored and promptly treated when decompensation occurred; this notion is supported by the higher rates of death reported in noninterventional cohort studies focused on this patient population.<sup>10</sup>

Fibrinolytic treatment is known to carry a risk of major bleeding, including intracranial hemorrhage. In two analyses of pooled data from trials of various fibrinolytic agents and regimens in patients with pulmonary embolism, intracranial bleeding rates were 1.8% and 2.2%.<sup>23,24</sup> The results of the present study, involving single-bolus tenecteplase, confirm these findings: the risk of hemorrhagic stroke was 2.0% among hemodynamically stable patients with acute pulmonary embolism.

In previous studies, increasing age and the presence of coexisting conditions have been associated with a higher risk of bleeding complications.<sup>25</sup> Our findings also suggest that fibrinolysis is associated with a lower risk of bleeding in younger patients than in patients over 75 years of age, although this difference was not significant. In a recently published trial of tenecteplase treatment in patients with ST-segment elevation myocardial infarction, there were no cases of intracranial hemorrhage when the dose was reduced by 50% in patients 75 years of age or older.<sup>26</sup> A reduced-dose strategy might also be beneficial in patients with intermediate-risk pulmonary embolism and warrants further investigation.<sup>27</sup> An alternative approach, consisting of ultrasound-assisted local administration of small doses of a fibrinolytic agent by means of a catheter, is currently being investigated (ClinicalTrials.gov number, NCT01513759), and a recently published randomized trial of this approach in 59 patients showed a promising safety profile.<sup>28</sup>

In conclusion, in normotensive patients with intermediate-risk pulmonary embolism, the composite primary outcome of early death or hemodynamic decompensation was reduced after treatment with a single intravenous bolus of tenecteplase. However, tenecteplase was also associated with a significant increase in the risk of



intracranial and other major bleeding. Therefore, great caution is warranted when considering fibrinolytic therapy for hemodynamically stable patients with pulmonary embolism, right ventricular dysfunction, and a positive cardiac troponin test.

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#### APPENDIX

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