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Randomized trial of low-dose, ultrasound-assisted thrombolysis or heparin for pulmonary embolism

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Aims

Intermediate high-risk pulmonary embolism (PE) is associated with increased risk of haemodynamic deterioration and death, but balancing the risk of thrombolytics or catheter-based treatment and efficacy has been challenging. This trial compared the additional efficacy of catheter-based ultrasound low-dose thrombolysis (USAT) over intravenous low-dose thrombolysis or heparin alone.

Methods and results

In an investigator-initiated randomized clinical multicentre trial, we randomized 210 adult patients with acute, intermediate high-risk PE admitted to emergency departments in two regions of Denmark. Patients were allocated 1:1:1 to one of three treatment strata: low-dose thrombolysis (20 mg alteplase administered over 6 h) by USAT, by intravenous administration, or heparin alone. The efficacy of the interventions was assessed by comparing the refined Modified Miller Score, rmMS, (0–40 points, higher score indicating higher thrombus burden) from CT angiographies performed at baseline and 48–96 h post-randomization. Two comparisons were investigated: the reduction of rmMS with low-dose thrombolysis (USAT or intravenously) compared to heparin alone and the reduction of rmMS with low-dose thrombolysis administered by USAT compared to the intravenous route. The safety endpoint included the risk of bleeding.

We included 210 patients with acute PE, 49% were female, the mean age was 70 (IQR 62–76), and the mean body mass index was 30 (26–34). Compared to heparin alone, low-dose thrombolysis reduced the rmMS by 3.6 points (95% CI 2.2–5.0, $P < 0.001$), but the reduction in rmMS was not different in the ultrasound-assisted thrombolysis (USAT) vs. the intravenous route, mean difference −0.1 (95% CI: −1.9–1.7), $P = 0.88$. Bleeding complications were numerically more frequent with low-dose thrombolysis, albeit not statistically significant. No differences in other outcomes were observed.

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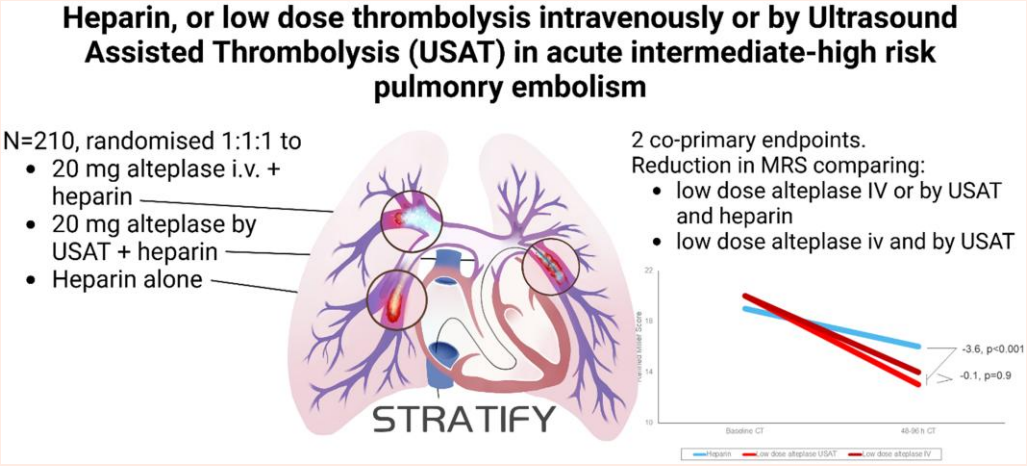
Conclusion Low-dose thrombolysis reduced thrombus burden more than heparin alone in patients with acute intermediate high-risk PE. However, USAT did not show greater thrombus reduction than intravenous thrombolysis. The rate of death and risk of bleeding complications were increased with low-dose thrombolysis.

Trial Registration clinicaltrials.gov, NCT04088292.

Graphical Abstract



Keywords Pulmonary embolism • Venous thromboembolism • Thrombolysis • Catheter-based thrombolysis

1. Introduction

Acute pulmonary embolism (PE) is a medical emergency, where thrombus, usually formed in and dislodged from the lower body, is carried by the bloodstream to the pulmonary arteries, causing a varying degree of obstruction. A subset of patients exhibits right ventricular pressure overload with evidence of myocardial injury and are categorized as intermediate high-risk, demonstrating a significant risk of clinical deterioration and death.[1] Conservative treatment with anticoagulation strategies does not seem to prevent deterioration in all, and thus, alternative and more aggressive treatment strategies have been investigated.

Previously, two randomized clinical trials assessing full-dose thrombolytics in patients with intermediate high-risk PE have failed to demonstrate a reduction in mortality,[1,2] since the number of fatal bleeding complications was comparable to the number of patients saved from haemodynamic deterioration.

As an alternative, reduced dose thrombolysis has been introduced, where a lower concentration of thrombolysis is administered over a similar or an extended period, thus reducing the concentration of the thrombolytic agent in the bloodstream at any given time point.[3] Since previous trials have shown similar efficacy as full-dose thrombolysis and, in some trials, reduced risk of bleeding, this approach could potentially represent a safer treatment strategy.[4,5] Furthermore, low-dose thrombolysis may outperform anticoagulation alone, but this has only been demonstrated in smaller populations.[6,7] The effect of low-dose thrombolysis may be further enhanced by ultrasound-assisted thrombolysis (USAT).[8] Though data from randomized trials are limited, USAT has been associated with faster normalization of right-to-left ventricular diameter ratio and reduction of tricuspid regurgitation gradient compared to anticoagulation alone.[9] Recently, a trial comparing four different combinations of duration of USAT and dose of alteplase showed similar efficacy.[10] Several case series have demonstrated that USAT is associated with good efficacy and an acceptable safety profile, with bleeding risk of approximately 10%,[8,11] and newer studies report bleeding risks as low as 1.6%.[12] Additionally, catheter-based thrombolysis includes both a mechanical thrombus manipulation from placing the catheters, an effect of the thrombolytics, and, with USAT, a potential additional augmentation of thrombolytics by ultrasound. Which components of the invasive treatment carry the main treatment effect that remains to be fully elucidated.

We report a head-to-head comparison of low-dose thrombolysis, administered via USAT catheters or intravenously, compared to anticoagulation with heparin in a prospective randomized trial in patients with acute intermediate high-risk PE.

2. Methods

2.1 Trial design

In the low dose thrombolysis, USAT or heparin for intermediate high-risk Pulmonary Embolism (STRATIFY) trial, an investigator initiated, open label, multicentre randomized trial, we randomly assigned 210 patients, who were diagnosed with acute PE and considered to be of intermediate-high risk[11] to one of three management strategies in a 1:1:1 ratio: therapeutic doses of heparin and low-dose thrombolysis administered by USAT, or as intravenous low-dose thrombolysis, or heparin alone. The option to administer full-dose thrombolysis in the event of clinical deterioration was available in all three treatment strata. Randomization was performed from March 2019 to June 2024 at four sites in the Capital Region of Denmark and Region of Zealand, using a REDCap®

webpage-based system with permuted blocks of sizes 6 and 9 patients.

Patients were included in the STRATIFY trial after obtaining written informed consent. The protocol was approved by the Regional Ethics Committee and the Danish Medicines Agency before initiation of the trial, and the investigation conformed to the principles outlined in the Declaration of Helsinki. The trial was designed and overseen by a steering committee (see Supplementary material online, Appendix). Data were collected by the authors and analysed by J.K. and E.S.-H. The first author vouches for the accuracy and completeness of the data and the fidelity of the trial to the protocol. Additional details of the trial design have been published previously.[13]

2.2 Patients

Adult patients (>18 years of age) who had been diagnosed with an acute PE on a computer tomography (CT) angiography less than 24 h prior to screening were eligible for inclusion if they were classified as intermediate high-risk according to the European Society of Cardiology criteria,[11] had thrombus visible in the main, lobar or segmental pulmonary arteries on CT angiography, had 14 days or less of symptom duration, and gave informed consent to participate in the trial. Key exclusion criteria were thrombolysis for PE within 14 days prior to screening and any contraindication to thrombolytic therapy. A complete list of inclusion and exclusion criteria, as well as a definition of right ventricular dysfunction and shock, is provided in the Supplementary material online, Appendix.

2.3 Treatment protocol

All patients received therapeutic doses of heparin, either as low molecular weight heparin (LMWH) or unfractionated heparin (UFH) according to European and national guidelines.[11] Patients in the three strata were then treated as follows:

In the USAT stratum, the patient was transferred to a tertiary heart centre (Rigshospitalet, Copenhagen), where USAT catheters were placed via ultrasound-guided access to the femoral vein and advanced under fluoroscopic guidance to the lower pulmonary lobar artery at the affected site, most frequently bilaterally. After placing the USAT catheters, the ultrasound-based mechanical stimulation was initiated along with a 20 mg alteplase infusion via the catheters over 6 h. The catheters were removed immediately after completion of the alteplase infusion, and after an additional 2 h, the sheaths were removed. The patient could be ambulated after an additional 1-h bedrest. In the low-dose thrombolysis stratum, 20 mg of alteplase was administered intravenously over 6 h in addition to heparin. The patient remained at the site where the patient was randomized. Finally, in the heparin-only stratum, patients were monitored for clinical deterioration. A full dose of alteplase (bolus and infusion over 2 h) could be administered at the discretion of the treating physician if signs of clinical deterioration developed in all three strata.

2.4 Trial intervention

The trial interventions were 20 mg of alteplase delivered intravenously or using USAT by EKOS™ endovascular system (Boston Scientific, Marlborough, Massachusetts, USA) over 6 h in addition to standard heparin therapy. Dose of UFH was guided by targeting an Activated Clotting Time of 160–180 s. If LMWH was chosen, the recommended therapeutic dose was administered. Heparin treatment was continued until a repeat CT angiography was performed between 48 and 96 h after randomization. The patient could then be put on oral anticoagulation therapy; the trial protocol suggested Direct Oral AntiCoagulant (DOAC) for no less than 6 months. Patients were reevaluated after 3 months with clinical assessment, a 6-min walk test, questionnaires, and Doppler echocardiography.

2.5 Outcome measures

The trial had two primary analyses, both testing change in thrombus burden assessed by a refined modified Miller score (rmMS), adapted from the original Miller score,[14] which quantified the extent of thrombus occlusion of the vascular tree on a pulmonary angiogram. This refined, modified score is used for the quantification of clot burden from CT angiographies.[15] The rmMS quantifies clot burden in proximal and segmental pulmonary arteries, and the scale ranges from 0 to 20 per lung, with a maximum of 40 in total, with a higher score corresponding to higher thrombus burden.[16] rmMS at baseline and at 48–96 h post-randomization was assessed in a core lab by an experienced radiologist (S.J.), blinded to treatment allocation. The analyses were as follows:

- Efficacy of 20 mg of alteplase administered intravenously or by USAT compared to UFH/LMWH alone, defined by reduction in the refined Miller score (rmMS)[16] at 48–96 h after randomization (n = 140 vs. n = 70) and
- Efficacy of 20 mg alteplase delivered by USAT catheters compared to intravenous administration (N = 70 vs. N = 70).

Additionally, the following secondary endpoints were prespecified:

Clinical endpoints:

- Duration of index admission, including hospital-based rehabilitation.
- Dyspnoea index (Visual analogue scale) after 48–96 h and after 3 months.
- Oxygen supplement, blood pressure, respiratory rate, and heart rate at time of follow-up CT pulmonary angiography.
- Incidence of tricuspid regurgitant (TR) gradient by continuous Doppler echocardiography >40 mmHg at 3 months follow-up.
- 6 min walking distance at 3 months follow-up.
- Health-related Quality of Life at 3 months follow-up by the Pulmonary Embolism Quality of Life (PEmb-QoL)[17] and the EQ-5D-5L.[18]

Safety endpoints:

- Bleeding complications (major and minor bleeding complications according to the Thrombolysis in Myocardial Infarction (TIMI) classification[19]). As a post hoc sensitivity analysis, bleeding complications were also assessed using the International Society on Thrombosis and Haemostasis classification.[20]
- Mortality in the three groups and hazard ratio in a multivariable analysis using the low-dose thrombolysis by intravenous route and UFH/LMWH as a reference.

Difference in right-to-left ventricle diameter ratio was also reported as a post hoc analysis.

2.6 Statistical analysis

Sample size estimation was based on previous trials, and we expected a mean rmMS of 18 ± 7 at baseline.[14] The comparator group treated by LMWH/UFH would only have a reduction in rmMS of 2 points (11%) after 48–96 h,[14] whereas the mean rmMS reduction in the thrombolysis groups (intravenously or by USAT) was expected to be 6 points (33%).[14]

With those assumptions and a power of 0.90 and alpha 0.01 for the first co-primary analyses of UFH/LMWH vs. low-dose thrombolysis, 210 patients were required (140 vs. 70 patients).

For the second co-primary, on the effect of low-dose thrombolysis administered intravenously or by USAT with a power of 0.9 and alpha 0.04, 140 patients (n = 70 vs. n = 70) were required, assuming a 22% or greater reduction in rmMS in the USAT group compared to the IV group.

Baseline characteristics of the patients were stratified into the three treatment allocation strata.

Analyses of primary and secondary endpoints were performed according to the statistical analysis plan.[13] For the primary analyses, a variance component model (proc mixed) was applied, adjusting for rmMS at baseline and for site. Patients who died before the follow-up CT angiography were assigned the highest rmMS score in the stratum. The site was defined as the site of randomization.

The remaining secondary endpoints were presented as mean difference and 95% CI or proportions and relative risk with 95% confidence intervals as appropriate in the same groups as defined for the primary analyses. Intraclass correlation coefficient (ICC) for the rmMS (primary endpoint) was calculated for 20 randomly selected angiographies and presented intra- and inter-rater variability.

Clinical and safety outcomes were assessed using the chi-squared test for dichotomous variables and the ANOVA test or *t*-test for continuous variables. The following are predefined design variables that were examined in subgroup analyses: sex, age above median, known renal failure (GFR <30 mL/min or current renal replacement therapy), known chronic obstructive pulmonary disease, saddle embolus at CT angiography, syncope before randomization, and cardiopulmonary resuscitation performed before randomization.

All statistical analyses were performed using the SAS Enterprise Guide, ver. 8.3, SAS Institute®, Cary, NC, USA.

3. Results

3.1 Patients

A total of 210 patients were enrolled in the trial from June 2019 to June 2024; the screening and selection of patients are shown in *Figure 1*. All patients provided informed consent, none withdrew the consent during the trial, and all patients underwent the allocated treatment regimen. Two patients, both in the low-dose USAT stratum, died from cardiac arrest before the 48–96 h follow-up pulmonary CT angiography, due to gastrointestinal and intracranial haemorrhage, respectively. An additional five patients did not have the follow-up CT angiography at 48–96 h (clinical deterioration, discharge per patient's request, logistical reasons, no intravenous access possible, and presumed allergy to intravenous contrast). Furthermore, 24 CT angiographies (6 at baseline and 18 at follow-up) were technically inadequate for assessment of rmMS. No patients were lost to follow-up; 19 patients were unable to attend the physical follow-up visit, partly due to COVID-19 restrictions and patient discretion. The baseline characteristics of the patients were well balanced in the three treatment allocation groups as well as in the groups used in the two co-primary endpoints.

3.2 Intervention

The three intervention strata consisted of 69 patients randomized to heparin alone, 70 patients treated with low-dose thrombolysis intravenously, and 71 patients with low-dose thrombolysis by USAT. Demography and clinical characteristics are provided in *Table 1*. The randomization was performed 14 h (IQR 7–23) from the onset of symptoms, with a median delay from randomization to initiation of the allocated treatment of 66 min (IQR 30–123) in the low-dose intravenous stratum and 261 min (IQR 30–123) in the low-dose USAT stratum. All patients in the low-dose thrombolysis strata received 20 mg alteplase, and in one patient, infusion via USAT catheters was interrupted prematurely due to bleeding complications. All patients in the low-dose thrombolysis by USAT stratum received two catheters, one in each lower pulmonary lobe artery. The follow-up CT angiography was performed a mean of 50 (IQR 49–63), 57 (49–65), and 60 (49–72) h, $P = 0.06$, for heparin alone, low thrombolysis iv and by USAT, respectively. The ICC for the rmMS was 0.93 (95% confidence interval 0.85–0.97) for intra-rater variability and 0.98 (0.94–1.00) for inter-rater variability.

3.3 Primary analyses

The reduction in rmMS in the 141 patients treated by low-dose thrombolysis was 6.2 (Standard deviation, SD 5.2) points vs. 2.6 (2.2) points in the 69 patients treated by heparin alone (mean difference −3.6, 95% CI −5.0 to −2.2, $P < 0.001$). The reduction in rmMS among the 71 patients treated by low-dose thrombolysis by USAT was 6.3 (5.3) points vs. 6.1 (5.0) points in the 70 patients treated by low-dose thrombolysis intravenously (mean difference −0.1, (95% CI: −1.9–1.7), $P = 0.88$), *Figure 2* and *Table 2*.

3.4 Clinical endpoint

Oxygen saturation was higher at time of follow-up CT angiography in the low-dose thrombolysis stratum, 97% (2%) compared to 96% (2%) in the heparin stratum (mean difference 0.8 (95% CI: 0.2–1.4)), and the dyspnoea index was 2 (2) vs. 3 (2) point, respectively (mean difference −1 (95% CI: −1.7 to −0.6). Other vital signs and days of hospitalization are presented in *Table 2*. The predefined subgroup analysis showed no differences between groups for the two primary analyses (*Figure 3*). No difference in RV/LV diameter ratio was found for either of the two comparisons (*Table 2*).

3.5 Safety endpoints

Full-dose thrombolysis was administered in five patients: two in the heparin only group, two in the low-dose intravenous group, and one in the USAT group, $P = 0.8$.

For the safety and 3-month outcomes, the risk of bleeding as classified by the TIMI definition was numerically higher in the low-dose thrombolysis groups compared to the heparin group, but the differences did not reach statistical significance ($n = 16$, 11% vs. = 3, 4%, $P = 0.10$, *Table 2*). Similar data were seen for the ISTH classification of bleeding events (*Table 2*). At 3-month follow-up, 6 (4%) patients in the low-dose thrombolysis groups had died (4 in the IV and 2 in the USAT groups) compared to 0 in the heparin group, $P = 0.08$, *Figure 1* and Supplementary material online, *Figure S2*.

No major or minor bleeding complications, but only three minimal bleeding events, according to the TIMI classification, were seen in the heparin-only group, even though two of the patients received full-dose thrombolysis for haemodynamic deterioration. Five patients died during index hospitalization, and one additional patient died before the 3 months follow-up, P = NS, See *Figure 1*. Causes of death during the first 3 days of hospitalization were haemodynamic deterioration in one case, gastrointestinal bleeding in one case, and intracranial haemorrhage in one case. Furthermore, two patients died while in the hospital, one from sudden cardiac arrest, and one from intracranial haemorrhage.

4. Discussion

In this randomized trial comparing low-dose alteplase administered by intravenous route or by USAT, we demonstrated a statistically significant greater reduction in thrombus burden after 48–96 h among patients treated with low-dose thrombolysis compared to patients treated only with heparin. We did not find an additional efficacy of low-dose thrombolysis administered by USAT compared to intravenously route of administration. The secondary outcomes showed no clinical and statistically significant differences between strata, but a trend towards increased risk of death in the thrombolysis strata.

PE management relies on early risk stratification.[11] All treatments, ranging from heparin to thrombolysis and mechanical clot

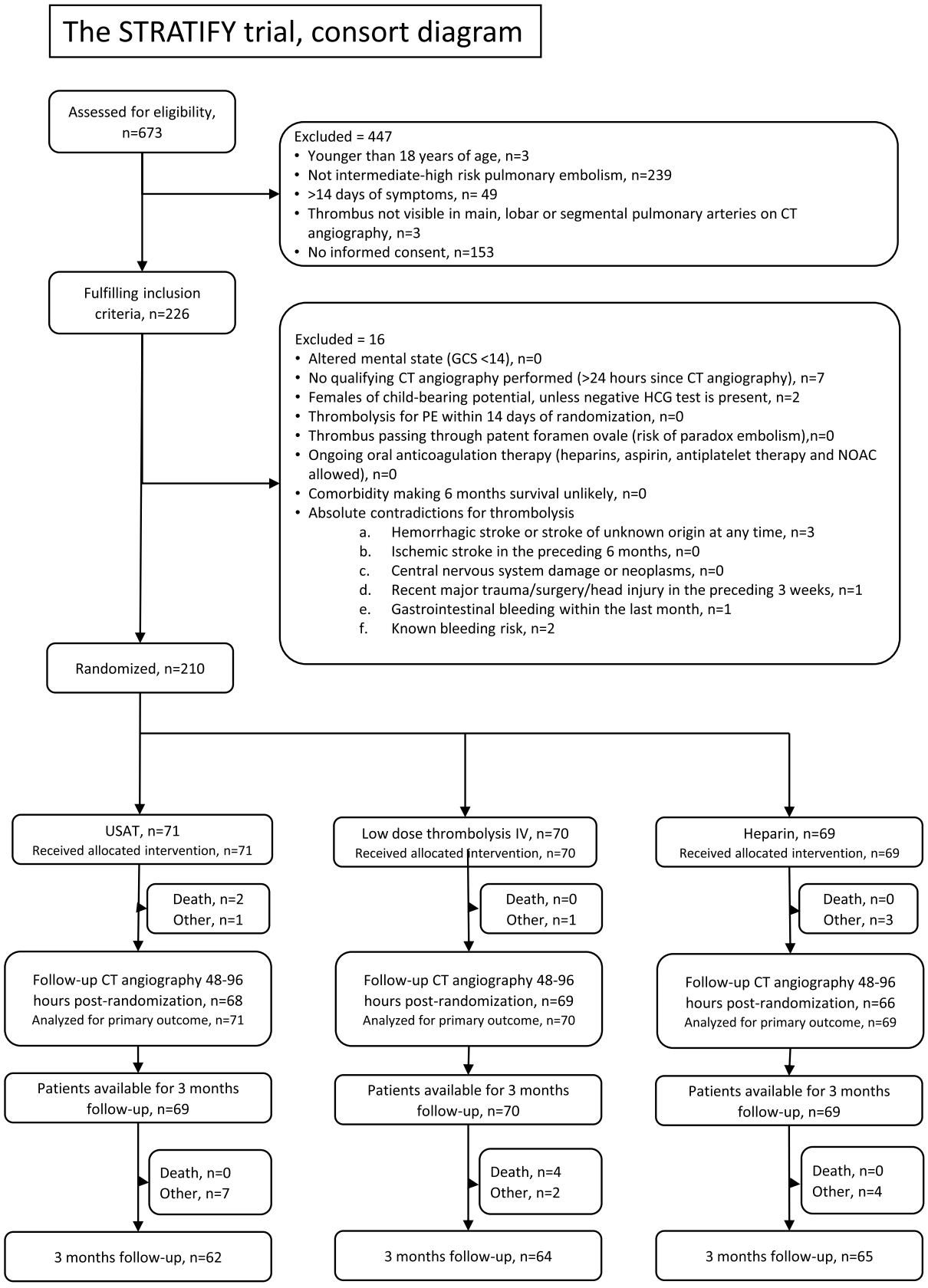


Figure 1 Consort diagram describing the trial population, treatment allocation, and follow-up data.

Table 1 Demographic and clinical variables

	USAT (*n* = 71)	IV (*n* = 70)	Heparin (*n* = 69)	*P* value
Female sex, no. (%)	31 (44)	37 (53)	34 (49)	0.55
Age, years (SD)	65 (15)	69 (12)	68 (12)	0.20
Body mass index, kg/m^2 (SD)	32 (7)	31 (7)	30 (6)	0.28
Medical history/risk factors				
Smoking, no. (%)	31 (44)	32 (46)	28 (41)	0.86
Alcohol abuse, no. (%)	1 (1)	3 (4)	3 (4)	0.54
Heart failure, no. (%)	1 (1)	0 (0)	1 (1)	0.60
Ischaemic heart disease, no. (%)	2 (3)	3 (4)	4 (6)	0.68
Arrhythmia, no. (%)	5 (6)	2 (3)	0 (0)	0.14
Hypertension, no. (%)	28 (39)	32 (46)	28 (41)	0.72
Stroke/transitory cerebral ischaemia, no. (%)	4 (6)	2 (3)	1 (1)	0.37
Diabetes, no. (%)	5 (7)	8 (11)	7 (10)	0.66
Asthma, no. (%)	9 (13)	6 (9)	4 (6)	0.36
Chronic obstructive pulmonary disease, no. (%)	2 (3)	4 (6)	3 (4)	0.70
Chronic kidney disease, no. (%)	1 (1)	4 (6)	5 (7)	0.24
Cancer, no. (%)	10 (14)	13 (19)	10 (15)	0.72
Coagulopathy, no. (%)	3 (4)	3 (4)	3 (4)	0.78
Previous deep venous thrombus, no. (%)	5 (7)	8 (11)	9 (13)	0.49
Previous pulmonary embolism, no. (%)	9 (13)	7 (10)	5 (7)	0.56
Clinical presentation				
Time from first symptom until admission, median h (IQR)	48 (4–138)	48 (4–105)	29 (4–80)	0.76
Heart rate, beats/min (SD)	105 (19)	100 (17)	99 (19)	0.15
Systolic blood pressure, mmHg (SD)	136 (21)	134 (22)	136 (21)	0.80
Arterial oxygen saturation, % (SD)	94 (5)	95 (3)	95 (4)	0.57
Oxygen supplement, median L/min (IQR)	2 (0–5)	1.5 (0–5)	0 (0–3)	0.29
Respiration rate, no. (SD)	21 (4)	20 (4)	20 (4)	0.63
Temperature, °C (SD)	36.6 (0.6)	36.6 (0.6)	36.6 (0.5)	0.77
pH (SD)	7.43 (0.05)	7.43 (0.05)	7.44 (0.04)	0.23
no. = 176				
Lactate, mmol/L (SD)	2.1 (1.5)	2.1 (1.7)	1.9 (0.9)	0.78
no. = 176				
D-dimér, mg/L (SD)	10.5 (8.3)	12.5 (9.2)	12.3 (10.8)	0.40
no. = 205				
Troponin I, g/L (SD)	718 (980)	607 (658)	746 (1130)	0.79
no. = 116				
Troponin T, g/L (SD)	129 (121)	165 (114)	154 (174)	0.48
no. = 111				
ECG at admission				
Arrhythmia, no. (%)	2 (3)	4 (6)	4 (6)	0.59
Atrial fibrillation, no. (%)	2 (3)	3 (4)	2 (3)	
Pace rhythm, no. (%)	0 (0)	0 (0)	1 (1)	
Other, no. (%)	0 (0)	1 (1)	1 (1)	
S1Q3T3, no. (%)	26 (37)	29 (41)	20 (29)	0.30
Negative T-wave V1–V3, no. (%)	32 (45)	28 (40)	29 (42)	0.83
Right bundle branch block (incl. incomplete), no. (%)	13 (18)	13 (19)	11 (16)	0.90
Echocardiography				
Left ventricular ejection fraction, % (SD)	58 (6)	59 (3)	58 (5)	0.35
Tricuspid annular systolic excursion, cm (SD)	15 (3)	17 (4)	17 (4)	0.11
Tricuspid regurgitation gradient, mmHg (SD)	44 (13)	42 (9)	44 (13)	0.59
CT angiography				
Saddle embolus, no. (%)	15 (21)	21 (30)	22 (32)	0.31

Continued

Table 1 *Continued*

	USAT (*n* = 71)	IV (*n* = 70)	Heparin (*n* = 69)	*P* value
Right to left ventricle diameter ratio, mean (SD) No. = 208	1.4 (0.3)	1.5 (0.4)	1.4 (0.4)	0.15

Differences are tested by Chi-square or ANOVA models. Troponins and D-dimer were given at the time of randomization.
CT, computerized tomography; ECG, electrocardiogram; IV, intravenous; SD, standard deviation; USAT, ultrasound-assisted thrombolysis.

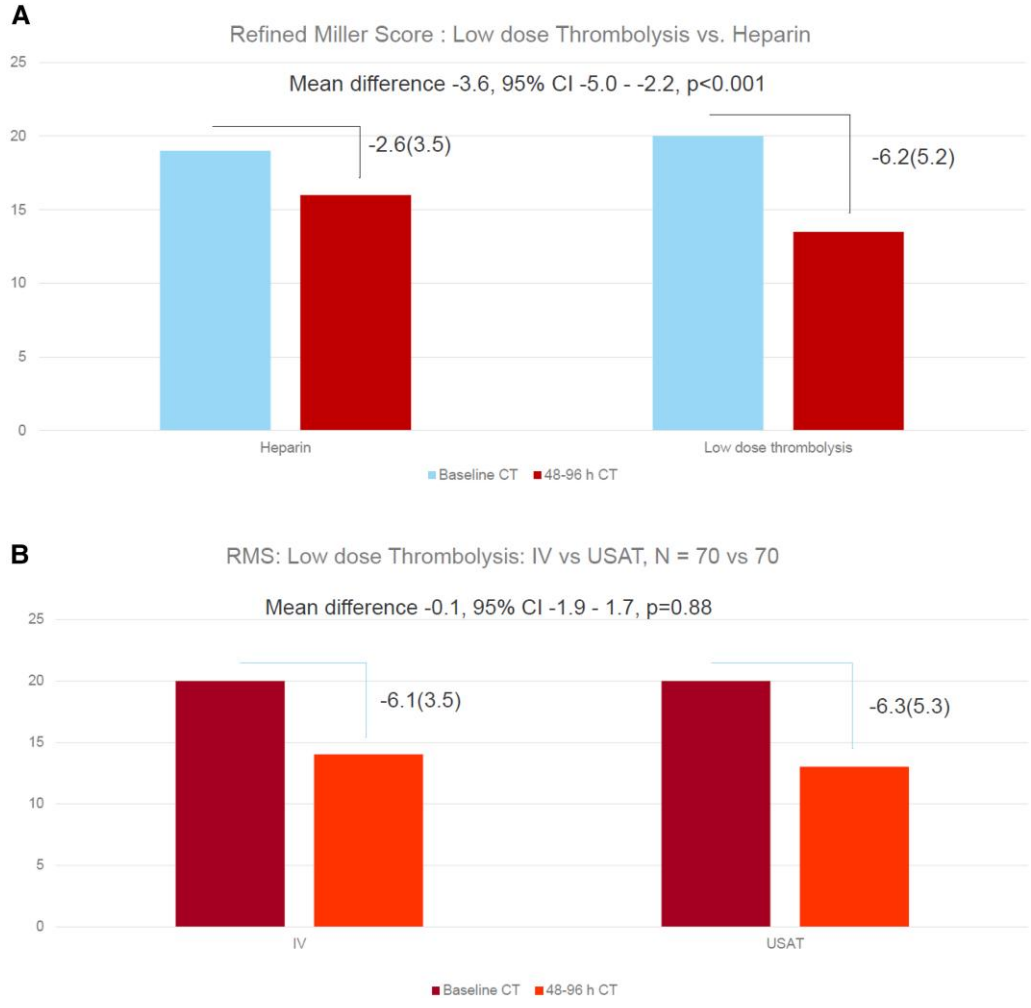


Figure 2 Refined Miller score at baseline and at 48–96 h follow-up CT pulmonary angiography. Comparison of the low-dose thrombolysis by ultrasound-assisted thrombolysis or intravenously compared to heparin alone (*A*) and low-dose thrombolysis by ultrasound-assisted thrombolysis compared to intravenous administration (*B*). *N* = 210. Differences were tested using a variance component model (proc mixed).

removal or thrombectomy, are associated with a risk of bleeding complications that generally increase with the efficacy of the intervention.[11] While high-risk PE mandates aggressive and urgent reperfusion therapy, the use of thrombolytics in intermediate high-risk PE has been demonstrated to reduce the risk of haemodynamic deterioration, but at the cost of an increased risk of severe adverse events and bleeding, which offset the advantages of reperfusion.[1,2] As the risk of bleeding may, at least partly, be dose dependent, the net efficacy of lower doses of thrombolytics has been investigated, finding similar efficacy as for high dose thrombolysis[5] and with a reduced risk of persistent pulmonary hypertension compared to anticoagulation alone.[7] The present study adds that reduced dose thrombolysis with 20 mg of alteplase is effective in reducing clot burden, but remains associated with an increased, albeit not statistically significant, increase in risk of bleeding. Therefore, choosing low-dose thrombolysis for intermediate

Table 2 Endpoints

	USAT	IV	Heparin	Mean diff. (95% CI) USAT/IV vs. heparin	Mean diff. (95% CI) USAT vs. IV
rmMS, baseline, mean (SD) no. = 204	20 (4)	20 (4)	19 (4)	0.99 (−0.14–2.13)	−0.29 (−1.58–1.01)
rmMS, 48–96 h follow-up, mean (SD) no. = 192	13 (5)	14 (6)	16 (4)	−2.27 (−3.70 to −0.85)	−0.41 (−2.17–1.34)
Primary endpoints					
Difference in RMS, baseline to 48–96 h follow-up, mean (SD) no. = 189	−6.3 (5.3)	−6.1 (5.0)	−2.6 (3.5)	−3.6 (−5.0 to −2.2) $P < 0.001$	−0.1 (−1.9–1.7) $P = 0.88$
Secondary endpoints					
Bleeding (TIMI classification), no. (%)	10 (14)	10 (14)	3 (4)	3.2 (0.93–11.2)	0.9 (0.4–2.5)
Major	2	2	0		
Minor	3	2	0		
Minimal	5	6	3		
Bleeding (ISTH classification), no. (%)	10 (14)	10 (14)	3 (4)	3.2 (0.93–11.2)	0.9 (0.4–2.5)
Major	6	6	1		
Minor	4	4	2		
Difference in RV/LV diameter ratio, baseline to 48–96 h follow-up, mean (SD) no. = 189	−0.3 (0.3)	−0.4 (0.4)	−0.3 (0.3)	−0.06 (−0.2–0.03)	0.03 (−0.08–0.1)
Days of hospitalization, median (IQR)	5 (4–6)	5 (4–7)	5 (4–7)	−0.1 (−1–1.0)	−0.7 (−2–1)
Dyspnoea index after 48–96 h, mean (SD) no. = 133	1 (2)	2 (1)	3 (2)	−1.2 (−1.7 to −0.6)	−0.5 (−1.1–0.1)
Dyspnoea index after 3 months, mean (SD) no. = 181	1 (2)	1 (2)	2 (5)	−0.9 (−1.9–0.2)	0.3 (−0.3–1.0)
Oxygen need, L/min, mean (SD)	0.3 (1.3)	0.3 (0.7)	2.3 (12.6)	−1.9 (−4.2–0.2)	0.1 (−0.3–0.5)
Heart rate, beats/min, mean (SD)	80 (12)	76 (12)	77 (13)	1.7 (−2.1–5.4)	3.5 (−0.7–7.8)
Systolic blood pressure, mmHg, mean (SD)	137 (16)	139 (16)	136 (20)	0.76 (−4.4–5.9)	−2.16 (−7.6–3.2)
O_2 Saturation, %, mean (SD)	98(2)	97 (2)	96 (2)	0.81 (0.24–1.38)	0.93 (0.32–1.53)
Respiration rate, mean (SD)	18 (3)	17 (3)	17 (2)	0.3 (−0.6–1.1)	0.02 (−1.0–1.0)
3-month follow-up					
Dead, *n* (%), odds ratio (95% CI)	2 (3)	4 (6)	0 (0)	NA	0.7 (0.4–1.3)
Tricuspid regurgitation gradient ≥40 mmHg, *n* (%), relative risk (95% CI) No. = 181	2 (1)	1 (1)	3 (4)	0.7 (0.3–1.5)	1.5 (0.3–7.5)
6-Min walk distance, m, mean (SD) No. = 166	476 (117)	458 (124)	472 (136)	−4 (−45–36)	19 (−27–64)
PEmb-Qol, 0–100, mean (SD) No. = 161	36 (13)	37 (12)	37 (11)	−0.7 (−4.6–3.1)	−1.5 (−6.4–3.4)
5Q-5D-5L, 0–5, mean (SD) No. = 161	1.7 (0.8)	1.5 (0.7)	1.5 (0.6)	0.1 (−0.1–0.3)	0.1 (−0.2–0.4)
Self-rated health, 0–100, mean (SD) No. = 161	75 (23)	77 (18)	76 (16)	−0.04 (−6.1–5.9)	−1.9 (−9.6–5.8)

The dyspnoea index is a scale from 0 to 10 measuring the severity of self-reported dyspnoea, with 10 representing the most extreme difficulty in breathing. *The PEmb-Qol scale* covers six dimensions, where scores are calculated by taking the mean of all items and finally transformed into a scale from 0 to 100. Higher scores indicate a worse quality of life. *The 5Q-5D-5L scale* from 1 to 5 where 5 indicates the worst outcome, and a visual analogue scale (EQ VAS) ranging from 0 to 100 where 100 indicates the best outcome. Differences in the primary and secondary outcomes were tested using a variance component model (proc mixed).
ISTH, International Society on Thrombosis and Haemostasis; USAT, ultrasound-assisted thrombolysis; RMS, Refined Miller Score; SD, standard deviation; TIMI, thrombolysis in myocardial infarction.

high-risk PE patients remains challenging and should be individualized, with thorough assessment of bleeding risk.[21]

Catheter-based interventions, predominantly catheter-based thrombolysis, have been introduced as a method to increase the efficacy of thrombolytics by delivering the drug in close proximity to the thrombus. The efficacy of this approach has been demonstrated in several case series, and the risk of complications, including bleeding, remains at an acceptable rate of around 5–10%.[22] A few small randomized trials have compared the efficacy of USAT with anticoagulation alone, finding a significant reduction in right to left ventricular diameter and a borderline reduction of tricuspid regurgitation gradient both after 48–72 h

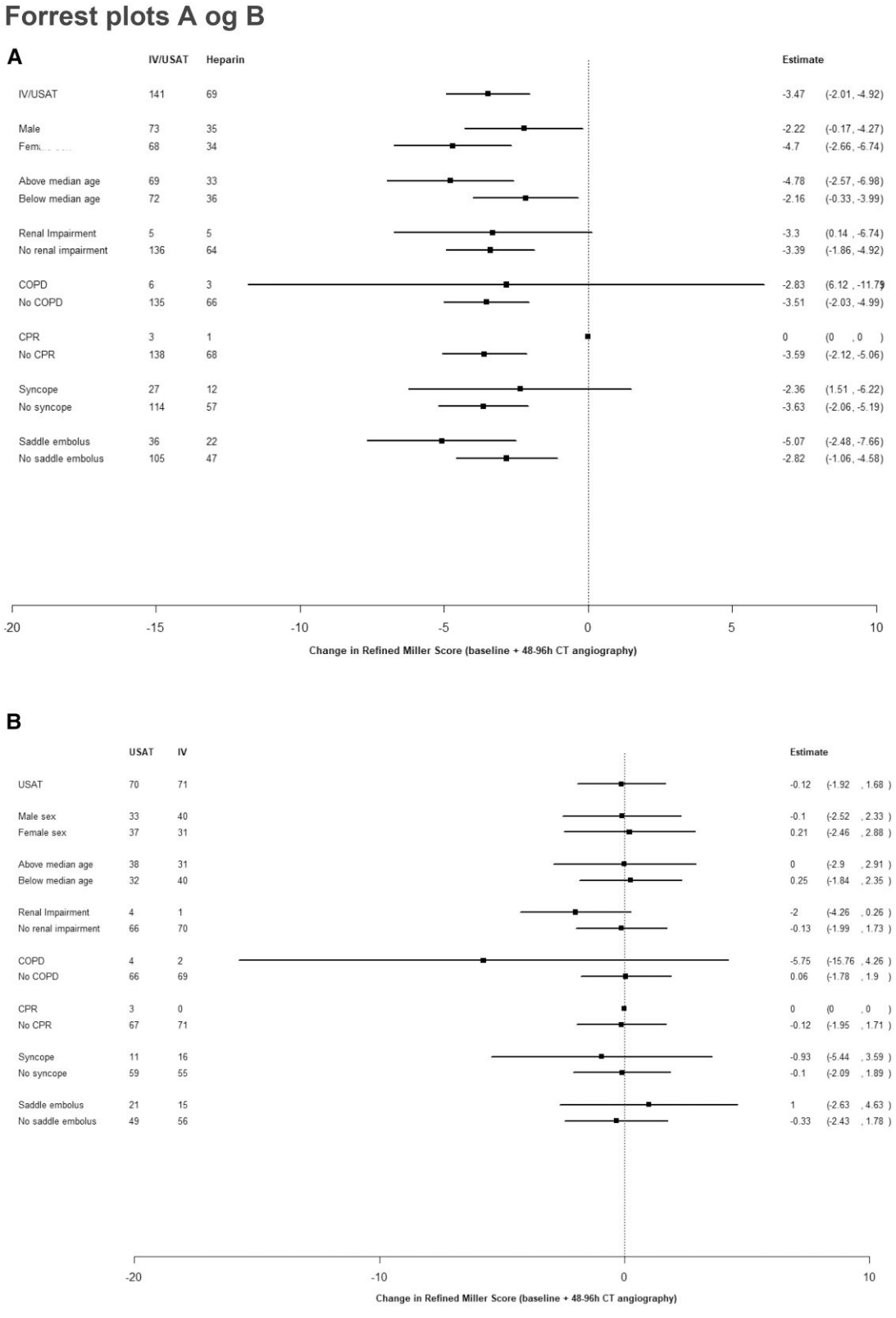


Figure 3 Forrest plot of predefined subgroups in the two co-primary endpoints: low-dose thrombolysis by IV or ultrasound-assisted thrombolysis vs. heparin alone (*A*) and low-dose thrombolysis by IV vs. USAT (*B*). *N* = 210. Differences were tested in a variance component model (proc mixed).

post-intervention[9,23] and at 3 months.[23] Catheter-based thrombolysis has been compared to USAT in one previous randomized trial (the SUNSET trial), finding similar efficacy in thrombus burden reduction but improved reduction in right ventricular to left ventricular diameter after 48 h,[24] suggesting the efficacy of the ultrasound of the USAT catheter may have minimal efficacy. The results of the present STRATIFY add that iv rTPA is equally efficacious as catheter-based thrombolysis. Furthermore, the OPTALYSE PE trial compared four different regimens of alteplase dose and duration in USAT for intermediate high-risk patients and found similar results across these regimens.[10] We chose a USAT intervention comparable to the highest dose and longest duration in the OPTALYSE trial to ensure sufficient time and dose and subsequently applied a similar 20 mg dose of alteplase in the intravenously low-dose thrombolysis group. The reduction in MRS was 2 points smaller than seen in a recent case series of catheter-based thrombolysis using another device.[25] A large-scale randomized trial of USAT compared to heparin alone, with PE-related mortality as the primary endpoint, is currently enrolling patients (NCT04790370).

Recently, catheter-based embolectomy has also been introduced. While no randomized clinical trials on this approach have yet been published, comparisons of published case series suggest that efficacy is similar to that of catheter-based thrombolysis and USAT.[26] Relevant upcoming randomized trials are the PEERLESS trials, of which the first has been published[27] and the other one has recently been initiated (NCT06055920).

Thrombus burden is a surrogate endpoint and should be interpreted with caution in relation to clinical outcomes, in particular, the risk of death, albeit used in previous trials in the field.[24,25] The STRATIFY trial was not powered to detect improvements in mortality or other clinical outcomes, and the rmMS was chosen as the best alternative to the hard clinical endpoint for the ability to have endpoint assessment blinded, and its previous use in literature, in particular in recent trials in the same population.[10,24] Larger trials are needed to evaluate the long-term effects of low-dose ultrasound or catheter-based treatments compared to other treatment options.

Given the invasive nature of USAT, the treatment allocation was open-label; however, the assessment of thrombus burden at baseline (re-reading of the qualifying CT angiography) and 48–96 h CT angiography was performed by an experienced radiologist who was blinded to the allocated treatment stratum. Twenty-four CT angiographies were deemed to be of insufficient quality for assessment of rmMS in the Core Lab, which is similar to previous trials[10] and lower than other trials.[24,25] We had no reason to believe this would result in systematic error and thus invalidate the results of the trial. Transfer for the USAT treatment introduced a delay from randomization to initiation of treatment, but the mean delay was less than 7 h, and the protocol defined the acceptable delay as 12 h. Whether the efficacy of USAT would be improved by a shorter delay in catheter placement cannot be assessed in the STRATIFY trial.[2]

Selection bias in the patient recruitment for the trial cannot be excluded, but the baseline characteristics seem to be representative of Danish PE patients.[28] However, previous reports on the mortality in patients presenting with PE and clinical symptoms and signs of right ventricular strain[29] suggest that the overall mortality of the present cohort was relatively low, albeit comparable to previous trials in intermediate high-risk PE patients. The risk of fatal bleeding in the first few days following randomization was similar to previous trials[10,24] and occurred only with thrombolysis. Doses of rTPA could be reduced in further trials to identify the optimal balance between efficacy and bleeding risk.[10]

5. Conclusion

Use of low-dose thrombolytics resulted in a significantly greater reduction in thrombus burden 48–96 h post-randomization compared to heparin alone. There was no additional benefit from administering low-dose thrombolysis via USAT catheters compared to intravenous administration. The rate of death, including risk of bleeding complications, was increased with low-dose thrombolysis, which should be considered when considering the implementation of this treatment.

Supplementary material

Supplementary material is available at *Cardiovascular Research* online.

Authors' contributions

J.K. and E.S.-H. drafted the work. The remaining authors reviewed the manuscript critically for important intellectual content and approved the final version of the manuscript. J.K., L.B., and J.C. designed the work. J.K., E.S.-H., M.G.L., K.E., S.F., M.E., O.P.K., and E.S. contributed significantly to the acquisition of data. J.K. and E.S.-H. analysed the data. All authors contributed to the interpretation of the data.

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Data availability

The data can be accessed by contacting the corresponding author.

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