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EDITORIAL COMMENT

Catheter-Directed Thrombolysis for Pulmonary Embolism

Where Do We Stand?*

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There have been 2 main treatments for acute pulmonary embolism (PE)—anticoagulant therapy alone or systemic thrombolytic therapy. Although systemic thrombolytic therapy is effective at preventing deaths from PE, it markedly increases bleeding, including intracranial and fatal bleeding (1). The recent PEITHO (Pulmonary Embolism Thrombolysis Study) (2), which compared tenecteplase with placebo in 1,000 PE patients without hypotension but with right ventricular dysfunction, found no clear net benefit from systemic thrombolytic therapy; the reduction in cardiovascular collapse (odds ratio: 0.30) was offset by the increase in major bleeding (odds ratio: 5.2). Consequently, systemic thrombolytic therapy is usually reserved for PE patients with hypotension (3). The ability to actively remove thrombus in patients with acute PE without increasing bleeding would be an important advance. Catheter-based therapy has that potential.

Catheter-directed thrombolysis (CDT) was initially developed for treatment of arterial, dialysis graft, and deep vein thromboses (leg or arm). When used to treat acute PE, a wire is usually passed through the embolus, followed by placement of a multiside hole infusion catheter through which a thrombolytic drug is infused over 12 to 24 h (4). The delivery of the drug directly into the thrombus is expected to be as effective as systemic therapy but to cause less bleeding because a much lower dose of the drug is used. If more rapid thrombus removal is required, such as in a decompensating patient, fragmentation, balloon maceration, and aspiration may be used as adjunct to CDT or instead of it (i.e., in patients with a high risk of bleeding). These mechanical techniques, however, are avoided in stable patients because they may cause pulmonary artery injury. The addition of an ultrasound-emitting wire to a multiside hole infusion catheter is thought to accelerate thrombolysis by ultrasonically disrupting thrombus (5). Although this approach has been used to treat arterial and deep venous thromboses for about 10 years, there is uncertainty that the addition of ultrasound emission increases the efficacy of CDT (6). Based partly on the findings of the SEATTLE II (A Prospective, Single-Arm Multi-Center Trial of EkoSonic Endovascular System and Activase for Treatment of Acute Pulmonary Embolism) study, which is reported in this issue of *JACC: Cardiovascular Interventions*, ultrasound-assisted CDT is now approved by the U.S. Food and Drug Administration for treatment of acute PE (7).

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SEATTLE II is a single-arm prospective cohort study in which 150 patients with lobar artery or more central PE (31 with and 119 without hypotension) were treated with ultrasound-assisted CDT using a standardized protocol (7). Tissue plasminogen activator was infused into each treated lung at a rate of 1 mg/h, to a total dose of 24 mg (over 12 h for bilateral lung infusions), and no additional mechanical maneuvers were used to disrupt or aspirate thrombus. When computed tomography pulmonary angiography was repeated after 48 h, the right ventricular to left ventricular ratio was decreased by 27% and thrombus burden was reduced

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by 30%. Pulmonary artery pressure also decreased by 27% between the start to the end of CDT. These 3 improvements were each highly statistically significant. There were 17 episodes of major bleeding in 15 patients (10%): one was associated with hypotension; all required transfusion; none was intracranial; and none was fatal. Strengths of the SEATTLE II study include its prospective design, inclusion of 150 patients, high patient retention, involvement of many clinical centers, standardized treatment protocol, and rigorous reporting. Limitations include that there was no comparison group (neither anticoagulation alone nor systemic thrombolytic therapy), short-term surrogate outcomes were used to assess efficacy, and that long-term outcomes such as quality of life or exercise capacity were not assessed. SEATTLE II also did not assess whether ultrasound-assisted CDT was more effective than standard CDT.

So, how effective and safe is CDT? The short-term improvements in right ventricular dimensions, thrombus burden, and pulmonary hypertension in SEATTLE II are consistent with the improvement in right ventricular dimension with ultrasound-facilitated CDT in 35 patients in the ULTIMA (Ultrasound Accelerated Thrombolysis of Pulmonary Embolism) study (8). In ULTIMA, there was almost no improvement in this outcome at 24 h in the 35 patients who were randomized to anticoagulant therapy alone, and the difference between the CDT and anticoagulant therapy alone groups was highly statistically significant. A recently published prospective registry of 101 patients with acute PE (PERFECT [Pulmonary Embolism Response to Fragmentation, Embolectomy, and Catheter Thrombolysis]) (9) reported similar efficacy of CDT, with or without ultrasound-assisted thrombolysis, to ULTIMA and SEATTLE. There was no major bleeding in this registry, although follow-up may not have been as standardized as the follow-up for the SEATTLE II and ULTIMA studies. The improvements in imaging and pulmonary artery pressure with ultrasound-assisted CDT in SEATTLE II and ULTIMA also appear to be at least as marked as the short-term improvements in these outcomes with systemic thrombolytic therapy (10). Therefore, based mostly on indirect comparisons of short-term surrogate outcomes, CDT appears to be effective compared with anticoagulant therapy alone and probably is as effective as systemic thrombolytic therapy, which uses much higher dose of the thrombolytic drug. The frequency of major bleeding in SEATTLE II, however, suggests that CDT may be associated with substantially more bleeding than anticoagulation alone. Although it is encouraging that there were no intracranial bleeds in the 150 patients in SEATTLE II, the upper boundary of the 95% confidence interval on this estimate is 2.4%. Although it seems likely that there is a lower risk of nonprocedural bleeding with CDT than with systemic thrombolytic therapy, this remains uncertain.

What then is the role of CDT in patients with PE? We think that current evidence suggests that CDT is preferred to systemic thrombolytic therapy in patients with acute PE who require active thrombus removal and have risk factors for bleeding. We suggest that venous puncture for CDT should always be ultrasound-guided and that the total dose of thrombolytic drug should be kept to a minimum in patients with a high risk of bleeding (3). If there is need for active thrombus removal in patients with a very high risk of bleeding, it may be necessary to use catheter-based therapy without thrombolytic drug or to use surgical embolectomy. We are not ready to encourage use of CDT in preference to anticoagulation alone in stable patients with acute PE and right ventricular dysfunction. We suggest that there is a need for evidence that the short- and long-term benefits of CDT outweigh the associated risk of bleeding before CDT can be recommended for such patients. We encourage randomized trials that compare CDT with systemic thrombolytic therapy in unstable patients with PE and compare CDT with anticoagulation alone in stable patients who have large PE and right ventricular dysfunction. Evidence from such studies would place the role of CDT for PE on a firmer footing.

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KEY WORDS catheter-directed, endovsacular therapy, pulmonary embolism, thrombolysis, treatment

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A Prospective, Single-Arm, Multicenter Trial of Ultrasound-Facilitated, Catheter-Directed, Low-Dose Fibrinolysis for Acute Massive and Submassive Pulmonary Embolism

The SEATTLE II Study

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ABSTRACT

OBJECTIVES This study conducted a prospective, single-arm, multicenter trial to evaluate the safety and efficacy of ultrasound-facilitated, catheter-directed, low-dose fibrinolysis, using the EkoSonic Endovascular System (EKOS, Bothell, Washington).

BACKGROUND Systemic fibrinolysis for acute pulmonary embolism (PE) reduces cardiovascular collapse but causes hemorrhagic stroke at a rate exceeding 2%.

METHODS Eligible patients had a proximal PE and a right ventricular (RV)-to-left ventricular (LV) diameter ratio ≥0.9 on chest computed tomography (CT). We included 150 patients with acute massive (n = 31) or submassive (n = 119) PE. We used 24 mg of tissue-plasminogen activator (t-PA) administered either as 1 mg/h for 24 h with a unilateral catheter or 1 mg/h/catheter for 12 h with bilateral catheters. The primary safety outcome was major bleeding within 72 h of procedure initiation. The primary efficacy outcome was the change in the chest CT–measured RV/LV diameter ratio within 48 h of procedure initiation.

RESULTS Mean RV/LV diameter ratio decreased from baseline to 48 h post-procedure (1.55 vs. 1.13; mean difference, −0.42; $p < 0.0001$). Mean pulmonary artery systolic pressure (51.4 mm Hg vs. 36.9 mm Hg; $p < 0.0001$) and modified Miller Index score (22.5 vs. 15.8; $p < 0.0001$) also decreased post-procedure. One GUSTO (Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries)-defined severe bleed (groin hematoma with transient hypotension) and 16 GUSTO-defined moderate bleeding events occurred in 15 patients (10%). No patient experienced intracranial hemorrhage.

CONCLUSIONS Ultrasound-facilitated, catheter-directed, low-dose fibrinolysis decreased RV dilation, reduced pulmonary hypertension, decreased anatomic thrombus burden, and minimized intracranial hemorrhage in patients with acute massive and submassive PE. (A Prospective, Single-arm, Multi-center Trial of EkoSonic® Endovascular System and Activase for Treatment of Acute Pulmonary Embolism (PE) [SEATTLE II]; NCT01513759) (J Am Coll Cardiol Intv 2015;8:1382–92) © 2015 by the American College of Cardiology Foundation.

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The Surgeon General estimates that 100,000 to 180,000 deaths occur annually from pulmonary embolism (PE) in the United States (1). Advanced therapies, such as systemic fibrinolysis and embolectomy, have the potential to reduce right ventricular (RV) pressure overload in massive (2) and submassive PE (3,4) and lower mortality by reversing pulmonary arterial obstruction and RV failure.

In the largest study of full-dose systemic fibrinolysis, tenecteplase reduced the risk of death or cardiovascular collapse by 56% in 1,006 submassive PE patients (5). However, this benefit was offset by a nearly 5-fold increased risk of major bleeding and a 10-fold increased risk of hemorrhagic stroke. Meta-analyses of trials of systemic fibrinolysis for acute PE have demonstrated similar findings (6,7).

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Concern over the risk of intracranial hemorrhage, which approaches 3% to 5% outside of clinical trials (8,9), has dampened clinician enthusiasm for full-dose systemic fibrinolysis and has sparked development of alternative advanced therapies with lower bleeding risk. Pharmacomechanical catheter-directed therapy combines fibrinolytic therapy with mechanical disruption of the thrombus (10–12). The high-frequency, low-power ultrasound component of ultrasound-facilitated, catheter-directed, low-dose fibrinolysis is hypothesized to disaggregate fibrin fibers, potentially allowing greater penetration of the fibrinolytic agent (13). This therapeutic strategy requires only a fraction of the systemic fibrinolytic dose. This dose reduction might improve the safety of fibrinolysis for PE. In a randomized, controlled trial of 59 patients with submassive PE in Europe, there were no major bleeding complications with ultrasound-facilitated, catheter-directed, low-dose fibrinolysis, which rapidly improved RV function compared with anticoagulation alone (14).

To expand our understanding of the efficacy and safety of ultrasound-facilitated, catheter-directed, low-dose fibrinolysis to reverse RV dysfunction in acute massive or submassive PE, we conducted a prospective, single-arm, multicenter trial (**Central Illustration**) (NCT01513759).

ABBREVIATIONS AND ACRONYMS

CT = computed tomography
DVT = deep vein thrombosis
PE = pulmonary embolism
RV = right ventricular
RV/LV = right ventricular-to-left ventricular
t-PA = tissue-plasminogen activator

METHODS

STUDY DESIGN. From June 2012 to February 2013, we screened 159 hospitalized patients with acute massive or submassive PE and enrolled 150 in this prospective, single-arm trial of ultrasound-facilitated, catheter-directed, low-dose fibrinolysis (**Figure 1**). Study patients were recruited at 22 sites across the United States, including urban, nonurban, teaching, and nonteaching hospitals. Institutional review board approval was obtained at all sites, and written informed consent was obtained for every patient. The results of this prospective, single-arm, multicenter trial were presented in abstract form on March 30, 2014, at the American College of Cardiology Annual

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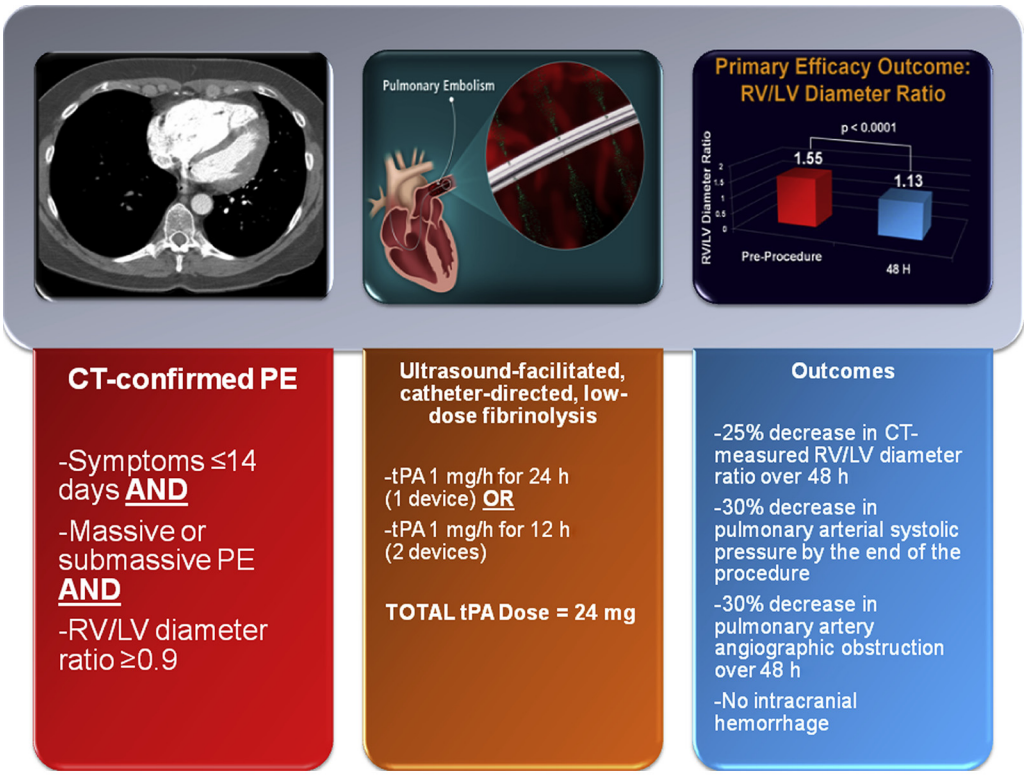
CENTRAL ILLUSTRATION **Ultrasound-Facilitated, Catheter-Directed, Low-Dose Fibrinolysis for Acute Massive and Submassive Pulmonary Embolism**



Piazza, G. et al. J Am Coll Cardiol Intv. 2015; 8(10):1382–92.

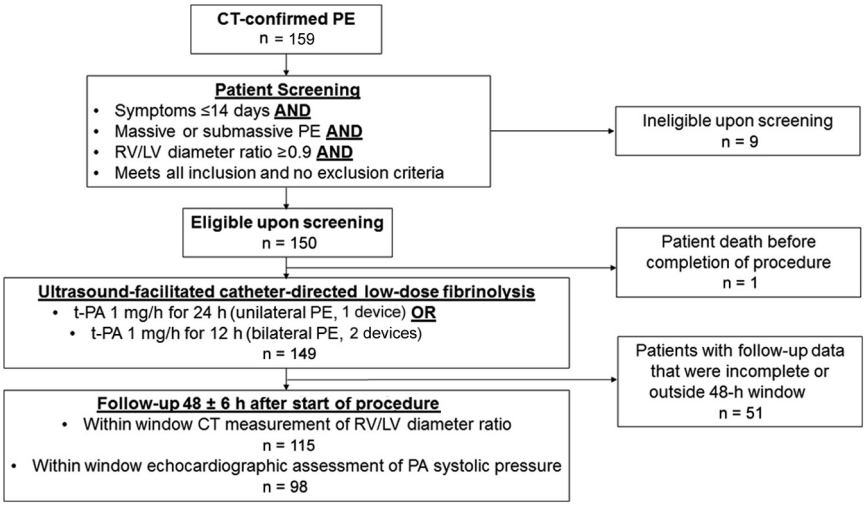
A total of 150 patients with computed tomography (CT)-confirmed pulmonary embolism (PE), symptoms for 14 days or less, and a right ventricular (RV)/left ventricular (LV) diameter ratio of at least 0.9 underwent ultrasound-facilitated, catheter-directed, low-dose fibrinolysis according to a standardized protocol. Ultrasound-facilitated, catheter-directed, low-dose fibrinolysis for acute massive and submassive pulmonary embolism (PE) improved RV function, decreased pulmonary hypertension, and minimized intracranial hemorrhage. PA = pulmonary artery; tPA = tissue plasminogen.

Scientific Sessions in Washington, DC. The trial was designed and led by an Executive Committee (G.P. and S.Z.G.) from the Study Coordinating Center. The Executive Committee established the data analysis plan and participated in the statistical analysis.

STUDY POPULATION. Patients were potentially eligible to participate if they had a proximal PE (filling defect in at least 1 main or lobar pulmonary artery), age 18 years or older, PE symptom duration ≤14 days, and RV/LV diameter ratio ≥0.9 on contrast-enhanced chest computed tomography (CT). We included patients with massive (defined as syncope, systemic arterial hypotension, cardiogenic shock, or resuscitated cardiac arrest) or submassive (defined as a normotensive patient with PE and evidence of RV dysfunction) PE. Major exclusion criteria were stroke or transient ischemic attack, head trauma, or other active intracranial or intraspinal disease within 12 months; major surgery within 7 days; recent active bleeding from a major organ; hematocrit <30%; platelets <100,000/μl; International Normalized Ratio >3; serum creatinine >2 mg/dl; and systolic blood pressure <80 mm Hg despite vasopressor or inotropic support (Online Appendix). Obesity was defined as a clinical diagnosis of obesity in the medical record.

ANTICOAGULATION. Anticoagulation was initiated with full-dose intravenous unfractionated heparin with a target activated partial thromboplastin time of 60 to 80 s. For patients who had already received low-molecular weight heparin or fondaparinux, the initiation of intravenous unfractionated heparin was delayed by 12 h. After completion of the procedure, all subjects received full anticoagulation. The drug,

FIGURE 1 Flow of Patients Through Each Stage of the Trial



One hundred fifty nine patients with acute pulmonary embolism (PE) were screened for eligibility across 22 study sites. One hundred fifty patients were eligible for enrollment. One patient died before the ultrasound-facilitated, catheter-directed, low-dose fibrinolytic procedure could be completed. One hundred fifteen patients had a within-window contrast-enhanced chest computed tomogram (CT) for measurement of change in right ventricular-to-left ventricular (RV/LV) diameter ratio. Ninety eight patients had a within-window echocardiogram to estimate 48-h pulmonary artery (PA) systolic pressure. t-PA = tissue-plasminogen activator.

dose, frequency, and duration of anticoagulation were selected by the attending physician.

ULTRASOUND-FACILITATED, CATHETER-DIRECTED, LOW-DOSE FIBRINOLYSIS. The EkoSonic Endovascular System (EKOS, Bothell, Washington) comprises 3 components: the Intelligent Drug Delivery Catheter, a removable MicroSonic device, and a reusable EkoSonic control unit. The procedure was performed by an experienced operator from Interventional Cardiology, Interventional Radiology, Vascular Surgery, or Cardiothoracic Surgery. Venous access was obtained, most often with ultrasound guidance, via the common femoral or internal jugular vein. After catheter placement but before activation of ultrasound and infusion of fibrinolytic therapy, baseline right heart pressures were transduced through the catheters. Because the catheters are placed in or adjacent to the PE, the fibrinolytic agent is delivered directly to the thrombus.

The fixed-dose regimen of tissue-plasminogen activator (t-PA) (Genentech, South San Francisco, California) was 24 mg at 1 mg/h with saline coolant at 35 ml/h for both unilateral and bilateral PEs. The fibrinolytic agent is not infused under pressure, but rather drips out of microscopic side holes. For patients with predominantly unilateral PE, a single continuous catheter-directed pulmonary artery infusion of t-PA was used for 24 h. For patients with bilateral PE, 2 drug delivery devices were placed, and a continuous infusion of t-PA was administered in each catheter for 12 h. No adjunctive interventional techniques to assist thrombus removal or dissolution were permitted. During the procedure, intravenous unfractionated heparin was continued at intermediate intensity with a target aPTT of 40 to 60 s. After removal of the drug delivery device(s), the access site was manually compressed for at least 5 min. Fifteen minutes after achieving hemostasis, full therapeutic anticoagulation was restarted.

FOLLOW-UP. After completion of the procedure but before catheter removal, right heart pressures were measured. Right heart pressure measurements were transduced once before activation of ultrasound and infusion of fibrinolytic therapy and once after completion of the procedure. The post-procedure invasive hemodynamic assessment was performed at either 12 or 24 h after the initiation of fibrinolysis. In the 86% of patients with bilateral PEs who underwent ultrasound-facilitated, catheter-directed, low-dose fibrinolysis via bilateral catheters, the post-procedure hemodynamic assessment was performed at 12 h after initiation of the procedure, before catheter removal. For the remaining patients who had unilateral ultrasound-facilitated, catheter-directed, low-dose fibrinolysis via a single catheter, the post-procedure hemodynamic assessment was performed at 24 h after initiation of the procedure, before

catheter removal. Multiple right heart pressure measurements or "averaging" values were not allowed for assessment of baseline and post-procedure pressures. Follow-up contrast-enhanced chest CT and transthoracic echocardiography were performed within 48 ± 6 h after initiation of the procedure. The changes in the RV/LV diameter ratio and modified Miller angiographic obstruction index score (15) were assessed by the contrast-enhanced chest CT performed at baseline and at 48 h. The maximal modified Miller Index score is 40, corresponding with occlusion of all pulmonary artery segments. Echocardiography was performed to estimate pulmonary artery systolic pressure at 48 ± 6 h. All CT scans and echocardiograms were analyzed at a dedicated, blinded imaging core laboratory (Syntactx, New York, New York).

Bleeding complications were assessed for 72 h after the procedure. Patients were assessed clinically for recurrent, symptomatic PE at 30 days after the procedure. Recurrent PE was defined as symptomatic and objectively confirmed with contrast-enhanced chest CT, ventilation-perfusion lung scanning, or invasive contrast pulmonary angiography. Overall, 149 of 150 patients (99.3%) completed the required clinical follow-up.

OUTCOMES. The primary efficacy outcome was the core laboratory-measured change in the RV/LV diameter ratio from baseline, as assessed by contrast-enhanced chest CT at baseline and at 48 ± 6 h after initiation of procedure (16). A secondary efficacy outcome was the change in pulmonary artery systolic pressure, as assessed by baseline right heart catheterization compared with measurements obtained at the conclusion of the procedure and as estimated by transthoracic echocardiography at 48 h. An additional secondary outcome was the change in the modified Miller angiographic obstruction index score, as assessed by the baseline contrast-enhanced chest CT and the follow-up scan performed at 48 h.

The primary safety outcome was major bleeding within 72 h of initiation of the procedure. Bleeding events were classified by the GUSTO (Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries) bleeding criteria (Online Appendix) (17). Severe or life-threatening bleeding was defined as either intracranial hemorrhage or bleeding that caused hemodynamic compromise and required intervention. Moderate bleeding required blood transfusion but did not result in hemodynamic compromise. Mild bleeding did not meet criteria for either severe/life-threatening or moderate bleeding. We defined major bleeding as either a GUSTO moderate or a GUSTO severe/life-threatening bleeding event. All monitoring for major bleeding within 72 h was performed during the hospitalization.

TABLE 1 Baseline Demographics and Clinical Characteristics (N = 150)

Patient	
Age, yrs	59 ± 16.1
Body mass index, kg/m^2	35.6 ± 9.1
Female	77 (51.3)
Ethnicity/race	
Caucasian	119 (79.3)
African American	22 (14.7)
Hispanic or Latino	9 (6)
Comorbid conditions	
Obesity	82 (54.7)
Concomitant use of antiplatelet medications	51 (34)
Immobility within 30 days of PE	45 (30)
Diabetes mellitus	42 (28)
Family history of venous thromboembolism	31 (20.7)
Previous DVT	30 (20)
Active tobacco use	27 (18)
Active infectious illness within 30 days of PE	20 (13.3)
Atherosclerotic cardiovascular disease	18 (12)
Previous PE	15 (10)

Values are mean ± SD or n (%).
DVT = deep vein thrombosis; PE = pulmonary embolism.

The secondary safety outcomes included symptomatic recurrent PE up to 30 days after the initiation of the procedure, all-cause mortality at hospital discharge and through 30 days, and technical procedural complications. Mortality was further classified as related to cancer, myocardial infarction, PE, or other causes. Death was attributed to PE if it was either sudden or unsuspected or if there was evidence to support an association with PE. All safety outcomes, including bleeding complications, were

TABLE 2 Characteristics of PE and Initial Anticoagulation (N = 150)

Any symptoms of PE	150 (100)
Duration of symptoms, days	
≤14	149 (99.3)
>14	1 (0.7)
PE subtype	
Submassive	119 (79.3)
Massive	31 (20.7)
Pre-procedure anticoagulation*	
Intravenous unfractionated heparin	76 (50.7)
Enoxaparin	54 (36)
Warfarin	16 (10.7)
Other	7 (4.7)
None	24 (16)

Values are n (%). *Patients could have received more than 1 anticoagulant.
PE = pulmonary embolism.

TABLE 3 Procedural Characteristics

Total dose of t-PA, mg*	23.7 ± 2.9
Successful device placement†	278 (97.5)
Access sites‡	
Right femoral vein	177 (63.7)
Left femoral vein	61 (21.9)
Right internal jugular vein	31 (11.2)
Other	9 (3.2)
No. of devices per patient*	
0	1 (0.7)
1	20 (13.3)
2	129 (86)
Completed infusion of t-PA‡	272 (97.8)

Values are mean ± SD or n (%). *N = 150 patients (1 patient died before devices could be placed). †Devices attempted = 285. ‡Devices placed = 278.
t-PA = tissue-plasminogen activator.

adjudicated by a designated independent Study Safety Monitor (M.R.J.).

STATISTICAL ANALYSIS. We estimated that at 48 h after the procedure, there would be at least a 0.27 mean decrease from baseline in the RV/LV diameter ratio, based on a study that compared RV/LV diameter ratios at baseline and after reperfusion in patients undergoing systemic fibrinolysis or surgical pulmonary embolectomy for acute PE (18). A 20% decrease in the RV/LV diameter ratio was observed in a previous systemic fibrinolysis study (19) and served as the basis for our sample size estimate. With recruitment of 118 evaluable subjects in our present study, the power was ~0.89 to detect a >0.2 mean RV/LV diameter ratio decrease, with a SD of 0.24, at a 2-sided $p < 0.05$ significance level by *t* test.

Results for continuous variables were compared with baseline using a paired *t* test or Wilcoxon signed rank test. For 2-group comparisons, a 2-sample *t* test or Wilcoxon rank sum test was used for continuous data, and the Fisher exact test was used for binary data. All reported p values were 2-sided, and a p value <0.05 was considered statistically significant. An intercept-only mixed model repeated measures analysis was conducted with change in RV/LV diameter ratio as the dependent variable and study site (n = 22) fitted as a random effect to assess the variance in the change in RV/LV diameter ratio across the study sites. All statistical analyses were performed using SAS statistical software version 9.2 (SAS Institute, Cary, North Carolina).

ROLE OF FUNDING. The sponsor had no role in data interpretation or writing the manuscript. G.P. and S.Z.G. had full access to the data and had final responsibility for the decision to submit for publication. The sponsor of the trial was in possession of the database.

RESULTS

BASELINE DEMOGRAPHICS AND CLINICAL CHARACTERISTICS. The mean age was 59 years (Table 1). The mean body mass index (35.6 kg/m^2) was consistent with an obese patient population. Common risk factors for PE included obesity (55%), immobility within 30 days of PE diagnosis (30%), family history of venous thromboembolism (21%), and personal history of deep vein thrombosis (DVT) (20%) or PE (10%). Mean serum creatinine was 1.0 mg/dl.

CHARACTERISTICS OF A PE. All patients had symptomatic PEs (Table 2). The duration of PE symptoms was 14 days or less, with the exception of a single patient who was subsequently found to have symptoms for more than 14 days. Submassive PE and massive PE were observed in 79% and 21% of patients, respectively.

PROCEDURAL CHARACTERISTICS. The mean total dose of t-PA was 24 mg (Table 3). Of 285 devices that were attempted to be placed, 98% were successfully placed. Right femoral venous access was most frequently used for device placement (64%). Ultrasound guidance was used in 73% of vascular access procedures for catheter placement. Bilateral devices were placed in 86% of patients. Bilateral catheters to treat bilateral PE were placed through a single-access site in the majority of patients (57%).

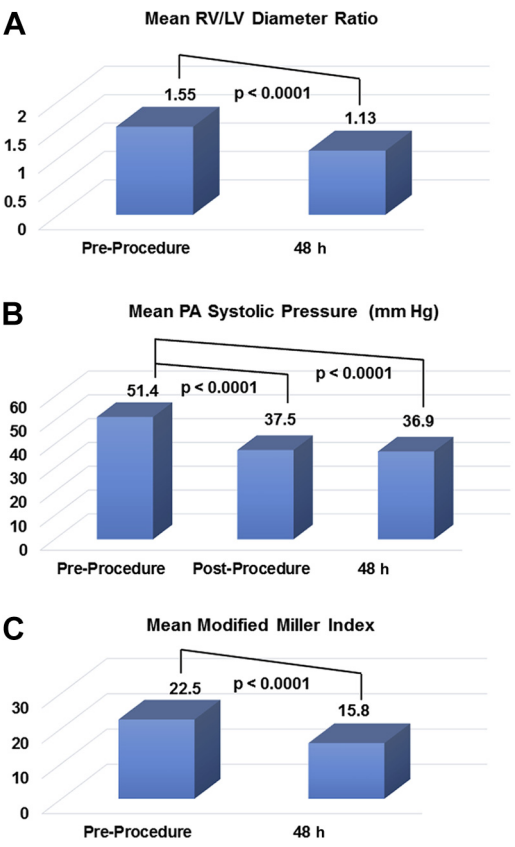
EFFICACY OUTCOMES. Thirty-five patients did not have follow-up chest CT performed within the 48 ± 6-h window. The mean RV/LV diameter ratio decreased from 1.55 at baseline to 1.13 at 48 ± 6 h after initiation of the procedure (mean difference, −0.42; $p < 0.0001$) (Table 4, Figure 2). Invasively measured mean pulmonary artery systolic pressure decreased from 51.4 mm Hg at baseline to 37.5 mm Hg at the completion of the procedure (mean difference,

TABLE 4 Efficacy Outcomes*

Outcome	Baseline	At Procedure Completion	Absolute Difference	48 h After Procedure	Absolute Difference
PA systolic pressure, mm Hg	51.4 ± 16	37.5 ± 11.9†	−14 ± 15	36.9 ± 14.9‡	−14.4 ± 15.4
RV/LV diameter ratio	1.55 ± 0.39	-	-	1.13 ± 0.2§	−0.42 ± 0.36
Modified Miller Index	22.5 ± 5.7	-	-	15.8 ± 5.9‖	−6.6 ± 6.3

Values are mean ± SD. *All p values <0.0001. †Patients with complete right heart catheterization data = 147. ‡Patients with transthoracic echocardiogram performed within both the baseline and the 48 ± 6-h window = 98. §Patients with contrast-enhanced chest computed tomography performed within both the baseline and the 48 ± 6-h window = 115. ‖Patients with contrast-enhanced chest computed tomography performed within both the baseline and the 48 ± 6-h window = 116.
PA = pulmonary artery; RV/LV = right ventricular-to-left ventricular.

FIGURE 2 Efficacy Outcomes



(A) Change in contrast-enhanced CT-determined mean RV/LV diameter ratio from baseline to 48 ± 6 h after initiation of the ultrasound-facilitated, catheter-directed, low-dose fibrinolytic procedure. **(B)** Change in invasively measured mean systolic pulmonary artery pressure from baseline to completion of the ultrasound-facilitated, catheter-directed, low-dose fibrinolysis and to 48 ± 6 h after the procedure as estimated by transthoracic echocardiogram. **(C)** Change in contrast-enhanced CT-determined mean modified Miller pulmonary angiographic obstruction index score from baseline to 48 ± 6 h after initiation of the ultrasound-facilitated, catheter-directed, low-dose fibrinolytic procedure. Abbreviations as in Figure 1.

TABLE 5 Safety Outcomes (N = 150)

Length of stay, SD, days	8.8 ± 5
In-hospital death	3 (2)
30-day mortality*	4 (2.7)
Serious and severe adverse events potentially related to device	3 (2)
Serious and severe adverse events potentially related to t-PA	2 (1.3)
IVC filter placed	24 (16)
Major bleeding within 30 days*	15 (10)
GUSTO moderate*	14 (9.3)
GUSTO severe*	1 (0.7)
Intracranial hemorrhage	0 (0)

Values are mean ± SD or n (%). *N = 149 (1 patient lost to follow-up).

GUSTO = Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries; IVC = inferior vena cava; t-PA = tissue-plasminogen activator.

−14 mm Hg; $p < 0.0001$). The decrease in mean pulmonary artery systolic pressure was sustained from baseline to 48 ± 6 h, as estimated by transthoracic echocardiography (51.4 mm Hg vs. 36.9 mm Hg; mean difference, −14.4; $p < 0.0001$). Mean modified Miller angiographic obstruction index score decreased from 22.5 at baseline to 15.8 at 48 ± 6 h (mean difference, −6.6; $p < 0.0001$).

An analysis was conducted to determine whether there was any difference in the change in RV/LV diameter ratio between patients who had a follow-up CT scan performed with the 48 ± 6-h window and those who had a follow-up CT scan performed but it fell outside of the 48 ± 6-h window. There was no difference in the change in RV/LV diameter ratio in patients who had a follow-up CT scan performed within the 48 ± 6-h window and those who had a follow-up CT scan performed but it fell outside of the 48 ± 6-h window (mean percentage of change, −24% vs. −29%; $p = 0.29$). Similarly, there was no difference in the change in pulmonary artery systolic pressure in patients who had follow-up echocardiography performed within the 48 ± 6-h window and those who had echocardiography performed outside of the 48 ± 6-h window (mean percentage of change, −14.4 mm Hg vs. −17.5 mm Hg; $p = 0.24$).

A random-effects model analysis was performed to assess whether there was significant variance in the change in RV/LV diameter ratio according to study site. There was no indication of significant study site variance ($p = 0.24$), and the 2-sided p value for comparing the mean change in RV/LV diameter ratio with the pre-specified control value of −0.2 remained significant ($p < 0.0001$).

SAFETY OUTCOMES. Three patients died while hospitalized, and 1 patient died after hospital discharge within 30 days of the procedure (Table 5). One patient died of massive PE before the procedure could be completed; 1 patient changed her code status and elected to receive hospice care after multisystem organ failure developed during a prolonged admission; 1 patient died of sepsis unrelated to the procedure; and 1 patient died of PE resulting in progressive respiratory failure. The patient who died before the procedure could be completed was a 61-year-old woman with diabetes, obesity, and recent infectious illness who presented hemodynamically stable with

TABLE 6 Summary of GUSTO Moderate Major Bleeds

Bleeding Event	Site of Bleed	Transfused Blood Products	Hgb (g/dl) or HCT (%) (From Baseline to Lowest)	Outcome and Complications
Access site hematoma	Right groin	2-U PRBCs	Hgb: 13.3 to 7.5	Recovered
Access site pseudoaneurysm	Right groin	2-U PRBCs	HCT: 34.5 to 23.8	Recovered
Gross hematuria	Genitourinary tract	4-U PRBCs	Hgb: 12.6 to 7.8	Recovered
Mucosal bleeding	Nasal and oropharyngeal	4-U PRBCs	Hgb: 10.7 to 7.5	Recovered
Hematoma	Left arm	6-U PRBCs	Hgb: 13.6 to 8.1	Recovered
Hemoptysis	Pulmonary	3-U PRBCs	Hgb: 16.5 to 8.9	Patient was intubated and ventilated; bronchoscopies were performed; recovered
Anemia	Unclear	4-U PRBCs	HCT: 38.8 to 23.2	Recovered
Hematoma	Scrotal surgery site (penile implant)	4-U PRBCs	Hgb: 14.6 to 7.5	Recovered
Hematoma	Abdominal surgery site (hysterectomy)	4-U PRBCs	HCT: 32.1 to 23.9	Recovered
Anemia	Unclear	1-U PRBCs	Hgb: 11.3 to 9.8	Recovered
Access site hematoma	Right groin	2-U PRBCs	HCT: 37.5 to 25.2	Recovered
Hematoma	Chest wall	2-U PRBCs	HCT: 43.8 to 29.7	Recovered after prolonged hospitalization
Hematoma	Retroperitoneal	2-U PRBCs	HCT: 43.8 to 29.7	Recovered after prolonged hospitalization
Hematoma	Chest wall	9-U PRBCs	HCT: 42.9 to 23.4	Recovered after prolonged hospitalization
Hemoptysis	Pulmonary	2-U PRBCs	HCT: 33.8 to 26.3	Died of pulmonary embolism
Anemia	Unclear	2-U PRBCs	Hgb: 11.7 to 8.2	Recovered

GUSTO = Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries; HCT = hematocrit; Hgb = hemoglobin; PRBC = packed red blood cell.

acute bilateral PEs to a local medical center and was started on heparin. Her initial RV/LV diameter ratio was 1.68, and her modified Miller Index score was 30. The following day, she was transferred to another medical center and enrolled in the SEATTLE II study. While the left infusion catheter was being placed, respiratory failure developed and the patient was intubated. She subsequently became bradycardic, experienced cardiac arrest, and could not be resuscitated.

Few serious adverse events were adjudicated to either the device (2%) or t-PA (1.3%). No patient experienced intracranial hemorrhage. There were 17 major bleeding events within 30 days of the procedure observed in 15 patients (10%) (Table 5). All but 1 took place within 72 h of the procedure. One of these major bleeding events was a GUSTO severe/life-threatening hemorrhage (a right groin vascular access site hematoma with transient hypotension requiring vasopressor support). The remainder (94%) were GUSTO moderate bleeds, 3 of which were related to vascular access (Table 6). Immobility within 30 days of PE diagnosis (57.1% vs. 27.8%, $p = 0.03$), recent trauma (21.4% vs. 3.7%, $p = 0.03$), and multiple vascular access attempts (25.9% vs. 4.0%, $p < 0.001$) were more frequent in patients with major bleeding compared with those who did not have major bleeding.

There was no significant difference in the proportion of major bleeding within 72 h of the procedure across the 22 study sites ($p = 0.91$).

MASSIVE VERSUS SUBMASSIVE PE. The decrease in mean RV/LV diameter ratio from baseline to 48 ± 6 h was similar in massive and submassive PE patients (−0.51 vs. −0.43, $p = 0.31$). Likewise, the decrease in mean pulmonary artery systolic pressure from baseline to procedure completion (−12.6 vs. −14.3, $p = 0.61$) and from baseline to 48 ± 6 h (−14.2 vs. −15.0, $p = 0.81$) was also similar in massive and submassive PE patients. Massive PE patients were more likely to experience major bleeding than submassive PE patients (23% vs. 7%, $p = 0.02$).

DISCUSSION

In our study, ultrasound-facilitated, catheter-directed, low-dose fibrinolysis resulted in no episodes of intracranial hemorrhage. We observed a 25% decrease in CT-measured RV/LV diameter ratio over 48 h, a 30% decrease in pulmonary arterial systolic pressure by the end of the procedure, and a 30% decrease in pulmonary artery angiographic obstruction over 48 h.

Systemic full-dose fibrinolysis has been the most extensively studied advanced therapy for patients with acute massive and submassive PE. However, its use even in the highest risk patients has decreased over the past 2 decades (20), presumably due to the high rate of intracranial hemorrhage. Clinical practice guidelines recommend against the use of full-dose systemic fibrinolytic therapy for acute submassive PE in all but the lowest bleeding risk patients (21–23).

The desire to reduce RV pressure overload and to minimize the risk of adverse outcomes, such as intracranial hemorrhage, spurred exploration of alternative lower-dose fibrinolytic strategies, including half-dose systemic fibrinolysis (24,25) and catheter-based pharmacomechanical therapy (26). In the European ULTIMA (Ultrasound Accelerated Thrombolysis of Pulmonary Embolism) trial of 59 patients with submassive PE, ultrasound-facilitated, catheter-directed, low-dose fibrinolysis plus anticoagulation improved RV function from baseline to 24 h to a greater extent than anticoagulation alone without causing major bleeding (14). Although both trials used the same equipment, the ULTIMA study used a slightly lower dose of t-PA (20 mg) than the current study (24 mg). The ULTIMA study evaluated the procedure in 30 patients with submassive PE, whereas the current study included 150 patients with submassive or massive PE. The difference in the definitions of major bleeding between the 2 trials may partly explain the variation in major bleeding with ultrasound-facilitated, catheter-directed, low-dose fibrinolysis (0% in the ULTIMA study vs. 10% in the current study). In contrast to the ULTIMA study, the current study also included massive PE patients who were more likely to experience major bleeding than those with submassive PE. Our study expands the experience of ultrasound-facilitated, catheter-directed, low-dose fibrinolysis in patients with massive and submassive PE and demonstrates the potential of this technique. On May 21, 2014, based on the data from our trial and previous studies, the U.S. Food and Drug Administration approved the EkoSonic Endovascular System for treatment of PE (27).

Increased RV/LV diameter ratio is a reproducible and well-validated tool for identifying PE patients at risk of adverse outcomes, in particular, increased 30-day mortality (28). Although a decrease in RV/LV diameter ratio is an important surrogate marker for the efficacy of ultrasound-facilitated, catheter-directed, low-dose fibrinolysis, the need for trials with clinical endpoints remains important (29). Clinical outcomes such as hemodynamic collapse, quality of life (30,31), and mortality will help guide the use of this technology.

STUDY LIMITATIONS AND STRENGTHS. The major limitation of our study was the lack of a comparator group. Because we did not include a comparator group, we cannot comment on the efficacy or safety of ultrasound-facilitated, catheter-directed, low-dose fibrinolysis compared with full-dose systemic fibrinolysis, half-dose systemic fibrinolysis, or anticoagulation alone.

Another potential comparator was catheter-directed, low-dose fibrinolysis without the ultrasound turned "on." A study evaluated the impact of ultrasound on catheter-directed, low-dose fibrinolysis for acute DVT and did not demonstrate that ultrasound bolstered efficacy (32). However, these findings in patients with DVT cannot be extrapolated to acute PE because PE thrombus is more acute, less organized, and less fibrotic than DVT.

An important statistical limitation relates to a subset of patients who did not undergo follow-up chest CT for assessment of RV/LV diameter ratio or echocardiography for estimation of pulmonary artery systolic pressure within the pre-specified 48 ± 6-h window. Missing data could have biased the results in favor of a greater treatment benefit by removing patients with a complicated post-procedure clinical course and limited improvement in our study outcomes. Alternatively, they or their physicians may have canceled follow-up imaging because they had excellent clinical improvement. We conducted an analysis to explore the possibility of important differences between the patients with and without missing follow-up imaging data. We observed no difference in baseline demographic, clinical characteristics, comorbid conditions, PE duration or subtype, anticoagulation, procedural characteristics, length of stay, or in-hospital mortality. Furthermore, we observed no difference in the change in RV/LV diameter ratio in patients who had a follow-up CT scan performed within the 48 ± 6-h window and those who had a follow-up CT scan performed but it fell outside of the 48 ± 6-h window.

In summary, we created a precise protocol for ultrasound-facilitated, catheter-directed, low-dose fibrinolysis with t-PA. Previously, there was no standardized approach. Our simplified study design facilitated expeditious enrollment of 150 patients within 9 months. One-half of the study population was female. The population was also racially and ethnically diverse, with substantial representation of African-American and Hispanic/Latino patients. We emphasized safety by using a definition of major bleeding (combining GUSTO severe/life-threatening and GUSTO moderate bleeds) that would capture a greater number of clinically relevant bleeding events.

FUTURE AREAS OF INVESTIGATION. Future considerations include determining which patients among those with hemodynamically stable PE are optimal candidates for ultrasound-facilitated, catheter-directed, low-dose fibrinolysis. Clinical studies with comparator groups of anticoagulation alone,

systemic fibrinolysis, or other catheter-based techniques will be critical in defining how ultrasound-facilitated, catheter-directed, low-dose fibrinolysis should be used in patients with acute PE. Strategies to reduce major bleeding related to the procedure should also be evaluated. Health economics and outcomes research will be critical for determining appropriate use of this technology.

CONCLUSIONS

Ultrasound-facilitated, catheter-directed, low-dose fibrinolysis improved RV function in acute PE, decreased pulmonary artery angiographic obstruction, reduced pulmonary artery systolic pressure, and did not result in intracranial hemorrhage. Ultrasound-facilitated, catheter-directed, low-dose fibrinolysis has the potential to improve outcomes and change treatment algorithms in higher risk PE patients.

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PERSPECTIVES

WHAT IS KNOWN? Ultrasound-facilitated, catheter-directed, low-dose fibrinolysis for acute massive and submassive PE improved RV function, decreased pulmonary artery angiographic obstruction, and reduced pulmonary hypertension.

WHAT IS NEW? The discussion of advanced therapies for patients with massive or submassive PE should include the option of ultrasound-facilitated, catheter-directed, low-dose fibrinolysis at medical centers with experience in the appropriate patient selection, performance of the procedure, and post-procedure care.

WHAT IS NEXT? Although ultrasound-facilitated, catheter-directed, low-dose fibrinolysis appeared to improve short-term, surrogate outcomes, subsequent studies focused on clinical and longer term outcomes will provide a better understanding of the optimal use of this therapy for acute PE. Subsequent studies with comparator groups of anticoagulation alone, systemic fibrinolysis, or other catheter-based techniques will be critical in defining how ultrasound-facilitated, catheter-directed, low-dose fibrinolysis should be applied to patients with acute PE.

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KEY WORDS catheter embolectomy, catheter thrombolysis, fibrinolysis, pulmonary embolism, right ventricular failure, thrombolysis

APPENDIX For supplemental material, please see the online version of this article.