Pulmonary Embolism International Thrombolysis Trial: A reduced dose of thrombolytic treatment for patients with intermediate high-risk acute pulmonary embolism: a randomized controlled trial.

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This study has been transitioned to CTIS with ID 2024-511321-54-00 check the CTIS register for the current data. Primary objective:To assess the efficacy of reduced dose thrombolytic therapy in patients with acute intermediate-high risk pulmonary...

Ethical review	Approved WMO
Status	Pending
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON56449

Source
ToetsingOnline

Brief title
PEITHO-3

Condition

- Other condition

Synonym
blockage in one of the pulmonary arteries in your lungs

Health condition

longembolie

Research involving
Human

Sponsors and support

Primary sponsor: Assistance Publique - Hôpitaux de Paris, Clinical Research and Innovation Direction (DRCI)
Source(s) of monetary or material Support: Academische Sponsor in Frankrijk; Assistance publique - Hôpitaux de Paris,Boehringer Ingelheim,Canadian Institutes of Health Research (CIHR),D. Collen Research Foundation,French Ministry of health - Programme hospitalier de Recherche Clinique - PHRC 2016 (PHRCN-16-0580),German Research Foundation - KO 1939/3-1, 2019

Intervention

Keyword: PEITHO, Pulmonary Embolism, thrombolytic treatment

Outcome measures

Primary outcome

The primary outcome is the composite of (1) death from any cause or (2)

hemodynamic decompensation or (3) objectively confirmed recurrent PE at day 30.

Secondary outcome

The following key secondary outcomes will be included in a hierarchical

analysis:

1) Fatal or GUSTO severe or life-threatening bleeding 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

The following secondary outcomes are not entered in the hierarchical analysis:

4) PE-related death within 30 days

5) Hemodynamic decompensation within 30 days

6) Need for rescue thrombolysis, catheter-directed treatment or surgical embolectomy within 30 days

7) Recurrent PE within 30 days

8) Ischemic or hemorrhagic stroke within 30 days

9) Serious adverse events within 30 days

10) All-cause mortality at two years

11) Persisting dyspnea assessed by the Medical Research Council (MRC) scale at day 180 and at 2 years

12) Functional outcome using the post-VTE functional scale at day 180 and at 2 years

13) Persistent RV dysfunction at day 180 and at 2 years defined as an intermediate or high probability of pulmonary hypertension on echocardiography according to ESC criteria

14) Confirmed chronic thromboembolic pulmonary hypertension at 2 years defined according to ESC criteria

15) Utilization of health care resources within 30 days and 180 days post randomization.

Study description

Background summary

In patients with intermediate-risk pulmonary embolism, thrombolytic treatment is associated with a reduction in the combined risk of hemodynamic decompensation and death but also with an increased risk of major and intracranial bleeding. The effect of thrombolytic treatment on the risk of death is still controversial in these patients. Previous studies suggest that reduced dose of thrombolytic treatment is as effective as the full dosage but

is associated with a decrease in the risk of bleeding. In this study, we will assess the efficacy and safety of a reduced dosage of thrombolytic therapy in patients with intermediate-high-risk acute pulmonary embolism.

Study objective

This study has been transitioned to CTIS with ID 2024-511321-54-00 check the CTIS register for the current data.

Primary objective:
To assess the efficacy of reduced dose thrombolytic therapy in patients with acute intermediate-high risk pulmonary embolism at day 30.

Secondary objectives:
• To assess the safety of reduced dose thrombolytic therapy in patients with intermediate-high-risk acute pulmonary embolism
• To assess the net clinical benefit of reduced dose thrombolytic therapy in patients with intermediate-high-risk acute pulmonary embolism
• To assess the effect of reduced dose thrombolytic therapy on overall mortality of patients with intermediate-high-risk acute pulmonary embolism
• To assess the effect of reduced dose thrombolytic therapy on long-term mortality, functional impairment, residual right ventricular (RV) dysfunction and chronic thromboembolic pulmonary hypertension
• To assess the effect of reduced-dose thrombolytic therapy on utilization of health care resources

Study design

Experimental design:
Randomized placebo-controlled double-blind multicenter, multinational trial with long-term follow-up.

Research period:
• The patients will be recruited over a 48-month period
• The duration of participation for the patient is 24 months
• The total duration of the study is 72 months

Number of sites:
About 90-100 centers in 13-14 countries

Intervention

After inclusion and exclusion criteria have been verified, study protocol will be explained to the patient and free and written informed consent will be

obtained.
Randomization will be performed with an IWRS no later than six hours after the confirmation of the inclusion criteria.
Study drug (alteplase or alteplase placebo) will be administered within 30 minutes of the randomization.
The follow-up study visits include a 30-day follow-up visit, a six-month follow-up visit and a 24-month follow-up visit. Echocardiography will be performed at six month and at 24 month-follow-up visits.

Study burden and risks

After inclusion and exclusion criteria have been verified, study protocol will be explained to the patient and free and written informed consent will be obtained.
Randomization will be performed with an IWRS no later than six hours after the confirmation of the inclusion criteria.
Study drug (alteplase or alteplase placebo) will be administered within 30 minutes of the randomization.
The follow-up study visits include a 30-day follow-up visit, a six-month follow-up visit and a 24-month follow-up visit. Echocardiography will be performed at six month and at 24 month-follow-up visits.

Burden for patient:
-respond to questions related to the utilization of Health Care resources at Day 30 and Day 180 visits
-Echocardiography taken at inclusion, Day 180 and 2 years visits

Benefit of study:
Improve standard of care treatment for patients with intemediate high risk pulmonary embolism

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Age 18 years or older;
* Objectively confirmed acute PE with first symptoms occurring 2 weeks or less before randomization. Objective confirmation is based on at least one of the following criteria: (a) at least one segmental ventilation-perfusion mismatch on lung scanning; (b) computed tomography pulmonary angiography (CTPA) or selective pulmonary angiography showing a filling defect or an abrupt obstruction of a segmental or more proximal pulmonary artery;
* *cute PE confirmed within 24 hours prior to randomization;
* Elevated risk of early death, or of hemodynamic collapse, or PE recurrence, indicated by at least one of the following criteria: (a) systolic blood pressure (SBP) <= 110 mm Hg over at least 15 min upon enrolment, (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 >= 90 mm Hg and adequate organ perfusion without catecholamine infusion; (c) respiratory rate > 20/min or SpO2 < 90% (or partial arterial oxygen pressure < 60 mm Hg) at rest while breathing room air, (d) documented history of chronic symptomatic heart failure defined as previous diagnosis of heart failure (i.e. heart failure with reduced, moderately reduced or preserved ejection fraction), or treatment for heart failure at any time during the past 12 months;
* 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);
* Serum troponin I or T concentration above the upper limit of local normal using a high-sensitivity assay;
* Ability to randomize the patient within 6 hours after the investigator

receives the result of the second of the two criteria for RV dysfunction (RV/LV diameter ratio > 1.0) and myocardial injury (serum troponin I or T concentration above the upper limit of local normal), whichever comes latest;
* Signed informed consent form;
* [France] Patient insured under a social security system

Exclusion criteria

* Hemodynamic instability, defined by at least one of the following criteria
- cardiac arrest;
- obstructive shock, defined as: (i) SBP < 90 mm Hg, or vasopressors required to achieve a SBP >= 90 mmHg despite an adequate filling status; and (ii) end-organ hypoperfusion (altered mental status; cold, clammy skin; oliguria/anuria; increased serum lactate);
- isolated persistent hypotension (SBP < 90 mm Hg, or a systolic pressure drop >= 40 mm Hg for > 15 min), if not caused by new-onset arrhythmia, hypovolemia, or sepsis
* Active bleeding
* History of non-traumatic intracranial bleeding, any time
* Acute ischemic stroke or transient ischemic attack (TIA) within the previous 6 months
* Known central nervous system neoplasm/metastasis
* Neurologic, ophthalmologic, abdominal, cardiac, thoracic, vascular or orthopedic surgery or trauma within the previous 3 weeks
* Platelet count < 100 x 109/L
* INR > 1.4. If INR not available: prothrombin time ratio < 60%. If both INR and prothrombin time ratio are measured, INR is relevant for the assessment of this criterion.
* Treatment with antiplatelet agents other than (a) acetylsalicylic acid (ASA) <= 100 mg once daily or (b) clopidogrel 75 mg once daily or (c) a single loading dose of ASA or clopidogrel. Dual anti-platelet therapy (ASA + clopidogrel) is not allowed.
* Any direct oral anticoagulant within 12 hours of inclusion
* Uncontrolled hypertension defined by SBP > 180 mm Hg at the time of inclusion
* Known pericarditis or endocarditis
* Known significant bleeding risk according to the investigator*s judgement
* Administration of thrombolytic agents within the previous 4 days
* Vena cava filter insertion or pulmonary thrombectomy within the previous 4 days
* [Italy and the Netherlands] Participation in another interventional clinical study within 30 days from the inclusion
* [All countries except Italy and the Netherlands] Current participation in another interventional clinical study
* Previous enrolment in this study
* Known hypersensitivity to alteplase, gentamicin (a residue of the Actilyse®

manufacturing process present in trace amounts), any of the excipients of Actilyse®, or low-molecular weight heparin (LMWH)
* Known previous immune heparin-induced thrombocytopenia
* Known severe liver disease (grade >= 3) including liver failure, cirrhosis, portal hypertension (esophageal varices) and active hepatitis
* Acute symptomatic pancreatitis
* Gastrointestinal ulcers or esophageal varices, documented within the past 3 months
* Known arterial aneurysm, arterial or venous malformations
* Pregnancy or parturition within the previous 30 days or current breastfeeding
* Women of childbearing potential who do not have a negative pregnancy test at the inclusion visit and do not use one of the following methods of birth control: hormonal contraception or intrauterine device or bilateral tubal occlusion
* Any other condition that in the investigator*s opinion would place the patient at increased risk upon start of the investigational treatment
* Life expectancy of less than 6 months, or inability to complete 6-month follow-up.
* Patient under legal protection

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-05-2022
Enrollment:	75
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Actilyse
Generic name:	Alteplase
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	02-11-2021
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	20-07-2022
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	20-09-2023
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	10-10-2023
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

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
EU-CTR	CTIS2024-511321-54-00
EudraCT	EUCTR2018-000816-96-NL
CCMO	NL77628.058.21