Catheter-Directed Interventions (CDIs) for Acute Pulmonary Embolism: a 10-year single-center experience

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Abstract:

Objectives: Catheter-directed interventions (CDIs) are increasingly used for patients with acute PE, primarily to prevent mortality. The purpose of this study was to evaluate the outcomes, the safety, and the comparative effectiveness of the various CDIs as they have evolved over the past 10 years.

Methods: Patients who underwent a CDI for acute intermediate-risk and high-risk PE between the years 2009 and 2019 were identified and grouped based on PE severity (high vs. intermediate risk) and type of interventions (catheter thrombolysis (CDT) vs. suction thrombectomy (ST)). In principle, ST was preferred for patients with a contraindication for lytics. Perioperative outcomes, including major bleeding and mortality, were assessed and compared between techniques. Clinical success was defined as survival without any adverse event. Statistical significance was set at P<.05.

Results: During the study period, 365 patients (59.36±19.4 years old, 50.7% males, 91.2% intermediate-risk PE) received a CDI (CDT=330 and ST=35). Clinical success was 94% for the intermediate risk and 56.3% for the high-risk cohort. Incidence of major bleeding was 4.2% [0.6% (n=2) strokes] in the intermediate-risk group vs 21.8% [9.3% (n=3) strokes] in the high-risk group, mainly driven by the need for transfusion. The mortality rate was 0.6% in the intermediate-risk group vs. 15.6% in the high-risk group. There were no statistically significant differences in mortality and major bleeding between CDT and ST in both the intermediate and high-risk groups. Length of hospital and ICU stay were significantly lower in patients who underwent CDT when compared to ST in the intermediate-risk group (5.87 ± 4.6 vs. 8.04 ± 4.4, P=0.003 and 2.23 ± 2.1 vs. 3.48 ± 2.5, P<0.001 respectively), likely mirroring the underlying condition related to the contraindication for lytics.

Conclusion: Catheter interventions for intermediate and high risk PE are safe life-saving procedures when performed in a high volume center with appropriate expertise. CDT and ST demonstrate similar efficacy. Further prospective studies are needed to determine their comparative cost-effectiveness.

Keywords: Pulmonary embolism, Catheter-directed interventions (CDIs), Catheter-directed thrombolysis (CDT), Ultrasound-assisted thrombolysis (USAT), Suction Thrombectomy (ST).

INTRODUCTION

Pulmonary embolism (PE) is the third most common vascular disease in the United States after myocardial infarction and stroke. Patients with acute PE present on a spectrum ranging from incidentally found clots without hemodynamic insult or cardiopulmonary dysfunction to sudden hypotension and possible death at another extreme.

The intensity and invasiveness of treatment modalities for acute PE should be commensurate with the level of hemodynamic, cardiac, and respiratory compromise. Conservative management with anticoagulation alone is the gold standard treatment modality for all PE patients and 3. Patients, however, who present with signs of right ventricular dysfunction or without hypotension require prompt debulking and reperfusion therapy to prevent high-anticipated morbidity and mortality (3-15% for intermediate, >15% for high-risk PE).

Benefits of systemic thrombolysis accrue from the rapid recanalization of pulmonary arteries, leading to improvements in pulmonary artery pressures, right ventricle (RV) function, ventilation/perfusion mismatches, and overall hemodynamics. However, frequent contraindications for lytics in this patient cohort as well as high rates of intracranial and other major hemorrhages have limited its use, even in cases of high-risk PE.

The local delivery of thrombolytic agents—catheter-directed thrombolysis (CDT)—has been an area of increasing interest. Navigating a catheter through an obstructed throm-
bus in the pulmonary arteries creates a channel for drug delivery and increases the surface area of the thrombus exposed to thrombolytic agents. More commonly performed those days in patients with absolute contraindications to thrombolysis is suction thrombectomy, which is presumed to provide similar therapeutic benefits to CDT without using thrombolytic agents. With a variety of options at hand, choice of treatment remains case-specific while taking into account physician preference.

Several observational series have been published regarding the ability of catheter-directed interventions (CDIs) to decrease PE clot burden and improve patient outcomes with less associated complications when compared to systemic thrombolysis. However, few have compared those techniques to each other. The purpose of this study is to review our experience on catheter interventions for PE and assess comparative effectiveness between different treatment modalities.

**METHODS**

**Patient Selection**

In this single-center retrospective study, patients who underwent CDT (Standard or Ultrasound-assisted) and suction thrombectomy (ST) for the treatment of acute PE from 2009 to 2019 were identified from our institution’s electronic medical records.

Patients were grouped per PE type/severity as high or intermediate risk. Per standard definition, patients who developed hypotension requiring vasopressors or inotropic support were classified as having a high-risk (massive) PE. Others who were hemodynamically stable but with signs of right ventricular dysfunction on imaging (echocardiography or CT angiography), or through positive biomarkers (troponin or brain natriuretic peptide), were considered as having an intermediate-risk (sub-massive) PE.

Patients who did not meet the above-mentioned criteria for intermediate-risk or high-risk PE, in addition to those who underwent a CDI at an outside institution before being transferred, were excluded from the study.

Clinical success was defined as survival to discharge with no major bleeding, perioperative stroke, decompensation, persistent shock, or any other procedure-related adverse event (i.e., heart or valve injury) for both groups.

Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) criteria were used to define major bleeding. Major bleeding events included GUSTO moderate (need for transfusion with no hemodynamic instability) and GUSTO severe (intracranial bleeding or leading to hemodynamic instability) cases.

This study was approved and exempted from informed consent by the institutional quality improvement review committee.

**Treatment Protocol**

Treatment options consisted of either CDT (Standard or Ultrasound-assisted) or ST and were initially chosen based on physician preference and availability of resources. During the reported time frame, experience and devices have evolved. A multidisciplinary response team (PERT) has been fully active since 2014. In today’s practice, a standard treatment algorithm has been implemented. All interventions were performed in a standard angiography suite or hybrid operating room with fixed-imaging fluoroscopic capacities.

The majority of patients were maintained on therapeutic heparin protocol (unfractionated or low molecular weight) throughout the interventional treatment. Early on, we used to discontinue systematic heparin during thrombolysis (similar to DVT or arterial lysis protocols) and maintained just a sheath drip (500 units per hour). This practice was later abandoned. All patients were eventually transitioned to systemic, oral, and long-term anticoagulation therapy (warfarin, enoxaparin, or factor Xa inhibitors) before discharge.

Either femoral or internal jugular vein access (based on physician preference) was obtained under ultrasound guidance in all patients. When CDT was planned for bilateral PEs, a dual lumen sheath (10 or 12F) was used.

Few patients (mainly high-risk PE) with a low cardiopulmonary reserve and/or with residual iliofemoral venous thrombus identified on duplex, had a retrievable inferior vena cava (IVC) filter placed before pulmonary artery catheterization.

Standard CDT was performed using Cragg-McNamara (Boston Scientific) or Uni-Fuse (AngioDynamics) multisidehole catheters, and Ultrasound-assisted CDT was performed using the EkoSonic system (EKOS Boston Scientific Corp) (Figure 1). Infusion of a loading dose of 2 to 4 mg of tissue plasminogen activator was started at the interventionist’s discretion, followed by a maintenance dose at a rate of 1 mg per hour per catheter. Patients were monitored in the intensive care unit (ICU) throughout infusion therapy. Fibrinogen levels and activated partial thromboplastin times were assessed and recorded at set intervals.

Suction thrombectomy was performed using Inari FlowTriever (Inari Medical, Irvine CA), Indigo CAT-8 (Penumbra, Alameda, CA), or AngioVac (AngioDynamics, Latham, NY) systems. (Figures 2 and 3)

Early on (2009-2011), lytics infusion time and dose were tailored according to clinical improvement, noted by more than 50% clot resolution on repeated angiography. Thrombolytics were discontinued if no improvement was noted after 48 hours. After 2011, termination was generally based on improved clinical (tachycardia and hypotension, dyspnea, or supplemental oxygen) and/or echocardiographic parameters (RV strain on repeat echocardiogram). Those were assessed 12 to 24 hours after the initiation of thrombolysis, and catheters were pulled out at the patient’s bedside. For the past few years, following the OPTALYSE results, thrombolytic infusion did not typically exceed 8 hours (Figure 4).
Figure 1. Ultrasound assisted thrombolysis. (a) Pulmonary arteriogram indicating bilateral thrombus; (b) EKOS catheters in the right and left main pulmonary arteries, notice the radiopaque ultrasound probes along the infusion length of the catheters.

Figure 2. Novel aspiration thrombectomy devices. (a) The FlowTriever (Inari Medical Inc., Irvine, Calif) consists of a flexible large-bore aspiration 0.035 guide catheter 20 or 24Fr (T20 and T24), and a catheter system of self-expanding nitinol discs (6-10, 11-14, and 15-18 mm), which can be advanced through the aspiration sheath to mechanically engage thrombi. The side port tubing of the sheath connects to a 60cc locking syringe that can generate up to 29mmHg negative pressure. Given the large bore access, the T20 sheath can remove up to 104mL/sec, the T24 up to 143mL/sec. A smaller T16 sheath/catheter is available but not recommended for routine use given its weak suctioning power. It is used complimentary to the larger sheaths to reach more distal targets. (b) The Indigo continuous aspiration mechanical thrombectomy (CAT) system (Penumbra, Inc, Alameda, Calif) has three components: a catheter, a separator, and a vacuum pump. It is an 8Fr catheter (CAT-8). The separator wire allows thrombus fragmentation and mobilization as well as cleaning of the catheter when it is obstructed by thrombus. The vacuum pump provides continuous suction and can aspirate up to 8mL/sec by applying and maintaining negative pressure of almost -29 mm Hg. A CAT-12 system is anticipated to enter the market by the end of 2020.
Figure 3. Aspiration thrombectomy using the Indigo CAT8 device. Notice the complete left main pulmonary artery obstruction and subsequent thrombectomy that led to complete thrombus removal. The pulmonary artery pressure had a significant drop from 53 to 49mmHg.

Figure 4. Thrombus reduction as seen in CT pulmonary arteriogram 48 hours after catheter directed thrombolysis.
Figure 5. Catheter interventions are not complication free procedures. (a) coronary sinus was accidentally cannulated and likely injured as 4 hours after initiation of thrombolysis patient developed cardiac tamponade that required emergent surgical evacuation; (b) 1st generation Angiovac (Angiodynamics, NY) thrombectomy, led to tricuspid valve rupture that required open repair. The device is not currently promoted for use in PE.

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<th>Intermediate-risk (n=333)</th>
<th>P-value</th>
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<td>4 (18.2%)</td>
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<td>16 (5.2)</td>
<td>14.6</td>
<td>21.68</td>
<td>0.62</td>
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<td>10 (8.8)</td>
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<td>2</td>
<td>4 (1.2)</td>
<td>4 (2.8)</td>
<td>5 (20)</td>
<td>45 (14.6)</td>
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<td>0.67</td>
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<td>154 (50)</td>
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<td>49.34±1.314.1</td>
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<td>16 (15.1)</td>
<td>1</td>
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<td>154 (50)</td>
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<td>154 (50)</td>
<td>154 (50)</td>
<td>154 (50)</td>
<td>0.40</td>
<td>0.47</td>
<td>60.30 ± 16.8</td>
<td>13 (52)</td>
<td>49.34±1.314.1</td>
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*P-value less than 0.05 considered as statically significant.

BNP; Brain Natriuretic Peptide, ASA: American Society of Anesthesiology, CHF Congestive Heart Failure, CAD: Coronary Artery Disease, DVT: Deep Vein Thrombosis, HTN: Hypertension, RV: Right Ventricle, LV: Left Ventricle, OCP: Oral Contraceptive Pills, PE: Pulmonary Embolism

Table 1. Patient demographics, risk factors and PE Characteristics across groups.


Data analysis

Data collected included demographic information, risk factors, and laboratory markers such as troponin and brain natriuretic peptide plasma levels. Major and minor lytic contraindications were defined based on current guidelines from the American Heart Association and European Society for Cardiology consensus guidelines.

Outcomes included periprocedural complications such as ischemic cerebrovascular or cardiac events, need for additional surgical intervention, length of ICU, and hospital stay, and supplemental oxygen use at discharge.

Comparisons were made using the Chi-square, Fisher exact, or Mann-Whitney U tests depending on the nature of the data. Kaplan-Meier (KM) analysis with log-rank test were used to compare long-term survival between PE groups. Binary logistic regression was performed to identify factors associated with clinical success.

Statistical analysis was performed using Statistical Package for the Social Sciences, version 25 (IBM Corp, Armonk, NY). A P-value of 0.05 was considered as cutoff for significance.

RESULTS

Over 10 years, 365 patients with acute PE underwent CDIs at our institution. Among these, 333 were in the intermediate-risk group, and 32 were in the high-risk group. Patients demographics, risk factors and PE characteristics are summarized in Table 1.

Overall clinical success was 90.7%. Clinical failure was mainly predicted by the severity of PE, troponin levels and female gender (Table 2). Perioperative details are described separately in each PE subgroup.

Kaplan-Meier analysis revealed a significant difference in 5-year survival between the intermediate-risk and high-risk PE groups (54% vs 40%, P < 0.001).

Intermediate-risk group

In this group, 92.4% (n= 308) received CDT and 7.6% (n= 25) received a ST. Mean age was 58.6 ±15-2 years and 50-1% (n= 167) were males. Major bleeding occurred in 4.2% (n= 14) of cases, and the rate of clinical success was 94% (n=313).

Patients who underwent CDT had significantly lower rate of contraindications to lytics when compared to the ST group (23.3% (n=69) vs. 16 64% (n=16), P< 0.01). There were no significant differences in other baseline characteristics (Table 1).

In-hospital death was very low in both groups (0.6% (n= 2) vs. 0, P=1.00). In the CDT group, major bleeding occurred in 3.9% (n=12), including 2 groin hematomas that required aspiration, 2 hemorrhagic strokes, 1 coronary sinus perforation and 8 transfusions ≥ 2 units. In the ST group, there were two major bleeding events (8%), including 1 hemorrhagic stroke, 1 tricuspid valve rupture and 2 transfusions ≥ 2 units. Overall, hospital stay and ICU stay were longer in the ST group when compared to the CDT group (8.04+4.4 vs 5.87+4.6 days, P= 0.003, and 3.48+2.5 vs 2.23+2.1 days, P= 0.001 respectively). (Table 2).

<table>
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<tr>
<th>Variable</th>
<th>Univariate logistic model</th>
<th>Multivariate logistic model</th>
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<tr>
<td>Age (years)</td>
<td>OR</td>
<td>95% C.I</td>
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<tr>
<td>Gender (female)</td>
<td>1.02</td>
<td>0.99-1.05</td>
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<tr>
<td>Type of PE (massive)</td>
<td>3.64</td>
<td>1.64-8.28</td>
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<td>Troponin(ng/mL)</td>
<td>12.17</td>
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<td>LOS</td>
<td>1.50</td>
<td>1.18-1.90</td>
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Table 2. Multivariate analysis for clinical failure.

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<th>Variable</th>
<th>Univariate logistic model</th>
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<tr>
<td>LOS</td>
<td>9.77±6.1</td>
<td>12.80±12.5</td>
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<td>ICU stay</td>
<td>6.18±5.9</td>
<td>9.89±13.5</td>
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<td>Clinical Success</td>
<td>13(59.1%)</td>
<td>5(50)</td>
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<td>Perioperative stroke</td>
<td>2.36</td>
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<tr>
<td>IVC filter</td>
<td>12(54.5)</td>
<td>5(50)</td>
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<tr>
<td>Discharge O2</td>
<td>4(18.2%)</td>
<td>1(10)</td>
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<tr>
<td>Perioperative MI</td>
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<td>In hospital death(mortality)</td>
<td>2(9.1%)</td>
<td>3(30%)</td>
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<td>Surgical conversion</td>
<td>2(9.1%)</td>
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<td>Major Bleeding</td>
<td>6 (27%)</td>
<td>1 (10%)</td>
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*P-value less than 0.05 considered as statistically significant.

LOS: Length of hospital stay, ICU: Intensive Care Unit, MI: Myocardial Infarction

Table 3. CDI outcomes.
HIGH-RISK GROUP
In this group, 68.7% (n= 22) received a CDT vs. 31.3% (n= 10) who received a ST. The mean age was 61 ±17.5 years. The overall rate of clinical success (survival without any complication) was 56.3% (n=18). Major bleeding occurred in 21.8% (n= 7) of cases.

Sub-analysis based on treatment modality (CDT vs ST groups) did not show significant differences in baseline characteristics except for a history of coronary disease (9.1% (n=2) for CDT vs. 50% (n=5) for ST, *P* = 0.01) and fewer lytic contraindications in the CDT group (36.3% (n=8) vs. 60% (n=6), *P* = 0.02) (Table 1).

In-hospital mortality was 15.6% for this cohort and did not differ between treatment groups (9.1% (n=2) for CDT vs 30% (n= 3) for ST, *P* = 0.13). Major bleeding occurred in 27% (n=6) of CDT patients (including 4 transfusions ≥ 2 units, 1 neck hematoma which required embolization and 1 hemorrhagic stroke). Of those, 2 patients with groin hematomas and 2 others with no identifiable source of bleeding were managed conservatively. On the other hand, major bleeding occurred in 10% (n=1) patient from the ST group (Hemoglobin drop <7 g/dl requiring multiple transfusions). Two patients in the CDT group but none in the ST group required open surgical conversion. Overall, hospital and length of ICU stay were similar (Table 2).

DISCUSSION
This study aimed to review our institution’s experience with acute PE patients who underwent endovascular revascularization and to compare the results of different interventions, including CDT (Standard and Ultrasound-assisted thrombolysis) and ST in both high-risk and intermediate-risk PE. Our results indicated high clinical success rates for the intermediate risk PE population and reasonable rates for the otherwise highly morbid high-risk PE population. No major differences were identified between the treatment alternatives of CDT versus ST.

Various clinical trials and consequent meta-analyses have demonstrated lower mortality with systemic thrombolysis in comparison with anticoagulants alone, but a high incidence of stroke and bleeding rates along with multiple contraindications have resulted in a higher desire for catheter interventions. Since the publication of the ULTIMA trial indicating the superiority of ultrasound assisted thrombolysis (USAT) over systemic anticoagulation in improving hemodynamic parameters without any significant increase in the bleeding complication rates, we’ve seen a tremendous increase of these interventions. Both standard and ultrasound assisted CDT techniques have demonstrated promising results in preventing mortality. An on-going trial (SUNSET sPE trial) aims at assessing whether ultrasound-assisted thrombolysis results in superior thrombus clearance compared with standard CDI in patients with intermediate-risk PE. While ultrasound assisted thrombolysis has been leading the field of interventions more recently non lytic techniques are entering the market targeting to provide an even safer alternative by eliminating the systemic bleeding effect that even locally administered tPA can have. Mechanical thrombus aspiration provides rapid clot removal while avoiding the use of thrombolytics. These devices are however bulkier and may introduce other risks, while the distal pulmonary arterial branches cannot be reached.

The novel suction thrombectomy systems that have been recently introduced to the US market and received FDA approval are the Indigo CAT 8 (Penumbra, Inc, Alameda, Calif) and Flowtriever (Inari Medical Inc., Irvine, Calif). Despite having some differences, both work with similar technical principles. Due to their relatively recent emergence, real world studies evaluating their safety and effectiveness and their comparison against CDT are limited. Ciampi-Dopazo et al. showed a technical success of 94.4% and a clinical success of 83.3% in 8 high-risk and 10 intermediate-risk cases of PE who underwent aspiration thrombectomy with CAT 8. Wible et al., in a single-center retrospective study, used suction thrombectomy using FlowTriever in acute PE in 8 high-risk and 38 intermediate-risk cases. Their results demonstrated technical success and significant improvement in mean pulmonary artery pressure, with a 100% survival rate and no procedure-related delayed complications. A previously published study by our institution showed no significant differences in clinical outcomes such as major bleeding, length of ICU stay, hospital stay, and clinical success between CDT and ST. However, due to the smaller number of patients when the study was conducted, no sub-analysis could be done after further stratification based on PE type.

In current study, we attempted to compare the outcomes of CDT to ST in both high-risk and intermediate-risk PEs. With the exception of length of stay being shorter for CDT in the intermediate-risk PE population, there were no significant differences in treatment outcomes. The increased ICU and hospital stay likely relates to the higher incidence of recent surgery and trauma in this sub-population (*P* = 0.019). Irrespective of technique used mortality rates remained close to 0 for the intermediate-risk PE population and 15% for the high-risk PE ones. The traditional quoted rates for anticoagulation treatment for these subgroups are 3-15% and >15% respectively. It is worth mentioning that this experience incorporates our learning curve which included poor patient selection and various complications. In 2019, we had no major bleeding and 97% clinical success for a total of 33 cases (intermediate and high risk).

Another important factor to be considered is cost-effectiveness. Device costs are roughly estimated as follows: standard multisidehole catheter approximately $120 (x2 for bilateral infusion), EKOS catheter approximately $2600 (x2 for bilateral infusion), Flowtriever approximately $5040 and Indigo CAT8 approximately $5580. Hospital resources usage will ultimately drive the final bill. In our comparative study the populations compared weren’t identical in terms of baseline disease as ST was used for those who had contraindications for lytics (recent surgery or trauma) thus reasons to stay longer in hospital. Although a randomized trial is unlikely to happen, comparing series from high-volume centers should be helpful in choosing the appropriate personalized treatment modality.
Our experience with CDIs highlights the importance of appropriate patient selection and bleeding risk assessment. Multiple techniques have been used throughout the years and a learning curve does exist, particularly as new devices are introduced in the field. While CDT is safe and effective for a subset of patients ST can be used for all PEs requiring an intervention and it remains the only option for patients with contraindications to lysis. The bulkiness and trackability of the ST devices along with a typically higher price account for their limitations against CDT. It is thus fair to say that the two techniques are complimentary. Systemic thrombolytics or surgical thrombectomy are otherwise a valid alternative for some patient subgroups or when appropriate interventional expertise is not available. These facts come in line with the interventional algorithm guided by the PERT Consortium consensus.

Our study is limited by its retrospective nature. Despite being among the largest series on CDIs for acute PE, the sample sizes in the high-risk PE group as well as in the ST group remain small, limiting the ability to draw inferences. Alongside, data on patient functional status and quality of life at follow up was not collected, limiting our ability to determine the effect of these interventions in longer term functional outcomes, mainly late PE sequelae and pulmonary hypertension.

CONCLUSION
CDT (Standard and Ultrasound-assisted) and ST for acute high-risk or intermediate-risk PE demonstrate similar safety and efficacy profiles when performed in high volume centers with appropriate expertise. Further prospective studies are needed to fully determine their comparative cost-effectiveness.

AUTHOR CONTRIBUTIONS
Conception and design: SA, PC, AAA, RC, EA
Data collection: SA, PC, AAA
Statistical analysis: SA, PC, AAA
Critical revision of the article: RC, EA
Final approval of the article: RC, EA
Obtained funding: Not applicable
Overall responsibility: EA

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