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ORIGINAL RESEARCH ARTICLE

Large-Bore Mechanical Thrombectomy Versus Catheter-Directed Thrombolysis in the Management of Intermediate-Risk Pulmonary Embolism: Primary Results of the PEERLESS Randomized Controlled Trial

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BACKGROUND: There are a lack of randomized controlled trial data comparing outcomes of different catheter-based interventions for intermediate-risk pulmonary embolism.

METHODS: PEERLESS is a prospective, multicenter, randomized controlled trial that enrolled 550 patients with intermediate-risk pulmonary embolism with right ventricular dilatation and additional clinical risk factors randomized 1:1 to treatment with large-bore mechanical thrombectomy (LBMT) or catheter-directed thrombolysis (CDT). The primary end point was a hierarchal win ratio composite of the following (assessed at the sooner of hospital discharge or 7 days after the procedure): (1) all-cause mortality, (2) intracranial hemorrhage, (3) major bleeding, (4) clinical deterioration and/or escalation to bailout, and (5) postprocedural intensive care unit admission and length of stay. Assessments at the 24-hour visit included respiratory rate, modified Medical Research Council dyspnea score, New York Heart Association classification, right ventricle/left ventricle ratio reduction, and right ventricular function. End points through 30 days included total hospital stay, all-cause readmission, and all-cause mortality.

RESULTS: The primary end point occurred significantly less frequently with LBMT compared with CDT (win ratio, 5.01 [95% CI, 3.68–6.97]; $P<0.001$). There were significantly fewer episodes of clinical deterioration and/or bailout (1.8% versus 5.4%; $P=0.04$) with LBMT compared with CDT and less postprocedural intensive care unit use ($P<0.001$), including admissions (41.6% versus 98.6%) and stays >24 hours (19.3% versus 64.5%). There were no significant differences in mortality, intracranial hemorrhage, or major bleeding between strategies or in a secondary win ratio end point including the first 4 components (win ratio, 1.34 [95% CI, 0.78–2.35]; $P=0.30$). At the 24-hour visit, respiratory rate was lower for patients treated with LBMT (18.3±3.3 versus 20.1±5.1; $P<0.001$), and fewer had moderate to severe modified Medical Research Council dyspnea scores (13.5% versus 26.4%; $P<0.001$), New York Heart Association classifications (16.3% versus 27.4%;

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P=0.002), and right ventricular dysfunction (42.1% versus 57.9%; *P*=0.004). Right ventricle/left ventricle ratio reduction was similar (0.32±0.24 versus 0.30±0.26; *P*=0.55). Patients treated with LBMT had shorter total hospital stays (4.5±2.8 overnights versus 5.3±3.9 overnights; *P*=0.002) and fewer all-cause readmissions (3.2% versus 7.9%; *P*=0.03), whereas 30-day mortality was similar (0.4% versus 0.8%; *P*=0.62).

CONCLUSIONS: PEERLESS met its primary end point in favor of LBMT compared with CDT in treatment of intermediate-risk pulmonary embolism. LBMT had lower rates of clinical deterioration and/or bailout and postprocedural intensive care unit use compared with CDT, with no difference in mortality or bleeding.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT05111613.

Key Words: percutaneous aspiration ■ pulmonary embolism ■ randomized controlled trial ■ thrombectomy ■ thrombolytic therapy

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Clinical Perspective

What Is New?

- The PEERLESS study is the first randomized controlled trial to compare interventional strategies for intermediate-risk pulmonary embolism.
- Results from 550 randomized patients demonstrate that large-bore mechanical thrombectomy has a significantly lower composite primary end point of all-cause mortality, intracranial hemorrhage, major bleeding, clinical deterioration and/or escalation to bailout therapy, and intensive care unit use through discharge or 7 days compared with catheter-directed thrombolysis (win ratio, 5.01 [95% CI, 3.68–6.97]; *P*<0.001).
- Large-bore mechanical thrombectomy is associated with significantly lower rates of clinical deterioration and/or escalation to bailout therapy and less postprocedural intensive care unit use compared with catheter-directed thrombolysis.

What Are the Clinical Implications?

- The PEERLESS study provides the first randomized data for mechanical thrombectomy and important new information to inform endovascular treatment selection for patients with intermediate-risk pulmonary embolism for whom the decision to intervene has been made by the patient's care team.
- In the intermediate-risk pulmonary embolism patient population, intervention with large-bore mechanical thrombectomy reduces the likelihood that patients will experience clinical deterioration and/or escalation to bailout therapy, and reduces intensive care unit admission, hospital length of stay, and 30-day readmission compared with catheter-directed thrombolysis.

Nonstandard Abbreviations and Acronyms

CDT	catheter-directed thrombolysis
CTPA	computed tomographic pulmonary angiogram
ICH	intracranial hemorrhage
ICU	intensive care unit
LBMT	large-bore mechanical thrombectomy
mMRC	modified Medical Research Council
NYHA	New York Heart Association
PE	pulmonary embolism
PEITHO	Pulmonary Embolism Thrombolysis
RCT	randomized controlled trial
RV	right ventricle
tPA	tissue-type plasminogen activator

Despite advances in care, by some estimates, pulmonary embolism (PE) remains the third leading cause of cardiovascular death.[1–4] Currently, high-risk PE is managed with rapid reperfusion therapy. However, given the high rate of bleeding, including intracranial hemorrhage (ICH), with systemic thrombolysis, societal guidelines recommend anticoagulation for patients with intermediate-risk PE with objective evidence of right ventricle (RV) dysfunction.[5,6] Early mortality rates in these patients range from 3% to 15%,[7,8] and clinical deterioration occurs in 5% to 18%[9–12]; thus, alternative therapies are needed to improve outcomes.

Observational studies of large-bore mechanical thrombectomy (LBMT) and catheter-directed thrombolysis (CDT) have separately reported positive outcomes in patients with intermediate-risk PE,[13–17] but no previous randomized controlled trials (RCTs) have directly compared these interventional strategies. The PEERLESS trial is the first RCT to evaluate mechanical thrombectomy and the first to compare 2 advanced therapies in the management of acute intermediate-risk PE with the objective of evaluating differences in acute clinical outcomes. We hypothesized that LBMT reduces the incidence of in-hospital adverse clinical outcomes compared

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with CDT by providing more rapid removal of emboli and relief of RV dysfunction.

METHODS

Data Availability

Data collected in this study will not be made available to others.

Study Oversight

The PEERLESS study (ClinicalTrials.gov identifier: NCT05111613) is a prospective, international multicenter, open-label device RCT comparing LBMT with CDT for acute intermediate-risk PE. Trial design details and rationale have been published previously.[18] The article was prepared by the senior author with input from all authors. The steering committee and the trial sponsor (Inari Medical) jointly designed the study. The steering committee comprised the global and European principal investigators of the study and a diverse group of field experts with various specialties who advised on regional treatment and operational considerations. A complete listing of committee members and investigators is provided in the Supplemental Material. Institutional review boards or ethics committees at participating sites approved the study, and all patients provided informed consent. Statistical analyses for the primary and secondary end points were performed independently by an external biostatistician (BAIM Institute for Clinical Research, Boston, MA) and the sponsor. All echocardiograms and computed tomographic pulmonary angiograms (CTPAs) provided by sites were assessed by a single independent, blinded physician who provided centralized review. An independent clinical events committee (Boston Clinical Research Institute, Newton, MA) adjudicated all safety-related primary and secondary end points.

Study Population

Eligible patients were ≥18 years of age with an intermediate-risk PE diagnosis per European Society of Cardiology guidelines.[5] In addition to RV dilatation or dysfunction on CTPA or echocardiogram, patients were required to have a proximal filling defect in ≥1 main or lobar pulmonary artery, symptom duration ≤14 days, and intervention planned ≤72 hours from diagnosis or arrival from a transferring hospital. For eligibility determination, assessment of RV dilatation or dysfunction was performed at the site level. The original study protocol required patients to have elevated cardiac troponin levels. The protocol was amended[18] to include elevated troponin in a broader list of other clinical risk factors (history of heart failure, history of chronic lung disease, heart rate ≥110 bpm, systolic blood pressure <100 mm Hg, respiratory rate ≥30 rpm, oxygen saturation <90%, syncope related to PE, elevated lactate), ≥1 of which was required. Patients were excluded if they could not receive therapeutic anticoagulation, right-sided heart clot in transit was identified, life expectancy was <30 days, or their intraprocedural systolic pulmonary artery pressure was ≥70 mm Hg on invasive hemodynamic measurement at the start of the index procedure before insertion of the therapeutic catheter. This last exclusion criterion of severely elevated systolic pulmonary artery pressure was a prespecified postrandomization exclusion intended to exclude patients with chronic PE, in whom interventional endovascular treatment may not convey benefit.[18] The Supplemental Material contains a complete list of eligibility criteria. With the aim of enrolling a diverse population, a total of 60 study sites across the United States and Europe were activated, including site investigators of varying specialties and practice setting types. The study design also included a parallel nonrandomized LBMT registry for patients who could not be randomized because of an absolute contraindication to thrombolytics.

Randomization was 1:1 and stratified by a VTE-BLEED score ≥2 (higher bleeding risk) or <2 (lower bleeding risk).[19–21] After completion of data entry of baseline patient information in the electronic data capture system, stratification and randomization occurred automatically, and the assignment was provided to the site electronically through the system. The original study protocol required ≥35% of patients to have a VTE-BLEED score ≥2; however, this requirement was removed by protocol amendment because of lower-than-expected enrollment of patients with elevated scores. Participants were followed up at 24 hours (±8 hours), hospital discharge, and at 30 days (+15 days). Postprocedural imaging was performed at the 24-hour visit; the specific modality (echocardiography or CTPA) was not mandated but was required to match that used for baseline RV assessment.

Treatment Strategies and Rationale

Permitted LBMT and CDT treatment strategies have been described previously.[18] Briefly, patients in the LBMT arm underwent aspiration/mechanical thrombectomy using the FlowTriever System (Inari Medical, Irvine, CA). Patients in the CDT arm underwent thrombolysis treatment per local standard for device selection and thrombolytic dosing. Devices included ultrasound-facilitated CDT (EKOS Endovascular System, Boston Scientific, Marlborough, MA), standard side-hole CDT (Cragg-McNamara Micro Therapeutics Infusion Catheter, Medtronic, Dublin, Ireland), standard side-slit CDT (Uni-Fuse Infusion Catheter, AngioDynamics, Latham, NY), pharmacomechanical CDT (BASHIR Endovascular Catheter, Thrombolex, New Britain, PA), and gradient side-hole CDT (Fountain Infusion Systems, Merit Medical, South Jordan, UT). Given the lack of clinical standards in the method or duration of delivery of local thrombolytics and the changing paradigm with multiple catheters on the market, the CDT arm was not standardized in an effort to simulate the most up-to-date clinical practice in experienced centers. The location of postprocedural care was determined by the treating team.

The PEERLESS study design did not include an anticoagulation treatment arm, the guideline-recommended front-line treatment for intermediate-risk PE. The aim of the study was to provide data on the comparability of interventional strategies after the decision to intervene was made by the treating physician or pulmonary embolism response team. Currently, the decision to use catheter-directed intervention is individualized and complex. The rationale for creating this RCT framework was to understand treatment risks and value between thrombolytic and nonthrombolytic strategies for patients undergoing catheter-directed intervention for the treatment of PE in current clinical practice.

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Analysis Population

All safety and effectiveness analyses were performed according to the modified intention-to-treat principle, including data from all randomized participants who were subsequently enrolled. The point of enrollment was when the therapeutic catheter entered the body.

End Points

The primary end point was a hierarchal win ratio composite[22] of the following clinical outcomes assessed at the sooner of discharge or 7 days after the procedure: (1) all-cause mortality, (2) ICH, (3) major bleeding per International Society for Thrombosis and Haemostasis definition,[23] (4) clinical deterioration and/or escalation to bailout therapy, and (5) postprocedural intensive care unit (ICU) admission and length of stay. Postprocedural ICU use was characterized hierarchically as follows: (1) no ICU admission, (2) admission lasting between 0 and 24 hours, and (3) admission lasting >24 hours. The first 4 components of the primary end point were evaluated in a win ratio as a secondary end point. Clinical deterioration consisted of objective worsening of hemodynamic or respiratory status meeting specific definitions for severity and duration described in the Supplemental Material. When determining the need for escalation to bailout therapy, treating physicians considered the patient's condition and documented the specific precipitating event(s) in the study records. All site-reported bailout events were then adjudicated by the clinical events committee to confirm the justification for therapy escalation. Specific precipitating events preceding escalation to bailout therapy included the following: persistent elevated respiratory rate; ongoing or increased requirement for supplemental oxygen; persistent or new-onset tachycardia; sustained or sudden bradycardia; sudden or persistent hypotension (not associated with a vagal episode) or signs of end-organ hypoperfusion; hemodynamic worsening or lack of hemodynamic improvement; lack of improved lung perfusion or inadequate thrombus resolution; and new-onset, persistent, or worsening symptoms of PE. Full end-point definitions and descriptions of objective clinical deterioration thresholds and therapy escalation triggers are included in the Supplemental Material.

Additional secondary end points included each component of the primary end point assessed individually; clinically relevant nonmajor bleeding per International Society for Thrombosis and Haemostasis definition[23] and minor bleeding events (any bleeding not classified as major or clinically relevant nonmajor bleeding per International Society for Thrombosis and Haemostasis definition) at discharge (maximum, 7 days); change in RV/left ventricle ratio from baseline to 24-hour visit; modified Medical Research Council (mMRC) dyspnea scores at the 24-hour and 30-day visits; Pulmonary Embolism Quality of Life and EuroQol 5-Dimension 5-Level scores at the 30-day visit; device- and drug-related serious adverse events through the 30-day visit; PE-related readmissions, all-cause readmissions, and all-cause mortality within 30 days; and total and postprocedural hospital length of stay. Exploratory assessments included estimated residual thrombus in treated vessel(s) and reduction in mean pulmonary artery pressure after treatment; heart rate, respiratory rate, and echocardiographic RV function at the 24-hour visit; and New York Heart Association (NYHA) heart failure classification and modified Borg dyspnea scores at rest at the 24-hour and 30-day visits. A blinded reviewer assessed the change in RV/left ventricle ratio using the same imaging modality (CTPA or echocardiogram) at both time points and determined categorization of RV dysfunction severity by visual assessment of ventricular wall motion following American Society of Echocardiography guidelines.[24] Symptom scores on mMRC, Pulmonary Embolism Quality of Life, EuroQol 5-Dimension 5-Level, NYHA, and Borg scales were assessed with structured questionnaires.

Win Ratio and Statistical Analysis

Win ratio is a generalized pairwise comparison method of evaluating a composite end point to determine treatment effect.[22] The primary advantage of a win ratio approach is the ability to rank the outcomes included in the composite by clinical importance and to assess them in a hierarchical manner. This is completed by comparing each patient treated with LBMT to each patient treated with CDT and assigning a result (LBMT winner, CDT winner, or tie) to the individual patient pairings. A winner is established by comparing the prioritized outcomes sequentially, meaning if neither patient experiences the first outcome (all-cause mortality), then the second outcome (ICH) is assessed and so on. The comparison terminates when a winner is established. The win ratio is calculated by dividing the number of LBMT winners by the number of CDT winners. Pairwise comparisons that terminate in a tie are not included in the win ratio calculation.

The win ratio end points were evaluated with a modified generalized Wilcoxon test[25] to examine performance differences between arms. The minimum sample size was determined to be 432 patients by requiring ≥80% power with a 1-sided α of 2.5% for the primary end point. The actual sample size was set at 550 patients to account for attrition. Site intracluster correlation was not accounted for in the power analysis, but analysis determining whether pooling across sites was appropriate based on random-effects modeling was planned (poolability analysis). Random-effects modeling using the inverse variance method was used to assess heterogeneity between sites in terms of the primary end point. This is done by using sites as the random effect and further quantifying the heterogeneity in terms of the Higgin and Thompson I^2 index for each arm. This analysis failed to reject the null hypothesis of no heterogeneity by site (P=0.94).

The statistical analysis plan specified 1-sided P values; however, 2-sided P values are reported to reflect the more conservative approach commonly used in RCTs. The remaining end points were compared using P values derived from Wilcoxon rank-sum tests with continuity correction for continuous variables and Fisher's exact tests for categorical variables. Details on the statistical methods related to controlling multiplicity can be found in the Supplemental Material. Statistical analyses were performed with SAS version 9.4 (Cary, NC).

RESULTS

Patients

In total, 599 patients underwent randomization, 550 of whom were enrolled and treated with LBMT (n=274) or CDT (n=276) at 57 sites in 3 countries between February 2022 and February 2024. Figure S1 shows progression of participants through the study and accounts for all 49

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postrandomization exclusions, 35 (71.4%) of which were attributable to the prespecified systolic pulmonary artery pressure requirement. A total of 142 patients with contraindications to thrombolytics (Table S1) were enrolled into the parallel nonrandomized registry.

Baseline characteristics are presented in Table 1. The mean age was 63.7 years for patients treated with LBMT and 61.2 years for those treated with CDT, and 54.4% and 51.4% were male, respectively. Elevated cardiac troponin levels were observed in 94.7%, indicating intermediate-high-risk PE per European Society of Cardiology guidelines.[5] Ultimately, 26.4% of patients had a VTE-BLEED score ≥2. Relative contraindications to thrombolytics (Table S2) were present in 4.2% of the randomized population. At baseline, 95.3% of patients in the LBMT arm and 96.7% of patients in the CDT arm were receiving parenteral anticoagulation with unfractionated heparin or low-molecular-weight heparin, with most patients receiving unfractionated heparin (80.7% and 85.5%, respectively). The time from study hospital presentation to treatment catheter insertion was similar between the LBMT and CDT arms (22.3±17.7 and 24.9±19.7 hours, respectively; P=0.08).

Procedural characteristics and periprocedural outcomes are reported in Table 2. All LBMT procedures were performed with common femoral or femoral vein access, whereas 35.1% of CDT cases were performed with jugular vein access. In the CDT arm (Table 3), bilateral catheters were used in 92.0% of patients, median total tissue-type plasminogen activator (tPA) dose was 16.0 mg (interquartile range, 12.0–24.0), and the median tPA infusion duration was 12.0 hours per lung (interquartile range, 6.0–15.6). Most tPA infusions were administered at a rate of 0.5 to 1.0 mg/h per lung (95.9%), for a duration of 6 to 24 hours (90.8%). Ultrasound-facilitated CDT was used in 59.8% of patients in the CDT arm, followed by standard side-hole CDT in 23.2% and standard side-slit CDT in 8.7%.

Win Ratios and Components

The primary end point significantly favored LBMT over CDT (Figure 1), with a corresponding win ratio of 5.01 (95% CI, 3.68–6.97; P<0.001). There were statistically significant differences in 2 of the 5 components of the primary end point: (1) a lower rate of clinical deterioration and/or escalation to bailout with LBMT compared with CDT (1.8% versus 5.4%; P=0.04); and (2) less postprocedural ICU use (P<0.001), including fewer admissions (41.6% versus 98.6%) and stays >24 hours (19.3% versus 64.5%). There were no significant differences in all-cause mortality (0.0% versus 0.4%; P=1.00), ICH (0.7% versus 0.4%; P=0.62), or major bleeding (6.9% versus 6.9%; P=1.00) or in the 4-component win ratio (1.34 [95% CI, 0.78–2.35]; P=0.30). Pairwise comparisons in the hierarchical win ratio end points are shown in Figure S2.

Table 1. Baseline and Preprocedural Characteristics

	LBMT (n=274)	CDT (n=276)
Age, y	63.7±13.0	61.2±14.8
Male sex	149 (54.4)	142 (51.4)
Race and ethnicity*		
White race	184 (72.4)	193 (74.5)
Black or African American race	67 (26.4)	56 (21.6)
Other races	3 (1.2)	10 (3.9)
Hispanic or Latino ethnicity	13 (5.2)	27 (10.8)
Body mass index, kg/m^2	34.5±8.6	36.3±9.4†
History of cancer	56 (20.4)	56 (20.3)
Active cancer	13 (4.7)	17 (6.2)
Prior pulmonary embolism	41 (15.0)	31 (11.2)
History of pulmonary hypertension	6 (2.2)	5 (1.8)
Prior deep vein thrombosis	60 (21.9)	58 (21.0)
Concomitant deep vein thrombosis	178 (65.0)	168 (60.9)
History of bleeding	5 (1.8)	9 (3.3)
Anemia	21 (7.7)	27 (9.8)
Renal dysfunction (CrCL 30–60 mL/min)	43 (15.7)	45 (16.3)
Relative contraindication to thrombolytics	12 (4.4)	11 (4.0)
VTE-BLEED score	1.55±1.30	1.56±1.31
≥2	68 (24.8)	77 (27.9)
<2	206 (75.2)	199 (72.1)
sPESI score	1.3±1.1†	1.3±1.1
0	70 (25.6)†	63 (22.8)
≥1	203 (74.4)†	213 (77.2)
Duration of symptoms, d	2.9±2.8	3.5±3.3
Elevated cardiac troponin levels‡	256 (93.4)	265 (96.0)
Pulmonary embolism location at screening		
Saddle	104 (38.0)	109 (39.5)
Right main pulmonary artery	184 (67.2)	190 (68.8)
Left main pulmonary artery	165 (60.2)	166 (60.1)
Right lobar	152 (55.5)	148 (53.6)
Left lobar	138 (50.4)	144 (52.2)
Right segmental	116 (42.3)	136 (49.3)
Left segmental	107 (39.1)	133 (48.2)
Right bundle-branch block	39 (14.2)	36 (13.0)
Heart rate, bpm	107.2±17.1	111.6±20.2
Respiratory rate, rpm	22.2±6.7	22.4±5.9†
Systolic blood pressure at diagnosis, mm Hg	134.0±22.4	132.1±21.7
Diastolic blood pressure at diagnosis, mm Hg	83.8±14.7	84.1±14.7
mMRC dyspnea score§		
0	16 (5.9)	12 (4.4)
1	23 (8.5)	17 (6.2)
2	37 (13.7)	39 (14.3)
3	87 (32.1)	79 (28.9)
4	108 (39.9)	126 (46.2)

(*Continued*)

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Table 1. Continued

	LBMT (n=274)	CDT (n=276)
NYHA class§		
I	26 (9.6)	19 (7.0)
II	54 (19.9)	51 (18.7)
III	122 (44.9)	127 (46.5)
IV	70 (25.7)	76 (27.8)
Modified Borg dyspnea score§	3.12±2.63	3.32±2.58
RV/LV ratio (CTPA or echocardiogram)§	1.27±0.26	1.31±0.27
RV function on echocardiogram§		
Normal	1 (0.6)	0 (0.0)
Mildly reduced	13 (7.3)	11 (6.4)
Moderately reduced	42 (23.6)	41 (24.0)
Severely reduced	122 (68.5)	119 (69.6)
Parenteral anticoagulation use at baseline		
UFH and/or LMWH	261 (95.3)	267 (96.7)
UFH	221 (80.7)	236 (85.5)
LMWH	25 (9.1)	24 (8.7)
UFH and LMWH	15 (5.5)	7 (2.5)
Another parenteral agent	0 (0.0)	1 (0.4)
None	13 (4.7)	8 (2.9)
Time from study hospital presentation to treatment catheter insertion, h§	22.3±17.7	24.9±19.7
mPAP, mm Hg§	30.0±7.6	31.1±7.2

Values are reported as mean±SD or number (percentage). CDT indicates catheter-directed thrombolysis; CrCL, creatinine clearance; CTPA, computed tomography pulmonary angiogram; LBMT, large-bore mechanical thrombectomy; LMWH, low-molecular-weight heparin; LV, left ventricle; mMRC, modified Medical Research Council; mPAP, mean pulmonary artery pressure; NYHA, New York Heart Association; rpm, respirations per minute; RV, right ventricle; sPESI, Simplified Pulmonary Embolism Severity Index; and UFH, unfractionated heparin.

*Patient-reported race was unavailable for 20 patients (7.3%) in the LBMT arm and 17 patients (6.2%) in the CDT arm. Other race category includes patients self-reporting as American Indian or Alaska Native, Asian, "other" race, or multiple races. Reported ethnicity was unavailable for 25 patients (9.1%) in the LBMT arm and 26 patients (9.4%) in the CDT arm.

†Assessment missing for 1 patient.

‡For subjects enrolled before protocol version 3.0, elevated cardiac troponin levels were required.

§Calculations based on non-missing values (missingness: mMRC dyspnea score, LBMT n=3 and CDT n=3; NYHA classification, LBMT n=2 and CDT n=3; modified Borg dyspnea score, LBMT n=0 and CDT n=2; RV/LV ratio, LBMT n=12 and CDT n=16; RV function on echocardiogram, LBMT n=96 and CDT n=105; time from study hospital presentation to treatment catheter insertion, LBMT n=3 and CDT n=5; and mPAP, LBMT n=0 and CDT n=6).

Table 2. Procedural Characteristics and Periprocedural Outcomes

	LBMT (n=274)	CDT (n=276)
Procedure time, min*	93.2±36.1	65.3±42.5
Fluoroscopy duration, min	21.5±14.2	10.1±6.6†
Treatment catheter dwell time, min‡	47.9±27.2	915.7±464.7†
Anesthesia used§		
Local	65 (23.7)	62 (22.5)
Local with sedation	217 (79.2)	218 (79.0)
General	2 (0.7)	3 (1.1)
Right access site of study device§		
Common femoral or femoral vein	265 (96.7)	171 (62.0)
Jugular vein	0 (0.0)	97 (35.1)
Other	1 (0.4)	4 (1.4)
Left access site of study device§		
Common femoral or femoral vein	9 (3.3)	25 (9.1)
Jugular vein	0 (0.0)	2 (0.7)
Other	0 (0.0)	1 (0.4)
Estimated blood loss, mL	87.7±87.6†	14.4±22.2†
Blood return used, mL	239 (87.2)	…
Estimated blood loss with blood return	79.7±76.1†	…
Estimated blood loss without blood return	149.8±136.3†	…
Estimated residual thrombus in treated vessels, %¶	16.2±15.7	29.6±29.3
Reduction in mPAP, mm Hg‖	5.9±6.3	3.6±7.2

Values are reported as mean±SD or number (percentage).

CDT indicates catheter-directed thrombolysis; LBMT, large-bore mechanical thrombectomy; and mPAP, mean pulmonary artery pressure.

*Procedure time measured from venous access time to the time of exit from index procedure room; LBMT n=272 and CDT n=274.

†Fluoroscopy duration (CDT n=273), treatment catheter dwell time (CDT n=271), estimated blood loss (LBMT n=245 [89.4%] vs CDT n=228 [82.6%]).

‡Treatment catheter dwell time measured from treatment catheter insertion time to treatment catheter removal time; LBMT n=272 and CDT n=269.

§Percentages do not sum to 100% because categories are not mutually exclusive.

¶Estimated residual thrombus was an optional site-entered periprocedural assessment collected in a limited number of patients (LBMT n=242 [88.3%] and CDT n=95 [34.4%]); exploratory comparison suggests a lower percentage of residual thrombus with LBMT vs CDT ($P<0.001$).

‖Reduction in mPAP from before to after the procedure was an optional periprocedural assessment collected in a limited number of patients (measured on table for LBMT n=247 [90.1%] and measured after 6 hours for CDT n=45 [16.3%]); exploratory comparison suggests a greater reduction in mPAP after LBMT vs CDT ($P=0.03$).

Clinical Deterioration and Therapy Escalation Events

There was a significantly lower rate of clinical deterioration and/or escalation to bailout therapy with LBMT compared with CDT (1.8% versus 5.4%; $P=0.04$). Clinical deterioration and therapy escalation events are summarized in Table 4. Among the 5 patients (1.8%) in the LBMT arm who experienced this end point, 4 (1.5%) had deteriorations and 1 (0.4%) underwent bailout; among the 15 patients (5.4%) in the CDT arm, 10 (3.6%) had deteriorations and 6 (2.2%) underwent bailout. In the LBMT arm, all deteriorations occurred during the index procedure and were resolved the same day, including 3 cases of hypotension and 1 case of increased oxygen requirement. In the CDT arm, all deteriorations or escalation events began after the index procedure, starting an average of 2.1±1.7 days after CDT initiation. The adjudicated CDT deteriorations included 2 cardiac arrests, 1 high-grade atrioventricular block, 3 cases of respiratory failure, and 4 cases of hypotension (1 of which required extracorporeal membrane oxygenation initiation). Five patients treated with CDT at 4 study sites underwent

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Table 3. Devices and Thrombolytic Agents Used in Patients Treated With CDT

Characteristics	CDT (n=276)
CDT system used	
Ultrasound-facilitated CDT	165 (59.8)
Standard side-hole CDT	64 (23.2)
Standard side-slit CDT	24 (8.7)
Other*	15 (5.4)
>1 Device type used†	8 (2.9)
Location of CDT catheter(s)	
Bilateral	254 (92.0)
Unilateral right	21 (7.6)
Unilateral left	1 (0.4)
Single catheterization laboratory session	252 (91.3)
Thrombolytic agent used	
tPA	266 (96.4)
tPA+other‡	8 (2.9)
Other‡	2 (0.7)
Total tPA dose per patient, mg§	16.0 (12.0, 24.0)
tPA infusion rate per lung, mg/h‖	1.0 (0.5, 1.0)
tPA infusion rate per lung, mg/h‖	
<0.5	14 (3.0)
0.5–1.0	448 (95.9)
>1.0	5 (1.1)
tPA infusion duration per lung, h‖	12.0 (6.0, 15.6)
tPA infusion duration per lung, h‖	
<6	26 (5.6)
6–12	291 (62.3)
>12–24	133 (28.5)
>24	17 (3.6)

Values are reported as median (quartile 1, 3) or number (percentage).

CDT indicates catheter-directed thrombolysis; and tPA, tissue-type plasminogen activator.

*Other devices include pharmacomechanical CDT catheter (n=12) and gradient side-hole CDT catheter (n=3).

†All 8 cases were completed at one study site that uses a standard side-hole catheter in combination with a pharmacomechanical CDT catheter.

‡Other thrombolytic agent was not captured.

§Total tPA dose is reported for 261 patients who received tPA only and includes amount used during all catheterization laboratory sessions.

‖Treated lungs (n=467) for 242 CDT patients who received only tPA and one infusion per catheter with nonmissing data.

successful bailout with LBMT. At the time of reintervention, all had completed CDT treatment with a total tPA dose of 12 to 20 mg. The remaining patient in the CDT arm who underwent bailout and the one patient in the LBMT arm who underwent bailout each had multiple unsuccessful bailout attempts and ultimately died after >7 days.

Bleeding Events

There were no statistically significant differences in ICH (0.7% versus 0.4%; *P*=0.62) or major bleeding (6.9% versus 6.9%; *P*=1.00) for patients treated with LBMT compared with CDT. There were 19 patients (6.9%) with 21 major bleeding events (2 patients with 2 events) in each arm. Adjudications per International Society for Thrombosis and Haemostasis criteria for patients treated with LBMT versus CDT were as follows: (1) fatal bleeding (0 versus 1), (2) symptomatic bleeding in a critical area or organ (2 versus 2), and (3) bleeding causing a fall in hemoglobin level (≥2 g/dL or 1.24 mmol/L) or leading to transfusion of ≥2 U (17 versus 16). The fatal bleed in the CDT arm occurred in a patient with thrombolytic- and anticoagulation-related intra-abdominal hematomas who died of hemorrhagic shock on postprocedural day 5. ICH accounted for 3 of the 4 cases of major bleeding in a critical area. In the LBMT arm, 1 ICH was a cerebral hemorrhage on postprocedural day 1 in a patient who had a fall with minor head trauma before treatment; the other ICH event was an ischemic stroke with hemorrhagic conversion occurring on postprocedural day 2; both events were adjudicated as anticoagulation related. In the CDT arm, the 2 major bleeds in critical areas were adjudicated as thrombolytic and anticoagulation related, occurred on postprocedural day 1, and included one patient with cerebral hemorrhage and one patient with knee hemarthrosis.

Among patients with adjudicated reason for major bleeding attributed to meeting the above thresholds for fall in hemoglobin or transfusion, the vascular access site was the most common source of bleeding for both arms (8 of 17 [47.1%] patients in the LBMT arm, 10 of 16 [62.5%] patients in the CDT arm). Among these same patients, transfusions were given to 1 of 17 patients (5.9%) treated with LBMT (2 units) and 8 of 16 patients (50.0%) treated with CDT (3.3±1.8 units). There was no significant difference in rates of clinically relevant nonmajor bleeding (2.6% versus 3.3%; *P*=0.80) or minor bleeding (2.2% versus 0.4%; *P*=0.07) for LBMT (n=274) compared with CDT (n=275).

Effectiveness at the 24-Hour Visit

Functional and imaging assessments at the 24-hour visit are shown in Figure 2. At the 24-hour visit, fewer patients treated with LBMT compared with CDT had mMRC dyspnea scores of 3 or 4 (13.5% versus 26.4%; *P*<0.001), NYHA classifications of III or IV (16.3% versus 27.4%; *P*=0.002), or moderately or severely reduced RV function on echocardiogram (42.1% versus 57.9%; *P*=0.004). Mean respiratory rate (18.3±3.3 versus 20.1±5.1; *P*<0.001) and modified Borg dyspnea scores (0.81±1.36 versus 0.99±1.35; *P*=0.03) were lower for patients in the LBMT arm compared with those in the CDT arm. Mean reduction in the RV/left ventricle ratio on CTPA or echocardiogram from baseline (0.32±0.24 versus 0.30±0.26; *P*=0.55) and mean heart rate at the 24-hour visit (83.2±13.3 bpm versus 83.9±14.6 bpm; *P*=0.86) were similar with LBMT compared with CDT.

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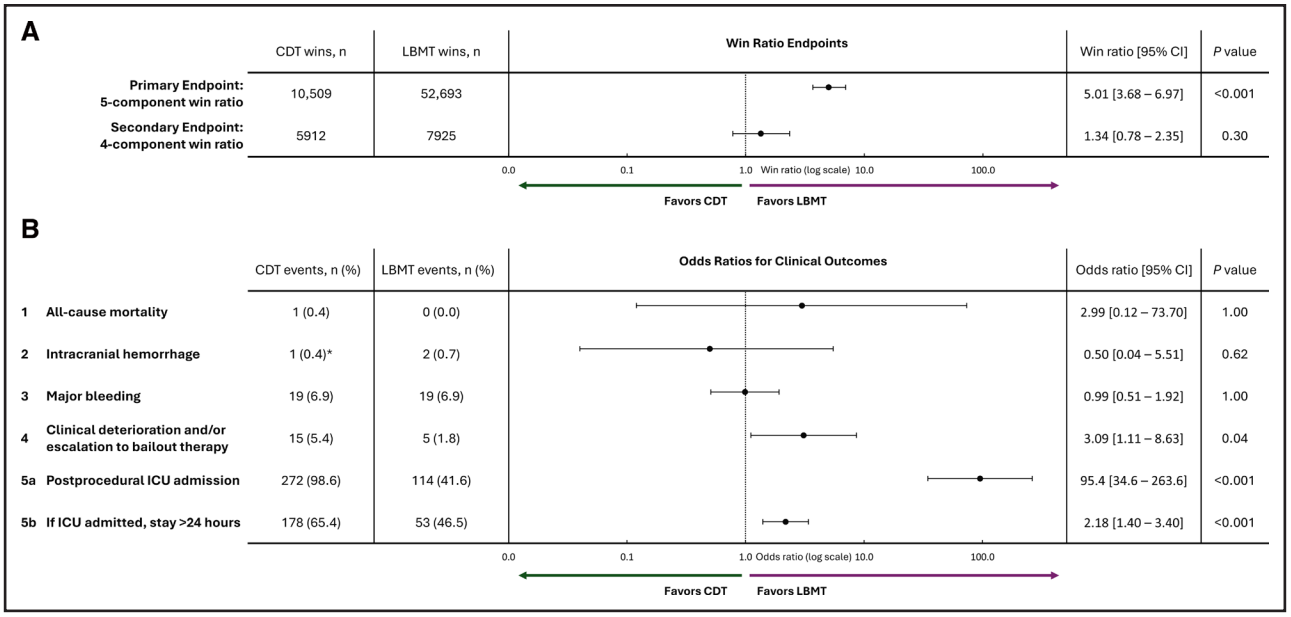

Figure 1. Win ratio end points and odds ratios for the win ratio components.
Shown are the primary and secondary win ratio end points (**A**) and the odds ratios for the clinical outcome components of the win ratios (**B**), assessed at the sooner of discharge or 7 days after the procedure. *P* values for the win ratio end points are derived with a modified generalized Wilcoxon test (F-S test), and *P* values for clinical outcomes of the win ratio are derived from the 2-sided Fisher exact test. Odds ratios and 95% Wald CIs are calculated with large-bore mechanical thrombectomy (LBMT) as the reference. *N=275 because of 1 death. CDT indicates catheter-directed thrombolysis; and ICU, intensive care unit.

ICU Use and Hospital Lengths of Stay

LBMT was associated with significantly less postprocedural ICU use compared with CDT (Figure 3). In the LBMT arm, 19.3% of patients were admitted to the ICU for stays >24 hours compared with 64.5% in the CDT arm ($P<0.001$). The average length of postprocedural ICU stay was 14.2±25.4 hours in the LBMT arm versus 39.3±28.0 hours in the CDT arm ($P<0.001$). Lengths of total hospital stay (4.5±2.8 overnights versus 5.3±3.9 overnights; $P=0.002$) and postprocedural hospital stay (3.2±2.7 days versus 4.0±3.7 days; $P<0.001$) were significantly shorter with LBMT compared with CDT.

Outcomes Through the 30-Day Visit

Secondary end points through the 30-day visit are reported in Table 5. There were no differences in mean modified Borg dyspnea score (0.38±1.05 versus 0.38±0.88; $P=0.55$) or the distributions of mMRC dyspnea score ($P=0.47$) and NYHA classification ($P=0.45$), with 53.1% versus 54.3% having an mMRC score of 0 and 63.8% versus 60.8% being NYHA class I. Average Pulmonary Embolism Quality of Life scores (19.33±18.91 versus 20.42±19.95; $P=0.64$) and EuroQol 5-Dimension 5-Level scores (0.829±0.218 versus 0.817±0.237; $P=0.99$) were similar for LBMT and CDT. A similar proportion of patients treated with LBMT and patients treated with CDT experienced device- and/or drug-related serious adverse events through the 30-day visit (13.3% versus 11.5%; $P=0.59$). A complete listing of all adjudicated treatment-related serious adverse events is provided in Table S3. All-cause mortality within 30 days of treatment was similar with LBMT compared with CDT (0.4% versus 0.8%; $P=0.62$). There were significantly fewer all-cause readmissions within 30 days after LBMT compared with CDT (3.2% versus 7.9%; $P=0.03$), whereas the number of PE-related readmissions was similar (0.0% versus 0.8%; $P=1.00$).

DISCUSSION

The PEERLESS study is the first RCT to evaluate the treatment effect of LBMT and the first to directly compare different primary interventional strategies in the acute intermediate-risk PE population. The win ratio primary end point of in-hospital adverse clinical outcomes and ICU use occurred significantly less often with LBMT compared with CDT. This finding favoring LBMT stemmed from the last 2 components of the composite primary end point: (1) significantly lower rates of clinical deterioration and/or escalation to bailout therapy, and (2) significantly less frequent ICU admissions and shorter postprocedural ICU lengths of stay, with no significant differences in in-hospital mortality, ICH, or major bleeding between arms.

In 2014, the PEITHO trial (Pulmonary Embolism Thrombolysis) showed that reperfusion with systemic fibrinolysis reduced early hemodynamic decompensation in patients with intermediate-risk PE compared with

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Table 4. Adjudicated Clinical Deterioration and Bailout Events

	LBMT (n=274)	CDT (n=276)
Clinical deterioration and/or escalation to bailout	5 (1.8)	15 (5.4)
Patients with clinical deterioration	4 (1.5)	10 (3.6)
Cardiac arrest	0 (0.0)	2 (0.7)
High-grade atrioventricular block	0 (0.0)	1 (0.4)
Respiratory failure	0 (0.0)	3 (1.1)
Increased oxygen requirement	1 (0.4)	0 (0.0)
Hypotension	3 (1.1)	4 (1.4)
Patients with escalation to bailout	1 (0.4)	6 (2.2)*
Patients with successful bailout†	0 (0.0)	5 (1.8)
Reason(s) for bailout		
Respiratory symptoms and inadequate thrombus resolution	0 (0.0)	3 (1.1)
Respiratory symptoms and hemodynamic worsening	0 (0.0)	1 (0.4)
Inadequate thrombus resolution	0 (0.0)	1 (0.4)
Patients with unsuccessful bailout‡	1 (0.4)	1 (0.4)
Reason(s) for bailout		
Hemodynamic worsening, hypotension, respiratory symptoms, and inadequate thrombus resolution, with/without tachycardia	1 (0.4)	1 (0.4)
Patients with clinical deterioration and/or escalation to bailout events leading to death§	1 (0.4)	2 (0.7)
Time to first clinical deterioration and/or escalation to bailout event, overnights	0.0±0.0	2.1±1.7

Values are reported as mean±SD or number (percent).

CDT indicates catheter-directed thrombolysis; LBMT, large-bore mechanical thrombectomy; and tPA, tissue-type plasminogen activator.

*n=275.

†Five patients in the CDT arm underwent successful bailout treatment with LBMT.

‡One patient in each arm had a pulmonary embolism that could not be treated after multiple bailout attempts and ultimately died after >7 days. The patient treated with LBMT had 3 bailout events (1 systemic tPA, 1 LBMT, and 1 CDT) after the index LBMT procedure was aborted and ultimately died on day 11. The patient treated with CDT experienced cardiac arrest after removal of the index CDT treatment catheter, received 19 minutes of cardiopulmonary resuscitation, was intubated, and had 2 bailout events (1 systemic tPA and 1 LBMT+CDT), in addition to venoarterial extracorporeal membrane oxygenation salvage therapy, before ultimately dying on day 10.

§The remaining death in the CDT arm occurred in a patient who experienced clinical deterioration (cardiac arrest/hemorrhagic shock on day 5) secondary to a thrombolytic- and anticoagulation-related major bleed (multiple large intra-abdominal hematomas).

anticoagulation alone, albeit at the cost of increased major bleeding.[9] Since PEITHO, studies of catheter-directed interventions have reported various measures of short- and long-term effectiveness[15–17,26,27]; however, no randomized trials have examined the incidence of in-hospital decompensation and therapy escalation for different interventional strategies. In PEITHO, the rate of hemodynamic decompensation within 7 days was 1.6% with tenecteplase plus heparin versus 5.0% with heparin alone (P=0.002). In PEERLESS, the rates of clinical deterioration and/or escalation to bailout were 1.8% with LBMT and 5.4% with CDT (P=0.04), with an equivalent rate of major bleeding (6.9% versus 6.9%; P=1.00). This suggests that LBMT may reduce deterioration and the need for reintervention through more effective early thrombus resolution without incurring any greater risk for major bleeding.

In addition to significant differences in event rates, there were notable contrasts in the nature and timing of clinical deterioration and bailout events between the arms. In the CDT arm, there were no intraprocedural deteriorations, with all events starting after CDT initiation. In the LBMT arm, all deteriorations were managed in the interventional suite and resolved on the day of procedure. Clinical deteriorations in the LBMT arm were clinically less severe with no instances of cardiac arrest, high-grade heart block, or respiratory failure. In terms of therapy escalation events, the study was designed in a pragmatic manner to allow treating physicians to consider each patient's holistic clinical status before determining whether bailout was necessary. Relatively few patients ultimately underwent bailout, representing only ≈1% of the total randomized cohort. Nearly every patient whose therapy was escalated had multiple clinical symptoms precipitating the need for bailout, including both clinical and imaging rationale. Because posttreatment computed tomography imaging was not mandated by the study protocol and was not part of routine postprocedural care at many sites, it is likely that patients whose therapy was escalated on the basis of imaging findings had a follow-up computed tomography ordered by their care team because they were not improving as expected after intervention. Although therapy escalation events were corroborated by the independent clinical events committee, this is nonetheless a possible source of bias in the trial.

The second component driving the hierarchal primary end point outcome was the significantly lower ICU use with LBMT, which is perhaps an intuitive outcome given that many hospital protocols require ICU monitoring for patients undergoing thrombolysis. We acknowledge that the ICU use outcomes may therefore be less impactful for informing clinical practice than other secondary end points evaluated in this trial. Nevertheless, ICU use trends among patients receiving different interventional therapies for intermediate-risk PE have not previously been evaluated in a large randomized trial. Previous retrospective studies have reported mixed results when attempting to compare ICU length of stay between these 2 therapies.[13,14] Although the significantly shorter post-procedural and total hospital stays reported for LBMT may have been driven at least partially by local standards for ICU monitoring of patients treated with CDT, the less frequent deterioration and/or bailout events and signals of earlier recovery after LBMT may also have contributed. Regardless of whether the underlying cause for ICU admission stemmed from standard hospital protocol

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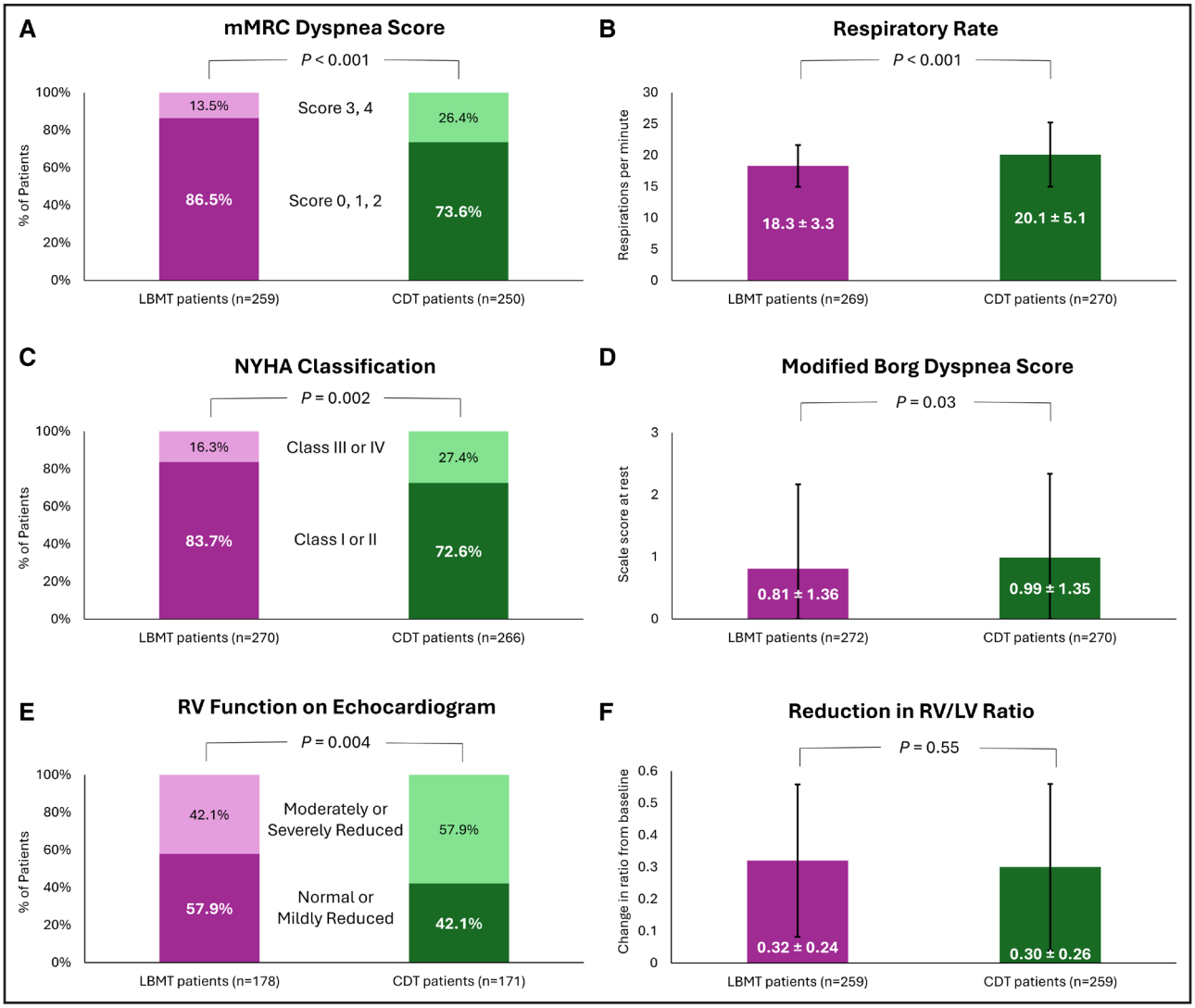

Figure 2. Functional and imaging assessments at the 24-hour visit.
Assessments at the 24-hour visit included the proportion of patients with a modified Medical Research Council (mMRC) dyspnea score <3 vs ≥3 (**A**), mean respiratory rate (**B**), proportion of patients New York Heart Association (NYHA) class I or II vs class III or IV (**C**), mean modified Borg dyspnea score at rest (**D**), proportion of patients with normal or mildly reduced vs moderately or severely reduced right ventricular (RV) function among those with echocardiograms at baseline and 24-hour visit (**E**), and mean reduction in RV/left ventricle (LV) ratio from baseline based on the same type of imaging (echocardiogram or computed tomography pulmonary angiogram) at baseline and 24-hour visit (**F**). *P* values are derived from the 2-sided Fisher exact test for categorical variables (mMRC score, NYHA classification, and RV function) and from Wilcoxon rank-sum tests with continuity correction for continuous variables (respiratory rate, modified Borg score, and reduction in RV/LV ratio). CDT indicates catheter-directed thrombolysis; and LBMT, large-bore mechanical thrombectomy.

or the need for high-acuity care, postprocedural ICU care is a significant driver of treatment cost and contributes to capacity strain in times of critical ICU bed shortages.[28–30] LBMT may be a resource sparing intervention with significantly lower ICU use, shorter total and postprocedural hospital stays, and fewer readmissions within the first 30 days, although further study is necessary to quantify any potential health economic impacts.

An intriguing outcome of this study is the emergence of significant differences in early recovery between LBMT and CDT at the 24-hour visit, which may suggest differing treatment effects for each therapy based on their mechanisms and anatomic sites of action.[31,32] At the 24-hour visit, a significantly lower proportion of patients in the LBMT arm had a moderate to severe mMRC dyspnea score, moderate to severe NYHA III or IV classification, and moderately or severely reduced RV function on echocardiography. In addition, the mean respiratory rate and modified Borg dyspnea score were lower in the LBMT arm compared with the CDT arm at the 24-hour visit. These findings suggest that the method of thrombus removal may affect outcomes in the acute posttreatment phase and provide a physiological rationale for the lower rate of in-hospital deterioration and/or bailout observed with LBMT. More effective early thrombus resolution may lead to quicker symptomatic and right-sided

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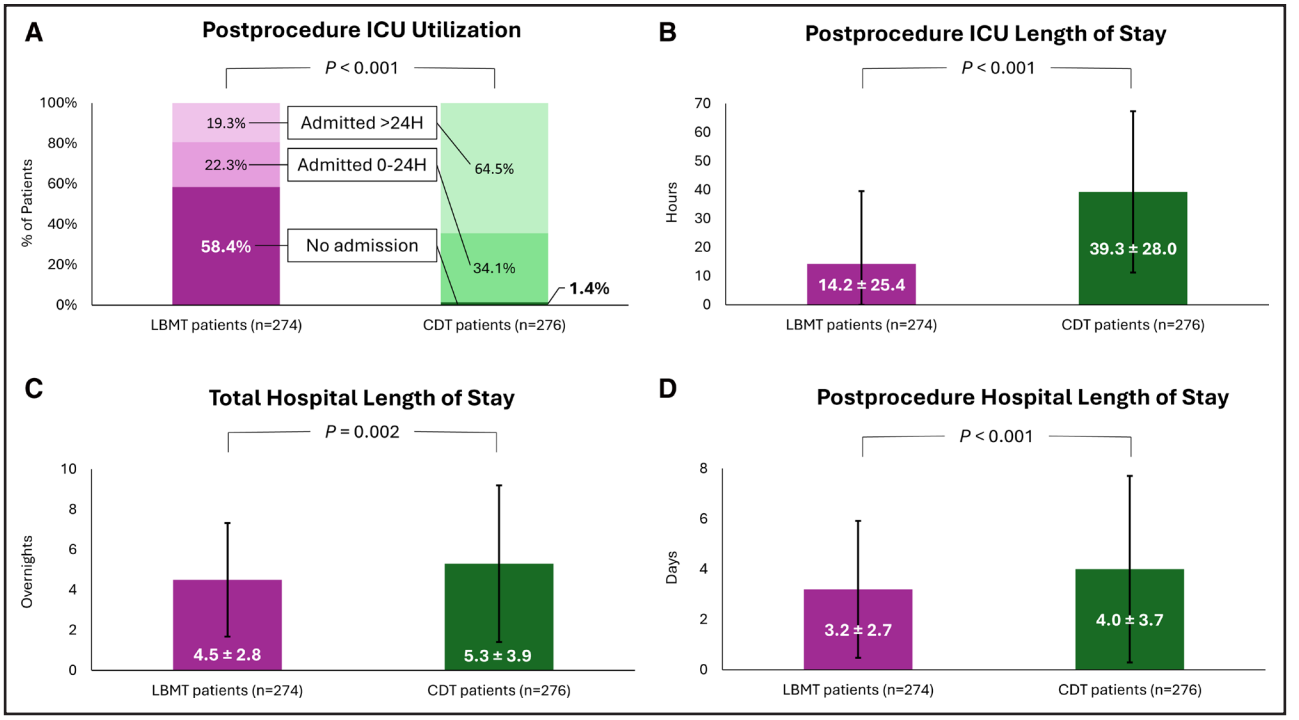

Figure 3. ICU use and length of stays.
Shown is postprocedural intensive care unit (ICU) use (proportion of patients with no ICU admission, ICU admission lasting 0–24 hours, and ICU admission lasting >24 hours; **A**) and the mean postprocedural ICU length of stay in hours among all patients (**B**). ICU length of stay is measured from the end of the index procedure or the time of ICU admission, whichever is later, until the time of an order to discharge from the ICU or transfer to a standard or lower-acuity unit. Total hospital length of stay is reported by number of overnights (**C**); postprocedural hospital length of stay is reported in days (**D**). *P* values are derived from the 2-sided Fisher exact test for categorical variables (postprocedural ICU admission) and from Wilcoxon rank-sum tests with continuity correction for continuous variables (postprocedural ICU, postprocedural hospital, and total hospital lengths of stay). CDT indicates catheter-directed thrombolysis; and LBMT, large-bore mechanical thrombectomy.

heart recovery and in turn prevent episodes of deterioration and reintervention. However, the longer-term clinical impact of early recovery is not clear from this study because symptom scores, quality of life assessments, and all-cause mortality were similar by the 30-day visit, although there were significantly fewer all-cause readmissions through 30 days with LBMT.

A positive finding across treatment arms was the overall low rate of all-cause mortality within 30 days of intervention, which was similar for LBMT and CDT (0.4% and 0.8%; *P*=0.62). PEITHO reported a 3.2% 30-day all-cause mortality rate with therapeutic anticoagulation.[9] Furthermore, a meta-analysis reported 2.9% acute mortality in patients with intermediate-risk PE treated with anticoagulation in 8 RCTs.[33] In PEERLESS, 94.7% of patients were classified as having intermediate-high-risk PE, indicating increased risk of early mortality.[5,34] The all-cause mortality rates observed for both interventions were nominally lower than historical reports for medical management, suggesting that this patient population can undergo catheter-based therapy with a low likelihood of mortality. However, although these mortality rates are encouraging for intervention broadly, the relative influence of treatment effect versus patient population on these outcomes remains unknown without comparison against conservative medical management. The lack of comparison with anticoagulation alone as the standard of care for intermediate-risk PE is a major limitation of this study. Several RCTs are investigating this important question, including the ongoing PEERLESS II trial, HI-PEITHO trial (Higher-Risk Pulmonary Embolism Thrombolysis), and PE-TRACT trial (Pulmonary Embolism–Thrombus Removal With Catheter-Directed Therapy).[35–37]

The extent to which clinical outcomes observed in this study can be generalized to the broader PE patient population at large is unknown, especially in terms of ICH and major bleeding outcomes. Despite careful efforts during study design, we were ultimately unable to enroll patients with bleeding risks representative of the PE population encountered in routine practice. Therefore, our ability to draw conclusions about comparative bleeding outcomes is limited. The low prevalence of relative contraindications to thrombolytics (4.2%) and VTE-BLEED scores ≥2 (26.4%), coupled with the brisk rate of enrollment in the nonrandomized LBMT registry for patients with contraindications to thrombolytics (n=142), including 57 (40.1%) who were enrolled because of a condition other than the absolute contraindications prespecified in the study protocol, suggests that clinical equipoise may have

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Table 5. Outcomes Through the 30-Day Visit

	LBMT (n=274)	CDT (n=276)	*P* value
Functional and quality of life assessments at the 30-day visit*			
mMRC dyspnea score			
0	137 (53.1)	138 (54.3)	0.47
1	74 (28.7)	63 (24.8)	
2	28 (10.9)	27 (10.6)	
3	14 (5.4)	23 (9.1)	
4	5 (1.9)	3 (1.2)	
NYHA class			
I	164 (63.8)	152 (60.8)	0.45
II	76 (29.6)	75 (30.0)	
III	16 (6.2)	23 (9.2)	
IV	1 (0.4)	0 (0.0)	
Modified Borg dyspnea score at rest	0.38±1.05	0.38±0.88	0.55
PEmb-QoL score	19.33±18.91	20.42±19.95	0.64
EQ-5D-5L score	0.829±0.218	0.817±0.237	0.99
Patients with SAEs through the 30-day visit			
Device- and/or drug-related SAE	34/256 (13.3)	28/244 (11.5)	0.59
Device-related SAE	19/254 (7.5)	12/240 (5.0)	0.27
Drug-related SAE	31/254 (12.2)	28/244 (11.5)	0.89
Mortality and readmissions within 30 days of the procedure			
All-cause mortality	1/251 (0.4)	2/240 (0.8)	0.62
All-cause readmission	8/251 (3.2)	19/239 (7.9)	0.03
PE-related readmission	0/251 (0.0)	2/239 (0.8)	1.00

Values are reported as mean±SD, number (percentage), or number/total (percentage). *P* values are derived from the 2-sided Fisher exact test for categorical variables (mMRC score, NYHA classification, SAEs, mortality, readmission) and from Wilcoxon rank-sum tests with continuity correction for continuous variables (modified Borg score, PEmb-QoL score, and EQ-5D-5L score).

CDT indicates catheter-directed thrombolysis; EQ-5D-5L; EuroQol 5-Dimension 5-Level questionnaire; LBMT, large-bore mechanical thrombectomy; mMRC, modified Medical Research Council; NYHA, New York Heart Association; PE, pulmonary embolism; PEmb-QoL; Pulmonary Embolism Quality of Life Questionnaire; and SAE; serious adverse event.

*Calculations based on nonmissing values (missingness: mMRC dyspnea score LBMT n=16 and CDT n=22; NYHA classification LBMT n=17 and CDT n=26; modified Borg dyspnea score LBMT n=12 and CDT n=21; PEmb-QoL score LBMT n=14 and CDT n=23; EQ-5D-5L score LBMT n=15 and CDT n=21).

shifted during the study. This observation is consistent with contemporary analyses from real-world administrative databases that report that mechanical thrombectomy is being used in an increasing proportion of acute PE cases at the expense of CDT.[38,39]

There are several limitations to this RCT. First, this was an open-label trial in which participants and investigators were unblinded to treatment. Furthermore, treatment in the CDT arm was not standardized, leading to variable device and thrombolytic dose use; however, the range of total tPA doses, infusion rates, and infusion durations reported in the CDT arm is generally consistent with common CDT therapy protocols,[7,40] and this variability reflects current clinical practice. The CDT arm included patients treated with ultrasound-facilitated CDT and conventional CDT methods. Although the majority of patients in the CDT arm were treated with ultrasound-facilitated CDT, we cannot currently comment on the potential benefit or lack of benefit from ultrasound application. In addition, newer contemporary CDT devices with different mechanisms of action, for example, pharmacomechanical thrombectomy that combines maceration with thrombolytics,[41] may use infusion durations shorter than the median time reported in this study. Trials comparing LBMT with newer catheters with more standard thrombolytic infusion protocols may be necessary in the future. Last, patient follow-up in PEERLESS was limited to clinical and quality of life metrics through the 30-day visit; therefore, long-term outcomes and quantitative assessments of residual pulmonary obstruction are not available. However, longer-term outcomes have been reported separately for LBMT and CDT from other studies.[17,26] Although 30-day all-cause readmissions were significantly lower for LBMT compared with CDT, no other differences were observed between strategies at 30 days; thus, it is unlikely that differences would be observed between study arms at later time points.

Conclusions

PEERLESS met its primary end point, demonstrating a statistically significant win ratio for LBMT compared with CDT for patients with acute intermediate-risk PE. Compared with CDT, LBMT was associated with significantly fewer clinical deteriorations and/or therapy escalations; less postprocedural ICU use; more favorable respiratory rates, symptom scores, and RV function measurements at the 24-hour visit; shorter hospital lengths of stay; and fewer readmissions within 30 days. Mortality rates and observed bleeding profiles were similar between strategies.

ARTICLE INFORMATION

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Supplemental Material

PEERLESS trial site principal investigators
PEERLESS trial site subinvestigators
PEERLESS trial organization and oversight
PEERLESS trial sponsor
Supplemental Methods: eligibility criteria
Supplemental Methods: trial end point definitions
Supplemental Methods: statistical methods controlling for multiplicity
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