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Impact of Thrombolytic Therapy on the Long-Term Outcome of Intermediate-Risk Pulmonary Embolism

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ABSTRACT

BACKGROUND The long-term effect of thrombolytic treatment of pulmonary embolism (PE) is unknown.

OBJECTIVES This study investigated the long-term prognosis of patients with intermediate-risk PE and the effect of thrombolytic treatment on the persistence of symptoms or the development of late complications.

METHODS The PEITHO (Pulmonary Embolism Thrombolysis) trial was a randomized (1:1) comparison of thrombolysis with tenecteplase versus placebo in normotensive patients with acute PE, right ventricular (RV) dysfunction on imaging, and a positive cardiac troponin test result. Both treatment arms received standard anticoagulation. Long-term follow-up was included in the third protocol amendment; 28 sites randomizing 709 of the 1,006 patients participated.

RESULTS Long-term (median 37.8 months) survival was assessed in 353 of 359 (98.3%) patients in the thrombolysis arm and in 343 of 350 (98.0%) in the placebo arm. Overall mortality rates were 20.3% and 18.0%, respectively ($p = 0.43$). Between day 30 and long-term follow-up, 65 deaths occurred in the thrombolysis arm and 53 occurred in the placebo arm. At follow-up examination of survivors, persistent dyspnea (mostly mild) or functional limitation was reported by 36.0% versus 30.1% of the patients ($p = 0.23$). Echocardiography (performed in 144 and 146 patients randomized to thrombolysis and placebo, respectively) did not reveal significant differences in residual pulmonary hypertension or RV dysfunction. Chronic thromboembolic pulmonary hypertension (CTEPH) was confirmed in 4 (2.1%) versus 6 (3.2%) cases ($p = 0.79$).

CONCLUSIONS Approximately 33% of patients report some degree of persistent functional limitation after intermediate-risk PE, but CTEPH is infrequent. Thrombolytic treatment did not affect long-term mortality rates, and it did not appear to reduce residual dyspnea or RV dysfunction in these patients. (Pulmonary Embolism Thrombolysis study [PEITHO]; NCT00639743) (J Am Coll Cardiol 2017;69:1536–44) © 2017 by the American College of Cardiology Foundation.

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Randomized controlled trials on anticoagulation and reperfusion treatment helped to develop and optimize risk-adjusted management strategies for the acute phase of pulmonary embolism (PE) (1). In contrast, however, little if any progress has been made in testing whether specific therapeutic interventions may increase long-term survival and prevent late sequelae of PE. In particular, the widespread belief among clinicians that early thrombolytic treatment may, by rapidly and effectively reducing the thrombotic burden, minimize the risk of persistent pulmonary hypertension and possibly (right-sided) heart failure over the long term, has not been prospectively investigated in a controlled randomized setting involving a large patient population.

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The international PEITHO (Pulmonary Embolism Thrombolysis) trial compared a single intravenous bolus of the thrombolytic agent tenecteplase plus heparin with placebo plus heparin in 1,006 patients with confirmed PE, right ventricular (RV) dysfunction detected by echocardiography or computed tomographic pulmonary angiography, and a positive troponin I or T test result (2). In the thrombolysis arm of the trial, the primary outcome

ABBREVIATIONS AND ACRONYMS

CTEPH = chronic thromboembolic pulmonary hypertension

PE = pulmonary embolism

RV = right ventricular

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TABLE 1 Baseline Characteristics of Patients Randomized by the Sites Participating in the 24-Month Follow-Up

	Tenecteplase (N = 359)	Placebo (N = 350)
Demographic data		
Age, yrs		
Mean	66.7 ± 15.1	66.4 ± 16.0
Median	70.0 (59.0-78.0)	71.0 (58.0-78.0)
Male	169 (47.1)	159 (45.4)
Mean weight, kg	82.6 ± 18.7	81.0 ± 17.1
Clinical status		
Systolic blood pressure, mm Hg	130.6 ± 17.9	132.3 ± 18.4
Missing data	3 (0.8)	3 (0.9)
Heart rate, beats/min	94.9 ± 17.2	91.5 ± 16.7
Missing data	6 (1.7)	6 (1.7)
Respiratory rate, respirations/min	21.8 ± 5.8	21.7 ± 5.6
Missing data	71 (19.8)	73 (20.9)
Oxygen treatment	315 (87.7)	298 (85.1)
Medical history or concomitant disease		
Chronic pulmonary disease	20 (5.6)	21 (6.0)
Missing data	4 (1.1)	4 (1.1)
Chronic heart failure	18 (5.0)	20 (5.7)
Missing data	4 (1.1)	3 (0.9)
Previous venous thromboembolism	84 (23.4)	93 (26.6)
Missing data	1 (0.3)	5 (1.4)
Active cancer	34 (9.5)	24 (6.9)
Missing data	11 (3.1)	8 (2.3)
Surgery or major trauma in the previous month	26 (7.2)	21 (6.0)
Missing data	1 (0.3)	2 (0.6)
Immobilization	40 (11.1)	37 (10.6)
Missing data	4 (1.1)	8 (2.3)
Estrogen use	19 (5.3)	22 (6.3)
Missing data	6 (1.7)	4 (1.1)

Values are mean ± SD, median (interquartile range), or n (%).

of all-cause death or hemodynamic decompensation within 7 days occurred less frequently than in the trial arm receiving heparin alone. In parallel, however, a higher incidence of hemorrhagic stroke and major nonintracranial bleeding was observed in patients allocated to tenecteplase than in the placebo arm of the trial (2). Following an amendment of the study protocol, 28 of the PEITHO sites having randomized approximately 70% of the entire study population consented to obtain 2-year survival data and prospectively conduct long-term clinical and echocardiographic follow-up of their patients. The present report, which summarizes these findings, may help to revisit the debate on the possible impact of thrombolysis on the long-term prognosis of patients after acute PE.

METHODS

PATIENT POPULATION, STUDY DESIGN, AND 30-DAY FOLLOW-UP. PEITHO was a multicenter, double-blind, placebo-controlled randomized trial. The study design has been described previously (3). Briefly, patients were eligible for the study if they met all the following criteria: age 18 years or older; objectively confirmed acute PE with first symptoms 15 days or less before randomization; RV dysfunction confirmed by echocardiography or spiral computed tomography of the chest; and myocardial injury confirmed by a positive troponin I or T test result. Eligible patients were centrally randomized using a computerized Internet-based system, and randomization was stratified by center. The protocol required randomization to be performed within 2 h after the investigator became aware of the presence of both RV dysfunction (by receiving the echocardiography or computed tomography report) and myocardial injury (by receiving a positive cardiac troponin test result).

Patients who were assigned to thrombolysis received a single weight-based intravenous bolus (administered over 5 to 10 s) of the thrombolytic agent tenecteplase. Patients assigned to placebo were administered a single intravenous bolus of the same volume and appearance. Unfractionated heparin was started in both arms of the trial as an intravenous bolus followed by infusion at a rate adjusted to achieve and maintain an activated partial thromboplastin time 2.0 to 2.5 times that of control. The use of anticoagulant agents other than unfractionated heparin was not allowed until 48 h after randomization; after that time, treatment with anticoagulant agents was continued according to local practice. The primary efficacy outcome was defined as the clinical composite of all-cause death or hemodynamic decompensation (or collapse) within 7 days of randomization. All patients were followed up for 30 days and were evaluated for death, hemodynamic decompensation (or collapse), bleeding, stroke, recurrent PE, and serious adverse events.

LONG-TERM FOLLOW-UP AND OUTCOMES ASSESSMENT. The third protocol amendment of the PEITHO trial, which focused on the long-term follow-up of randomized patients, was approved by the central ethics committee in March 2012. The patients' vital, clinical, and hemodynamic status was recorded 24 months or later after randomization. Clinical and (whenever possible) echocardiographic assessment was performed during an appointment at the participating center. If the assessment was performed earlier, follow-up was repeated at or after month 24. If the patient had died, the date and primary cause of death were recorded by contacting the patient's physician. In patients whose symptoms and/or echocardiogram indicated pulmonary hypertension,

further diagnostic work-up was performed as recommended by guidelines available at the time of the trial (1,4). The diagnostic work-up and management of chronic thromboembolic pulmonary hypertension (CTEPH) were considered standard medical care and were not part of the study protocol.

STATISTICAL ANALYSIS. The statistical analysis of the PEITHO trial has been described previously (2,3). In the present study, the basis of the analysis of the patients' long-term outcome consisted of events that occurred in the intention-to-treat population, defined as all randomized patients who signed the informed consent form and participated in the follow-up at the 28 sites. Analysis of the long-term mortality rates in the 2 treatment arms, and of the patients' clinical and echocardiographic parameters at long-term follow-up, was carried out using a 2-sided chi-square test of proportions. In addition, Kaplan-Meier curves representing survival estimates were compared using log-rank statistics. In patients who were alive on the date of the last contact with the study site, the date of this contact was the censoring date. For continuous variables, the Student *t* test was used for comparison of means. All results are presented in the intention-to-treat population. All tests were performed using SAS software version 9.2 (SAS Institute, Cary, North Carolina).

RESULTS

BASELINE CHARACTERISTICS OF STUDY PATIENTS AND 2-YEAR MORTALITY RATE. Between November 2007 and July 2012, 1,006 patients were enrolled at 76 sites in 13 countries. The intention-to-treat population consisted of 1,005 patients, 506 randomly assigned to treatment with tenecteplase plus unfractionated heparin and 499 randomly assigned to placebo plus unfractionated heparin. All but 5 patients received the assigned study drug. Overall, 28 PEITHO study sites, which had randomized a total of 709 patients, participated in the long-term follow-up (median 37.8 months; interquartile range: 24.6 to 54.8 months). At these sites, the survival rate and causes of death were assessed in 353 of 359 (98.3%) patients in the tenecteplase arm of the trial and in 343 of 350 (98.0%) in the placebo arm. The demographic data, clinical status at baseline, and medical history of these patients are shown in Table 1. Comparison of baseline parameters between the patients followed over the long term and analyzed in the present study and the subpopulation of "nonfollowed" patients did not reveal significant differences between the 2 treatment arms, with the exception of body weight and a history of previous venous thromboembolism (Table 2).

TABLE 2 Comparison of Baseline Characteristics Between Patients Who Did and Those Who Did Not Participate in the 24-Month Follow-Up

	With 24-Month Follow-Up (N = 709)	Without 24-Month Follow-Up (N = 296)	p Value
Demographic data			
Age, yrs			
Mean	66.6 ± 15.5	65.2 ± 14.7	0.184
Median	70.0 (58.0–78.0)	67.0 (57.0–76.5)	
Male,	328 (46.3)	145 (49.0)	0.430
Mean body weight, kg	81.8 ± 17.9	84.4 ± 18.3	0.043
Clinical status			
Systolic blood pressure, mm Hg	131.5 ± 18.2	130.1 ± 18.9	0.282
Missing data	6 (0.8)	1 (0.3)	
Heart rate, beats/min	93.2 ± 17.0	93.9 ± 16.7	0.547
Missing data	12 (1.7)	1 (0.3)	
Respiratory rate, respirations/min	21.7 ± 5.7	21.5 ± 5.8	0.594
Missing data	144 (20.3)	58 (19.6)	
Oxygen treatment	613 (86.5)	244 (82.4)	0.101
Medical history or concomitant disease			
Chronic pulmonary disease	41 (5.8)	19 (6.4)	0.692
Missing data	8 (1.1)	4 (1.4)	
Chronic heart failure	38 (5.4)	9 (3.0)	0.117
Missing data	7 (1.0)	5 (1.7)	
Previous venous thromboembolism	177 (25.0)	96 (32.4)	0.012
Missing data	6 (0.8)	5 (1.7)	
Active cancer	58 (8.2)	15 (5.1)	0.118
Missing data	19 (2.7)	21 (7.1)	
Surgery or major trauma in previous month	47 (6.6)	11 (3.7)	0.072
Missing data	3 (0.4)	2 (0.7)	
Immobilization	77 (10.9)	34 (11.5)	0.814
Missing data	12 (1.7)	2 (0.7)	
Estrogen use	41 (5.8)	22 (7.4)	0.340
Missing data	10 (1.4)	2 (0.7)	

Values are mean ± SD, median (interquartile range), or n (%).

Table 3 displays the rates of overall and cause-specific early (within 30 days of randomization) death, as well as the late mortality rates (i.e., deaths occurring between 30 days and long-term follow-up in the 2 treatment arms). The corresponding Kaplan-Meier curves representing the long-term survival estimates are shown in the Central Illustration. The overall mortality rate in the entire study population was 19.2%; no significant differences were observed between patients who underwent thrombolysis with tenecteplase and patients randomized to heparin anticoagulation alone (p = 0.43). Most late deaths occurring between day 30 and long-term follow-up resulted from cancer, acute or chronic respiratory failure, or other illness (mostly acute infections or chronic systemic inflammatory diseases). The cause of death could not be identified in 32 and 35 cases in

TABLE 3 Overall and Cause-Specific 30-Day and Long-Term Mortality

	Tenecteplase (N = 359)	Placebo (N = 350)	p Value
Death from any cause between randomization and day 30	8 (2.2)	10 (2.9)	0.595
Hemodynamic collapse	1 (0.3)	1 (0.3)	
Stroke (ischemic or hemorrhagic)	4 (1.1)	0 (0.0)	
Recurrent pulmonary embolism	0 (0.0)	2 (0.6)	
Respiratory failure	0 (0.0)	2 (0.6)	
Extracranial bleeding	1 (0.3)	0 (0.0)	
Sudden unexplained death	0 (0.0)	2 (0.6)	
Other	2 (0.6)	3 (0.9)	
Death from any cause between day 30 and long-term follow-up	65 (18.1)	53 (15.1)	
Stroke	1 (0.3)	2 (0.6)	
Acute myocardial infarction	0 (0.0)	1 (0.3)	
Respiratory failure	2 (0.6)	1 (0.3)	
Sudden unexplained death	2 (0.6)	0 (0.0)	
Cancer	8 (2.2)	9 (2.6)	
Bleeding	0 (0.0)	1 (0.3)	
Chronic heart failure	1 (0.3)	0 (0.0)	
Other	19 (5.3)	4 (1.1)	
Unknown cause	32 (8.9)	35 (10.0)	
Death from any cause between randomization and long-term follow-up	73 (20.3)	63 (18.0)	0.430

Values are n (%).

the tenecteplase and placebo arms of the trial, respectively (Table 3).

LONG-TERM CLINICAL AND ECHOCARDIOGRAPHIC FOLLOW-UP. Clinical and echocardiographic follow-up examination of PE was performed in survivors. The clinical status could be obtained in 175 and 183 patients in the tenecteplase and placebo arms of the trial, respectively. Sixty-three (36.0%) of the patients in the tenecteplase arm and 55 (30.1%) in the placebo arm reported persistent clinical symptoms after PE ($p = 0.23$). In most of these cases (55 of 63 and 50 of 55 patients, respectively), the leading symptom was mild exertional dyspnea; only 21 patients (12.0%) randomized to tenecteplase and 20 (10.9%) randomized to placebo were in New York Heart Association functional class III or IV. Peripheral edema was recorded in 9 (5.1%) and 4 patients (2.2%), respectively. Other symptoms or clinical signs indicating heart failure (syncope or pre-syncope on exertion, chest pain at rest or on exertion, prominent RV impulse, accentuation or splitting of the second heart sound, auscultation of a third [S_3] or fourth [S_4] heart sound, jugular venous distention, hepatomegaly, or ascites) were distinctly rare and were documented in <2% of the patients in each treatment arm.

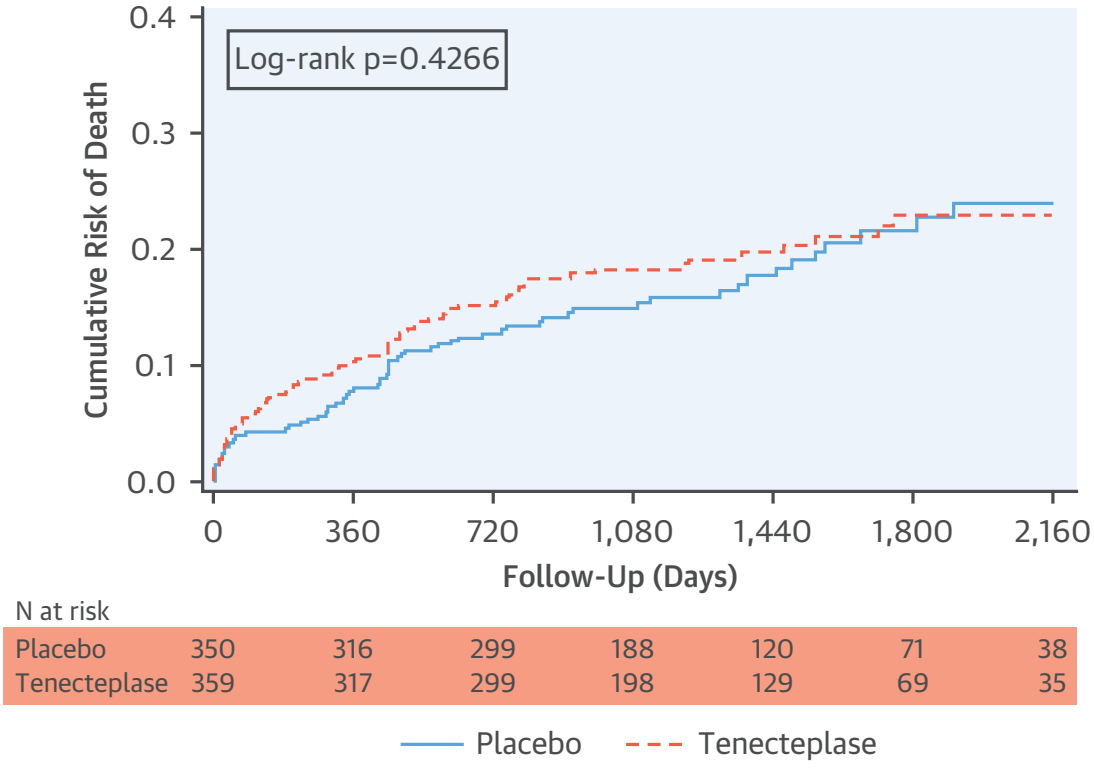
Echocardiography was performed as part of the long-term follow-up in 144 and 146 patients in the thrombolysis and control arms, respectively. The findings, which are summarized in Table 4, did not reveal significant differences between the 2 treatment arms regarding the presence of residual pulmonary hypertension or RV dysfunction. Among patients with data obtained on at least 4 of the echocardiographic parameters shown in Table 4, 1 or more indicators of pulmonary hypertension and/or RV dysfunction were recorded in 63 (44.1%) of the patients randomized to tenecteplase and in 52 (36.6%) of those who received placebo ($p = 0.20$). However, echocardiographically estimated systolic pulmonary artery pressures were mildly elevated in the majority of cases (median 30.0 mm Hg; interquartile range: 25.0 to 35.0 mm Hg) (Table 4). Post hoc application of the echocardiographic criteria proposed in the 2015 European Society of Cardiology/European Respiratory Society Guidelines for the diagnosis and treatment of pulmonary hypertension (5) classified the probability of (chronic) pulmonary hypertension as low in 60% of the patients randomized to tenecteplase and 68% of the patients who received placebo ($p = 0.26$) and as intermediate in 25% and 28% of the patients, respectively, in the 2 groups.

A definitive diagnosis of CTEPH was made in 4 of 190 (2.1%) patients randomized to tenecteplase and in 6 of 186 (3.2%) allocated to placebo ($p = 0.79$). All these patients were alive and had not (yet) undergone surgical treatment at the time of follow-up.

DISCUSSION

In PEITHO, a large randomized thrombolysis trial of acute PE, treatment with tenecteplase significantly reduced the incidence of the combined primary outcome "death or hemodynamic collapse at 7 days," but it was also associated with a 2% rate of hemorrhagic stroke and a 6.3% rate of major extracranial bleeding (2). The present analysis of the trial patients who underwent long-term follow-up revealed no impact of thrombolysis on the overall long-term mortality rate, which was relatively low (20.3% and 18.0%, respectively) in both treatment arms. Persisting symptoms were reported by 33% of the study patients, but the degree of functional limitation and the elevation of echocardiographically estimated systolic pulmonary artery pressure were mild in most cases, regardless of whether the patients had initially been treated with thrombolysis or anticoagulation alone. In agreement with these findings, most patients (85% and 96% in the tenecteplase and placebo

CENTRAL ILLUSTRATION **Thrombolysis for Pulmonary Embolism: Kaplan-Meier Survival Curves of Patients Randomized to Tenecteplase Compared With Placebo**



Konstantinides, S.V. et al. J Am Coll Cardiol. 2017;69(12):1536–44.

Kaplan-Meier curves showing the cumulative risk of death in patients with intermediate-risk pulmonary embolism who were randomized to tenecteplase versus placebo in the PEITHO (Pulmonary Embolism Thrombolysis) trial. A total of 709 patients, corresponding to 71% of the overall intention-to-treat population, were randomized by 28 study sites that signed the third protocol amendment extending the follow-up period to at least 24 months. Long-term follow-up extended over a median period of 37.8 months, with an interquartile range of 24.6 to 54.8 months. Survival status was assessed in 353 of 359 (98.3%) patients in the thrombolysis arm and in 343 of 350 (98.0%) patients in the placebo arm. Overall long-term mortality rates did not differ significantly between the 2 treatment arms: 20.3% and 18.0%, respectively (log-rank; $p = 0.43$).

arms, respectively) had a low or intermediate ultrasound-based probability of chronic pulmonary hypertension. The diagnosis of CTEPH was confirmed in 2.1% and 3.2% of the patients randomized to tenecteplase and placebo, respectively.

Since 2005, several controlled randomized trials (6) contributed to substantial improvement in the management of acute PE, mainly by optimizing diagnostic algorithms as well as anticoagulation and reperfusion strategies. In parallel, data obtained from registries (7) and population studies (8-10) consistently documented a decrease in case-fatality rates in the acute phase of PE, even though some doubts remain that overdiagnosis of the disease could exert a confounding effect on these favorable trends (10,11). The 30-day mortality rates in the PEITHO trial (2), which focused on a population with elevated risk of an adverse outcome (termed "intermediate-high-risk" PE), are in agreement with these observations. PEITHO thus provides solid evidence to support the recommendations of current guidelines, which emphasize that prompt initiation of anticoagulation treatment may, along with hemodynamic monitoring and the option of rescue reperfusion if signs of hemodynamic decompensation appear, result in high early survival rates even in patients with "severe" PE (1,12). In contrast, the existing data on the long-term outcome of patients with PE, and particularly on the possible impact of early therapeutic interventions on the risk of late death, are much less conclusive. In 1992, investigators

TABLE 4 Findings in Patients With Echocardiographic Long-Term Follow-Up

	Tenecteplase (N = 144)	Placebo (N = 146)	p Value
Right ventricular end-diastolic diameter >30 mm	34 (23.6)	22 (15.1)	0.058
Missing data	12 (8.3)	11 (7.5)	
Right/left ventricular end-diastolic diameter >0.9	34 (23.6)	22 (15.1)	0.834
Missing data	12 (8.3)	11 (7.5)	
Hypokinesia of the right ventricular free wall (any view)	6 (4.2)	5 (3.4)	0.740
Missing data	4 (2.8)	4 (2.7)	
Tricuspid annulus plane systolic excursion reduced	14 (9.7)	7 (4.8)	0.107
Mean, mm Hg	23.6 ± 4.8	23.9 ± 3.6	
Median, mm Hg	24.0 (20.0–27.0)	24.0 (21.0–26.0)	0.551
Missing data,	19 (13.2)	18 (12.3)	
Tricuspid systolic velocity >2.6 m/s	22 (15.3)	27 (18.5)	0.412
Missing data	11 (7.6)	14 (9.6)	
Systolic pulmonary artery pressure, mm Hg			
Mean	31.6 ± 12.3	30.7 ± 10.2	0.527
Median	30.0 (24.0–35.0)	30.0 (25.0–35.0)	
Missing data	33 (22.9)	39 (26.7)	

Values are n (%), mean ± SD, or median (interquartile range).

reported that as many as 24% of patients with PE were dead at 1-year follow-up, and most deaths were the result of cancer or serious cardiopulmonary comorbidity (13). In another cohort study, published in 2004, a lower cumulative all-cause mortality rate of 13% at 1 year was reported (14). Importantly, none of the randomized thrombolysis trials (15) was powered to permit reliable assessment of late clinical outcomes. In the present study, the long-term all-cause mortality rate was 19.2%, and no significant differences were observed between patients who were randomized to thrombolysis with tenecteplase and patients who initially received heparin anticoagulation alone. As in the previous reports, most deaths occurring after the first 30 days resulted from comorbidity or underlying disease, and there was no evidence that they might have resulted from progressive right-sided heart failure following the index event or from recurrent PE thereafter. Consequently, it is not surprising that early thrombolysis did not appear capable of preventing these late deaths.

It is conceivable that early thrombolysis may exert favorable prolonged effects other than reducing overall mortality rates. In fact, some degree of persistent pulmonary hypertension or RV dysfunction has been reported in as many as 40% of survivors followed over 6 months to 1 year after acute PE (16). However, the number of patients followed in cohort studies was rather small, standardization of the echocardiographic parameters remains a largely unresolved issue, and, most importantly, a correlation of ultrasound findings with the severity of patients' symptoms or the degree of functional limitation at follow-up could not be demonstrated (17). In the present study, echocardiographic follow-up, which was performed in 290 randomized patients, yielded 1 or more indicators of pulmonary hypertension and/or RV dysfunction in a high proportion (44%) of the patient population. However, persistent clinical symptoms, which were reported by 33% of the patients evaluated, were mostly mild, with 11.5% of the patients in New York Heart Association functional class III or IV. Moreover, there was no indication that early thrombolysis had a positive impact on the presence or severity of symptoms, the patients' functional status, or the echocardiographic parameters over the long term. These results do not appear to support the hypothesis generated by 2 small randomized trials, namely that thrombolysis might improve, compared with anticoagulation alone, functional capacity (as part of a combined clinical outcome) at 3 months (18) or the persistence (or development) of pulmonary hypertension at 28 months (19). However, in the former study, the absolute numbers of late events were low in both treatment arms, and the small difference in favor of thrombolysis over the long term appeared to be mainly driven by the rates of "low perception of wellness" determined on the basis of the 36-Item Short Form (SF-36) survey (18). In the latter study, which used nonstandardized criteria to define "moderate" acute PE and allocate patients to reduced-dose alteplase treatment versus heparin alone, mean estimated systolic pulmonary artery pressure at 28-month follow-up was 43 ± 6 mm Hg in the control (anticoagulation-only) arm, and as many as 57% of the patients in that group were reported to have an estimated systolic pressure higher than 40 mm Hg (19). Late morbidity of such severity appears surprising in view of the findings of the present study, in which mean systolic pulmonary pressures were approximately 31 mm Hg in either treatment arm, even though we focused on patients with elevated-risk (intermediate- to high-risk) acute PE.

STUDY LIMITATIONS. First, long-term follow-up was performed by only 28 of the 76 PEITHO sites, which had included, in total, 709 patients or approximately two-thirds of the entire randomized population. However, selection bias is unlikely because randomization was, by protocol, stratified by center and, within centers, performed in blocks to ensure balanced distribution of the treatment groups; moreover, comparison between the patients who were followed over the long term and analyzed in the present study and patients who

did not participate in the follow-up did not, with the exception of body weight and a history of previous venous thromboembolism, reveal significant differences with regard to baseline characteristics. Second, the causes of late death (beyond the first 30 days) were not centrally adjudicated and remained unidentified in some cases. Third, clinical and echocardiographic examinations could not be performed in all survivors. The echocardiographic findings analyzed in the present study therefore cannot be considered definitive evidence of how often pulmonary hypertension or RV dysfunction persists (or develops) after acute PE and cannot ascertain the possible impact of thrombolysis on the long-term hemodynamic course of these patients.

Finally, and despite the relatively large number of randomized patients and patients in follow-up, the PEITHO trial cannot resolve the debate on the true incidence of CTEPH after acute PE and on whether thrombolysis might help to prevent this late complication. Over a median follow-up exceeding 3 years, CTEPH was diagnosed in 2.7% of the study patients. This rate appears slightly lower than that observed in some of the earlier cohort studies (14,20), but extrapolation of previous data and of our data to the general population is limited by the possibility that an unknown proportion of patients may have had pre-existing pulmonary hypertension at baseline (20). The diagnostic algorithm for suspected CTEPH was not part of the PEITHO trial protocol, and confirmed cases were not externally adjudicated.

CONCLUSIONS

In a large, prospective randomized controlled trial of patients with intermediate- to high-risk PE, thrombolytic treatment with tenecteplase did not affect long-term mortality rates, and it did not appear to reduce residual dyspnea, functional limitation, or persisting RV dysfunction, which were mostly mild in both treatment arms. These results suggest that future trials investigating advanced reperfusion regimens and modalities for acute PE should primarily focus on early efficacy and, particularly, safety outcomes while also prospectively including an adequately long period of prospective follow-up that will permit the assessment of the patients' clinical and hemodynamic course as well as their functional status and quality of life.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Systemic thrombolysis in the acute phase of PE in normotensive patients with RV dysfunction (intermediate-risk PE) did not affect mortality rates over more than 3 years of follow-up, nor did it reduce residual dyspnea, functional limitation, or echocardiographic signs of RV pressure overload. Thus, an expectant strategy of anticoagulation, early monitoring, and rescue reperfusion in cases of hemodynamic decompensation is the preferable initial approach to patients with intermediate-risk PE.

TRANSLATIONAL OUTLOOK: Future trials of alternative reperfusion strategies for acute PE should focus on early efficacy and safety and include sufficient follow-up with standardized assessment of clinical, hemodynamic, and functional outcomes.

REFERENCES

1. Konstantinides SV, Torbicki A, Agnelli G, et al. 2014 ESC guidelines on the diagnosis and management of acute pulmonary embolism. Eur Heart J 2014;35:3033–69.

2. Meyer G, Vicaut E, Danays T, et al. Fibrinolysis for patients with intermediate-risk pulmonary embolism. N Engl J Med 2014;370:1402–11.

3. PEITHO Steering Committee. 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. Am Heart J 2012;163:33–8.

4. Galie N, Hoeper MM, Humbert M, et al. Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Respir J 2009;34:1219–63.

5. Galie N, Humbert M, Vachiery JL, et al. 2015 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension: the Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Heart J 2016;37:67–119.

6. Konstantinides SV, Barco S, Lankeit M, Meyer G. Management of pulmonary embolism: an update. J Am Coll Cardiol 2016;67:976–90.

7. Jimenez D, de Miguel-Diez J, Guijarro R, et al. Trends in the management and outcomes of acute pulmonary embolism: analysis from the RIETE registry. J Am Coll Cardiol 2016;67:162–70.

8. Dentali F, Ageno W, Pomero F, Fenoglio L, Squizzato A, Bonzini M. Time trends and case fatality rate of in-hospital treated pulmonary embolism during 11 years of observation in northwestern Italy. Thromb Haemost 2016;115:399–405.

9. de Miguel-Diez J, Jimenez-Garcia R, Jimenez D, et al. Trends in hospital admissions for pulmonary embolism in Spain from 2002 to 2011. Eur Respir J 2014;44:942–50.

10. Wiener RS, Schwartz LM, Woloshin S. Time trends in pulmonary embolism in the United States: evidence of overdiagnosis. Arch Intern Med 2011;171:831–7.

11. Konstantinides SV. Trends in incidence versus case fatality rates of pulmonary embolism: good news or bad news? Thromb Haemost 2016;115:233–5.

12. Kearon C, Akl EA, Ornelas J, et al. Antithrombotic therapy for VTE disease: CHEST guideline and expert panel report. Chest 2016;149:315–52.

13. Carson JL, Kelley MA, Duff A, et al. The clinical course of pulmonary embolism. N Engl J Med 1992;326:1240–5.

14. Pengo V, Lensing AW, Prins MH, et al. Incidence of chronic thromboembolic pulmonary hypertension after pulmonary embolism. N Engl J Med 2004;350:2257–64.

15. Marti C, John G, Konstantinides S, et al. Systemic thrombolytic therapy for acute pulmonary embolism: a systematic review and meta-analysis. Eur Heart J 2015;36:605–14.

16. Stevinson BG, Hernandez-Nino J, Rose G, Kline JA. Echocardiographic and functional cardiopulmonary problems 6 months after first-time pulmonary embolism in previously healthy patients. Eur Heart J 2007;28:2517–24.

17. Chung T, Emmett L, Mansberg R, Peters M, Kritharides L. Natural history of right ventricular dysfunction after acute pulmonary embolism. J Am Soc Echocardiogr 2007;20:885–94.

18. Kline JA, Nordenholz KE, Courtney DM, et al. Treatment of submassive pulmonary embolism with tenecteplase or placebo: cardiopulmonary outcomes at 3 months: multicenter double-blind, placebo-controlled randomized trial. J Thromb Haemost 2014;12:459–68.

19. Sharifi M, Bay C, Skrocki L, Rahimi F, Mehdipour M. Moderate pulmonary embolism treated with thrombolysis (from the "MOPETT" trial). Am J Cardiol 2013;111:273–7.

20. Guerin L, Couturaud F, Parent F, et al. Prevalence of chronic thromboembolic pulmonary hypertension after acute pulmonary embolism: prevalence of CTEPH after pulmonary embolism. Thromb Haemost 2014;112:598–605.

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