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

Published: 16-06-2022
Last updated: 06-04-2024

The primary aim of the study is to evaluate whether treatment with the EKOS device on top of anticoagulation in patients with severe pulmonary embolism results in a better clinical outcome than treatment with anticoagulation alone. The primary...

Ethical review	Approved WMO
Status	Pending
Health condition type	Pulmonary vascular disorders
Study type	Interventional

Summary

ID

NL-OMON51732

Source
ToetsingOnline

Brief title
Hi-PEITHO - S2479

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 the occurrence of pulmonary embolism-related mortality, cardiorespiratory decompensation or collapse or non-fatal symptomatic and objectively confirmed recurrent pulmonary embolism within 7 days of randomization.

Cardiorespiratory decompensation or collapse is defined as:

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

b) Signs of shock: first-onset persistent hypotension (SBP below 90 mmHg or decrease in SBP of at least 40 mmHg for at least 15 minutes, and despite adequate filling status; or vasopressors/inotropics required to maintain an SBP of at least 90 mmHg), along with end-organ hypoperfusion (altered mental status; oliguria/anuria; increased serum lactate) at any time between randomization and day 7;

c) placement of 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 at least 2 measurements spaced at least 15 minutes apart.

Secondary outcome

1. Change in the right ventricular (RV) to left ventricular (LV) end diastolic diameter ratio (RV/LV) 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. Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) bleeding scale major (moderate and severe) bleeding within 7 days;

6. International Society on Thrombosis and Haemostasis (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: World Health Organization (WHO) functional class and Post-Venous Thromboembolism (VTE) Functional Status (PVFS) scale at discharge, 30 days, 6 and 12 months; 6-Minute Walk Test (6MWT) at 30 days, 6 and 12 months;

16. Quality of life: Pulmonary Embolism Quality of Life (PEmb-QOL), Short Form 36 (SF-36), EuroQuol-5 Dimension (EQ-5D) at 6 and 12 months;

17. Diagnosis of chronic thromboembolic pulmonary hypertension (CTEPH) within 12 months;

18. Health economic analysis (length of hospital stay, resource utilization, indirect costs) at 30 days and at 12 months (selected sites and countries)

Study description

Background summary

Intravenous thrombolysis is the "prototyped standard" for reperfusion therapy in severe acute pulmonary embolism. This is only administered in case of haemodynamic instability due to the pulmonary embolism (*high risk pulmonary embolism*); although patients recover faster haemodynamically and have a better survival after administration of thrombolysis, there is also a greatly increased risk of major bleeding. Also in patients with a so-called intermediate-high risk pulmonary embolism, defined as maintained blood pressure with signs of right ventricular overload and cardiac ischaemia, thrombolysis also protects against progression to shock or death due to pulmonary embolism. Due to the large number of bleeding events, thrombolysis in this patient group does not protect against death from any cause. For this reason, it is not the standard treatment for this group.

Several steps have been taken to improve the treatment of the group of patients with an intermediate-high risk pulmonary embolism. First of all, safer ways of reperfusion therapy have been developed, namely catheter-guided treatment with thrombosuction and/or local low-dose thrombolysis. Both techniques are known to restore right heart function more quickly compared to anticoagulation alone,

and have a low risk of bleeding. In addition, better selection criteria have been developed to identify hemodynamically stable patients with a risk of progression to shock and death greater than 20%, by adding clinical signs of severity on top of cardiac imaging and biomarkers of ischemic heart damage. The researchers of the HI-PEITHO study are testing the hypothesis that reperfusion therapy using catheter-guided low-dose thrombolysis in the latter group of patients will lead to better outcomes (less death from pulmonary embolism or progression to shock) than treatment with anticoagulation alone.

Study objective

The primary aim of the study is to evaluate whether treatment with the EKOS device on top of anticoagulation in patients with severe pulmonary embolism results in a better clinical outcome than treatment with anticoagulation alone. The primary endpoint is the occurrence of pulmonary embolism-related mortality, cardiorespiratory decompensation or collapse or non-fatal symptomatic and objectively confirmed recurrent pulmonary embolism within 7 days of randomization. Secondary endpoints are to determine the effect of the intervention on the individual components of the primary endpoint, quality of life, and speed of physical recovery. The safety and cost-effectiveness of the treatment is also examined.

Study design

The study is a Phase 4, randomized, controlled, adaptive, open-label, multicenter, parallel group, blinded assessment of primary composite outcome. Subjects are randomized 1:1 to treatment with EKOS plus anticoagulation or anticoagulation alone. The randomization is stratified by age (< 75 years versus >= 75 years) and RV/LV ratio on CTPA (< 1.5 versus >= 1.5). After randomization to the intervention arm, EKOS treatment should start within 6 hours of determining eligibility to participate in the study. In both study arms, the first 24 hours is treated with unfractionated or twice daily dosed low molecular weight heparin. In the intervention arm, this treatment is continued until 24 hours after the end of the intervention. The local investigator can then proceed to oral anticoagulation according to the applicable international guideline and local protocol.

The target number of study patients is 406. These patients are being recruited from approximately 65 hospitals in the United States and Europe. Based on the interim analysis after 50% of the intended inclusions, there is a possibility to increase the sample size to a maximum of 544 patients. All patients are followed for 12 months; it is expected that the study can be completed 3 to 4 years after the start.

Intervention

Patients meeting all of the inclusion criteria and none of the exclusion criteria will be included in the study upon written informed consent. They are randomized in a 1:1 ratio to receive ultrasound-facilitated catheter-directed thrombolysis (USCDT) in combination with anticoagulants or anticoagulants alone. Randomization and initiation of assigned treatment should be followed as soon as possible, but no later than six (6) hours after confirmation of the diagnosis of intermediate to high risk pulmonary embolism, as defined in inclusion criteria 2-5. Randomization should be performed as soon as practicable after the investigator confirms the diagnosis. The assigned treatment should be started as soon as possible after randomization. For subjects assigned to the USCDT group, it is strongly recommended that the intervention be initiated within two (2) hours of randomization.

Study burden and risks

The intervention is associated with a higher risk of bleeding due to thrombolysis, and procedure-related risks such as bleeding at the insertion site, damage to the heart or bypassed blood vessels, pneumothorax and haemoptysis. However, the absolute risk of this is low (<3%) and should be viewed in the context of the estimated risk of developing shock or death (20%). If a patient in the control arm of the study, or who is not included, becomes hemodynamically unstable, reperfusion therapy should still be administered, whereby the risk of bleeding and complications is higher than that 3% due to the acute setting.

Contacts

Public
Boston Scientific Corporation

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

300 Boston Scientific Way 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 SBP of >= 90 mmHg 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 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, 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:	Pending
Start date (anticipated):	01-05-2022
Enrollment:	45
Type:	Anticipated

Medical products/devices used

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

Ethics review

Approved WMO Date:	16-06-2022
Application type:	First submission
Review commission:	METC NedMec

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	NL81278.041.22