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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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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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.

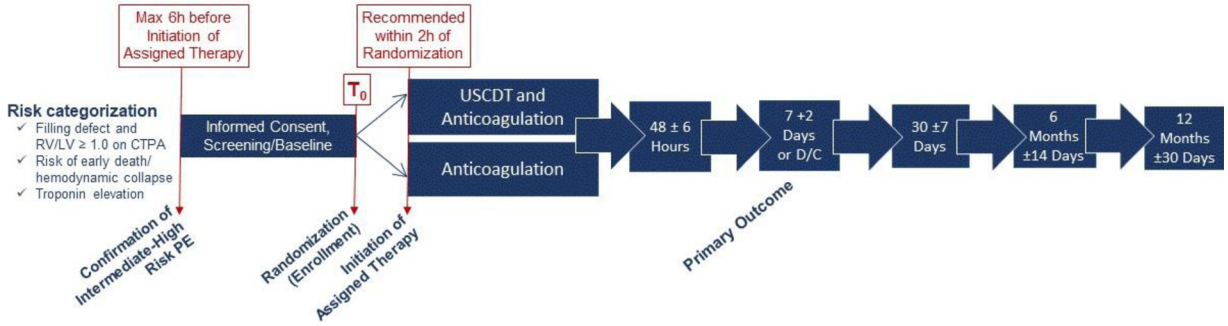
Assignment to the USCDT arm will include both treatment with the USCDT procedure and treatment with anticoagulation. The USCDT procedure will entail delivery of alteplase using the EkoSonic Endovascular System (Boston Scientific Corporation, Marlborough, MA). Alteplase will be delivered using a specified 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.

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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

S. Barco reports grants or contracts from Bayer, Sanofi, Boston Scientific, and Medtronic; consulting fees from Inari Medical and Boston Scientific; and honoraria from Inari Medical, Boston Scientific, Concept Medical, and Bayer. S. Barco reports participation on a Data Safety Monitoring Board or Advisory Board for Inari Medical. S.Z. Goldhaber reports support for the present manuscript from Boston Scientific and grants from Bayer, Boston Scientific, The National Heart, Lung, and Blood Institute, Bristol Myers Squibb, Janssen, and Pfizer. S.Z. Goldhaber reports honoraria from Lankenau Ground Rounds in Medicine, The Brigham Board Review in Critical Care, Latin American Anticoagulation Series Conference, Mount Sinai Ground Rounds, West Chester Medical Grand Rounds, Bakken Symposium at The University of Minnesota, New York Cardiovascular Symposium, Jeresaty Symposium at Trinity Health of New England, SBACV Symposium at Brazil Society of Angiology and Vascular Medicine, and the Philippine Society of Vascular Medicine Annual Convention. M.R. Jaff reports support for the present manuscript from Boston Scientific, honoraria from Gilde Healthcare, and stock in Embolitech. F.A. Klok reports grants from Bayer, Bristol Myers Squibb, Boehringer-Ingelheim, MSD, Daiichi-Sankyo, Actelion, Boston Scientific, The Netherlands Organisation for Health Research and Development, the Dutch Thrombosis Association, and the Dutch Heart Foundation. S.V. Konstantinides reports support for the present manuscript from Boston Scientific; consulting fees from Bayer AG, Daiichi-Sankyo, and Boston Scientific; and honoraria from Bayer AG, Inari Medical, MSD, Pfizer, and Bristol-Myers Squibb. N. Kucher reports honoraria from Boston Scientific. I.M. Lang reports manuscript writing support from Janssen, grants and consulting fees from Janssen and AOP Health, honoraria from Janssen, AOP Health, and Bayer, and support for attending meetings from Janssen, AOP Health, and Ferrer. F. Ní Ainle reports support for the present manuscript from Boston Scientific; grants and consulting fees from Actelion, Bayer, Sanofi, and Daiichi-Sankyo; honoraria from the American Society of Hematology; and support for attending World Thrombosis Day International Steering Committee meetings. F. Ní Ainle reports 2 patents planned, issued, or pending: UK 1616853.3 and European Application No. 20166826.6. F. Ní Ainle reports leadership on boards, societies, or committees including World Thrombosis Day Steering Committee, Director at Large and Member International Network of VENous Thromboembolism Clinical Research Networks (INVENT Council), Section Coordinator (Pulmonary Embolism and Pregnancy Section), Task Force to develop the 2019 European Society of Cardiology (ESC) Guidelines on the diagnosis and management of acute pulmonary embolism, Member of European Society of Cardiology Working Group of Pulmonary Circulation and Right Ventricular Function, Panel Member on International Society on Thrombosis and Haemostasis task force, Member, Scientific Topic Theme Committee on Women's Health, Congress of the International Society on Thrombosis and Haemostasis, Scientific Program Committee/Advisory Board member, European Haematology Association (EHA) Congress, Member, International Advisory Board, XXXI Congress of the International Society of Thrombosis and Haemostasis, Founder and member, VTE Ireland, Advisory Committee for Human Medicine (ACHM) of the Irish Health Products Regulatory Authority (HPRA). G. Piazza reports support for the present manuscript from Boston Scientific, research grants from Bristol Myers Squibb, Pfizer, Janssen, Boston Scientific, Bayer, Amgen, Inc., and Alexion Pharmaceuticals; consulting fees for scientific advisory from Amgen, Inc., Boston Scientific, Janssen, Bristol Myers, Squibb, Pfizer, PERC, and Syntactx. K. Rosenfield reports support for the present manuscript from Boston Scientific; grants from NIH; consulting fees from

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