Ultrasound-Accelerated Catheter-Directed Thrombolysis

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Abstract

Venous thromboembolism is a very common presentation in the hospital setting. In patients with high-risk pulmonary embolism (PE) or PE and hemodynamic instability, systemic thrombolytic treatment is generally indicated. In those with contraindications to systemic thrombolysis, catheter-directed local thrombolytic therapy and surgical embolectomy are currently considered. In particular, catheter-directed thrombolysis (CDT) is a drug delivery system coupling the endovascular drug administration nearby in the thrombus and the local facilitating effect of ultrasounds. The applications of CDT are currently debated. Here we provide a systematic review of the clinical utilization of CDT.

Keywords: Venous thromboembolism; Catheter-directed thrombolysis; Embolectomy; Pulmonary embolism; Deep venous thrombosis

Introduction

Pulmonary embolism (PE) and deep venous thrombosis (DVT) are part of venous thromboembolism (VTE) disease spectrum. Blood clots that form in the deep veins of the extremities, most frequently in the leg, are what define DVT. When a portion of a DVT clot separates, it can cause PE by passing through the right heart and being lodged in the pulmonary artery. More than half of individuals with DVT in the iliac, femoral, and popliteal veins of the lower limbs also have PE [1]. PE is a prevalent condition that affects 60 - 112 persons per 100,000 each year. According to prospective cohort studies, the case fatality rate during the acute phase ranges from 7% to 11% [2]. Anticoagulation (AC) alone is suggested for patients who have low-risk PE. For patients with high- and intermediate-

risk PE, more aggressive options have been suggested. In 2014 and 2016, the European Society of Cardiology (ESC) and the American College of Chest Physicians (CHEST) published specific guidelines for the therapy of PE in intermediate- and high-risk patients, respectively. Primary systemic thrombolysis is not indicated in intermediate-risk PE, according to both organizations. However, both the 2014 ESC and the 2016 CHEST guidelines suggest systemic thrombolytic treatment in high-risk PE patients. The ESC guidelines also recommend surgical pulmonary embolectomy and catheter-directed therapies for high-risk individuals for whom full-dose thrombolysis is contraindicated or has failed. Catheter-directed thrombolysis (CDT) is a type of pharmacological thrombolysis that involves injecting a thrombolytic agent directly into the pulmonary artery (PA) circulation via a catheter [3]. A smart drug delivery catheter, a detachable device with many miniature ultrasonic transducers spreading over the treatment zone, and the control unit make up the CDT system. The lytic medication is delivered through the catheter, while non-cavitational ultrasonic energy gently pushes the drug deeper into the clot, limiting the quantity of medicine that escapes into the systemic circulation [4]. In this article, we conduct a literature review in regard to CDT use in patients with VTE.

CAVA

The CAVA trial [5] is a multi-center, single-blind, randomized, superiority, parallel-group study to assess the effects of extra ultrasound-accelerated catheter-directed thrombolysis (USCDT) on the development of post-thrombotic syndrome (PTS) following acute iliofemoral DVT in comparison to standard post-thrombotic therapy. The study included 184 individuals. Ninety-one participants were randomized to receive additional USCDT, whilst 93 patients received only the normal course of therapy. At the conclusion of the trial, 58 patients from the control group and 62 patients from the experimental group had completed all long-term follow-ups. Fifteen institutions in the Netherlands took part in the study. Patients between the ages of 18 and 85 years who have never previously developed an acute iliofemoral DVT but whose maximum symptom duration was 14 days were included. Patients received either standard treatment alone or standard treatment combined with USCDT. Anticoagulant therapy administered in accordance with international guidelines was the treatment standard. Within 21 days of the onset of symptoms, patients who had been allocated to the interventional group were brought to one of the six interventional centers to begin thrombolysis. Instead of getting the

traditional oral anticoagulant treatment, the intervention group was administered low molecular weight heparin at therapeutic concentrations. At 3, 6, and 12 months following the intervention, in addition to yearly afterward, the outpatient clinic completed routine follow-up study visits. The main result was the percentage of patients who had PTS during follow-up later than 12 months as determined by the original definition: the occurrence of venous ulceration or two occurrences of a Villalta score more than 5 that were at least 3 months apart. The Villalta score is a score stratification system used to measure the severity of PTS in patients diagnosed with lower-extremity DVT. A PTS diagnosis is made after the acute phase of DVT (3 - 6 months). The score is calculated using the presence or absence of clinical symptoms and signs of lower-extremity DVT. The level of clinical severity can guide further management of patients diagnosed with PTS, with conservative treatment of mild to moderate severities and potential endovascular intervention of moderate to severe and lifestyle-limiting syndromes. A score greater than 5 indicates the presence of PTS, scores 5 - 9 are mild, 10 - 14 moderate, and greater than 15 is considered severe. Additionally, PTS was analyzed to allow external comparisons using the accepted criteria provided by the International Society on Thrombosis and Homeostasis (ISTH).

Nineteen of the 62 patients in the intervention group (30.6%) and 26 of the 44 patients in the control group (44.8%) developed PTS at the median follow-up of 39 months (odds ratio (OR), 0.54; 95% confidence interval (CI), 0.26 to 1.15 (P = 0.11)). Vilalta scores between the two groups did not show any differences in PTS severity. A significant decline in PTS was seen in accordance with the ISTH consensus criteria (46.8% (29) against 69.0% (40); OR, 0.40; 95% CI, 0.19 - 0.84 (P = 0.01)), the absolute difference between the group was 22.2% (95% CI, 39.8% to 2.8%).

With no statistically significant difference groups at the 12-month follow-up, the number of patients forgoing compression therapy increased. Only the physical health quality of life (QOL) measure showed a significant difference, favoring conventional treatment, between the QOL data from the 12-month follow-up and final follow-up. No difference here affects how a clinical trial turns out.

The CAVA trial was limited by the overall sample size of the study. The effects of this sample size were especially notable in the analysis of the long-term follow-up of the study. The length of the recruitment period and strict inclusion criteria may have affected the generalizability of the results. The high rate of withdrawals prior to allocated treatment and high numbers of PTS diagnosis in the standard group affected the power of the study.

ACCESS PTS

The ACCESS PTS [6] is an open-label, single-arm, prospective study that involved multiple centers. The aim of this prospective study was to evaluate the efficacy of combined percutaneous transluminal venoplasty (PTV) and ultrasound-accelerated thrombolysis (USAT) in the management of symptoms and QOL in PTS patients with chronic veno-occlusive disease. Selected participants ranged in age from 18 to 75 years and had undergone an acute DVT episode in one or more proximal veins at least 6 months before the trial. Within 60 days before the study procedure, chronic venous occlusion was proven to exist. Body mass index (BMI) greater than 40, complete occlusion of the popliteal vein, isolated DVT in the ipsilateral vein, and thrombus extending more than 3 cm into the inferior vena cava were all exclusion criteria, as well as mechanical thrombectomy within 2 weeks or thrombolytic therapy within 48 h of the study procedure. Additional exclusion standards included a history of current bleeding or recent gastrointestinal bleeding, as well as laboratory standards for hemoglobin (9 g/dL), international normalized ratio (INR) ($\geq$ 1.5), platelet count, and serum creatinine. Of the 113 participants who were eligible, 81 patients gave their assent to the trial. Seventy-five participants underwent evaluation at a 30-day follow-up visit after 78 patients successfully completed the study intervention. Prior to the start of the research, patients were taking enoxaparin to prevent clotting for at least 48 h. After gaining venous access, venography was used to assess the severity of the chronic thrombotic illness. The afflicted segments were crossed using a standard catheter and wire procedures, and USAT was not inserted if the occlusion could not be crossed (three patients excluded from original enrollment). The key efficacy endpoint was a drop of $\geq$ 4 points in the Villalta score from baseline to 30 days.

Eighty-one patients were enrolled; 78 underwent the surgery and are part of the intent-to-treat population (mean age 54.6 $\pm$ 12.7 years; 32.1% women). The 30-day follow-up for 75 patients (79 limbs) was successful, and they were counted in the primary efficacy endpoint. At 30 days, the main endpoint had been reached in 64.6% of the limbs. At 1 year, the Villalta score had decreased by $\geq$ 4 in 77.3% of the limbs. The average Villalta score at the outset was 15.5 ($\pm$ 5.2). At 30, 90, 180, and 365 days after surgery, the Villalta scores changed by -5.9 ($\pm$ 5.8), -6.9 ($\pm$ 6.5), -7.8 ($\pm$ 6.1), and -8.2 ($\pm$ 6.4), respectively (P = 0.0001).

In this experiment, the use of PTV and USAT in combination to treat chronic venous obstruction following DVT led to clinical improvements over a year as well as a quantitative and long-lasting improvement in venous patency. PTV and USAT therapy increases both long-term venous potency and clinical PTS as measured by the Villalta scale in patients with PTS brought on by chronic venous obstruction.

The ACCESS PTS trial was a single-arm study design. This design was compensated for by pre-randomization treatment requirements. All the patients that were included in the study had previously failed 3 months of conservative therapy that consisted of therapeutic AC and compression stockings. If a control arm that consisted of standard-of-care therapy was present, then patients would have been enrolled in a treatment arm that they had already failed. There was no independent adjudication of the primary endpoint of the study, resulting in a potentially exaggerated report of benefit.

ULTIMA

The ULTIMA [7] trial is a randomized, open-label trial examining whether AC alone is more effective than USAT in re-

versing right ventricular (RV) dilatation in intermediate-risk PE patients. Low-power, high-frequency ultrasound, and traditional CDT are combined in USAT.

Fifty-nine patients with intermediate-risk PE from eight tertiary care facilities were randomized between receiving unfractionated heparin (UFH) and a USAT regimen of 10 mg recombinant tissue plasminogen activator (tPA) over 15 h using the USCDT, or UFH alone, between November 2010 and January 2012. Chest computed tomography (CT) was used to diagnose 363 individuals. The RV/left ventricular (LV) ratio had to be less than 1 and acute symptoms of PE had to be present, as determined by contrast-enhanced CT and four-chamber echocardiographic tests, respectively. Patients with ages between 18 and 80 years, PE symptoms lasting more than 14 days, insufficient ECHO measures of the RV/LV ratio or a ratio of less than 1, known bleeding concerns, recently administered thrombolytic medications, life expectancy under 90 days, and high-risk PE were excluded. Three hundred four patients were excluded because of screening failure, or 84% of the total. The 59 patients who were still alive got heparin alone in 29 cases and USAT with heparin in 30 cases, with primary evaluable outcomes of 25 and 28 respectively. The RV/LV ratio's deviation from baseline at 24 h was the major ULTIMA endpoint. The average age of the 59 patients was 63 ± 14 years, and 53% of them were female. Cancer (12%), renal insufficiency (15%), diabetes mellitus (17%), and hypertension (59%) were the most prevalent comorbidities, with no variation across research groups. Core laboratory chest CT findings of the pulmonary occlusion score and RV/LV ratio, as well as baseline vital signs like respiratory and heart rates, arterial pressure, and oxygen saturation, were identical amongst the groups.

The mean RV/LV ratio in the USAT group decreased from 1.28 ± 0.19 at baseline to 0.99 ± 0.17 at 24 h ($P = 0.001$). The average RV/LV ratio in the heparin group was 1.20 ± 0.14 at baseline and 1.17 ± 0.20 at 24 h ($P = 0.31$). The mean RV/LV ratio changed by 0.30 ± 0.20 and 0.03 ± 0.16 ($P = 0.001$), respectively, from baseline to 24 h.

In PE patients at intermediate risk of death, a standardized USAT regimen was more effective than AC with heparin alone in reversing RV dilatation after 24 h, and this was achieved without an increase in bleeding issues. In ULTIMA, early improvement in ECHO parameters following a standardized USAT regimen was observed, whereas the majority of echocardiographic parameters in the control group of patients receiving only heparin treatment did not improve at 24 h. Invasive hemodynamic testing revealed a significant decrease in pulmonary artery pressure and a rise in the cardiac index within 24 h in the USAT group, according to the experiment. In short, the ULTIMA study demonstrated that a fixed-dose USAT regimen was more effective at reducing RV dysfunction at 24 h than AC with heparin alone. In patients with acute PE, it was the first randomized trial to evaluate a standardized catheter intervention technique.

The ULTIMA study had several limitations. There was no thrombolysis control group without the use of ultrasound, so the overall effect of ultrasound with regards to thrombolytic effect could not be appreciated. Selection bias could not be ruled out because only the most eligible patients were enrolled during the screening process, and consequently some eligible patients may have been excluded as a result. Dose adjustments of anticoagulant therapy were managed by the investigators and not outlined specifically by the study itself. No assessment of residual embolic burden via CT angiography (CTA) was done.

DUET

The DUET [8] study is a multi-center, randomized, and controlled study that included 60 patients (average age 64 years; 44 men) with acute limb ischemia (Rutherford category I or IIa) due to recently (7 - 49 days) thrombosed infrainguinal bypass grafts or native arteries. They were randomly assigned to receive either standard thrombolysis (ST) (n = 32) or USAT with the endowave system (n = 28). Patients below or above the day range were excluded. Acute limb ischemia patients with recent (7 - 49 days) thrombosed infrainguinal native arteries or bypass grafts were included.

The time required to achieve continuous flow by thrombolysis was the primary outcome (> 95% thrombus destruction) with at least one below-the-knee artery achieving outflow. Using a 5-F Unifuse infusion catheter and a 250,000 International Unit (IU) bolus dose of urokinase followed by a 100,000 IU/h continuous infusion, ST was performed.

It took substantially less urokinase ($2.8 \pm 1.6 \times 10^6$ IU in the ST group vs. $1.8 \pm 1.0 \times 10^6$ IU in the USAT group, $P = 0.01$) and thrombolysis was completed much quicker (17.7 ± 2.0 h) in the USAT group than in the ST group (29.5 ± 3.2 h, $P = 0.009$) to achieve a continuous flow. Technical success was attained in 27 (84%) of the ST patients vs. 21 (75%) of the USAT patients ($P = 0.52$). In the ST group, the cumulative 30-day death and serious adverse event rate was 19%, but in the USAT group, it was 29% ($P = 0.54$). The ST group's 30-day patency rate was 82% compared to the USAT group's 71% ($P = 0.35$).

Magnetic resonance angiography with contrast enhancement of the leg was done as part of the follow-up at 30 (± 7) days. Five patients experienced re-occlusion in the ST group compared to six patients in the patients treated with UAST.

In comparison to ST, USAT significantly shortened the time required for thrombolysis in patients with freshly thrombosed infrainguinal native arteries or bypass grafts.

The DUET trial's study population was small (60 patients), which reduced the research's power but was randomized and properly balanced with 32 patients in the control group and 28 patients in the study group. Patients who experienced symptoms for less than a week were not included in the research, nor were those with active cancer or those who had surgery within the previous 6 weeks, both of which are recognized to be patient populations with a greater risk of blood clot formation.

SEATTLE II

The SEATTLE II study [9] is a multi-center, single-arm, and prospective trial evaluating ultrasound-facilitated, low-dose fibrinolysis that was catheter-directed. Acute massive (n = 31)

or sub-massive (n = 119) PE was seen in 150 individuals. Patients were required to be at least 18 years old, have a proximal PE (filling defect in at least one major or lobar pulmonary artery) and have a PE symptom duration equal to or less than 14 days, have a RV to LV diameter ratio greater than or equivalent to 0.9 on chest CT and a proximal PE.

The primary effectiveness outcome was the core laboratory-measured change in the RV/LV diameter ratio from baseline, as assessed by contrast-enhanced chest CT imaging at baseline and at 48 ± 6 h after the start of the treatment. The primary safety outcome was major bleeding within 72 h of the procedure starting. A unilateral catheter was used to provide a total of 24 mg of tPA at 1 mg/h, or a bilateral catheter was used to deliver 1 mg of tPA each catheter every hour for 12 h for another total of 24 mg as well.

From baseline to 48 h post-surgery, mean pulmonary artery systolic pressure (51.4 mm Hg vs. 36.9 mm Hg; $P < 0.00001$), mean RV/LV diameter ratio (1.55 vs. 1.13; mean difference, - 0.42; $P < 0.00001$), and modified Miller index score (22.5 vs. 15.8; $P < 0.00001$) were all seen to decrease. Fifteen patients experienced moderate bleeding events and one patient experienced a severe bleeding event, as defined by Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO). No patient suffered from intracranial hemorrhage.

In patients suffering from acute massive and sub-massive PE, ultrasound-facilitated, low-dose fibrinolysis that was catheter-directed lowered pulmonary hypertension, RV dilatation, anatomic thrombus load, and minimized intracranial hemorrhage.

The study population included 150 patients, and 149 of them completed the necessary follow-up. The study's primary flaws were that it was a single-arm trial without a control group, randomization, or blinding. The average BMI of the study cohort was 35.6 kg/m^2, which is consistent with an obese study population.

OPTALYSE

The OPTALYSE [10] study is a randomized, multi-center, parallel-group trial for the purpose of determining the lowest ideal tPA delivery and dose duration using USCDT. Participants (aged 18 to 75 years) totaling 101 were enrolled who had a proximal PE in one main or proximal lobar pulmonary artery, intermediate-risk acute PE (less than 14 days in duration), normal systolic blood pressure (> 90), RV to LV diameter ratio greater than or equal to 0.9 on chest CTA, and were symptomatic.

One of four USCDT regimens was used to treat patients. The tPA dosage per lung varied from 4 to 12 mg, and the infusion time was 2 to 6 h. The CTA-measured decrease in the RV-to-LV diameter ratio served as the primary efficacy endpoint. Embolic load by refined modified Miller score, assessed on CTA 48 h after the start of USCDT, was a significant secondary endpoint.

All of the groups showed improvement in the refined modified Miller score: arm 1 through arm 4: 0.40 (24%; $P = 0.0001$), 0.35 (22.6%; $P = 0.0001$), 0.42 (26.3%; $P = 0.0001$), and 0.48 (25.5%; $P = 0.0001$), respectively. All showed improvements in

the RV to LV diameter ratio as well. Four persons (4%) experienced major bleeding. One of the two instances of intracranial hemorrhage was related to tPA administered via USCDT.

In comparison to baseline, treatment with USCDT utilizing a shorter delivery period and lower-dose tPA was linked to enhanced RV function and decreased clot load. One intracranial hemorrhage episode brought on by tPA administered via USCDT did occur despite the low major bleeding rate.

The trial had 101 patients who were randomly assigned to one of four distinct treatment plans, which reduced the study's overall statistical power when comparing each group. Each patient received a USCDT catheter treatment regimen, and there was neither a conventional thrombolysis control group nor a heparin AC control group (Table 1).

Conclusion

CDT therapy remains a controversial topic on the rise. There is general agreement that in high-risk PE patients for whom full-dose thrombolysis is contraindicated or has failed, CDT therapy should be used as a second-line treatment option alongside surgical embolectomy. SEATTLE II study, OPTALYSE and ULTIMA trials show improvement in RV strain after the use of CDT. Both delivery and thrombolysis time were reduced using CDT, as shown in DUET trial. However, none of the aforementioned trials shows mortality or morbidity benefit. We are hopeful that further studies would guide us better on the utility and effectiveness of CDT therapy.

Conflict of Interest

The authors affirm that they have no conflict of interest.

Author Contributions

Mrhaf Alsamman: abstract, introduction, conclusion; Ali Mohsin Choudhry: studies 1-3; Abdulaziz Mheri AlSaadi: studies 4-6; Rakesh Prashad: final edits and review.

Data Availability

The authors declare that data supporting the findings of this study are available within the article.

Table 1. Summary of Each Trial

Study	Study design	Sample size	Purpose	Findings	Conclusion
CAVA	Multi-center, single-blind, randomized, superiority, parallel-group study	184 individuals. 91 participants were randomized to receive additional ultrasound-accelerated catheter-directed treatment, whilst 93 patients received only the normal course of therapy.	To assess the effects of USCDT on the development of PTS following acute iliofemoral DVT in comparison to standard post-thrombotic therapy.	19 of the 62 patients in the intervention group (30.6%) and 26 of the 44 patients in the control group (44.8%) developed PTS at the median follow-up of 39 months (OR, 0.54; 95% CI, 0.26 to 1.15 (P = 0.11)).	With no statistically significant difference groups at the 12-month follow-up, the number of patients forgoing compression therapy increased.
ACCESS PTS	Open-label, single-arm, prospective study that involved multiple centers	113 participants were eligible, 81 patients gave their assent to the trial. 75 participants underwent evaluation at a 30-day follow-up visit after 78 patients successfully completed the study intervention.	To evaluate the efficacy of combined PTV and USAT in the management of symptoms and QOL in PTS patients with chronic veno-occlusive disease	At 1 year, the Villalta score had decreased by ≥ 4 in 77.3% of the limbs. The average Villalta score at the outset was 15.5 ($\pm$ 5.2). At 30, 90, 180, and 365 days after surgery, the Villalta scores changed by -5.9 ($\pm$ 5.8), -6.9 ($\pm$ 6.5), -7.8 ($\pm$ 6.1), and -8.2 ($\pm$ 6.4), respectively (P = 0.0001).	The use of PTV and USAT in combination to treat chronic venous obstruction following DVT led to clinical improvements over a year as well as a quantitative and long-lasting improvement in venous patency.
ULTIMA	Randomized, open-label	363 individuals, 304 patients were excluded because of screening failure, or 84% of the total. The 59 patients who were still alive got heparin alone in 29 cases and USAT with heparin in 30 cases, with primary evaluable outcomes of 25 and 28, respectively.	To examine whether AC alone is more effective than USAT in reversing RV dilatation in intermediate-risk PE patients	The mean RV/LV ratio in the USAT group decreased from 1.28 $\pm$ 0.19 at baseline to 0.99 $\pm$ 0.17 at 24 h (P = 0.001). The average RV/LV ratio in the heparin group was 1.20 $\pm$ 0.14 at baseline and 1.17 $\pm$ 0.20 at 24 h (P = 0.31).	In PE patients at intermediate risk of death, a standardized USAT regimen was more effective than AC with heparin alone in reversing RV dilatation after 24 h, and this was achieved without an increase in bleeding issues.
DUET	Multi-center, randomized, and controlled study	60 patients with acute limb ischemia due to recently (7 - 49 days) thrombosed infrainguinal bypass grafts or native arteries were randomly assigned to receive either ST (n = 32) or USAT with the endowave system (n = 28).	The time required to achieve continuous flow by thrombolysis was the primary outcome (> 95% thrombus destruction) with at least one below-the-knee artery achieving outflow.	It took substantially less urokinase (2.8 $\pm$ 1.6 $\times$ 10^6 IU in the ST group vs. 1.8 $\pm$ 1.0 $\times$ 10^6 IU in the USAT group, P = 0.01) and thrombolysis was completed much quicker (17.7 $\pm$ 2.0 h) in the USAT group than in the ST group (29.5 $\pm$ 3.2 h, P = 0.009) to achieve a continuous flow.	In comparison to ST, USAT significantly shortened the time required for thrombolysis in patients with freshly thrombosed infrainguinal native arteries or bypass grafts.
SEATLE II	Multi-center, single-arm, and prospective trial	150 individuals with acute massive (n = 31) or sub-massive (n = 119) PE.	The primary effectiveness outcome was the core laboratory-measured change in the RV/LV diameter ratio from baseline, as assessed by contrast-enhanced chest CT imaging at baseline and at 48 $\pm$ 6 h after the start of the treatment.	From baseline to 48 h post-surgery, mean pulmonary artery systolic pressure (51.4 mm Hg vs. 36.9 mm Hg; P < 0.00001), mean RV/LV diameter ratio (1.55 vs. 1.13; mean difference, - 0.42; P < 0.00001), and modified Miller index score (22.5 vs. 15.8; P < 0.00001) were all seen to decrease.	In patients suffering from acute massive and sub-massive PE, ultrasound-facilitated, low-dose fibrinolysis that was catheter-directed lowered pulmonary hypertension, RV dilatation, anatomic thrombus load, and minimized intracranial hemorrhage.
OPTALYSE	Randomized, multi-center, parallel-group trial	101 were enrolled who had a proximal PE in one main or proximal lobar pulmonary artery, intermediate-risk acute PE (less than 14 days in duration), normal systolic blood pressure (> 90), RV to LV diameter ratio greater than or equal to 0.9 on chest CTA, and were symptomatic.	To determine the lowest ideal tPA delivery and dose duration using USCDT.	All of the groups showed improvement in the refined modified Miller score: arm 1 through arm 4: 0.40 (24%; P = 0.0001), 0.35 (22.6%; P = 0.0001), 0.42 (26.3%; P = 0.0001), and 0.48 (25.5%; P = 0.0001), respectively.	In comparison to baseline, treatment with USCDT utilizing a shorter delivery period and lower-dose tPA was linked to enhanced RV function and decreased clot load.

AC: anticoagulation; CI: confidence interval; CTA: computed tomography angiography; DVT: deep venous thrombosis; LV: left ventricular; OR: odds ratio; PE: pulmonary embolism; PTS: post-thrombotic syndrome; PTV: percutaneous transluminal venoplasty; QOL: quality of life; RV: right ventricular; ST: standard thrombolysis; tPA: tissue plasminogen activator; USAT: ultrasound-accelerated thrombolysis; USCDT: ultrasound-facilitated catheter-directed thrombolysis.

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