The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 28, 2026 VOL. 394 NO. 20

Ultrasound-Facilitated, Catheter-Directed Fibrinolysis for Acute Pulmonary Embolism

K. Rosenfield,[1] F.A. Klok,[2,3] G. Piazza,[4,5] A.S.P. Sharp,[6,7] F. Ní Áinle,[6] M.R. Jaff,[8] S. Barco,[3,9] S.Z. Goldhaber,[4,5] N. Kucher,[9] I.M. Lang,[10] I. Schmidtmann,[11] K.M. Sterling,[8] A. Araszkiewicz,[12] V. Arora,[13] R. Cires-Drouet,[14] J. Coghlan,[15] L. Hobohm,[3,16] W.D. Ito,[17] K. Jacobson,[18] C. Kaiser,[19] G. Kopec,[20,21] K. Marx,[22] S. McElwee,[23] N. Meneveau,[24-26] P. Monteleone,[27] J.M. Montero-Cabezas,[28] C.B. Olivier,[29,30] J. Park,[31] M. Roik,[32] R. Sakhuja,[1] A. Tego,[22] M. Theurl,[33] G. Visveswaran,[34] J.A. Vos,[35] M.N. Young,[36,37] F.M. Asch,[38] and S.V. Konstantinides,[3,39] for the HI-PEITHO Investigators*

ABSTRACT

BACKGROUND

Whether anticoagulation alone is an adequate treatment for acute, intermediate-risk pulmonary embolism is uncertain.

METHODS

We conducted a multinational, adaptive-design trial with blinded outcome adjudication. Patients with intermediate-risk pulmonary embolism (with a ratio of right ventricular end-diastolic diameter to left ventricular end-diastolic diameter of ≥1.0 and an elevated troponin level) were eligible if they had at least two indicators of cardiorespiratory distress (systolic blood pressure of ≤110 mm Hg, a heart rate of ≥100 beats per minute, or a respiratory rate of >20 breaths per minute). Patients were randomly assigned to undergo ultrasound-facilitated, catheter-directed fibrinolysis with alteplase plus anticoagulation (the intervention group) or anticoagulation alone (the control group) according to prespecified treatment protocols. The primary outcome was a composite of pulmonary embolism–related death, cardiorespiratory decompensation or collapse, or symptomatic recurrence of pulmonary embolism within 7 days.

RESULTS

The intention-to-treat population comprised 544 patients: 273 in the intervention group and 271 in the control group. The mean (±SD) age was 58.2±13.5 years, and 42.6% of the patients were women. A primary-outcome event occurred in 11 patients (4.0%; 95% confidence interval [CI], 2.3 to 7.1) in the intervention group and 28 (10.3%; 95% CI, 7.2 to 14.5) in the control group (relative risk, 0.39; 95% CI, 0.20 to 0.77; P=0.005). The effect was driven primarily by a lower risk of cardiorespiratory decompensation or collapse in the intervention group. Major bleeding occurred within 7 days after randomization in 11 patients (4.1%) in the intervention group and 6 (2.2%) in the control group (P=0.32); major bleeding occurred within 30 days in 11 patients (4.1%) and 8 patients (3.0%), respectively (P=0.64). No substantial between-group differences in the incidence of other serious adverse events were observed up to 30 days after randomization; no intracranial hemorrhage occurred.

CONCLUSIONS

In patients with acute, intermediate-risk pulmonary embolism, ultrasound-facilitated, catheter-directed fibrinolysis plus anticoagulation led to a lower risk of the composite of pulmonary embolism–related death, cardiopulmonary decompensation or collapse, or symptomatic recurrence of pulmonary embolism within 7 days than anticoagulation alone. (Funded by Boston Scientific; HI-PEITHO ClinicalTrials.gov number, NCT04790370.)

The authors' full names, academic degrees, and affiliations are listed at the end of the article. Stavros V. Konstantinides can be contacted at stavros.konstantinides@unimedizin-mainz.de or at the Center for Thrombosis and Hemostasis, University Medical Center of the Johannes Gutenberg University Mainz, Langenbeckstrasse 1, 55131 Mainz, Germany.

*A complete list of the HI-PEITHO investigators is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on March 28, 2026, at NEJM.org.

N Engl J Med 2026;394:1979-90.
DOI: 10.1056/NEJMoa2516567

CME

A Quick Take is available at NEJM.org

Acute pulmonary embolism encompasses a broad spectrum of clinical severity, a fact that emphasizes the need for risk-informed therapy.[1] For patients who present with hemodynamic instability, the consensus is that early thrombus removal by means of systemically administered fibrinolysis, percutaneous catheter-directed interventions, or surgical embolectomy is indicated.[2-4] On the other hand, the appropriate treatment strategy for patients whose condition appears to be stable but who have evidence of right ventricular dysfunction and clinical or laboratory signs that suggest a risk of cardiorespiratory decompensation remains unclear.[5] In a large, randomized, controlled trial, intravenous fibrinolytic therapy prevented hemodynamic collapse in patients with intermediate-risk pulmonary embolism, but at the cost of an increased risk of major hemorrhage and stroke.[6]

High-frequency, low-power ultrasound energy may potentiate fibrinolytic effects[7]; the use of a device that administers such energy as adjunctive therapy with catheter-delivered tissue-type plasminogen activator (alteplase) may allow for lower doses of alteplase and a shorter duration of infusion while maintaining efficacy. Ultrasound-facilitated, catheter-directed fibrinolysis has been associated with early recovery of right ventricular function.[8-12] To date, however, evidence has been lacking from randomized, controlled trials of the effect of this intervention, or of any other catheter-directed treatment, on relevant clinical outcomes in patients with acute pulmonary embolism, as compared with current usual care.[13,14] We conducted the Higher-Risk Pulmonary Embolism Thrombolysis (HI-PEITHO) trial to assess whether ultrasound-facilitated, catheter-directed fibrinolysis combined with anticoagulation improves patient outcomes as compared with anticoagulation alone.

METHODS

TRIAL DESIGN AND OVERSIGHT

We conducted this postmarket, multinational, adaptive-design, open-label, randomized trial with blinded adjudication for the primary composite outcome. The steering committee was responsible for the design and oversight of the trial, the development of the protocol, the analysis of the data, the writing of the manuscript, and the decision to submit the manuscript for publication. The HI-PEITHO investigators gathered the data. The last author wrote the first draft of the manuscript. The authors 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 conducted in accordance with the International Council for Harmonisation guidelines for Good Clinical Practice, the principles of the Declaration of Helsinki, and local regulations. The protocol, which has been published previously,[15] was approved by the institutional review board, independent ethics committee, or research ethics board at each trial site. All the patients provided written informed consent.

The trial was conducted by a tripartite partnership consisting of Boston Scientific (the sponsor), the University Medical Center of the Johannes Gutenberg University of Mainz, and the not-for-profit PERT Consortium, with guidance from an executive committee with representatives from these entities and leading investigators from North America and Europe. A clinical-events committee whose members were unaware of the treatment assignments independently adjudicated prespecified outcome events. Echocardiograms were assessed by an independent core laboratory (MedStar Health Research Institute). An independent data and safety monitoring board periodically reviewed all safety data and assessed the interim primary-outcome analysis. The members of the trial committees are listed in the Supplementary Appendix, available at NEJM.org.

PATIENTS, RANDOMIZATION, AND TRIAL INTERVENTIONS

Adult patients 18 to 80 years of age with acute, intermediate-risk pulmonary embolism in at least one main or proximal lobar pulmonary artery as confirmed by computed tomographic pulmonary angiography were eligible if they presented with a ratio of right ventricular end-diastolic diameter to left ventricular end-diastolic diameter of 1.0 or higher and abnormal cardiac troponin levels[5] and met at least two criteria for cardiorespiratory distress (systolic blood pressure of ≤110 mm Hg, tachycardia with a heart rate of ≥100 beats per minute, or tachypnea with a respiratory rate of >20 breaths per minute or hypoxemia) within the 6-hour window preceding randomization. Patients with persistent hemodynamic instability were excluded. The complete

criteria for exclusion and inclusion are listed in the Supplementary Appendix.

Patients were randomly assigned in a 1:1 ratio to undergo ultrasound-facilitated, catheter-directed fibrinolysis with alteplase plus anticoagulation (the intervention group) or to receive the current usual care, which is anticoagulation alone (the control group). Assignment was computer-randomized and stratified according to age (<75 vs. ≥75 years) and ratio of right ventricular end-diastolic diameter to left ventricular end-diastolic diameter (<1.5 vs. ≥1.5). The catheter-directed procedures were performed with the EkoSonic endovascular system (Boston Scientific),[16] in accordance with the instructions of the manufacturer and established standards. Randomization and initiation of the assigned therapy were required to occur no more than 6 hours after confirmation of pulmonary embolism and fulfillment of the additional risk criteria. For patients assigned to the intervention group, the protocol recommended initiation of therapy within 2 hours after randomization. The prespecified fibrinolysis dosing schedule and standardized anticoagulation regimens are described in the Supplementary Appendix. Outcomes within 7 days were assessed at the 7-day follow-up visit, which took place at least 7 days and no more than 9 days after randomization, or at discharge; outcomes within 30 days were assessed at the 30-day follow-up visit, which took place between 23 and 37 days after randomization.

OUTCOME MEASURES

The primary outcome was a composite of pulmonary embolism–related death, cardiorespiratory collapse or decompensation, or nonfatal, symptomatic recurrence of pulmonary embolism, as confirmed by computed tomographic angiography, within 7 days after randomization. The criteria for the primary outcome are described in the Supplementary Appendix. Cardiorespiratory collapse or decompensation was defined as at least one of the following: cardiac arrest or indication for cardiopulmonary resuscitation, signs of shock (new-onset persistent arterial hypotension accompanied by end-organ hypoperfusion), placement on extracorporeal membrane oxygenation, intubation or initiation of noninvasive mechanical ventilation, or a National Early Warning Score (NEWS)[17] that rose to or persisted at 9 or higher, as confirmed by two consecutive measurements 15 minutes apart, between 24 hours and 7 days after randomization. NEWS (Table S1 in the Supplementary Appendix) is a clinical tool that permits standardized serial assessments of a patient's vital status. Scores range from 0 to 20, with higher scores indicating greater risk; elevated scores have shown high discrimination for admission to the intensive care unit or early death.[18] In this trial, escalation to rescue treatment required documented cardiorespiratory decompensation, with fulfillment of at least one of the aforementioned criteria.

Additional outcomes assessed included major bleeding as defined according to the criteria of the International Society on Thrombosis and Haemostasis[19] within 72 hours, 7 days, and 30 days after randomization and as defined according to the criteria of the Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO)[20] within 7 days after randomization; ischemic stroke or intracranial hemorrhage within 7 days and 30 days; the change in the ratio of right ventricular end-diastolic diameter to left ventricular end-diastolic diameter within 48±6 hours; death from any cause within 7 days and 30 days; recurrence of pulmonary embolism and the occurrence of serious adverse events within 30 days; World Health Organization (WHO) functional class and the score on the Post-Venous Thromboembolism Functional Status scale (scores range from 0 to 4, with higher scores indicating more severe limitations) at 7 days and 30 days; and 6-minute walking distance at 30 days. All primary-outcome events, major bleeding, and other serious adverse events were adjudicated by the clinical-events committee.

STATISTICAL ANALYSIS

The primary analysis of the primary composite efficacy outcome was performed in the intention-to-treat population, which comprised all the patients who had undergone randomization. The hypothesis that the probability of a primary-outcome event in patients who underwent ultrasound-facilitated, catheter-directed fibrinolysis would be lower than that in patients treated with anticoagulation alone was tested with Fisher's exact test (with a two-sided alpha boundary of <0.02938; details are provided in the Supplementary Appendix). Relative risks and 95% confidence intervals are reported. In addition, an analysis was conducted in the per-protocol population, which

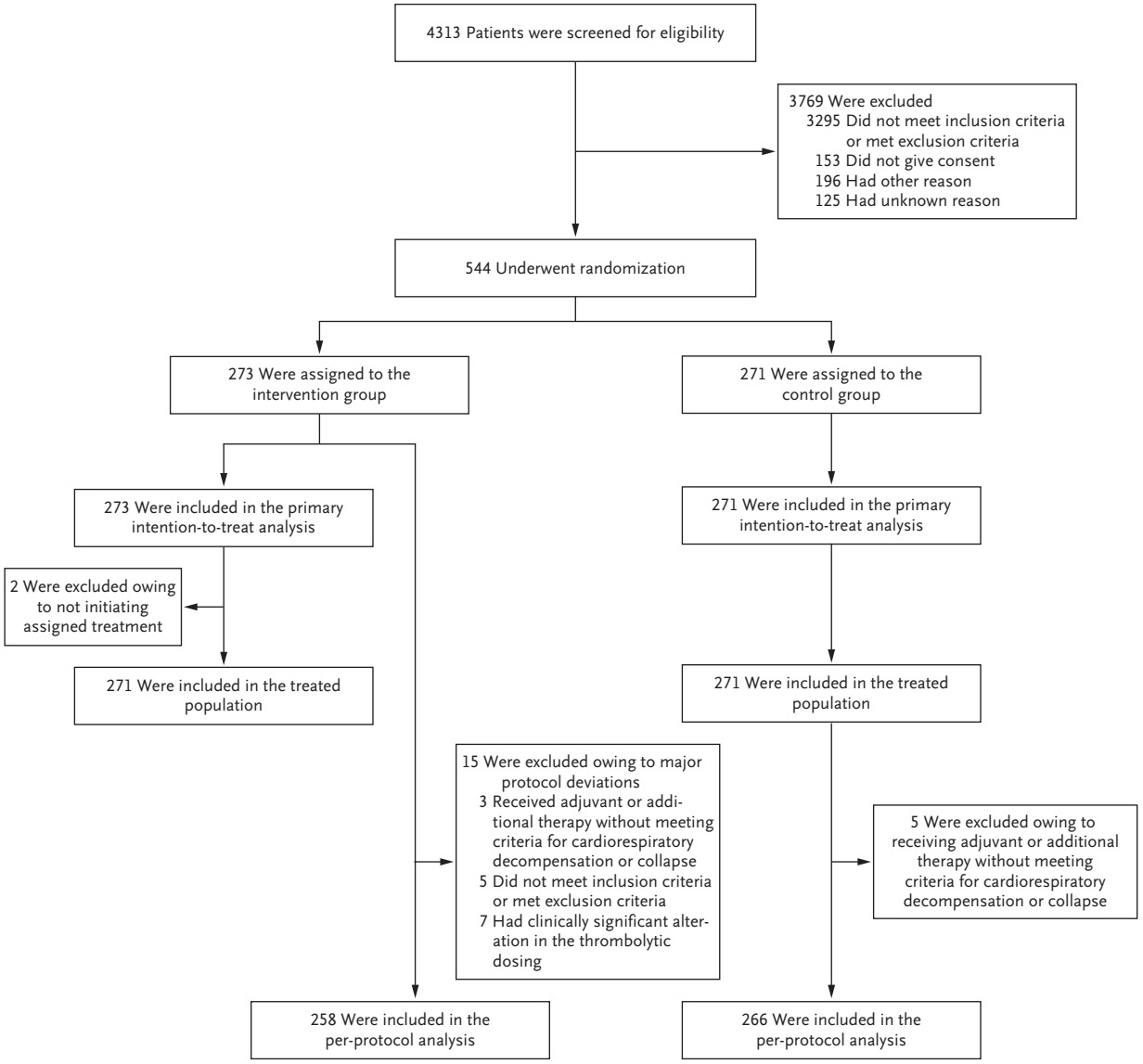

Figure 1. Randomization and Treatment.

Of 4313 patients with pulmonary embolism who were screened for eligibility, a total of 3769 were excluded. Of these patients, 3295 did not meet at least one criterion for inclusion or met at least one criterion for exclusion. Other reasons included physician discretion (88 patients), the lack of an available local investigator (41 patients), inability to meet the 6-hour window (29 patients), use of other treatment (25 patients), the patient traveling or not living near a trial site (10 patients), and participation of the patient in another clinical trial (3 patients). The treated population comprised all the patients who had undergone randomization and received treatment: ultrasound-facilitated, catheter-directed fibrinolysis (defined as activation of the EkoSonic device and initiation of fibrinolytic infusion) with anticoagulation, or anticoagulation alone. Of the 2 patients who did not begin fibrinolysis as assigned, 1 died before treatment was initiated and was excluded from the treated population but was included in the per-protocol analysis, and 1 was excluded from both the treated population and the per-protocol population because of a major protocol deviation. Major protocol deviations included receipt of adjuvant or additional therapy by a patient who did not meet the criteria for cardiorespiratory decompensation or collapse, clinically significant alterations in the thrombolytic dosing that may have posed a risk to the patient's safety or the efficacy of the assigned treatment, or violation of inclusion or exclusion criteria that may have posed a risk to the patient's safety or the efficacy of the assigned treatment.

included all the patients who had undergone randomization and had no major protocol deviations (Fig. 1). Major protocol deviations included receipt of adjuvant or additional therapy by a patient who did not meet the criteria for cardiorespiratory decompensation or collapse according to the primary-outcome definition, clinically significant alterations in the thrombolytic dosing that may have posed a risk to the patient's safety or the efficacy of the assigned treatment, or a violation of inclusion or exclusion criteria that may have posed a risk to the patient's safety or the efficacy of the assigned treatment.

The originally planned sample size of 406 patients was increased to 544 patients after the interim analysis according to prespecified criteria.[15] Assumptions about the sample size and the rules for the interim analysis are described in the Supplementary Appendix and in the statistical analysis plan, available with the protocol. A sensitivity analysis of the primary outcome was performed with logistic regression, with stratification factors and the treatment group included as covariates. Safety analyses, including analyses of adverse events and serious adverse events, were performed in the treated population, which comprised all the patients who had undergone randomization and received treatment: ultrasound-facilitated, catheter-directed fibrinolysis (defined as activation of the EkoSonic device and initiation of fibrinolytic infusion) with anticoagulation, or anticoagulation alone. Confidence intervals were not adjusted for multiplicity, and the intervals may not be used in place of hypothesis testing. Missing data for 7- and 30-day outcomes were expected for only a small number of patients, and it was assumed that data would be missing completely at random. No imputation was performed for missing data. All P values are two-sided. Analyses were performed with SAS software, version 9.4 (SAS Institute).

RESULTS

PATIENTS AND TREATMENTS

From August 2021 through July 2025, a total of 4313 patients from 59 sites in the United States and Europe were screened, and 544 patients were randomly assigned to a treatment group and included in the intention-to-treat analysis: 273 in the intervention group and 271 in the control group (Fig. 1). Of the patients who underwent randomization, 20 (3.7%) with major protocol deviations were excluded from the per-protocol analysis. The 7-day (discharge) visit was completed by 266 patients (97.4%) in the intervention group and 266 patients (98.2%) in the control group, and 30-day follow-up visits were completed by 253 (92.7%) and 250 (92.3%), respectively. Of a total of 41 patients who did not complete the 30-day visit, 9 patients (6 in the intervention group and 3 in the control group) discontinued participation in the trial before that visit; the remaining 32 patients completed later visits, which permitted recording of 30-day safety outcomes.

The mean (±SD) age of the patients who underwent randomization was 58.2±13.5 years; 42.6% were women, and 15.8% identified their race as non-White. The representativeness of the patients is shown in Table S2. Demographic and clinical characteristics are shown in Table 1; additional characteristics of the patients at baseline are summarized in Table S3. The mean symptom duration associated with acute pulmonary embolism was 3.7±3.4 days; the mean NEWS at baseline was 6.0±1.9. Ultrasound-facilitated, catheter-directed fibrinolysis was initiated no more than 2 hours after randomization in 200 patients (73.3%) in the intervention group. The mean total dose of alteplase was 8.85±0.67 mg for the 20 patients who had catheter placement on one side only and 16.92±3.47 mg for the 251 patients who had catheter placement into both the right and left pulmonary arteries; the mean total infusion duration was 7.16±0.52 hours (Table S4). Unfractionated heparin was the most commonly used anticoagulant agent in both the intervention group (in 71.6% of the patients) and the control group (in 55.7%), followed by low-molecular-weight heparin (used in 50.6% and 53.9%, respectively).

EFFICACY OUTCOMES

In the intention-to-treat population, a primary-outcome event occurred in 11 patients (4.0%) in the intervention group and in 28 patients (10.3%) in the control group (relative risk, 0.39; 95% confidence interval [CI], 0.20 to 0.77; P=0.005) (Table 2). Cardiorespiratory decompensation or collapse occurred in 10 patients (3.7%; 95% CI,

2.0 to 6.6) in the intervention group, as compared with 28 patients (10.3%; 95% CI, 7.2 to 14.5) in the control group (relative risk, 0.4; 95% CI, 0.2 to 0.7). Causes of cardiorespiratory decompensation or collapse are presented in Table S5. A NEWS of 9 or higher at least 24 hours after randomization was the only criterion for cardiopulmonary decompensation or collapse that was met in 15 patients (1 in the intervention group and 14 in the control group); the score represented a deterioration from baseline by at least 2 points in all but 1 patient, whose baseline score of 9 improved within 24 hours after randomization but subsequently worsened. The relative risk of pulmonary embolism–related death was 3.0 (95% CI, 0.3 to 28.5), and the relative risk of recurrence of pulmonary embolism within 7 days was 1.0 (95% CI, 0.1 to 15.8). Subgroup

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline (Intention-to-Treat Population).*

Characteristic	Intervention (N=273)	Control (N=271)	Standardized Difference†
			percent
Demographic data			
Age — yr	58.2±13.6	58.2±13.4	0.2
Female sex — no. (%)	114 (41.8)	118 (43.5)	3.6
Clinical status			
Body-mass index‡	32.9±8.5	33.4±8.2	5.0
Frailty index§	1.9±0.7	1.9±0.7	2.0
Duration of symptoms (current episode) — days¶	3.5±3.3	3.9±3.5	12.5
Dyspnea — no. (%)	254 (93.0)	242 (89.3)	13.2
Chest pain — no. (%)	87 (31.9)	101 (37.3)	11.4
Syncope — no. (%)	67 (24.5)	64 (23.6)	2.2
Tachycardia — no. (%)‖	210 (76.9)	215 (79.3)	5.8
Prolonged hypotension — no. (%)	4 (1.5)	6 (2.2)	5.6
Tachypnea — no. (%)**	118 (43.2)	142 (52.4)	18.4
Hypoxemia — no. (%)	135 (49.5)	130 (48.0)	3.0
National Early Warning Score††	6.0±1.9	6.0±1.9	2.2
Concomitant ultrasound-confirmed, lower-extremity deep-vein thrombosis — no. (%)			
Yes	107 (39.2)	109 (40.2)	2.1
No	82 (30.0)	86 (31.7)	
Ultrasound not performed	84 (30.8)	76 (28.0)	
Imaging findings			
Bilateral pulmonary embolism — no. (%)‡‡	251 (91.9)	262 (96.7)	20.6
RV:LV ratio§§	1.6±0.5	1.5±0.4	12.5
Medical history — no. (%)			
Congestive heart failure			
Yes	4 (1.5)	9 (3.3)	12.2
No	267 (97.8)	259 (95.6)	
Unknown	2 (0.7)	3 (1.1)	
Transient ischemic attack or stroke			
Yes	7 (2.6)	11 (4.1)	8.4
No	266 (97.4)	259 (95.6)	
Unknown	0	1 (0.4)	

Table 1. (Continued.)

Characteristic	Intervention (N=273)	Control (N=271)	Standardized Difference†
			percent
Current or previous cancer¶¶			
Yes	29 (10.6)	21 (7.7)	10.0
No	236 (86.4)	249 (91.9)	
Unknown	8 (2.9)	1 (0.4)	
Chronic obstructive pulmonary disease			
Yes	13 (4.8)	14 (5.2)	1.9
No	256 (93.8)	247 (91.1)	
Unknown	4 (1.5)	10 (3.7)	

* Plus–minus values are means ±SD. The intention-to-treat population included all the patients who underwent randomization.
† The standardized difference between groups was calculated as the difference in means or percentages divided by the pooled standard deviation, with the type of calculation dependent on the type of variable.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters. Data were missing for 1 patient (0.4%) in each group.
§ The frailty index is the age in years divided by the body-mass index. Data were missing for 1 patient (0.4%) in each group.
¶ Data were missing for 1 patient (0.4%) in each group.
‖ Tachycardia was reported by the investigator.
** Tachypnea was reported by the investigator.
†† National Early Warning Scores range from 0 to 20, with higher scores indicating greater risk. Data were missing for 2 patients (0.7%) in the control group.
‡‡ Data were missing for 2 patients (0.7%) in the intervention group.
§§ The ratio of right ventricular end-diastolic diameter to left ventricular end-diastolic diameter (RV:LV ratio) was determined on the basis of computed tomographic pulmonary angiography.
¶¶ Current or previous cancer includes active cancer and cancer in remission.

analyses of the primary outcome according to randomization strata and according to country are presented in Figures S1 and S2, respectively. Results for the primary outcome were consistent in the per-protocol population (Table S6) and in the sensitivity analysis that accounted for the stratification factors of age and ratio of right ventricular end-diastolic diameter to left ventricular end-diastolic diameter (odds ratio, 0.36; 95% CI, 0.18 to 0.75).

ADDITIONAL ASSESSMENTS

No apparent between-group differences in the incidence of major bleeding[19] were observed up to 30 days after randomization (4.1% vs. 3.0%; relative risk, 1.4; 95% CI, 0.6 to 3.4; P=0.64), and no intracranial hemorrhage occurred in either group in the treated population; detailed results are shown in Table 3. Results were consistent in the intention-to-treat population (Table S7) and the per-protocol population (Table S8). Within 30 days after randomization, the incidence of death from any cause, recurrence of symptomatic pulmonary embolism, and serious adverse events did not appear to differ substantially between the treatment groups; outcomes in the treated population are shown in Table 4, and outcomes in the intention-to-treat and per-protocol populations are shown in Tables S9 and S10, respectively.

Of the nine deaths that occurred in the intention-to-treat population during the period from randomization through 30 days after randomization, four deaths (three of six in the intervention group and one of three in the control group) were adjudicated to be pulmonary embolism–related. One patient who was enrolled despite the presence of exclusion criteria and assigned to the intervention group died from inguinal hemorrhage 9 days after randomization. Information on the causes of all the deaths is provided in Table S11; serious adverse events through the 30-day follow-up are listed in Table S12, and site-reported adverse events are listed in Table S13. Changes in

Table 2. Clinical Efficacy Outcomes (Intention-to-Treat Population).*

Outcome	Intervention (N=273)		Control (N=271)		Relative Risk (95% CI)†
	no. of patients	*% (95% CI)†*	*no. of patients*	*% (95% CI)†*	
Any primary-outcome event	11	4.0 (2.3–7.1)	28	10.3 (7.2–14.5)	0.39 (0.20–0.77)‡
Components of the primary outcome					
Pulmonary embolism–related death	3	1.1 (0.4–3.2)	1	0.4 (0.1–2.1)	3.0 (0.3–28.5)
Cardiorespiratory decompensation or collapse	10	3.7 (2.0–6.6)	28	10.3 (7.2–14.5)	0.4 (0.2–0.7)
Recurrence of pulmonary embolism	1	0.4 (0.1–2.0)	1	0.4 (0.1–2.1)	1.0 (0.1–15.8)

* The primary composite efficacy outcome was evaluated in the intention-to-treat population of 544 patients at 7 days (or as late as 9 days in some cases) after randomization or at discharge; 2 patients (1 in each group) withdrew from the trial before the 7-day visit and were considered to have missing data. All outcome events were independently adjudicated by a clinical-events committee whose members were unaware of the treatment assignments.

† The 95% confidence intervals were determined with the Wilson method[21] and were not adjusted for multiplicity.

‡ P=0.005. The two-sided P value was calculated with Fisher's exact test; a value of less than 0.02938 was considered to indicate significance.

right ventricular dysfunction by 48±6 hours after randomization in the two treatment groups, as assessed by the ratio of right ventricular end-diastolic diameter to left ventricular end-diastolic diameter on transthoracic echocardiograms and determined by a core laboratory, are shown in Table S14.

After randomization, 8 patients (2.9%) in the intervention group underwent rescue therapy, as compared with 25 (9.2%) in the control group; escalation to rescue treatment followed documented cardiorespiratory collapse or decompensation, with fulfillment of at least one prespecified criterion, in 78.8% of the cases. The criteria for rescue therapy that were fulfilled and the rescue procedures that were performed are summarized in Table S15. The mean duration of the hospital stay was 5.77±5.02 days in the intervention group and 6.48±4.88 days in the control group (mean difference, −0.71 days; 95% CI, −1.55 to 0.12; data were missing for 1 patient [0.4%] in the intervention group). In the intervention group, 71.1% of the patients were admitted to the intensive care unit, as compared with 50.2% in the control group, and the mean duration of stay in the intensive care unit was 2.19±3.02 days and 2.78±3.09 days, respectively (mean difference, −0.59 days; 95% CI, −1.27 to 0.09; data were missing for 7 patients [2.6%] in the intervention group).

The WHO functional class, which was assessed at 7 days after randomization (or at discharge) and at 30 days, is shown in Table S16; the Post-Venous Thromboembolism Functional Status is shown in Table S17. At 30 days, the median distance walked in 6 minutes was 405.0 m (interquartile range, 311.0 to 501.4) in the intervention group and 393.0 m (interquartile range, 280.0 to 502.0) in the control group; data were available for 228 patients and 225 patients, respectively.

DISCUSSION

In this randomized, controlled trial involving patients with acute, intermediate-risk pulmonary embolism, ultrasound-facilitated, catheter-directed fibrinolysis plus anticoagulation led to a lower risk of the composite of pulmonary embolism–related death, cardiopulmonary decompensation or collapse, or recurrence of pulmonary embolism than anticoagulation alone, with a relative risk of 0.39 (95% CI, 0.20 to 0.77). The difference between the two groups was driven by a lower incidence of cardiorespiratory decompensation or collapse within 7 days after randomization in the intervention group than in the control group. No clear differences were observed between the two treatment groups with regard to the incidence of major bleeding or other serious adverse events through 30 days of follow-up, and no intracranial hemorrhage occurred in either group.

For decades, systemic fibrinolytic therapy has consistently been shown to restore hemodynamic stability and right ventricular function, which prevents cardiorespiratory collapse and possibly death.[6,22-24] However, the increased risk of major

Table 3. Cumulative Major Bleeding Events through 30 Days (Treated Population).*

Event	Intervention (N=271)	Control (N=271)	Relative Risk (95% CI)†	P Value‡
	no. of patients (%)			
Major bleeding according to ISTH criteria				
Within 72 h	10 (3.7)	4 (1.5)	2.5 (0.8–7.9)	0.17
Within 7 days	11 (4.1)	6 (2.2)	1.8 (0.7–4.9)	0.32
Within 30 days	11 (4.1)	8 (3.0)	1.4 (0.6–3.4)	0.64
Moderate-to-severe bleeding within 7 days according to GUSTO criteria	9 (3.3)	4 (1.5)	2.3 (0.7–7.2)	0.26
Ischemic stroke				
Within 7 days	1 (0.4)	0	NE	1.00
Within 30 days	1 (0.4)	0	NE	1.00
Intracranial hemorrhage				
Within 7 days	0	0	NE	1.00
Within 30 days	0	0	NE	1.00

* All major bleeding events and strokes were evaluated in the treated population of 542 patients, which comprised all the patients who had undergone randomization and received treatment: ultrasound-facilitated, catheter-directed fibrinolysis (defined as activation of the EkoSonic device and initiation of fibrinolytic infusion) with anticoagulation, or anticoagulation alone. The numbers shown reflect the cumulative number of events from randomization to the indicated time point. All the events reported were independently adjudicated by a clinical-events committee whose members were unaware of the treatment assignments. Outcomes within 7 days were assessed at the 7-day follow-up visit, which took place at least 7 days and no more than 9 days after randomization, or at discharge; outcomes within 30 days were assessed at the 30-day follow-up visit, which took place between 23 and 37 days after randomization. At 72 hours and 7 days, 1 patient (0.4%) in the control group had missing data; at 30 days, 6 patients (2.2%) in the intervention group and 3 (1.1%) in the control group had missing data because they had withdrawn from the trial before the 30-day visit. GUSTO denotes Global Use of Strategies to Open Occluded Coronary Arteries, ISTH International Society on Thrombosis and Haemostasis, and NE not evaluable.

† Confidence intervals were not adjusted for multiplicity.

‡ Two-sided P values were determined with Fisher's exact test.

bleeding associated with fibrinolytic therapy, particularly intracranial hemorrhage,[25,26] has limited the widespread adoption of this treatment in clinical practice.[27,28] Ultrasound-facilitated, catheter-directed fibrinolysis allows low doses of alteplase to be infused locally, with the aim of maintaining efficacy while reducing the risk of major bleeding. The present trial was designed to validate the clinical efficacy and safety of this procedure in direct comparison to the currently recommended usual care for this risk category.[5]

We enrolled patients with intermediate-risk pulmonary embolism as defined by an earlier trial[6] and current guidelines[5]; the additional criteria of cardiorespiratory distress, defined according to blood pressure, heart rate, and respiratory function at presentation, allowed for better focus on the patients most likely to benefit from advanced treatment.[3,29] These criteria were chosen on the basis of findings from a large, randomized trial of systemic fibrinolysis as compared with anticoagulation, as well as an observational study of large patient cohorts.[30,31] In the intervention group, ultrasound-facilitated, catheter-directed fibrinolysis was initiated no later than 2 hours after randomization in 73.3% of the cases, which minimized selection bias toward patients who were already recovering from the acute episode.

The mandated protocol of ultrasound-facilitated, catheter-directed fibrinolysis was based on insights from previous studies and real-world experience.[8-11] This protocol was in contrast to the approach in previous trials, which left the catheter-based fibrinolytic regimen to the discretion of local investigators.[32,33] Similarly, a standardized anticoagulation regimen was stipulated for both treatment groups. In view of the strong adherence of the participating sites to the trial protocol, our results indicate that the inter-

Table 4. Mortality, Recurrence of Pulmonary Embolism, and Serious Adverse Events through 30 Days (Treated Population).*

Event	Intervention (N=271)	Control (N=271)	Relative Risk (95% CI)†
	no. of patients (%)		
Death from any cause through 7 days	3 (1.1)	2 (0.7)	1.5 (0.3–8.9)
Outcomes through 30 days			
Death from any cause	5 (1.8)	3 (1.1)	1.7 (0.4–6.9)
Symptomatic recurrence of pulmonary embolism	1 (0.4)	2 (0.7)	0.5 (0.0–5.5)
Any serious adverse event‡	40 (14.8)	44 (16.2)	0.9 (0.6–1.3)§

* The numbers shown reflect the cumulative number of events from randomization to the indicated time point. Deaths and symptomatic recurrences of pulmonary embolism were independently adjudicated by a clinical-events committee whose members were unaware of the treatment assignments. At 7 days, 1 patient (0.4%) in the control group had missing data; at 30 days, 6 patients (2.2%) in the intervention group and 3 (1.1%) in the control group had missing data because they had withdrawn from the trial before the 30-day visit.

† Confidence intervals were not adjusted for multiplicity.

‡ The numbers shown include all the patients with reported serious adverse events, regardless of the adjudication of the events by the clinical-events committee.

§ P=0.64. The two-sided P value was determined with a Cochran–Mantel–Haenszel test with stratification according to age (<75 vs. ≥75 years) and ratio of right ventricular end-diastolic diameter to left ventricular end-diastolic diameter (<1.5 vs. ≥1.5).

vention tested has a favorable efficacy and safety profile in this patient population with intermediate risk. Patient follow-up over a 12-month period is ongoing to address the possible effects of ultrasound-facilitated, catheter-directed fibrinolysis on late outcomes after pulmonary embolism.[15]

In trials testing catheter interventions, open-label randomization introduces the risk of expectation bias on the part of investigators, who may proceed to treatment escalation early when they believe that a patient's condition is not improving fast enough. To mitigate this risk, rescue treatment was not an outcome itself in this trial, but it could be used only after at least one criterion for cardiorespiratory decompensation or collapse had been fulfilled. However, the trial protocol also addressed the need for standardized, early recognition of failure of the assigned treatment.[29] Specifically, the criteria for cardiorespiratory decompensation or collapse included a persistently high NEWS (≥9) after the first 24 hours after randomization. Helping to reproducibly quantify a patient's vital status, this score is broadly used in hospitals in many countries and has repeatedly been validated as a reliable monitoring tool for detecting clinical decompensation, with values similar to or lower than the one used in the present trial considered to indicate a medical emergency.[18,34,35]

The present trial has limitations. Patient randomization was not blinded, but all primary-outcome and safety events were independently adjudicated by a committee whose members were unaware of the treatment assignments. Mortality was low in both treatment groups, despite the inclusion criteria for intermediate risk; however, this result largely reflects a principal safety aspect of the trial, which was to prevent hemodynamic collapse and death. Objective documentation of cardiorespiratory decompensation allowed for rescue treatment in 2.9% of the patients in the intervention group and 9.2% of those in the control group, which may have prevented deaths.

Owing to the overall low frequency of events, the trial did not have the power to compare treatment efficacy in specified patient subgroups or to allow for firm conclusions with regard to differences in bleeding complications between the two treatment groups. Standardized differences larger than 10% suggest possible imbalance of some baseline variables between the two treatment groups. In addition, only 10.1% of the patients were 75 years of age or older, and the mean frailty index (the age in years divided by the body-mass index) of the patients was moderate. Because randomization was not stratified by site, potential center-level effects cannot be excluded. The results may differ in more ethnically diverse

populations. Finally, we did not test whether similar results might be obtained with other catheter-based interventions or reduced-dose systemic fibrinolysis. Trials testing various methods of advanced treatment were recently reported[36] or are currently under way[37-39]; together with the present trial, they may provide the evidence to inform future guideline recommendations.

In this trial, ultrasound-facilitated, catheter-directed fibrinolysis plus anticoagulation led to a lower risk of the composite of pulmonary embolism–related death, cardiopulmonary decompensation or collapse, or symptomatic recurrence of pulmonary embolism within 7 days than anticoagulation alone in patients with acute, intermediate-risk pulmonary embolism. No apparent differences between the two treatment groups with regard to major bleeding complications were observed.

Supported by Boston Scientific.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

We thank Elizabeth Davis, Ph.D. (Boston Scientific), who helped coordinate the manuscript writing process.

AUTHOR INFORMATION

Kenneth Rosenfield, M.D.,[1] Frederikus A. Klok, M.D., Ph.D.,[2,3] Gregory Piazza, M.D.,[4,5] Andrew S.P. Sharp, M.D.,[6,7] Fionnuala Ní Áinle, M.D.,[6] Michael R. Jaff, D.O.,[8] Stefano Barco, M.D., Ph.D.,[3,9] Samuel Z. Goldhaber, M.D.,[4,5] Nils Kucher, M.D.,[9] Irene M. Lang, M.D.,[10] Irene Schmidtmann, Ph.D.,[11] Keith M. Sterling, M.D.,[8] Aleksander Araszkiewicz, M.D.,[12] Vishal Arora, M.D.,[13] Rafael Cires-Drouet, M.D.,[14] John Coghlan, M.D.,[15] Lukas Hobohm, M.D.,[3,16] Wulf D. Ito, M.D.,[17] Kurt Jacobson, M.D., M.H.S.A,[18] Christoph Kaiser, M.D.,[19] Grzegorz Kopec, M.D.,[20,21] Kristin Marx, M.D.,[22] Samuel McElwee, M.D.,[23] Nicolas Meneveau, M.D., Ph.D.,[24-26] Peter Monteleone, M.D.,[27] Jose M. Montero-Cabezas, M.D., Ph.D.,[28] Christoph B. Olivier, M.D.,[29,30] John Park, M.D.,[31] Marek Roik, M.D., Ph.D.,[32] Rahul Sakhuja, M.D., M.P.P.,[1] Andi Tego, M.D.,[22] Markus Theurl, M.D., Ph.D.,[33] Gautam Visveswaran, M.D.,[34] Jan Albert Vos, M.D.,[35] Michael N. Young, M.D.,[36,37] Federico M. Asch, M.D.,[38] and Stavros V. Konstantinides, M.D.[3,39]

[1] Division of Cardiology, Massachusetts General Hospital, Boston; [2] Division of Thrombosis and Hemostasis, Department of Medicine, Leiden University Medical Center, Leiden, the Netherlands; [3] Center for Thrombosis and Hemostasis, University Medical Center of the Johannes Gutenberg University, Mainz, Germany; [4] Thrombosis Research Group, Brigham and Women's Hospital, Harvard Medical School, Boston; [5] Division of Cardiovascular Medicine, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston; [6] University College Dublin School of Medicine, Dublin; [7] Boston Scientific, Galway, Ireland; [8] Boston Scientific, Marlborough, MA; [9] Department of Vascular Medicine, University Hospital Zurich, Zurich, Switzerland; [10] Department of Internal Medicine II, Division of Cardiology, Medical University of Vienna, Vienna; [11] Department of Biostatistics and Bioinformatics, Institute of Medical Biostatistics, Epidemiology and Informatics, University Medical Center of the Johannes Gutenberg University, Mainz, Germany; [12] Department of Cardiology, Poznan University of Medical Sciences, Poznań, Poland; [13] Augusta University, Augusta, GA; [14] University of Texas Southwestern Medical Center, Dallas; [15] Royal Free Hospital, London; [16] Department of Cardiology, University Medical Center of the Johannes Gutenberg University, Mainz, Germany; [17] Department of Angiology and Cardiology, Heart and Vascular Center Klinikverbund Allgäu, Klinik Immenstadt, Immenstadt, Germany; [18] Division of Cardiovascular Medicine, University of Wisconsin Hospitals and Clinics, Madison; [19] University Hospital Basel, Basel, Switzerland; [20] Department of Cardiac and Vascular Diseases, Pulmonary Circulation Center, Jagiellonian University Medical College, Krakow, Poland; [21] Department of Cardiac and Vascular Diseases, St. John Paul II Hospital, Krakow, Poland; [22] Department of Cardiology and Intensive Care Medicine, University Hospital Ostwestfalen-Lippe of Bielefeld University, Campus Klinikum Bielefeld, Bielefeld, Germany; [23] University of Alabama at Birmingham, Birmingham; [24] Department of Cardiology, University Hospital Besançon, Besançon, France; [25] Marie and Louis Pasteur University, Besançon, France; [26] Sinergies Laboratory, Besançon, France; [27] Ascension Texas Cardiovascular, University of Texas Austin Dell School of Medicine, Austin; [28] Department of Cardiology, Leiden University Medical Center, Leiden, the Netherlands; [29] Department of Cardiology and Angiology, University Heart Center Freiburg Bad Krozingen, Bad Krozingen, Germany; [30] Faculty of Medicine, University of Freiburg, Freiburg, Germany; [31] Nebraska Methodist Hospital, Omaha; [32] Department of Internal Medicine and Cardiology with Center for Venous Thromboembolism, Medical University of Warsaw, Warsaw, Poland; [33] Divisions of Cardiology and Angiology, University Hospital of Internal Medicine III, Medical University of Innsbruck, Innsbruck, Austria; [34] Newark Beth Israel Medical Center, Newark, NJ; [35] St. Antonius Ziekenhuis, Nieuwegein, the Netherlands; [36] Division of Cardiology, Dartmouth Hitchcock Medical Center, Lebanon, NH; [37] Geisel School of Medicine at Dartmouth, Hanover, NH; [38] MedStar Health Research Institute, Washington, DC; [39] Department of Cardiology, Democritus University of Thrace, Alexandroupolis, Greece.

REFERENCES

1. Piazza G. Advanced management of intermediate- and high-risk pulmonary embolism: JACC focus seminar. J Am Coll Cardiol 2020;76:2117-27.

2. Jaff MR, McMurtry MS, Archer SL, et al. Management of massive and submassive pulmonary embolism, iliofemoral deep vein thrombosis, and chronic thromboembolic pulmonary hypertension: a scientific statement from the American Heart Association. Circulation 2011;123:1788-830.

3. Giri J, Sista AK, Weinberg I, et al. Interventional therapies for acute pulmonary embolism: current status and principles for the development of novel evidence: a scientific statement from the American Heart Association. Circulation 2019;140(20):e774-e801.

4. Goldberg JB, Giri J, Kobayashi T, et al. Surgical management and mechanical circulatory support in high-risk pulmonary embolisms: historical context, current status, and future directions: a scientific statement from the American Heart Association. Circulation 2023;147(9):e628-e647.

5. Konstantinides SV, Meyer G, Becattini C, et al. 2019 ESC guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS). Eur Heart J 2020;41:543-603.

6. Meyer G, Vicaut E, Danays T, et al. Fibrinolysis for patients with intermediate-

risk pulmonary embolism. N Engl J Med 2014;370:1402-11.
7. Ariëns RAS, Sharp ASP, Duval C. Ultrasound-mediated catheter delivery of tissue plasminogen activator promotes thrombolysis by altering fibrin fiber thickness and clot permeability. Haematologica 2025;110:665-72.
8. Kucher N, Boekstegers P, Müller OJ, et al. Randomized, controlled trial of ultrasound-assisted catheter-directed thrombolysis for acute intermediate-risk pulmonary embolism. Circulation 2014;129:479-86.
9. Piazza G, Hohlfelder B, Jaff MR, et al. A prospective, single-arm, multicenter trial of ultrasound-facilitated, catheter-directed, low-dose fibrinolysis for acute massive and submassive pulmonary embolism: The SEATTLE II Study. JACC Cardiovasc Interv 2015;8:1382-92.
10. Tapson VF, Sterling K, Jones N, et al. A randomized trial of the optimum duration of acoustic pulse thrombolysis procedure in acute intermediate-risk pulmonary embolism: the OPTALYSE PE Trial. JACC Cardiovasc Interv 2018;11:1401-10.
11. Sterling KM, Goldhaber SZ, Sharp ASP, et al. Prospective multicenter international registry of ultrasound-facilitated catheter-directed thrombolysis in intermediate-high and high-risk pulmonary embolism (KNOCOUT PE). Circ Cardiovasc Interv 2024;17(3):e013448.
12. Draxler DF, Johannes JK, Nakase M, et al. Clinical outcomes in patients with acute pulmonary embolism undergoing ultrasound-assisted catheter-directed thrombolysis. J Am Heart Assoc 2025;14(9):e035916.
13. Dhruva SS, Redberg RF. Coverage of transvenous pulmonary embolectomy — Medicare's missed opportunity for evidence generation. N Engl J Med 2022;386:904-6.
14. Stevens SM, Woller SC, Kreuziger LB, et al. Antithrombotic therapy for VTE disease: second update of the CHEST guideline and expert panel report. Chest 2021;160(6):e545-e608.
15. Klok FA, Piazza G, Sharp ASP, et al. Ultrasound-facilitated, catheter-directed thrombolysis vs anticoagulation alone for acute intermediate-high-risk pulmonary embolism: rationale and design of the HI-PEITHO study. Am Heart J 2022;251:43-53.
16. Hobohm L, Keller K, Münzel T, Gori T, Konstantinides SV. EkoSonic endovascular system and other catheter-directed treatment reperfusion strategies for acute pulmonary embolism: overview of efficacy and safety outcomes. Expert Rev Med Devices 2020;17:739-49.
17. Smith GB, Prytherch DR, Meredith P, Schmidt PE, Featherstone PI. The ability of the National Early Warning Score (NEWS) to discriminate patients at risk of early cardiac arrest, unanticipated intensive care unit admission, and death. Resuscitation 2013;84:465-70.
18. Liu VX, Lu Y, Carey KA, et al. Comparison of early warning scoring systems for hospitalized patients with and without infection at risk for in-hospital mortality and transfer to the intensive care unit. JAMA Netw Open 2020;3(5):e205191.
19. Schulman S, Kearon C, Subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. J Thromb Haemost 2005;3:692-4.
20. GUSTO investigators. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. N Engl J Med 1993;329:673-82.
21. Wilson EB. Probable inference, the law of succession, and statistical inference. J Am Stat Assoc 1927;22:209-12 (https://www.jstor.org/stable/2276774?seq=1).
22. Dalla-Volta S, Palla A, Santolicandro A, et al. PAIMS 2: alteplase combined with heparin versus heparin in the treatment of acute pulmonary embolism: plasminogen activator Italian multicenter study 2. J Am Coll Cardiol 1992;20:520-6.
23. Goldhaber SZ, Haire WD, Feldstein ML, et al. Alteplase versus heparin in acute pulmonary embolism: randomised trial assessing right-ventricular function and pulmonary perfusion. Lancet 1993;341:507-11.
24. Konstantinides S, Geibel A, Heusel G, Heinrich F, Kasper W; Management Strategies and Prognosis of Pulmonary Embolism-3 Trial Investigators. Heparin plus alteplase compared with heparin alone in patients with submassive pulmonary embolism. N Engl J Med 2002;347:1143-50.
25. Chatterjee S, Chakraborty A, Weinberg I, et al. Thrombolysis for pulmonary embolism and risk of all-cause mortality, major bleeding, and intracranial hemorrhage: a meta-analysis. JAMA 2014;311:2414-21.
26. 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.
27. Keller K, Hobohm L, Ebner M, et al. Trends in thrombolytic treatment and outcomes of acute pulmonary embolism in Germany. Eur Heart J 2020;41:522-9.
28. Stein PD, Matta F. Thrombolytic therapy in unstable patients with acute pulmonary embolism: saves lives but underused. Am J Med 2012;125:465-70.
29. Pruszczyk P, Klok FA, Kucher N, et al. Percutaneous treatment options for acute pulmonary embolism: a clinical consensus statement by the ESC Working Group on Pulmonary Circulation and Right Ventricular Function and the European Association of Percutaneous Cardiovascular Interventions. EuroIntervention 2022;18(8):e623-e638.
30. Barco S, Vicaut E, Klok FA, Lankeit M, Meyer G, Konstantinides SV. Improved identification of thrombolysis candidates amongst intermediate-risk pulmonary embolism patients: implications for future trials. Eur Respir J 2018;51:1701775.
31. Jaureguízar A, Jiménez D, Bikdeli B, et al. Heart rate and mortality in patients with acute symptomatic pulmonary embolism. Chest 2022;161:524-34.
32. Jaber WA, Gonsalves CF, Stortecky S, et al. Large-bore mechanical thrombectomy versus catheter-directed thrombolysis in the management of intermediate-risk pulmonary embolism: primary results of the PEERLESS randomized controlled trial. Circulation 2025;151:260-73.
33. Avgerinos ED, Jaber W, Lacomis J, et al. Randomized trial comparing standard versus ultrasound-assisted thrombolysis for submassive pulmonary embolism: the SUNSET sPE trial. JACC Cardiovasc Interv 2021;14:1364-73.
34. Price C, Prytherch D, Kostakis I, Briggs J. Evaluating the performance of the National Early Warning Score in different diagnostic groups. Resuscitation 2023;193:110032.
35. Janata K, Lipa AJ, Merrelaar A, et al. Enhancing pulmonary embolism risk stratification: the National Early Warning Score and its integration into the European Society of Cardiology Classification. Thromb Haemost 2026;126:192-201.
36. Lookstein RA, Konstantinides SV, Weinberg I, et al. Randomized controlled trial of mechanical thrombectomy with anticoagulation versus anticoagulation alone for acute intermediate-high risk pulmonary embolism: primary outcomes from the STORM-PE trial. Circulation 2026;153:21-34.
37. Giri J, Mahfoud F, Gebauer B, et al. PEERLESS II: a randomized controlled trial of large-bore thrombectomy versus anticoagulation in intermediate-risk pulmonary embolism. J Soc Cardiovasc Angiogr Interv 2024;3:101982.
38. Sista AK, Troxel AB, Tarpey T, et al. Rationale and design of the PE-TRACT trial: a multicenter randomized trial to evaluate catheter-directed therapy for the treatment of intermediate-risk pulmonary embolism. Am Heart J 2025;281:112-22.
39. Sanchez O, Charles-Nelson A, Ageno W, et al. Reduced-dose intravenous thrombolysis for acute intermediate-high-risk pulmonary embolism: rationale and design of the Pulmonary Embolism International THrOmbolysis (PEITHO)-3 trial. Thromb Haemost 2022;122:857-66.