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Study Design

PEERLESS II: A Randomized Controlled Trial of Large-Bore Thrombectomy Versus Anticoagulation in Intermediate-Risk Pulmonary Embolism

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ABSTRACT

Background: Anticoagulation (AC) is the guideline-recommended treatment for intermediate-risk pulmonary embolism (PE); however, it remains unclear whether mechanical thrombectomy provides benefit over AC alone. The PEERLESS II study aims to evaluate outcomes in intermediate-risk PE patients randomized to treatment with large-bore mechanical thrombectomy and AC vs AC alone.

Methods: PEERLESS II is an international randomized controlled trial enrolling up to 1200 patients with intermediate-risk PE and additional clinical risk factors from up to 100 sites. Treatment is randomized 1:1 to large-bore mechanical thrombectomy with the FlowTriever System (Inari Medical) and AC or AC alone. Outcomes will be evaluated for up to 3 months, with safety events independently adjudicated. The primary end point is a hierarchical composite win ratio of (1) all-cause mortality by 30 days, (2) clinical deterioration (earlier of discharge or 30 days), (3) all-cause hospital readmission by 30 days, (4) bailout therapy (earlier of discharge or 30 days), and (5) Modified Medical Research Council (mMRC) dyspnea score of $\geq$1 at the 48-hour visit. Secondary end points include all-cause and PE-related mortality (30-day and 90-day), all-cause and PE-related readmission (30-day and 90-day), major bleeding (30-day and 90-day), clinical deterioration (earlier of discharge or 30 days), bailout (earlier of discharge or 30 days), right ventricle-to-left ventricle diameter ratio (48-hour visit), mMRC dyspnea score (48-hour, 1-month, and 3-month visits), quality of life using Pulmonary Embolism Quality of Life and EuroQol-5 Dimensions-5 Levels (1-month and 3-month visits), 6-minute walk distance (1-month visit), and post-PE impairment diagnosis (3-month visit).

Conclusions: PEERLESS II will inform the understanding of mechanical thrombectomy treatment for intermediate-risk PE and provide evidence for consideration in future treatment guidelines.

Introduction

Current consensus guidelines recommend anticoagulation (AC) alone as first-line therapy for patients with acute intermediate-risk pulmonary embolism (PE), defined as those with hemodynamic stability and objective evidence of right ventricular (RV) dysfunction based on imaging and/or cardiac biomarkers.[1–4] Active thrombus removal strategies receive lower levels of recommendation in this population, with some guidelines recommending utilization of advanced therapies beyond AC alone only in cases of acute decompensation and others recommending careful selection of patients deemed to be at high risk of deterioration for these approaches. These recommendations are largely based on evidence derived from several randomized trials examining the utility of systemic thrombolysis in this population, which demonstrated an equivocal risk-to-benefit ratio characterized by reductions in short-term mortality but significant increases in major bleeding including intracranial hemorrhage.[5]

In efforts to improve the outcomes of patients with acute PE, a variety of novel devices have been developed to facilitate active thrombus removal with a more optimal safety profile. These include locally administered catheter-directed thrombolysis (CDL) approaches as well as mechanical thrombectomy (MT) approaches that eschew the utilization of thrombolytic agents. Several of these have

Abbreviations: AC, anticoagulation; CDL, catheter-directed thrombolysis; mMRC, Modified Medical Research Council; MT, mechanical thrombectomy; PE, pulmonary embolism; RV, right ventricular; RV/LV, right ventricle-to-left ventricle diameter.

Keywords: anticoagulation; mechanical thrombectomy; pulmonary embolism; randomized controlled trial.

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received the US Food and Drug Administration clearance for marketing based on the results of prospective single-arm studies, demonstrating acute improvements in RV performance with favorable safety profiles.[6–9] Postmarketing registries have largely confirmed these results in larger and more unselected patient populations.[10–12] However, in the absence of large-scale randomized evidence supporting their use, the overall utilization of these therapies remains infrequent.[13–15]

Against this background, the PEERLESS II trial (ClinicalTrials.gov identifier: NCT06055920) aims to evaluate the comparative safety and effectiveness of large-bore MT with the FlowTriever System (Inari Medical) plus AC against AC alone in a population of patients with acute intermediate-risk PE. The trial aims to have sufficient power to evaluate end points that are clinically meaningful to both patients and physicians, further differentiating it from published studies in the space, which have largely relied on surrogate measures as their primary assessment of effectiveness.

Materials and methods

Study design overview

PEERLESS II is a prospective, multicenter, international, randomized controlled trial of large-bore MT with the FlowTriever System plus AC vs AC alone for the treatment of intermediate-risk PE (Central Illustration). The objective is to determine whether this intervention is clinically superior to guideline-recommended standard medical management in this patient population. Up to 1200 patients with intermediate-risk PE and additional clinical risk factors will be enrolled from up to 100 global study sites, using a 1:1 randomization scheme. Data on clinical, imaging, functional, and quality of life outcomes will be collected across 48-hour, 1-month, and 3-month follow-up visits. The primary end point is a hierarchical win ratio assessing short-term mortality, clinical deterioration, hospital readmission, bailout therapy, and dyspnea outcomes between the 2 randomized arms.

Patient population

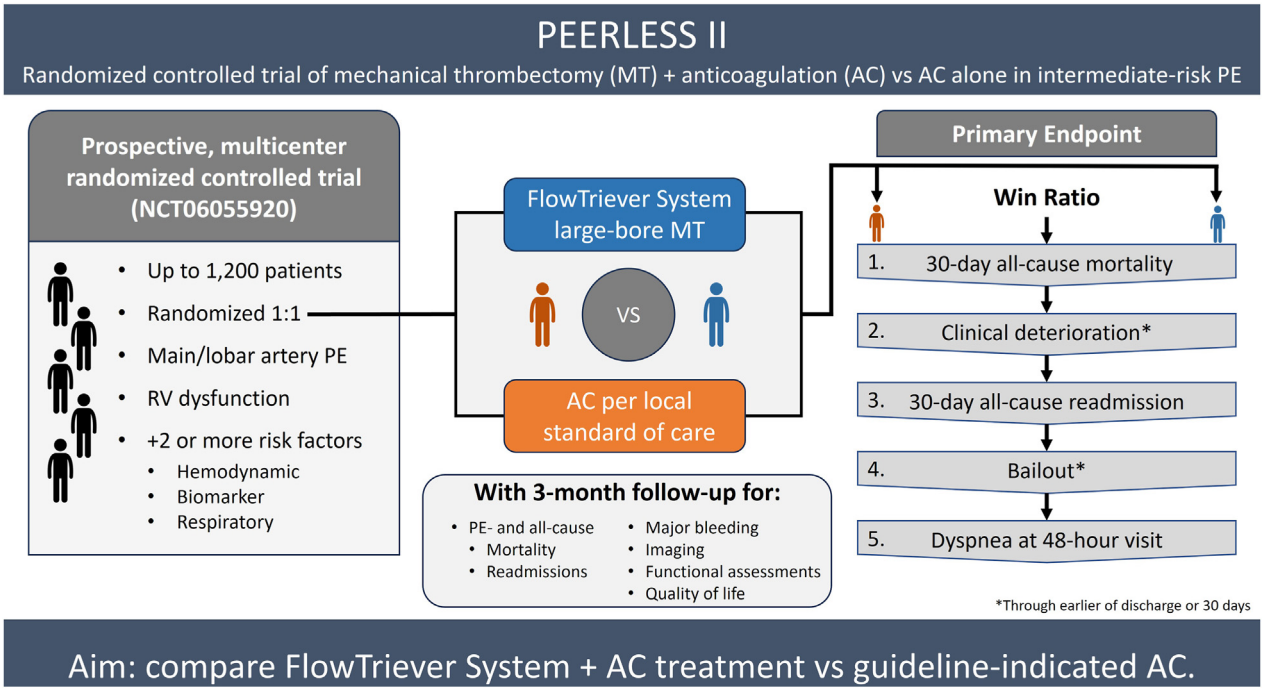
Patients aged 18 years or older with symptom onset within 14 days of PE diagnosis plus imaging evidence of a proximal filling defect in at least 1 main or lobar pulmonary artery will be eligible for inclusion. Evidence of RV dysfunction (right ventricle-to-left ventricle diameter [RV/LV] ratio $\geq$ 0.9 or RV dilation or hypokinesis) plus additional factors indicating elevated risk from at least 2 categories (hemodynamic, biomarker, and respiratory) are also required for inclusion to ensure that PE severity is significant enough to potentially benefit from intervention beyond AC. Key exclusion criteria include patients with hemodynamic instability meeting the high-risk definition in the 2019 European Society of Cardiology guidelines[1]; patients with no imaging evidence of RV dysfunction; those with <3 months of life expectancy; and those with chronic thromboembolic pulmonary hypertension, chronic thromboembolic disease, or RV systolic pressure of >70 mm Hg on standard-of-care echocardiography before enrollment. Full eligibility inclusion and exclusion criteria are listed in Table 1.

Consent, enrollment, and randomization

Patients meeting the study eligibility criteria must sign an informed consent form approved by the site's institutional review board/independent ethics committee prior to participation in any study-related procedures and/or sharing of any medical record or personal health information. Patients providing informed consent are enrolled in the study and then randomized 1:1 using the electronic data capture system to be treated with either (a) large-bore MT using the FlowTriever System plus AC per local practice standards or (b) AC alone per local practice standards. Randomization is considered time 0 and the reference for determining all follow-up visit windows.

Interventions

Index treatment. In both randomized arms, initial treatment begins upon first administration of AC, which may occur prior to the baseline



Central illustration.
Inclusion criteria, study design, and endpoints of the PEERLESS II randomized controlled trial.

Table 1. Inclusion and exclusion eligibility criteria.

Inclusion
- Aged 18 years or older at enrollment
- Objective evidence of a proximal filling defect in at least 1 main or lobar pulmonary artery, as confirmed by CTPA, pulmonary angiography, or other imaging modality
- RV dysfunction, defined as one or more of the following: RV/LV ratio ≥0.9 or RV dilation or hypokinesis
- One or more risk factors from at least 2 separate categories noted below:
  - Hemodynamic:
    - Systolic blood pressure 90-100 mm Hg
    - Resting heart rate >100 beats per minute
  - Biomarker:
    - Elevated[a] cardiac troponin (troponin I or troponin T, conventional or high sensitivity)
    - Elevated[a] B-type natriuretic peptide or N-terminal pro B-type natriuretic peptide
    - Elevated venous lactate ≥2 mmol/L
  - Respiratory
    - Oxygen saturation <90% on room air
    - Supplemental oxygen requirement ≥4 L/min
    - Respiratory rate ≥20 breaths/min
    - mMRC dyspnea score >0
- Symptom onset within 14 days of confirmed PE diagnosis
- Willing and able to provide informed consent

Exclusion
- Unable to be anticoagulated with heparin, enoxaparin, or other parenteral antithrombin
- Presentation with hemodynamic instability[b] that meets the high-risk PE definition in the 2019 ESC Guidelines,[1] including any of the following:
  - Cardiac arrest

OR
  - Systolic blood pressure <90 mm Hg or vasopressors required to achieve a blood pressure ≥90 mm Hg despite adequate filling status, AND end-organ hypoperfusion

OR
  - Systolic blood pressure <90 mm Hg or systolic blood pressure drop ≥40 mm Hg, lasting longer than 15 min and not caused by new-onset arrhythmia, hypovolemia, or sepsis
- Known sensitivity to radiographic contrast agents that, in the investigator's opinion, cannot be adequately pretreated
- Imaging evidence or other evidence that suggests, in the opinion of the investigator, the patient is not appropriate for catheter-based intervention (eg, inability to navigate to target location, clot limited to segmental/subsegmental distribution, and predominately chronic clot)
- End-stage medical condition with life expectancy <3 months, as determined by the investigator
- Current participation in another drug or device study that, in the investigator's opinion, would interfere with participation in this study
- Current or a history of chronic thromboembolic pulmonary hypertension or chronic thromboembolic disease diagnosis, per 2019 European Society of Cardiology Guidelines[1]
- If objective testing was performed,[c] estimated RV systolic pressure >70 mm Hg on standard of care echocardiography
- Administration of advanced therapies (thrombolytic bolus, thrombolytic drip/infusion, catheter-directed thrombolytic therapy, mechanical thrombectomy, or extracorporeal membrane oxygenation) for the index PE event within 30 d before enrollment
- Ventricular arrhythmias refractory to treatment at the time of enrollment
- Known to have heparin-induced thrombocytopenia
- Patient has any condition for which, in the opinion of the investigator, participation would not be in the best interest of the patient (eg, compromise the well-being or that could prevent, limit, or confound the protocol-specified assessments). This includes a contraindication to use of FlowTriever System per local approved labeling
- Patient is currently pregnant
- Patient has previously completed or withdrawn from this study

CTPA, computed tomography pulmonary angiography; mMRC, Modified Medical Research Council; PE, pulmonary embolism; RV, right ventricular; RV/LV, right ventricle-to-left ventricle diameter.

[a] Meaning at or above the upper limit of normal, per local standards for the assay used. [b] Patients who are stable at time of screening or randomization (ie, systolic blood pressure ≥90 mm Hg and adequate organ perfusion without catecholamine or vasopressor infusion) may be included despite initial presentation including temporary, low-dose catecholamines or vasopressors, or temporary fluid resuscitation. [c] If clinical suspicion of acute-on-chronic PE, chronic obstruction, or chronic thromboembolism, echocardiographic estimated RV systolic pressure must be confirmed to be ≤70 mm Hg to meet eligibility. Pressure assessment not required if investigator attests to absence of such clinical suspicion.

visit in some circumstances. The assigned treatment based on randomization allocation must begin no later than 24 hours post-randomization. For patients randomized to the large-bore MT arm, the index procedure begins at the time of vascular access.

Anticoagulation considerations. Patients randomized to the AC treatment arm will either confirm prior initiation of an AC regimen or begin AC administration. The study protocol recommends patients in the AC arm receive a minimum of 48 hours of parenteral low molecular weight heparin or unfractionated heparin at therapeutic doses before transitioning to oral AC. The type of AC regimen will follow local standard of care and the instructions for use for the assigned therapy. The rationale for not requiring a standardized AC protocol in PEERLESS II is as follows: (1) guidelines include a range of acceptable AC strategies[1,16]; (2) inclusion of only those sites willing to adhere to a mandated AC regimen may decrease generalizability and external validity; and (3) PEERLESS II aims to generate data reflecting real-world practice patterns, including variable AC approaches. The initial AC regimen and dosing strategy will be recorded as will all changes throughout the follow-up period so that AC medications, routes, and dosing can be summarized with the potential for exploratory analyses on study conclusion.

FlowTriever MT. Patients randomized to the large-bore MT arm will be treated with the FlowTriever System plus AC per local standards and the instructions for use. The FlowTriever System is a catheter-based MT device comprised a large-bore aspiration catheter and self-expanding nitinol mesh disks enabling mechanical thrombus retrieval. To generate data reflective of actual practice patterns, no specific requirements are dictated for access site, technique, or when to terminate the procedure beyond standard information provided in the instructions for use. The MT procedure will begin when vascular access for treatment is obtained and conclude when the study catheter exits the body. All study investigators performing MT will have a minimum of 5 cases of prior experience using the FlowTriever System for thrombectomy in acute PE.

Follow-up, end points, and other outcomes

The study assessments and follow-up are depicted in Figure 1. Patients will have follow-up visits at 48 hours (±12 hours), 1 month (day 30-

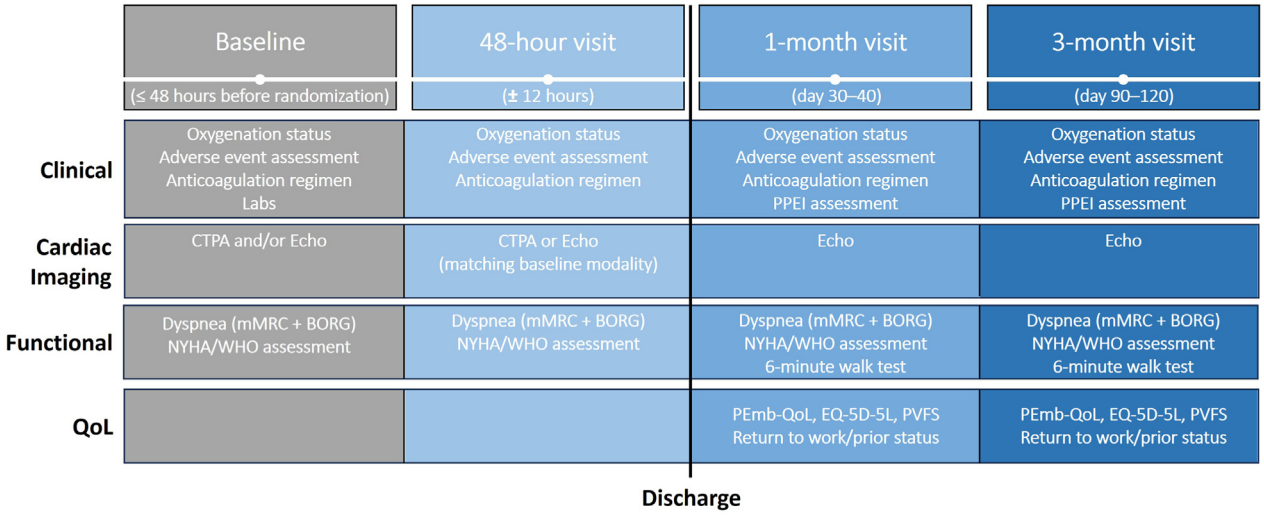


Figure 1.
Assessments and follow-up. CTPA, computed tomography pulmonary angiography; EQ-5D-5L, EuroQol-5 Dimensions-5 Levels; mMRC, Modified Medical Research Council; NYHA, New York Heart Association; PEmb-QoL, Pulmonary Embolism Quality of Life; PPEI, postpulmonary embolism impairment; PVFS, Postvenous Thromboembolism Functional Scale; WHO, World Health Organization.

40), and 3 months (day 90-120) postrandomization. Expert clinical consensus among the trial's steering committee members was reached to determine the follow-up window based on (1) current clinical practice of continued outpatient follow-up for development of chronic thromboembolic pulmonary hypertension or the post-PE syndrome if persistent pulmonary hypertension or clinically significant functional limitations are reported at 3 months posttreatment, and (2) guidelines for AC management after acute PE routinely recommend AC continuation for a minimum 3-month duration, unless the PE was provoked by an underlying coagulopathy requiring ongoing management.[1,16] An independent clinical events committee will adjudicate all safety-related primary and secondary end points throughout the 3-month follow-up.

Primary end point. PEERLESS II's hierarchical win ratio primary end point consists of the following: (1) all-cause mortality through 30 days, (2) clinical deterioration through the earlier of discharge or 30 days, (3) all-cause hospital readmission through 30 days, (4) bailout therapy through the earlier of discharge or 30 days, and (5) Modified Medical Research Council (mMRC) dyspnea score[17] $\geq$ 1 at the 48-hour visit. The win ratio primary end point incorporates these 5 components because they represent some of the most important clinical, procedural, and functional outcomes relevant for assessing the safety and effectiveness of large-bore MT compared with conservative medical management. Table 2 provides full definitions and details on each of the 5 components of the hierarchical primary end point.

Win ratios are composite end points that allow for prioritization of each end point component by clinical importance.[18] They have been used in cardiovascular[19] and PE[20] randomized controlled trials. PEERLESS II uses an unmatched win ratio design where each patient in the large-bore MT treatment arm is compared pairwise with every patient in the AC treatment arm. In each pairing, win ratio components are evaluated in order of clinical importance until a patient does not meet a component of the win ratio that their paired patient does. This patient is considered the "winner." The win ratio is calculated by dividing the number of large-bore MT "winners" by the total number of AC "winners" in the study. Pairs without a "winner" (ie, those tied for all end point components) are excluded from the calculation.

Bailout therapy qualification and timing. Bailout therapy is an unplanned escalation of therapy for treating the index PE when a patient's condition has worsened or not improved as expected. Bailout is assessed through the earlier of discharge or 30 days. It is only permitted by protocol in response to clinical deterioration at any time after randomization or in response to failure to progress after at least 72 hours after randomization. The criteria for clinical deterioration and failure to progress are detailed in Table 2. The type of bailout therapy will be determined at the discretion of the treating physician and recorded. All unplanned escalations of therapy will be adjudicated by an independent clinical events committee. Those that do not meet the abovementioned definitions for bailout therapy will be considered protocol deviations.

Secondary end points. Secondary end points of the study will be used to assess safety, effectiveness, and utility measures of large-bore MT (Table 3). These include an additional win ratio comprised the first 3 components of the primary end point to ascertain the impact of therapy on the most clinically important components of the primary end point. Additionally, each component of the primary end point will be assessed individually, including all-cause and PE-related mortality and readmission through 30 and 90 days. Major bleeding will be evaluated through 30 and 90 days using a simple composite of the Bleeding Academic Research Consortium levels 3b, 3c, 5a, or 5b definitions.[21] Dyspnea severity will be measured by mMRC score at the 48-hour, 1-month, and 3-month visits. When completing the mMRC assessment in a hospital setting, patients will be asked to make their best estimate of how their breathing would feel in the out-of-hospital settings described in the mMRC scoring rubric. General (EuroQol-5 Dimensions-5 Levels) and PE-specific (Pulmonary Embolism Quality of Life) quality of life will be measured at the 1-month and 3-month visits and 6-minute walk distance determined at the 1-month visit. Site-reported RV/LV ratio will be assessed at the 48-hour visit using the same imaging modality as was used for the baseline assessment. Post-PE impairment[22] based on the site-reported presence of echocardiographic and clinical, functional, or laboratory markers will be evaluated at the 3-month visit.

Exploratory outcomes

Additional measures assessing patient function, quality of life, and other clinical factors will be collected during follow-up to better understand the course of disease after acute PE therapy but are not intended to be statistically powered comparisons (Figure 1).

Table 2. Hierarchical win ratio primary end point.

Outcome	Description
All-cause mortality	• Any mortality through 30 d
Clinical deterioration	• Objective hemodynamic or respiratory worsening not present at enrollment that occurs at any time from randomization through the earlier of discharge or 30 d, including: • Qualifying events when occurring at any time • Cardiac arrest requiring cardiopulmonary resuscitation • Need for intubation in a previously nonintubated patient • Unplanned use of extracorporeal membrane oxygenation • Qualifying events when occurring outside of the periprocedural window • Hypotension with systolic blood pressure <90 mm Hg lasting at least 30 min, unresponsive to fluid resuscitation, and requiring the addition of or increased dose of vasopressors • Fall in systolic blood pressure by 40 mm Hg or more, lasting at least 30 min, and accompanied end-organ hypoperfusion (such as oliguria, mental status changes, and ischemic extremities) • Bradycardia lasting more than 10 min, accompanied by hypotension, and requiring pharmacologic intervention or insertion of a pacemaker • New-onset ventricular tachycardia, ventricular fibrillation, or other sustained cardiac tachyarrhythmia requiring emergent pharmacologic intervention or defibrillation • Drop in arterial oxygen saturation requiring a sustained increase in supplemental oxygen (ie, from standard to high-flow nasal cannula, face mask, or mechanical ventilation) to maintain saturation at or above 90% at rest, lasting longer than 30 min and with documented attempts to wean supplemental oxygen
All-cause readmission	• Any return visit to the hospital after discharge from the index hospital stay lasting ≥24 h through 30 d
Bailout therapy	• Any unplanned escalation of therapy for treating the index pulmonary embolism through the earlier of discharge or 30 d in response to clinical deterioration (defined above) or failure to progress: • Persistence or worsening of any of the following, ≥72 h after randomization: • >20 breaths/min at rest • Ongoing or increased requirement for supplemental oxygen ≥4 L/min at rest to maintain arterial saturation ≥90% • Tachycardia >100 beats/min at rest • Bradycardia <40 beats/min at rest • Nonvagal hypotension (systolic blood pressure <100 mm Hg at rest) • SpO_2 ≤85% upon ambulation (with room air or supplemental oxygen per investigator discretion) • Venous lactate ≥2 mmol/L • Inability to perform basic functions, limited by severity or changes in vitals and/or symptoms that are attributable to the pulmonary embolism in the opinion of the investigator
Dyspnea	• Modified Medical Research Council dyspnea score[17] ≥1 at 48-h visit

Statistical analysis

Sample size calculation and planned interim analyses. The study sample size was calculated by simulation to determine the appropriate sample size for an adaptive design with a 1-sided α of 2.5% and >90% power for evaluating the 5-component win ratio primary end point. Three interim analyses with sample sizes of 500, 800, and 1000 patients are planned with a final sample size of 1200 patients, randomized 1:1 to the 2 study arms. At each interim analysis, comparison with a predetermined 2-sided α threshold for the findings of the primary end point analysis ($\alpha = 0.00103$ for $n = 500$; $\alpha = 0.01176$ for $n = 800$; $\alpha = 0.02446$ for $n = 1000$; and $\alpha = 0.04096$ for $n = 1200$) will occur. This analysis, combined with assessment of secondary end points, will inform whether the study continues to the next analysis, at the discretion of the sponsor and steering committee.

Endpoint analyses. All patients who meet the inclusion/exclusion criteria, provide informed consent, are randomized to the study, and receive some treatment will be included in the intention-to-treat population. Patients for whom all aspects of study participation are adherent to the study protocol will be included in the per-protocol population. Primary and secondary end points will be analyzed separately for both the intention-to-treat and per-protocol populations.

Win ratio components are measured as binary end points and will be analyzed sequentially in order of clinical importance using a modified generalized Wilcoxon test (F-S test)[23] to determine a win ratio[18]

Table 3. Secondary end points.

Outcome	Description and assessment time points
3-Component win ratio	All-cause mortality through 30 d Clinical deterioration as defined in Table 2 through the earlier of discharge or 30 d All-cause readmission through 30 d
All-cause mortality	Any mortality through 30 and 90 d
PE-related mortality	Any PE-related mortality through 30 and 90 d
All-cause readmission	Any return visit to the hospital after discharge from the index hospital stay lasting ≥24 h through 30 and 90 d
PE-related readmission	Any PE-related return visit to the hospital after discharge from the index hospital stay lasting ≥24 h through 30 and 90 d
Clinical deterioration	Clinical deterioration as defined in Table 2 through the earlier of discharge or 30 d
Bailout therapy	Bailout therapy as defined in Table 2 through the earlier of discharge or 30 d
Major bleeding	Bleeding Academic Research Consortium, level 3b, 3c, 5a, or 5b,[21] through 30 and 90 d
Dyspnea severity	mMRC dyspnea score ≥1 at 48-h, 1-mo, and 3-mo visits
Quality of life	PEmb-QoL at the 1-mo and 3-mo visits EQ-5D-5L at the 1-mo and 3-mo visits
6-min walk distance	6-minute walk distance at the 1-mo visit
RV/LV ratio	RV/LV ratio at the 48-h visit
Post-PE impairment	Post-PE impairment[22] based on echocardiographic and clinical, functional, or laboratory markers at the 3-mo visit

EQ-5D-5L, EuroQol-5 Dimensions-5 Levels; mMRC, Modified Medical Research Council; PE, pulmonary embolism; PEmb-QoL, Pulmonary Embolism Quality of Life; RV/LV, right ventricle-to-left ventricle diameter.

summarizing the performance differences between the 2 treatment arms. In the case where ties are abundant, win odds defined by Brunner et al[24] will also be reported. A 95% CI for the win ratio and the win odds will be estimated via the bootstrap method and reported with each.

Differences in outcomes between the treatment arms for individual components of the win ratio, incidence of major bleeding through 30 and 90 days, PE-related mortality and readmissions through 30 and 90 days, all-cause mortality and readmissions through 90 days, mMRC scores at the 1-month and 3-month visits, and post-PE impairment at the 1-month and 3-month visits will be assessed using *P* values calculated from Fisher exact tests. Differences in RV/LV ratio at the 48-hour visit, 6-minute walk distance at 1 month, and Pulmonary Embolism Quality of Life and EuroQol-5 Dimensions-5 Levels scores at the 1-month and 3-month visits will be evaluated using *P* values calculated from Wilcoxon rank sum tests. *P* values of $<.05$ will be considered statistically significant.

Discussion

PEERLESS II is the first randomized clinical trial comparing large-bore MT with standard AC against AC alone for the management of acute intermediate-risk PE. The trial design aims to evaluate patient-centric clinical and functional end points as opposed to surrogate measures related to RV function.

Two prior studies have compared CDL strategies against AC alone in intermediate-risk PE patients. Both demonstrated more rapid improvement in RV function with CDL but both were insufficiently powered to evaluate clinical or functional outcomes.[25,26] A larger study, HI-PEITHO, is currently randomizing up to 544 patients to ultrasound-assisted CDL with AC against AC alone to evaluate the rates of short-term mortality, hemodynamic collapse, or recurrent PE (ClinicalTrials.gov identifier: NCT04790370).[27] Additionally, the PE-TRACT study aims to evaluate intermediate to long-term functional outcomes among 500 patients with acute intermediate-risk PE randomized to any endovascular treatment strategy vs AC alone (ClinicalTrials.gov identifier: NCT05591118).

PEERLESS II both complements and extends the efforts of these contemporaneous randomized trials in patients with acute PE. The inclusion criteria aiming to create an "enriched" population of intermediate-risk patients includes several novel vital sign, biomarker, and clinical symptom elements that may serve to more carefully guide clinicians in their therapeutic decisions in this population. Moreover, PEERLESS II remains the only trial with an exclusive focus on MT as the initial therapeutic strategy for acute PE that aims to produce high-level comparative evidence regarding the safety and effectiveness of this treatment. The planned sample size of up to 1200 patents will represent the largest ever prospective randomized study evaluating an active thrombus removal strategy in patients with acute PE. In addition to providing appropriate power to evaluate important short-term to intermediate-term clinical and functional outcomes, this sample size will allow for hypothesis-generating examination of important patient subgroups, components of the primary end point, and secondary end points. Finally, this study is expected to provide a rigorous assessment of the natural history of acute intermediate-risk PE treated with large-bore MT and AC alone.

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Declaration of competing interests

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This study was sponsored by Inari Medical. The role of the sponsor includes study design, overseeing, logistic support, and review of study reports. All authors are members of the PEERLESS II Steering Committee and contributed significantly to the overall design of the study protocol, which served as the basis for this publication.

Ethics statement and patient consent

Each investigator is responsible for securing study approval from an appropriate institutional review board/ethics committee before implementing the clinical trial. Investigators are also responsible for ensuring informed consent is obtained for each patient prior to enrollment in the study and any study-specific tests or procedures are performed.

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