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Pulmonary Embolism Response to Fragmentation, Embolectomy, and Catheter Thrombolysis (PERFECT)

Initial Results From a Prospective Multicenter Registry

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BACKGROUND: Systemic thrombolysis for acute pulmonary embolism (PE) carries up to a 20% risk of major bleeding, including a 2% to 5% risk of hemorrhagic stroke. We evaluated the safety and effectiveness of catheter-directed therapy (CDT) as an alternative treatment of acute PE.

METHODS: One hundred one consecutive patients receiving CDT for acute PE were prospectively enrolled in a multicenter registry. Massive PE (n = 28) and submassive PE (n = 73) were treated with immediate catheter-directed mechanical or pharmacomechanical thrombectomy and/or catheter-directed thrombolysis through low-dose hourly drug infusion with tissue plasminogen activator (tPA) or urokinase. Clinical success was defined as meeting all the following criteria: stabilization of hemodynamics; improvement in pulmonary hypertension, right-sided heart strain, or both; and survival to hospital discharge. Primary safety outcomes were major procedure-related complications and major bleeding events.

RESULTS: Fifty-three men and 48 women (average age, 60 years [range, 22-86 years]; mean BMI, 31.03 ± 7.20 kg/m^2) were included in the study. The average thrombolytic doses were 28.0 ± 11 mg tPA (n = 76) and 2,697,101 ± 936,287 International Units for urokinase (n = 23). Clinical success was achieved in 24 of 28 patients with massive PE (85.7%; 95% CI, 67.3%-96.0%) and 71 of 73 patients with submassive PE (97.3%; 95% CI, 90.5%-99.7%). The mean pulmonary artery pressure improved from 51.17 ± 14.06 to 37.23 ± 15.81 mm Hg (n = 92) ($P < .0001$). Among patients monitored with follow-up echocardiography, 57 of 64 (89.1%; 95% CI, 78.8%-95.5%; $P < .0001$) showed improvement in right-sided heart strain. There were no major procedure-related complications, major hemorrhages, or hemorrhagic strokes.

CONCLUSIONS: CDT improves clinical outcomes in patients with acute PE while minimizing the risk of major bleeding. At experienced centers, CDT is a safe and effective treatment of both acute massive and submassive PE.

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ABBREVIATIONS: CDT = catheter-directed therapy; IVC = inferior vena cava; PE = pulmonary embolism; PERFECT = Pulmonary Embolism Response to Fragmentation, Embolectomy, and Catheter Thrombolysis; RCT = randomized controlled trial; SEATTLE II = A Prospective, Single-Arm, Multi-center Trial of EkoSonic Endovascular System and Activase for Treatment of Acute Pulmonary Embolism; tPA = tissue plasminogen activator; ULTIMA = Ultrasound Accelerated Thrombolysis of Pulmonary Embolism; USAT = ultrasound-assisted thrombolysis

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Acute pulmonary embolism (PE) remains a significant cause of cardiovascular morbidity and mortality worldwide. Although treatment escalation with systemic thrombolysis may reduce mortality, it is also associated with a higher risk of hemorrhagic complications, including a 2% to 5% risk of hemorrhagic stroke.[1] An alternative to systemic thrombolysis is catheter-directed therapy (CDT), which uses pharmacomechanical methods and low-dose thrombolytic infusion. Recently, CDT has demonstrated efficacy in alleviating right-sided heart strain and pulmonary hypertension in trial populations[2,3] with no increase in bleeding complications; however, prospective data showing the effectiveness of CDT in a real-world population are lacking. We present the initial results from a prospective multicenter registry evaluating the safety and effectiveness of CDT for acute massive and submassive PE.

Materials and Methods

Study Design

This study was conducted after obtaining institutional review board or ethics board approval from all study centers, including six sites in the United States and one site in Europe (e-Appendix 1). Over a 3-year period (2011-2014), 101 consecutive patients with PE treated with CDT were enrolled in this prospective multicenter registry after obtaining informed consent. All data were collected using case report forms, and enrollment was capped at 101 patients for this initial analysis.

Study Population

Patients were included if they had acute massive or submassive PE presenting within 14 days and CT scan evidence of proximal PE defined as a filling defect in at least one main or lobar pulmonary artery. Massive PE was defined as acute PE with sustained hypotension as follows: systolic BP < 90 mm Hg for at least 15 min or requiring inotropic support. Submassive PE was defined as acute PE causing right ventricular dilatation and hypokinesis confirmed on echocardiography, chest CT scan, or both without systemic hypotension. Patients were excluded if they were aged < 18 years, had contraindications to therapeutic anticoagulation, or had tumor thrombus in the pulmonary arteries.

Catheter-Directed Therapy

Submassive PE was treated with catheter-directed thrombolysis through low-dose hourly drug infusion into the clot with tissue plasminogen activator (tPA) 0.5 to 1.0 mg/h or urokinase 100,000 International Units/h using ultrasound-guided transfemoral or transjugular venous access per a previously described protocol.[4] Thrombolytic drugs were delivered using standard infusion catheters such as the Unifuse (AngioDynamics) or multi-side hole pigtail catheter (COOK) or through an ultrasound-assisted thrombolysis (USAT) infusion catheter (EKOS Corporation).

Massive PE was treated with immediate catheter-directed mechanical or pharmacomechanical thrombectomy using defined modern CDT techniques,[5] including low-profile catheters (≤ 10F), catheter-directed fragmentation of PE, intraclot lytic injection (if drug was given), and aspiration. The rheolytic AngioJet device (Possis Medical Inc) was not used in this study due to prior reports of related serious adverse events.[5] Following mechanical clot debulking, a potential low-dose hourly drug infusion was administered as just described for residual submassive PE. During all thrombolytic infusions, full therapeutic anticoagulation was suspended, and only a small dose of heparin (300-500 units/h) was continued to minimize the risk of perisheath clot formation per established protocol.[4] After completion of CDT, all patients resumed therapeutic parenteral anticoagulation bridging to warfarin, an injectable anticoagulant as monotherapy, or rivaroxaban. The concomitant use of inferior vena cava (IVC) filters was at the discretion of each institution.

Clinical Outcomes

Clinical success was defined as meeting all three end points: stabilization of hemodynamics; improvement in pulmonary hypertension, right-sided heart strain, or both; and survival to hospital discharge. Stabilization of hemodynamics was defined as prevention or resolution of hemodynamic shock (systolic BP < 90 mm Hg) with no need for pressor support. Improvement in pulmonary hypertension was defined as a reduction in systolic pulmonary artery pressure below the baseline as confirmed by invasive pressure measurements through a catheter. Right-sided heart dysfunction was qualitatively assessed with echocardiography by independent cardiology laboratory interpretation at each institution before and after CDT based on published guidelines[6] and classified into four steps (normal, mild, moderate, severe). Improvement in right ventricular dysfunction was defined as one or more step changes toward normal right ventricular function. Primary safety outcomes were major procedure-related complications and major bleeding events. Secondary safety outcomes were minor bleeding complications. All complications were defined according to Society of Interventional Radiology clinical practice guidelines.[7]

Statistics

The paired Wilcoxon test was used to evaluate changes in invasive pulmonary artery pressures after CDT, and the Bowker test of symmetry was used to assess changes in the degree of right-sided heart strain. The Mann-Whitney test was used to compare changes in pretreatment and posttreatment pulmonary artery pressures, mean drug doses, and mean infusion times between patients treated with USAT vs standard infusion catheters. The Kolmogorov-Smirnov test was used to test the equality of distributions. $P < .05$ was considered statistically significant. CIs were calculated using the exact binomial method, and all statistics were calculated using Stata 13.1 software (StataCorp LP).

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Results

Fifty-three men and 48 women (average age, 60 years [range, 22-86 years]; mean BMI, 31.03 ± 7.20 kg/m^2, consistent with an obese population) were included in the study. The baseline demographics and clinical characteristics are summarized in Table 1. Acute submassive PE and massive PE were observed in 73% (73 of 101) and 28% (28 of 101) of patients, respectively.

Procedural Characteristics

CDT for acute PE was first-line therapy beyond anticoagulation in 97% (98 of 101). The three remaining patients had a prior failure of systemic tPA, and all three (one with massive PE, two with submassive PE) were successfully rescued with CDT. The average thrombolytic doses infused through catheter were 28.0 ± 11.0 mg tPA (n = 76) and 2,697,101 ± 936,287 International Units urokinase (n = 23). One patient with submassive PE (1%) did not receive any thrombolytic drug and was treated only with mechanical CDT. Among patients receiving catheter-directed thrombolytic infusions (n = 100), 64% were treated using standard infusion catheters, and 36% were treated with USAT.

TABLE 1] Baseline Patient Demographics and Clinical Characteristics

Demographic	Value
No. patients	101
Age, y	60.3 ± 14.9
BMI, kg/m^2	31.03 ± 7.20
Female sex	48 (47.5)
Ethnicity/race	
White	93 (92)
Black	3 (3)
Hispanic or Latino	1 (1)
Asian	1 (1)
Other	3 (3)
Comorbid conditions	
Acute DVT	68 (67)
Obesity	50 (50)
Hypertension	21 (21)
Immobility within 30 d of PE	17 (17)
Diabetes mellitus	14 (14)
Cancer	12 (12)
Atherosclerotic cardiovascular disease	5 (5)
None	5 (5)

Data are presented as mean ± SD or No. (%) unless otherwise indicated. PE = pulmonary embolism.

Outcomes

Clinical success was achieved in 24 of 28 patients with massive PE (85.7%; 95% CI, 67.3%-96.0%) and 71 of 73 patients with submassive PE (97.3%; 95% CI, 90.5%-99.7%). Four of six deaths were due to massive PE, and two were due to submassive PE. Safety outcomes are summarized in Table 2. Among nine patients with absolute contraindications to systemic tPA, one received mechanical CDT only (no thrombolytic), and eight received catheter-directed tPA infusion (average dose, 24.0 ± 13.2 mg) with no major bleeding events. Eight of the nine survived, and one died of massive PE.

Among patients monitored with follow-up echocardiography, 57 of 64 (89.1%; 95% CI, 76.8%-94.4%) showed improvement in right ventricular strain, and this improvement occurred significantly more often than worsening of heart strain ($P < .0001$) (Fig 1). Among patients monitored with invasive pulmonary artery pressures, 84.8% (78 of 92; 95% CI, 75.8%-91.4%) showed significant improvement in pulmonary artery pressures (pretreatment, 51.17 ± 14.06 mm Hg; post-CDT, 37.23 ± 15.81 mm Hg; $P < .0001$) (Fig 2). A test of equality of distributions suggested that CDT changes may be less variable than USAT ones ($P = .032$), but a Wilcoxon test showed no significant difference in median pressure drops between these groups ($P = .900$) (Figs 2E, 2F). Subgroup analyses comparing patients treated with USAT vs standard CDT revealed no significant differences in pretreatment and posttreatment pulmonary artery pressures, average pressure changes, average thrombolytic doses, and average infusion times (Table 3).

Complications

There were no major procedure-related complications, major hemorrhages, or hemorrhagic strokes. Minor

TABLE 2] Safety Outcomes in 101 Patients After CDT

Outcome	Value
Hospital stay, d	8.23 ± 4.82
In-hospital death	6 (5.9)
> 30-d mortality	1[a] (1.0)
IVC filter placed	65 (64.4)
Major bleeding within 30 d	0
Intracranial hemorrhage	0

Data are presented as mean ± SD or No. (%). Four deaths were due to massive PE, and two were due to submassive PE. CDT = catheter-directed therapy; IVC = inferior vena cava. See Table 1 legend for expansion of other abbreviation.

[a]One patient with massive PE died 24 wk after hospital discharge.

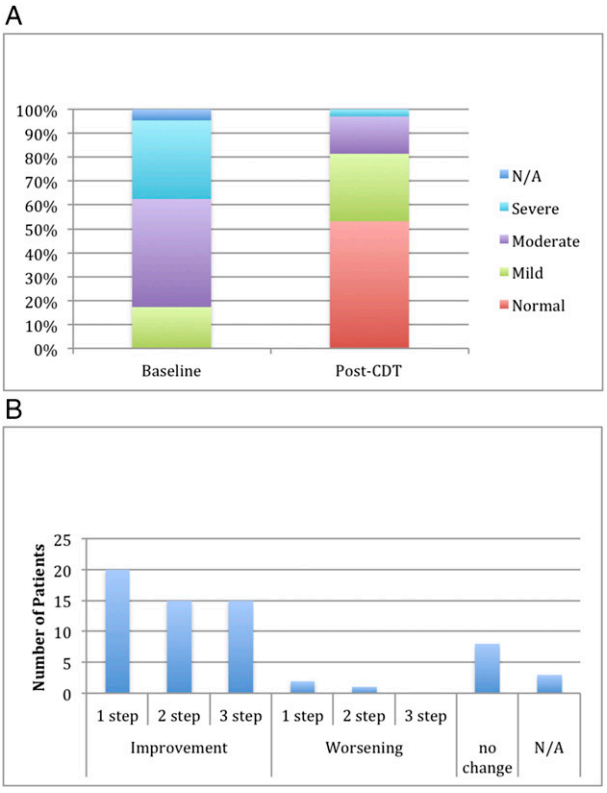

Figure 1 – *A, Distribution of systolic right ventricular (RV) dysfunction in 64 patients pre- and post-CDT. Following CDT, 89.1% (95% CI, 76.8%-94.4%) had alleviation of RV strain, and this improvement occurred significantly more often than worsening of heart strain (P < .0001). B, Stepwise changes in RV dysfunction. CDT = catheter-directed therapy; N/A = presence of heart strain but classification unavailable (A) or presence of heart strain improvement but precise classification unavailable (B).*

bleeding events occurred in 13 of 101 patients (12.9%; 95% CI, 7.0%-21.0%) as follows: five neck access hematomas, one groin access hematoma, one IV access site, two hemoptysis, two hematuria, one epistaxis, and one vaginal bleeding in a patient with uterine fibroids. All minor bleeding episodes were self-limited and required no blood transfusions.

Discussion

The role of CDT for acute PE is rapidly evolving, and guidelines have acknowledged CDT as a viable treatment option for acute massive PE[8] in patients who have (1) contraindications to thrombolysis, (2) failed thrombolysis, or (3) shock likely to cause death before systemic thrombolysis can take effect (eg, within hours) if appropriate expertise and resources are available. Nevertheless, large prospective studies are lacking, and the ideal CDT protocol, particularly for submassive PE, remains unclear. In 2007, Goldhaber[9] announced the need for a multicenter registry to study CDT for acute PE, and other experts have called for more prospective registry data to resolve areas of uncertainty and to determine the optimal CDT methods for acute PE.[10,11]

The initial results from the present prospective multicenter registry demonstrate clinical CDT success rates of 85.7% for massive PE and 97.3% for submassive PE. These results were achieved in a real-world population while incurring no major procedure-related complications, major bleeding events, and hemorrhagic strokes. The results for massive PE are consistent with a prior meta-analysis reporting 86.5% clinical success for massive PE,[5] and we believe that the present success rate was also high because we used the same modern methods of immediate catheter-directed mechanical or pharmacomechanical thrombectomy.

The 0% rate of major complications in the current study is lower than the 2.4% complication rate previously reported,[5] and we believe this is due to elimination of the AngioJet device from the present protocol. Indeed, when used to treat PE, the rheolytic AngioJet device is associated with a high rate of complications, including procedure-related death.[5,9] As a result, the US Food and Drug Administration has issued a black box warning on the device label,[12] and for all these reasons, we believe that the AngioJet should not be used to treat patients with acute PE.

The present results for submassive PE support two recent trials showing a high success rate of CDT for submassive PE (Fig 3) with a low risk of significant bleeding complications.[2,3] However, in the SEATTLE II (A Prospective, Single-Arm, Multi-center Trial of EkoSonic Endovascular System and Activase for Treatment of Acute Pulmonary Embolism)[3] and ULTIMA (Ultrasound Accelerated Thrombolysis of Pulmonary Embolism)[2] trials, high-cost USAT infusion catheters were used in all patients, and these studies did not permit comparison of USAT with standard CDT infusion catheters. Conversely, the present study design allowed enrollment of patients treated with either method. Interestingly, we found no advantage in patients treated with USAT vs standard CDT (Table 3), and these data suggest that CDT may be performed effectively without the added cost associated with USAT infusion catheters.

In a large meta-analysis, systemic thrombolysis for acute massive and submassive PE was associated with lower all-cause mortality; however, there was also a higher risk of major bleeding, including a higher risk of hemorrhagic stroke.[1] Consequently, the authors acknowledged that future research should focus on standardization of thrombolytic dosages and the ideal

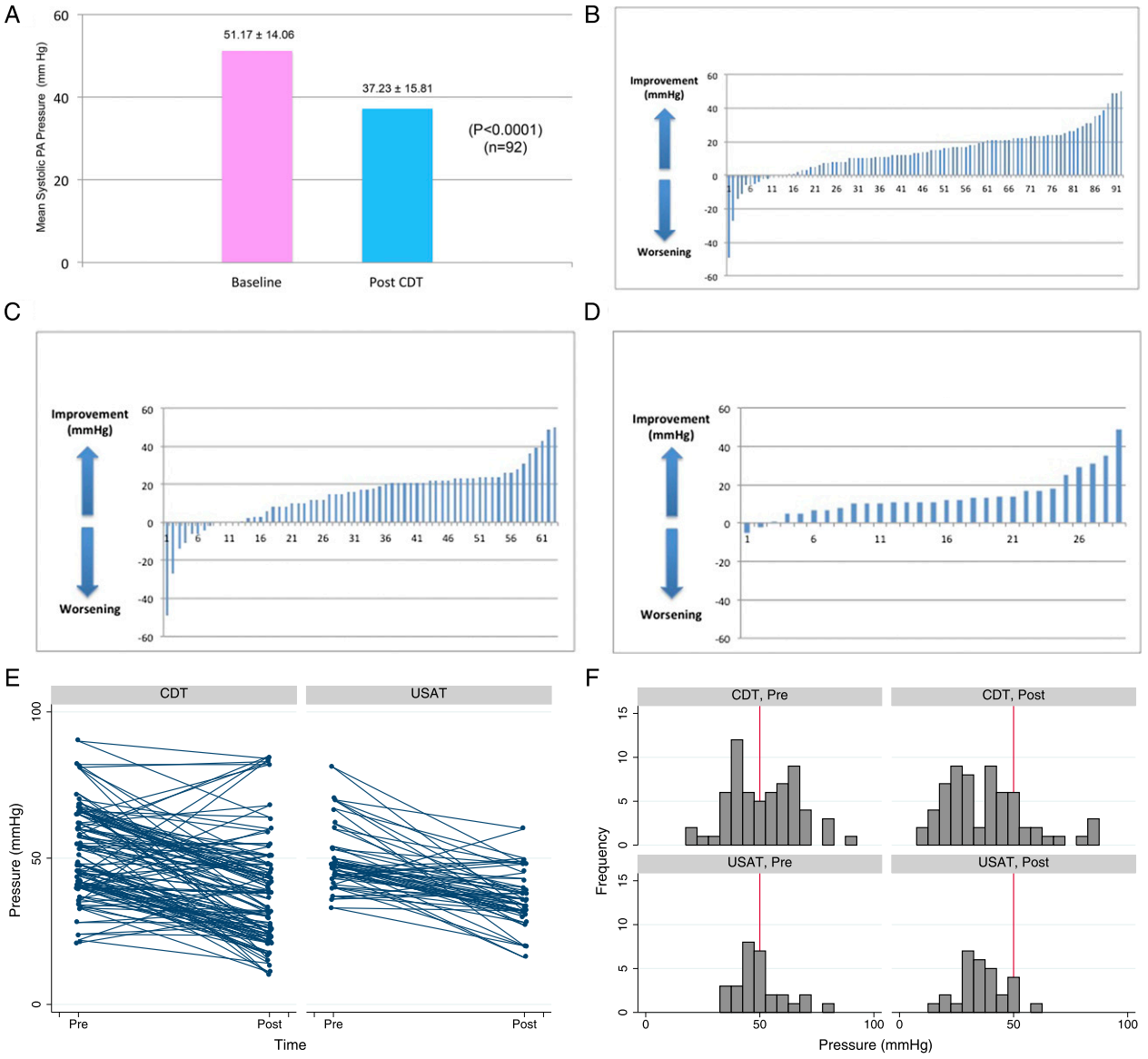

Figure 2 – *A, Invasive PA pressures pre- and post-CDT. B, Individual changes in PA pressure (n = 92). C, Individual changes in PA pressure after standard CDT (n = 63). D, Individual changes in PA pressure after USAT (n = 29). E, Graphs of pre- and post-PA pressures after standard CDT and USAT. There was no significant difference in pressure drops between these groups (P = .900). F, Distributions of pre- and post-PA pressures after standard CDT and USAT. A test of the equality of distributions suggests that CDT changes may be less variable than USAT ones (P = .032), but there was no significant difference in median pressure drops between these groups (P = .900). PA = pulmonary artery; USAT = ultrasound-assisted thrombolysis. See Figure 1 legend for expansion of other abbreviation.*

method of administration (peripheral IV vs CDT into the pulmonary arteries) to maximize clinical benefit and minimize bleeding risk.[1] Indeed, we found that the use of CDT allowed a much lower average thrombolytic dose (24 mg tPA through 1.0 mg/h infusion) vs systemic tPA regimens that infuse 50 to 100 mg IV within 1 to 2 h.[1,13] We believe that this explains the low risk of major bleeding complications associated with low-dose CDT, and the present results support earlier studies using similar dosing regimens.[2,3] In the SEATTLE II trial, there were no hemorrhagic strokes and only one severe bleeding event,[3] and the ULTIMA trial reported no major bleeding events.[2]

The randomized ULTIMA trial demonstrated that a standardized CDT regimen with USAT to treat submassive PE was superior to anticoagulation alone in reversing right ventricular dilatation and alleviating pulmonary hypertension at 24 h[2]; however, the trial was limited by selection bias and enrollment of an idealized trial population,[11] and there was no comparison of USAT with standard CDT infusions. The current study registry enrolled patients from a real-world population

TABLE 3] USAT vs Standard CDT

Available Pressure Data	USAT	Standard CDT	*P* Value
PA pressure at baseline, mm Hg	49.83 ± 11.14 (n = 29)	51.79 ± 15.26 (n = 63)	.697
PA pressure post-CDT, mm Hg	36.07 ± 9.62 (n = 29)	37.77 ± 18.01 (n = 63)	.897
Pressure change post-CDT, mm Hg	−13.76 ± 11.20 (n = 29)	−14.02 ± 16.39 (n = 63)	.900
Available tPA data			
tPA dose, mg	30.27 ± 9.07 (n = 36)	25.63 ± 11.71 (n = 40)	.055
Infusion time,[a] h	23.19 ± 8.09 (n = 36)	20.76 ± 11.51 (n = 27)	.103

Data are presented as mean ± SD. No significant difference was identified between these groups. PA = pulmonary artery; tPA = tissue plasminogen activator; USAT = ultrasound-assisted thrombolysis. See Table 2 legend for expansion of other abbreviation.
[a]Data from overnight infusions.

with very few exclusion criteria and showed an effective reduction in pulmonary artery pressure following CDT (Fig 3). Furthermore, the present registry data revealed no added advantage with USAT vs standard CDT (Table 3).

Despite early intervention, some patients did not improve, and two died of submassive PE, emphasizing the real mortality associated with the presence of right ventricular strain from acute PE. The possible reasons for treatment failure are development of irreversible right-sided heart strain and irreversible pulmonary hypertension prior to initiation of treatment and/or presence of a chronic PE component not amenable to thrombolysis. Fortunately, the success rate was 97% in this group, and this supports the concept of early CDT intervention prior to hemodynamic collapse to prevent death from submassive PE. Given the results from this study along with other trial data[2,3] (Fig 3), a low-dose CDT infusion appears to improve pulmonary hypertension, right ventricular strain, and hemodynamic parameters without the serious side effects of major hemorrhage and intracerebral hemorrhage that may be encountered with full-dose thrombolysis.

PERFECT (Pulmonary Embolism Response to Fragmentation, Embolectomy, and Catheter Thrombolysis) is a registry, and these data are not from a randomized controlled trial (RCT); therefore, they need confirmation by RCTs. However, for real-world medical practice settings, the RCT may not be practical or provide the best evidence,[14] and RCTs must be confirmed by observational studies and registry data.[14] Therefore, the strength of this multicenter study is the prospective collection of data from actual practice based on a modern CDT protocol[4] used across a wide range of institutions. Although we incidentally reported the concomitant use of IVC filters in the present study population, the registry was not designed to assess the potential risks vs benefits of long-term IVC filter use, and further studies are warranted. Another limitation of the study is the lack of data evaluating long-term right ventricular function and the risk of chronic thromboembolic pulmonary hypertension. Although trial data for systemic thrombolysis[15]

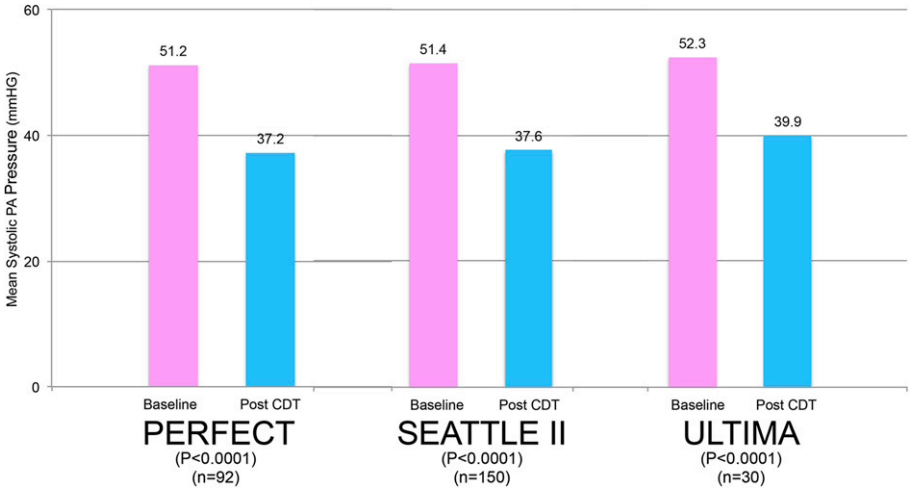

Figure 3 – *Comparison of studies on CDT for acute pulmonary embolism: PERFECT, SEATTLE II,[3] and ULTIMA.[2] PERFECT = Pulmonary Embolism Response to Fragmentation, Embolectomy, and Catheter Thrombolysis; SEATTLE II = A Prospective, Single-Arm, Multi-center Trial of EkoSonic Endovascular System and Activase for Treatment of Acute Pulmonary Embolism; ULTIMA = Ultrasound Accelerated Thrombolysis of Pulmonary Embolism. See Figure 1 and 2 legends for expansion of other abbreviations.*

support the notion that thrombolytic therapy may reduce long-term sequelae from PE, further studies examining the impact of low-dose catheter-directed thrombolysis on long-term quality of life are needed.

Conclusions

To our knowledge, PERFECT is the first multicenter PE registry to demonstrate the clinical safety and effectiveness of CDT in a real-world population with acute PE. These data support an optimal CDT protocol of rapid clot debulking for massive PE that avoids using the AngioJet device to minimize procedure-related complications. These data also support the use of low-dose thrombolytic infusion through standard catheters for patients with submassive PE without the need for high-cost USAT catheters. In this study, CDT was successfully used as first-line therapy for acute massive or submassive PE, and overall, CDT improved clinical outcomes while minimizing the risk of major bleeding.

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Author contributions: W. T. K. had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. W. T. K. wrote the initial draft of the manuscript and revised subsequent drafts based on input from all coauthors and W. T. K., A. B., P. S. K., F. J. D., J. R. L., F. R. F., K. U., M. J. B., A. K. S., M. J. H., J. K. R., and M. A. D. G. vouched for the accuracy, completeness, and analysis of the reported data and agreed to publish the manuscript.

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Additional information: The e-Appendix can be found in the Supplementary Materials section of the online article.

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