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A Randomized Trial of the Optimum Duration of Acoustic Pulse Thrombolysis Procedure in Acute Intermediate-Risk Pulmonary Embolism

The OPTALYSE PE Trial

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ABSTRACT

OBJECTIVES The aim of this study was to determine the lowest optimal tissue plasminogen activator (tPA) dose and delivery duration using ultrasound-facilitated catheter-directed thrombolysis (USCDT) for the treatment of acute intermediate-risk (submassive) pulmonary embolism.

BACKGROUND Previous trials of USCDT used tPA over 12 to 24 h at doses of 20 to 24 mg for acute pulmonary embolism.

METHODS Hemodynamically stable adults with acute intermediate-risk pulmonary embolism documented by computed tomographic angiography were randomized into this prospective multicenter, parallel-group trial. Patients received treatment with 1 of 4 USCDT regimens. The tPA dose ranged from 4 to 12 mg per lung and infusion duration from 2 to 6 h. The primary efficacy endpoint was reduction in right ventricular-to-left ventricular diameter ratio by computed tomographic angiography. A major secondary endpoint was embolic burden by refined modified Miller score, measured on computed tomographic angiography 48 h after initiation of USCDT.

RESULTS One hundred one patients were randomized, and improvements in right ventricular-to-left ventricular diameter ratio were as follows: arm 1 (4 mg/lung/2 h), 0.40 (24%; $p = 0.0001$); arm 2 (4 mg/lung/4 h), 0.35 (22.6%; $p = 0.0001$); arm 3 (6 mg/lung/6 h), 0.42 (26.3%; $p = 0.0001$); and arm 4 (12 mg/lung/6 h), 0.48 (25.5%; $p = 0.0001$). Improvement in refined modified Miller score was also seen in all groups. Four patients experienced major bleeding (4%). Of 2 intracranial hemorrhage events, 1 was attributed to tPA delivered by USCDT.

CONCLUSIONS Treatment with USCDT using a shorter delivery duration and lower-dose tPA was associated with improved right ventricular function and reduced clot burden compared with baseline. The major bleeding rate was low, but 1 intracranial hemorrhage event due to tPA delivered by USCDT did occur. (J Am Coll Cardiol Intv 2018;11:1401–10)

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ABBREVIATIONS AND ACRONYMS

CDT = catheter-directed therapy

CTA = computed tomographic angiography

ICH = intracranial hemorrhage

ITT = intention to treat

LV = left ventricular

mPP = modified per protocol

PE = pulmonary embolism

RV = right ventricular

tPA = tissue plasminogen activator

USCDT = ultrasound-facilitated catheter-directed thrombolysis

Thrombolysis has been studied in intermediate-risk (submassive) pulmonary embolism (PE), but concern over intracranial hemorrhage (ICH) with systemic thrombolysis (1,2) has resulted in limited use of this approach except in high-risk (massive) PE. Bleeding complications with systemic thrombolysis have also generated interest in alternative therapies with lower bleeding risk. Ultrasound-facilitated catheter-directed thrombolysis (USCDT) is a form of pharmacomechanical thrombolysis (3,4) that uses the energy transmitted by high-frequency (2 to 3 MHz), low-power ultrasound waves. In vitro and in animal models, this technique has been shown to separate fibrin strands, increasing thrombus surface area and making more plasminogen activator receptor sites available for facilitating thrombolysis (5).

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The EkoSonic Endovascular System (Ekos/BTG, Bothell, Washington) ultrasound device has been described previously (6,7). Prior trials of USCDT in acute intermediate-risk PE evaluated infusion durations of 12 to 24 h. In most cases, both the right and left pulmonary arteries were treated (6,7).

In intermediate-risk PE, the randomized controlled ULTIMA (Ultrasound Accelerated Thrombolysis of Pulmonary Embolism) trial demonstrated that right ventricular (RV)-to-left ventricular (LV) diameter ratio is improved at 24 h with USCDT compared with anticoagulation alone and with no major bleeding (6). In the SEATTLE II (A Prospective, Single-Arm, Multi-Center Trial of EkoSonic Endovascular System and Activase for Treatment of Acute Pulmonary Embolism) trial, use of this technique was associated with RV-to-LV diameter ratio improvement at 48 h compared with baseline in predominantly intermediate-risk PE and a smaller population of patients with massive PE (21%), with a major bleeding rate of 10%. There were no ICH events (7). Other studies have shown an association between the use of USCDT and significant improvement in PA pressure ($p < 0.001$), cardiac index ($p < 0.001$), RV-to-LV diameter ratio ($p < 0.001$) (8), and shorter length of hospital stay (9). This USCDT device was approved by the U.S. Food and Drug Administration on May 21, 2014, for treatment of acute PE.

We hypothesized that even lower doses of tissue plasminogen activator (tPA) and shorter durations of USCDT than were used in prior studies would be associated with improvement in RV function in this intermediate-risk population.

METHODS

STUDY DESIGN. The trial (NCT02396758) was designed by our steering committee with participation of the sponsor (Ekos/BTG). The 101 trial participants were enrolled at 17 centers in the United States and Europe. Institutional Review Board approval was obtained at all sites, and written consent was obtained from all patients. Imaging analysis was conducted by Syntactx (New York, New York). Statistical support was provided and reviewed independently in an unblinded manner by Claire Daugherty (BTG) and Ping-Yu Liu (Liu Associates Consulting). This was a multicenter, parallel-group study in which participants were randomly assigned to 1 of 4 USCDT regimens, varying in duration and total tPA dose.

STUDY POPULATION. Patients 18 to 75 years of age were eligible to participate if they had symptomatic, intermediate-risk, acute PE, defined as PE symptoms

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for <14 days with normal systolic blood pressure (>90 mm Hg), RV-to-LV diameter ratio ≥0.9 on chest computed tomographic angiography (CTA), and proximal PE located in at least 1 main or proximal lobar pulmonary artery. Troponin and brain natriuretic protein were obtained but not required for inclusion. Major exclusion criteria included stroke or transient ischemic attack, head trauma, other active intracranial or intraspinal disease within 1 year, recent active bleeding from a major organ within 1 month, major surgery within 7 days of screening, systolic blood pressure <90 mm Hg or use of vasopressors, hematocrit <30%, platelet count <100,000/μl, international normalized ratio >3, creatinine outside the normal range, and, as of June 8, 2016, any hematologic disease potentially involving abnormal platelet number or function. Additional exclusion criteria were perceived high risk for catastrophic bleeding, history of heparin-induced thrombocytopenia, catheter-based pharmacomechanical treatment for PE within 3 days of study enrollment, cardiac arrest requiring active cardiopulmonary resuscitation, evidence of irreversible neurological compromise, life expectancy <1 year, use of thrombolytics or glycoprotein IIb/IIIa receptor antagonists within 3 days before USCDT procedure, pregnancy or breastfeeding, and allergy or hypersensitivity to tPA or iodinated contrast except for mild to moderate contrast allergies for which steroid pre-medication can be used. Patients with active cancer (metastatic, progressive, or treated within the past 6 months) were excluded; patients with nonmelanoma primary skin cancer, however, were eligible.

TREATMENT REGIMENS. Patients were randomized to 1 of 4 groups (block randomization with block size 4). This was changed to block size 3 after arm 4 was closed. Subject identification information was entered in the electronic case report form to produce the randomization assignment. The 4 arms were as follows: arm 1, USCDT × 2 h with tPA infused at 2 mg/h per catheter (range 4 to 8 mg; 1 vs. 2 lungs); arm 2, USCDT × 4 h with tPA infused at 1 mg/h per catheter (range 4 to 8 mg; 1 vs. 2 lungs); arm 3, USCDT × 6 h with tPA infused at 1 mg/h per catheter (range 6 to 12 mg; 1 vs. 2 lungs); arm 4, USCDT × 6 h with tPA infused at 2 mg/h per catheter (range 12 to 24 mg; 1 vs. 2 lungs).

All patients received therapeutic anticoagulation; the heparin dose was reduced to 300 to 500 U/h during the thrombolytic infusion and increased to full therapeutic dosing after USCDT. Patients receiving low-molecular-weight heparin received therapeutic doses. After the USCDT procedure, the type and duration of anticoagulation were determined by the responsible physician.

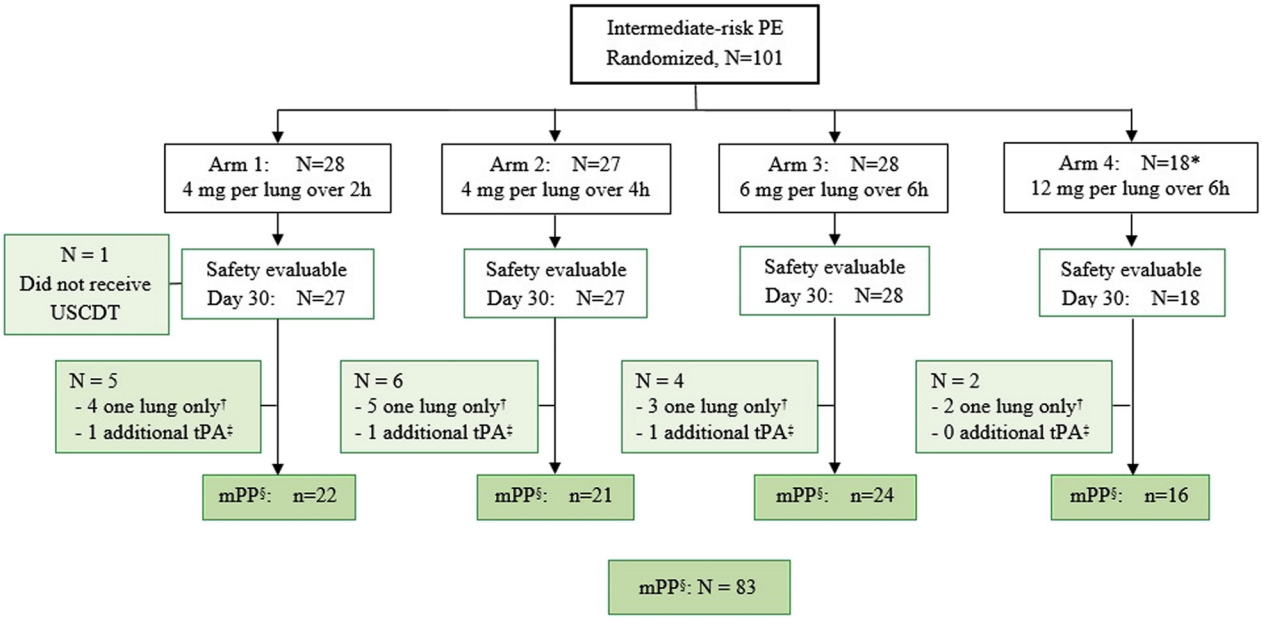
THE USCDT PROCEDURE. The USCDT procedure was performed in an angiographic suite by interventional radiologists or cardiologists or vascular surgeons within 48 h of diagnostic CTA. The 5.2-F infusion catheter contains 3 lumens, 1 for the inner ultrasound cable, 1 for drug infusion, and 1 for the coolant (normal saline). Placement of the Ekos catheter was guided by fluoroscopy or focused pulmonary arteriography. For unilateral PE in 1 main or proximal lobar pulmonary artery, 1 catheter was placed in the involved vessel (these patients received half of the dose that bilateral patients received). With bilateral PE in the main or proximal lobar pulmonary arteries, 2 catheters were placed, 1 in each of the involved vessels. Site of venous access was at the discretion of the treating physician. Venous access was obtained using ultrasound guidance. Physicians could use jugular or femoral venous access for placing 1 catheter or bilateral or ipsilateral femoral venous access for placing 2 devices in the pulmonary arteries. Treatment began with infusion of tPA and saline coolant at 35 ml/h per catheter. The MicroSonic core of the EkoSonic device was then activated to deliver low-energy ultrasound.

DETERIORATION OR NONRESPONSE TO USCDT PROCEDURE. Cessation of the procedure in favor of alternative therapy could be undertaken for adverse events such as recurrent PE, clinical deterioration, or bleeding. If there was no significant clinical or echocardiographic improvement but the patient was clinically stable, investigators were encouraged not to add additional advanced therapy beyond the USCDT protocol and simply to resume full anticoagulation.

OUTCOMES: EFFICACY AND SAFETY ENDPOINTS. The primary efficacy endpoint was change in RV-to-LV diameter ratio as measured by CTA from baseline to 48 ± 6 h after the start of USCDT. A secondary efficacy endpoint was change from baseline in embolic burden determined by refined modified Miller score by chest CTA at 48 ± 6 h after the procedure (Online Appendix). Although we initially considered determining Miller score and hemodynamic status by pulmonary arteriography before and within 4 h after the end of the USCDT procedure, the protocol was amended to make these follow-up measurements optional because of the logistics of returning to the catheterization laboratory within 4 h after treatment.

The primary safety outcome was frequency of major bleeding within 72 h after the start of the USCDT procedure by International Society on

FIGURE 1 Patient Flow and Evolution From ITT to mPP



A total of 101 patients with proven acute intermediate-risk pulmonary embolism (PE) by computed tomographic angiography (CTA) were randomized to 1 of 4 treatment arms at 17 centers in the United States and Europe. Clot burden was assessed by refined modified Miller score, and right ventricular (RV)/left ventricular (LV) diameter ratio was measured by CTA in all patients.

Thrombosis and Haemostasis criteria (10): 1) fatal bleeding; or 2) symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular, pericardial, or intramuscular with compartment syndrome; or 3) bleeding causing a decrease in hemoglobin of ≥2 g/dl or bleeding leading to transfusion of ≥2 U of whole blood or red blood cells. Clinically relevant nonmajor bleeding was also assessed as a secondary endpoint in the first 72 h (10).

Other secondary safety outcomes included symptomatic recurrent PE and mortality. For the diagnosis of symptomatic recurrent PE, documentation of clinical symptoms or signs suggesting recurrent PE was required in combination with objective confirmation with CTA, ventilation-perfusion lung scanning, or pulmonary arteriography. Hemoglobin, hematocrit, platelet count, activated partial thromboplastin time, international normalized ratio, blood urea nitrogen, and creatinine were measured at baseline or screening, within 4 h post-USCDT procedure, and at 48 h after the start of USCDT. A safety monitor adjudicated all major bleeding events during the study but was not blinded to the specific treatment arms. The adjudication committee reviewed diagnoses of symptomatic recurrent PE, and events that occurred up to the 365-day follow-up visit are reported.

STATISTICAL ANALYSIS. The intention-to-treat (ITT) patient population comprised all randomized patients. Unless otherwise specified, analyses were performed for primary and secondary efficacy endpoints for the ITT and modified-per-protocol (mPP) population (**Figure 1**). Analyses were performed separately for each treatment arm. Continuous measures are summarized as numbers, mean, SD, median, minimum, and maximum. Categorical data are

TABLE 1 Baseline Characteristics and Demographics (ITT Population*)

	Arm 1† (n = 28)‡	Arm 2† (n = 27)	Arm 3† (n = 28)	Arm 4† (n = 18)	All Patients (N = 101)‡
Age, yrs	58.5 (31–74)	62.0 (29–77)	60.0 (36–77)	58.5 (29–76)	60.0 (29–77)
Sex					
Female	12 (42.9)	12 (44.4)	17 (60.7)	7 (38.9)	48 (47.5)
Male	16 (57.1)	15 (55.6)	11 (39.3)	11 (61.1)	53 (52.5)
Race					
Caucasian	16 (57.1)	14 (51.9)	19 (67.9)	11 (61.1)	60 (59.4)
African American	12 (42.9)	10 (37.0)	9 (32.1)	6 (33.3)	37 (36.6)
Hispanic or Latino	0	2 (7.4)	0	0	2 (2.0)
Asian or Pacific Islander	0	1 (3.7)	0	0	1 (1.0)
Other§	0	0	0	1 (5.6)	1 (1.0)
Weight, lbs	246.3 ± 82.7	238.3 ± 60.7	254.9 ± 59.4	195.8 ± 39.3	237.5 ± 66.5
BMI, kg/m^2	36.1 ± 11.4	36.3 ± 11.0	39.5 ± 8.6	29.1 ± 6.7	35.8 ± 10.3
Congestive heart failure	2 (7.1)	4 (14.8)	4 (14.3)	1 (5.6)	11 (10.9)
Diabetes	11 (39.3)	10 (37.0)	11 (39.3)	3 (16.7)	35 (34.7)
Tobacco use	10 (35.7)	11 (40.7)	9 (32.1)	9 (50.0)	39 (38.6)
BMI ≥30 kg/m^2	19 (67.9)	17 (63.0)	26 (92.9)	7 (38.9)	69 (68.3)
Previous PE	7 (25.0)	4 (14.8)	6 (21.4)	2 (11.1)	19 (18.8)
Previous DVT	11 (39.3)	10 (37.0)	14 (50.0)	11 (61.1)	46 (45.5)

Values are median (range), n (%), or mean ± SD. *The intention-to-treat (ITT) patient population comprised all randomized patients; analyses were performed for primary and secondary efficacy endpoints for the ITT population. †Arm 1: ultrasound-facilitated catheter-directed thrombolysis (USCDT) for 2 h with tissue plasminogen activator (tPA) infused at 2 mg/h per catheter (i.e., 4 mg per lung); arm 2: USCDT for 4 h with tPA infused at 1 mg/h per catheter (i.e., 4 mg per lung); arm 3: USCDT for 6 h with tPA infused at 1 mg/h per catheter (i.e., 6 mg per lung); arm 4: USCDT for 6 h with tPA infused at 2 mg/h per catheter (i.e., 12 mg per lung). ‡n = 27 for weight and body mass index (BMI) in arm 1, resulting in n = 100 for weight and BMI in the column for all patients. §One patient reported race of black/white.

DVT = deep vein thrombosis; PE = pulmonary embolism.

summarized as frequency and percentage for each data category. Missing data were not imputed for the efficacy and safety analyses. Changes from baseline (absolute and percentage change) were summarized at 48 h with 95% confidence intervals for mean changes. Statistical significance for changes from baseline were assessed using the Student's *t*-test.

EFFICACY ANALYSES. The primary efficacy outcome was change in RV-to-LV diameter ratio from baseline to 48 ± 6 h after the start of the USCDT procedure. The main primary endpoint analyses reported are for the ITT and mPP populations. For each treatment arm, the post-procedural RV-to-LV diameter ratio was compared with baseline. Assuming a standard deviation of 0.41, as observed in the SEATTLE II study, and a 1-sided p value of 0.15, 24 evaluable subjects would provide 95% power in each arm to detect a mean RV-to-LV diameter ratio reduction of 0.23 or more. The power for simultaneous success in all 4 arms is approximately 0.81. A 1-sided $p < 0.15$ Student's *t*-test rejecting the null hypothesis of no reduction was regarded as a positive sign for further investigating a treatment regimen. To limit the 4-arm total false-positive error rate to 0.15, the Hochberg procedure was used for statistical testing (11).

The main secondary efficacy outcome reported is change from baseline in pulmonary embolic burden by refined modified Miller score as assessed by CTA at 48 h after the start of the USCDT procedure (95% confidence intervals for mean changes). Statistical significance for changes from baseline were assessed by Student's *t*-test. This secondary analysis was also performed for both the ITT and mPP populations.

SAFETY ANALYSES. The safety population included patients in whom venous access was attempted specifically for USCDT. This population was used for all safety analyses. For the primary safety analysis, the number and percentage of subjects with major bleeding events within 72 h of start of USCDT procedure were reported with a 95% Wilson confidence interval. The frequencies and proportions of patients with symptomatic recurrent PE and death during the 30- and 365-day follow-up periods are reported with 95% Wilson score confidence intervals.

RESULTS

We randomized 101 patients, and patient disposition is shown in **Figure 1**. Baseline demographics are shown in **Table 1** and were similar across treatment groups, although arm 3 had more women and arm 4 had lower weight and body mass index than the other groups. Presenting symptoms, signs, biomarkers, and leg ultrasound results are shown in **Table 2**. Seventy-nine

TABLE 2 Presenting Symptoms and Signs (Intention-to-Treat Population*)

	Arm 1 (n = 28)	Arm 2 (n = 27)	Arm 3 (n = 28)	Arm 4 (n = 18)	All Patients (N = 101)
Dyspnea	24 (85.7)	24 (88.9)	27 (100.0)	18 (100.0)	94 (93.1)
Tachycardia†	15 (53.6)	9 (33.3)	13 (46.4)	5 (27.8)	42 (41.6)
Hypoxemia	5 (17.9)	9 (33.3)	7 (25.0)	4 (22.2)	25 (24.8)
Dizziness/lightheadedness	11 (39.3)	6 (22.2)	12 (42.9)	4 (22.2)	33 (32.7)
Syncope	4 (14.3)	5 (18.5)	6 (21.4)	5 (27.8)	20 (19.8)
Chest pain	15 (53.6)	11 (40.7)	13 (46.4)	8 (44.4)	47 (46.5)
Swollen lower extremity	5 (17.9)	5 (18.5)	7 (25.0)	4 (22.2)	21 (20.8)
Leg pain	8 (28.6)	3 (11.1)	3 (10.7)	4 (22.2)	18 (17.8)
DVT (ultrasound)	12 (42.9)	11 (40.7)	10 (35.7)	10 (55.6)	43 (42.6)
Elevated BNP or troponin I‡	20 (77.0)	23 (92.0)	23 (82.0)	11 (61.0)	77 (79.0)
Elevated BNP and troponin I§	9 (35.0)	8 (32.0)	6 (21.0)	5 (28.0)	28 (29.0)

Values are n (%). *The ITT patient population comprised all randomized patients; analyses were performed for primary and secondary efficacy endpoints for the ITT population. †Heart rate >100 beats/min. ‡Arm 1, n = 26; arm 2, n = 25; arm 3, n = 28; arm 4, n = 18; all patients, N = 97. §Arm 1, n =26; arm 2, n = 25; arm 3, n = 28; arm 4, n = 18; all patients, N = 96.

BNP = B-type natriuretic peptide; other abbreviations as in Table 1.

percent of patients were at intermediate or high risk (abnormal right ventricle by echocardiography or CTA and abnormal biomarkers). Randomization to arm 4 was stopped after an ICH developed that was considered probably related to thrombolytic therapy and anticoagulation by the safety monitor. After review of the medical records, the steering committee determined that the patient may have been at increased risk for bleeding and required the protocol to be amended to exclude patients with histories of any hematologic disease likely to be associated with bleeding and to no longer enroll in arm 4 (12 mg of tPA per lung over 6 h). Of note, the concentration of tPA in the 24-mg infusion in our study was higher than in the ULTIMA (6) and SEATTLE II (7) trials (2 mg/h per catheter rather than 1 mg/h per catheter), and our infusion rates were shorter.

EFFICACY. Mean baseline RV-to-LV diameter ratio (Table 3) and mean refined modified Miller score improved from baseline in both the ITT and mPP populations. The patients treated with bilateral catheters had slightly higher but similar baseline RV-to-LV diameter ratios as those treated with unilateral catheters. In both the ITT and mPP populations, there was a stepwise reduction in refined modified Miller score (Table 4).

SAFETY. Bleeding. No major bleeding events occurred in arm 1 during the 72 h after the start of the USCDT procedure. In the other study arms, 4 patients had a total of 5 major bleeding events. Two of these patients received additional tPA beyond that designated by randomization after study treatment (Table 5). In arm 2, a 61-year-old woman developed anemia and ICH. Syncope resulted in facial trauma and anemia; the latter was considered related to the thrombolytic agent administered as USCDT. The USCDT procedure led to a significantly improved RV-to-LV diameter ratio. However, she developed probable recurrent PE causing hypotension 48 h after USCDT treatment and received a rapid infusion of 50 mg of intravenous tPA, which was followed by a nonfatal ICH, believed precipitated by the systemic tPA. At 2 years, she is alive, with mild right-hand neurological deficit (incoordination). In arm 3, a 35-year-old woman developed anemia in the setting of a bleeding uterine fibroid after receiving an additional 12 mg of tPA, beyond the assigned 12 mg. The anemia was likely related to or exacerbated by tPA. In

TABLE 3 RV-to-LV Diameter Ratio by CTA

	Arm 1	Arm 2	Arm 3	Arm 4
ITT population,* n	27	27	28	18
RV/LV diameter ratio at baseline	1.47 ± 0.39	1.43 ± 0.33	1.49 ± 0.37	1.51 ± 0.58
Change from baseline at 48 h	−0.40 ± 0.37	−0.35 ± 0.27	−0.42 ± 0.32	−0.48 ± 0.51
Percentage change from baseline at 48 h	−24.0 ± 15.9‡	−22.6 ± 14.1‡	−26.3 ± 16.8§	−25.5 ± 22.7
95% CI, %	−30.5 to −17.6	−28.3 to −16.9	−32.9 to −19.7	−36.8 to −14.2
p value† (2-sided Student's *t*-test comparing with baseline)	<0.0001	<0.0001	<0.0001	0.0011
mPP population,* n	22	21	24	16
RV/LV diameter ratio at baseline	1.51 ± 0.40	1.52 ± 0.31	1.51 ± 0.36	1.55 ± 0.60
Change from baseline at 48 h	−0.46 ± 0.38	−0.40 ± 0.27	−0.44 ± 0.32	−0.52 ± 0.52
Percentage change from baseline at 48 h	−26.9 ± 15.9‖	−24.8 ± 13.5	−26.9 ± 16.3	−27.26 ± 21.6
95% CI	−34.1 to −19.6	−30.9 to −18.7	−33.8 to −20.1	−38.8 to −15.7
p value† (2-sided Student's *t*-test comparing with baseline)	<0.0001	<0.0001	<0.0001	0.0013

Values are mean ± SD. *The intention-to-treat (ITT) patient population comprised all randomized patients; analyses were performed for primary and secondary efficacy endpoints for the ITT population. The modified-per-protocol (mPP) population comprised randomized patients who were treated with bilateral catheters and did not receive additional thrombolytic therapy as rescue therapy. †The p value is given for change from baseline to 48 h. ‡n = 26; 1 patient did not undergo follow-up computed tomographic angiography (CTA). §n = 27; 1 patient did not undergo follow-up CTA. ‖n = 21; 1 patient did not undergo follow-up CTA.

CI = confidence interval; LV = left ventricular; RV = right ventricular.

TABLE 4 Refined Modified Miller Score by CTA

	Arm 1	Arm 2	Arm 3	Arm 4
ITT population,* n	27	27	28	18
Baseline	20.33 ± 2.99	19.70 ± 4.62	21.14 ± 2.37	20.44 ± 4.12
Percentage change from baseline at 48 h	−5.5 ± 9.0‡	−9.2 ± 10.6§	−14.0 ± 11.7§	−25.7 ± 26.0
95% CI, %	−9.3 to −1.7	−13.4 to −4.9	18.7 to −9.2	38.6 to −12.8
p value† (1-sided)	0.0032	<0.0001	<0.0001	0.0003
mPP population,* n	22	21	24	16
Baseline	20.68 ± 1.73	20.95 ± 2.11	21.29 ± 1.30	21.06 ± 2.43
Percentage change from baseline at 48 h	−6.0 ± 10.0‖	−9.0 ± 9.9	−12.5 ± 11.0¶	−21.7 ± 24.7
95% CI, %	−10.8 to −1.2	−13.5 to −4.5	−17.2 to −7.7	−34.9 to −8.6
p value† (1-sided)	0.0085	0.0002	<0.0001	0.0016

Values are mean ± SD. *The ITT patient population comprised all randomized patients; analyses were performed for primary and secondary efficacy endpoints for the ITT population. The mPP population comprised randomized patients who were treated with bilateral catheters and did not receive additional thrombolytic therapy as rescue therapy. †The p value is given for percentage change from baseline at 48 h. ‡n = 24. §n = 26. ‖n = 19. ¶n = 23. See Online Appendix.

Abbreviations as in Tables 1 and 3.

arm 4, 2 patients each had an event considered related to thrombolysis: a 73-year-old man with hypertension developed ICH and died 11 days after USCDT while in a rehabilitation facility. His platelet count was low normal at 133,000/μl at admission, and there was a history of pancytopenia. He developed hypertension to 181/92 mm Hg after USCDT. The head computed tomographic scan revealing the ICH suggested the possibility of an arteriovenous malformation. Another patient had bleeding after USCDT from a splenic pseudoaneurysm treated with coil embolization with full recovery. Seven patients developed clinically relevant nonmajor bleeding (medical intervention required) in the first 72 h, including 2 with bleeding or hematoma at the USCDT insertion site, 1 bleeding from the venous sheath after placement of an RV assist device, 2 cases of hematuria, 1 case of epistaxis, and 1 scalp laceration.

Recurrent PE. Symptomatic recurrent PE confirmed by CTA occurred in 1 patient (1%) in arm 3, 18 days after the index event. He was not anticoagulated at the time, because he had not filled his anticoagulation prescription.

TABLE 5 Major Bleeding Within 72 h (Primary Safety Endpoint)

	Safety Population*			mPP*		
	n	n (%)	Events (%)	n	n (%)	Events (%)
Arm 1	27	0 (0)	0 (0)	22	0 (0)	0 (0)
Arm 2	27	1 (3.7)	2 (7.4)	21	1 (4.7)†	1 (4.7)†
Arm 3	28	1 (3.6)	1 (3.6)	24	0 (0)	0 (0)
Arm 4	18	2 (11.1)	2 (11.1)	16	2 (11.1)	2 (11.1)
All patients	100	4 (4)	5 (5)	83	3 (3.6)	3 (3.6)

*See text for definition of safety and mPP populations and details of major bleeding cases. †A major bleeding event of anemia is included here even though the patient subsequently received systemic tPA and had a second major bleeding event, which excluded her from the mPP population.

Abbreviations as in Tables 1 and 3.

Mortality. One patient (1%) died during the initial 30 days. The estimated 365-day mortality rate was 2% by the Kaplan-Meier method, which accounts for cases that were withdrawn and lost to follow-up. (Table 6).

DISCUSSION

In OPTALYSE PE (A Randomized Trial of the Optimum Duration of Acoustic Pulse Thrombolysis Procedure in Acute Intermediate-Risk Pulmonary Embolism) trial, USCDT with lower doses of thrombolytic therapy ranging from 4 to 12 mg per lung and shorter infusion times (2 to 6 h) than previously studied in intermediate-risk PE patients was associated with statistically significant improvement in RV-to-LV diameter ratio (the primary endpoint) for all arms in the ITT and mPP populations, compared with baseline. The RV-to-LV diameter ratio improved in each of the 4 arms by approximately 25%. The refined modified Miller score also statistically improved from baseline in each arm in both ITT and mPP patients, although the improvement increased as the tPA dose and infusion duration increased. Most patients (86%) underwent treatment of both lungs (2 catheters). Patients in whom 1 lung (1 catheter) was treated were equally divided among the 4 arms, and the numbers were too small to meaningfully analyze separately.

The major bleeding rate was 4.0% for the ITT population and 3.6% for the mPP group, 1 of which was an ICH. This event appeared related to USCDT. A second ICH occurred after delivery of systemic tPA 50 mg for probable recurrent massive PE and was likely due to the subsequent systemic thrombolysis. There were no ICH events in the ULTIMA and SEATTLE II trials and 2 such events in OPTALYSE PE trial (6,7). Thus, in the 277 patients in these 3 USCDT trials, the ICH event rate was 0.72%, with only 1 attributable to USCDT (0.36%).

TABLE 6 All-Cause Mortality and Recurrent Pulmonary Embolism in Safety Population*

		All-Cause Mortality		Confirmed Recurrent PE		Suspected Recurrent PE	
	n	Within 30 Days	Within 365 Days	Within 30 Days	Within 365 Days	Within 30 Days	Within 365 Days
Arm 1	27	0 (0)	1 (3.7)†	0 (0)	0 (0)	0 (0)	0 (0)
Arm 2	27	0 (0)	0 (0)	0 (0)	1 (3.7)	1 (3.7)‡	1 (3.7)‡
Arm 3	28	0 (0)	0 (0)	1 (3.6)	1 (3.6)	0 (0)	0 (0)
Arm 4	18	1 (5.6)§	1 (5.6)§	0 (0)	0 (0)	0 (0)	0 (0)
All patients	100	1 (1)	2 (2‖)	1 (1)	2 (2)	1 (1)	1 (1)

Values are n (%). *At 30 days, 2 patients were lost to follow-up, 1 had died, and 1 had withdrawn; thus, 96 patients were assessed for safety through 30 days. At 1-year follow-up, 1 more patient had withdrawn (total 2), and 1 more had died (total 2). Although 13 more were lost to follow-up (total 15), 12 of the 15 were confirmed alive at 365 days. †Patient death attributed to complications of chronic obstructive pulmonary disease and multiple organ failure 177 days after USCDT. PE noted on imaging but believed to be chronic by adjudication committee. ‡Subject was symptomatic, but no diagnostic imaging was collected before treatment with systemic tissue-type plasminogen activator for suspected recurrent massive PE. §Death was attributed to cardiac arrest. No follow-up imaging or autopsy was performed to rule out recurrent PE. ‖Estimated mortality rate was 2% by Kaplan-Meier method.

Abbreviations as in Table 1.

We believed that the RV-to-LV diameter ratio serves as a reproducible and well-validated tool for identifying patients with PE at risk for adverse outcomes, including increased 30-day mortality (12–14). Therefore, we chose change in the RV-to-LV diameter ratio as our primary endpoint. We are not certain why the RV-to-LV diameter ratio improved similarly across all arms, while the refined modified Miller score representing clot burden improved as the dose increased and the infusion duration increased. This observation suggests that there is not a direct correlation between the pulmonary arterial embolic burden and RV dilation. Perhaps relatively low doses of thrombolytic agents can improve functional vessel radius enough to improve pulmonary perfusion (Poiseuille's law) (15) and thus RV-to-LV diameter ratio, but to produce a similar reduction in overall clot burden, higher doses or longer infusions of thrombolytic are required.

The rate of recurrent PE in this trial was 1% at 30 days (1 patient confirmed), which is similar to the rate reported with standard anticoagulation (16). This observation emphasizes the need to be vigilant with outpatient follow-up, because our patient who experienced recurrent PE had not filled his prescription for anticoagulant medication.

STUDY LIMITATIONS. Limitations of our study include the relatively small number of patients in each arm. However, we had a combined group of 100 patients undergoing USCDT, and all arms demonstrated statistically significant improvement in both RV-to-LV diameter ratio and refined modified Miller score. The absence of a heparin control was a limitation. Although the ULTIMA trial (head-to-head USCDT vs. heparin) proved that USCDT results in more rapid improvement in RV-to-LV diameter ratio (and pulmonary artery pressure) than anticoagulation alone, the endpoint was 24 h, not 48 h as in our study. Thus, we cannot rule out that continued anticoagulation and endogenous thrombolysis contributed to the improved RV-to-LV diameter ratio and refined modified Miller score at 48 h. Furthermore, there has been no head-to-head comparison of USCDT with other delivery catheters, and the lack of a standard catheter thrombolytic infusion arm was a limitation. Although this would have been ideal, we did not have the resources to include such an arm.

A primary strength of the study included the use of lower doses of tPA delivered over a shorter period than traditionally studied. The randomized design was also important in minimizing bias, which, for example, might have favored administering higher doses or longer infusions of tPA to patients with higher RV-to-LV diameter ratios or higher refined modified Miller score values. Another strength was including the refined modified Miller score as a secondary endpoint, demonstrating that RV-to-LV diameter ratio can improve significantly even without a substantial (although still a statistically significant) improvement in obstruction score. Importantly, all imaging studies were read by a central laboratory in a blinded manner, without knowledge of tPA dose or infusion duration.

Our study demonstrated that lower doses of tPA than previously studied with USCDT were associated with favorable improvement in RV-to-LV diameter ratio and with low major bleeding rates. This is consistent with data suggesting that lower doses of systemic tPA also achieve favorable results, with less bleeding (17). In intermediate-risk PE, it has been shown that RV-to-LV diameter ratio is improved at 24 h with USCDT compared with anticoagulation alone (6) and is associated with improvement at 48 h compared with baseline in intermediate-risk patients and in a small population of massive PE (7) patients, with a low major bleeding rate without ICH.

There remains a paucity of high-quality randomized trials of catheter-directed thrombolysis with

adequate controls in acute PE (18–20). Such trials are needed to determine short- and long-term benefit, to identify patients most likely to benefit, and to learn whether this strategy prevents adverse long-term outcomes such as post-PE syndrome and chronic thromboembolic pulmonary hypertension. Future trials examining other clinical endpoints should also be considered (21). Studies examining health care costs and outcomes, such as hemodynamic deterioration and quality of life, will also inform the optimal use of this technology (22).

CONCLUSIONS

We have demonstrated that USCDT using lower doses and shorter infusions of thrombolytic therapy in acute intermediate-risk PE is associated with an improvement in RV-to-LV diameter ratio as well as a reduction in clot burden at 48 h. We believe that USCDT using lower dose and shorter infusion regimens has potential in this setting and should be further studied and refined in future trials.

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PERSPECTIVES

WHAT IS KNOWN? Acute intermediate-risk PE patients are critically important to study because they are common in clinical practice and because the parameters that define them, including abnormal RV function and elevated B-type natriuretic peptide and troponin, are associated with increased mortality. USCDT using doses of tPA in the range of 20 to 24 mg delivered over 12 to 24 h has been associated with improved RV-to-LV diameter ratio within 24 to 48 h, although improved mortality has not been demonstrated.

WHAT IS NEW? Lower doses of tPA and shorter infusion durations than previously studied appear to be safe and effective in acute intermediate-risk PE patients with improved RV-to-LV diameter ratio and reduced clot burden demonstrated at 48 h.

WHAT IS NEXT? Future clinical trials should focus on carefully selected acute intermediate- and high-risk patients with goals of refining the ideal USCDT regimen. These trials should include comparator groups of anticoagulation alone, systemic fibrinolysis, or other catheter-based techniques focusing on very short-term as well as longer-term clinical outcomes, which will be critical in defining how USCDT should be applied to patients with acute PE. Registries that include "real-world data" may complement such research.

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APPENDIX For the calculation of pulmonary embolism burden (obstruction score), please see the online version of this paper.