Randomized Controlled Trial of Mechanical Thrombectomy Versus Catheter-directed Thrombolysis For Acute Pulmonary Embolism: The PEERLESS Study Design And Rationale

Stefan Stortecky MD, MPH
Department of Cardiology, Inselspital, Bern University Hospital, University of Bern, Switzerland

On behalf of the PEERLESS Study Steering Committee
I have the following potential conflicts of interest to report:

- Consulting fees from BTG / Boston Scientific, Teleflex
- Employment in industry
- Stockholder of a healthcare company
- Owner of a healthcare company
- Other(s) Research grants to the institution from Abbott, Edwards Lifesciences, Medtronic, Boston Scientific, Guerbet AG

I do not have any potential conflict of interest.
BACKGROUND

• Current guidelines recommend normotensive patients with PE receive front-line treatment with anticoagulation therapy¹

• However, there remains unmet potential to improve short-term mortality and long-term outcomes following PE in these patients²-⁴

• This led to technologic advancements and studied use of catheter-based therapies for hemodynamically stable PE patients⁵-⁷

• Subsequently, a rapid increase in catheter-based interventional treatment has been observed in clinical practice⁸,⁹

STUDY RATIONALE

• Previous studies of large-bore mechanical thrombectomy (MT)\(^1\) and catheter-directed thrombolysis (CDT)\(^2,3\) have separately reported positive surrogate outcomes in normotensive PE patients.

• However, it is currently unknown whether the interventional method of PE thrombus removal impacts the clinical outcomes of patients.

• Robust prospective evidence is needed to identify the safest and most effective interventional treatment for PE patients\(^4\).

PEERLESS (NCT05111613) is a currently enrolling prospective international RCT of patients with acute hemodynamically stable PE.

The study objective is to compare the clinical outcomes of patients treated with large-bore MT using the FlowTriever System versus CDT conducted according to local standard of care.
**Key Inclusion Criteria:**
- ≥18 years of age
- PE symptom onset ≤14 days of diagnosis
- SBP>90, central clot, RV dysfunction, and ≥1 of the following additional clinical risk factors at diagnosis:
  - Elevated cardiac troponin
  - History of heart failure
  - History of chronic lung disease
  - Heart rate ≥110 bpm
  - SBP <100 mmHg
- Intervention planned to begin ≤72 hours following diagnosis or arrival at the treating hospital

**Key Exclusion Criteria:**
- Unable to receive anticoagulation with heparin, enoxaparin, or another parenteral antithrombin
- Right heart clot in transit
- Life expectancy <30 days
- Presence or history of CTEPH or CTED
- sPAP measurement ≥70 mmHg at the beginning of the index procedure
Large-bore MT: with the FlowTriever System
• Extracts PE thrombus by large-bore syringe-based aspiration (16–24F catheter):
  • Includes option for mechanical thrombus removal with nitinol mesh disks:
  • Does not utilize thrombolytics

CDT: with any commercially available device
• Dose and duration of thrombolytic is guided by Investigator discretion per local standard of care

Cragg-McNamara™ (Medtronic):

Uni-Fuse™ (AngioDynamics):

EKOS™ (Boston Scientific):
Eligible patients

- **YES**
  - Absolute contraindication to thrombolytics?
    - **No**
      - 1:1 randomization stratified by VTE-BLEED score ≥2 or <2
      - **MT arm** (FlowTriever System)
      - **CDT arm** (per local standard of care)
      - **NONRANDOMIZED MT COHORT (FlowTriever System)**

- **Index procedure → 24-hour visit → Hospital discharge → 30-day visit**
RANDOMIZATION

• 550 patients will undergo 1:1 randomization stratified by VTE-BLEED score ≥2 or <2

VTE-BLEED Score:

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active cancer</td>
<td>2</td>
</tr>
<tr>
<td>Male with uncontrolled hypertension (≥140 mmHg)</td>
<td>1</td>
</tr>
<tr>
<td>Anemia</td>
<td>1.5</td>
</tr>
<tr>
<td>History of bleeding</td>
<td>1.5</td>
</tr>
<tr>
<td>Renal dysfunction (CrCL 30–60 mL/min)</td>
<td>1.5</td>
</tr>
<tr>
<td>Age ≥60 years</td>
<td>1.5</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>9</strong></td>
</tr>
</tbody>
</table>

• An elevated VTE-BLEED score (≥2 vs <2) indicates a higher risk of bleeding on stable anticoagulation following an acute VTE event\(^1\)

• At least 35% of randomized patients will have a VTE-BLEED score ≥2 to approximate a real-world distribution of bleeding risks\(^2,3\)

• Patients with absolute contraindications to thrombolytics are not randomized, however, up to 150 such patients may be enrolled into a separate MT cohort

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PRIMARY ENDPOINT

• Composite endpoint of 5 clinical outcomes assessed at hospital discharge or 7 days post procedure, whichever is sooner

• The 5 components of the composite endpoint represent the outcomes which were considered most important to patients, physicians, and hospitals, prioritized hierarchically as follows:

1. All-cause mortality
2. Intracranial hemorrhage
3. Major bleeding per ISTH definition\(^1\)
4. Clinical deterioration and/or escalation to a bailout therapy
5. ICU admission and length of ICU stay

• A win ratio will be used to evaluate the primary endpoint and summarize the treatment difference between the randomized MT and CDT study arms\(^2\)

SECONDARY ENDPOINTS

At the 24-hour visit (± 8 hours):
- RV/LV ratio
- mMRC Dyspnea score

At discharge or 7 days post procedure, whichever is sooner:
- 4 component win ratio without ICU admission and length of stay outcome
- Individual assessment of the 5 clinical outcomes included in the win ratio
- Minor bleeding events

Within 30 days of index procedure:
- All-cause mortality
- PE-related and all-cause readmission
- Total and postprocedural length of hospital stay

At the 30-day visit (+ 15 days):
- Device- or drug-related SAEs
- mMRC Dyspnea score
- PEmb-QoL and EQ-5D-5L
IMPLICATIONS AND STATUS

• PEERLESS is the first RCT to compare 2 different interventional treatment strategies for acute hemodynamically stable PE
• Results from PEERLESS will be crucial to inform treatment decisions for patients who will undergo interventional therapies for PE

• Enrollment status as of May 18, 2023:
  • 59 study sites activated
  • 389 total patients enrolled
  • 315 randomized and 74 in the contraindication cohort
Patients followed for 3 months

Intermediate-risk acute PE

1200 patients randomized 1:1

FlowTriever Arm  AC Arm

Primary endpoint hierarchy (win ratio):
- All-cause mortality by 30 days
- Clinical deterioration and/or bailout by 30 days
- All-cause hospital readmission by 30 days
- Dyspnea score at 48-hour visit

Global Principal Investigators:
Jay Giri, MD
Interventional Cardiology
Penn Medicine

Frances Mae West, MD
Pulmonary and Critical Care Medicine
Jefferson Health

EU Principal Investigators:
Bernhard Gebauer, MD
Interventional Radiology
Charité University Hospital Berlin

Felix Mahfoud, MD
Interventional Cardiology
Saarland University Hospital Homburg

Designed to evaluate whether anticoagulation alone or large-bore volume-controlled aspiration thrombectomy should be standard of care for intermediate-risk PE
Win Ratio

• The primary advantage of using a win ratio is the prioritization of the most important outcomes of the composite endpoint\textsuperscript{1,2}

• In this unmatched approach, each patient in the MT arm will be compared to each patient in the CDT arm to determine a “winner” for each patient pair\textsuperscript{1,2}

• The 5 endpoint components are compared sequentially until a “winner” is identified

• Pairwise MT vs CDT patient comparisons without a “winner” (e.g., neither patient experiences one of the 5 outcomes) are not included in the win ratio calculation

• 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

Primary Endpoint
Constructed as a Hierarchal Win Ratio

Outcome in CDT patient \( \text{vs} \) Outcome in FlowTriever patient

- All-cause mortality
  - Tie
- Intracranial hemorrhage
  - Tie
- Major bleeding
  - Tie
- Clinical deterioration and/or escalation to bailout
  - Tie
- ICU admission and length of ICU stay
  - Tie

Win ratio = \( \frac{\# \text{ FlowTriever winners}}{\# \text{ CDT winners}} \)

\( \# \text{ FlowTriever winners} \) \( \# \text{Ties} \) \( \# \text{ CDT winners} \)