Catheter-Directed Thrombolysis versus Anticoagulation Monotherapy in Patients with Acute Intermediate-High Risk Pulmonary Embolism: The CANARY Randomized Clinical Trial

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1. BACKGROUND

Treatment of intermediate-risk pulmonary emboli (PE) is still debated. Despite the promising results of small studies on the efficacy and safety of systemic thrombolytic therapy, larger trials failed to show a net clinical benefit (1). The Pulmonary Embolism THrombolysis (PEITHO) trial which compared the full-dose systemic thrombolysis (i.e., tenecteplase) versus anticoagulation monotherapy in patients with intermediate-risk PE, showed significantly lower incidence of all-cause mortality or hemodynamic collapse in the first seven days after randomization in patients who received tenecteplase (2.6% vs 5.6%, odds ratio (OR), 0.44; 95% confidence interval (CI), 0.23 to 0.87; P= 0.02). However, the mortality benefit was neutralized by the increased risk of major extracranial bleeding (6.3% vs 1.2%; OR, 5.55; 95% CI, 0.23 to 0.87; P< 0.001) and hemorrhagic stroke (2.0% vs 0.2%; OR, 10.04; 95% CI, 1.28 to 78.73) in the thrombolytic arm (2).

The dose of the thrombolytic therapy has been discussed as one of the potential explanations of the lack of net clinical benefit in PEITHO trial. Some investigators hypothesize that lower-dose thrombolytic regimens might result in the same efficacy but with lower bleeding events. Sharifi et al. in the Moderate Pulmonary Embolism Treated with Thrombolysis (MOPETT trial), reported the efficacy and safety of half-dose systemic thrombolytic therapy (i.e., alteplase) compared to anticoagulation monotherapy in 121 patients with moderate PE (i.e., CT pulmonary angiogram (CTPA) involvement of >70% involvement of thrombus in ≥ 2 lobar or left or right main pulmonary arteries). Patients treated with lower-dose thrombolytic therapy experienced significantly fewer primary outcome events (composite of pulmonary hypertension and recurrent PE) compared to those treated with anticoagulation monotherapy (16% versus 63%, P<0.001) during 28-month follow up. No bleeding events among the study participants (3).

Catheter directed thrombolysis (CDT) claims to potentially optimize thrombolytic therapy by direct delivery of thrombolytic agents into pulmonary arteries and consequently decreasing the required dose which might translate to lower bleeding events. In a meta-analysis of retrospective studies, the technique provided a success rate of 91.2% in restoration of hemodynamic stability and resolution of hypoxemia with minor and major complication rates of 7.9% and 2.4%, in treating massive and submassive PE (4). In the only available randomized controlled trial (RCT),
the Ultrasound Accelerated Thrombolysis of Pulmonary Embolism (ULTIMA) study, 59 patients with intermediate-risk PE were randomized into ultrasound-assisted catheter-directed thrombolysis (USAT) or anticoagulation monotherapy. USAT improved surrogate markers such as mean RV/LV ratios (from 1.28±0.19 at baseline to 0.99±0.17 during 24 hours (P<0.001) in the USAT group compared to no improvement in the mean RV/LV ratios in heparin group (1.20±0.14 and 1.17±0.20, at baseline and 24 hours, respectively, P=0.31). During 3-month follow-up no major bleeding or recurrent venous thromboembolism events were detected in either groups; only one death in anticoagulation monotherapy group occurred (5). The Prospective, Single-Arm, Multicenter Trial of Ultrasound-Facilitated, Catheter-Directed, Low-Dose Fibrinolysis for Acute Massive and Submassive Pulmonary Embolism (SEATTLE II) again showed that the use of USAT was associated with improvement in mean RV/LV diameter ratios (1.55 vs. 1.13; mean difference, -0.42; p < 0.0001), pulmonary artery systolic pressure (51.4 mm Hg vs. 36.9 mm Hg; p < 0.0001) and modified Miller Index score (22.5 vs. 15.8; p < 0.0001) from baseline to 48 h post-procedure on 150 patients with an acute massive or submassive proximal PE and RV/LV ratio ≥ 0.9 on chest computed tomography. Fatal or intracranial bleeding was not reported in any of the study population (6). These studies have suggested a potential utility of CDT (in the form of USAT) for patients with intermediate-risk or high-risk PE.

The superiority of USAT to conventional CDT (i.e., without ultrasound facilitation) for improving RV function and preventing hemodynamic instability remains uncertain. In an RCT of 48 patients with acute iliofemoral deep vein thrombosis, Engelberger et al. compared conventional CDT and USAT (with fixed-dose of 20 mg r-tPA in 15 hours in both arms). There was no significant difference between the two groups with respect to thrombus resolution (thrombus load reduction of 55%±27% with USAT and 54%±27% with CDT, P=0.91). Three-month follow-up data did not showsignificant difference in the rates of post-thrombotic syndrome severity (mean Villalta score of 3.0 ± 3.9 and 1.9 ± 1.9 in USAT and CDT, respectively, P=0.21) and primary venous patency (100% in USAT and 96% in CDT; P= 0.33) (7). No RCTs have still compared USAT and conventional CDT in patients with PE. However, compared with conventional CDT, USAT is more expensive and it is unclear whether USAT is truly superior to conventional CDT. Consequently, generating additional information related to comparative effects of conventional CDT compared to anticoagulation monotherapy remains of clinical relevance.
It remains unknown whether conventional CDT is safe and has the potential to confer benefit, compared with anticoagulation monotherapy. In an open-label parallel groups randomized clinical trial with blinded outcome adjudication, we aim to evaluate the 3-month effects of conventional CDT vs anticoagulation monotherapy in patients with acute intermediate-high risk pulmonary embolism. The hypothesis is that conventional CDT compared to anticoagulation monotherapy will have a superior efficacy on decreasing the proportion of patients with a RV/LV ratio > 0.9 at a 3-month follow-up assessed by an imaging core laboratory with an acceptable major bleeding event rate.

2. Objectives

2.1. Primary objective

- To assess the feasibility of enrollment in a trial of conventional CDT plus anticoagulation vs. anticoagulation monotherapy in patients with acute intermediate-high risk PE and to determine the proportion of patients with imaging-based RV/LV ratio >0.9 at 3-month follow-up as assessed by an imaging core laboratory.

2.2. Secondary objectives

- To compare conventional CDT vs. anticoagulation monotherapy in patients with acute intermediate-high risk PE with respect to the proportion of patients with a RV/LV ratio > 0.9 at 72 hours post-randomization assessed by an imaging core laboratory
- To compare conventional CDT vs anticoagulation monotherapy in patients with acute intermediate-high risk PE toward the proportion of patients with an unrecovered RV function at the 3-month follow-up assessed by an imaging core laboratory
- To compare the conventional CDT vs anticoagulation monotherapy in patients with acute intermediate-high risk PE toward all-cause mortality during the 3-month follow-up
- To compare the conventional CDT vs anticoagulation monotherapy in patients with acute intermediate-high risk PE toward the rates of major bleeding (based on
Bleeding Academic Research Consortium (BARC) type 3 or 5) during 3-month follow up

3. Design

Open-label parallel groups randomized controlled trial with 1:1 allocation ratio, concealed allocation sequence, and blinded outcome adjudication.

4. Setting

Two large cardiovascular tertiary centers in Tehran, Iran:

- Rajaie Cardiovascular Medical and Research Center
- Tehran Heart Center

5. Participants

Patients with acute intermediate-high risk PE confirmed by CTPA who fulfill the eligibility criteria will be considered for enrollment in the trial. Risk stratification will be based on the classification of the latest guideline of ESC (8). Patients with confirmed PE with signs of RV dysfunction on imaging tests along with positive cardiac biomarkers will be categorized as intermediate-high risk PE.

6. Inclusion criteria

Study participants must meet all the following criteria:

- Adult patients (≥18 years), with an acute intermediate-high risk PE confirmed by CTPA and symptom onset ≤ 14 days
- Elevated N-terminal pro b-type natriuretic peptide (NT-proBNP) (≥ 600 pg/mL) and cardiac high-sensitive troponin T (≥14 pg/mL for patients aged <75 years and ≥45 pg/mL for those ≥ 75 years)(8)
- RV/LV ratio >0.9 in CTPA
- Simplified pulmonary embolism severity index score ≥1
• Randomized within 48 hours since initiation of anticoagulation therapy
• Not enrolled in another blinded randomized trial study
• Willing to participate, and provide signed and dated informed consent form

7. Exclusion criteria

• Pulmonary emboli diagnosed with modalities other than CTPA
• Patients with involvement limited to segmental and sub-segmental branches of pulmonary arteries
• High-risk (massive) PE (i.e., patients with confirmed PE with unstable hemodynamics were categorized as high-risk PE according to the latest guideline of ESC (8))
• Severe renal dysfunction (creatinine clearance [CrCl] below 30 mL/min calculated based on Cockcroft-Gault formula)
• Terminal illness, as assessed by the treating clinicians
• Surgery within prior 2 weeks
• Platelet count <50 x 10^3/μL
• Absolute contraindication to thrombolytic therapy (8):  
  o Active internal bleeding (excluding menstrual bleeding)
  o History of intracranial hemorrhage
  o Ischemic stroke within the past 3 months
  o Cerebral vascular malformation (aneurysm)
  o Primary or metastatic intracranial malignancy
  o Presence of signs or symptoms of an acute aortic dissection
  o Major trauma or head injury in the previous three weeks

• Concomitant right heart thrombi
• Allergic reaction to study medications
• Lack or withdrawal of informed consent

8. Randomization
Permuted block randomization with block size of four via a web-based system will be proceeded for this study. The random allocation specifications will be provided by the study biostatistician and the steering committee. An independent biostatistician, not otherwise part of the study team, will generate the randomization sequence.

9. Intervention and comparator

a. Intervention

Patients assigned into the intervention arm will be treated with CDT via a unified approach between the two enrolling centers. An ultrasound-guided vascular access will be obtained. For patients needing bilateral pulmonary artery catheters, unilateral femoral access with 2 punctures will be selected. Thereafter, 2 infusion catheters (Cragg–McNamara Valved Infusion Catheters, Medtronic, Plymouth, MN) will be deployed, one in the left and one in the right pulmonary artery. For patients with unilateral involvement of the pulmonary arteries, a single catheter will be placed in the affected pulmonary artery.

A fixed dose of alteplase (Actilyse, Boehringer Ingelheim, Germany), 0.5 mg/h per catheter, (i.e., 1mg/h if bilateral catheters were placed) for 24 hours, with a maximum dose of 24mg/24h will be infused. A fixed dose of unfractionated heparin infusion (UFH) of 500 units/hour will be administered to all the patients in the CDT group during thrombolytic therapy. After the termination of CDT and removal of catheter(s), therapeutic dose of UFH will be substituted. UFH will be changed to twice-daily subcutaneous enoxaparin (1 mg/kg) in patients without procedural complication (e.g., major vascular access complication or bleeding events) or unstable hemodynamic necessitating other invasive therapies. Enoxaparin will be continued for the first 48 hours after completion of thrombolytic therapy. Thereafter, oral anticoagulation (OAC) will be started at the discretion of treating physician.

b. Comparator
Patients assigned to anticoagulation monotherapy group will receive twice-daily subcutaneous enoxaparin (1mg/kg) doses in the first 48 hours of enrollment. OAC will be started at the discretion of treating physician.

10. Outcomes

Primary outcome

- The proportion of patients with a RV/LV ratio >0.9 at a 3-month follow-up assessed by an imaging core laboratory blinded to treatment assignment

Secondary and exploratory outcomes

- The proportion of patients with a RV/LV ratio >0.9 at 72 hours post-randomization, assessed by an imaging core laboratory blinded to treatment assignment
- The proportion of patients with unrecovered RV (see imaging core lab section) at the 3-month follow-up assessed by an imaging core laboratory blinded to treatment assignment
- 3-month rate of all-cause mortality
- A composite of 3-month rate of all-cause mortality or the primary outcome
- 3-month rate of PE-related mortality
- Hospital length of stay (index hospitalization)
- Six-minute walk test (6MWT) at three-month follow up

Main Safety outcomes:

- Major bleeding will be defined based on the BARC criteria. BARC 3 or 5 will be considered as major bleeding (9)

Additional safety outcome:

- Severe thrombocytopenia
- Vascular access complication
- Clinically relevant non-major bleeding (CRNMB) (BARC 2)
11. Imaging core laboratory:

Three specific TTE examinations will be performed for all the participants: on admission, at 72-hour post-randomization, and at 3-month follow-up. The first TTE will be performed by the on-call cardiologist for the primary risk stratification and investigation of eligibility criteria (e.g., the presence of right heart thrombosis). The next 2 TTE examinations (72-hour post-randomization and at the 3-month follow-up) will be sent to an independent imaging core laboratory. The core laboratory will constitute of two experienced cardiologists with subspecialty in echocardiology who will be blinded to study group assignment and will assess the images according to a uniform criteria. All the conventional measurements will be performed based on the latest guidelines on performing TTE (10). RV and LV diameter for the RV/LV ratio at 72-hour post-randomization and 3-month follow up, will be measured at apical four chamber view. The 3-month RV recovery will be based on PEITHO definition (11), as follows: 1) RV size (measured at mid RV end diastolic diameter in the RV focused view) <35 mm, 2) pulmonary artery pressure <35 mm Hg (estimated from the highest tricuspid regurgitation gradient acquired from multiple views plus right atrial pressure based on inferior vena cava diameter and its respiratory collapse), 3) an RV/LV ratio <0.9, and 4) the normalization of RV free wall motion (in RV focused view). The fulfillment of all the criteria, some criteria, and none of the criteria was defined as complete, partial, and no recovery, respectively (11). Intra-and-inter-observer variability will be tested by recirculating a series of deidentified cases for a second evaluation by the same and second operator of the core laboratory. Potential discrepancies will be resolved by a third operator.
12. STUDY FLOW DIAGRAM

Inclusion Criteria
- Men and women aged ≥18 years with an acute intermediate-high risk PE* confirmed by CTPA and symptom onset ≤ 14 days
- Elevated NT-proBNP and cardiac troponin
- RV/LV ratio >0.9 in CTPA
- Simplified pulmonary embolism severity index score ≥ 1
- Less than 48 hours since initiation of anticoagulation therapy
- Willing to participate with provision of signed and dated informed consent form

Exclusion criteria
- PE diagnosed with modalities other than CTPA
- Involvement limited to segmental and sub-segmental branches of pulmonary arteries
- High-risk (massive) PE
- Severe renal dysfunction (CrCl < 30 mL/min)
- Terminal illness
- Surgery within 2 weeks
- Platelet count <50 x 10^3/μL
- Contraindication to thrombolytic therapy
- Concomitant right heart thrombi
- Allergic reaction to allocated medications
- Lack or withdrawal of informed consent

Patients meeting eligibility criteria

Randomized 1:1 open label

Conventional CDT

Anticoagulation monotherapy

BARC; Bleeding Academic Research Consortium, CDT; Catheter directed thrombolysis, CrCI; creatinine clearance, CTPA; computed tomography pulmonary angiography, NT-proBNP; N-terminal pro b-type natriuretic peptide, PE; Pulmonary embolism, RV/LV; right ventricular/left ventricular, t-pa; tissue plasminogen activator

* Risk stratified based on the classification of the 2014 latest guideline of the European Society of Cardiology (ESC)^4
^ Calculated based on Cockcroft-Gault formula
13. Study baseline variables and outcomes

<table>
<thead>
<tr>
<th>Variable Name</th>
<th>Unit</th>
<th>Definitions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Years</td>
<td>Years that have passed from the person’s date of birth</td>
</tr>
<tr>
<td>Gender</td>
<td>Male/Female</td>
<td>Self-report by patients</td>
</tr>
<tr>
<td>Weight</td>
<td>Kg</td>
<td></td>
</tr>
<tr>
<td>Baseline blood pressure</td>
<td>mmHg</td>
<td>Blood pressure measured by automated noninvasive blood pressure system in the emergency department on admission</td>
</tr>
<tr>
<td>Baseline heart rate</td>
<td>Beats per minute</td>
<td>The number of the heart beats within a minute on admission</td>
</tr>
<tr>
<td>Baseline Respiratory rate</td>
<td>Breaths per minute</td>
<td>The number of breaths per minute on admission</td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>Yes/No</td>
<td>History of diabetes by medical history</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Yes/No</td>
<td>History of hypertension by medical history</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>Yes/No</td>
<td>History of total cholesterol ≥ 240 mg/dL, LDL-cholesterol ≥ 190 mg/dL, HDL-cholesterol ≤ 40 mg/dL, and triglycerides ≥ 500 mg/dL</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>Yes/No</td>
<td>History of established coronary artery disease by non-invasive and invasive diagnostic tests or history of coronary artery revascularization</td>
</tr>
<tr>
<td>Obstructive airway disease</td>
<td>Yes/No</td>
<td>History of obstructive airway disease by medical history</td>
</tr>
<tr>
<td>Baseline imaging and laboratory characteristics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline RV/LV &gt;0.9</td>
<td></td>
<td>RV/LV ratio measured on the axial view at the baseline CTPA</td>
</tr>
<tr>
<td>Main PA diameter</td>
<td>mm</td>
<td>Defined as the widest diameter perpendicular to the long axis of main PA, at the level of PA bifurcation in the baseline CTPA</td>
</tr>
<tr>
<td>PA obstruction index (12)</td>
<td>%</td>
<td>Calculated according to the Qanadli score on the baseline CTPA</td>
</tr>
<tr>
<td>High-sensitivity troponin</td>
<td>ng/L</td>
<td>High-sensitivity troponin level at baseline, assessed by a uniform assay in both study sites</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Measure</td>
<td>Definitions</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
<td>---------</td>
<td>-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>NT-proBNP</td>
<td>pg/L</td>
<td>NT-proBNP level at baseline, assessed by a uniform assay in both study sites</td>
</tr>
<tr>
<td>3-month RV/LV ratio &gt;0.9</td>
<td>Yes/No</td>
<td>The proportion of patients with a RV/LV ratio &gt;0.9 at 3-month follow-up assessed by an imaging core laboratory blinded to treatment assignment measured by TTE (apical 4-chamber view)</td>
</tr>
<tr>
<td>72-hour post-randomization RV/LV &gt;0.9</td>
<td>Yes/No</td>
<td>The proportion of patients with a RV/LV ratio &gt;0.9 at 72 hours post-randomization assessed by an imaging core laboratory blinded to treatment assignment measured by TTE (apical 4-chamber view)</td>
</tr>
<tr>
<td>RV recovery (13)</td>
<td>Complete, partial, and no recovery</td>
<td>The 3-month RV recovery will be based on PEITHO definition (11), as follows: 1) RV size (measured at mid RV end diastolic diameter in the RV focused view) &lt;35 mm, 2) pulmonary artery pressure &lt;35 mm Hg (estimated from the highest tricuspid regurgitation gradient acquired from multiple views plus right atrial pressure based on inferior vena cava diameter and its respiratory collapse), 3) an RV/LV ratio &lt;0.9, and 4) the normalization of RV free wall motion (in RV focused view). The fulfillment of all the criteria, some criteria, and none of the criteria was defined as complete, partial, and no recovery, respectively. The criteria will be based on TTE measurement and will be assessed by an imaging core laboratory blinded to treatment assignment</td>
</tr>
<tr>
<td>3-month rate of all-cause mortality</td>
<td>Dead/Alive</td>
<td>Survival status of the patients ascertained by the CEC. Death will be classified into cardiovascular (also defining PE or non-PE related), non-cardiovascular and undetermined causes as below:</td>
</tr>
<tr>
<td>Death (14)</td>
<td>Yes/No</td>
<td>Death resulting from an acute MI, sudden cardiac death, death due to HF, death due to PE, death due to stroke, death due to CV procedures, death due to CV hemorrhage, and death due to other CV causes.</td>
</tr>
<tr>
<td>a. Cardiovascular</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### b. Non-cardiovascular

<table>
<thead>
<tr>
<th>PE-related (13)</th>
<th>Yes/No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-cardiovascular death is defined as any death with a specific cause that is not thought to be CV in nature</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Undetermined Cause</th>
<th>Yes/No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Undetermined cause of death refers to a death not attributable to one of the above categories of CV death or to a non-CV cause. Inability to classify the cause of death may be due to lack of availability of sufficient information (e.g., the only available information is “patient died”) or when there is insufficient supporting information or detail to assign the cause of death between competing potential causes.</td>
<td></td>
</tr>
</tbody>
</table>

### Hospital length of stay

<table>
<thead>
<tr>
<th>Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>The total duration of the hospitalization</td>
</tr>
</tbody>
</table>

### 3-month 6MWT

<table>
<thead>
<tr>
<th>meters</th>
</tr>
</thead>
<tbody>
<tr>
<td>The distance which an individual is able to walk over a total of six minutes on a hard, flat surface (15) measured at three-month follow up</td>
</tr>
</tbody>
</table>

### 3-month VTE recurrence

<table>
<thead>
<tr>
<th>Yes/No</th>
</tr>
</thead>
<tbody>
<tr>
<td>The recurrence of new objectively-confirmed VTE after the first episode with nonfatal symptoms during three-month follow up. New VTE composed of:</td>
</tr>
<tr>
<td>1. New distal or proximal DVT which has been confirmed by ultrasonography or venography</td>
</tr>
<tr>
<td>2. New PE confirmed by CTPA. New PE limited to one new subsegment will not accounted.</td>
</tr>
</tbody>
</table>

### In-hospital hemodynamic decompensation

<table>
<thead>
<tr>
<th>Yes/No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemodynamic decompensation consisted of as at least one of the following criteria:</td>
</tr>
<tr>
<td>a. Cardiac arrest or need for CPR at any time after randomization and during the index hospitalization</td>
</tr>
<tr>
<td>Condition</td>
</tr>
<tr>
<td>-----------</td>
</tr>
<tr>
<td>Signs of shock: new-onset persistent arterial hypotension SBP below 90 mmHg or SBP drop by at least 40 mm Hg, over at least 15 minutes and despite an adequate volume status; or need for vasopressors to maintain SBP of at least 90 mmHg), accompanied by end-organ hypoperfusion (altered mental status; oliguria/anuria; or increased serum lactate) at any time after randomization and during the index hospitalization</td>
</tr>
<tr>
<td>Placement on ECMO at any time after randomization and during the index hospitalization</td>
</tr>
<tr>
<td>Intubation, or initiation of noninvasive mechanical ventilation at any time after randomization and during the index hospitalization (16)</td>
</tr>
<tr>
<td>Major bleeding events based on BARC criteria (BARC 3 or 5) during three-month follow up</td>
</tr>
<tr>
<td>BARC 3: decrease in the hemoglobin of &gt; 3 g per deciliter, any transfusion, cardiac tamponade, or intracranial or ocular involvement</td>
</tr>
<tr>
<td>BARC 5: fatal bleeding</td>
</tr>
<tr>
<td>Clinically-significant bleeding that warranted attention from the medical personnel, but not fulfilling criteria for major bleeding (BARC 2) during three-month follow up</td>
</tr>
<tr>
<td>Platelet count &lt; 20,000 /μL during index hospitalization</td>
</tr>
<tr>
<td>Complications that potentially necessitated intervention and consisted of major bleeding, large hematoma, pseudoaneurysm, arteriovenous fistula, arterial occlusion, and retroperitoneal bleeding during the index hospitalization</td>
</tr>
</tbody>
</table>

BARC; Bleeding Academic Research Consortium, CEC; Clinical event committee, CPR; Cardiopulmonary resuscitation, CTPA; Computed Tomography pulmonary angiography, CV; cardiovascular, ECMO; extracorporeal membrane oxygenation, HF; heart failure, LV; left ventricle, LVEDD; Left ventricular end-diastolic diameter, MI; myocardial infarction, NT-proBNP; N-terminal-proB-type natriuretic peptide, PA; pulmonary artery, PE; pulmonary emboli, RV; Right ventricle, RVEDD; Right ventricular end-diastolic
diameter, SBP; systolic blood pressure, 6MWT; Six-minute walk test, TTE; transthoracic echocardiography, VTE; venous thromboembolism

14. Statistical considerations and sample size calculation

Based on the long-term follow-up of the PEITHO trial (17), a 15.3% event rate for the primary outcome of an RV/LV ratio >0.9 in the control group was presumed. Considering a 2-sided α of 0.05 and using the Z approximation formula for comparing 2 proportions between independent groups, a sample size of 144 patients in each group was calculated to reach a power of 80% for the detection of a 10% absolute risk reduction in the primary outcome with CDT by comparison with anticoagulation monotherapy.

Data will be expressed as mean values ± standard error of mean or medians (interquartile ranges) for interval variables and counts (%) for categorical variables. The categorical variables will be compared by using the χ² test or the Fisher exact test. The continuous variables will be compared between the 2 groups with the aid of the independent t test (or its nonparametric equivalent, the Mann–Whitney U test). The effects of the intervention on the outcomes were reported through odds ratio (OR) with 95% CI.

15. Ethical considerations

The study protocol and patient informed consent will be approved by the Rajaie Cardiovascular Medical and Research Center (RHC) Ethics Committee which is also valid in the other contributing center. The patients will be fully informed about the possible risks and benefits of participation in the study, afterward signed and dated written informed consent will be provided. Patients will be closely monitored for any adverse event or complication associated with the study drugs and appropriate medical care will be provided for them in case of any complication occurrence.

16. Registration

The trial will be registered at Iranian Registry of Clinical Trials and clinicaltrials.gov.
17. Serious adverse events

All patients will be closely monitored for any serious adverse events immediately after their enrolment and they will be under observation of their physician until consent withdrawal, death, or the end of the study. Any adverse event detected by the study physician or reported by the patient will be recorded carefully and the patient will be followed until the resolution or stabilization of the condition. Serious adverse events include major bleeding (BARC type 3 or 5), severe thrombocytopenia, complication of vascular access, and mortality.

18. Clinical event committee (CEC)

The members of CEC are listed in appendix B. Clinical events which will be assessed and adjudicated by the CEC include VTE recurrence, mortality (all-cause-mortality, cardiovascular mortality and PE related morality), bleeding events, severe thrombocytopenia and procedural related complication (e.g., vascular access complication). Members of the CEC will be meeting in virtual sessions where all de-identified data elements will be presented to them. The meeting will be valid only if the all three members of CEC participating. The data will be de-identified, and the treatment arms will remain blinded when the data are being provided to the CEC. De-identified imaging tests, laboratory values or surgical/interventional procedural reports will be presented as a proof of related events. The Committee will adjudicate the reported outcomes. The adjudicated data will be registered to the electronic database by a research nurse separate from recruiting centers. An official report will be made at the end of each CEC meeting.

19. Data and safety monitoring board (DSMB)

Safety oversight will be under the direction of the Data and Safety Monitoring Board (DSMB) composed of individuals with the appropriate expertise (Appendix C), and no members of the steering committee or the authors group of the study and free from conflict of interest. The DSMB meetings will be held according to the occurrence of the adverse events. No pre-specified criteria were decided by the steering committee to terminate the trial for efficacy. However, a stopping rule for harm (bleeding events) was defined. Considering the lack of large RCTs reporting bleeding events rate in patients undergone CDT, stopping rule for bleeding were defined according to data acquired from SEATTLE II Study (8).
The SEATTLE II tested similar dosage of thrombolytic agents during CDT as the currently planned trial. However, bleeding events were defined differently in SEATTLE study compared to the current investigation. BARC definition was applied for the present investigation (please see Appendix one) due to its more frequent use in modern studies concentrating on thrombolytic and antithrombotic therapies. In contrast, SEATTLE II used GUSTO (Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries) definition which categorized patients into GUSTO moderate bleeding (defined as bleeding that requires blood transfusion but does not result in hemodynamic compromise) and GUSTO severe bleeding (defined as either intracranial hemorrhage or bleeding that causes hemodynamic compromise and requires intervention). Fortunately, the detailed description of bleeding events reported in SEATTLE II, allows reclassification of bleeding endpoints by BARC definition. In SEATTLE II, 15 patients were complicated by GUSTO moderate and severe major bleeding from whom 12 (8.0%) patients had either or both hemoglobin drop more than 3 g/dL or blood transfusion for overt bleeding (BARC 3a and 3b respectively). Since bleeding events may become more frequent with thrombolytic therapy, an absolute 8% excess in major non-fatal bleeding events for the CDT arm compared to anticoagulation monotherapy will be considered for early stopping for harm after 25%, 50%, or 75% recruitment. Since no fatal bleeding or intracranial bleeding (ICH) were reported by SEATTLE II, any ICH or fatal bleeding will be immediately assessed by the DSMB for appropriate consideration and potential early termination of the trial.

20. Data collection and management responsibilities

Data collection is the responsibility of the study physician in each site under the supervision of the site PI. The site PI is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. Data recorded in the electronic case report form (eCRF) derived from source documents should be consistent with the data recorded on the source documents.
Appendix

Appendix A. Bleeding Academic Research Consortium (BARC) definition for Bleeding (9)

Type 0: no bleeding

Type 1: bleeding that is not actionable and does not cause the patient to seek unscheduled performance of studies, hospitalization, or treatment by a healthcare professional; may include episodes leading to self-discontinuation of medical therapy by the patient without consulting a healthcare professional

Type 2: any overt, actionable sign of hemorrhage (eg, more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for type 3, 4, or 5 but does meet at least one of the following criteria: (1) requiring nonsurgical, medical intervention by a healthcare professional, (2) leading to hospitalization or increased level of care, or (3) prompting evaluation

Type 3

Type 3a: Overt bleeding plus hemoglobin drop of 3 to 5 g/dL* (provided hemoglobin drop is related to bleed) Any transfusion with overt bleeding

Type 3b: Overt bleeding plus hemoglobin drop 5 g/dL* (provided hemoglobin drop is related to bleed) Cardiac tamponade Bleeding requiring surgical intervention for control (excluding dental/nasal/skin/hemorrhoid) Bleeding requiring intravenous vasoactive agents

Type 3c: Intracranial hemorrhage (does not include microbleeds or hemorrhagic transformation, does include intraspinal) Subcategories confirmed by autopsy or imaging or lumbar puncture Intraocular bleed compromising vision

Type 4: CABG-related bleeding Perioperative intracranial bleeding within 48 h Reoperation after closure of sternotomy for the purpose of controlling bleeding Transfusion of 5 U whole blood or packed red blood cells within a 48-h period† Chest tube output 2L within a 24-h period

Type 5: Fatal bleeding

Type 5a: Probable fatal bleeding; no autopsy or imaging confirmation but clinically suspicious

Type 5b: Definite fatal bleeding; overt bleeding or autopsy or imaging confirmation

CABG indicates coronary artery bypass graft. Platelet transfusions should be recorded and reported but are not included in these definitions until further information is obtained about the relationship to outcomes. If a CABG-related bleed is not adjudicated as at least a type 3 severity event, it will be classified as not a bleeding event. If a bleeding event occurs with a clear temporal relationship to CABG (ie, within a 48-h time frame) but does not meet type 4 severity criteria, it will be classified as not a bleeding event.

*Corrected for transfusion (1 U packed red blood cells or 1 U whole blood 1 g/dL hemoglobin).

†Cell saver products are not counted.
Appendix B. Clinical Events Committee members:

Behnood Bikdeli, MD, MS (Chair)
Hamidreza Pouraliakbar, MD
Melody Farrashi, MD

Appendix C. Data and Safety Monitoring Board members:

Hooman Bakhshandeh, MD, PhD
Ata Firouzi, MD
Shiva Khaleghparast, MD
Reference