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Design and rationale of PRAGUE-26: a multicentre, randomised trial of catheter-directed thrombolysis for intermediate-high risk acute pulmonary embolism

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ABSTRACT

The PRAGUE-26 trial (ClinicalTrials.gov: NCT05493163) is a non-industry-sponsored, prospective, multicentre, randomised, active-controlled, unblinded, parallel-group study evaluating clinical outcomes in patients with intermediate-high risk acute pulmonary embolism (PE), comparing catheter-directed thrombolysis (CDT) to standard anticoagulation therapy. Patients with intermediate-high risk acute PE meeting inclusion criteria and not having any exclusion criteria are randomised at a 1:1 ratio to receive either CDT or standard anticoagulation therapy alone. The primary outcome is a clinical composite endpoint of all-cause mortality, PE recurrence, or cardiorespiratory decompensation or collapse, assessed within 7 days of randomisation. The secondary outcomes include bleeding complications, first-line therapy failure, cost-effectiveness analysis, and a broad spectrum of functional and patient-reported outcomes over a 2-year follow-up period. The trial aims to enrol 558 patients. As of 24 November 2024, 258 patients have been randomised. PRAGUE-26 seeks to assess the clinical benefits of simple CDT compared to anticoagulation alone in intermediate-high risk acute PE and aims to contribute to the understanding of this interventional approach.

Over the past decade, percutaneous treatment options for intermediate-high and high-risk acute pulmonary embolism (PE) have rapidly evolved. Since 2014, there has been growing evidence for the efficacy and safety of catheter-based treatments for acute PE, supported by data coming from registries, prospective cohorts, and small randomised controlled trials (RCTs)[1]. However, no large-scale randomised studies comparing interventional to standard treatment have yet been conducted[1,2].

Currently, two main interventional strategies are under extensive investigation: (a) catheter-directed thrombolysis (CDT), and (b) mechanical thrombectomy. Each approach offers distinct advantages and disadvantages, potentially challenging the current standard of care, particularly in intermediate-high risk PE[3]. In these patients, CDT has shown some promising results regarding safety and efficacy, regardless of whether simple catheter-directed local thrombolysis or ultrasound-facilitated, catheter-directed thrombolysis (USCDT; EKOS [Boston Scientific]) is used[4-7]. To date, no evidence suggests that one method is more effective than the other[8,9].

The industry-sponsored, randomised HI-PEITHO trial, with an adaptable design allowing for up to 544 participants, is currently underway. This trial is comparing USCDT to anticoagulation alone (the current standard of care) in a preselected group of patients with intermediate-high risk PE and is expected to provide much-needed robust clinical data[10].

KEYWORDS: acute pulmonary embolism; anticoagulation; catheter-directed thrombolysis; local thrombolysis; randomised controlled trial

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In parallel, the investigator-initiated, non-industry-sponsored, academic RCT, titled "A Multicentre, Randomized Trial of Catheter-directed Thrombolysis in Intermediate-high Risk Acute Pulmonary Embolism (PRAGUE-26)" (ClinicalTrials.gov: NCT05493163), is now in progress. This trial will compare simple CDT (without ultrasound facilitation) to standard anticoagulation alone.

Methods

STUDY DESIGN

PRAGUE-26 is an academic, prospective, multicentre, randomised, active-controlled, unblinded, parallel-group trial designed to evaluate clinical outcomes in patients with intermediate-high risk acute PE, comparing CDT to standard anticoagulation therapy. The study was approved by the Multicentric Ethics Committee at University Hospital Kralovske Vinohrady in Prague and by the official regulatory authority, the State Institute for Drug Control in the Czech Republic.

A flow diagram of the study is shown in **Figure 1**. The list of PRAGUE-26 investigators and participating institutions is provided in **Supplementary Appendix 1**. This study adheres to the CONSORT 2010 guidelines for the reporting of randomised controlled trials. A detailed checklist is provided in **Supplementary Appendix 2**.

ELIGIBILITY CRITERIA

PRAGUE-26 is enrolling intermediate-high risk PE patients as defined in the European Society of Cardiology (ESC) 2019 Guidelines on Acute Pulmonary Embolism, including patients directly admitted to the cardiocentre as well as patients transferred from peripheral hospitals (referral centres); these patients meet the inclusion criteria and do not have any exclusion criteria, as outlined in **Table 1**.

PRIMARY OUTCOME

The primary outcome of the PRAGUE-26 study is a combined clinical endpoint, a composite of any of the following three events within 7 days of randomisation: all-cause mortality, PE recurrence (non-fatal, symptomatic, and objectively confirmed), or cardiorespiratory decompensation or collapse.

Cardiorespiratory decompensation or collapse is defined by at least one of the following criteria: (a) cardiac arrest or the need for cardiopulmonary resuscitation (CPR) at any time between randomisation and day 7; (b) signs of shock, defined as new-onset persistent arterial hypotension (systolic blood pressure below 90 mmHg or systolic blood pressure drop of at least 40 mmHg, sustained for more than 15 minutes despite an adequate volume status, or the need for vasopressors to maintain systolic blood pressure of at least 90 mmHg), accompanied by end-organ hypoperfusion (altered mental status, oliguria/anuria, or increased serum lactate >2 mmol/L) at any time between randomisation and day 7; (c) commencement of extracorporeal membrane oxygenation; (d) intubation or initiation of non-invasive mechanical ventilation at any time between randomisation and day 7; (e) National Early Warning Score (NEWS) of 9 or higher, between 24 hours and 7 days after randomisation, confirmed by consecutive measurements taken twice, 15 minutes apart[11].

The NEWS score is an internationally standardised scoring system used in critical care medicine to objectively assess patient deterioration and potential treatment failure.

SECONDARY OUTCOMES

The secondary outcomes of the trial include all the individual components of the primary endpoint, as well as the following: first-line therapy failure (defined as the administration of systemic thrombolysis during the index hospitalisation); ischaemic or haemorrhagic stroke; all serious adverse events; duration of hospitalisation (intensive care unit/coronary care unit and overall hospital stay); hospitalisation cost (cost-effectiveness analysis); bleeding complications classified by GUSTO as major (moderate and severe) bleeding, by the International Society on Thrombosis and Haemostasis (ISTH) as major bleeding, and all bleeding complications according to the Bleeding Academic Research Consortium (BARC) criteria; echocardiographic measures of right ventricle recovery and pulmonary artery hypertension; functional status assessed by the World Health Organization (WHO) functional class; functional status as measured by the 6-minute walk test (6MWT); quality-of-life assessment using the EuroQol 5-Dimension (EQ-5D) scale; and diagnosis of chronic thromboembolic pulmonary hypertension (CTEPH).

All primary and secondary objectives are summarised in **Supplementary Appendix 3**, including prespecified time frames for evaluation.

ENROLMENT

PRERANDOMISATION EVALUATION

All patients, including those directly admitted to the cardiocentre and those transferred from cooperating peripheral hospitals, will undergo routine clinical evaluation and standard-of-care testing (computed tomography angiography [CTA], transthoracic echocardiography, and laboratory testing) for diagnosis and risk stratification of acute PE. Patients with intermediate-high risk PE who meet the inclusion criteria and do not meet any exclusion criteria will be deemed suitable for study participation. The State

Abbreviations

aPTT	activated partial thromboplastin time
CDT	catheter-directed thrombolysis
CTEPH	chronic thromboembolic pulmonary hypertension
ISTH	International Society on Thrombosis and Haemostasis
LMWH	low-molecular-weight heparin
LV	left ventricle
NEWS	National Early Warning Score
PE	pulmonary embolism
PESI	Pulmonary Embolism Severity Index
RCT	randomised controlled trial
RV	right ventricle
sPAP	systolic pulmonary artery pressure
sPESI	simplified Pulmonary Embolism Severity Index
STEMI	ST-segment elevation myocardial infarction
USCDT	ultrasound-facilitated, catheter-directed thrombolysis

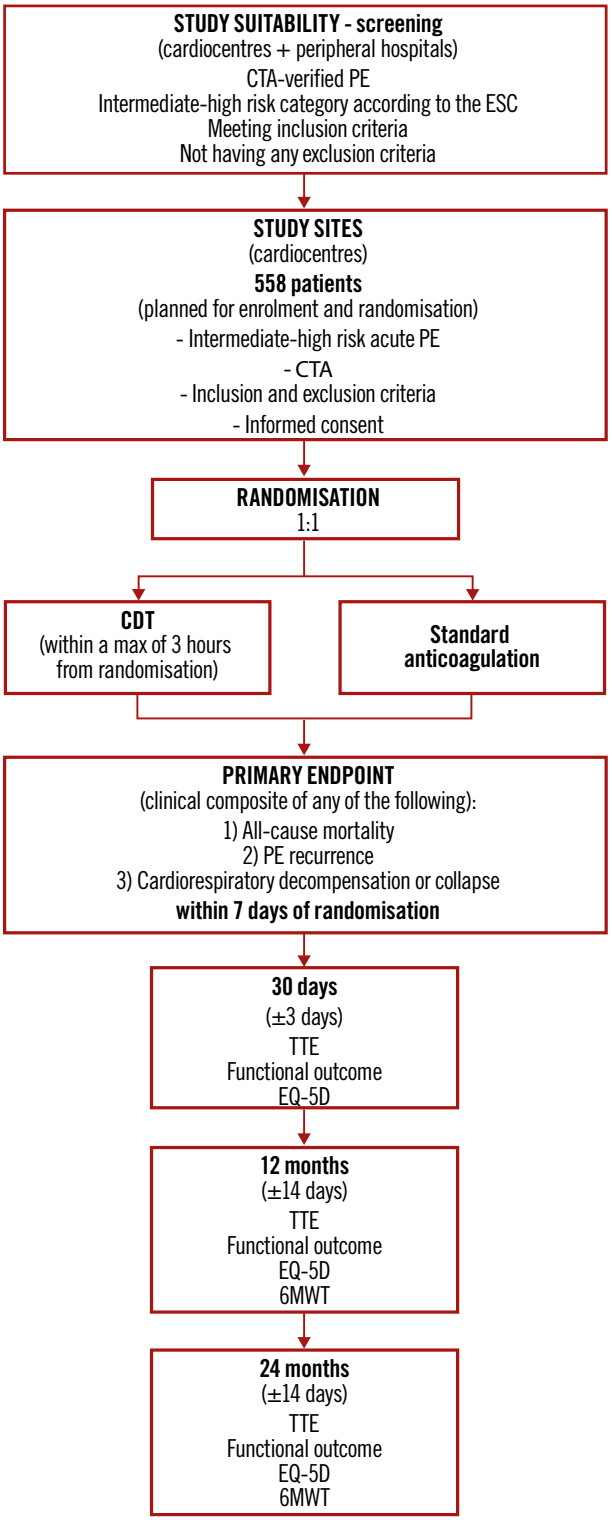

Figure 1. *Study flow diagram – PRAGUE-26. CDT: catheter-directed thrombolysis; CTA: computed tomography angiography; EQ-5D: EuroQol 5-Dimension; ESC: European Society of Cardiology; PE: pulmonary embolism; TTE: transthoracic echocardiography; 6MWT: 6-minute walk test*

Institute for Drug Control (Czech Republic, regulatory authority) insisted on the exclusion of elderly patients (over 80 years of age) due to the perceived higher risk of bleeding from thrombolysis in this population.

There is no time limit from the CTA-confirmed diagnosis of acute PE to randomisation, but investigators are encouraged to take measures to minimise the duration from diagnosis to randomisation.

RANDOMISATION

The randomisation of study participants takes place at study sites (tertiary care cardiocentres) capable of percutaneous interventions for ST-segment elevation myocardial infarction on a 24/7 basis. After providing written informed consent, the participants are randomised via a web-based software, with a 1:1 allocation to either the interventional group (CDT) or the standard care group (anticoagulation alone).

Randomisation into treatment groups is stratified by the following criteria: age, sex, unilateral or bilateral acute PE, time from the diagnosis of acute PE (diagnostic CTA at <24 h or >24 h), and direct admission to the cardiocentre.

Patients randomised to the interventional CDT group should undergo the procedure as soon as possible after randomisation, ideally within a maximum of 3 h, per protocol.

INVASIVE PROCEDURE, ANTICOAGULATION MANAGEMENT

Following prior exclusion of deep vein thrombosis via ultrasound or CTA, venous access is obtained under ultrasound guidance via the common femoral vein. The choice of a double-lumen 8 Fr introducer (single access site) or two 4 Fr introducers (two ipsilateral access sites) is left to the operator's discretion. Subsequent procedural steps are detailed in a previously published pilot study[4]. Operators are strongly advised against the use of hydrophilic wires in the pulmonary arteries because of the risk of vessel perforation. Any 4 Fr valved infusion catheter with an active zone of 10 cm may be used at the operator's discretion.

After each catheter placement, a bolus of 1 mg alteplase (Actilyse [Boehringer Ingelheim]) per catheter is administered, followed by a continuous infusion at 1 mg/h per catheter for 9 h (total dose of 10 mg for unilateral and 20 mg for bilateral PE).

During CDT, intravenous unfractionated heparin is administered to maintain a target activated partial thromboplastin time (aPTT) of 50-60 s. Following local thrombolysis, the catheters are removed, and anticoagulation with unfractionated heparin (without a bolus) is continued to reach a target aPTT of 70-90 s. The 8 Fr introducer (or two 4 Fr introducers) is removed from the femoral vein 60 min after the end of the alteplase infusion, and the access site is manually compressed for 10 min.

In patients undergoing the CDT procedure, additional laboratory tests (blood count, aPTT, international normalised ratio, fibrinogen) are recommended 6 hours after alteplase infusion initiation.

ANTICOAGULATION

Before randomisation, all patients are treated with intravenous unfractionated heparin (to a target aPTT of 70-90 s) or a full therapeutic dose of subcutaneous low-molecular-weight heparin (LMWH). For patients treated with LMWH who are

Table 1. PRAGUE-26: inclusion and exclusion criteria.

Inclusion criteria	1. Age >18 years and ≤80 years
	2. CTA-verified proximal* PE and symptom onset <14 days prior
	3. Intermediate-high risk PE with a sPESI score ≥1 and RV dysfunction# and an elevated biomarker§ (hs-troponin or NT-proBNP) level
	4. Signed informed consent
Exclusion criteria	1. Active clinically significant bleeding
	2. Any haemorrhagic stroke or a recent (<6 months) ischaemic stroke/transient ischaemic attack
	3. Recent (<3 months) cranial trauma or another active intracranial/intraspinal process
	4. Major surgery within 7 days prior
	5. Active malignancy or other severe illness with expected survival <2 years
	6. Haemoglobin level <80 g/L; international normalised ratio >2.0; platelet count ≤100x10^9; creatinine level >200 µmol/L
	7. Pregnant or breastfeeding, fertility without previous exclusion of gravidity
	8. Allergy to thrombolytics or heparin or low-molecular-weight heparin, contrast allergy, a history of heparin-induced thrombocytopaenia
	9. Floating thrombi in transit through a patent foramen ovale
	10. Participation in another clinical trial

*A perfusion defect in at least one main or one lobar pulmonary artery evident on CTA. #RV/LV ratio ≥0.9 on transthoracic echocardiography or CTA. §hs-troponin I (TnI) >53 ng/L (males) or >34 ng/L (females), hs-troponin T (hs cTnT) >14 ng/l; NT-proBNP level >600 pg/mL, BNP >100 pg/mL. CTA: computed tomography angiography; LV: left ventricular; NT-proBNP: N-terminal pro-brain natriuretic peptide; PE: pulmonary embolism; RV: right ventricular; sPESI: simplified Pulmonary Embolism Severity Index

randomised to CDT, the procedure should be postponed for 8 h after the last LMWH dose. Anticoagulation management during CDT is as described above. Patients in the standard care group continue therapeutic anticoagulation with either unfractionated heparin or LMWH, in accordance with current guidelines. A subsequent switch to oral anticoagulation is at the discretion of the treating physician, but not earlier than 24 hours post-randomisation.

FOLLOW-UP EVALUATION

Study participants will be followed for a period of 2 years after randomisation. The study assessment schedule, along with all subsequent procedures, is summarised in **Table 2**.

DATA MANAGEMENT

Pseudonymised data will be entered into an electronic case report form provided and managed by the Third Faculty of Medicine, Charles University, Prague. All data and relevant study documentation will be stored at the trial sites for at least 25 years in compliance with Czech Republic law.

DATA MONITORING

All clinical events (endpoints, adverse events, and others) will be assessed and reviewed by a clinical adjudication event committee.

The data safety monitoring board (DSMB) will oversee the study's progress and ensure the safety of patients is maintained. The DSMB will review accumulating data on a regular basis, with planned analyses at 25%, 50%, and 75% of study enrolment.

SAMPLE SIZE CALCULATION

Based on three studies – the PEITHO study (with a primary composite endpoint of death or haemodynamic collapse, showing an incidence of 5.6% in the standard arm)[12], a study published by Becattini (reporting early mortality of 6.0-7.7%)[13] and our randomised pilot study[4] – we estimated an incidence of the primary composite endpoint of 1.5% in the CDT group and 6.0% in the standard care group. The power calculation is shown in **Table 3**.

RECRUITMENT STATUS

As of 24 November 2024, 258 participants have been enrolled and randomised into the PRAGUE-26 study across 8 active sites in the Czech Republic. Completion of enrolment and reporting of the primary endpoint are anticipated in January 2026. The number of centres may be increased depending on the enrolment rate.

STATISTICAL ANALYSIS PLAN

Data will be analysed on an intention-to-treat basis, with a secondary per-protocol analysis also planned. Interim efficacy and safety analyses are scheduled at 25%, 50%, and 75% of the enrolled patient target, with alpha spending adjusted using the O'Brien-Fleming method to control the overall type I error rate. Based on the review of clinical and safety events, the DSMB will provide recommendations on the study's continuation or may advise early termination.

Discussion

The interventional treatment of acute PE is rapidly advancing, and there is an urgent need for RCTs that are specifically designed and adequately powered to assess the safety and real clinical benefits of interventional approaches, particularly in intermediate-high risk PE. To this end, several large-scale clinical trials are underway, comparing different interventional methods[14] against each other or evaluating various catheter-based interventions relative to the standard of care[10,15].

Table 2. Study assessment schedule.

Period	Screening	Randomisation			Follow-up			
		Day 1	Day 2 (24±3 hours)	Day 3 (48±6 hours)	Discharge	Day 30 (±3 days)	12 months (±14 days)	24 months (±14 days)
Informed consent	x							
Inclusion/exclusion criteria	x	x						
Demography/medical history	x							
Concomitant medication	x				x	x	x	x
Height and weight[a]	x						x	x
Vital signs[b]	x	x	x	x	x	x	x	x
Biochemistry[c]	x							
Haematology[c]	x							
Coagulation[c]	x							
Transthoracic echocardiography		x	x			x	x	x
CDT procedure[d]		x						
WHO Functional Class					x	x	x	x
EQ-5D						x	x	x
6MWT							x	x
AE assessment[e]		x	x	x	x	x	x	

[a]Height in cm, weight in kg. [b]Blood pressure in mmHg, heart rate in beats/min, body temperature in °C, respiratory rate in breaths/min. [c]Laboratory tests – components of routine clinical care (including hs-troponin and NT-proBNP and pregnancy [serum or urine] testing in women before menopause). [d]Only in patients allocated to the CDT group. [e]At each study visit, the investigator will determine whether any (serious) adverse events ([S]AE) have occurred. All serious adverse events and adverse events, depending on local regulatory requirements, will be recorded in a timely manner on the electronic case report form by the investigator (or any dedicated site personnel) and will include the event start and stop date, description of event, severity, and relatedness to the index procedure and the study medication. Notification of suspected unexpected serious adverse events will be in accordance with guidelines KLH-21. CDT: catheter-directed thrombolysis; EQ-5D: EuroQol 5-Dimensional; WHO: World Health Organization; 6MWT: 6-minute walk test

To the best of our knowledge, the PRAGUE-26 study is the second largest interventional, multicentre, randomised trial currently being conducted in this field (after PEERLESS II; ClinicalTrials.gov: NCT06055920). Similar to the industry-sponsored HI-PEITHO study (NCT04790370), the academic PRAGUE-26 trial is challenging the current standard of care in intermediate-high risk acute PE by employing a simple, low-cost CDT approach. With its rigorous design and well-defined endpoints, the PRAGUE-26 study is sufficiently powered to determine whether CDT (without ultrasound facilitation) is superior to standard anticoagulation alone in intermediate-high risk patients. In addition, the study is expected to provide valuable information on bleeding complications, patient-oriented functional outcomes, and the cost-effectiveness of the interventional approach.

PRAGUE-26 is enrolling patients who are either directly admitted to tertiary care interventional centres or referred from peripheral hospitals. The impact of routinely transporting patients with intermediate-high risk acute PE for CDT is not yet known, although this strategy may potentially benefit these patients.

The optimal timing of the interventional procedure, thrombolytic dose, and infusion duration remain unclear. In our trial, we chose a total dose of 20 mg of alteplase for bilateral acute PE (10 mg for unilateral PE). Previous studies that have used local thrombolysis have employed similarly low doses, and it is reassuring that the risk of intracranial or life-threatening bleeding does not appear to be increased[5-7,16]. One small study has investigated dosing and infusion duration for alteplase, with a total dose range of 8 mg to 24 mg; a higher dose appeared to be numerically more effective[5]. These data provided the scientific rationale for our selected dose of alteplase. Independently, the ongoing multicentre HI-PEITHO study of ultrasound-assisted local thrombolysis has chosen a similar dosing approach, with 9 mg for unilateral and 18 mg for bilateral PE[10].

Finally, PRAGUE-26 will assess the feasibility of percutaneous pulmonary interventions (CDT) in cardiac interventional laboratories without prior extensive experience with these procedures (PE-naïve interventional centres). The simplicity and relatively low cost of this intervention might encourage broader adoption among interventional centres worldwide that are not currently offering PE interventions.

Limitations

The PRAGUE-26 study is being conducted at high-volume, primarily tertiary care centres with 24/7 access to cardiac catheterisation, providing the highest level of care available. Although the study enrols intermediate-high risk patients initially admitted and diagnosed in peripheral hospitals, the randomisation process and subsequent care are conducted

Table 3. Study parameters, power calculation.

Primary endpoint – composite of any death, PE recurrence, cardiorespiratory decompensation/collapse (time frame: within 7 days of randomisation)	
Incidence (in CDT group; N=279)	1.5%
Incidence (in standard anticoagulation group; N=279)	6%
Alpha (N=558)	0.05
Beta (N=558)	0.2
Power (N=558)	0.8

Power calculation – sample size calculator: https://clincalc.com/stats/samplesize.aspx. CDT: catheter-directed thrombolysis; PE: pulmonary embolism

exclusively at high-volume centres, even for patients in the standard care group. It is important to note that in a real-world setting, only about half of all patients with acute PE are treated at high-volume centres, while the remaining stay at low-volume (peripheral) hospitals[17]. To demonstrate the superiority of CDT over anticoagulation therapy alone, it is necessary to avoid potential bias arising from differences in care levels between high- and low-volume centres by conducting the trial solely at high-volume centres.

Conclusions

PRAGUE-26 (ClinicalTrials.gov: NCT05493163) aims to evaluate the clinical benefits of simple catheter-directed thrombolysis compared to anticoagulation alone in patients with intermediate-high risk acute PE. The PRAGUE-26 trial will provide insights into whether simple CDT is superior to standard anticoagulation alone in intermediate-high risk acute PE. Regardless of outcome, it will also offer valuable information on the efficacy, safety, and cost-effectiveness of this straightforward interventional approach.

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Conflict of interest statement

J. Kroupa reports receiving consultation fees from Terumo and Boston Scientific; and holds stocks in Medtronic and Inari Medical. V. Kocka reports receiving consultation fees from Medtronic, Abbott, and Philips. M. Poloczek reports receiving consultation fees from Abbott. P. Tousek reports receiving consultation fees from Medtronic. M. Pliva holds stocks in Inari Medical. M. Sluka reports receiving consultation fees from Abbott; and lecturer fees from Edwards Lifesciences. The other authors have no conflicts of interest to declare related to this work.

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Supplementary data

Supplementary Appendix 1. PRAGUE-26 investigators and participating institutions.

Supplementary Appendix 2. CONSORT 2010 checklist of information to include when reporting a randomised trial.

Supplementary Appendix 3. Primary and secondary objectives of the PRAGUE-26 study, including prespecified time frames for evaluation.

Supplementary Appendix 4. Author contributions.

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Supplementary data

Supplementary Appendix 1. PRAGUE-26 investigators and participating institutions.

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8. 2nd Department of Medicine – Department of Cardiovascular Medicine of 1st Faculty of Medicine and General University Hospital in Prague, Prague, Czech Republic – **Jan Pudil, Johana Horakova**

Supplementary Appendix 2. CONSORT 2010 checklist of information to include when reporting a randomised trial*.

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	4
	2b	Specific objectives or hypotheses	4
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	4, 6
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	No changes yet
Participants	4a	Eligibility criteria for participants	5, 12
	4b	Settings and locations where the data were collected	6-7
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	6-7
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	5 + Supp. appendix
	6b	Any changes to trial outcomes after the trial commenced, with reasons	None
Sample size	7a	How sample size was determined	8, 14
	7b	When applicable, explanation of any interim analyses and stopping guidelines	8
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	6
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	6

Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	6
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	6
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	Unblinded study
	11b	If relevant, description of the similarity of interventions	Unblinded study
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	8
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	8
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	8
	13b	For each group, losses and exclusions after randomisation, together with reasons	8
Recruitment	14a	Dates defining the periods of recruitment and follow-up	6-8
	14b	Why the trial ended or was stopped	Left for DSMB decision
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Not applicable – design paper
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	Not applicable – design paper
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	Not applicable – design paper
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	Not applicable – design paper
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	Not applicable – design paper
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	Not applicable – design paper

Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	9
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	10
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	Not applicable – design paper
Other information			
Registration	23	Registration number and name of trial registry	2-3
Protocol	24	Where the full trial protocol can be accessed, if available	Clinicaltrials.gov
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	10

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

Supplementary Appendix 3. Primary and secondary objectives of the PRAGUE-26 study, including prespecified time frames for evaluation.

Primary endpoint – combined; clinical composite of any of the following parameters

1) **All-cause mortality** – [Time Frame: Within 7 days of randomization]
2) **PE recurrence** (non-fatal symptomatic and objectively confirmed recurrence of PE by repeated CTA) – [Time Frame: Within 7 days of randomization]
3) **Cardiorespiratory decompensation or collapse*** – [Time Frame: Within 7 days of randomization]

** Defined as at least one of following criteria:*

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

b) signs of shock, defined as new-onset persistent arterial hypotension (systolic blood pressure below 90 mmHg or systolic blood pressure drop by at least of 40 mmHg, sustained for more than 15 minutes despite an adequate volume status, or the need for vasopressors to maintain systolic blood pressure of at least 90 mmHg), accompanied by end-organ hypoperfusion (altered mental status, oliguria/anuria, or increased serum lactate >2 mmol/L) at any time between randomization and day 7;

c) commencement of extracorporeal membrane oxygenation (ECMO);

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 by consecutive measurements taken twice, 15 min apart.

Secondary endpoints

1. All individual components of primary endpoint – [Time Frame: Within 7 days, 30 days, and 12 months]
2. First-line therapy failure** – [Time Frame: Hospitalization]

*** Defined as administration of systemic thrombolysis during first (index) hospitalization for acute PE.*

3. Ischemic or haemorrhagic stroke [Time Frame: Within 7 days and 30 days]
4. Serious adverse events – [Time Frame: Within 12 months]
5. Duration of hospitalization for the index acute PE event (Time from admission to discharge from hospital) – [Time Frame: Within 30 days]
6. Duration of stay at the intensive, intermediate or coronary care unit during hospitalization for the index acute PE event (Time from admission to discharge from ICU, intermediate, or CCU) – [Time Frame: Within 30 days]
7. Hospitalization cost (cost-effectiveness analysis) – [Time Frame: Within 30 days]
8. GUSTO major (moderate and severe) bleeding*** – [Time Frame: Within 30 days]

**** Major bleeding will be adjudicated according to the GUSTO criteria:*

GUSTO severe or life-threatening bleeding: A bleeding episode that leads to hemodynamic compromise requiring emergency intervention (such as replacement of fluid and/or blood products, inotropic support, or surgical treatment), or is life-threatening or fatal.

GUSTO moderate bleeding (a bleeding episode requiring blood transfusion(s), but which is not deemed life-threatening and does not lead to hemodynamic compromise requiring emergency fluid replacement, inotropic support, or interventional treatment).

9. International Society on Thrombosis and Hemostasis (ISTH) major bleeding**** – [Time Frame: Within 30 days]

***** Major bleeding will be adjudicated according to the ISTH criteria:*

Fatal bleeding and/or

Symptomatic bleeding in a critical area or organ (intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome) and/or

Bleeding causing a fall in hemoglobin level of 20 g/L (2 g/dL) or more, or leading to transfusion of two or more units of whole blood or red blood cells.

10. All bleeding complications scored by the Bleeding Academic Research Consortium (BARC) classification – [Time Frame: Within 30 days and 12 months]
11. Change in the RV-to-LV diameter ratio, systolic pulmonary artery pressure (sPAP), Tricuspid annular plane systolic excursion (TAPSE), Tissue Doppler imaging-derived Tricuspid lateral annular Systolic Velocity (S´ TDI) as measured by echocardiography – [Time Frame: Between Randomization and 24±3 hours, at 30 days, 12 months and 24 months]
12. Functional status as measured by World Health Organization (WHO) functional class***** – [Time Frame: Discharge, 30 days, 12 months and 24 months]

***** *The World Health Organization (WHO) Functional Class assessment is a system for assessing the severity of dyspnea in patients with pulmonary hypertension. Subjects will be classified as Class 1-4 at time points throughout their participation in the study.*

13. Functional status as measured by 6-Minute Walk Test (6MWT) ****** – [Time Frame: 12 months and 24 months]

****** *The 6MWT measures the distance a patient can walk on a flat surface in a period of 6 minutes. A 100-meter distance is measured in a hallway and the patient is asked to walk quickly as many laps as they can over the course of the timed test. The total distance is measured. The patient's baseline vitals and symptoms are compared to their condition at the completion of the test.*

14. Quality of life using EQ-5D scale******* – [Time Frame: 30 days, 12 months and 24 months]

******* *The EQ-5D is a patient reported outcome that provides a simple descriptive profile and single index value for health status. The questionnaire consists of 5 questions pertaining to specific health dimensions, including mobility, self-care, usual activities, pain/discomfort, anxiety/depression, and overall health status rating scale.*

15. Diagnosis of chronic thromboembolic pulmonary hypertension (CTEPH) – [Time Frame: Within 24 months]

Supplementary Appendix 4. Author contributions.

J. Kroupa and V. Kocka designed the study and serve as the principal investigators. J. Kroupa drafted and edited the manuscript, while H. Voberkova reviewed and edited the manuscript. V. Kocka provided supervision, critically reviewed the content, and edited the manuscript. All other authors contributed to manuscript revisions.