A randomized trial of ultrasound-facilitated, catheter-directed, thrombolysis versus anticoagulation for acute intermediate-high risk pulmonary embolism: The higher-risk pulmonary embolism thrombolysis study

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The primary objective of the study is to assess whether ultrasound-facilitated, catheter-directed, thrombolysis and anticoagulation are associated with a significant reduction in the composite outcome of PE-related mortality, cardiorespiratory...

Ethical review	Not approved
Status	Will not start
Health condition type	Pulmonary vascular disorders
Study type	Interventional

Summary

ID

NL-OMON52149

Source
ToetsingOnline

Brief title
S2479 - Hi-PEITHO

Condition

- Pulmonary vascular disorders

Synonym
Pulmonary embolism; blood clot in lung

Research involving

Human

Sponsors and support

Primary sponsor: Boston Scientific Corporation
Source(s) of monetary or material Support: Industry Boston Scientific

Intervention

Keyword: anticoagulation, embolism, pulmonary, thrombolysis

Outcome measures

Primary outcome

The primary endpoint is a composite of PE-related mortality, cardiorespiratory decompensation or collapse (as defined below), or non-fatal symptomatic and objectively confirmed recurrence of PE, within seven (7) days of randomization.

Cardiorespiratory collapse or decompensation should fulfill at least one of the following criteria:

a) cardiac arrest or need for CPR at any time between randomization and day 7;

b) signs of shock: new-onset persistent arterial hypotension (SBP below 90 mmHg or SBP drop by at least 40 mmHg over at least 15 minutes, and despite an adequate filling status; or need for vasopressors to maintain SBP of at least 90 mmHg), 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 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 consecutive measurements, taken twice.

Secondary outcome

1. Change in the RV-to-LV diameter ratio as measured by echocardiography between baseline and 48±6 hours

2. PE-related death within 7 days;

3. Cardiorespiratory decompensation within 7 days;

4. Placement on ECMO or mechanical ventilation within 7 days;

5. GUSTO major (moderate and severe) bleeding within 7 days;

6. ISTH major bleeding within 7 days, 30 days, and 6 months;

7. Ischemic or hemorrhagic stroke within 7 days and 30 days;

8. All-cause mortality within 7 days, 30 days, 6 months, and 12 months;

9. Serious adverse events within 30 days;

10. All-cause mortality, cardiorespiratory collapse or recurrence of PE within 30 days;

11. Symptomatic PE recurrence within 30 days and 6 months;

12. Change from baseline in RV dysfunction on echocardiography at 6 months;

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 days, 6 months, and 12 months, including:

a) WHO functional class (and discharge),

b) PVFS scale (and discharge),

c) 6-Minute Walk Test;

16. Quality of life (PEmb-QOL, SF-36, and EQ-5D scales) at 6 months and 12

months;

17. Diagnosis of CTEPH within 12 months;

18. Health economic analysis (length of hospital stay, resource utilization,

indirect costs) at 30 days and 12 months (selected sites and countries).

Study description

Background summary

Intravenously administered thrombolysis is the *prototype* of reperfusion therapy for acute PE. Early studies reported significant hemodynamic improvement after full-dose systemic thrombolysis, and a meta-analysis of 15 randomized controlled trials with a total of 2057 patients confirmed that thrombolysis may improve early survival (odds ratio [OR] 0.59; 95% confidence interval [CI] 0.36-0.96), and reduce PE-related death (OR 0.29; 95% CI 0.14-0.60) and recurrent PE (OR 0.50; 95% CI 0.27-0.94) compared to anticoagulation alone (3). Today, PE guidelines recommend primary systemic thrombolytic therapy only for *high-risk* patients with overt right ventricular (RV) failure, i.e. those presenting with hemodynamic instability (4-6).

The majority of patients with acute PE appear hemodynamically stable at presentation (7). However, patients with imaging or laboratory findings of RV dysfunction may have an *intermediate* but still substantial (up to 8%) risk of early death (7). It has been hypothesized that intermediate-risk patients may benefit from early thrombolysis. In the randomized, placebo-controlled, Pulmonary Embolism International Thrombolysis (PEITHO) trial, patients had combined echocardiographic and laboratory evidence of RV dysfunction. All-cause death or hemodynamic decompensation within 7 days was reduced in the thrombolysis group, from 5.6% to 2.6% (OR 0.44; 95% CI 0.23-0.88). However, this was offset by higher rates of hemorrhagic stroke (OR 12.10; 95% CI 1.57* 93.39) (8). High rates of major and intracerebral bleeding were confirmed by a meta-analysis of thrombolysis trials, most of which employed systemic *full-dose* thrombolysis (9).

Consequently, the current state of the art on thrombolysis for PE can be summarized as follows:

a) Acute intermediate-risk (submassive) PE remains potentially life-threatening when treated with anticoagulation alone.
b) Early reperfusion with standard-dose intravenous thrombolysis offers the potential of improving hemodynamics as well as early clinical outcomes.
c) Reperfusion treatment is nevertheless not recommended for patients without cardiogenic shock, because the bleeding risk of standard-dose thrombolytic treatment is considered prohibitive.
This unsatisfactory situation, which deprives many patients with acute PE of a potentially life-saving therapeutic option, can be resolved only if future research focuses on the following key aspects:

a) Improve the safety of thrombolysis. Pharmacomechanical reperfusion, notably ultrasound-facilitated catheter-directed thrombolysis (USCDT), has the potential of reversing RV dilation, pulmonary hypertension, and anatomic thrombus burden (10). 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 dimension ratio > 1.0, ultrasound-assisted local infusion of 10*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 (11). Supportive of the efficacy and safety of this approach are also the results of (i) a prospective, single-arm multicenter trial on 150 patients with submassive or massive PE (12); (ii) a registry on catheter-directed, either purely mechanical or pharmacomechanical thrombus removal including 28 patients with massive and 73 with submassive PE (13); and (iii) 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 four USCDT regimens using a shorter delivery duration for the primary efficacy endpoint defined as the reduction in right ventricular*to*left ventricular diameter ratio by computed tomographic angiography (14).

b) Advance the concept of intermediate-high risk and the PE severity criteria, to better identify patients who may clinically benefit from thrombolysis. In the PEITHO trial, baseline imaging and laboratory findings, but not clinical parameters (apart from the requirement for hemodynamic *stability* at presentation), were used as inclusion criteria (1). The combined primary outcome and particularly early mortality rates were low both in the thrombolysis and in the placebo (anticoagulant-only) arm (8). This generates the hypothesis that better identification of *intermediate-high risk* PE may be necessary to justify early thrombolysis. In a recent post-hoc analysis of the PEITHO trial, baseline clinical variables were identified, which may be used (in addition to RV dysfunction and troponin elevation) as additional criteria to identify patients with an elevated risk of *imminent* hemodynamic decompensation and an adverse early outcome (1). For the purpose of this post-hoc analysis, the composite clinical outcome was defined as PE-related death, hemodynamic collapse, or non-fatal symptomatic recurrent PE between

randomization and day 30. In the placebo arm, the rate of the composite clinical outcome was 20% in patients with at least two clinical criteria of severity, and this was reduced to 7.0% in the thrombolysis arm; this corresponds to a relative risk reduction of 65%. In contrast, in patients who fulfilled none of these clinical criteria, the rate of the composite clinical outcome was only 2.3% in the placebo arm and higher, 3.8%, in the thrombolytic arm. These findings must be regarded as exploratory and hypothesis-generating. However, keeping in mind this limitation, they appear to support the requirement for disease-specific clinical indicators of PE severity at presentation on top of established imaging and biochemical criteria, to be used as inclusion criteria in future trials testing safer reperfusion modalities in intermediate-risk PE.

Study objective

The primary objective of the study is to assess whether ultrasound-facilitated, catheter-directed, thrombolysis and anticoagulation are associated with a significant reduction in the composite outcome of PE-related mortality, cardiorespiratory decompensation or collapse, or non-fatal symptomatic and objectively confirmed recurrence of PE compared to anticoagulation alone within seven days of randomization.

Additional objectives are to contribute further evidence to the existing data 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 that is currently recommended in the guidelines.

Study design

The trial is a post-market, randomized, controlled, adaptive, open-label, multicenter parallel-group trial with blinded adjudication of the primary composite outcome. Subjects will be randomized 1:1 to treatment with USCDT and anticoagulation or anticoagulation alone. The study is unblinded to Investigators and subjects, but adjudication of the outcome measure and other safety outcomes will be completed by a blinded CEC.

Initially, 406 subjects are planned to be enrolled at up to 65 sites in the US and Europe. There will be a planned interim analysis after 50% are enrolled, with the potential to enroll up to 544 subjects. The follow up period for each subject is 12 months, so the overall study duration is anticipated to be at least 36 months.

Subjects will be randomized 1:1 to receive either the USCDT intervention with anticoagulation or will be treated with anticoagulation alone. Randomization will be stratified by the following parameters:

* Age: <75 years vs *75 years
* RV/LV ratio on CTPA: <1.5 vs *1.5

Basic demographic, pseudonymized information about the subject will be entered into the EDC. The research staff will confirm that all eligibility criteria are met. The subject will be assigned a subject ID number and will receive a randomized assignment to the USCDT treatment arm or anticoagulation-only control arm. If they are assigned to receive USCDT, treatment should be initiated as soon as practical, but no later than six (6) hours of confirmation of diagnosis of intermediate-high risk PE. It is strongly recommended that it begins within two hours of randomization.

Test (USCDT) Arm

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 EkoSonicTM Endovascular System. Alteplase will be delivered using a specified treatment protocol (see section 10.3.4.1.1 for the full protocol). Treatment must be initiated as soon as practical but no more than six (6) hours after confirmation of diagnosis of intermediate-high risk PE. It is strongly recommended that it begins within two (2) hours of randomization.
Assignment to the experimental USCDT arm will also include initiation or continuation of anticoagulation therapy according to a specified treatment protocol. If a subject is already being treated with low molecular weight heparin (LMWH) or unfractionated heparin (UFH), the treatment protocol for continuation of therapy from the time of randomization is provided. See section 10.3.4.1.2.

Control (Anticoagulation) arm:

Assignment to the anticoagulation-only control arm will include either initiation or continuation of anticoagulation therapy according to a specified treatment protocol (see section 10.3.4.2 for the full protocol). Therapeutic anticoagulation is the current standard of care in the treatment of acute intermediate-high risk PE.
The control arm will not receive an interventional procedure. Note: there are mechanisms in place if a subject requires an escalation in therapy with a documented hemodynamic collapse or decompensation. In the absence of hemodynamic collapse or decompensation, or documentation of such, institution of any PE treatment beyond the therapy to which the subject was randomly assigned will be considered a protocol deviation.

Intervention

Patients who fulfill all inclusion criteria and meet none of the exclusion criteria will be enrolled in the study after providing written informed

consent. They will be randomized with a 1:1 ratio to ultrasound-facilitated, catheter-directed thrombolysis (USCDT) combined with anticoagulation versus anticoagulation alone.

Randomization and initiation of assigned therapy should follow as soon as possible, but no more than six (6) hours after confirmation of diagnosis of intermediate-high risk PE as defined by inclusion criteria #2-5. Randomization should occur as soon as practical after the Investigator confirms diagnosis. Initiation of assigned therapy should follow as soon as possible after randomization. For subjects randomized to receive USCDT, it is strongly recommended the intervention is initiated within two (2) hours of randomization.

Study burden and risks

Risks associated with participation in this study are listed in the IFU and ICF.

Additional risks may exist. Risks can be minimized through compliance with the protocol, performing procedures in the appropriate hospital environment, adherence to subject selection criteria, close monitoring of the subject*s physiologic status during research procedures and/or follow-ups and by promptly supplying BSC with all pertinent information required by this protocol.
Data will be monitored as they are submitted to sponsor. Qualified employees at sponsor, or a designee under contract, will conduct monitoring visits at the initiation of the study and at interim intervals described in the monitoring plan throughout the course of the study to evaluate protocol compliance and determine if there are any issues that could affect the safety or welfare of any subject in the study.

All study-specific tests and assessments completed by patients in the study are considered part of routine care for patients with pulmonary embolism. Study subjects may complete more questionnaires to assess symptoms and quality of life, but they are not asked to undergo any procedures or examinations outside standard care for this patient population.

However taking part in the study may be associated with a significant reduction in the composite outcome of pulmonary embolism (PE)-related mortality, cardiorespiratory decompensation or collapse, or nonfatal symptomatic and objectively confirmed recurrence of PE.

Contacts

Public
Boston Scientific Corporation

300 Boston Scientific Way
Marlborough MA 01752
US
Scientific
Boston Scientific Corporation

300 Boston Scientific Way
Marlborough MA 01752
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1) Age 18-80 years, inclusive

2) Objectively confirmed acute PE, based on CTPA showing a filling defect in at least one main or proximal lobar pulmonary artery (PA)

3) Elevated risk of early death/hemodynamic collapse, indicated by at least two of the following new-onset clinical criteria:
i. Electrocardiogram (ECG)-documented tachycardia with heart rate *100 beats per minute, not due to hypovolemia, arrhythmia, or sepsis;
ii. SBP * 110 mm Hg for at least 15 minutes;
iii. respiratory rate > 20 x min-1 or oxygen saturation on pulse oximetry (SpO2) < 90% (or partial arterial oxygen pressure < 60 mmHg) at rest while breathing room air;

4) Right-to-left ventricular (RV/LV) diameter ratio * 1.0 on CTPA

5) Serum troponin I or T levels above the upper limit of normal

6) Signed informed consent.

Exclusion criteria

1) Hemodynamic instability*, i.e. at least one of the following present:
a) cardiac arrest or need for cardiopulmonary resuscitation;
b) need for ECMO, or ECMO initiated before randomization
c) PE-related shock, defined as: (i) SBP < 90 mmHg, or vasopressors required to achieve SBP * 90 mmHg, despite an adequate volume status; and (ii) end-organ hypoperfusion (altered mental status; oliguria/anuria; increased serum lactate);
d) isolated persistent hypotension (SBP < 90 mmHg, or a systolic pressure drop by at least 40 mmHg for at least 15 minutes), 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 hours of admission and maintain

2) Need for admission to an intensive care unit for a reason other than the index PE episode. Note: Patients who test positive for severe acute respiratory syndrome coronavirus 2 (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 39oC / 102.2oF
4) Logistical reasons limiting the rapid availability of interventional procedures to treat acute PE (e.g., during the outbreak of an epidemic)
5) Index PE symptom duration > 14 days
6) Active bleeding
7) History of intracranial or intraocular bleeding at any time
8) Stroke or transient ischemic attack within the past 6 months, 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 weeks
11) Platelet count < 100 x 109 x L-1
12) Patients who have received a once-daily therapeutic dose of LMWH or a therapeutic dose of fondaparinux within 24 hours prior to randomization
13) Patients who have received one of the direct oral anticoagulants apixaban or rivaroxaban within 12 hours 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 days
15) Administration of a thrombolytic agent or a glycoprotein IIb/IIIa receptor

antagonist during the current hospital stay and/or within 30 days, for any reason
16) Chronic treatment with antiplatelet agents other than low-dose acetylsalicylic acid or clopidogrel 75 mg once daily (but not both). Dual antiplatelet therapy is excluded.
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 an International Normalized Ratio (INR) > 1.5
19) Pregnancy or lactation
20) Previous inclusion in the study
21) Known hypersensitivity to alteplase, LMWH or UFH, or to any of the excipients
22) Life expectancy less than 6 months

Study design

Design

Study type:	Interventional
Intervention model:	Other
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	45
Type:	Anticipated

Medical products/devices used

Generic name:	EkoSonicTM Endovascular System
Registration:	Yes - CE intended use

Ethics review

Not approved

Date:	29-03-2022
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
ClinicalTrials.gov	NCT04790370
CCMO	NL77735.041.21