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Pharmacomechanical Catheter-Directed Thrombolysis With the Bashir Endovascular Catheter for Acute Pulmonary Embolism

The RESCUE Study

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ABSTRACT

BACKGROUND Catheter-directed thrombolysis (CDT) has been associated with rapid recovery of right ventricular (RV) function. The Bashir catheter was developed for enhanced thrombolysis in large vessels such as the pulmonary arteries (PAs) with lower doses of tissue plasminogen activator (tPA).

OBJECTIVES The aim of this study was to evaluate the efficacy and safety of tPA infused using a pharmacomechanical (PM) CDT device called the Bashir endovascular catheter in patients with intermediate-risk acute pulmonary embolism (PE).

METHODS Patients with symptoms of acute PE with computed tomographic evidence of RV dilatation were enrolled. The Bashir catheter was used to deliver 7 mg tPA into each PA over 5 hours. The primary efficacy endpoint was the core laboratory–assessed change in computed tomographic angiography–derived RV/left ventricular (LV) diameter ratio at 48 hours, and the primary safety endpoint was serious adverse events (SAEs) including major bleeding at 72 hours.

RESULTS At 18 U.S. sites, 109 patients were enrolled. The median device placement time was 15 minutes. At 48 hours after PM-CDT, the RV/LV diameter ratio decreased by 0.56 (33.3%; $P < 0.0001$). PA obstruction as measured by the refined modified Miller index was reduced by 35.9% ($P < 0.0001$). One patient (0.92%) had 2 SAEs: a retroperitoneal bleed (procedure related) and iliac vein thrombosis (device related). Two other procedure-related SAEs were epistaxis and non-access site hematoma with anemia.

CONCLUSIONS PM-CDT with the Bashir endovascular catheter is associated with a significant reduction in RV/LV diameter ratio and a very low rate of adverse events or major bleeding in patients with intermediate-risk acute PE. The notable finding was a significant reduction in PA obstruction with low-dose tPA. (Recombinant tPA by Endovascular Administration for the Treatment of Submassive PE Using CDT for the Reduction of Thrombus Burden [RESCUE]; NCT04248868) (J Am Coll Cardiol Intv 2022;15:2427–2436) © 2022 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

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ABBREVIATIONS AND ACRONYMS

CDT = catheter-directed thrombolysis

CTA = computed tomographic angiography

ITT = intention-to-treat

LV = left ventricular

PA = pulmonary artery

PE = pulmonary embolism

PM = pharmacomechanical

PMT = percutaneous mechanical thrombectomy

RMMI = refined modified Miller index

r-tPA = recombinant tissue plasminogen activator

RV = right ventricular

SAE = serious adverse event

Acute pulmonary embolism (PE) is the third most common cause of cardiovascular morbidity and mortality. Each year it leads to more than 350,000 hospitalizations and more than 100,000 deaths in the United States alone.[1] Advanced therapies such as systemic thrombolysis have been shown to improve mortality and hemodynamic decompensation in patients with intermediate-risk PE; however, this has been associated with major bleeding rates of 10% to 20%, including intracranial hemorrhage rates of 2% to 3%.[2,3] In an effort to mitigate bleeding risk, there has been an impetus for the development of catheter-based thrombus removal therapies such as catheter-directed thrombolysis (CDT) and percutaneous mechanical thrombectomy (PMT). CDT has been shown to more rapidly improve right ventricular (RV)-to-left ventricular (LV) diameter ratio compared with anticoagulation alone.[4,5] However, this therapy has also been associated with major bleeding rates of 4% to 10%, which has been ascribed to anticoagulation plus thrombolytics in patients undergoing invasive procedures.[6,7] Unfortunately, all these CDT studies have used single-lumen infusion catheters, designed for small-diameter vessels.[8] Therefore, these catheters might have needed relatively higher doses of fibrinolytic agents to reduce pulmonary vascular obstruction and restore alveolar perfusion. Recently PMT has been associated with RV/LV diameter ratio reduction in patients with intermediate-risk PE with low rates of major bleeding; however, this therapy has been associated with very modest reductions in pulmonary vascular obstruction (9.3% with the Inari Medical FlowTriever and 11.3% with the Penumbra Indigo catheter).[9,10]

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The Bashir endovascular catheter (Thrombolex) is a new pharmacomechanical (PM) infusion catheter consisting of an expandable basket of 6 Nitinol-reinforced infusion limbs.[11] First-in-human evidence suggests that using this technology, which disperses the fibrinolytic agent across a wider cross section of a large vessel filled with thrombus, may be more effective in reducing pulmonary vascular obstruction at lower doses and with fewer adverse events.[11]

We hereby report the results of the RESCUE (recombinant tPA by Endovascular Administration for the Treatment of Submassive PE Using CDT for the Reduction of Thrombus Burden; NCT04248868) investigational device exemption study, describing the outcomes of PM-CDT with the Bashir catheter in patients with acute intermediate-risk PE.

METHODS

STUDY DESIGN. The RESCUE trial is a prospective, multicenter, single-arm study to assess the safety and efficacy of PM-CDT with the Bashir catheter in patients with acute intermediate-risk PE. The study was sponsored by a National Heart, Lung, and Blood Institute Small Business Innovation Research grant, the Department of Health of the Commonwealth of Pennsylvania, and Thrombolex. It was conducted under an investigational device exemption approval from the U.S. Food and Drug Administration. Institutional Review Board approval was obtained at all sites, and informed consent was obtained from every patient.

STUDY POPULATION. The RESCUE trial enrolled patients 18 to 75 years of age with filling defects in at least 1 main or lobar pulmonary artery (PA) as determined by computed tomographic angiography (CTA) of the chest, RV/LV diameter ratio >0.9, and symptom duration <14 days. The key exclusion criteria were active bleeding or major surgery within 2 weeks; head trauma or active intracranial or intraspinal disease; and systolic blood pressure <90 mm Hg for >15 minutes, need for vasopressors, or cardiac arrest. For detailed inclusion and exclusion criteria see the Supplemental Appendix.

DEVICE DESCRIPTION AND PROCEDURAL TECHNIQUES. The Bashir catheter is a 7-F device intended for the localized infusion of therapeutic agents into the vasculature. It has a distal infusion segment that contains an expandable radial array of

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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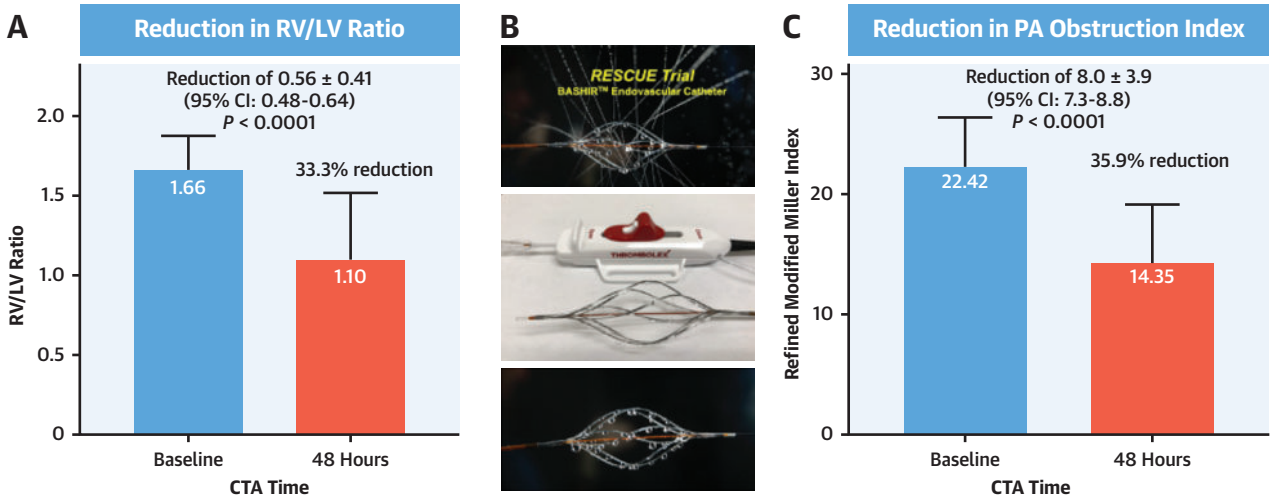
CENTRAL ILLUSTRATION **Primary Efficacy and Safety Endpoint Results of the RESCUE Trial**



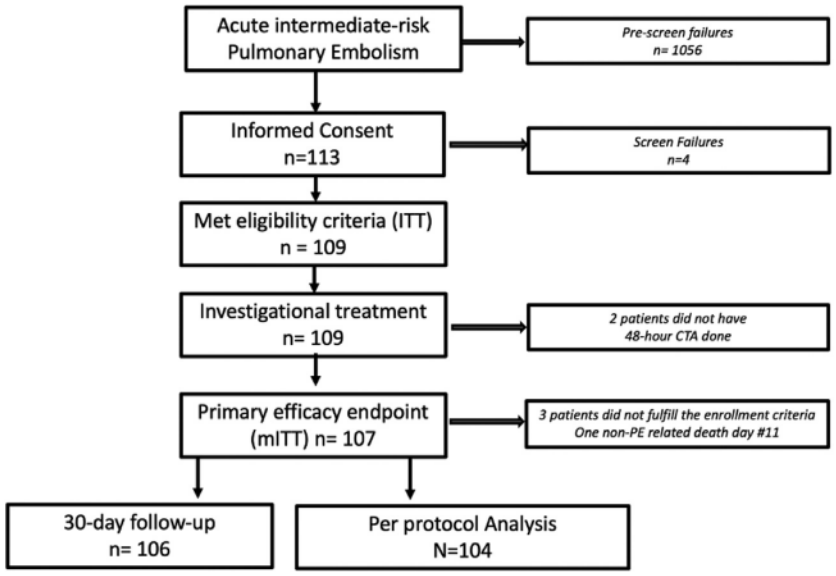
Mean reduction in RV/LV ratio	Mean reduction in PA obstruction index	Major adverse events within 72 hours	Major bleeding within 72 hours	Median BASHIR catheter placement time	Median hospital length of stay
33.3%	35.9%	0.92%	0.92%	15 mins	2.8 days

Bashir R, et al. J Am Coll Cardiol Intv. 2022;15(23):2427–2436.

Computed tomographic angiographic parameters before and after pharmacomechanical (PM) catheter-directed thrombolysis (CDT) using the Bashir endovascular catheter. **(A)** Reduction in right ventricular (RV)/left ventricular (LV) diameter ratio at 48 hours after PM-CDT. At 48 hours, the mean RV/LV diameter ratio had decreased from 1.66 ± 0.45 to 1.10 ± 0.24 ($P < 0.0001$), a mean difference of 0.56 ± 0.41 (95% CI: 0.48-0.64; 33.3% reduction). **(B)** The Bashir endovascular catheter, with collapsed and expanded infusion basket showing pulse spray and infusion. **(C)** Reduction in pulmonary artery obstruction at 48 hours after PM-CDT. Mean total pulmonary artery obstruction as measured using the refined modified Miller index decreased from 22.42 ± 3.93 to 14.35 ± 4.77 ($P < 0.0001$), a mean difference of 8.05 ± 3.89 (95% CI: 7.3 to 8.8; 35.9% reduction).

helical conduits (infusion basket) with a total of 48 laser-drilled orifices used for the delivery of the therapeutic agents at multiple cross-sectional points of the target vessel. This infusion basket can be expanded and collapsed by an actuator (slider) located on the handle at the proximal end of the device (**Central Illustration B**). The helical infusion basket can be expanded up to a maximum diameter of 45 mm. The Bashir catheter has previously been described in detail,[11] and the **Central Illustration** highlights the pulse spray and infusion characteristics of this device. Venous access, using ultrasound guidance and a micropuncture needle, were mandated via either the femoral or internal jugular vein. The Bashir catheter was advanced over an 0.018-inch guidewire through a long 7-F sheath and positioned such that the infusion basket was placed within the thrombus in the PA. Once in place, the sheath was retracted, and the infusion basket was expanded under fluoroscopy by retracting the actuator on the handle. Then a pulse spray of 1 mg recombinant tissue plasminogen activator (r-tPA) (alteplase) diluted in 10 mL normal saline was administered. The basket was collapsed and re-expanded for administration of a second pulse spray of another 1 mg r-tPA. In patients with bilateral PE, the same steps were repeated to administer the pulse sprays in the contralateral lung. Following this, the basket was again collapsed and re-expanded before commencing the infusion of an additional dose of 5 mg r-tPA into each lung over 5 hours. The total r-tPA dose administered was 7 mg in patients with unilateral PE and 14 mg in patients with bilateral PE. The rationale for expanding and collapsing the basket 3 times before starting the infusion is that every time the helical Nitinol basket is expanded, it creates fissures along different planes within the thrombus. This creates multiple channels for the blood and endogenous fibrinolytic agent to percolate into the thrombus. Additionally, a pulse spray of diluted r-tPA

FIGURE 1 Patient Screening, Enrollment, and Follow-Up



A total of 113 patients were consented for the RESCUE (rtPA by Endovascular Administration for the Treatment of Submassive PE Using CDT for the Reduction of Thrombus Burden) trial, and 4 of them failed screening. Therefore 109 patients were enrolled and treated with pharmacomechanical catheter-directed thrombolysis and constituted the intention-to-treat (ITT) population. Two patients did not undergo 48-hour computed tomographic angiography (CTA), and therefore 107 patients were used for primary efficacy endpoint assessment. This formed the modified ITT (mITT) population. One patient died of a non-pulmonary embolism (PE)–related cause, so 106 patients were eligible for 30-day follow-up. Three patients did not meet the enrollment criteria, so 104 patients formed the per protocol population.

within these different planes traps the thrombolytic within the thrombus, which continues to convert the fibrin-bound plasminogen into plasmin until blood flow is restored. Patients were monitored in an intensive care unit or the catheterization laboratory recovery area while undergoing PM-CDT, per institutional policy. After completion of the infusion, the devices were removed at the bedside after recording PA pressure and mixed venous oxygen saturations. During r-tPA infusion, patients were anticoagulated with a lower dose (5-8 mg/kg/h, maximum 1,000 U/h) of unfractionated heparin with a target activated partial thromboplastin time of 50 to 60 seconds. Patients were restarted on therapeutic anticoagulation within 45 minutes of sheath removal and hemostasis. Data collection and patient follow-up were done at 24 hours, 72 hours, and 30 days after treatment.

EFFICACY AND SAFETY ENDPOINTS. The primary efficacy endpoint was change in RV/LV diameter ratio as measured by the core laboratory using contrast-enhanced chest CTA at 48 ± 8 hours after PM-CDT therapy. The primary safety endpoint was serious adverse events (SAEs), including the major bleeding rate within 72 hours after PM-CDT, defined by International Society on Thrombosis and Haemostasis criteria as fatal bleeding and/or bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome, and/or bleeding causing a decrease in hemoglobin level of 2.0 g/dL (1.24 mmol/L) or more or leading to transfusion of 2 or more units of whole blood or red cells. The secondary endpoints included: 1) change in PA obstruction index as assessed by the core laboratory using the refined modified Miller index (RMMI) on chest CTA at 48 ± 8 hours after completion of PM-CDT compared with baseline; 2) all-cause mortality at 30 days; 3) SAEs through 30-day follow-up; 4) unanticipated (nonserious) AEs through 30-day follow-up; 5) recurrent PE through 30-day follow-up; 6) clinically relevant nonmajor bleeding, defined as any sign or symptom of hemorrhage (eg, more bleeding than would be expected for a clinical circumstance, including bleeding found on imaging alone) that does not fit the criteria for the International Society on Thrombosis and Haemostasis definition of major bleeding but does meet at least 1 of the following criteria: requiring medical intervention by a health care professional or leading to hospitalization or increased level of care or prompting a face-to-face (ie,

not just a telephone or electronic communication) evaluation[12]; 7) technical procedural complications; 8) a change from baseline in systolic PA pressure measured at the completion of infusion or removal of catheters; 9) changes from baseline in cardiac output and cardiac index as measured using the modified Fick method following the completion of infusion or removal of infusion catheters; and 10) device success (the percentage of devices used successfully to deliver therapy).

Changes in RV/LV diameter ratio and PA obstruction index were measured by a dedicated imaging core laboratory using anonymized chest computed tomographic angiographic studies at baseline and 48 hours after treatment. RV/LV diameter ratio was measured using the reformatted 4-chamber view.[13] PA obstruction was measured using the RMMI,[14] which is a refinement of the modified Miller scoring system. The RMMI assesses the degree of obstruction in 10 segmental arteries in the right lung and 10 in the left lung and assigns a score of 0 (no obstruction), 0.5 (1%-33% obstruction), 1 (34%-66% obstruction), 1.5 (67%-99% obstruction), or 2 (total occlusion) to each of these arteries. A cumulative score is calculated by adding the scores for all arteries. Total scores can range from 0 to 40 (20 per side). The proximal PA branch scores are calculated on the basis of the number of segmental arteries that arise from that proximal artery, as long as the highest possible scores are ascribed to each branch. These proximal branches included the 2 main PAs, 2 upper lobe truncus branches, and 2 lower lobe interlobar arteries. A data and safety monitoring board and clinical events committee adjudicated all adverse events, and the final judgement of the data and safety monitoring board and clinical events committee was reported to the Food and Drug Administration and in this paper. The primary analysis is based on an intention-to-treat (ITT) analysis using all patients who received the investigational treatment. We also performed a per protocol analysis.

DATA ANALYSIS. Analysis populations. All enrolled subjects who received the study treatment were included in the ITT population. The ITT population was used to analyze the primary and secondary safety endpoints, including device-related adverse events. The modified ITT population included all patients who had all data available to assess change in RV/LV diameter ratio as measured on CTA at screening and 48 hours after the completion of PM-CDT treatment. This population was used to analyze the primary efficacy endpoint. The per protocol population was used to analyze secondary endpoints that required 30 days of follow-up, such as all-cause mortality, SAEs, adverse events, and recurrent PE.

TABLE 1 Baseline Demographic and Clinical Characteristics (N = 109)

Age, y	57 ± 13.3
Body mass index, kg/m^2	33.3 ± 6.05
Male	67 (61.5)
Female	42 (38.5)
White/non-Hispanic	64 (58.7)
Black/African American	32 (29.4)
Hispanic	10 (9.2)
Other	3 (2.8)
BNP, pg/mL	1,101 ± 1,950
Troponin, ng/mL	0.52 ± 2.1
History of cancer	17 (15.6)
Diabetes mellitus	27 (24.7)
Previous deep vein thrombosis	28 (25.7)
History of pulmonary embolism	15 (13.8)
Unilateral pulmonary embolism	7 (6.4)
Bilateral pulmonary embolism	102 (93.6)
Elevated troponin or BNP	98/109 (89.9)
Elevated troponin	78/109 (66.1)
Elevated BNP	78/105 (74.3)
Negative biomarkers	69/109 (8.3)
sPESI score > 1	41/109 (37.6)

Values are mean ± SD, n (%), or n/N (%).
BNP = brain type natriuretic peptide; sPESI = simplified pulmonary embolism severity index.

The study was allowed to enroll up to 125 patients, with the goal of having 100 evaluable subjects (after accounting for a 20% attrition rate). The other assumptions used to determine the required sample size for the study included the following: we estimated a mean reduction of 28% in the primary efficacy endpoint (RV/LV diameter ratio) at 48 hours after PM-CDT on the basis of prior reperfusion studies in acute PE.[13] We planned to compared this with the performance goal of a 20% reduction in RV/LV diameter ratio at 48 hours, which was observed in a previous systemic fibrinolysis study.[15]

A prespecified interim analysis was conducted once data on 60 participants had been collected, in order to obtain preliminary efficacy results using the primary efficacy endpoint. To constrain the overall type I error rate, an O'Brien-Fleming alpha spending function was used, in which a stringent type I error rate of alpha = 0.0038 was used for the interim analysis, leaving alpha = 0.0212 for the final analysis, when the study was completed. On the basis of the assumptions stated, the sample size needed for 80%

TABLE 2 Procedural Characteristics (N = 109)

Total dose of tPA, mg	
Unilateral PE (pulse spray + infusion)	7 (2 + 5)
Bilateral PE (pulse spray + infusion)	14 (4 + 10)
Total procedure time, min	54.2 ± 28.8
Bashir catheter placement time, min	15 ± 14
Number of devices per patient	
1	7 (6.4)
2	102 (93.6)
Completed r-tPA infusion (N = 109)	109 (100)

Values are n, mean ± SD, or n (%).
PE = pulmonary embolism; r-tPA = recombinant tissue plasminogen activator; tPA = tissue plasminogen activator.

power to test the primary efficacy hypothesis in the final analysis was 83 subjects. This estimate is based on a 1-sided 1-sample *t*-test with a predicted 20% reduction in mean percentage change in RV/LV diameter ratio from baseline to 48 hours with an SD of 25%. A *t*-test was performed twice to assess the change in RV/LV diameter ratio, once in the interim analysis (with $\alpha = 0.0038$) and once in the final analysis (with $\alpha = 0.0212$). If the *P* value was less than α at either analysis, then the test was considered statistically significant.

The primary safety endpoint was assessed using a 1-sided, 1-sample exact test. The hypothesis test for the primary safety endpoint was not done in the interim analysis, only at the end of the study. This test would comply with a type I error rate of 0.025. Descriptive statistics were used for the secondary endpoints listed previously. For continuous measures (eg, RMMI), the mean and 95% confidence limits were calculated, along with the SD and range; *P* values were computed using a 2-sided paired *t*-test. For frequency outcomes (eg, device success), results were reported as the overall frequency of occurrence as well as the percentage of subjects. We also evaluated study site variance for primary and secondary efficacy endpoints.

The study was monitored by a clinical research organization (Eminence Clinical Research) and an independent data and safety monitoring board. Electronic data capture (Medrio) was used to record all study data. The analyses of the computed tomographic scans were performed by the core laboratory (NAMSA/Syntactx); the metrics analyzed included measurements of RV/LV diameter ratio and PA obstruction using the RMMI. Statistical analyses were performed by PharmaLex.

TABLE 3 Efficacy Outcomes

	Baseline	After PM-CDT	Difference	*P* Value
RV/LV diameter ratio by CTA (n = 107)	1.66 ± 0.41	1.10 ± 0.21	0.56± 0.41	0.0001
Refined modified Miller index (n = 106)	22.42 ± 3.93	14.35 ± 4.77	8.05± 3.89	<0.0001
Systolic PA pressure, mm Hg (n = 93)	49.53 ± 13.39	43.74 ± 13.51	5.94± 10.69	<0.0001
Cardiac output, L/min (n = 98)	4.81 ± 1.43	5.31 ± 1.59	0.49± 1.59	0.0029
Cardiac index, L/minm^2 (n = 98)	2.29 ± 0.60	2.47 ± 0.71	0.19± 0.76	0.0156

Values are mean ± SD.
CDT = catheter-directed thrombolysis; CTA = computed tomographic angiography; LV = left ventricular; PA = pulmonary artery; PM = pharmacomechanical; RV = right ventricular.

RESULTS

BASELINE CHARACTERISTICS. A total of 109 patients were enrolled across 18 U.S. sites from October 2020 to May 2022 (**Figure 1**). All patients met the criteria for acute intermediate-risk PE as defined in the European Society of Cardiology guidelines.[16] The mean age was 57 ± 13 years, 61.5% were men, and 102 (93.6%) had bilateral PE. The mean body mass index was 33.31 ± 6.05 kg/m^2. Histories of PE were present in 13.8% of patients, histories of deep vein thrombosis were present in 25.7% of patients, and 15.6% of patients had histories of cancer (**Table 1**). Ninety-eight patients (89.9%) had elevated troponin and/or brain type natriuretic peptide levels. Preprocedural anticoagulant agents were heparin in 93.6% of subjects and enoxaparin sodium in 6.4% of subjects.

PROCEDURAL CHARACTERISTICS. A total of 214 devices were placed in the 109 enrolled patients: 2 each in 102 patients with bilateral PEs and 1 each in 7 patients with unilateral PEs. All but 3 devices (98.2%) were successfully placed. All patients received pulse sprays of 2 mg r-tPA into each lung, followed by 5 mg over 5 hours for a total of 7 mg r-tPA for unilateral and 14 mg for bilateral PEs. The median device placement time was 15 ± 14 minutes, and total procedure time was 54.2 ± 28.8 minutes. Additional procedural characteristics are shown in **Table 2**. The names of sites are shown in Supplemental e-Table 1.

EFFICACY OUTCOMES. Two patients did not undergo follow-up CTA at 48 hours, so a total of 107 evaluable patients were used for assessment of the primary efficacy endpoint (modified ITT population). All studies were of good imaging quality for this analysis. At 48 hours after PM-CDT, the mean RV/LV diameter ratio had decreased from 1.66 ± 0.41 to 1.10 ± 0.21 ($P < 0.0001$), a mean difference of 0.56 ± 0.41 (95% CI: 0.48-0.64; 33.3% reduction) (**Central Illustration A, Table 3**). Mean total PA obstruction as measured using the RMMI decreased from 22.42 ±

3.93 to 14.35 ± 4.77 ($P < 0.0001$), a mean difference of 8.05 ± 3.89 (95% CI: 7.3-8.8; 35.9% reduction) (**Central Illustration C, Table 3**).

SAFETY OUTCOMES. One major bleeding event (0.92%) occurred within 72 hours, and the same patient had device-related left common iliac vein thrombosis while off anticoagulation. There was 1 non-PE-related death (0.92%) within 30 days. Three patients (2.7%) had 4 procedure-related SAEs: epistaxis requiring silver nitrate cautery, non-access site hematoma, anemia, and retroperitoneal bleeding (**Table 4**). There were 2 nonmajor device-related adverse events: left lower lobe intraparenchymal hematoma and inability to perform a pulse spray with one device, which was safely removed and replaced with another device without any adverse events. Seven patients had 14 SAEs within 30 days of follow-up (**Table 5**). There was no significant study site variance in the efficacy outcome of RV/LV diameter ratio reduction ($P = 0.91$) or reduction in PA obstruction index ($P = 0.24$).

TABLE 4 Safety Outcomes (N = 109)

Procedural success (n = 109)	109 (100)
Major bleeding within 72 h (ISTH criteria)[a] (n = 109)	1 (0.92)
Major device-related AEs[b] (n = 109)	1 (0.92)
Clinically relevant nonmajor bleeding (n = 109)	1 (0.92)
Nonmajor device-related AEs[c] (n = 109)	2 (1.8)
Recurrent PE through 30-d follow-up (n = 104)	0 (0)
SAEs through 30-d follow-up[d] (n = 104)	7 (6.7)
All-cause mortality at 30 d (n = 104)	1 (0.92)
Intracranial hemorrhage	0 (0)
Median length of hospital stay, d (n = 109)	2.88 ± 1.6

Values are n (%) or mean ± SD. [a]Major bleeding as defined by the (ISTH in nonsurgical patients. [b]Left common iliac vein thrombosis in a patient with May-Thurner syndrome with ipsilateral popliteal deep vein thrombosis and off anticoagulation because of retroperitoneal bleeding. [c]Left lower lobe intraparenchymal hematoma and inability to perform a pulse spray with one device, which was safely removed and replaced with another device without any AEs. [d]14 adverse events were seen in 7 patients. Three of these patients had 4 procedure-related SAEs, which included epistaxis requiring silver nitrate cautery, non-access site hematoma with anemia, and retroperitoneal bleeding.

AE = adverse event(s); ISTH = International Society on Thrombosis and Haemostasis; PE = pulmonary embolism; SAE = serious adverse event.

DISCUSSION

This prospective, multicenter study of patients with intermediate-risk PE showed a significant reduction in RV/LV diameter ratio at 48 hours after PM-CDT following deployment of the Bashir endovascular catheter, with minimal bleeding complications and device-related adverse events. Additionally, PA obstruction was reduced by 35.9% at 48 hours. The magnitude of this reduction is 3-fold higher than with other PMT devices and 2-fold higher than with other thrombolysis catheters at a similar dose of tissue plasminogen activator. This improvement was associated with improvement in hemodynamic parameters such as cardiac output and PA pressures within 5 hours of initiating PM-CDT.

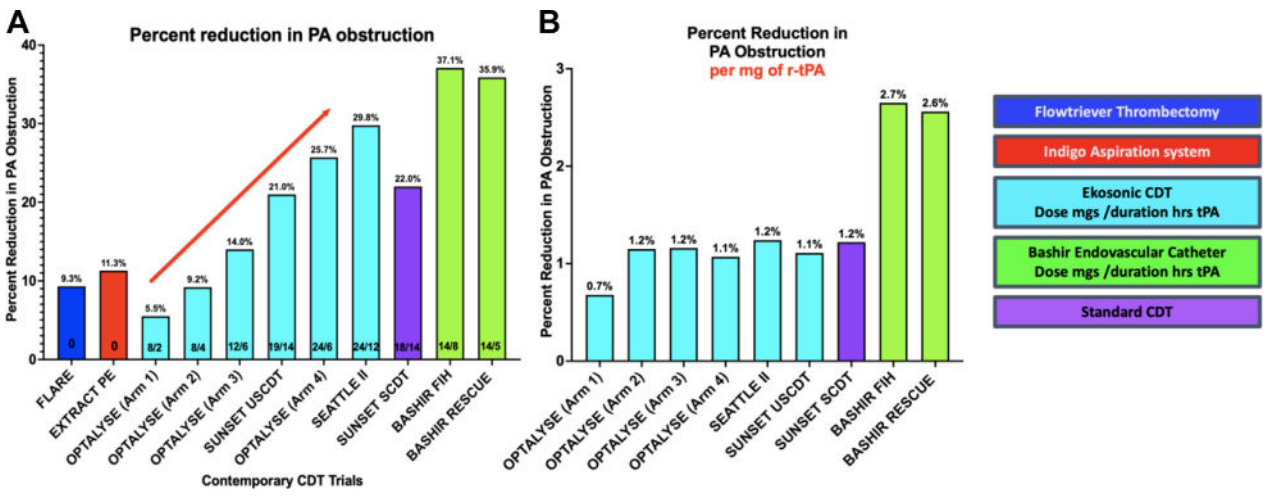
The RV/LV diameter ratio improvement noted in this study following PM-CDT was 33.3%, which compared very favorably with systemic thrombolysis[13] and with most contemporary catheter-directed therapies.[6-9,10] The percentage reduction in RV/LV diameter ratio reported with systemic thrombolysis was 31%, with EkoSonic CDT was 22% to 26%, with Indigo thrombectomy was 27%, and with FlowTriever thrombectomy was 25%. The 2 small randomized controlled trials that compared CDT plus anticoagulation with anticoagulation alone showed that CDT leads to faster restoration of RV/LV diameter ratio as well as greater reduction in PA pressures compared with anticoagulation alone.[4,5] To know whether this ultimately improves short- and long-term clinical outcomes, we need to await the results of RCTs such as PE-TRACT (Pulmonary Embolism: Thrombus Removal with Adjunctive Catheter-Directed Thrombolysis)[16] and HI-PEITHO (Ultrasound-Facilitated, Catheter-Directed, Thrombolysis in Intermediate-High Risk Pulmonary Embolism; NCT04790370).

The safety profile of PM-CDT with the Bashir catheter is a key finding of this study. The rate of major bleeding was minimal (0.9%) and lower than in any multicenter EkoSonic CDT trial, in which rates ranged from 4% to 10%. This bleeding rate compares very favorably with those seen with contemporary

TABLE 5 Serious Adverse Events Within 30 Days

Patient #	Events
1	Anemia
2	Alcohol withdrawal Pleural effusion
3	Epistaxis
4	Bleeding associated with fall in hemoglobin Thromboembolism
5	Acute respiratory failure Hemoptysis Hematoma Anemia Acute kidney injury Infection (septicemia, multisystem organ failure)
6	Allergic reaction
7	Recurrent gluteal abscess

FIGURE 2 Percentage Pulmonary Artery Obstruction Index Reduction Across Various Contemporary PE Trials



Reduction in pulmonary artery obstruction. **(A)** Percentage reduction in pulmonary artery (PA) obstruction across various contemporary catheter-based therapy trials. The **red arrow** suggests a dose response curve with Ekosonic CDT. **(B)** Percentage reduction in PA obstruction index per milligram recombinant tissue plasminogen activator (r-tPA) in contemporary catheter-directed thrombolysis (CDT) trials. BEC = Bashir endovascular catheter; EXTRACT PE = Evaluating the Safety and Efficacy of the Indigo® Aspiration System in Acute Pulmonary Embolism; FIH = first-in-human; FLARE = FlowTriever Pulmonary Embolectomy Clinical Study; OPTALYSE = Optimum Duration of Acoustic Pulse Thrombolysis Procedure in Acute Pulmonary Embolism; PE = pulmonary embolism; RESCUE = rt-PA by Endovascular Administration for the Treatment of Submassive PE Using CDT for the Reduction of Thrombus Burden; SEATTLE II = Submassive and Massive Pulmonary Embolism Treatment With Ultrasound Accelerated Thrombolysis Therapy; SUNSET = Standard vs. Ultrasound-Assisted Catheter Thrombolysis for Submassive Pulmonary Embolism; tPA = tissue plasminogen activator; USCDT = ultrasound-facilitated catheter-directed thrombolysis.

PMT devices, which also cause procedural blood loss related to suction thrombectomy. Additionally, serious device- or procedure-related adverse events in these PMT trials (1.7% with Penumbra Indigo thrombectomy and 3.8% with the FlowTriever device) makes PM-CDT with the Bashir catheter an attractive alternative in patients with intermediate-risk PE. In this study there were very few device- or procedure-related major adverse events despite enrolling 90% of patients with a combination of RV dysfunction and elevated biomarkers.

Another salient finding of this study is the 35.9% reduction in PA obstruction as measured by the core laboratory using the RMMI. It is the first time that this magnitude of reduction in PA obstruction has been noted with any catheter-based therapy (Figure 2) with such a low dose of tissue plasminogen activator. The reduction in PA obstruction index was shown to be similar between standard CDT and EkoSonic CDT in a randomized controlled trial.[8] Several studies of EkoSonic CDT have shown a very predictable dose-response relationship in terms of reduction in PA obstruction (Figure 2). However, all PMT therapies have shown very modest (9%-11%) reductions in PA obstruction index, which may be related to downstream embolization of some embolic material leading to distal segmental artery occlusions.[17] As relief of PA obstruction with restoration of perfusion to the alveolar capillary bed is an important goal of this therapy,[18] PM-CDT with the Bashir catheter may be an important technological advance in the treatment of patients with acute PE.

The advantage of using the Bashir catheter in the treatment of patients with acute PE is its low profile (7-F) and its ease of use compared with large-bore PMT devices (up to 24-F), which may be challenging to position and operate in these very sick patients with PE.[19] This multicenter study confirmed that Bashir catheters can be placed in both PAs in <15 minutes, which is significantly shorter than for any PMT device. Additionally, the median length of hospital stay in these patients with intermediate-risk PE was only 2.8 days, which is again shorter than that seen in any CDT or PMT trials and should reduce the health care costs of treating these patients. The efficacy and safety of this treatment approach, combined with the ease of use and a very short procedure time, should facilitate the adoption of this therapy across a wide spectrum of health care institutions globally, particularly if future randomized controlled trials

confirm the superiority of catheter-based interventions over anticoagulation alone.

STUDY LIMITATIONS. The limitations of this study include the lack of long-term clinical follow-up and patient-centered clinical outcomes. This was a single-arm study without any comparison group with anticoagulation alone. We did not enroll patients with high-risk acute PE, and future studies are needed to evaluate the role of this therapy in these patients. Future randomized controlled trials should evaluate these imaging outcomes in addition to long-term clinical outcomes.

CONCLUSIONS

This multicenter investigational device exemption study showed that PM-CDT with the Bashir catheter in patients with intermediate-risk acute PE is associated with a significant reduction in the RV/LV diameter ratio and relief of PA obstruction. The safety profile of the Bashir catheter and its ease of use should facilitate the adoption of this therapy across a wide spectrum of health care institutions globally, particularly if randomized controlled trials confirm the benefit of PM-CDT in patients with intermediate-risk acute PE. Future studies are also needed to assess the direct effect of acute reduction in PA obstruction on long-term clinical outcomes, including chronic thromboembolic pulmonary disease or hypertension, post-PE syndrome, and long-term mortality.

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PERSPECTIVES

WHAT IS KNOWN? The role of advanced therapies in treatment of patients with intermediate-risk acute PE is uncertain. Systemic thrombolysis is effective but associated with very high major bleeding rates, including intracranial hemorrhage.

WHAT IS NEW? PM-CDT with the Bashir endovascular catheter is associated with a significant reduction in RV/LV diameter ratio and very low bleeding and adverse event rates. It is also associated with a significant reduction in PA obstruction with low doses of tissue plasminogen activator.

WHAT IS NEXT? The safety and effectiveness of PM-CDT with the Bashir catheter with a low dose and short duration of tissue plasminogen activator makes it important that future randomized controlled trials consider comparing this treatment with other therapies, such as mechanical thrombectomy or anticoagulation alone.

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KEY WORDS catheter-directed therapy, pulmonary embolism, thrombolysis, refined modified Miller index, RV/LV ratio

APPENDIX For a supplemental table and the inclusion and exclusion criteria, please see the online version of this paper.