Randomized Controlled Trial of Mechanical Thrombectomy Versus Catheter-directed Thrombolysis for Acute Hemodynamically Stable Pulmonary Embolism: Rationale and Design of the PEERLESS Study

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Trial Design

Title: Randomized Controlled Trial of Mechanical Thrombectomy Versus Catheter-directed Thrombolysis for Acute Hemodynamically Stable Pulmonary Embolism: Rationale and Design of the PEERLESS Study

Abbreviated Title: The PEERLESS Study Design and Rationale

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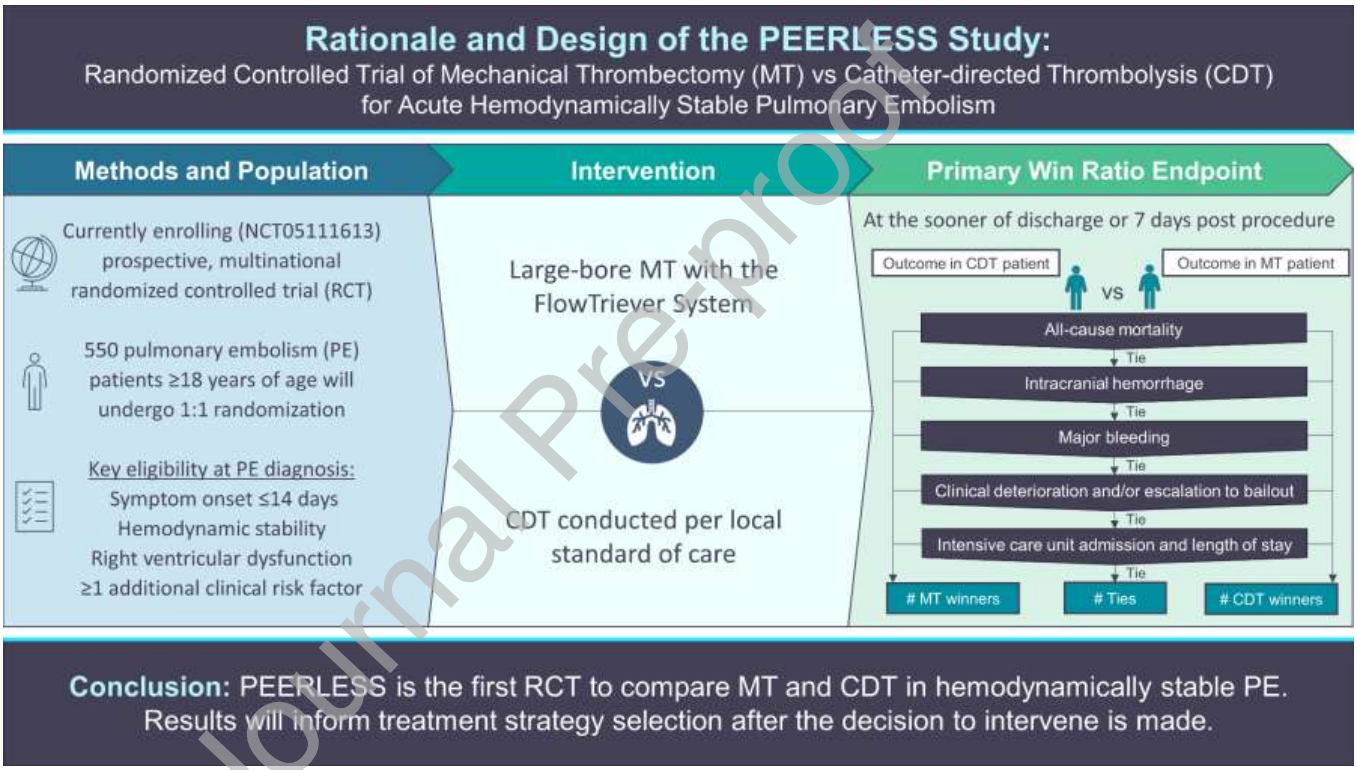
Summary abstract

Background: The identification of hemodynamically stable pulmonary embolism (PE) patients who may benefit from advanced treatment beyond anticoagulation is unclear. However, when intervention is deemed necessary by the PE patient's care team, data to select the most advantageous interventional treatment option are lacking. Limiting factors include major bleeding risks with systemic and locally delivered thrombolytics and the overall lack of randomized controlled trial (RCT) data for interventional treatment strategies. Considering the expansion of the Pulmonary Embolism Response Team (PERT) model, corresponding rise in interventional treatment, and number of thrombolytic and non-thrombolytic catheter-directed devices coming to market, robust evidence is needed to identify the safest and most effective interventional option for patients.

Methods: The PEERLESS study (ClinicalTrials.gov identifier: NCT05111613) is a currently enrolling multinational RCT comparing large-bore mechanical thrombectomy (MT) with the FlowTriever System (Inari Medical, Irvine, CA) vs catheter-directed thrombolysis (CDT). A total of 550 hemodynamically stable PE patients with right ventricular (RV) dysfunction and additional clinical risk factors will undergo 1:1 randomization. Up to 150 additional patients with absolute thrombolytic contraindications may be enrolled into a non-randomized MT cohort for separate analysis. The primary endpoint will be assessed at hospital discharge or 7 days post procedure, whichever is sooner, and is a composite of the following clinical outcomes constructed as a hierarchal win ratio: 1) all-cause mortality, 2) intracranial hemorrhage, 3) major bleeding, 4) clinical deterioration and/or escalation to bailout, and 5) intensive care unit admission and length of stay. The first 4 components of the win ratio will be adjudicated by a Clinical Events Committee, and all components will be assessed individually as secondary endpoints. Other key secondary endpoints include all-cause mortality and readmission within 30 days of procedure and device- and drug-related serious adverse events through the 30-day visit.

Implications: PEERLESS is the first RCT to compare two different interventional treatment strategies for hemodynamically stable PE and results will inform strategy selection after the physician or PERT determines advanced therapy is warranted.

Graphical abstract



Background

Pulmonary embolism (PE) is the third leading cause of cardiovascular death. Over the last 2 decades, the steady rise in incidence and stagnant 10% overall 30-day mortality rate underscore the unmet need for more effective PE treatment with advanced therapy.[1-3] However, clinical evidence generation for advanced therapies has lagged behind the pace of innovation. There is consensus that high-risk PE, which is defined by hemodynamic instability, necessitates rapid reperfusion treatment due to an early mortality rate exceeding 30%.[4-6] Intermediate-risk PE however, is characterized by apparent hemodynamic stability, often in the presence of right ventricle (RV) dysfunction, and is associated with an early all-cause mortality rate that ranges broadly from 3–15%.[7, 8] In-hospital PE-related mortality ranges from 2–6%.[6, 9, 10] Although patients present without overt hemodynamic instability, intermediate-risk PE encompasses a heterogenous spectrum of disease severity, and normotensive cardiogenic shock has been identified in 30–40% of patients upon invasive measurement.[11, 12] Current guidelines recommend anticoagulation (AC) therapy as front-line treatment for intermediate-risk PE patients and if deterioration occurs, reperfusion treatment is recommended.[5, 13]

In the absence of hemodynamic deterioration, the decision to use reperfusion treatment for intermediate-risk PE patients is more ambiguous and controversial in clinical practice. The PEITHO (Pulmonary Embolism Thrombolysis) study showed early reperfusion with systemic thrombolysis reduced the likelihood of early death or hemodynamic decompensation compared with AC alone.[14] In PEITHO, the treatment benefit was primarily driven by prevention of hemodynamic decompensation, while a meta-analysis showed an additional association with decreased likelihood of PE-related mortality.[15] These benefits, however, are tempered by the relatively high frequency of major bleeding events with thrombolytics.[5, 14, 15] Difficulties in clearly identifying hemodynamically stable PE patients who could benefit from early advanced therapy, coupled with demonstrated challenges in identifying

those at higher risk of bleeding with thrombolytics, has prohibited front-line use of systemic thrombolysis in these patients.[13, 16, 17]

The recently published European Society of Cardiology (ESC) clinical consensus statement states reperfusion treatment can be considered when there is no improvement in vital signs after 24–48 hours of therapeutic AC or when there are signs of worsening which are expected to precede deterioration.[13] Precisely when to intervene based on treatment failure or early warning signs remains a primary research question. Without clear data, in clinical practice, a multidisciplinary Pulmonary Embolism Response Team (PERT) would convene to make these decisions. PERT activations commonly occur in hemodynamically stable PE cases with additional risk indicators and are associated with higher utilization of catheter-directed interventions.[8, 18]

Percutaneous catheter-directed interventions, including mechanical thrombectomy (MT) and catheter-directed thrombolysis (CDT), remain an alternative to reperfusion with systemic thrombolysis.[5] Catheter-directed interventions have been studied in hemodynamically stable PE patients, with the aim of providing clinical benefits similar to those observed with systemic thrombolytics while reducing the risk of major bleeding.[6, 11, 19, 20] These interventional therapies have been shown in single-arm studies to rapidly relieve RV strain, with low reported rates of acute clinical deterioration, hemodynamic worsening, or death.[21-25] As a result of these observations, there has been rapid adoption of interventional treatment in clinical practice.[26, 27]

Study rationale

Although the uptake of catheter-based treatment has been accompanied by observational clinical evidence, there is an overall lack of randomized controlled trial (RCT) data for interventional strategies. This is particularly true for trials with clinical outcome-based measures of treatment effectiveness. While foundational studies of both MT and CDT have separately reported positive outcomes in patients with

intermediate-risk PE, there are no prospective studies directly comparing these different strategies in randomized trials.[28-30] As a result, it is currently unknown whether different interventional treatment strategies provide similar clinical benefits to patients. As multiple new thrombolytic and non-thrombolytic catheter-directed devices come to market, it is important to understand if the method of thrombus removal impacts outcomes following treatment. Large-bore MT may provide added clinical benefit due to the immediacy of thrombus extraction and RV strain relief,[31, 32] but it has also been suggested that the ability of CDT to address thrombus in the distal pulmonary vasculature could be linked to improved outcomes.[33] As clinical outcome-based data become available for devices with varying mechanisms of action, the interpretation and generalizability of results could be complicated by study differences and the lack of understanding regarding comparability of interventional strategies. Therefore, it is necessary to create a RCT framework to evaluate the safety and effectiveness of currently available interventional strategies.[29]

The PEERLESS Study (ClinicalTrials.gov Identifier: NCT05111613) is a currently enrolling prospective, multicenter, international RCT with the primary objective of comparing the clinical outcomes of patients following large-bore MT versus CDT for the treatment of acute hemodynamically stable PE, with the goal of informing treatment decisions for patients who the physician or PERT feels are likely to benefit from catheter-based interventional management.

Methods

Patient population

The PEERLESS study will enroll 550 patients who will be randomized 1:1 to receive treatment with large-bore MT, using the FlowTriever System (Inari Medical, Irvine, CA), or CDT, using any commercially available system, at up to 60 study sites located in the US and Europe. The study enrollment flowchart is shown in **Figure I**. A separate cohort of up to 150 patients who meet eligibility criteria but have absolute

contraindications to thrombolytic agents (**Supplemental Table SI**) may be enrolled into a non-randomized MT cohort for independent analysis if their planned primary treatment includes the FlowTriever System.

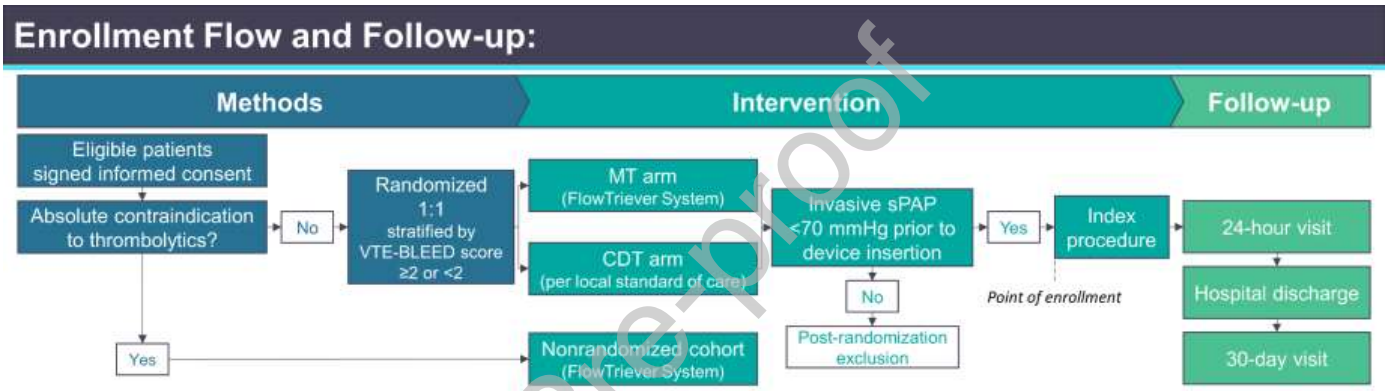
Patients ≥18 years of age with hemodynamically stable PE and evidence of proximal filling defect in at least one main or lobar pulmonary artery (PA) on echocardiogram or imaging (computed tomographic pulmonary angiogram [CTPA] or pulmonary angiogram) will be included. Additionally, symptom onset must have occurred within 14 days of confirmed PE diagnosis, and intervention must be planned to begin within 72 hours following diagnosis or arrival at the treating hospital if transferring from another hospital, whichever was later. Patients will be excluded if they are unable to receive AC with heparin, enoxaparin, or another parenteral antithrombin, or if they have a right heart clot in transit, life expectancy <30 days, or current diagnosis or documented history of chronic thromboembolic pulmonary hypertension (CTEPH) or chronic thromboembolic disease (CTED). A complete list of study inclusion and exclusion criteria can be found in **Table I**.

Randomization will be stratified by bleeding risk as measured by VTE-BLEED score ≥2 or <2 (**Table II**), which will occur automatically in the Electronic Data Capture system upon data entry. Following an acute VTE (venous thromboembolism) event, a VTE-BLEED score ≥2 or <2 identifies patients with high or low risk of bleeding, respectively, during stable AC.[34] The VTE-BLEED score was not designed to predict early bleeding due to interventional treatment for VTE and therefore, stratification should not be interpreted as predictive of outcomes. The VTE-BLEED score was selected because it is an extensively validated disease-specific score with population-based distribution data.[35, 36] The proportion of the randomized population with an elevated VTE-BLEED score will be tracked and reported. All patients who give informed consent and fulfill baseline inclusion/exclusion criteria will be randomized. The point of enrollment is when the patient meets all eligibility criteria and the primary therapeutic catheter enters

the body. As shown in **Table I**, patients will be excluded post-randomization if their systolic pulmonary artery pressure (sPAP) is ≥70 mmHg on invasive measurement at the beginning of the index procedure, prior to enrollment and insertion of the primary therapeutic catheter. A sPAP ≥70 mmHg suggests chronic or acute-on-chronic thrombus, and patients with this degree of pre-existing elevation in sPAP are fundamentally different from the acute PE patient population intended to be studied in PEERLESS. Patients affected by this prespecified post-randomization exclusion criterion will not be included in the analysis population. However, screen failures or post-randomization exclusions will be tracked along with the reason for exclusion.

In the original study protocol, enrolled patients were required to meet the classification of intermediate-high-risk PE determined per the 2019 ESC Guidelines[5] fulfilling all of the following: 1) clinical signs and symptoms consistent with acute PE or risk stratification of Pulmonary Embolism Severity Index (PESI) class III-V or simplified PESI (sPESI) score ≥1; 2) hemodynamic stability; 3) RV dysfunction on echocardiogram or CTPA; and 4) elevated cardiac troponin levels. After the enrollment phase had started, concerns were raised by Investigators regarding the inability to enroll patients selected for intervention during the normal course of practice-based treatment due to the criteria requiring elevated troponin levels. Reported concerns noted the observed transient pattern of troponin increases. Consequently, the PEERLESS Steering Committee expanded the inclusion criteria to include elevated cardiac troponin levels as one component of a broader clinical risk factor profile identified at the time of diagnosis, as shown in **Table I**.

Figure I. Enrollment Flowchart and Follow-up Assessments



CDT, catheter-directed thrombolysis; MT, mechanical thrombectomy; sPAP, systolic pulmonary artery pressure.

Table I. Full Inclusion and Exclusion Eligibility Criteria

Inclusion
1. Age ≥18 years
2. Echocardiographic, CTPA, or pulmonary angiographic evidence of any proximal filling defect in at least one main or lobar pulmonary artery
3. ALL of the following characteristics: a. Clinical signs and symptoms consistent with acute PE or PESI class III–V or sPESI score ≥1, AND b. Hemodynamically stable, AND c. RV dysfunction on echocardiography or CT, AND d. Any one or more of the following at the time of diagnosis: • Elevated cardiac troponin levels • History of heart failure • History of chronic lung disease • Heart rate ≥110 beats per minute • SBP <100 mmHg • Respiratory rate ≥30 breaths per minute • Oxygen saturation <90% • Syncope related to PE • Elevated lactate
4. Intervention planned to begin within 72 hours of the later of either: a. Confirmed PE diagnosis, OR b. If transferring from another hospital, arrival at the treating hospital
5. Symptom onset within 14 days of confirmed PE diagnosis

Exclusion
1. Unable to receive AC with heparin, enoxaparin, or other parenteral antithrombin
2. Index presentation with hemodynamic instability that are part of the high-risk PE definition in the ESC 2019 Guidelines, including ANY of the following: a. Cardiac arrest, OR b. SBP <90 mmHg or vasopressors required to achieve a SBP ≥90 mmHg despite adequate filling status, AND end-organ hypoperfusion, OR c. SBP <90 mmHg or SBP drop ≥40 mmHg, lasting longer than 15 minutes and not caused by new-onset arrhythmia, hypovolemia, or sepsis
3. Known sensitivity to radiographic contrast agents that, as determined by the Investigator, cannot be adequately pre-treated
4. Imaging evidence or other evidence that suggests, in the opinion of the Investigator, the patient is not appropriate for catheter-based intervention
5. Patient has right heart clot in transit identified at baseline screening
6. Life expectancy <30 days as determined by the Investigator
7. Current participation in another drug or device study that, in the opinion of the Investigator, would interfere with participation in this study
8. Current or history of CTEPH or CTED diagnosis, per ESC 2019 Guidelines
9. Invasive sPAP ≥70mmHg prior to the primary therapeutic catheter entering the body
10. Administration of bolus or drip/infusion thrombolytic therapy or mechanical thrombectomy for the index PE event within 48 hours prior to enrollment
11. Ventricular arrhythmias refractory to treatment at the time of enrollment
12. Known to have heparin-induced thrombocytopenia

13. Patient has any condition for which, in the opinion of the Investigator, participation would not be in the best interest of the patient. This includes a contraindication to use of the FlowTriever System or CDT System per local approved labeling
14. Patient has previously completed or withdrawn from this study
15. Patient unwilling or unable to conduct the follow up visits per protocol

AC, anticoagulation; CDT, catheter-directed thrombolysis; CT, computed tomography; CTED, chronic thromboembolic disease; CTEPH, chronic thromboembolic pulmonary hypertension; CTPA, computed tomographic pulmonary angiography; ESC, European Society of Cardiology, PE, pulmonary embolism; PESI, Pulmonary Embolism Severity Index; sPESI, simplified PESI; RV, right ventricle; SBP, systolic blood pressure; sPAP, systolic pulmonary artery pressure.

Table II. VTE-BLEED Algorithm

Parameter	Points
Active cancer	2
Male patient with uncontrolled hypertension (≥140 mmHg)	1
Anemia	1.5
History of bleeding	1.5
Renal dysfunction (creatinine clearance 30–60 mL/min)	1.5
Age ≥60 years	1.5
Total	9 points

Catheter-directed thrombolysis in PEERLESS

Patients randomized to the CDT arm in PEERLESS may be treated with any commercially available CDT system cleared for use per local regulations at the discretion of the treating physician; this includes conventional (e.g., Cragg-McNamara Micro Therapeutics Infusion Catheter, Medtronic, Dublin, Ireland; and Uni-Fuse Infusion Catheters, AngioDynamics, Latham, NY) and ultrasound-assisted CDT systems (EKOS Endovascular System, Boston Scientific, Marlborough, MA). Treatment with CDT in the PEERLESS study is supported by evidence from several clinical studies of both conventional and ultrasound-assisted CDT systems that included hemodynamically stable PE patients. Two studies of ultrasound-assisted CDT without comparator treatment arms reported a statistically significant decrease in RV/left ventricle (LV) ratio at 48 hours after initiation of procedure; major bleeding events occurred in 10% and 4% of patients and 30-day mortality rates were 2.7% and 1%, respectively.[21, 22] The SUNSET sPE RCT, assessed the additive benefit of ultrasound-assisted CDT over conventional CDT and showed no difference in PA thrombus reduction between the two therapies.[37] Additionally, 2 small RCTs, one with ultrasound-assisted CDT and one with conventional CDT, suggested surrogate outcomes are improved with CDT versus AC alone in patients with hemodynamically stable PE. The ULTIMA (Ultrasound Accelerated Thrombolysis of Pulmonary Embolism) study (N=59) reported greater mean reduction in RV/LV ratio at 24 hours post procedure with ultrasound-assisted CDT plus AC vs AC alone for intermediate-risk PE (0.30 ±0.20 vs 0.03 ±0.16, respectively; *P* <0.001). In ULTIMA, there were no major bleeding events and only 1 patient (AC arm) death (1.7%) occurred through 90 days.[19] The more recently published CANARY (Catheter-Directed Thrombolysis vs Anticoagulation in Patients with Acute Intermediate-High-Risk Pulmonary Embolism) study (N=94) of conventional CDT plus AC vs AC alone for intermediate-high-risk PE suggested improvement of RV/LV ratio among patients treated with CDT. However, this study was stopped early due to the COVID-19 pandemic and, therefore, statistical

significance of the primary endpoint was not reached. In CANARY, 1 (2.1%) non-fatal major bleeding event occurred in the CDT arm.[20]

Mechanical thrombectomy in PEERLESS

In contrast to the various CDT systems permitted in the PEERLESS study, patients randomized to the MT arm will be treated with the FlowTriever System. The FlowTriever System is a MT device that extracts PE thrombus by large-bore syringe-based aspiration (16–24F catheter) and/or mechanical (nitinol mesh disks) modes, without employing thrombolytics. There are other smaller-bore MT devices intended to be used without a thrombolytic agent for the treatment of PE. However, given the paucity of data for their different modes of action, particularly for device safety, they are not included in this study.

Evidence supporting study treatment with the FlowTriever System includes results from two previously conducted single-arm sponsored studies, FLARE and FLASH,[23-25, 38] in addition to independently conducted studies.[39-41] FLARE (FlowTriever Pulmonary Embolectomy Clinical Study) was a prospective and multicenter investigational device exemption trial, which led to US FDA clearance of the FlowTriever System for PE treatment in 2018.[25] Results were confirmed by the large, prospective, and multicenter FLASH (FlowTriever All-Comer Registry for Patient Safety and Hemodynamics) registry in patients with intermediate- or high-risk PE. Available outcomes through the 30-day visit were recently published for the full US cohort (n=800).[24] The primary endpoint, a major adverse event composite of device-related mortality and major bleeding within 48 hours and intraprocedural device- or procedure-related adverse events, was observed in 1.8% of patients. There were no intracranial hemorrhages or device-related deaths, and all-cause mortality was 0.8% at the 30-day visit. Immediately following the procedure, mean pulmonary artery pressure decreased by 7.6 mmHg on average. Echocardiographic

assessments at the 48-hour visit showed an improvement in the baseline mean RV/LV ratio from 1.23 to 0.98, in addition to improvements in RV systolic pressure and RV function.[24]

Interventional procedure

In this study, interventional treatment with either MT or CDT will be conducted per standard local practice and in a manner consistent with the device manufacturer's Instructions for Use. There is no specific guidance on when to terminate the procedure. The goal of PEERLESS is to compare treatment outcomes of patients treated in the standard course of clinical practice. Invasive PA pressure measurement is required prior to insertion of the primary therapeutic catheter. For patients treated with CDT, PA pressure measurement is requested, but not required per protocol, at both ≥10 minutes after beginning infusion through the primary therapeutic catheter and 6 ±2 hours post procedure. For patients treated with MT, PA pressure measurement is requested, but not required per protocol, after the FlowTriever System is removed for the last time. Estimated procedural blood loss is recorded.

The use of pre-, intra-, and post-procedural AC is guided by investigator discretion, local standard of care, and in accordance with the Instructions for Use for the assigned therapy. The dose and duration of thrombolytic agents used for patients assigned to CDT is guided in the same manner, and no standardized thrombolytic dosing protocol is enforced. A partial thromboplastin time of 40–60 seconds is suggested to avoid bleeding during CDT administration.[21] The rationale for the decision to not require a standardized thrombolytic dosing protocol in patients randomized to CDT is multifaceted: 1) the ultimate goal of PEERLESS is to provide data reflective of current practice patterns, which include variable thrombolytic dosing regimens during CDT; 2) as described in ESC treatment guidelines,[5, 13] the optimal thrombolytic dosing strategy for CDT is not settled and therefore institutions generally establish their own protocols; and 3) excluding sites unwilling to participate based on enforcement of a strictly controlled thrombolytic regimen could introduce bias. It is important to note, however, that the initial

thrombolytic dosing strategy will be recorded, along with any dose adjustments throughout infusion, including the extension of infusion duration. Therefore, this information will be available for analysis when data become available.

Follow-up and outcomes

Follow-up assessments

Patients will have post-procedure follow-up evaluations at 24 hours (±8 hours), hospital discharge, and 30 days (+15 days). The full schedule of assessments is shown in **Supplemental Table SII**.

Primary endpoint

The primary study endpoint is a composite endpoint constructed as a win ratio,[42] which is a hierarchy of the following clinical outcomes assessed at hospital discharge or 7 days post procedure, whichever is sooner: 1) all-cause mortality, 2) intracranial hemorrhage, 3) major bleeding per the International Society for Thrombosis and Haemostasis (ISTH) definition,[43] 4) clinical deterioration and/or escalation to a bailout therapy, and 5) intensive care unit (ICU) admission and ICU length of stay (LOS) during the index hospitalization and following the index procedure. The first 4 components of the win ratio will be adjudicated by a Clinical Events Committee. The definitions for events included in the primary endpoint can be found in **Table III**.

The win ratio defined by Pocock et al.[42] will be used to evaluate the primary endpoint and summarize the treatment difference between the randomized MT and CDT study arms. Each randomized patient treated with MT will be compared to each patient treated with CDT to determine a "winner". Within each pair, the 5 endpoint components of the win ratio are compared sequentially, in the order of clinical outcome priority, until a "winner" is identified. Pairwise MT vs CDT patient comparisons without a "winner" (i.e., "tie") are not included in the win ratio calculation (e.g., neither

patient experiences one of the 5 outcomes). After all patient pairs have been compared, the win ratio is calculated by dividing the total number of MT winners by the total number of CDT winners in the study.

In PEERLESS, an unmatched win ratio approach is utilized, in that each randomized MT patient will be compared to each CDT patient. To our best knowledge, this is the first PE RCT to employ a win ratio approach. Experience based on other cardiovascular win ratio RCTs indicates an unmatched approach is favored if a validated patient matching process is challenging to pre-define,[42, 44] as is the case in hemodynamically stable PE patients. An unmatched win ratio approach was used in the COAPT trial (heart failure and functional mitral regurgitation) and the PARTNER B trial (severe symptomatic aortic stenosis), among others.[42, 44] Treatment effect determined by win ratio analysis is considered transparent and high quality.[42] The primary advantage of using a win ratio is the prioritization of the most crucial endpoints. In contrast to conventional composite endpoints, all components are not treated equally in a win ratio composite endpoint design; instead, the components are prioritized by clinical importance.

Secondary endpoints

Another composite hierarchic win ratio consisting of only the first 4 components of the primary endpoint will be evaluated as a secondary endpoint to demonstrate comparative treatment effect without considering ICU admission or ICU LOS. Other secondary endpoints include the individual assessment of each of the 5 components of the primary endpoint, in addition to clinically relevant non-major (CRNM) and minor bleeding events at hospital discharge or 7 days post procedure if sooner. CRNM bleeding is defined as any sign or symptom of hemorrhage that does not fit the criteria for the ISTH definition of major bleeding but does meet at least one of the following criteria: 1) requiring medical intervention by a healthcare professional, 2) leading to hospitalization or increased level of care,

or 3) prompting a face-to-face evaluation. Minor bleeding is defined as any bleeding not classified as major or CRNM bleeding.

Additionally, the change in RV/LV ratio and modified Medical Research Council (mMRC) Dyspnea scores from baseline to 24-hour visit and 30-day visit will be evaluated. The mMRC Dyspnea Scale was used in the FLASH registry and is a patient-reported assessment tool with scores from 0 to 4, with higher scores representing worse dyspnea.[24, 45] All-cause mortality and all-cause and PE-related readmission will be assessed within 30 days after index procedure. Device- and drug-related serious adverse events will be captured through the 30-day visit. The total hospital and post-index-procedure LOS will be captured through a maximum of 30 days. Other assessments at the 30-day visit include disease-specific and general health-related quality of life, assessed by PEmb-QoL and EQ-5D-5L, respectively.

Table III. Hierarchal Win Ratio Primary Endpoint

Primary Endpoint	Hierarchical Clinical Outcome Events and Definitions
Win Ratio	**1. All-cause mortality** **2. Intracranial hemorrhage:** • Any bleeding involving the brain parenchyma, ventricular system, or subarachnoid, subdural, or epidural regions as identified by CT scan or MRI regardless of symptoms **3. Major bleeding according to the ISTH definition in non-surgical subjects:** • Fatal bleeding, AND/OR • Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, or intramuscular with compartment syndrome, AND/OR • Bleeding causing a fall in hemoglobin level of ≥2 g/dL (1.24 mmol/L) or leading to transfusion of ≥2 units of whole blood or red cells **4. A. Clinical deterioration AND/OR B. escalation to a bailout therapy** **4A. Clinical deterioration:** defined by documented objective hemodynamic or respiratory worsening that is not present at the time of enrollment, including one or more of the following: • Hypotension with SBP <90 mmHg lasting at least 30 minutes, unresponsive to fluid resuscitation, and

	requiring the addition of, or increased dose of, vasopressors • Fall in SBP by ≥40 mmHg lasting at least 30 minutes and accompanied end-organ hypoperfusion • Cardiac arrest requiring cardiopulmonary resuscitation • Bradycardia lasting >10 minutes, accompanied by hypotension and requiring pharmacologic intervention or insertion of a pacemaker • Ventricular tachycardia or fibrillation requiring pharmacologic intervention or defibrillation • Requirement for an increase in fraction of inspired oxygen requirements ≥0.20, lasting longer than 30 minutes • Need for intubation in a previously non-intubated patient, or unplanned use of ECMO **4B. Escalation to a bailout therapy**: defined by surgical thrombectomy; unplanned use of additional mechanical, pharmacomechanical, or pharmacologic catheter-based therapies, or systemic thrombolytics; or changing from the assigned treatment strategy after initial treatment strategy was assigned: • If CDT was assigned and emergent or clinically driven systemic thrombolytic administration was required after CDT was initiated, this would be considered a bailout. If length of administration is simply extended and is not emergent or clinically driven, this would not qualify as a bailout • If MT was assigned, low-dose catheter-directed adjunctive thrombolytic therapy (<10 mg tPA) that is administered intra-procedurally or post-procedurally will be strongly discouraged but not considered a bailout

	5. ICU admission and ICU LOS during the index hospitalization and following the index procedure: • ICU admission and ICU LOS are characterized hierarchically as follows: 1) no ICU admission, 2) ICU admission lasting between 0–24 hours, 3) ICU admission lasting >24 hours

CDT, catheter-directed thrombolysis; CT, computed tomography; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; ISTH, International Society on Thrombosis and Haemostasis; LOS, length of stay; MRI, magnetic resonance imaging; MT, mechanical thrombectomy; SBP, systolic blood pressure; tPA, tissue plasminogen activator.

Statistical analysis

Sample size calculation

Assuming 80% power with one-sided alpha of 2.5%, the win ratio methodology was applied to the primary endpoint, consisting of the five components described previously, to determine the required sample size. Under these assumptions, the required sample size was determined to be 432 patients, with 216 randomized to each arm. Considering follow-up attrition and the planned assessment of secondary endpoints, the study aims to enroll a total of 550 patients in the randomized cohort.

Endpoint analyses

The hierarchic win ratio composite endpoint will be evaluated using a modified generalized Wilcoxon test (F-S test) proposed by Finkelstein and Schoenfeld[46] to examine the performance differences between the two randomized treatment arms. The 95% confidence interval (CI) of the win ratio estimate will be derived via bootstrap method.

Outcomes for each of the 5 individual components of the primary endpoint, incidence of CRNM and minor bleeding events at the sooner of discharge or 7 days post procedure, all-cause mortality and all-cause and PE-related readmission within 30 days of index procedure, device- and drug-related serious adverse events through 30-day visit, and mMRC dyspnea score at 24-hour and 30-day visits will be compared between treatment arms using *P* values derived using Fisher's or Fisher's exact tests as appropriate. The change in RV/LV ratio from baseline to 24-hour visit and overall PEMB-QoL and EQ-5D-5L scores at the 30-day visit will be assessed with *P* values derived using the Wilcoxon rank sum test. *P*

values ≤0.05 will be considered statistically significant. Data from the non-randomized cohort of patients with absolute contraindications to thrombolytics will not be used for any protocol-defined hypothesis testing nor used to calculate any primary or secondary endpoints.

Funding and ethical considerations

This study is being sponsored by Inari Medical. The initial draft of this manuscript was developed with writing assistance provided by the study sponsor. All authors are members of the PEERLESS Steering Committee and contributed significantly to the overall design and study protocol, which served as the basis for this publication.

Investigators are responsible for obtaining written or, if applicable, electronic Informed Consent for each study patient in accordance with pertinent regulations. This study is approved by an appropriate institutional review board or ethics committee at each site. Boston Clinical Research Institute is serving as the Clinical Events Committee in this study, which will be utilized for the purposes of adjudicating safety-related primary and secondary endpoints. Site-reported safety and outcome data will be provided to the committee for review and adjudicated for all patients enrolled in the study.

Discussion

Expected impact of PEERLESS

PEERLESS is the first RCT comparing two different interventional strategies for the treatment of hemodynamically stable PE. This study will address the comparability of clinical outcomes following MT with the FlowTriever System versus CDT conducted per local standard of care. The PEERLESS study design is intended to generate important data to support decision-making after the physician or PERT determines intervention is

warranted. The adoption of interventional treatment in real-world clinical practice is increasing based on single-arm studies demonstrating reduced short- and long-term mortality and morbidity in intermediate-risk PE patients. With the recent and ongoing emergence of multiple catheter-based systems for interventional PE management, there is a fundamental and topical imperative to understand treatment risks and value between thrombolytic and non-thrombolytic strategies.

Remaining uncertainties

PEERLESS does not include an anticoagulation treatment arm, the guideline recommended treatment for hemodynamically stable PE, and this is a significant limitation of the study. This study will not determine if interventional treatment is superior to conservative treatment with AC for these patients and does not include a specified analysis to identify patients most likely to benefit from interventional treatment. Other RCTs either in development or underway will study patients with hemodynamically stable PE to assess outcomes for intervention compared to conservative therapy alone, including HI-PEITHO, PE-TRACT, STORM-PE, and the forthcoming PEERLESS II study.[47-49] PEERLESS is designed to provide data supporting treatment strategy selection after the decision to intervene is made. In the absence of hemodynamic worsening, the individualized decision to use catheter-directed intervention is complex and currently made without standardized algorithmic guidance.

The results from PEERLESS will provide insight on the comparability of cardinal clinical outcomes with MT versus CDT through 30 days post intervention. However, it is important to recognize that long-term outcomes following intervention are an increasingly important part of the discussion concerning interventional therapies and are not being addressed in this study. Additionally, the rate of long-term sequelae, such as CTEPH and CTED, is a key treatment outcome and will need to be investigated in follow-on studies.

Current enrollment status

As of April 30, 2023, 59 study sites were activated with a total of 370 patients enrolled, 298 in the randomized arms and 72 in the non-randomized MT cohort.

Author Disclosures

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