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Catheter-Directed Thrombolysis vs Anticoagulation in Patients With Acute Intermediate-High–risk Pulmonary Embolism
The CANARY Randomized Clinical Trial

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IMPORTANCE The optimal treatment of intermediate-high–risk pulmonary embolism (PE) remains unknown.

OBJECTIVE To assess the effect of conventional catheter-directed thrombolysis (cCDT) plus anticoagulation vs anticoagulation monotherapy in improving echocardiographic measures of right ventricle (RV) to left ventricle (LV) ratio in acute intermediate-high–risk PE.

DESIGN, SETTING, AND PARTICIPANTS The Catheter-Directed Thrombolysis vs Anticoagulation in Patients with Acute Intermediate-High–Risk Pulmonary Embolism (CANARY) trial was an open-label, randomized clinical trial of patients with intermediate-high–risk PE, conducted in 2 large cardiovascular centers in Tehran, Iran, between December 22, 2018, through February 2, 2020.

INTERVENTIONS Patients were randomly assigned to cCDT (alteplase, 0.5 mg/catheter/h for 24 hours) plus heparin vs anticoagulation monotherapy.

MAIN OUTCOMES AND MEASURES The proportion of patients with a 3-month echocardiographic RV/LV ratio greater than 0.9, assessed by a core laboratory, was the primary outcome. The proportion of patients with an RV/LV ratio greater than 0.9 at 72 hours after randomization and the 3-month all-cause mortality were among secondary outcomes. Major bleeding (Bleeding Academic Research Consortium type 3 or 5) was the main safety outcome. A clinical events committee, masked to the treatment assignment, adjudicated clinical outcomes.

RESULTS The study was prematurely stopped due to the COVID-19 pandemic after recruiting 94 patients (mean [SD] age, 58.4 [2.5] years; 27 women [29%]), of whom 85 patients completed the 3-month echocardiographic follow-up. Overall, 2 of 46 patients (4.3%) in the cCDT group and 5 of 39 patients (12.8%) in the anticoagulation monotherapy group met the primary outcome (odds ratio [OR], 0.31; 95% CI, 0.06-1.69; $P = .24$). The median (IQR) 3-month RV/LV ratio was significantly lower with cCDT (0.7 [0.6-0.7]) than with anticoagulation (0.8 [0.7-0.9]); $P = .01$). An RV/LV ratio greater than 0.9 at 72 hours after randomization was observed in fewer patients treated with cCDT (13 of 48 [27.0%]) than anticoagulation (24 of 46 [52.1%]; OR, 0.34; 95% CI, 0.14-0.80; $P = .01$). Fewer patients assigned to cCDT experienced a 3-month composite of death or RV/LV greater than 0.9 (2 of 48 [4.3%] vs 8 of 46 [17.3%]; OR, 0.20; 95% CI, 0.04-1.03; $P = .048$). One case of nonfatal major gastrointestinal bleeding occurred in the cCDT group.

CONCLUSIONS AND RELEVANCE This prematurely terminated randomized clinical trial of patients with intermediate-high–risk PE was hypothesis-generating for improvement in some efficacy outcomes and acceptable rate of major bleeding for cCDT compared with anticoagulation monotherapy and provided support for a definitive clinical outcomes trial.

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Visual Abstract

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Supplemental content

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The role of reperfusion therapy in intermediate-risk pulmonary embolism (PE) is still debated. Patients with accompanying right ventricular (RV) dysfunction and/or elevated cardiac biomarkers have a higher risk for decompensation or death compared with patients who have lower-risk PE.[1] In the Pulmonary Embolism Thrombolysis (PEITHO) trial, full-dose systemic fibrinolytic therapy was tested in patients with intermediate-high-risk PE compared with anticoagulation monotherapy.[2] Although the risk of clinical deterioration was lower in patients treated with fibrinolytic therapy, the higher incidence of bleeding events counterbalanced the benefit.[2]

Catheter-directed thrombolysis (CDT) may optimize fibrinolytic drug delivery into the pulmonary arteries and consequently decrease the required dose, which may translate to fewer bleeding events. In prior observational studies and relatively small clinical trials of CDT, potentially beneficial effects were observed on short-term metrics, such as RV function.[3-6] However, it remains unknown whether there is a durable beneficial effect on improving RV function (lasting beyond short-term follow-up) for CDT compared with anticoagulation monotherapy. Accordingly, we compared the effect of conventional CDT (cCDT) plus anticoagulation vs anticoagulation monotherapy on decreasing the 3-month proportion of patients with an RV to left ventricle (LV) ratio (RV/LV) greater than 0.9 in patients with acute intermediate-high-risk PE.

Key Points

Question What are the effects of conventional catheter-directed thrombolysis (cCDT) plus anticoagulation in patients with acute intermediate-high–risk pulmonary embolism (PE)?

Findings In this prematurely terminated randomized clinical trial of 94 patients with intermediate-high–risk PE, cCDT compared with anticoagulation monotherapy did not significantly decrease the proportion of patients with a 3-month right ventricle to left ventricle ratio of greater than 0.9 but was associated with improvement in other imaging parameters. There was only 1 case of nonfatal major bleeding with cCDT.

Meaning The findings are encouraging for the design and execution of a definitive clinical outcomes trial.

Methods

Trial Oversight and Design

The Catheter-Directed Thrombolysis vs Anticoagulation Monotherapy in Patients With Acute Intermediate-High-Risk Pulmonary Embolism (CANARY) trial was an open-label, parallel-group, masked-end point, randomized clinical trial performed in 2 large cardiovascular centers in Tehran, Iran: the Rajaie Cardiovascular, Medical and Research Center and the Tehran Heart Center. The study protocol (Supplement 1) was approved by the ethics committee of the Rajaie Cardiovascular, Medical and Research Center and accepted by Tehran Heart Center. All patients provided written informed consent. An independent Data and Safety Monitoring Committee monitored the trial results. This study followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guidelines.

Study Population

Adult patients (≥18 years) presenting within 14 days from symptom onset with acute intermediate-high-risk PE (according to the latest classification of the European Society of Cardiology guidelines at the time of trial design[7]), simplified PE severity index score of 1 or more,[8] and PE confirmation with computed tomography pulmonary angiography (CTPA) were considered for inclusion. Excluded from the study were patients with creatinine clearance less than 30 mL/min (to convert to milliliter per second per meter squared, multiply by 0.0167), contraindications to fibrinolytic therapy (such as history of intracranial bleeding or recent ischemic stroke), concomitant right heart thrombosis, or terminal illness. Information regarding patient race and ethnicity was not systematically gathered in this study. A full list of eligibility criteria can be found in Supplement 1.

Randomization and Treatment Strategy

Randomization was carried out in a 1:1 ratio to cCDT plus anticoagulation vs anticoagulation monotherapy via an electronic web-based system with permuted blocks of 4 and concealed allocation sequences. For the patients assigned to the anticoagulation monotherapy group, twice-daily subcutaneous enoxaparin (1 mg/kg) was started for the first 48 hours of enrollment.[9]

For patients assigned to cCDT, 1 infusion catheter was used per involved pulmonary artery, 1 in the left and 1 in the right pulmonary artery in case of bilateral involvement (Cragg-McNamara Valved Infusion Catheters; Medtronic). A fixed dose of alteplase (Actilyse; Boehringer Ingelheim) at a rate of 0.5 mg per catheter per hour for 24 hours (ie, a total of 12 mg for unilateral and 24 mg for bilateral involvement of pulmonary arteries, respectively) was administered. A fixed dose of unfractionated heparin (UFH; 500 units/hour) was administered to all the patients in the cCDT group during fibrinolytic therapy. After the termination of cCDT and removal of catheter(s), UFH was increased to therapeutic levels. Afterward, UFH was changed to twice-daily subcutaneous enoxaparin (1 mg/kg) in patients without procedural complication (eg, major vascular access complication or bleeding events) or unstable hemodynamics necessitating other invasive therapies. Enoxaparin was planned to be continued for the first 48 hours after completion of fibrinolytic therapy. For both groups, transition to oral anticoagulation was permissible at the discretion of treating clinicians. Details about the treatment strategy in each group can be found in Supplement 1.

Follow-up Clinical and Transthoracic Echocardiographic Examination

During the hospital course, every patient was monitored daily by the study team. A structured 3-month follow-up program was designed. The 3-month follow-up session was planned with detailed history taking, a transthoracic echocardiographic (TTE) examination, and a 6-minute walk test.

In the course of the trial, 3 TTE examinations were planned for each trial participant: on admission, 72 hours after randomization, and at the 3-month follow-up (Supplement 1). The first TTE was performed by the on-call cardiologist for risk stratification and investigation of eligibility criteria (eg, the presence of right heart thrombosis). The 2 subsequent TTE examinations (at 72 hours after randomization and at the 3-month follow-up) were recorded and sent to an imaging core laboratory, masked to treatment assignment. All the conventional measurements were performed based on the latest American Society of Echocardiography guidelines[10]; RV/LV ratio at 72 hours after randomization and at the 3-month follow-up was measured in the apical 4-chamber view. Three-month echocardiographic RV recovery was based on the PEITHO definition[11] as follows: (1) RV size (end-diastolic diameter measured at mid-RV in the RV-focused view) less than 35 mm, (2) pulmonary artery pressure less than 35 mm Hg (estimated from the highest tricuspid regurgitation gradient acquired from multiple views plus right atrial pressure based on inferior vena cava diameter and its respiratory collapse), (3) an RV/LV ratio less than 0.9, and (4) the normalization of RV free wall motion (in RV-focused view). The fulfillment of all the criteria, some criteria, and none of the criteria was defined as completely recovered, partially recovered, and unrecovered RV, respectively.[11] Additional details are summarized in Supplement 1.

Study Outcomes

The primary outcome was the proportion of patients with an RV/LV ratio greater than 0.9 at the 3-month follow-up assessed by the imaging core laboratory. Secondary outcomes included the proportion of patients with an RV/LV ratio greater than 0.9 at 72 hours after randomization and the proportion of patients with unrecovered RV at the 3-month follow-up and the 3-month rate of all-cause mortality.

Exploratory outcomes included a composite of the 3-month rate of all-cause mortality or the proportion of patients with an RV/LV ratio greater than 0.9 at the 3-month follow-up (ie, the primary outcome), 3-month rate of PE-related mortality, hospital length of stay (index hospitalization), and 6-minute walk test at 3-month follow-up. The main prespecified safety outcome was major bleeding based on the classification of the Bleeding Academic Research Consortium (BARC) (Supplement 1). BARC type 3 or 5 was considered as major bleeding.[12] Additional safety outcomes were severe thrombocytopenia (platelet count <20 × 10^3/μL; to convert to 10^9 thrombocytes/L, multiply by 1), vascular access complication, and clinically relevant nonmajor bleeding (BARC type 2). A clinical events committee, masked to the treatment assignment, adjudicated the clinical outcomes.

Statistical Analysis

Power calculation was performed for 2-sided superiority testing for the primary outcome in all the patients randomly assigned to treatment groups. Based on the pooled prevalence of RV dysfunction in the systematic review performed by Sista et al,[13] an 18.3% event rate for the primary outcome of an RV/LV ratio greater than 0.9 in the control group was presumed. Considering a 2-sided α of 0.05 and using the *z* approximation formula for comparing 2 proportions between independent groups, a sample size of 144 patients in each group (288 total) was calculated to reach a power of 80% for the detection of a 10% absolute risk reduction in the primary outcome with cCDT by comparison with anticoagulation monotherapy. However, midway through the conduct of the current study, in February 2020, the COVID-19 pandemic affected the study sites. Due to unprecedented strain on the health care system in the enrolling centers, which affected the care even for patients with non–COVID-19 venous thromboembolism,[14] the steering committee made the decision to stop patient recruitment on February 4, 2020. The primary outcome, unrecovered RV at the 3-month follow-up and the 6-minute walk test at the 3-month follow up, were analyzed in patients with valid values, ie, those who were alive and agreed to participate in the 3-month follow-up visit. Other outcomes were analyzed on all randomly assigned patients.

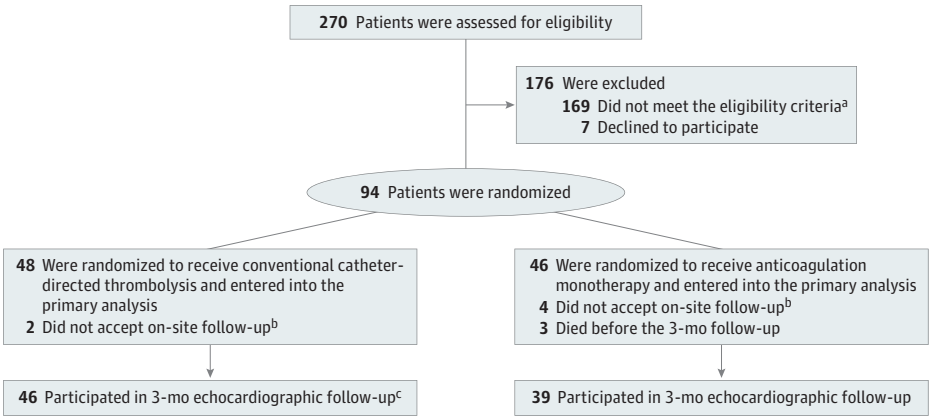
Categorical variables were expressed as frequencies with percentages. Continuous variables were described as the mean and SEM, if normal distribution was confirmed. The effect of the intervention on the outcomes was reported with odds ratio (OR) as the effect measure. A *P* value < .05 was considered significant for the primary outcome. Other *P* values were not adjusted for multiplicity of comparisons and should be considered exploratory.

After completion of enrollment but before completing the analyses of the trial data, it was planned to conduct a random-effect meta-analysis from the CDT groups of prior randomized trials plus the current trial with the goal of assessing pooled relative frequency of bleeding events (eMethods in Supplement 2). Subgroup analyses among the participants of the current trial were performed based on age, sex, body mass index (BMI; ≥30 or <30; calculated as weight in kilograms divided by height in meters squared), history of diabetes, hypertension, coronary artery disease, and heart rate on admission (≥110 or <110 beats/minute).

Results

From December 22, 2018, through February 2, 2020, a total of 270 patients were screened for eligibility. Overall, 94 patients were randomly assigned to the cCDT (48 [51%]) and control (46 [49%]) groups (mean [SD] age, 58.4 [2.5] years; 27 women [29%]; 67 men [71%]) (**Figure 1**). Six patients (6.3%)—2 patients assigned to cCDT and 4 patients assigned to the anticoagulation monotherapy—refused to participate in the onsite 3-month in-person follow-up required for the primary outcome due to difficulties imposed by the COVID-19 pandemic. However, these patients agreed to a phone interview to ascertain survival and symptoms. Three patients, all assigned to anticoagulation monotherapy, died before the 3-month follow-up. Consequently, from the initial 94 patients, 85 patients completed the 3-month echocardiographic follow-up, which was required for the primary outcome (eResults, eTables 1, 2, and 3 in Supplement 2).

Figure 1. Enrollment and Randomization



[a] Among 169 patients not meeting the eligibility criteria, 91, 48, and 11 patients were categorized as having low, intermediate-low, and high risk of developing pulmonary emboli. Ten patients had 1 or more contraindication to fibrinolytic therapy. Eight patients experienced end-stage kidney disease. One patient had allergy to iodine-based contrast.

[b] Six patients in the study (2 in the conventional catheter-directed thrombolysis group and 4 in the anticoagulation group) did not agree to participate in the 3-month on-site imaging follow-up, but they did agree to have off-site clinical follow-up assessment by phone interview.

[c] All images obtained from patients participating in the echocardiographic 3-month follow-up were considered acceptable by the core laboratory.

The 2 study groups were balanced in terms of baseline characteristics (**Table 1**).[15,16] Baseline RV/LV ratio greater than 0.9 was consistent between CTPA and bedside TTE at the time of enrollment in all patients. One patient with active cancer, assigned to anticoagulation monotherapy, was discharged with low-molecular-weight heparin; all other surviving patients were discharged with oral anticoagulation. Considering the bilateral involvement of the pulmonary arteries in all patients randomly assigned to cCDT, all patients were assigned to receive a fixed dose of alteplase, 24 mg, over 24 hours.

Efficacy Outcomes

At 3-month follow-up, the primary efficacy outcome (the proportion of patients with an RV/LV ratio >0.9 at 3-month follow-up) was not significantly different in the cCDT group compared with the anticoagulation monotherapy group (2 of 46 patients [4.3%] vs 5 of 39 patients [12.8%]; OR, 0.31; 95% CI, 0.06-1.69; P = .24) (**Table 2**). The median (IQR) RV/LV ratio at 3-month follow-up was significantly lower in the cCDT group compared with the anticoagulation monotherapy group (0.7 [0.6-0.7] vs 0.8 [0.7-0.9]; P = .01) (eFigure 1 in Supplement 2).

For the secondary efficacy outcomes, fewer patients assigned to cCDT had an RV/LV ratio greater than 0.9 at 72 hours after randomization (13 of 48 patients [27.0%]) compared with those assigned to anticoagulation monotherapy (24 of 46 patients [52.1%]; OR, 0.34; 95% CI, 0.14-0.80; P = .01). The median (IQR) RV/LV ratio was lower in the cCDT group at 72 hours after randomization (0.8 [0.7-0.9] vs 0.9 [0.8-1.1]; P = .001) (eFigure 1 in Supplement 2).

The rate of unrecovered RV function was lower at 3-month follow-up with cCDT compared with anticoagulation monotherapy (3 of 46 patients [6.2%] vs 11 of 39 patients [28.2%]; OR, 0.18; 95% CI, 0.06-0.77; P = .009) (Table 2). Clinical deterioration (ie, hemodynamic instability despite treatment with vasopressor agent) occurred in 1 of 46 patients (2.1%) in the anticoagulation monotherapy group. The patient subsequently received open-label cCDT as part of routine care. Patients in both groups had similar hospital lengths of stay (median [IQR], 6 [5-8] days; P = .45). All patients were discharged from the hospital alive.

Three patients died during the 3-month follow-up, all in the anticoagulation monotherapy group, of whom 2 events were adjudicated as PE-related mortality. For the third patient, PE-related death and cancer-related death were the 2 possible etiologies. However, the clinical events committee concluded that sufficient information was not available to ascertain the cause. A composite of 3-month mortality or having an RV/LV ratio greater than 0.9 at a 3-month follow-up was observed in 2 of 48 patients (4.3%) in the cCDT group and 8 of 46 patients (17.3%) in the anticoagulation monotherapy group (OR, 0.20; 95% CI, 0.04-1.03; P = .048) (Table 2). The TTE-based 3-month estimated pulmonary artery systolic pressure had reliable measurements according to the core laboratory in 79 patients (92%) and were not significantly different between the 2 groups (median [IQR], 30 [25-35] mm Hg vs 34 [27-45] mm Hg in the cCDT and anticoagulation monotherapy groups, respectively; P = .33).

Due to logistical limitations, the 6-minute walk test at 3-month follow-up was performed in only 1 of 2 enrolling centers (34 patients). There was no significant difference in the median (IQR) walk distance among patients randomly assigned to cCDT (415 [339-455] m) vs those randomized to standard anticoagulation (368 [270-442] m; P = .31).

Table 1. Baseline Characteristics in Patients Who Completed the 3-Month Follow-up[a]

Characteristic	No. (%)	
	cCDT + anticoagulation (n = 46)	Anticoagulation monotherapy (n = 39)
Age, mean (SEM), y	57.7 (2.2)	57.5 (2.4)
Sex		
Female	13 (28)	11 (28)
Male	33 (72)	28 (72)
Body mass index, mean (SEM)[b]	28.3 (0.7)	29.3 (1.0)
Vital signs on admission, mean (SEM)		
Systolic blood pressure, mm Hg	129.1 (3.3)	122.9 (2.6)
Heart rate, beats/min	102.6 (2.7)	105.0 (3.2)
Coexisting conditions		
Diabetes	6 (13)	9 (23)
Hypertension	13 (28)	14 (36)
Dyslipidemia	5 (11)	7 (18)
Coronary artery disease	8 (17)	8 (21)
Obstructive airway disease	2 (4)	3 (8)
Previous cerebrovascular accident	1 (2)	0
Previous history of PE	1 (2)	1 (2)
Active malignancy	0	0
Immobility ≥3 d	10 (23)	9 (22)
Surgery within prior 4 wk	3 (7)	3 (8)
Anemia[c]	6 (13)	5 (13)
Previous statin therapy	3 (7)	6 (15)
BACS bleeding score[d]		
Low risk	35 (76)	31 (79)
Intermediate risk	11 (23)	8 (20)
Baseline CTPA indices, mean (SEM)		
Right-to-left ventricle ratio[e]	1.2 (0.1)	1.2 (0.3)
Pulmonary artery obstruction index, %[f]	55.1 (1.4)	55.2 (1.2)
Baseline laboratory tests, mean (SEM)[g]		
High-sensitivity troponin, ng/L	169.9 (68.2)	168.1 (73.3)
NT-proBNP, pg/L	1804.2 (524.1)	1762.4 (792.6)

Abbreviations: cCDT, conventional catheter-directed thrombolysis, CTPA, computed tomography pulmonary angiogram, NT-proBNP, N-terminal-pro–brain natriuretic peptide; PE, pulmonary embolus.

SI conversion factor: To convert troponin to micrograms per liter, divide by 1000 and multiply by 1.

[a] Baseline characteristics were analyzed in 85 patients who were alive and participated in the 3-month follow-up visit (eTable 1 in Supplement 2).

[b] Calculated as weight in kilograms divided by height in meters squared.

[c] Anemia defined as hemoglobin level less than 13 g/dL (130 g/L) in men and less than 12 g/dL (120 g/L) in nonpregnant women.

[d] The Bleeding Age Cancer Syncope (BACS) scoring system consists of recent major bleeding (3 points), age older than 75 years (1 point), active cancer (1 point), and syncope (1 point). A score of 0 signifies a low risk, 1 to 3 an intermediate risk, and greater than 3 a high risk.[15]

[e] Mean (SEM) baseline echocardiographic right-to-left ventricle ratio was 1.1 (0.2) and 1.1 (0.3) in CDT and anticoagulation monotherapy groups.

[f] Calculated based on Qanadli score.[16]

[g] Normal limit for highly sensitive troponin and NT-proBNP were less than 19 ng/L and 125 pg/L, respectively, for both sexes.

Safety Outcomes

One case of BARC type 3a major bleeding (nonfatal gastrointestinal bleeding) occurred in the cCDT group. Spontaneous intramural esophageal hematoma was noted during the final hour of fibrinolytic infusion and was managed conservatively. No fatal or intracranial bleeding occurred in either group. Three cases of minor bleeding (vascular access-site hematoma, BARC type 2) were reported in the intervention group. Two patients had superficial hematomas larger than 5 cm in the greatest diameter, and 1 patient had a superficial hematoma smaller than 5 cm in the greatest diameter; the hematomas resolved spontaneously. There were no cases of severe thrombocytopenia.

The pooled proportion estimate for fatal bleeding, intracranial hemorrhage, and major bleeding in the CDT group of randomized clinical trials—including Ultrasound-Accelerated Thrombolysis of Pulmonary Embolism (ULTIMA),[4] Optimum Duration of Acoustic Pulse Thrombolysis Procedure in Acute Pulmonary Embolism (OPTALYSE-PE),[6] Standard vs Ultrasound-Assisted Catheter Thrombolysis for Submassive Pulmonary Embolism (SUNSET-PE),[3] and CANARY—was estimated at 0.02% (95% CI, 0-1.15%), 0.44% (95% CI, 0-2.17%), and 1.76% (95% CI, 0.20%-4.27%), respectively (eFigure 2 in Supplement 2). No statistically significant heterogeneity was observed between CDT groups of these controlled trials regarding major bleeding (P value for Q = 0.39; I^2 = 5.52%), intracranial hemorrhage (P value for Q = 0.67; I^2 = 0.01%), or fatal bleeding (P value for Q = 0.91; I^2 = 0) (eFigure 2 in Supplement 2). The CDT protocols of these trials are summarized in eTable 2 in Supplement 2. Subgroup analysis did not show significant treatment interaction for the primary outcome in prespecified subgroups (**Figure 2**).

Discussion

In this randomized clinical trial of 94 patients with acute intermediate-high-risk PE, we observed numerically fewer patients who had an RV/LV ratio greater than 0.9 at 3-month follow-up with cCDT compared with those in the anticoagulation monotherapy group. In addition, cCDT was associated with lower median 72-hour and 3-month RV/LV ratios, a decrease in the proportion of patients with an RV/LV ratio greater than 0.9 at 72 hours after randomization, and a decrease in the number of patients with an unrecovered RV at 3-month follow-up. cCDT resulted in low major bleeding events (ie, only a single nonfatal gastrointestinal major bleeding event) compared with anticoagulation monotherapy. Three patients, all assigned to the anticoagulation monotherapy group, died during the study follow-up; 2 deaths were adjudicated to be caused by PE.

One of the major drawbacks of systemic fibrinolysis is major bleeding, which is related to the dose of fibrinolytic agent and administration over a short period of time. The markedly smaller dose of fibrinolytic agents with cCDT in the current study resulted only in 1 major bleeding event (2%), and no fatal or intracranial hemorrhage. Similarly, the dose of fibrinolytic agents in all other major RCTs on CDT has been at least 4-fold smaller than the standard dosage of systemic fibrinolytic therapy. Based on pooled analyses that were performed as a part of the current study, fatal and intracranial bleeding event rates were less than 1% with

Table 2. Study Outcomes in the Study Population

Outcome	No. (%)		Odds ratio (95% CI)	Risk ratio (95% CI)	*P* value[a]
	cCDT + anticoagulation	Anticoagulation monotherapy			
Primary outcome[b]					
3-mo Echocardiographic RV/LV ratio >0.9	2/46 (4.3)	5/39 (12.8)	OR, 0.31 (0.06 to 1.69)	0.33 (0.07 to 1.65)	.24
Other efficacy outcomes					
72-h RV/LV ratio >0.9[c]	13/48 (27.0)	24/46 (52.1)	OR, 0.34 (0.14 to 0.80)	0.52 (0.30 to 0.89)	.01
3-mo Unrecovered RV[b,d]	3/46 (6.2)	11/39 (28.2)	OR, 0.18 (0.06 to 0.77)	0.23 (0.07 to 0.770)	.009
3-mo All-cause mortality[c]	0/48	3/46 (6.5)	−6.50 (−13.06 to 6.14)		.40
Composite of 3-mo all-cause mortality or the primary outcome	2/48 (4.2)	8/46 (17.3)	OR, 0.20 (0.04 to 1.03)	0.24 (0.05 to 1.07)	.048
PE-related mortality[c]	0[e]	2/46 (4.3)	−4.35 (−11.34 to 2.66)	0.34 (0.07 to 1.65)	.34
Hospital length of stay, median (IQR), d[c]	6 (5-8)	6 (5-8)	NA	NA	.45
3-mo 6-min Walk test, median (IQR), m[f]	415 (339-455)	368 (270-442)	NA	NA	.31
Safety outcomes[c]					
BARC type 3 or 5	1/48 (2.1)	0	2.1 (−1.9 to 6.52)	NA	.86
CRNMB	3/48 (6.2)	0[e]	6.25 (−1.53 to 14.03)		.43
Major or nonmajor bleeding	4/48 (8.3)	0[e]	8.33 (−0.27 to 16.94)		.27
Vascular access complication	3/48 (6.2)	0[e]	6.25 (−1.53 to 14.03)		.43
Severe thrombocytopenia[h]	0	0	NA		NA

Abbreviations: BARC, Bleeding Academic Research Consortium; cCDT, conventional catheter-directed thrombolysis, CRNMB, clinically relevant nonmajor bleeding; LV, left ventricle; NA, not applicable; PE, pulmonary embolism; RV, right ventricle.

[a] Apart from primary outcome, other *P* values are exploratory. *P* values are calculated by Pearson χ^2 tests, or exact test, as needed.

[b] Primary outcome (3-month RV/LV ratio >0.9) and unrecovered RV, were analyzed in 85 patients (46 and 39 patients in CDT and anticoagulation monotherapy groups, respectively) who were alive and participated in the 3-month follow-up visit. Three patients died within 3 months, and 6 patients responded to the telephone follow-up but did not agree to proceed to the visit.

[c] Assessed in all 94 randomly assigned patients.

[d] The Pulmonary Embolism Thrombolysis (PEITHO) definition for echocardiographic RV recovery was used as follows: (1) RV size (in the modified 4-chamber view) less than 35 mm, (2) pulmonary artery pressure less than 35 mm Hg, (3) an RV/LV ratio less than 0.9, and (4) the normalization of RV free wall motion. The fulfillment of all the criteria, some criteria, and none of the criteria was defined as complete, partial, and no recovery, respectively.

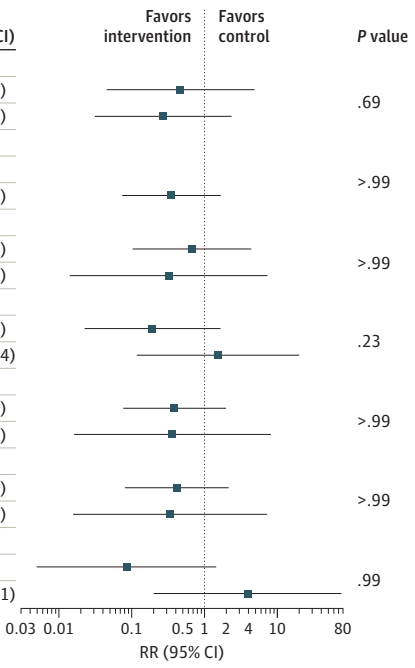
[e] For events with 0 incidence in 1 group, only absolute risk difference was reported.

[f] Six-minute walk test was only evaluated in 1 center and tested in patients who participated in the follow-up visit and were able to exercise (14 patients in the CDT group and 20 patients in the anticoagulation-monotherapy group).

[g] Defined as platelet counts less than 20 × 10^3/μL (20 × 10^9/L).

Figure 2. Subgroup Analysis for the Primary Outcome

Subgroup (total No.)	CDT No./ total No. (%)	Anticoagulation monotherapy No./total No. (%)	Risk ratio (95% CI)	*P* value
Age, y				
<65 (53)	1/28 (3)	2/25 (8)	0.45 (0.04-4.63)	.69
≥65 (32)	1/18 (5)	3/14 (21)	0.26 (0.03-2.23)	
Sex				
Female (24)	0/13 (0)	0/11 (0)	NR	>.99
Male (61)	2/33 (6)	5/28 (17)	0.34 (0.07-1.62)	
BMI[a]				
<30 (48)	2/29 (6)	2/19 (10)	0.66 (0.10-4.26)	>.99
>30 (37)	0/17 (0)	2/20 (10)	0.23 (0.01-4.55)	
Diabetes				
No (70)	1/40 (2)	4/30 (13)	0.19 (0.02-1.59)	.23
Yes (15)	1/6 (16)	1/9 (11)	1.50 (0.11-19.64)	
Hypertension				
No (58)	2/33 (6)	4/25 (16)	0.38 (0.08-1.91)	>.99
Yes (27)	0/13 (0)	1/14 (7)	0.26 (0.02-8.06)	
CAD				
No (69)	2/38 (3)	4/31 (12)	0.41 (0.08-2.08)	>.99
Yes (16)	0/8 (3)	1/8 (12)	0.33 (0.02-7.14)	
Heart rate, beats/minute				
≥110 (46)	0/24 (0)	5/22 (22)	0.08 (0-1.43)	.99
<110 (39)	2/22 (9)	0/17 (0)	3.91 (0.20-76.51)	



BMI indicates body mass index; CAD, coronary artery disease; CDT, catheter-directed thrombolysis; NR, not reported; RR, risk ratio.

[a] BMI calculated as weight in kilograms divided by height in meters squared.

CDT. The pooled estimate for major bleeding is 1.76%, compared with pooled major bleeding event rate of 7.7% for systemic fibrinolysis reported in prior analyses.[17] In the ongoing Ultrasound-Facilitated, Catheter-Directed, Thrombolysis in Intermediate-High-Risk Pulmonary Embolism (HI-PEITHO) trial, ultrasonography-assisted CDT and anticoagulation monotherapy will be compared in patients with intermediate-high-risk PE for a primary composite outcome of 7-day PE-related mortality, cardiorespiratory collapse, and recurrent PE.[18] Considerations for lower doses of fibrinolytic therapy have been made in observational studies,[19] and small trials of systemic fibrinolysis, as well.[20] The ongoing Pulmonary Embolism International Thrombolysis Study 3 (PEITHO-3) trial will compare reduced-dose systemic fibrinolytic therapy with anticoagulation monotherapy in patients with intermediate-high-risk PE.[21]

In the current study, compared with anticoagulation monotherapy, fewer patients treated with cCDT had an RV/LV ratio greater than 0.9 in 72 hours after randomization. Further, the 72 hours after randomization and 3-month median RV/LV ratio were smaller in patients treated by cCDT. It is known that patients receiving anticoagulant monotherapy have late catch-up improvement in the imaging markers of PE over time.[22,23] In addition, the median RV/LV ratio in both groups in the current trial were within normal range at 3-month follow-up. Nevertheless, prior investigations have suggested a progressive association between the increase in echocardiographic-based RV/LV ratio value and short- and long-term mortality.[24] The current study suggests a more favorable durable effect for cCDT compared with anticoagulation monotherapy on several 3-month imaging indices. Future RCTs should determine whether such hypothesis-generating imaging changes translate to relevant improvement in clinical outcomes.

The choice of the study intervention in the current trial deserves some discussion. Most available trials of CDT that have shown improvement in short-term imaging metrics, such as reduction in the RV/LV ratio[3,4,6] or computed tomography-based thrombus burden,[3] used ultrasound-assisted CDT vs anticoagulation monotherapy. The selection of cCDT in the current trial was due to higher cost and limited availability of ultrasound-assisted CDT in the study centers. Recently, the SUNSET-PE trial did not report a significant difference in the degree of thrombus resolution 48 hours after intervention with ultrasound-assisted CDT compared with cCDT.[3] Of note, the current study did not aim to compare the 2 modalities, and further studies in this regard are needed.

Limitations

The present study has several limitations. First, due to logistic restriction imposed by the pandemic, we prematurely discontinued the study, which made the trial underpowered for the prespecified primary outcome. Although this remains an important limitation, findings from the primary outcome and several secondary and exploratory analyses suggest favorable outcomes with cCDT compared with anticoagulation monotherapy, which should be verified in large trials. Second, the assessment of exercise capacity by the 6-minute walk test was performed in only half the patients. Future studies should assess such functional metrics, as well as quality of life in an adequately powered group of patients. Third, at the time of analysis, we recognized that women were underrepresented in our study (approximately 30%). Both enrolling centers are tertiary cardiovascular centers, accepting a high volume of referral patients. A careful assessment of the referred patients for screening indicated that 86 of 270 screened patients (32%) were female. The trial was offered similarly to women and men, and the rate of participation was also similar. We cannot exclude the possibility of chance alone but remain vigilant for our future randomized investigations. Additional studies are needed to understand whether intermediate-high-risk PE is more common among men in Iran or if disparities exist in treatment or referral to tertiary care centers. Fourth, only 2 patients had a prior history of PE. However, the relative frequency of previously undiagnosed chronic thromboembolic pulmonary hypertension in these patients is uncertain. Fifth, the assigned dosage of alteplase in the current study was based on available evidence at the time of trial design and is higher than a few more recently published or ongoing trials (eTable 2 in Supplement 2) in which a lower dose of alteplase per pulmonary artery has been considered. Finally, the majority of our study population had low baseline bleeding risk. Careful patient selection is always needed to consider the treatment tradeoffs of fibrinolytic therapy, including CDT.

Conclusions

To conclude, in the setting of premature termination, this randomized clinical trial was underpowered to detect a statistically significant difference between cCDT and anticoagulation monotherapy with regard to its primary outcome of proportion of patients with a 3-month RV/LV ratio of greater than 0.9. However, results suggest a hypothesis-generating improvement in secondary and exploratory outcomes, such as short-term and 3-month echocardiographic RV recovery, with cCDT compared with anticoagulation and also a low risk of major bleeding in patients treated with cCDT. These results are encouraging for the design and execution of a definitive outcomes trial. Results from the ongoing HI-PEITHO, PEITHO-3, PE-TRACT, and nonfibrinolysis mechanical-thrombectomy trials will be similarly enlightening for assessment of other treatment alternatives for intermediate-high-risk PE.

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Invited Commentary

Catheter-Directed Treatment of Submassive Pulmonary Embolism—A Cautious Step Closer?

Elaine M. Hylek, MD, MPH

Thrombolytic therapy is recommended for patients with pulmonary embolism and hemodynamic compromise, as associated mortality rates are reported to be as high as 50% by 90 days.[1-3] However, use of thrombolytic therapy for intermediate-risk or submassive pulmonary embolism, defined by right ventricular dysfunction without hemodynamic compromise, remains controversial due to the high risk of bleeding, including intracranial bleeding, associated with this treatment.[2-4] Sadeghipour and colleagues[5] report results from the Catheter-Directed Thrombolysis vs Anticoagulation in Patients With Acute Intermediate-High–Risk Pulmonary Embolism (CANARY) randomized clinical trial. The trial was designed as an open-label randomized assessment of conventional catheter-directed thrombolysis (cCDT) plus anticoagulation vs anticoagulation monotherapy in improving echocardiographic measures, specifically the right ventricle to left ventricle (RV/LV) ratio, measured at 3 months. As noted by the investigators, the trial was stopped early due to enrollment challenges during the COVID-19 pandemic. Among the 94 patients recruited, 46 were randomized to receive catheter-directed alteplase. Primary outcome data were available for 85 of 94 randomized patients (90%). As noted, 2 of 46 patients (4.3%) in the cCDT group and 5 of 39 (12.8%) in the anticoagulation monotherapy group met the primary outcome (odds ratio [OR], 0.31; 95% CI, 0.06-1.69; $P = .24$). Fewer patients who were randomized to cCDT experienced a 3-month composite outcome of death or RV/LV greater than 0.9 (2 of 48 [4.3%] vs 8 of 46 [17.3%]; OR, 0.20; 95% CI, 0.04-1.03; $P = .048$). One case of nonfatal major gastrointestinal bleeding occurred in the cCDT group.

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For perspective, the Pulmonary Embolism Thrombolysis (PEITHO) trial[6] also studied fibrinolytic therapy in an intermediate-risk population defined by right ventricular dysfunction, positive troponin, and normal blood pressure. Using a double-blind trial design, patients were randomized to a single-bolus injection of tenecteplase plus standard heparin therapy vs standard anticoagulation monotherapy. The primary efficacy outcome was the composite of death from any cause or hemodynamic decompensation within 7 days after randomization. Of the 506 patients in the tenecteplase group, death or hemodynamic decompensation occurred in 13 (2.6%) compared to 28 of 499 patients (5.6%) in the standard treatment group (OR, 0.44; 95% CI, 0.23-0.87; $P = .02$). In the safety analysis, 10 patients in the tenecteplase group (2%) sustained a hemorrhagic stroke compared to 1 patient (0.2%) in the standard anticoagulation group ($P = .003$). Extracranial bleeding occurred in 32 patients (6.3%) in the tenecteplase group and 6 patients (1.2%) in the placebo group ($P < .001$). The PEITHO trial documented the efficacy of thrombolytic treatment and

Ultrasound-facilitated, catheter-directed thrombolysis vs anticoagulation alone for acute intermediate-high-risk pulmonary embolism: Rationale and design of the HI-PEITHO study

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Leiden, The Netherlands; MA, USA; Cardiff, United Kingdom; Dublin, Ireland; Massachusetts, USA; Zurich, Switzerland; Mainz, Germany; Vienna, Austria; Mainz, Germany; VA, USA; Greece

Abstract

Background Due to the bleeding risk of full-dose systemic thrombolysis and the lack of major trials focusing on the clinical benefits of catheter-directed treatment, heparin antiocoagulation remains the standard of care for patients with intermediate-high-risk pulmonary embolism (PE).

Methods and results The Higher-Risk Pulmonary Embolism Thrombolysis (HI-PEITHO) study (ClinicalTrials.gov Identifier: NCT04790370) is a multinational multicenter randomized controlled parallel-group comparison trial. Patients with: (1) confirmed acute PE; (2) evidence of right ventricular (RV) dysfunction on imaging; (3) a positive cardiac troponin test; and (4) clinical criteria indicating an elevated risk of early death or imminent hemodynamic collapse, will be randomized 1:1 to treatment with a standardized protocol of ultrasound-facilitated catheter-directed thrombolysis plus anticoagulation, vs anticoagulation alone. The primary outcome is a composite of PE-related mortality, cardiorespiratory decompensation or collapse, or non-fatal symptomatic and objectively confirmed PE recurrence, within 7 days of randomization. Further assessments cover, apart from bleeding complications, a broad spectrum of functional and patient-reported outcomes including quality of life indicators, functional status and the utilization of health care resources over a 12-month follow-up period. The trial plans to include 406 patients, but the adaptive design permits a sample size increase depending on the results of the predefined interim analysis. As of May 11, 2022, 27 subjects have been enrolled. The trial is funded by Boston Scientific Corporation and through collaborative research agreements with University of Mainz and The PERT Consortium.

Conclusions Regardless of the outcome, HI-PEITHO will establish the first-line treatment in intermediate-high risk PE patients with imminent hemodynamic collapse. The trial is expected to inform international guidelines and set the standard for evaluation of catheter-directed reperfusion options in the future. (Am Heart J 2022;251:43–53.)

Background and rationale

Risk-adjusted treatment of pulmonary embolism: limits and caveats of systemic thrombolysis

Despite recent advances in prevention, diagnosis and (anticoagulation) treatment, acute pulmonary embolism

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(PE) remains an important cause of global morbidity and mortality.[1-3] The progressive reduction in case fatality reported over the past 2 decades has been challenged by increasing annual incidence and hospitalization rates.[4-6] Thus, a substantial PE-related burden persists, which warrants the need for further improvement in patient outcomes.

Acute PE leading to overt right ventricular (RV) failure and hemodynamic instability places the patient at particularly high risk of early death.[7,8] Consequently, there is global consensus in international guidelines that massive or high-risk PE is a medical emergency requiring revascularization by dissolving or removing pulmonary arterial thrombus.[9-11] Reperfusion treatment consists of systemic administration of thrombolytic (fibrinolytic) drugs or, in case of contraindications, catheter-directed (pharmaco) mechanical treatment or surgical embolectomy. However, a much larger (up to 25% of all patients with PE) group of patients in the so-called intermediate-risk category may also benefit from direct thrombus dissolution and/or disruption.[12] These latter patients appear hemodynamically stable but present with various combinations of clinical abnormalities, RV dysfunction on echocardiography or computed tomography pulmonary angiography (CTPA), and/or myocardial injury detected by laboratory biomarkers.[10]

Addressing a longstanding debate over treatment of intermediate-risk PE, the Pulmonary Embolism International Thrombolysis (PEITHO) trial enrolled 1006 normotensive patients presenting with *both* RV dysfunction on imaging and a positive cardiac troponin I or T test.[13] These inclusion criteria were considered to define a patient population with *intermediate-high-risk PE*. Patients received either full-dose intravenous thrombolysis (tenecteplase) plus heparin, or heparin anticoagulation alone. In PEITHO, clinical efficacy of reperfusion treatment was confirmed by a reduction in the clinical composite of death from any cause or hemodynamic collapse within 7 days of randomization (odds ratio [OR], 0.44; 95% confidence interval [CI], 0.23-0.87; $P = .02$). However, stroke occurred in 12 patients (2.4%) randomized to the thrombolysis arm (OR, 12.10; 95% CI, 1.57-93.39 vs heparin alone; $P = .003$), and was hemorrhagic in 10 cases.[13]

In view of the bleeding risk of full-dose intravenous thrombolytic treatment and the lack of major trials focusing on the clinical benefits of alternative strategies, current guidelines recommend neither systemic thrombolysis nor any other form of reperfusion treatment as first-line therapy in intermediate-risk PE.[10,11,14] Indeed, administrative data indicate that systemic thrombolysis is only rarely used (in <4% of all cases) in the treatment of acute PE in the United States and Europe.[15,16] This reality has created an urgent medical need for developing and properly validating advanced modalities of reperfusion treatment, with particular focus on patients with intermediate-high risk PE.

Improving the risk-benefit ratio of reperfusion: catheter-directed treatment

The search for safer reperfusion strategies in acute PE has driven interest towards regimens using lower thrombolytic doses. While the risk-benefit ratio of reduced-dose systemic (intravenous) thrombolysis remains to be determined,[17,18] technical innovations have led to the development of catheter systems infusing low doses of a thrombolytic agent into the affected branches of one or both pulmonary arteries, often coupled with mechanical disruption of pulmonary emboli. Pharmacomechanical reperfusion, notably USCDT, has the potential of reversing RV dilation, pulmonary hypertension, and anatomic thrombus burden at a considerably lower risk of major bleeding and hemorrhagic stroke than systemic thrombolysis.[19] In the randomized phase II Ultrasound Accelerated Thrombolysis of Pulmonary Embolism Trial (ULTIMA), which enrolled 59 patients with acute PE and a right–to–left ventricular (RV/LV) diameter ratio >1.0, ultrasound-assisted local infusion of 10 to 20 mg recombinant tissue-type plasminogen activator (r-tPA) led to significant recovery of RV function at 24 hours, with no increased risk of major hemorrhage or stroke.[20] Supportive of the efficacy and safety of USCDT are for instance the results of a prospective, single-arm multicenter study on 150 patients with submassive or massive PE (SEATTLE II), showing an impact both on RV/LV diameter ratio (primary end point) and on peripheral pulmonary artery perfusion.[21,22] Also, a registry on catheter-directed, either purely mechanical or pharmacomechanical thrombus removal (only 1 patient did not receive thrombolysis) in 28 patients with massive and 73 with submassive PE showed clinical success in 71 of 73 patients with submassive PE with no bleeding events recorded.[23] Lastly, the prospective multicenter, parallel-group Optimum Duration of Acoustic Pulse Thrombolysis Procedure in Acute Intermediate-Risk Pulmonary Embolism (OPTALYSE-PE) trial, which randomized 101 hemodynamically stable adult patients, testing 4 USCDT regimens with a shorter delivery duration, showed that shorter delivery duration and lower-dose thrombolysis still resulted in fast improvement in RV function and reduced clot burden.[24]

Taken together, over a decade of cohort studies and randomized trials on USCDT to date suggest a favorable safety profile of pharmacomechanical reperfusion, with low rates of major and particularly intracranial or other life-threatening bleeding.[25,26] Furthermore, these studies reported a reduction in RV size and improvement in RV function. Hemodynamic (systolic pulmonary artery pressure) and imaging (Miller score on CTPA) parameters improved using a broad range of treatment protocols. Promising results, always using surrogate end points,

were also reported by cohort studies which tested alternative forms of catheter-directed PE treatment.[27,28]

Remaining uncertainties and the need for a large randomized controlled trial

Although the existing data appear favorable, they are not sufficient to establish USCDT, or any other catheter-directed intervention,[29] as first-line treatment for patients with intermediate-risk PE. The most important remaining gaps in evidence, now needing to be addressed by a major, state-of-the-art randomized controlled trial, are:

1) Direct comparison, in terms of efficacy and safety, of USCDT vs heparin anticoagulation alone, which remains the standard of care for acute PE without hemodynamic compromise at presentation.[10,11,14]
2) Demonstration of the clinical benefits of USCDT; having documented favorable effects on surrogate hemodynamic or imaging end points, the primary end point should now consist of a valid composite clinical outcome, convincingly showing a positive impact on prognosis and quality of life.
3) Refinement of the patient selection criteria to ensure the inclusion of patients with the highest potential to gain from interventions; in this regard, a *post hoc* analysis of the PEITHO study identified clinical baseline parameters which might, in combination with indicators of RV dysfunction on imaging and elevated cardiac troponin levels, better define the "optimal" candidates for reperfusion treatment.[30]
4) Agreement upon a standardized USCDT protocol (bolus, infusion rate and total dose of the thrombolytic agent; duration of the procedure; concomitant anticoagulation regimen) to be clinically tested and validated; this will ensure that the results of the trial will be translated into precise clinical recommendations and shape future practice.

Study overview

Study design and objectives

The Higher-Risk Pulmonary Embolism Thrombolysis (HI-PEITHO) trial (ClinicalTrials.gov Identifier: NCT04790370) is a multinational controlled randomized adaptive-design multicenter parallel-group comparison trial, with concealed sequence of randomization allocation. The primary objective of HI-PEITHO is to assess whether USCDT plus anticoagulation is associated with a significant reduction in the composite outcome of PE-related mortality, cardiorespiratory decompensation or collapse, or non-fatal symptomatic and objectively confirmed PE recurrence compared to anticoagulation alone, within 7 days of randomization. Additional objectives are to contribute further evidence on the treatment and outcomes of acute intermediate-high-risk PE, and to provide controlled data comparing a catheter-based intervention to the standard of care.

Study patients will be randomized 1:1 to treatment with USCDT plus anticoagulation vs anticoagulation alone. Randomization is stratified by age (<75 years vs ≥75 years) and RV/LV ratio (<1.5 vs ≥1.5) as assessed on CTPA. Allocation to the treatment arms is open-label to investigators and patients, but adjudication of the composite primary outcome and safety outcomes will be performed by a blinded Clinical Events Committee.

Patient population and eligibility

All patients who present to the emergency department for evaluation and treatment of PE will be considered for inclusion in the trial. Clinical evaluation and a series of standard-of-care imaging (eg, CTPA, echocardiogram) and laboratory tests (eg, biomarkers) will be performed to diagnose and risk stratify patients with acute PE. Upon confirmation of intermediate-high-risk PE, patients will be screened for specific clinical criteria indicating an elevated risk of early death and/or imminent hemodynamic collapse. These include: (1) heart rate ≥100 beats per minute; (2) systolic blood pressure (SBP) ≤110 mm Hg; 3) respiratory rate >20/min^{-1} and/or oxygen saturation on pulse oximetry (SpO2) <90% (or partial arterial oxygen pressure <60 mm Hg) at rest while breathing room air. Patients are required to demonstrate 2 or more of the above 3 clinical categories of cardiorespiratory distress, as well as the remaining broader inclusion criteria and none of the exclusion criteria (Table I). They will then be randomized after providing written informed consent.

Intervention and treatment regimens

The study flow diagram is shown in Figure. If a study patient is assigned to receive USCDT, treatment will be initiated as soon as possible, but no later than 6 hours after confirmation of study eligibility (Table I). The trial protocol strongly recommends starting USCDT within 2 hours of randomization.

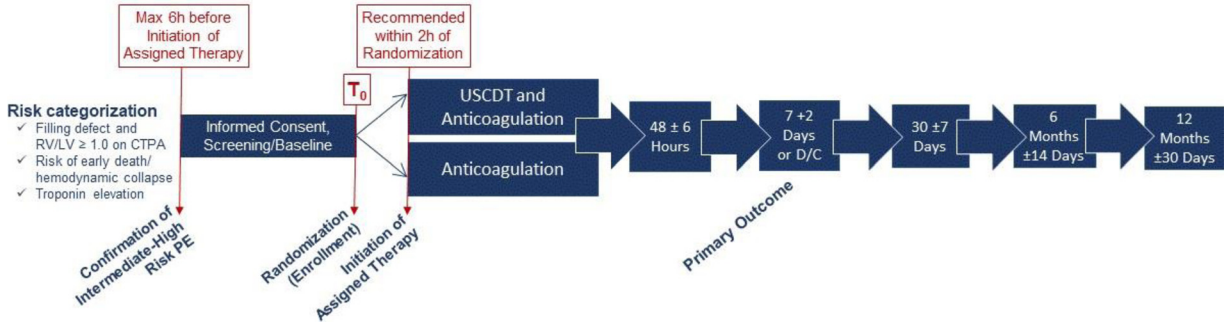
Assignment to the USCDT arm will include both treatment with the USCDT procedure and treatment with anticoagulation. The USCDT procedure will entail delivery of alteplase using the EkoSonic Endovascular System (Boston Scientific Corporation, Marlborough, MA). Alteplase will be delivered using a specified treatment protocol: the infusion time will be 7 hours, with a total r-tPA dose of 9 mg (2 mg bolus followed by infusion of 1 mg/h) if 1 catheter is used to treat unilateral PE; if 2 catheters are used to treat bilateral PE, the total r-tPA dose will be 18 mg (2 mg bolus per catheter followed by infusion of 1 mg/h/catheter). The Steering Committee of HI-PEITHO agreed upon this regimen after carefully reviewing the efficacy and safety results of randomized trials[20,24] and a cohort study[21] as well as real-life data (K. Sterling et al KNOCOUT PE: Retrospective

Table I. Key inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
1) Age 18-80 y 2) Objectively confirmed acute PE, based on CTPA showing a filling defect in at least 1 main or proximal lobar pulmonary artery 3) Elevated risk of early death/hemodynamic collapse, indicated by at least 2 of the following new-onset clinical criteria: a. ECG-documented tachycardia with heart rate ≥100 beats per minute, not due to hypovolemia, arrhythmia, or sepsis; b. SBP ≤110 mm Hg over at least 15 min; c. respiratory rate >20 x min^{-1} or oxygen saturation on pulse oximetry (SpO2) <90% (or partial arterial oxygen pressure <60 mm Hg) at rest while breathing room air 4) Right-to-left ventricular diameter ratio ≥1.0 on CTPA 5) Serum troponin I or T levels above the upper limit of normal 6) Signed informed consent	1) Hemodynamic instability*, ie, at least one of the following present: i. cardiac arrest or need for cardiopulmonary resuscitation; ii. need for ECMO, or ECMO initiated before randomization; iii. PE-related shock, defined as: (i) SBP <90 mm Hg, or vasopressors required to achieve SBP ≥90 mm Hg, despite an adequate volume status; *and* (ii) end-organ hypoperfusion (altered mental status; oliguria/anuria; increased serum lactate); iv. isolated persistent hypotension (SBP <90 mm Hg, or a systolic pressure drop by at least 40 mm Hg for at least 15 min), not caused by new-onset arrhythmia, hypovolemia, or sepsis * Patients who presented with *temporary* need for fluid resuscitation and/or low-dose catecholamines may be included, provided that they could be stabilized within 2 h of admission and maintain SBP of ≥90 mm Hg and adequate organ perfusion without catecholamine infusion 2) Need for admission to an intensive care unit for a reason other than the index PE episode. Note: Patients who test positive for SARS-CoV-2 can be enrolled where the investigator believes that the pulmonary embolism is the dominant pathology in the patient's clinical presentation and qualifying cardiorespiratory parameters 3) Temperature above 39 °C / 102.2 °F 4) Logistical reasons limiting the rapid availability of interventional procedures to treat acute PE (eg, during the outbreak of an epidemic) 5) Index PE symptom duration >14 d 6) Active bleeding. 7) History of intracranial or intraocular bleeding at any time 8) Stroke or transient ischemic attack within the past 6 mo, or previous stroke at any time if associated with permanent disability 9) Central nervous system neoplasm, or metastatic cancer 10) Major neurologic, ophthalmologic, abdominal, cardiac, thoracic, vascular or orthopedic surgery or trauma (including syncope-associated with head strike or skeletal fracture) within the past 3 wk 11) Platelet count $<100 \times 10^9$ x L^{-1} 12) Patients who have received a *once-daily* therapeutic dose of LMWH or a therapeutic dose of fondaparinux within 24 h prior to randomization 13) Patients who have received one of the direct oral anticoagulants apixaban or rivaroxaban within 12 h prior to randomization 14) Patients who have received one of the direct oral anticoagulants dabigatran or edoxaban for the index PE episode, as these drugs are not approved for patients who have not received heparin for at least 5 d 15) Administration of a thrombolytic agent or a glycoprotein IIb/IIIa receptor antagonist during the current hospital stay and/or within 30 d, for any reason 16) Chronic treatment with antiplatelet agents other than low-dose acetylsalicylic acid or clopidogrel 75 mg once daily (but not both) 17) Chronic treatment with a direct oral anticoagulant (apixaban, dabigatran, edoxaban or rivaroxaban) 18) Chronic treatment with a vitamin K antagonist, or known coagulopathy including severe hepatic dysfunction, with INR >1.5 19) Pregnancy or lactation 20) Previous inclusion in the study 21) Known hypersensitivity to alteplase, LMWH, UFH, or to any of the excipients 22) Life expectancy less than 6 months

CTPA, computed tomography pulmonary angiography; ECMO, extracorporeal membrane oxygenation; INR, international normalized ratio; LMWH, low molecular weight heparin; PE, pulmonary embolism; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2; SBP, systolic blood pressure; UFH, unfractionated heparin; USCDT, ultrasound-facilitated catheter-directed thrombolysis.

Figure



Flow diagram of the Higher-Risk Pulmonary Embolism Thrombolysis (HI-PEITHO) trial (ClinicalTrials.gov Identifier: NCT04790370) CTPA indicates computed tomography pulmonary angiography; *LV*, left ventricular; *PE*, pulmonary embolism; *RV*, right ventricular; *USCDT*, ultrasound-facilitated catheter-directed thrombolysis.

and Prospective International EKoSoNic Registry of the Treatment and Clinical Outcomes of Patients with Pulmonary Embolism. Presented at the Vascular InterVentional Advances Conference, Las Vegas, NV, October 5, 2021). Assignment to the experimental USCDT arm will also include initiation or continuation of anticoagulation therapy according to a specified treatment protocol. The study patients will receive low molecular weight heparin (LMWH) subcutaneously at a twice-daily therapeutic dose, or a therapeutic, activated partial thromboplastin-guided intravenous infusion of unfractionated heparin (UFH) until the start of the USCDT procedure. During the procedure, intravenous UFH will be used at an infusion rate of 300 to 600 units/hour, the exact infusion rate being left to the investigator's discretion, and will be continued for up to 4 hours after catheter removal. After the procedure, the study patient should be transitioned to full-dose parenteral anticoagulation, either twice-daily LMWH or UFH, no more than 4 hours after the end of the USCDT procedure, unless there are documented bleeding concerns. Study patients may be transitioned to any commercially available oral anticoagulant, at the discretion of the clinical care team, no sooner than 24 hours after the end of the USCDT procedure.

Assignment to the control (anticoagulation) arm will consist of receiving LMWH subcutaneously twice daily or UFH intravenously at a therapeutic dose according to labeling and established protocols. The patient may be transitioned to oral anticoagulation of the investigator's choice no sooner than 24 hours after initiation of their randomized treatment.

Outcomes

An overview of the tests to be performed and parameters to be collected upon enrollment and at the follow-up visits is provided in Table II; the primary outcome and secondary outcomes of the trial are presented in Table III. The primary outcome is a composite of PE-related mortality, cardiorespiratory decompensation or collapse, or non-fatal symptomatic and objectively confirmed recurrence of PE, within 7 days of randomization. Cardiorespiratory collapse or decompensation is defined as at least one of the following criteria:

a) Cardiac arrest or need for cardiopulmonary resuscitation at any time between randomization and day 7;
b) Signs of shock, ie, new-onset persistent arterial hypotension (SBP <90 mm Hg, or SBP drop by ≥40 mm Hg over ≥15 minutes, despite an adequate volume status; or need for vasopressors to maintain SBP ≥90 mm Hg), accompanied by end-organ hypoperfusion (altered mental status; oliguria/anuria; or increased serum lactate) at any time between randomization and day 7;
c) Placement on extracorporeal membrane oxygenation (ECMO) at any time between randomization and day 7;
d) Intubation, or initiation of non-invasive mechanical ventilation at any time between randomization and day 7;
e) National Early Warning Score (NEWS) of 9 or higher, between 24 hours and 7 days after randomization, confirmed on 2 consecutive measurements 15 minutes apart.

NEWS is a standardized, easy-to-use clinical tool, which determines the degree of illness and mortality risk of a patient and can be used to prompt critical care intervention.[31,32] The score assesses and integrates the following vital parameters: respiratory rate (breaths per minute); oxygen saturation; breathing room air or need for supplemental oxygen; temperature; SBP; pulse rate;

Table II. Trial visit plan and data collection schedule

Procedure/Assessment	Screening (baseline)	Enrollment	Index procedure	48±6 h post-randomization	Follow-up			
					7+2 d (or discharge)[¶]	30 ± 7 d	6 mo ± 14 d	12 mo ± 30 d
CTPA	X							
Laboratory tests[*]	X			X				
Informed consent process	X							
Demographics	X							
Transthoracic echocardiogram	X[†]			X		X	X[#]	X
Medical history, risk factors	X[‡]							
Confirmation of eligibility		X						
Randomization		X						
Initiation[§] of assigned therapy (USCDT or anticoagulation alone)			X					
NEWS	X[†,‖]			X[‖]	X[‖,¶]			
Vitals	X			X	X[¶]	X	X	
WHO functional class					X[¶]	X	X	X
6MWT						X	X	X
PVFS interview					X	X	X	X
PEmb-QOL							X	X
SF-36							X	X
EQ-5D							X	X
Adverse event assessment		X	X	X	X[¶]	X	X	X
Review of anticoagulation medication	X		X	X	X[¶]	X	X	X

CTPA, computed tomography pulmonary angiography; EQ-5D, EuroQol-5 dimension; NEWS, national early warning score; PEmb-QOL, pulmonary embolism quality of life; PVFS, post-venous thromboembolism functional status scale; SF-36, generic quality of life short form-36; USCDT, ultrasound-facilitated catheter-directed thrombolysis; WHO, world health organization; 6MWT, 6-min walk test.

[*] At baseline and 48 ± 6 h post-randomization, complete blood count, chemistry, and biomarkers will be collected. Troponin I or T is required for eligibility. The troponin assay is not standardized across the study sites, as it is in the practice-based setting. Hence, each hospital will use its local assay with threshold as indicated by the manufacturer. In the case of a bleeding event, hemoglobin, hematocrit, and platelet count shall be entered in the Bleeding Event form.

[†] Baseline may be completed before or after randomization, but must be completed prior to initiation of assigned therapy, ie, within six (6) h of confirmation of intermediate-high risk PE.

[‡] Medical history includes collection of anticoagulation medications since presentation to hospital.

[§] Continuation of anticoagulation protocol for patients who are assigned to anticoagulation and already receiving therapy.

[‖] NEWS score is collected at baseline and then daily, starting at 24 h post-randomization through 7 d post-randomization.

[¶] When patients are discharged prior to 7 d post-randomization, indicated assessments shall be performed on day of discharge. At 7 (+2) d post-randomization, a follow-up telephone call will be made to the patient to complete the PVFS and assess changes to health status.

[#] At select sites, where standard of care, up to 100 patients.

and level of consciousness (Table IV). NEWS is recommended by the National Health System in the United Kingdom for initial assessment, serial monitoring, and assessment of patients for triage, but it has also been validated in other countries including the United States.[31] Employing the NEWS score in HI-PEITHO will permit, for the first time in an interventional randomized controlled trial in acute PE, a standardized, objective assessment and monitoring of each patient's vital status after randomization. This will facilitate early detection of imminent decompensation and, if needed, prompt institution of rescue therapy before overt hemodynamic collapse occurs. At the same time, NEWS is a valuable tool for preventing arbitrary or premature crossover from the control to the intervention arm, or to other rescue reperfusion treatment outside the trial protocol. It helps to provide clear rules and transparent criteria on how and when the investigator should declare "failure" of the assigned treatment.

The secondary outcomes of the trial include the individual components of the primary outcome, bleeding complications, echocardiographic measures of RV recovery, recurrent venous thromboembolism and patient reported outcomes including disease specific (Pulmonary Embolism Quality of Life [PEmb-QOL]) and generic quality of life (Short Form 36 [SF-36], EuroQuol-5 Dimension [EQ-5D]), functional limitations (post-venous thromboembolism functional status [PVFS] scale], 6-minute walk test (6MWT), and health care resource utilization.[33-38]

Sample size calculation and statistical analysis

The null hypothesis (H_0) is that the probability of a primary outcome event in the control group (π_c) and in

Table III. Primary and secondary outcomes

Primary outcome	Composite of PE-related mortality, cardiorespiratory decompensation or collapse, or non-fatal symptomatic and objectively confirmed recurrence of PE, within 7 d of randomization
Secondary outcomes	1) Change in RV/LV diameter ratio on echocardiography between baseline and 48 ± 6 h 2) PE-related death within 7 d 3) Cardiorespiratory decompensation within 7 d 4) Placement on ECMO or mechanical ventilation within 7 d 5) GUSTO major (moderate and severe) bleeding within 7 d[40] 6) ISTH major bleeding within 7 d, 30 d, and 6 mo[41] 7) Ischemic or hemorrhagic stroke within 7 d and 30 d 8) All-cause mortality within 7 d, 30 d, 6 mo, and 12 mo 9) Serious adverse events within 30 d 10) All-cause mortality, cardiorespiratory collapse or recurrence of PE within 30 d 11) Symptomatic PE recurrence within 30 d and 6 mo 12) Change from baseline in RV dysfunction on echocardiography at 6 mo 13) Duration of hospitalization for the index PE event 14) Duration of stay at the intensive, intermediate or coronary care unit during hospitalization for the index PE event 15) Functional status at 30 d, 6 mo, and 12 mo, including: WHO functional class (and at discharge), PVFS scale (and at discharge) and 6-min walk test 16) Quality of life (PEmb-QOL, SF-36, and EQ-5D scales) at 6 mo and 12 mo 17) Diagnosis of CTEPH within 12 mo 18) Health economic analysis (length of hospital stay, resource utilization, indirect costs) at 30 d and 12 mo (selected sites and countries)

CT images used for enrollment will be assessed locally at each site, to enable swift inclusion of the patients. Echocardiograms will be assessed in a central laboratory. CTEPH, chronic thromboembolic pulmonary hypertension; ECMO, extracorporeal membrane oxygenation; EQ-5D, EuroQol-5 dimension; GUSTO, global utilization of streptokinase and tissue plasminogen activator for occluded coronary arteries; ISTH, international society on thrombosis and haemostasis; LV, left ventricular; NEWS, national early warning score; PE, pulmonary embolism; PEmb-QOL, pulmonary embolism quality of life; PVFS, post-venous thromboembolism functional status scale; RV, right ventricular; SF-36, generic quality of life short form-36; USCDT, ultrasound-facilitated catheter-directed thrombolysis; WHO, world health organization.

Table IV. The national early warning score (NEWS)[31,32]

Vital signs	3	2	1	0	1	2	3
Respiration rate (rpm)	≤8		9-11	12-20		21-24	≥25
Oxygen saturations (%)	≤91	92-93	94-95	≥96.0			
Any supplemental oxygen		Yes		No			
Temperature	≤35		35.1-36.0	36.1-38.0	38.1-39.0	≥ 39.1	
Systolic blood pressure (mm Hg)	≤90	91-100	101-110	111-219			≥220
Heart rate (bpm)	≤40		41-50	51-90	91-110	111-130	≥131
Level of consciousness				A			V, P, or U

AVPU scale (level of consiousness): Alert, Verbal, Pain, Unresponsive; bpm, beats per minute; rpm; respirations per minute.

the treatment group (π_t) is identical; the alternative hypothesis (H_1) is that the probability of an event is lower in the treatment group than in the control group. The study is designed to detect a 15% vs 5% difference (OR, 0.298) in the primary end point event rates. A total of 406 patients will yield 90% power to detect the target difference in event rates with a one-sided alpha of 0.025 using a Pocock alpha spending group sequential design; adaptation of the trial, including a sample size increase, will be possible based on the results of the interim analysis (see below).

Analysis of the primary end point will be performed on the Intention-To-Treat (ITT) population and, as a second step, the per-protocol population. The ITT population will comprise all randomized patients who met study eligibility criteria. The per-protocol population will comprise all patients of the ITT population without major protocol deviations. A Cochran-Mantel-Haenszel test accounting for stratification factors at randomization will be used to compare the primary end point between the treatment and control groups; the OR and corresponding 95% CI will be presented. A logistic regression including the stratification factors used at randomization as covariates will be performed as a sensitivity analysis. Multicollinearity will be assessed using the variance inflation factor.

An efficacy interim analysis will be assessed by the independent Data Safety Monitoring Board after 50% of the expected number of patients have been randomized. The superiority of the treatment group vs the control group will be tested by a Cochran-Mantel-Haenszel test. If the interim analysis takes place with exactly 50% of the patients, the one-sided significance level for the interim analysis is $\alpha_1 = 0.01469$, and is $\alpha_2 = 0.01469$ for the final

analysis using Pocock alpha spending. If the interim analysis does not occur at exactly 50% of the patients, the efficacy boundaries will be re-calculated using the Pocock alpha spending function. A conditional power of ≤15% at the interim analysis could result in the study stopping early for futility. A sample size increase to 544 patients will be considered at the interim analysis according to a simplification of the Promising Zone methodology described in Mehta and Pocock,[39] to ensure control of Type I error. A sample size of 544 patients will give 90% power to to detect a smaller, 15% vs 6% (OR, 0.362), difference in the primary end point event rates.

Implications and expected impact of HI-PEITHO

We have witnessed great technical progress in catheter-directed treatment of acute PE. Modalities involving pharmacomechanical thrombolysis or purely mechanical thrombus fragmentation and aspiration have been investigated in cohort studies or small randomized trials using surrogate end points. Among these, USCDT using the EkoSonic Endovascular System has undergone more than a decade of clinical investigation, with consistently promising results regarding efficacy and safety. Consequently, we designed HI-PEITHO as a state-of-the-art randomized controlled trial, aiming to establish the clinical benefits of USCDT for patients with intermediate-high-risk PE. With its rigorous design and protocol, HI-PEITHO is expected to provide answers to a large number of remaining questions concerning the efficacy and safety profile of USCDT. More specifically:

1) HI-PEITHO is the only ongoing trial directly comparing, in terms of efficacy and safety, catheter intervention (USCDT) with heparin anticoagulation, which is the current standard of care for acute PE in this risk category.
2) The primary end point of HI-PEITHO is a composite clinical outcome which builds on the experience gained from a previous landmark trial in the field.[13] Besides early mortality, it includes clear and unambigious clinical indicators of life-threatening hemodynamic decompensation or collapse, and is thus suitable for determining the impact of the intervention on the patients' prognosis. Moreover, HI-PEITHO is the first PE trial to include the NEWS score in its primary end point. This standardized practical tool will be used for monitoring the patient's vital status and permit timely escalation of therapy in case of imminent hemodynamic collapse, while preventing unjustified crossover between treatment arms. NEWS is thus expected to maximize the safety of patients enrolled in HI-PEITHO while ensuring the scientific integrity of the trial and the validity of its results.
3) HI-PEITHO has refined patient selection criteria which go beyond those mentioned in risk stratification tables of current guidelines.[10] The additional clinical inclusion criteria of the trial represent an evolution of the definition of intermediate-high-risk PE based on recent analyses,[30] and aim to include an "enriched" patient population that will be most likely to benefit from USCDT.
4) The HI-PEITHO steering committee, consisting of PE experts from interventional cardiology and radiology, internal and vascular medicine, and hematology, critically reviewed the existing evidence and agreed on a standardized USCDT protocol to be used and validated in the present trial. Thus, apart from the main results, the expected service of HI-PEITHO to the interventional community and the PE response teams around the world will be the harmonization of USCDT procedures, including their thrombolytic and anticoagulation regimens. A clearly described procedure tested in a major trial may also prove useful for specifying future guideline recommendations.
5) Finally, the comprehensive assessment plan and long-term follow-up schedule of HI-PEITHO extends the scope of the trial far beyond patient survival over the first few days. In fact, HI-PEITHO has been designed to assess the impact of USCDT not only on severe late sequelae of PE such as chronic thromboembolic pulmonary hypertension, but also on a broad spectrum of functional and patient-reported outcomes, including various quality of life indicators, as well as on the utilization of health care resources.

Treatment of pulmonary embolism is evolving at a rapid pace. The increasing complexity of managing patients with severe PE warrants a multifaceted and nuanced approach to decision-making on a case-by-case basis, taking into account patient characteristics, clinical presentation, and local resources and expertise. If the treatment arm is confirmed to be superior to the control arm, catheter-directed treatment and particularly USCDT will have provided, for the first time, the solid evidence which is necessary to establish it as first-line treatment in selected patients with acute PE. If the treatment arm is not shown to be superior to the control arm, heparin anticoagulation will continue to be the standard of care for intermediate-risk PE, reducing healthcare costs and possible harm to the patients. In either case, HI-PEITHO is expected to inform international guidelines and set the standard for state-of-the-art evaluation of catheter-directed reperfusion options in the future.

Current enrollment status

As of May 11, 2022, a total of 27 patients have been enrolled at 29 active sites. The estimated completion of enrolment and the primary end point is December 2023.

Study committees

Steering committee

Stefano Barco, MD, Zurich, Switzerland; Samuel Z Goldhaber, MD, Boston, MA; Michael R. Jaff, DO, Maple Grove, MN; Frederikus A. Klok, MD, Leiden, The Netherlands; Stavros V. Konstantinides, MD, Mainz, Germany; Nils Kucher, MD, Zurich, Switzerland; Irene M Lang, MD, Vienna, Austria; Fionnuala Ní Ainle, Dublin, Ireland; Gregory Piazza, MD, Boston, MA; Kenneth Rosenfield, MD, Boston, MA; Irene Schmidtmann, PhD, Mainz, Germany; Andrew S. P. Sharp, MD, Cardiff, United Kingdom; Keith M Sterling, MD, Alexandria, VA.

Trial statisticians

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Data safety monitoring board (DSMB)

Deepak L Bhatt, MD, MPH, Boston, MA (Chair); Cecilia Becattini, MD, Perugia, Italy; Stephan Ogenstad, PhD, Wake Forest, NC; Adam Torbicki, MD, PhD, Otwock, Poland

Clinical events adjudication committee (CEC)

Eric A Secemsky, MD, MSc, Boston, MA; Patrick J Troy, MD, Hartford Hospital, Hartford, CT; Mitchell D Weinberg, MD, Staten Island, NY; Robin Condliffe, MD, MBChB, Sheffiled, UK

Trial sponsor and collaborating institutions

Sponsor: Boston Scientific Corporation, Marlborough, MA.

Collaborating institutions: The PERT Consortium (Brookline, NH), University Mainz/PEITHO Network (Mainz, Germany).

Conflict of interest

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Reduced-Dose Intravenous Thrombolysis for Acute Intermediate–High-risk Pulmonary Embolism: Rationale and Design of the Pulmonary Embolism International THrOmbolysis (PEITHO)-3 trial

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Abstract

Intermediate–high-risk pulmonary embolism (PE) is characterized by right ventricular (RV) dysfunction and elevated circulating cardiac troponin levels despite apparent hemodynamic stability at presentation. In these patients, full-dose systemic thrombolysis reduced the risk of hemodynamic decompensation or death but increased the risk of life-threatening bleeding. Reduced-dose thrombolysis may be capable of improving safety while maintaining reperfusion efficacy. The Pulmonary Embolism International THrOmbolysis (PEITHO)-3 study (ClinicalTrials.gov Identifier: NCT04430569) is a randomized, placebo-controlled, double-blind, multicenter, multinational trial with long-term follow-up. We will compare the efficacy and safety of a reduced-dose alteplase regimen with standard heparin anticoagulation. Patients with intermediate–high-risk PE will also fulfill at least one clinical criterion of severity: systolic blood pressure $\leq$110 mm Hg, respiratory rate $>$20 breaths/min, or history of heart failure. The primary efficacy outcome is the composite of all-cause death, hemodynamic decompensation, or PE recurrence within 30 days of randomization. Key secondary outcomes, to be included in hierarchical analysis, are fatal or GUSTO severe or life-threatening bleeding; net clinical benefit (primary efficacy outcome plus severe or life-threatening bleeding); and all-cause death, all within 30 days. All outcomes will be adjudicated by an independent committee. Further outcomes include PE-related death, hemodynamic decompensation, or stroke within 30 days; dyspnea, functional limitation, or RV dysfunction at 6 months and 2 years; and utilization of health care resources within 30 days and 2 years. The study is planned to enroll 650 patients. The results are expected to have a major impact on risk-adjusted treatment of acute PE and inform guideline recommendations.

Keywords
- pulmonary embolism
- intermediate–high-risk
- reduced-dose thrombolysis
- prognosis
- randomized trial

Background and Rationale

Advanced Risk Stratification of Pulmonary Embolism

Assessment of the clinical severity of acute pulmonary embolism (PE) is based on the estimated risk of early (in-hospital or 30-day) mortality. High-risk PE, defined by the presence of hemodynamic instability at presentation, is a life-threatening condition in which prompt reperfusion treatment is needed to increase the chances of survival.[1] However, the vast majority of patients with acute PE do not present with overt hemodynamic compromise.[2,3] Within this large, apparently stable group, prediction scores derived from clinical variables permit further risk stratification. For example, a Pulmonary Embolism Severity Index (PESI) risk class of I or II, a simplified PESI (sPESI) of 0, or the absence of Hestia criteria all have a high negative predictive value for ruling out an early adverse outcome (low-risk PE).[4–6] On the other hand, hemodynamically stable patients who do not fulfill these criteria belong to the intermediate-risk category. Numerous studies could show that, in intermediate-risk PE, imaging parameters and laboratory biomarkers possess additive prognostic value, complementing each other[7,8] as well as baseline clinical parameters.[9,10] Accordingly, patients are classified into the *intermediate–high-risk* category if they have evidence of right ventricular (RV) dysfunction on echocardiography or computed tomography pulmonary angiography, in combination with elevated plasma cardiac troponin levels.[1]

Unfavorable Risk-to-benefit Profile of Full-Dose Systemic Thrombolysis

The superior hemodynamic effects and faster onset of action (compared with heparin anticoagulation alone) of systemic thrombolytic (fibrinolytic) treatment have been established, and its use is recommended in the emergency setting of acute high-risk PE.[11] However, it has remained controversial for decades whether systemic thrombolysis might also improve the clinical outcome of hemodynamically stable patients,[12] particularly those with intermediate–high-risk PE. Following first promising data in the early 2000s,[13] the Pulmonary Embolism International THrOmbolysis (PEITHO) trial confirmed the clinical efficacy of full-dose thrombolysis (using tenecteplase) in this risk group.[14] That study showed a significant reduction (odds ratio [OR]: 0.44; 95% confidence interval [CI]: 0.23–0.87) in the clinical composite of death from any cause or hemodynamic collapse within 7 days after randomization. However, this benefit came at a high price: in PEITHO, stroke occurred in 12 patients (2.4%) randomized to the thrombolysis arm (OR: 12.10; 95% CI: 1.57–93.39 vs. heparin alone), being hemorrhagic in 10 cases.[14] Considering the high risk of intracranial or other life-threatening bleeding events, which was subsequently confirmed by meta-analyses,[15] current guidelines do not recommend systemic thrombolysis as first-line treatment in intermediate–high-risk PE.[1,16] Lastly, the PEITHO trial had not been designed to answer the question whether early systemic thrombolysis may prevent the development of late sequelae thromboembolic pulmonary hypertension (chronic thromboembolic pulmonary hypertension) after intermediate-risk PE.[17]

Reduced-Dose Thrombolysis Might Improve Safety While Maintaining Efficacy

In patients with acute PE, three small randomized trials compared a reduced dose of alteplase with the conventional 100 mg regimen (received by a total of 162 and 99 patients, respectively, in the pooled study population).[18–20] The reduced-dosage regimens varied amongst the studies: in one of them, 50 mg of alteplase was infused over 2 hours,[20] whereas in the two other studies, a weight-adapted dose of 0.6 mg/kg, up to a total of 50 mg, was given over 15 minutes.[18,19] There were no significant differences in efficacy between the reduced-dose and the standard-dose regimen, as judged by changes in pulmonary artery pressure, cardiac index or residual vascular obstruction at 24 hours, or the incidence of PE recurrence.[18–20] In addition, and importantly, a meta-analysis suggested that a reduced dosage may be associated with reduction in the risk of major bleeding (OR: 0.33; 95% CI: 0.12–0.91).[21]

The efficacy of the reduced-dose regimen is further supported by two studies comparing alteplase, at the dose of 0.6 mg/kg[22] or 0.5 mg/kg (maximum of 50 mg),[23] with heparin alone in patients with acute PE. A greater improvement of vascular obstruction was observed with alteplase in the former study,[22] whereas the latter reported a reduction in the combined endpoint of persistent pulmonary hypertension or recurrent PE over the long term.[23]

Taken together, reperfusion treatment employing systemic thrombolysis exerts favorable hemodynamic effects, and thrombolytic regimens may be capable of improving the prognosis of patients with acute intermediate–high-risk PE. Nevertheless, the bleeding risk of full-dose intravenous thrombolysis is too high to justify its use as first-line therapy in this risk category. Today, reduced-dose regimens are becoming increasingly popular in clinical practice worldwide, despite the explicit warning by scientific societies and guidelines that the available evidence is not (yet) sufficient to support their efficacy and safety. This potentially dangerous gap in knowledge must therefore be closed as soon as possible. An adequately powered randomized placebo-controlled clinical trial, focusing on clinically relevant efficacy and safety outcomes, is the only way to determine the benefits versus risks of reduced-dose thrombolysis in acute PE.

Study Overview

Study Design and Objectives

The Pulmonary Embolism International Trial (PEITHO)-3 study (ClinicalTrials.gov Identifier: NCT04430569) is a randomized, placebo-controlled, double-blind, multicenter, multinational trial with long-term follow-up. The primary objective is to assess the efficacy (defined as the ability to prevent death, hemodynamic decompensation, or PE recurrence) of reduced-dose intravenous thrombolytic therapy with alteplase, against the background of standard care (heparin anticoagulation), in patients with acute intermediate–high-risk PE, 30 days after randomization. The secondary objectives are to assess (1) the safety, net clinical benefit, and impact of reduced-dose thrombolytic therapy on overall mortality in patients with intermediate–high-risk PE, as well as (2) the effect on long-term mortality, functional impairment, residual RV dysfunction, and the incidence of chronic thromboembolic pulmonary hypertension.

Patient Population and Eligibility

The key inclusion and exclusion criteria are summarized in ►**Table 1**. In this context, it is important to explain the rationale for the advanced definition of intermediate–high-risk PE used in the present study. In fact, both past[24] and current[1] guidelines defined intermediate–high-risk PE based "exclusively" on imaging (evidence of RV dysfunction) and biochemical (circulating levels of elevated laboratory biomarkers) criteria. Although these modalities generally possess high sensitivity, validated in several cohort studies and a randomized trial (reviewed in Konstantinides et al[24]), their prognostic specificity as standalone tools may be too low to predict threatening cardiorespiratory decompensation.[13,14] They may thus not suffice to identify the patients closer to the "upper border" of the intermediate-risk zone, who are expected to obtain the largest possible clinical benefit from early thrombolytic treatment. To address this limitation, we sought to identify additional baseline predictors of early life-threatening events in the population of the large PEITHO trial, in which overall early mortality was low.[14] We found that initial systolic blood pressure $\leq$110 mm Hg, respiratory

Table 1 Key inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
1. Age 18 years or older 2. Objectively confirmed acute PE with first symptoms $\leq$2 weeks before randomization, $\geq$1 of the following criteria required: a. $\geq$1 segmental ventilation-perfusion mismatch on lung scan b. CTPA/pulmonary angiography showing filling defect or abrupt obstruction of a segmental/more proximal pulmonary artery 3. Elevated risk of early death or hemodynamic collapse, indicated by $\geq$1 of the following criteria: a. SBP $\leq$ 110 mm Hg over $\geq$15 minutes b. Temporary need for fluid resuscitation and/or treatment with low-dose catecholamines because of arterial hypotension at presentation, provided that the patient could be stabilized within 2 hours of admission and maintains SBP of $\geq$90 mm Hg and adequate organ perfusion without catecholamine infusion c. Respiratory rate $>$ 20 per minute *or* oxygen saturation on pulse oximetry (SpO_2) $<$ 90% *or* partial arterial oxygen pressure $<$ 60 mm Hg at rest while breathing room air d. History of chronic heart failure, defined as previous diagnosis of heart failure with reduced, moderately reduced, or preserved ejection fraction, *or* treatment for heart failure at any time during the past 12 months 4. RV dysfunction, indicated by RV/LV diameter ratio $>$ 1.0 on echocardiography (apical four-chamber or subcostal four-chamber view) *or* on CTPA (transverse plane) 5. Serum troponin I or T concentration above the upper limit of local normal using a high-sensitive assay 6. Signed informed consent *Note*: Patients who test positive for SARS-CoV-2 may be randomized, if the investigator judges that the acute PE (and not the infection with SARS-CoV-2) is responsible for the patient's clinical, imaging, and hemodynamic parameters meeting the trial's inclusion criteria.	1. High-risk PE with hemodynamic instability[1] 2. Active bleeding 3. History of nontraumatic intracranial bleeding 4. Acute ischemic stroke or transient ischemic attack in the past 6 months 5. Neurosurgery or eye surgery; abdominal, cardiac, thoracic, or vascular surgery; or orthopaedic surgery or trauma, in the past 3 weeks 6. Known central nervous system neoplasm or metastasis 7. Platelet count $< 100 \times 10^9$/L 8. INR $>$ 1.4 9. Administration of thrombolytic agents in the preceding 4 days 10. Antiplatelet agents other than ASA $\leq$100 mg once daily; clopidogrel 75 mg once daily or a single loading dose of ASA or clopidogrel 11. Any direct oral anticoagulant within 12 hours of randomization 12. Known significant bleeding risk according to investigator's judgment 13. Vena cava filter insertion in the preceding 4 days 14. Current participation in another clinical trial 15. Previous enrolment in this study 16. Known hypersensitivity to alteplase, gentamicin, any of the excipients of the trial drug, or low-molecular weight heparin 17. Known severe hepatic disease, portal hypertension (with esophageal varices), or active hepatitis 18. Peptic ulcer diagnosed in the past 3 months 19. Pregnancy or parturition within the previous 30 days, or current breastfeeding 20. Women of childbearing potential who do not have a negative pregnancy test and do not use an effective method of birth control 21. Any other condition that the investigator feels would place the patient at increased risk upon start of the investigational treatment 22. Life expectancy $<$6 months or inability to participate at 6-month follow-up visit

Abbreviations: ASA, acetylsalicylic acid; CTPA, computed tomography pulmonary angiography; INR, international normalized ratio; LV, left ventricular; PE, pulmonary embolism; RV, right ventricular; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SBP, systolic blood pressure.

rate $>$20 breaths/min (or, as a surrogate, an arterial oxygen saturation $<$90% on room air) at presentation, or a history of chronic heart failure, predicted, alone or in combination, death from any cause, hemodynamic decompensation, or objectively confirmed recurrent PE within 30 days of randomization. The presence of at least one of these criteria thus defined an enriched patient population (53% of the patients enrolled in that study), in which the incidence of the composite clinical outcome was 11.2% in the control group as opposed to as low as 3.7% in the thrombolysis group.[25] This group was defined as the target population in the present trial, with the aim to obtain an optimized benefit-to-risk ratio from early thrombolysis.

Treatment Regimens

The diagram shown in ►**Fig. 1** depicts the study flow and the allowed time intervals between consecutive trial procedures and visits. An overview of the tests to be performed and parameters to be collected upon enrolment and at the follow-up visits is provided in ►**Table 2**. Patients fulfilling all the inclusion criteria and none of the exclusion criteria (►**Table 1**) will be randomized into the experimental or the reference treatment arm. Patients will receive alteplase (if randomized into the experimental arm) or placebo (if randomized into the reference arm), to be given within 30 minutes of randomization as a 15-minute intravenous infusion; the dosage will be 0.6 mg/kg, with the total dose not exceeding 50 mg. If the experimental treatment cannot be given within 30 minutes of randomization, the patient will be analyzed according to the intention-to-treat (ITT) principle.

Both treatment arms will receive anticoagulant treatment using low-molecular-weight heparin (LMWH) or any other type of heparin approved for the treatment of acute PE, according to local practice. If anticoagulation has been initiated using unfractionated heparin (UFH) and a switch to LMWH is envisaged after randomization, the UFH infusion will be stopped at the time of randomization and the first LMWH subcutaneous injection will be given within 3 hours

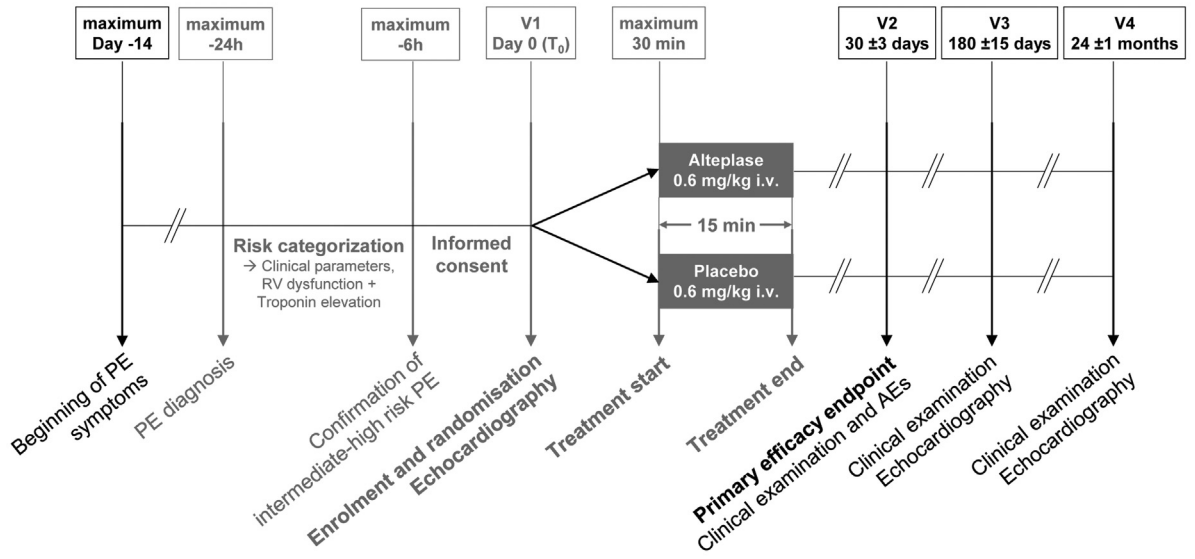

Fig. 1 Overview of design of the Pulmonary Embolism International THrOmbolysis (PEITHO)-3 trial. AEs, adverse events; PE, pulmonary embolism, RV, right ventricular; i.v., intravenously; V, visit.

Table 2 Trial visit plan and data collection schedule

	Day (D)0 Inclusion visit	D30 ± 3 days after randomization	Month (M)6 ± 15 days after randomization	M24 ± 30 days after randomization/end of study
	In hospital	*Outpatient follow-up*		
Verification of inclusion and exclusion criteria	X			
Signed informed consent	X			
Randomization	X			
Medical interview - Demographics - Medical history - Concomitant antiplatelet and anticoagulant treatment	X			
Clinical examination[a]	X	X	X	X
Troponin I and/or *t*-test	X			
Further laboratory tests[b]	X			
RV/LV diastolic diameter ratio	X			
sPESI	X			
Study drug administration	X			
Echocardiography	X		X	X
Pregnancy test (for women of childbearing age)	X			
Documentation of (serious) adverse events[c]	X	X		
Utilization of health care resources		X	X	

Abbreviations: LV, left ventricular; RV, right ventricular; sPESI, simplified Pulmonary Embolism Severity Index.
[a]Including body weight, blood pressure, heart rate, arterial oxygen saturation, respiratory rate, clinical signs of right heart failure.
[b]Creatinine, international normalized ratio, hemoglobin (1 day after randomization), platelet count (before and after randomization).
[c]Patients will be continuously monitored for early detection of hemodynamic instability or major bleeding.

of the end of UFH infusion. If anticoagulation has been initiated with LMWH as a twice-daily regimen, the next LMWH injection will be given 12 hours after the previous one. If fondaparinux, or LMWH as once-daily injection, has been given before randomization, the next injection will be given 24 hours after the previous one. Due to the longer half-life of fondaparinux as compared with LMWH, a switch from that drug to LMWH (or UFH) is generally recommended over the first 48 hours. The use of direct oral anticoagulants (apixaban, betrixaban, dabigatran, edoxaban, rivaroxaban) and vitamin K antagonists will not be allowed within the first 48 hours after randomization. All approved anticoagulant regimens will be allowed 48 hours after randomization.

As recommended by current guidelines,[1] all patients will receive therapeutic anticoagulation for at least 3 months. After the first 3 months, discontinuation or extension of the anticoagulant treatment will be at the discretion of the treating physician.

Outcomes

The efficacy and safety outcomes of the PEITHO-3 trial are summarized in ►**Table 3**. The primary efficacy outcome is the clinical composite of death from any cause, hemodynamic decompensation, or objectively confirmed recurrent PE within 30 days of randomization. When defining the primary efficacy outcome, we took into account that early mortality is relatively low in patients with intermediate-risk PE receiving contemporary, state-of-the-art supportive care such as that provided in the setting of a randomized controlled trial.[14] Thus, the sample size required for a trial aiming to show a "pure mortality benefit" from thrombolysis would be prohibitively large. On the other hand, other relevant adverse outcomes, notably early hemodynamic collapse or decompensation, are more frequent in patients with intermediate–high-risk PE treated with anticoagulation, and they represent a valid component of overall clinical efficacy.[14] In addition, by including all-cause (and not only PE-related) mortality in the composite primary outcome, we aim to ensure that, if superiority of reduced-dose thrombolysis over heparin alone is shown in the present study, it will have accounted for any thrombolysis-related fatal bleeding events. In the same context, the GUSTO definition of bleeding was chosen because it directly reflects the possible impact of bleeding complications on death or hemodynamic compromise/decompensation. Consequently, possible opposing effects of reduced-dose thrombolysis on efficacy and safety (such as prevention of PE-related death or decompensation at the cost of excessive fatal bleeding or hemorrhage-induced hemodynamic compromise) will both be taken into account in the primary clinical outcome. PEITHO-3 thus aims to provide a clear message to physicians regarding the overall clinical benefit of thrombolysis in patients with intermediate–high-risk PE rigorously defined by clinical, imaging, and biochemical criteria.[25]

All primary and secondary outcomes will be adjudicated by an independent clinical events committee.

Sample Size Calculation and Statistical Analysis Plan

To calculate the sample size for the present study, we performed a post hoc analysis of the population of the PEITHO trial, the largest (full-dose) thrombolysis trial with

Table 3 Primary and secondary outcomes

Primary outcome	Clinical composite of death from any cause *or* hemodynamic decompensation *or* objectively confirmed recurrent PE within 30 days of randomization
Secondary outcomes	To be included in a hierarchical analysis:
	1. Fatal or GUSTO severe or life-threatening bleeding, defined as either intracranial bleeding or bleeding leading to significant hemodynamic compromise requiring treatment,[38] within 30 days 2. Net clinical benefit, defined as the composite of the primary efficacy outcome and GUSTO severe or life-threatening bleeding, within 30 days 3. All-cause mortality within 30 days
	Not to be included in the hierarchical analysis:
	4. PE-related death within 30 days of randomization 5. Hemodynamic decompensation within 30 days 6. Recurrent PE within 30 days 7. Need for rescue thrombolysis, catheter-directed treatment, or surgical embolectomy within 30 days 8. Ischemic or hemorrhagic stroke within 30 days 9. Serious adverse events within 30 days 10. Utilization of health care resources within 30 days and 6 months 11. All-cause mortality at 2 years 12. Persisting dyspnea assessed by the Medical Research Council (MRC) scale at 6 months and at 2 years 13. Functional outcome, using the post-VTE functional scale,[39] at 6 months and at 2 years 14. Persistent RV dysfunction, defined as an intermediate or high probability of pulmonary hypertension on echocardiography according to ESC criteria,[40] at 6 months and 2 years 15. Confirmed chronic thromboembolic pulmonary hypertension according to ESC criteria[40] at 2 years

Abbreviations: ESC, European Society of Cardiology; GUSTO, Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries; PE, pulmonary embolism; RV, right ventricular; VTE, venous thromboembolism.

clinical outcomes conducted to this date.[25] This analysis helped to estimate the incidence of the primary efficacy outcome (death from any cause or hemodynamic collapse or objectively confirmed recurrent PE within 30 days of randomization) as defined in the present study, PEITHO-3. More specifically, in the subgroup of patients included in PEITHO, who would have fulfilled the "enriched" inclusion criteria of the present study, the rates were 11.2 and 3.7% in the control and (standard-dose) thrombolysis groups, respectively (relative risk reduction 67%). For estimating efficacy in PEITHO-3, we conservatively assumed a 55% relative risk reduction, corresponding to a 5.0% expected incidence in the reduced-dose thrombolysis group. Taking into account a planned interim analysis (see below) with the Lan and DeMets methods, we calculated that several ($n = 305$) patients per treatment arm will allow a 80% power to show the expected relative risk reduction. The nominal α at final analysis will be set at 0.049 for the primary analysis according to the Lan–DeMets[26] monitoring boundary with an O'Brien–Fleming stopping rule, provided that no sample size modification will be needed; otherwise, the final significance level will be adjusted accordingly.[27] Accounting for possible early dropouts, it is planned to enroll and randomize a total of 650 patients; the final size of the trial population will depend on the results of the interim analysis as explained below.

The primary analysis on the primary outcome will be performed in the ITT population applying a logistic regression analysis to account for stratification factors[28,29]; the group variables age (>75 vs. ≤75 years) and country will be included in the model. Results will be presented as OR and associated 95% CI. In addition, two exploratory subgroup analyses will be performed for the primary outcome in the ITT population, according to the following variables: (1) >75 versus ≤75 years, and (2) presence of ≥2 clinical criteria of PE severity at presentation (among the following inclusion criteria: systolic blood pressure ≤ 110 mm Hg; respiratory rate > 20/min or, as a surrogate, arterial oxygen saturation < 90% on room air; history of chronic heart failure) versus one criterion. An interaction term between subgroup variable and the treatment variable will be included in the logistic model, to assess whether the interaction is significantly associated to the primary outcome. Results will be presented as a forest plot.

In addition to improving early clinical outcomes, utilization of health care resources will be recorded for each patient at two time points (30 days and 180 days) postrandomization. For outpatient visits and periods of hospitalization, country-specific standardized unit costs will be applied, representing costs from a societal perspective. In addition, PE-related resource utilization will be recorded.

Safety Monitoring, Interim Analysis, and Stopping Rules

An independent data and safety monitoring board (DSMB) will be assessing the safety of the study. The DSMB will periodically review the serious adverse events (SAEs) with a special attention to the major bleeding events and will communicate its recommendations to the sponsor about stopping or continuing the trial. As specified in a dedicated charter, the frequency of DSMB meetings will be scheduled every 20 SAEs. Additional meetings may be arranged, especially if the SAE numbers are higher than anticipated. An independent statistician will conduct a formal efficacy interim analysis and sample size re-estimation based on the adjudicated primary efficacy outcome of 50% of the expected total number of patients. The superiority of the experimental treatment versus the control arm will be assessed by the chi-square test. To provide an overall two-sided significance level close to 0.05 for the study, the interim analysis will have a Lan–DeMets monitoring boundary with an O'Brien–Fleming stopping rule.[26] The study will stop for efficacy if the *p*-value provided by the chi-square test is <0.003. The study will stop for futility if the conditional probability (based on the observed treatment effect) of rejecting the null hypothesis is <0.5.

Implications of PEITHO-3

It has been almost 18 years since the first PEITHO trial was launched. The PEITHO investigators set out to resolve a long-lasting controversy concerning the efficacy versus safety of reperfusion treatment for patients with acute PE presenting with findings of acute RV pressure overload and dysfunction despite apparently normal systemic blood pressures.[30,31] PEITHO helped to advance the definition of intermediate-risk PE, and it showed that patients belonging to the intermediate–high-risk class may clinically benefit from systemic thrombolysis as first-line treatment. However, that trial also showed that the bleeding risks of full-dose intravenous thrombolysis predominate over its clinical and hemodynamic effects.[14] In view of these results, the focus of the debate has shifted toward identifying safer reperfusion modalities. Percutaneous catheter-directed treatment of acute PE, aiming a mechanical thrombus removal with or without local thrombolysis, has shown promising effects on surrogate imaging or hemodynamic parameters.[32–35] However, for the majority of countries and hospitals around the world, intravenous thrombolysis is expected to remain a more affordable and more feasible option in terms of required expertise, infrastructure, and resources. The present randomized controlled trial will address a large unmet need by testing the hypothesis that reduced-dose systemic thrombolysis may improve the prognosis of patients with acute intermediate–high-risk PE at an acceptably low risk of major bleeding complications. In this context it is further anticipated, as also suggested by the results of meta-analyses,[15,36] that the use of alteplase in the present trial will be associated with a lower risk of intracranial hemorrhage and other major bleeding compared with tenecteplase used in PEITHO.[14] If the hypothesis of PEITHO-3 is confirmed, international clinical practice guidelines will most likely revisit their recommendations by including reperfusion and particularly reduced-dose systemic thrombolysis as first-line treatment in this risk class. If the hypothesis is rejected, catheter-directed treatment may become the only option for improving the prognosis of patients with intermediate–high-risk PE,[37] provided that it can demonstrate clinical efficacy and

safety in future state-of-the-art randomized controlled trials. In any case, the results of the present trial are expected to have a major impact on future risk-adjusted treatment strategies for patients with acute PE.

Study Committees and Investigators

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Conflict of Interest

O.S. has received institutional research grants from Bayer, Leo Pharma, Bristol-Myers Squibb, Merck Sharp and Dome, Daiichi-Sankyo, Boehringer Ingelheim, and Sanofi, and personal consultancy/speaker fees from Bayer, Bristol-Myers Squibb, Pfizer, Boston Scientific, Merck Sharp and Dome, Boehringer Ingelheim, Sanofi, and Chiesi. S.B. has received congress and travel payments from Daiichi-Sankyo and Bayer AG, honoraria from BTG Pharmaceuticals, Boston Scientific, Bayer HealthCare, and Leo Pharma, and institutional grants from Sanofi, outside the submitted work. W.A. reports research support from Bayer; activity in advisory boards for Bayer, Boehringer Ingelheim, Daiichi Sankyo, Portola, Janssen, Aspen, and Sanofi. D.D. has received speaker's honoraria from Bayer Vital, Daiichi-Sankyo, and Pfizer/Bristol-Myers Squibb, and consulting fees from Bayer Vital and Daiichi-Sankyo. In addition, D.D. is a member of SFB1425, funded by the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation #422681845). K.E. reports lecture fees from AstraZeneca, Bayer Vital, Berlin Chemie, Boehringer Ingelheim, and Novartis, and consulting fees from Bayer Vital, Boehringer Ingelheim, Novartis, and Novo Nordisk. M.F. reports lecture fees and travel grants from Bayer, Bristol-Myers Squibb, and Pfizer, and travel grants from Daiichi-Sankyo and Leo Pharma. M.V.H. reports grants from ZonMW Dutch Healthcare Fund, and grants and personal fees to the hospital from Boehringer Ingelheim, Bristol-Myers Squibb/Pfizer, Bayer Health Care, Aspen, and Daiichi-Sankyo, all outside the submitted work. D.J. has served as an advisor or consultant for Bayer HealthCare Pharmaceuticals, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi-Sankyo, Leo Pharma, Pfizer, ROVI, and Sanofi; served as a speaker or a member of a speakers' bureau for Bayer HealthCare Pharmaceuticals, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi-Sankyo, Leo Pharma, ROVI, and Sanofi; received grants for clinical research from Daiichi-Sankyo, Sanofi, and ROVI. M.K. reports speaker fees from Pfizer, Boehringer Ingelheim, and Bayer AG, outside the submitted work. M.L. reports consultant and speaker fees from Actelion, Bayer, Thermo Fisher Scientific, Daiichi-Sankyo, MSD, and Bristol-Myers Squibb-Pfizer, and project funding from Thermo Fisher Scientific. N.M. reports consulting fees, speaker fees, and project funding from Bayer AG and Bristol-Myers Squibb/Pfizer; speaker fees from AstraZeneca and Boehringer Ingelheim; and consulting fees from Abbott and Terumo. A.P. reports speaker fees from S.C. Pfizer Romania SRL, Servier Pharma SRL, Novartis Pharma Services Romania SRL, Bayer SRL, and SC Sanience SRL.

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