



Clinical trial results:

Low dose catheter directed thrombolysis for acute intermediary-high risk pulmonary embolism.

Summary

EudraCT number	2018-003564-31
Trial protocol	DK
Global end of trial date	21 January 2025

Results information

Result version number	v1 (current)
This version publication date	22 January 2026
First version publication date	22 January 2026

Trial information

Trial identification

Sponsor protocol code	190580-001
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03854266
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Aarhus University Hospital
Sponsor organisation address	Palle Juul Jensens Boulevard 99, Aarhus N, Denmark, 8200
Public contact	Asger Andersen, Aarhus University Hospital, 45 26363226, asger.andersen@clin.au.dk
Scientific contact	Asger Andersen, Aarhus University Hospital, 45 26363226, asger.andersen@clin.au.dk

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	21 January 2025
Is this the analysis of the primary completion data?	Yes
Primary completion date	21 January 2025
Global end of trial reached?	Yes
Global end of trial date	21 January 2025
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To investigate if low dose catheter directed fibrinolysis for 2 h is superior to unfractionated heparin with regards to unloading the right ventricle in acute intermediate-high risk pulmonary embolism.

Protection of trial subjects:

The study adhered to Danish laws of ethics and management of personal data. The study was approved by "Datatilsynet", the Regional Ethics Committee and Lægemiddelstyrelsen. The study adhered to the standards of good clinical practice and was monitored by the local GCP unit. The study has payed the outmost respect to the included patients mental and physical health and their personal integrity.

The patients included in the trial was exposed to an extra CTA which exposes the patient to 4-8 msievert which approximates the background radiation a person receives over 3 years and increases the risk of a fatal cancer from 25% to 25.045%. Patients randomized to CDT received an additional 1-2 msievert from the fluoroscopy. The patients included in this study had an estimated 30 day mortality of 15% and solid preliminary data suggest the treatment to be effective and safe. Therefore it is the investigators opinion that the benefits of doing this study outweighed the risks.

The treatment is considered safe and previous studies suggest that this approach may be better than conventional therapy. All patients will be monitored closely during the study period and in the catheterization laboratorium when treated with low dose heparin. The invasive procedure will be performed by a trained invasive cardiologist whose expertise is to catheterize the pulmonary circulation. Using the low dose short period regime suggested in this protocol there have not been reported any bleedings in clinical studies.

Background therapy:

Standard unfractionated heparin infusion.

Evidence for comparator:

The treatment of low and intermediate-low risk pulmonary embolism patients is anticoagulation and for high-risk patients treatment it is reperfusion. These treatment strategies are well documented, but in patients with intermediate-high risk the choice of treatment is more tricky. Anticoagulation does not introduce a quick relief of the struggling right ventricle and despite being effective at reducing thrombus burden, the risk of major bleedings outweighs the benefit of systemic thrombolysis. The optimal treatment should quickly reduce thrombus mass without increasing bleeding risk. Based on this principle, local catheter based trombolysis (CDT) could be ideal. In combination with low frequency ultrasound, CDT unloads the right ventricle more efficiently than anticoagulation and without increasing bleeding risk. And it has been reported to be as effective to use a low dose of the fibrinolytic agent for a shorter period of time making the approach more applicable in the clinical setting. The ultrasound assisted CDT is however more complicated to use and more expensive than conventional CDT and it is highly speculative if ultrasound have any additive effect to CDT alone. But, there are no data from randomized trials that have investigated the effect of CDT in PE. This was the first randomized trial to investigate if low dose CDT is superior to anticoagulation in PE.

Actual start date of recruitment	01 April 2019
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Denmark: 60
Worldwide total number of subjects	60
EEA total number of subjects	60

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	26
From 65 to 84 years	34
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Between August 2020 and October 2024, 60 patients with acute intermediate-high risk PE were randomized to receive UFH plus CDT (n = 30) or UFH alone (n = 30).

Pre-assignment

Screening details:

Patients presenting with acute PE at one of the hospitals in the two Danish regions were eligible if they were older than 17 years and younger than 81 years, had symptom onset within 14 days before diagnosis, and had acute intermediate-high risk PE according to the European Society of Cardiology (ESC) guidelines.

Period 1

Period 1 title	Overall study period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Data analyst ^[1]

Blinding implementation details:

Analyst of CT data was blinded to the study arm

Arms

Are arms mutually exclusive?	Yes
Arm title	Unfractionated Heparin alone

Arm description:

Standard treatment is unfractionated heparin infusion alone. Treatment is initiated at the time of study inclusion. Initial dose is 80 IE/kg bolus followed by 18 IE/kg as continuous infusion with dose adjustment every 6 h and once daily when APTT is 1.5-2.3 times control value. Dose adjustment is guided by APTT according to ESC guidelines

Arm type	No intervention
No investigational medicinal product assigned in this arm	
Arm title	Catheter Directed Thrombolysis + Unfractionated Heparin

Arm description:

Patients randomized to CDT were transferred to the cardiac catheterization laboratory and treated within 48 hours of PE diagnosis. The procedure was performed by experienced interventional cardiologists under continuous hemodynamic and electrocardiographic monitoring. Two Uni*Fuse side-hole infusion catheter (AngioDynamics, USA) (one for each lung) were placed for all patients. Recombinant tissue plasminogen activator (r-tPA) was infused at a dose of 4 mg per catheter over 2 hours (2 mg/h, diluted in saline at an infusion rate of 35 mL/h).

Patients also recieved UFH similar to controls.

Arm type	Experimental
Investigational medicinal product name	Actilyse
Investigational medicinal product code	PR1
Other name	Alteplase
Pharmaceutical forms	Powder and solution for solution for injection
Routes of administration	Intravascular use

Dosage and administration details:

A continuous infusion of Actilyse 2 mg/h mixed in saline for an infusion rate of 35 ml/h in two catheters administered to the pulmonary circulation for a total time of 2 h. Total dosage of 8 mg.

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Pharmaceutical forms	Powder and solution for solution for injection

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A continuous infusion of Actilyse 2 mg/h mixed in saline for an infusion rate of 35 ml/h in two catheters administered to the pulmonary circulation for a total time of 2 h. Total dosage of 8 mg.

Notes:

[1] - The roles blinded appear inconsistent with a simple blinded trial.

Justification: The person analyzing the CT scans at baseline and 24 hour follow up was blinded to the treatment arm.

The investigators and patients were not blinded.

Number of subjects in period 1	Unfractionated Heparin alone	Catheter Directed Thrombolysis + Unfractionated Heparin
Started	30	30
Completed	29	29
Not completed	1	1
Adverse event, serious fatal	1	-
Screening failure. Right atrial mass. Excluded.	-	1

Baseline characteristics

Reporting groups

Reporting group title	Unfractionated Heparin alone
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Reporting group description:

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Patients also recieved UFH similar to controls.

Reporting group values	Unfractionated Heparin alone	Catheter Directed Thrombolysis + Unfractionated Heparin	Total
Number of subjects	30	30	60
Age categorical			
Age categorical			
Units: Subjects			
Adults (18-64 years)	17	9	26
From 65-84 years	13	21	34
Age continuous			
Age Continuous			
Units: years			
median	64	61	
standard deviation	± 16	± 15	-
Gender categorical			
Units: Subjects			
Female	11	12	23
Male	19	18	37

End points

End points reporting groups

Reporting group title	Unfractionated Heparin alone
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Reporting group description:

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Patients also received UFH similar to controls.

Primary: Right ventricular to left ventricular diameter ratio

End point title	Right ventricular to left ventricular diameter ratio
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End point description:

End point type	Primary
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End point timeframe:

Change from baseline to 24 hours follow up compared between the two arms.

End point values	Unfractionated Heparin alone	Catheter Directed Thrombolysis + Unfractionated Heparin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	29		
Units: ratio				
arithmetic mean (standard deviation)	-0.17 ($\pm$ 0.33)	0.02 ($\pm$ 0.25)		

Statistical analyses

Statistical analysis title	Paired t-test
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Comparison groups	Catheter Directed Thrombolysis + Unfractionated Heparin v Unfractionated Heparin alone
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Number of subjects included in analysis	58
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.01
Method	t-test, 2-sided

Secondary: CT obstruction score

End point title	CT obstruction score
End point description:	
End point type	Secondary
End point timeframe:	
Change in obstruction score from baseline to 24 hours follow up.	

End point values	Unfractionated Heparin alone	Catheter Directed Thrombolysis + Unfractionated Heparin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	29		
Units: score				
arithmetic mean (standard error)	-2.76 ($\pm$ 0.07)	-0.58 ($\pm$ 0.65)		

Statistical analyses

Statistical analysis title	Paired t-test
Comparison groups	Catheter Directed Thrombolysis + Unfractionated Heparin v Unfractionated Heparin alone
Number of subjects included in analysis	58
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.26
Method	t-test, 2-sided

Secondary: Mortality

End point title	Mortality
End point description:	
End point type	Secondary
End point timeframe:	
30 day mortality	

End point values	Unfractionated Heparin alone	Catheter Directed Thrombolysis + Unfractionated Heparin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30	29		
Units: 1	1	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Major bleedings

End point title	Major bleedings
End point description:	
End point type	Secondary
End point timeframe:	
24 hours	

End point values	Unfractionated Heparin alone	Catheter Directed Thrombolysis + Unfractionated Heparin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30	30		
Units: 1	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Minor bleeding

End point title	Minor bleeding
End point description:	
End point type	Secondary
End point timeframe:	
24 hours	

End point values	Unfractionated Heparin alone	Catheter Directed Thrombolysis + Unfractionated Heparin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30	30		
Units: 1	3	1		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

3 months

Assessment type	Non-systematic
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Dictionary used

Dictionary name	None
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Dictionary version	0
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Reporting groups

Reporting group title	UFH alone
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Reporting group description: -

Reporting group title	UFH + CDT
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Reporting group description: -

Serious adverse events	UFH alone	UFH + CDT	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 30 (3.33%)	1 / 30 (3.33%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events	1	0	
Cardiac disorders			
Death	Additional description: Cardiogenic shock due to pulmonary embolism leading to cardiac arrest. Attempts to resuscitate not successful.		
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiogenic shock	Additional description: During CDT the patient had hemodynamic decompensation. Resolved by Actilyse bolus 8mg.		
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	UFH alone	UFH + CDT	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 30 (3.33%)	1 / 30 (3.33%)	
Cardiac disorders			

Chest discomfort	Additional description: Chest discomfort following CDT. All exams normal. Resolved with no interventions.		
	subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)
	occurrences (all)	0	1
Skin and subcutaneous tissue disorders			
	Rash	Additional description: Rash following treatment with Eliquis. Changed to Xarelto. Resolved.	
	subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)
	occurrences (all)	1	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
17 March 2020	Due to the COVID pandemic, the study was temporarily suspended for inclusion fra March 17 2020 to August 20 2020.	20 August 2020

Notes:

Limitations and caveats

None reported