

ORIGINAL ARTICLE

Catheter-Directed Thrombolysis in Intermediate-High-Risk Pulmonary Embolism

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ABSTRACT

BACKGROUND

Whether catheter-directed thrombolysis improves clinical outcomes in patients with intermediate-high-risk pulmonary embolism, as compared with anticoagulation alone, is uncertain.

METHODS

In this multicenter, open-label, randomized trial, we randomly assigned patients with intermediate-high-risk acute pulmonary embolism (defined by hemodynamic stability, a simplified Pulmonary Embolism Severity Index score of ≥ 1 , and right ventricular dysfunction plus an elevated level of cardiac troponin or natriuretic peptide) in a 1:1 ratio to receive catheter-directed thrombolysis with alteplase plus anticoagulation therapy (thrombolysis group) or anticoagulation therapy alone (standard-care group). The primary outcome was a composite of death from any cause, recurrence of pulmonary embolism, or cardiorespiratory decompensation or collapse within 7 days after randomization. Secondary outcomes included clinically relevant bleeding as defined by the Bleeding Academic Research Consortium, major bleeding as defined in the Global Use of Strategies to Open Occluded Coronary Arteries guidelines, and intracranial hemorrhage.

RESULTS

A total of 558 patients underwent randomization; 280 were assigned to the thrombolysis group, and 278 to the standard-care group. The median age was 64 years, and 40.9% were female. A primary-outcome event occurred in 2 patients (0.7%) in the thrombolysis group and in 19 patients (6.8%) in the standard-care group (relative risk, 0.10; 95% confidence interval, 0.02 to 0.44; $P < 0.001$); this difference was driven mainly by the lower incidence of cardiorespiratory decompensation or collapse in the thrombolysis group. By day 7, clinically relevant bleeding had occurred in 13 patients (4.6%) in the thrombolysis group and in 14 patients (5.0%) in the standard-care group ($P = 0.85$); major bleeding in 4 (1.4%) and 6 (2.2%), respectively ($P = 0.54$); and intracranial hemorrhage in 2 (0.7%) and none. One patient in the thrombolysis group died within 30 days, and 4 patients in the standard-care group died within 7 days.

CONCLUSIONS

Among patients with intermediate-high-risk acute pulmonary embolism, catheter-directed thrombolysis with alteplase plus anticoagulation therapy led to a lower risk of death from any cause, recurrent pulmonary embolism, or cardiorespiratory decompensation or collapse within 7 days after randomization than anticoagulation therapy alone. (Funded by the Ministry of Health of the Czech Republic and others; PRAGUE-26 ClinicalTrials.gov number, NCT05493163; EudraCT number, 2022-002218-18; European Union Clinical Trials number, 2024-516144-25-00.)

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PULMONARY EMBOLISM IS A GLOBAL CLINICAL challenge associated with substantial mortality.¹ Patients with intermediate-high-risk acute pulmonary embolism represent a clinically important subgroup because they remain at increased risk for early hemodynamic deterioration despite standard therapeutic anticoagulation. Although systemic thrombolysis reduces the risk of clinical deterioration, its routine use in this subgroup is not recommended because this benefit is offset by an increased risk of major bleeding, including intracranial hemorrhage.² Catheter-directed delivery of low-dose fibrinolytic therapy has emerged as an alternative reperfusion strategy that may preserve efficacy while limiting bleeding complications.³⁻⁵ In a recent trial, ultrasound-facilitated catheter-directed thrombolysis was shown to reduce the risk of early clinical deterioration in a selected population of patients with intermediate-high-risk pulmonary embolism and additional clinical features associated with impending decompensation.⁶

Whether similar clinical benefit can be achieved with conventional catheter-directed thrombolysis in patients with intermediate-high-risk acute pulmonary embolism, as defined in the 2019 European Society of Cardiology (ESC) guidelines,⁷ remains uncertain. The PRAGUE-26 trial, which was conducted without industry sponsorship, was designed to compare conventional catheter-directed thrombolysis plus anticoagulation therapy with anticoagulation therapy alone in this population.⁸

METHODS

TRIAL DESIGN

The current trial was an investigator-initiated, open-label, randomized trial comparing catheter-directed thrombolysis plus anticoagulation therapy with anticoagulation therapy alone in patients with intermediate-high-risk acute pulmonary embolism, as defined in the 2019 ESC guidelines. The trial was conducted at 11 tertiary care cardiovascular centers in the Czech Republic, with oversight by the Third Faculty of Medicine, Charles University. The trial design and methods have been described previously.⁸

The investigators conducted the trial, collected the data, and vouch for the completeness and accuracy of the data and for the fidelity of the trial to the protocol (available with the full text of this article at NEJM.org). The trial was performed in

accordance with the principles of the Declaration of Helsinki, the International Council for Harmonisation guidelines for Good Clinical Practice, and applicable regulatory requirements. The protocol was approved by the institutional review board or independent ethics committee at each participating center and by the relevant national regulatory authority in the Czech Republic (the State Institute for Drug Control). All the patients provided written informed consent before enrollment.

The clinical events committee adjudicated all prespecified outcome events. An independent data and safety monitoring board reviewed safety data and performed the prespecified interim analyses of the primary outcome. The clinical events committee and data and safety monitoring board were aware of the trial-group assignments.

PATIENTS, RANDOMIZATION, AND TRIAL INTERVENTIONS

Patients 18 to 80 years of age who had intermediate-high-risk pulmonary embolism, including those who had been directly admitted to a participating tertiary care cardiovascular center and those who had been transferred to a trial center from a referring hospital, were screened for eligibility. Intermediate-high-risk pulmonary embolism was defined by hemodynamic stability, a simplified Pulmonary Embolism Severity Index score of at least 1 (range, 0 to 6; higher scores indicate a greater risk of death or serious complications at 30 days), and right ventricular dysfunction plus an elevated level of cardiac troponin or natriuretic peptide. Pulmonary embolism was diagnosed and risk stratification conducted on the basis of computed tomography (CT) pulmonary angiographic imaging, transthoracic echocardiographic imaging, and laboratory testing performed according to routine clinical practice. Patients who met all inclusion criteria and none of the exclusion criteria underwent randomization (Table 1).

Patients were randomly assigned in a 1:1 ratio to receive catheter-directed thrombolysis with alteplase plus anticoagulation therapy (thrombolysis group) or to receive anticoagulation therapy alone (standard-care group). Simple stratified randomization was performed with the use of a computer-generated sequence; the randomization strata were age (18 to 64 years or 65 to 80 years), sex, whether the pulmonary embolism was unilateral or bilateral, time since diagnostic CT pulmonary angiography (≤ 24 hours or > 24 hours), and mode of

Table 1. Trial Inclusion and Exclusion Criteria.***Inclusion criteria**

1. Age of 18 to 80 yr
2. Proximal pulmonary embolism verified on CT angiography and symptom onset <14 days before randomization†
3. Intermediate-high-risk pulmonary embolism with a simplified PESI score of ≥ 1 , RV dysfunction, and an elevated level of cardiac troponin or natriuretic peptide‡
4. Signed informed consent

Exclusion criteria

1. Active clinically significant bleeding
2. Any hemorrhagic stroke, or ischemic stroke or transient ischemic attack <6 mo before randomization
3. Cranial trauma <3 mo before randomization, or another active intracranial or intraspinal process
4. Major surgery ≤ 7 days before randomization
5. Active cancer or other severe illness with expected survival of <2 yr
6. Hemoglobin level of <80 g/liter, international normalized ratio of >2.0, platelet count of $\leq 100 \times 10^9$ per liter, and creatinine level of >200 $\mu\text{mol/liter}$ (2.26 mg/dl)
7. Pregnant or breastfeeding, or fertility without previous exclusion of gravidity
8. Allergy to thrombolytic drugs or heparin or low-molecular-weight heparin, contrast allergy, or a history of heparin-induced thrombocytopenia
9. Floating thrombi in transit through a patent foramen ovale
10. Participation in another clinical trial

* Patients were eligible for randomization if they met all four inclusion criteria. Patients who met 1 or more of the 10 exclusion criteria were ineligible.

† Proximal pulmonary embolism was defined as a perfusion defect in at least one main pulmonary artery or one lobar pulmonary artery detected on computed tomographic (CT) angiography.

‡ The simplified Pulmonary Embolism Severity Index (PESI) is used to estimate the risk of death from any cause within 30 days after acute pulmonary embolism (Table S1). One point is assigned for each of six risk factors: age of more than 80 years, history of cancer, chronic cardiopulmonary disease, heart rate of at least 110 beats per minute, systolic blood pressure of less than 100 mm Hg, and arterial oxygen saturation of less than 90%. The total score is calculated by summing the points; a score of 0 indicates low risk, whereas a score of at least 1 indicates higher risk. Right ventricular (RV) dysfunction was defined as a ratio of right ventricular end-diastolic diameter to left ventricular end-diastolic diameter of at least 0.9 on transthoracic echocardiography or CT angiography. An elevated level of cardiac troponin was defined as a high-sensitivity troponin (hs-troponin) I level of more than 53 ng per liter for males and more than 34 ng per liter for females or a hs-troponin T level of more than 14 ng per liter. An elevated level of natriuretic peptide was defined as an N-terminal pro-B-type natriuretic peptide level of more than 600 pg per milliliter or a B-type natriuretic peptide level of more than 100 pg per milliliter.

admission (direct admission or transfer from a referring hospital). As recommended in the protocol, initiation of catheter-directed thrombolysis was to begin within 3 hours after randomization, whenever feasible.

Catheter-directed thrombolysis was performed with the use of a standard 4-French valved infusion catheter with a 10-cm infusion segment (e.g., Cragg–McNamara 4-French valved infusion catheter [Medtronic] or similar). After catheter placement, alteplase was administered as a 1-mg bolus through each catheter and then infused at a dose of 1 mg per hour per catheter up to a total dose of 20 mg (10 mg in patients with unilateral pulmonary embolism).

Unfractionated heparin or low-molecular-

weight heparin was administered to the patients before randomization. During the alteplase infusion, patients in the thrombolysis group continued to receive reduced-intensity unfractionated heparin, with a recommended target activated partial-thromboplastin time of 50 to 60 seconds. After completion of thrombolysis, the catheters were removed and therapeutic anticoagulation was continued without interruption according to standard clinical practice. Patients in the standard-care group received therapeutic unfractionated heparin or low-molecular-weight heparin during the trial treatment period. Transition to oral anticoagulation therapy was permitted no earlier than 24 hours after randomization and was at the discretion of the treating physician.

OUTCOMES

The primary outcome was a composite of death from any cause, recurrence of pulmonary embolism, or cardiorespiratory decompensation or collapse within 7 days after randomization. Cardiorespiratory decompensation or collapse was defined by the presence of at least one of following features: cardiac arrest or need for cardiopulmonary resuscitation, signs of shock (new-onset of persistent arterial hypotension accompanied by end-organ hypoperfusion), initiation of extracorporeal membrane oxygenation (ECMO), or intubation or initiation of noninvasive mechanical ventilation between randomization and day 7 or a National Early Warning Score of 9 or higher (see Table S2 in the Supplementary Appendix, available at NEJM.org) between 24 hours and 7 days that was confirmed on the basis of two consecutive measurements performed 15 minutes apart. Arterial hypotension was defined by a systolic blood pressure of less than 90 mm Hg or a decrease of 40 mm Hg or more that lasts for at least 15 minutes despite an adequate volume status or by an indication for vasopressors in order to maintain a systolic blood pressure of at least 90 mm Hg. End-organ hypoperfusion was defined by altered mental status, oliguria or anuria, or a serum lactate level of more than 2 mmol per liter.

Secondary outcomes through 30 days were assessed at the scheduled follow-up visit (± 3 days) and included the individual components of the primary outcome; failure of the assigned first-line therapy (defined as systemic or local thrombolysis administered during the index hospitalization); ischemic or hemorrhagic stroke; serious adverse events; echocardiographic features, including the ratio of right ventricular end-diastolic diameter to left ventricular end-diastolic diameter (right-to-left ventricular ratio); World Health Organization (WHO) functional class (range, class I to IV; higher classes indicate greater functional limitations); and lengths of stay in the intensive care unit (ICU) and hospital. All bleeding events were recorded as secondary-outcome events. Major bleeding is defined in the protocol and was assessed on the basis of GUSTO (Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries) criteria and International Society on Thrombosis and Haemostasis guidelines. Clinically relevant bleeding was defined as bleeding events of Bleed-

ing Academic Research Consortium (BARC) type 2 or higher (types range from 1 [minimal bleeding, not actionable] to 5 [fatal bleeding]). Additional details about the primary and secondary outcomes are provided in the Supplementary Appendix. Long-term follow-up is ongoing and will continue through 2 years after randomization.

STATISTICAL ANALYSIS

We estimated that 558 patients would provide the trial with 80% power to detect an absolute difference of 4.5 percentage points in the risk of a primary-outcome event in the thrombolysis group as compared with the standard-care group (1.5% vs. 6.0%) as assessed with a two-sided test for superiority. The sample size was not changed during the trial. The primary analysis was performed according to the intention-to-treat principle and included all the patients who underwent randomization.

Categorical variables are summarized as counts and percentages; continuous variables are presented as medians with interquartile ranges or as means with standard deviations. Missing values for the primary or secondary clinical outcomes for the 7-day and 30-day follow-up were expected to be minimal and were assumed to be missing completely at random; therefore, no imputation was performed.

The Fisher's exact test was used for between-group comparisons of the primary composite outcome and all categorical variables. The Mann-Whitney test was used for comparisons of continuous variables. Relative risks and corresponding 95% confidence intervals are reported for the evaluated outcomes. Confidence intervals for secondary outcomes have not been adjusted for multiplicity and should not be used to infer definitive treatment effects. A prespecified per-protocol analysis that included all the patients in the intention-to-treat population who did not have a protocol deviation (per-protocol population) was performed as a secondary, supportive analysis. All reported P values are two-sided. A P value of less than 0.047, calculated with an O'Brien-Fleming boundary in two interim analyses and a final analysis, was considered to be significant. Statistical analyses were performed with the use of SPSS software, version 31.0.1.0 (IBM).

RESULTS

PATIENTS AND TREATMENT

From October 2022 through March 2026, a total of 558 patients underwent randomization at 11 tertiary care cardiovascular centers in the Czech Republic. A total of 280 patients were assigned to the thrombolysis group and 278 to the standard-care group; all were included in the intention-to-treat population (Fig. 1).

Follow-up through 7 days was completed in 280 patients (100%) in the thrombolysis group and 278 patients (100%) in the standard-care group. Follow-up through 30 days was completed in 278 patients (99.3%) and 263 patients (94.6%), respectively.

The median age was 64 years, 40.9% of the patients were women, and 49.5% had been transferred from referring hospitals. Pulmonary embolism was bilateral in 548 patients (98.2%). Base-

line demographic and clinical characteristics were generally similar in the two groups, with minor variations (Table 2). The representativeness of the trial population is shown in Table S3.

In the thrombolysis group, the median time from randomization to initiation of catheter-directed thrombolysis was 76 minutes (interquartile range, 49 to 126), and catheter-directed thrombolysis was initiated within 3 hours after randomization in 250 patients (89.3%). Successful catheter placement and initiation of alteplase infusion were achieved in 279 patients (99.6%); in one patient, the procedure was unsuccessful because the operator was unable to access the pulmonary artery. The mean ($\pm$ SD) total dose of alteplase was 19.9 ± 1.2 mg among patients with bilateral pulmonary embolism and 10.0 ± 0.0 mg among those with unilateral pulmonary embolism. The mean duration of alteplase infusion was 9.3 ± 0.95 hours.

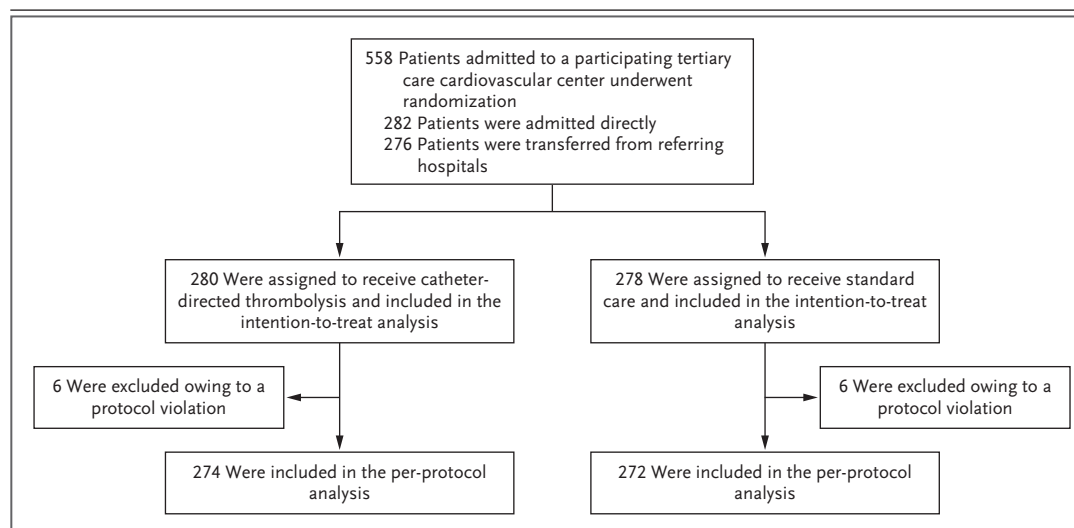


Figure 1. Randomization and Follow-up.

We randomly assigned, in a 1:1 ratio, 558 patients with intermediate-high-risk acute pulmonary embolism to receive catheter-directed thrombolysis with alteplase plus anticoagulation therapy (thrombolysis group) or anticoagulation therapy alone (standard-care group). All the patients had been admitted from October 2022 through March 2026, either directly or by transfer from referring hospitals, to 1 of 11 participating tertiary care cardiovascular centers. Screening logs were not maintained at the referring hospitals or the trial sites. The intention-to-treat analysis included all the patients who underwent randomization. The per-protocol analysis included all the patients in the intention-to-treat population who did not have a protocol deviation. Four patients in the thrombolysis group were excluded from the per-protocol analysis because they did not meet the inclusion criterion for elevated cardiac biomarker level (or natriuretic peptide), and 2 were excluded because of a platelet count of 100×10^9 per liter or less. Three patients in the standard-care group were excluded from the per-protocol analysis because they did not meet the inclusion criterion for elevated cardiac biomarker level: 1 because of a platelet count of 100×10^9 per liter or less, 1 because of an international normalized ratio of greater than 2, and 1 because of a creatinine level of greater than $200 \mu\text{mol}$ per liter (2.26 mg per deciliter).

Table 2. Characteristics of the Patients at Baseline (Intention-to-Treat Population).*

Characteristic	Thrombolysis (N=280)	Standard Care (N=278)	Standardized Mean Difference† <i>percent</i>
Demographic characteristic			
Median age (IQR) — yr	64.0 (51.5–72.0)	64.0 (51.0–72.0)	1.4
Age >65 yr — no. (%)	138 (49.3)	135 (48.6)	1.4
Female sex — no. (%)	115 (41.1)	113 (40.6)	0.9
Median body-mass index (IQR)‡	30.9 (27.2–35.8)	31.8 (27.8–35.8)	4.9
Clinical characteristic			
Bilateral acute pulmonary embolism — no. (%)	275 (98.2)	273 (98.2)	2.5
Direct admission to trial cardiovascular center — no. (%)	142 (50.7)	140 (50.4)	0.7
Median time from hospital admission to randomization (IQR) — hr	17.8 (6.3–22.5)	16.9 (5.8–22.4)	1.6
Diagnostic CT angiography >24 hr before randomization — no. (%)	51 (18.2)	51 (18.3)	0.3
Median PESI score (IQR)§	94.0 (78.5–105.5)	93.0 (80.0–108.0)	1.8
Simplified PESI score — no. (%)			
1	187 (66.8)	175 (62.9)	8.2
2	81 (28.9)	87 (31.3)	5.2
3	12 (4.3)	15 (5.4)	5.1
4	0	1 (0.4)	9.0
Vital sign			
Median systolic blood pressure (IQR) — mm Hg	135.0 (120.0–150.0)	134.5 (120.0–148.0)	2.9
Median heart rate (IQR) — beats/min	105.0 (91.0–115.0)	110.0 (93.0–116.0)	7.0
Medical history			
Arterial hypertension — no. (%)	161 (57.5)	165 (59.4)	3.8
Diabetes mellitus — no. (%)	56 (20.0)	49 (17.6)	6.1
Coronary artery disease — no. (%)	11 (3.9)	11 (4.0)	0.1
Chronic heart failure — no. (%)	9 (3.2)	17 (6.1)	13.8
Ischemic stroke — no. (%)	10 (3.6)	6 (2.2)	8.5
Chronic kidney disease — no. (%)	15 (5.4)	24 (8.6)	12.9
Previous thromboembolism — no. (%)¶	63 (22.5)	90 (32.4)	22.3
Cancer — no. (%)	34 (12.1)	30 (10.8)	4.2
Receiving treatment for active cancer — no. (%)	9 (3.2)	6 (2.2)	6.5
Any bleeding, according to GUSTO criteria — no. (%)	6 (2.1)	7 (2.5)	2.5
Active smoking — no. (%)	52 (18.6)	48 (17.3)	3.2
Contraceptive use among women — no./total no. (%)	24/115 (20.9)	16/113 (14.2)	17.7
Biochemical feature			
Median creatinine level — $\mu\text{mol/liter}$	92.0 (75.0–108.0)	89.0 (77.0–107.0)	6.6
Median cardiac troponin:ULN ratio (IQR)**	4.6 (2.1–9.8)	4.7 (2.2–10.5)	7.9
Median natriuretic peptide:ULN ratio (IQR)††	3.1 (1.1–6.5)	4.0 (1.7–7.1)	13.9

Table 2. (Continued.)

Characteristic	Thrombolysis (N=280)	Standard Care (N=278)	Standardized Mean Difference† percent
Echocardiographic feature			
Median RV:LV ratio (IQR)‡‡	1.13 (1.03–1.27)	1.14 (1.02–1.26)	5.0
Median TAPSE (IQR) — mm§§	16.0 (13.0–20.0)	16.0 (14.0–19.0)	2.1
Median S' wave velocity (IQR) — cm/sec¶¶	10.0 (8.0–12.0)	10.0 (8.0–12.0)	9.1
Median pulmonary-artery systolic pressure (IQR) — mm Hg	49.5 (42.0–58.0)	48.0 (40.0–56.0)	9.5

* Patients with intermediate-high-risk pulmonary embolism were randomly assigned to received catheter-directed thrombolysis with alteplase plus anticoagulation therapy (thrombolysis group) or anticoagulation therapy alone (standard-care group). The intention-to-treat population included all patients who underwent randomization. The pattern of missing data was consistent with data missing completely at random ($P=0.40$ by Little's missing-completely-at-random test). IQR denotes interquartile range.

† Standardized mean differences of more than 20% were considered to be potentially indicative of baseline imbalance. Values should be interpreted in the clinical context, accounting for the relevance of each variable.

‡ Body-mass index is calculated as the weight in kilograms divided by the square of the height in meters.

§ The distribution of PESI scores is shown in Table S4.

¶ Previous thromboembolism was defined as previous pulmonary embolism or deep-vein thrombosis.

|| According to the Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) criteria, severe or life-threatening bleeding is defined as intracranial hemorrhage or bleeding causing hemodynamic compromise that results in an intervention, moderate bleeding as bleeding that results in blood transfusion without hemodynamic compromise, and mild bleeding as bleeding that did not meet the criteria for severe or moderate bleeding.

** Data for the ratio of the cardiac troponin level to the upper limit of the normal range (ULN) were available for 279 patients (99.6%) in the thrombolysis group and 277 (99.6%) in the standard-care group.

†† Data for the ratio of the natriuretic peptide level to the ULN were available for 259 patients (92.5%) in the thrombolysis group and 258 (92.8%) in the standard-care group.

‡‡ Data for the ratio of right ventricular end-diastolic diameter to left ventricular end-diastolic diameter (RV:LV ratio) were available for 265 patients (94.6%) in the thrombolysis group and 267 (96.0%) in the standard-care group.

§§ Data for the tricuspid annular plane systolic excursion (TAPSE) were available for 273 patients (97.5%) in the thrombolysis group and 275 (98.9%) in the standard-care group.

¶¶ The S' wave velocity was measured at the tricuspid annulus with tissue Doppler imaging. Data were available for 248 patients (88.6%) in the thrombolysis group and 239 (86.0%) in the standard-care group.

|| Data were available for 216 patients (77.1%) in the thrombolysis group and 205 (73.7%) in the standard-care group.

Before randomization, unfractionated heparin was administered to 52.0% of the patients in the thrombolysis group and to 51.1% of those in the standard-care group and low-molecular-weight heparin to 48.0% and 48.6%, respectively. After randomization, patients in the thrombolysis group were treated according to the protocol, and unfractionated heparin was administered to 99.3% of these patients. At 24 hours after randomization, before the transition to oral anticoagulation therapy, unfractionated heparin was administered to 40.1% of the patients in the thrombolysis group and to 31.9% of those in the standard-care group and low-molecular-weight heparin to 56.3% and 65.2%, respectively.

PRIMARY OUTCOME AND ITS COMPONENTS

In the intention-to-treat population, a primary-outcome event occurred in 2 patients (0.7%) in the

thrombolysis group and in 19 patients (6.8%) in the standard-care group (relative risk, 0.10; 95% confidence interval [CI], 0.02 to 0.44; $P<0.001$) (Table 3). The risk difference was -6.1 percentage points (95% CI, -9.2 to -3.0 ; $P<0.001$), favoring catheter-directed thrombolysis. The results for the primary outcome in the per-protocol population were consistent with those in the intention-to-treat population (Table S5).

The between-group difference in the percentage of patients with a primary-outcome event was driven primarily by a lower incidence of cardiorespiratory decompensation or collapse in the thrombolysis group. Cardiorespiratory decompensation or collapse by day 7 occurred in 2 patients (0.7%) in the thrombolysis group, as compared with 15 patients (5.4%) in the standard-care group (relative risk, 0.13; 95% CI, 0.03 to 0.57) (Table S6). Recurrent pulmonary embolism by day 7

Table 3. Outcomes (Intention-to-Treat Population).*

Outcome	Thrombolysis (N=280)		Standard Care (N=278)		Relative Risk (95% CI)
	<i>no. of patients</i>	<i>% of patients (95% CI)†</i>	<i>no. of patients</i>	<i>% of patients (95% CI)†</i>	
Primary outcome					
Death from any cause, recurrence of pulmonary embolism, or cardiorespiratory decompensation or collapse	2	0.7 (0.0–2.7)	19	6.8 (4.4–10.5)	0.10 (0.02–0.44)‡
Secondary outcomes					
Death from any cause	0	0 (0.0–1.6)	4	1.4 (0.4–3.8)	0
Recurrence of pulmonary embolism	2	0.7 (0.0–2.7)	1	0.4 (0.0–2.2)	1.99 (0.18–21.77)
Cardiorespiratory decompensation or collapse	2	0.7 (0.0–2.7)	15	5.4 (3.2–8.8)	0.13 (0.03–0.57)

* Outcome events that occurred through day 7 after randomization were included in the analysis.

† The 95% confidence intervals were calculated with the Wilson method. Confidence intervals for secondary outcomes were not adjusted for multiplicity and should not be used to infer definitive treatment effects.

‡ $P < 0.001$ for the comparison of the trial groups. The two-sided P value was calculated with Fisher's exact test. A P value of less than 0.047 was considered to be significant.

occurred in 2 patients (0.7%) in the thrombolysis group and in 1 patient (0.4%) in the standard-care group (relative risk, 1.99; 95% CI, 0.18 to 21.77). Between randomization and day 7, no deaths occurred in the thrombolysis group, whereas four deaths (1.4%) occurred in the standard-care group. Between days 8 and 30, there was one death (0.4%) in the thrombolysis group and no deaths in the standard-care group. Causes of death through day 30 are shown in Table S7.

SAFETY

Bleeding events of BARC type 2 or higher occurred through day 7 in 13 patients (4.6%) in the thrombolysis group and in 14 patients (5.0%) in the standard-care group ($P=0.85$); between days 8 and 30, such events occurred in 3 patients (1.1%) and 5 patients (1.9%), respectively. Major bleeding as defined according to GUSTO criteria occurred in 4 patients (1.4%) in the thrombolysis group and in 6 patients (2.2%) in the standard-care group ($P=0.54$) and intracranial hemorrhage in 2 patients (0.7%) and no patients, respectively. Additional details regarding bleeding events are provided in Table 4.

Within 7 days after randomization, stroke occurred in 3 patients; 2 patients (0.7%) in the thrombolysis group had a hemorrhagic stroke, and 1 patient (0.4%) in the standard-care group had

an ischemic stroke. No patients had a stroke between days 8 and 30. Of the 2 patients with a hemorrhagic stroke, one event occurred shortly after completion of the alteplase infusion during a hypertensive episode, and one event occurred on day 5 in the context of a documented overdose of low-molecular-weight heparin. Fatal bleeding occurred in 1 patient (0.4%) in the standard-care group after cardiorespiratory collapse (shock) on day 3, which had led to the escalation to systemic thrombolysis, mechanical thrombectomy, and ECMO. The cumulative incidence of serious adverse events through day 30 was similar in the two groups — 6.4% (in 18 patients) in the thrombolysis group and 7.6% (in 21 patients) in the standard-care group (Table S8).

OTHER SECONDARY OUTCOMES

At 24 hours after randomization, the median right-to-left ventricular ratio on transthoracic echocardiography was 0.94 (interquartile range, 0.83 to 1.05) in the thrombolysis group and 1.07 (interquartile range, 0.94 to 1.15) in the standard-care group. Data for other echocardiographic features are provided in Table S9. The median time from admission to discharge from the ICU was 2.1 days (interquartile range, 1.7 to 3.0) in the thrombolysis group and 2.8 days (interquartile range, 1.7 to 4.0) in the standard-care group.

Table 4. Cumulative Bleeding Events and Stroke after Randomization (Intention-to-Treat Population).

Variable	Thrombolysis (N=280) <i>no. of patients (%)</i>	Standard Care (N=278) <i>no. of patients (%)</i>	Relative Risk (95% CI)	P Value*
Clinically relevant bleeding according to BARC criteria†				
Within 7 days	13 (4.6)	14 (5.0)	0.92 (0.44–1.93)	0.85
Within 30 days	16 (5.7)	16 (5.8)	0.99 (0.51–1.95)	1.00
Major bleeding according to GUSTO criteria‡				
Within 7 days	4 (1.4)	6 (2.2)	0.66 (0.19–2.32)	0.54
Within 30 days	5 (1.8)	6 (2.2)	0.83 (0.26–2.68)	0.72
Major bleeding according to ISTH criteria‡				
Within 7 days	5 (1.8)	7 (2.5)	0.71 (0.23–2.21)	0.58
Within 30 days	6 (2.1)	7 (2.5)	0.85 (0.29–2.50)	0.79
Intracranial hemorrhage				
Within 7 days	2 (0.7)	0		0.50
Within 30 days	2 (0.7)	0		0.50
Ischemic stroke				
Within 7 days	0	1 (0.4)		0.50
Within 30 days	0	1 (0.4)		0.50

* P values are two-sided and were calculated with Fisher's exact test. Little's missing-completely-at-random test was used to assess 30-day outcome data and showed no evidence against the assumption that missing 30-day outcome data in the standard-care group were missing completely at random ($P=0.36$).

† Data are for bleeding events that were classified according to Bleeding Academic Research Consortium (BARC) criteria as events of type 2 or higher. BARC types range from 1 (minimal bleeding, not actionable) to 5 (fatal bleeding), with types 3 and 4 indicating major bleeding.

‡ According to International Society on Thrombosis and Haemostasis (ISTH) criteria, major bleeding is defined as fatal bleeding, symptomatic bleeding in a critical area or organ, or bleeding associated with a decrease of at least 20 g per liter in the hemoglobin level or resulting in transfusion of at least 2 units of whole blood or red cells.

The median duration of hospitalization was 4.3 days (interquartile range, 3.2 to 6.2) in the thrombolysis group and 5.1 days (interquartile range, 4.0 to 7.0) in the standard-care group. Failure of the assigned first-line therapy without the occurrence of a primary-outcome event occurred in no patients in the thrombolysis group and 12 patients (4.3%) in the standard-care group. Escalation of treatment was prompted by worsening clinical status or a lack of clinical improvement (Table S10), as assessed by the treating physician, often in consultation with the pulmonary embolism response team. At 30 days, WHO functional class I was present in 58.2% of patients in the thrombolysis group and in 44.6% of those in the standard-care group; detailed results are provided in Table S11.

DISCUSSION

In this trial, catheter-directed thrombolysis with alteplase plus anticoagulation therapy resulted in a lower risk of death from any cause, recurrent pulmonary embolism, or cardiorespiratory decompensation or collapse than anticoagulation therapy alone in patients with intermediate-high-risk acute pulmonary embolism. The observed reduction in the risk of a primary-outcome event was driven mainly by a lower rate of cardiorespiratory decompensation or collapse in the thrombolysis group. No apparent between-group differences in major bleeding events or serious adverse events were observed through 30 days of follow-up.

Mortality in the trial population was very low.

This finding may reflect close monitoring within the trial environment, as well as the tertiary care setting, where there was immediate access to rescue reperfusion therapy.⁹ However, a substantial proportion of patients with pulmonary embolism are treated in smaller regional hospitals, where cardiorespiratory decompensation may be associated with increased mortality.¹⁰ In this context, prevention of cardiorespiratory decompensation or collapse may represent a clinically meaningful treatment effect, although further study is needed to confirm this hypothesis. Wider access to interventional treatment for pulmonary embolism might be facilitated by adapting established regional networks and transfer pathways that are already used in the treatment of patients with ST-segment elevation myocardial infarction.¹¹

The treatment-response pattern observed in the current trial was similar to that reported in the Higher-Risk Pulmonary Embolism Thrombolysis (HI-PEITHO) trial. In that trial, the reduction in the risk of a primary-outcome event among patients with intermediate-risk pulmonary embolism who underwent ultrasound-facilitated, catheter-directed fibrinolysis was also driven predominantly by fewer episodes of cardiorespiratory decompensation or collapse.⁶ Although the populations in our trial and the HI-PEITHO trial were broadly similar, the HI-PEITHO trial included additional indicators of cardiorespiratory distress among the eligibility criteria and may therefore have enrolled a population of patients who were at higher risk for early complications related to pulmonary embolism. Differences in the risk of a primary-outcome event may partly reflect these differences in patient selection. Nevertheless, the results of our trial extend the available evidence to catheter-directed thrombolysis without ultrasound facilitation in patients with intermediate-high-risk acute pulmonary embolism as defined by the 2019 ESC guidelines.⁷ The benefit of catheter-directed thrombolysis in the absence of ultrasound may be particularly relevant in resource-constrained health care systems, where access to more advanced catheter-based techniques may be limited.¹

The clinical relevance of the composite primary outcome is supported by consistent results with regard to secondary-outcome analyses, which suggested more rapid early recovery with catheter-directed thrombolysis, including the right-to-left ventricular ratio at 24 hours (consistent with the

findings in the ULTIMA trial¹²), durations of ICU and hospital stay, and the percentage of patients in WHO functional class I at 7 and 30 days.

The potential benefit of early reperfusion must be weighed against the risk of bleeding. In our trial, no clear between-group differences were observed in major bleeding complications or serious adverse events through 30 days of follow-up. However, two intracranial bleeding events occurred in the thrombolysis group, underscoring the importance of careful patient selection, adherence to a low-dose thrombolytic protocol, blood-pressure control, and standardized anticoagulation management. Conversely, hemodynamic collapse with subsequent escalation of treatment may expose patients to an increased risk of bleeding or procedural complications,¹³ as illustrated by one fatal bleeding event in the standard-care group after escalation of therapy. These findings may have implications for the management of intermediate-high-risk acute pulmonary embolism. Current practice often relies on anticoagulation therapy, with rescue reperfusion reserved for severe clinical deterioration.¹⁴ The results of our trial support the concept that, in selected patients treated in interventional centers, earlier catheter-based reperfusion may prevent deterioration before overt collapse occurs and may facilitate faster recovery.¹⁵ A similar suggestion of clinical stabilization has been observed with mechanical thrombectomy — an alternative catheter-based reperfusion strategy — in the PEERLESS trial.¹⁶

The current trial has several limitations. The trial was conducted in a single country with a predominantly White population, which may limit generalizability to other racial and geographic populations. The organization of the trial included transfer of patients from a cooperating network of referring hospitals; screening logs were not collected, limiting the ability to assess the representativeness of the enrolled population. The trial was open-label, as is common in interventional trials. Although clinical events were prospectively defined and adjudicated, the lack of blinding, including the clinical events committee's awareness of the trial-group assignments, may have influenced management decisions and outcome reporting. The trial was not designed to compare catheter-directed thrombolysis with ultrasound-facilitated catheter-directed fibrinolysis, systemic thrombolysis, or mechanical thrombec-

tomy. The exclusion of patients older than 80 years of age precludes conclusions regarding this elderly population. Finally, although no obvious between-group difference in major bleeding was observed, the trial was not powered to exclude small differences in rare but serious adverse events.

In patients with intermediate-high-risk acute pulmonary embolism, catheter-directed thrombolysis with alteplase plus anticoagulation therapy led to a lower risk of death from any cause, recurrent pulmonary embolism, or cardiorespiratory decompensation or collapse at 7 days than anticoagulation therapy alone.

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