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Predictors of failure and complications of catheter-directed interventions for pulmonary embolism

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Abstract

Objective: Catheter-directed interventions (CDIs) are increasingly performed for acute pulmonary embolism (PE) as they are presumed to provide similar therapeutic benefits to systemic thrombolysis while decreasing the dose of thrombolytic required and the associated risks. This study aimed to identify factors associated with CDI failure and to describe anticipated complications.

Methods: Consecutive patients who underwent CDI for massive or submassive PE between 2009 and 2015 were identified; outcomes and complications were retrospectively collected. CDI clinical failure was defined as major bleeding, perioperative stroke or other major adverse procedure-related event, decompensation for submassive or persistent shock for massive PE, need for surgical thromboembolectomy, or in-hospital death. Univariate analysis was used to study the factors associated with CDI failure.

Results: There were 102 patients who received a CDI during the study period (36 standard catheter thrombolysis, 60 ultrasound assisted, 6 other; age, 59.2 ± 15.9 years; male, 50 [49.0%]; massive PE, 14 [13.7%]). Five patients (4.9%) had a major contraindication and 15 patients (14.7%) had a minor contraindication to systemic thrombolysis. The mean alteplase dose was 28.2 ± 18.8 mg (range, 0–123 mg; three patients had already received systemic lysis). CDI failure occurred in 15 patients (14.7%; 7 in massive PE, 8 in submassive PE). Of these patients, seven had

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major bleeding events, whereas eight patients decompensated. Ten (9.8%) patients had minor bleeding events (four access related). Factors associated with CDI failure and major bleeding included massive PE, age > 70 years, and major contraindication to thrombolytics. Both failures and bleeding events were independent of lysis dose and CDI technique.

Conclusions: CDIs for acute PE are not risk-free procedures, and their use should be individualized on the basis of a risk-benefit ratio. Particularly for patients with major contraindications to systemic thrombolytics, CDIs should be used selectively. Lytic dose, within the low-volume range administered in CDI, and type of CDI seem to have no impact on adverse events. (*J Vasc Surg: Venous and Lym Dis* 2017;5:303–10.)

Acute pulmonary embolism (PE) is a leading cause of morbidity and mortality.¹ Its increased incidence during the past two decades, in part due to the higher diagnosis rate and the aging population, has driven practice toward newer treatment modalities.² The goal of treatment is primarily focused on preventing mortality and secondarily PE recurrence and late-onset chronic thromboembolic pulmonary hypertension. Recent guidelines reiterate the standard of care treatment (anticoagulation) for low-risk PE while escalating therapy to systemic thrombolytics for high-risk PE associated with hypotension.^{3–5} In selected patients without hypotension but with evidence of cardiopulmonary deterioration (eg, right ventricular strain, elevated cardiac biomarkers), the risk-benefit ratio may also favor thrombolytic therapy to prevent decompensation.^{3–5} Whereas current evidence is derived from trials using systemic thrombolytics, their limitations have driven contemporary practice toward catheter-directed interventions (CDIs) that are presumed to provide similar therapeutic benefits while decreasing complication rates because of the lower doses or even the absence of lytics.^{6–9}

The Ultrasound Accelerated Thrombolysis of Pulmonary Embolism (ULTIMA) randomized trial, the prospective Single-arm, Multicenter Trial of EkoSonic Endovascular System and Activase for Treatment of Acute Pulmonary Embolism (SEATTLE II) trial, the Pulmonary Embolism Response to Fragmentation, Embolectomy, and Catheter Thrombolysis (PERFECT) registry, and multiple case series have demonstrated a relative safety and potential efficacy of CDI, triggering more interest in CDI as first-line treatment for acute massive and high-risk submassive PE.^{7,10–14} However, studies are still controversial and have shown that CDI may not be without complications as the reported major bleeding rate ranges widely between 0% and 10%; failures do exist, although they are not uniformly reported.^{6,7,12–14}

The purpose of this study was to study the factors associated with CDI failure and to describe anticipated complications of CDI for acute PE.

METHODS

The study protocol was approved and exempted from informed consent by the Quality Review Board of the University of Pittsburgh Medical Center.

Study design.

Consecutive patients who received in-hospital treatment for acute PE between January 2009 and October 2015 were identified from our institution's electronic medical records. Patients with low-risk PE on presentation and those who received anticoagulation or systemic thrombolysis only were excluded from the analysis, leaving for analysis patients with acute high-risk (massive) and intermediate-risk (submassive) PE treated with CDI. This classification of PE types is in accordance with published guidelines.^{3,5} High-risk PE is defined as sustained hypotension for at least 15 minutes or requiring vasopressors. Intermediate-risk PE is defined as a simplified Pulmonary Embolism Severity Index (sPESI) 1 and positive cardiac biomarkers or signs of right ventricular dysfunction on echocardiography or computed tomography scans.

Records were reviewed for demographics, baseline risk factors, baseline laboratory markers such as glomerular filtration rate (which is calculated using the Modification of Diet in Renal Disease method), lower extremity studies, indications, biomarkers at baseline (troponin and brain natriuretic peptide plasma levels), intraprocedural data, and periprocedural complications. Patients were stratified into intermediate-risk vs high-risk PE groups, depending on their sPESI score, cardiac biomarkers, and echocardiographic findings.^{5,15} An sPESI score of 1 is obtained if any of the following conditions are present: age >80 years, cancer, chronic cardiopulmonary disease (either chronic heart failure or chronic pulmonary disease or both), pulse rate >110 beats/min, systolic blood pressure <100 mm Hg, and oxygen saturation <90%. If none of these are present, the patient receives an sPESI score of 0 and is considered at low risk (30-day mortality, 0.0%–2.1%); patients with a score of 1 are classified at high risk (30-day mortality, 8.5%–13.2%).¹⁵

Our primary outcome, CDI failure, was assessed at hospital discharge. CDI failure was defined as death, decompensation for submassive or persistent shock for massive PE, major bleeding events, surgical embolectomy, and other potential procedure-related complications (heart injury or acute kidney injury requiring long-term hemodialysis). Major bleeding events were defined according to the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) classification, whereby both GUSTO moderate and GUSTO severe constituted major bleeding.¹⁶ GUSTO moderate includes bleeding requiring transfusions without hemodynamic compromise, whereas GUSTO severe includes bleeding that causes hemodynamic instability and requires an intervention or bleeding that is intracranial. Absolute and relative contraindications were defined per the American Heart Association guidelines.¹⁷

Treatment protocol.

Patients not receiving heparin at the time of admission were given an intravenous bolus of 80 units/kg, followed by an infusion of 18 units/kg/h. If the patient was receiving heparin at admission, infusion was continued to maintain an activated partial thromboplastin time of 68 to 106 seconds per institutional protocol. The decision to undergo CDI for PE treatment was determined by the institution's multidisciplinary PE response team (PERT) consisting of pulmonary, critical care, cardiology, vascular surgery, and cardiothoracic services. The decision was based on an evolving protocol that considers intermediate- to high-risk

(echocardiographic right ventricular dysfunction and positive cardiac biomarkers [troponin >0.1 ng/mL and brain natriuretic peptide >100 pg/mL]) and high-risk (systolic blood pressure <90 mm Hg for at least 15 minutes or requiring inotropic support) PE patients as potential candidates for CDI. Right ventricular dysfunction was defined as echocardiographic or computed tomography right ventricle/left ventricle ratio >0.9. The majority of the patients (>90%) had a baseline echocardiogram.⁷ Systemic lysis was favored in severely unstable cases and CDI in patients with risk factors for bleeding. An inferior vena cava filter was generally used in patients with contraindication to anticoagulation and selectively in high-risk patients with low cardiopulmonary reserve. In controversial cases, the PERT was consulted. The filter was usually placed before pulmonary artery catheterization. Our heparinization protocol during catheter-directed lysis shifted from subtherapeutic dosing early in our experience to full low therapeutic dosing (activated partial thromboplastin time of 40 to 60 seconds). After intervention, all patients remained on full systemic anticoagulation, after which they were transitioned to long-term oral anticoagulation.

Catheter intervention technique.

Ultrasound-guided femoral or internal jugular vein access is used in all patients. Dual-lumen jugular or femoral sheaths or two single-lumen femoral sheaths are used for bilateral PEs. If necessary, an inferior vena cava filter is inserted before pulmonary artery catheterization. A wire is then navigated toward the pulmonary arteries. As the wire crosses from the right atrium into the right ventricle, it may go through the chordae tendineae of the tricuspid valve. As long as the catheter or device used is a small-bore (8F) one, this will be uneventful. When larger catheters are used, the chordae can rupture, leading to tricuspid valve insufficiency. To prevent this, when large devices are considered, crossing of the tricuspid valve should be done either with a pigtail or with an inflated balloon catheter (eg, Swan-Ganz). A pulmonary arteriogram is obtained to assess the clot's location. Standard CDI protocol includes placement of unilateral or bilateral 5-cm multi-side-hole catheters (5F Cragg-McNamara [Boston Scientific, Marlborough, Mass] or UniFuse [AngioDynamics, Latham, NY]) across the heaviest clot burden (unilateral or bilateral). On-table infusion of 2 to 4 mg of tissue plasminogen activator is given if it is deemed necessary, followed by the initiation of lysis at a rate of 0.5 to 1 mg/h. Another CDI technique involves the use of ultrasound-assisted thrombolysis (USAT) with the EkoSonic catheter (EKOS Corp, Bothell, Wash). In a few cases, aspiration thrombectomy with the AngioVac device (AngioDynamics), rheolysis with the AngioJet device (Boston Scientific) or the Arrow-Trerotola thrombolytic device (PTD; Arrow, Reading, Pa), catheter-based mechanical fragmentation, and on-table-only catheter-directed infusion (without initiation of continuous infusion) were used per the physician's preference. Patients undergoing CDI are monitored in the intensive care unit. No adjunct medications (eg, prostanoids) are used for pulmonary hypertension. Termination of catheter-directed thrombolysis gradually evolved through operating room lysis check to bedside catheter removal based on improvement of clinical, hemodynamic, and echocardiographic parameters or any complication that necessitates discontinuation of treatment. Pulmonary artery pressures are transduced before catheter removal at bedside and compared with the intraoperative ones. Filter retrieval is performed at a later date, if applicable.

Statistical analysis.

Descriptive characteristics are reported as mean $\pm$ standard deviation or as number of cases and percentages. Comparison of binary data between and within groups was performed using the χ^2 and Fisher exact tests. Factors associated with CDI failure and major bleeding were assessed using univariate analysis.¹⁸ Results were considered statistically significant if $P < .05$. Data analysis was performed using Statistical Package for the Social Sciences, version 22 (IBM Corp, Armonk, NY).

RESULTS

During the study period, 102 patients received CDI, 14 (13.7%) for massive and 88 (86.3%) for submassive PE. The mean age of the cohort was 59.2 ± 15.9 years, and 52 (51.0%) were women. Baseline characteristics are presented in Table I. Twenty patients (19.6%) had either a major or minor contraindication to thrombolytics. CDIs were used as complementary to systemic lysis in three patients who had no improvement with systemic thrombolytics alone.

Procedural data.

The majority of CDI patients received USAT (60 [58.8%]); 38 (37.3%) received standard catheter-directed lysis, 2 (2.0%) patients received aspiration thrombectomy, and 2 (2.0%) patients underwent rheolytic thrombectomy. The mean alteplase dose was 28.2 ± 18.8 mg (range, 0–123 mg), and mean infusion time was 17.0 ± 9.1 hours (range, 0–51 hours). Interventions were bilateral in most cases (90 [88.2%]). Inferior vena cava filter was inserted in 46 (45.1%) patients; 59 (57.8%) patients required a single trip to the angiography suite with catheters removed at bedside and termination of infusion based on clinical and echocardiographic parameters.

In-hospital outcomes.

Outcomes stratified per PE type are reported in Table II. CDI failure occurred in 15 patients (14.7%; 7 in massive PE, 8 in submassive PE). Of these patients, seven had major bleeding events; eight patients decompensated. The seven major bleeding events break down as follows: one patient with a recent (<3 months) stroke experienced an intracranial hemorrhage and later died, two patients experienced access bleeds requiring blood transfusions, three other patients experienced systemic bleeds (intraperitoneal, rectus sheath, and gastrointestinal bleeds) requiring blood transfusions, and one patient had a cardiac tamponade secondary to hemopericardium from a coronary sinus rupture (procedure-related complication). As for the eight decompensation patients, seven of those were PE related (three required surgical embolectomy, three patients died, and one patient eventually recovered). The last patient decompensated as a result of a tricuspid valve rupture requiring open repair (procedure-related complication).

CDIs were used in 7 (6.9%) patients with absolute contraindications and 13 (12.7%) patients with relative contraindications. Of the patients with absolute contraindications, five experienced CDI failure, although two of those were unrelated to the contraindication itself and did not involve any bleeding (surgical embolectomy and tricuspid valve injury requiring open repair). The other three patients with major contraindications experienced

intraperitoneal, gastrointestinal, and intracranial bleeds. Of the patients with relative contraindications, no CDI failure was documented. Four patients required extracorporeal membrane oxygenation (ECMO). All the ECMO cases followed unsuccessful CDI. The AngioVac technique involved a venovenous nonoxygenating bypass circuit and thus was not considered part of the ECMO group.

Minor bleeding events occurred in 10 (9.8%) patients, 4 of which were access related. Other minor bleeding events included nosebleeds, blood-tinged sputum, incisional bleeds, breast hematoma, and two gastrointestinal bleeds. None required reintervention or transfusion.

The average hospital and intensive care unit length of stay for CDI were 8.5 ± 7.9 days and 3.8 ± 5.7 days, respectively.

Overall, in-hospital death occurred in four (3.9%) patients receiving CDI. Of these, three were PE related and one was due to hemorrhagic stroke. Of the three patients who died of PE-related causes, two of them received prior systemic thrombolytics.

Twenty-one patients had no follow-up beyond 30 days because of either loss of follow-up (17 patients) or death from an unidentified cause (4 patients). At 90 days, two additional patients died, one of a known pancreatic tumor and one of non-PE-related medical comorbidities (an infectious process in his biliary tree). These were not included in our analysis.

Factors associated with CDI failure and major bleed. Using univariate analysis, massive PE and pre-existing major contraindication to thrombolytics were associated with higher odds of CDI failure. Age ≥ 70 years and pre-existing major contraindication to thrombolytics were associated with higher odds of major bleed ($P < .05$; Table III).

Excluding the four CDI cases without the use of standard or ultrasound-directed thrombolysis, the factors associated with CDI failure and major bleeding remained the same. None of the four cases had major bleeding events.

DISCUSSION

Our study demonstrated that CDI can be effective and safe when it is used selectively, but it can also be detrimental without appropriate selection of patients. Patients at risk to experience failure or major bleed are those with massive PE, age ≥ 70 years, or a major contraindication to thrombolytic therapy.

Currently, CDIs appear to have a significant role in the management of acute PE, especially for intermediate-risk PEs.^{8,9} This current appeal for CDI comes as an extrapolation from the Pulmonary Embolism Thrombolysis (PEITHO) trial and a subsequent meta-analysis showing superior mortality and decompensation prevention for systemic thrombolytics compared with anticoagulation alone for intermediate-risk PEs.^{8,9} There is also evidence for superior midterm benefits of systemic thrombolysis compared with anticoagulation with respect to exercise tolerance and quality of life.^{19–21} There is still no study to date focusing on quality of life outcomes after CDI. CDI was also shown to improve early right ventricular

function recovery compared with anticoagulation, with higher reductions in the right ventricle/left ventricle ratio.²² Appropriate selection of patients for this subset of PEs is important, given the higher major bleeding rates with systemic thrombolytics, the low mortality rates of intermediate-risk PEs, and that the main benefit from thrombolytics is derived from decompensation prevention rather than mortality benefit.⁸

The majority of CDI studies focus on their complications, but failures should also be taken into account and uniformly reported. We used a composite clinical success end point incorporating hemodynamic stabilization and echocardiographic parameter improvement to assess CDI and to allow meaningful comparisons.^{7,13,22}

Our CDI failure rate of 14.7% and major bleeding rate of 6.9% reveal that CDIs are not risk-free procedures. Our results are consistent with CDI failure and major bleeding rates in the literature. Apart from one randomized study, real-world studies have revealed a CDI failure rate roughly ranging between 6% and 14%.^{6,12–14} The most recent National Inpatient Sample study revealed a failure rate of 16.6% (in-hospital mortality rate, 13.36%; hemorrhage requiring transfusion, 3.23%) while having a major bleeding rate of 3.2%.⁶ The SEATTLE II also had a CDI failure rate of 14.7% (in-hospital mortality, 2.7%; adverse events related to device, 2.0%; major bleeding, 10.0%) while having a major bleeding rate of 10.0%.¹³ Despite the ULTIMA trial's showing no CDI failure or major bleeding events, the study was limited by a small sample size and an idealized sample population of patients that might not represent actual clinical scenarios.⁷ The recent PERFECT study, however, revealed a CDI failure rate of 5.9% with no major bleeding events.¹⁴ The absence of major bleeding events is surprising in this cohort of patients, especially because some patients had an absolute contraindication to thrombolytics. Unclear inclusion criteria, unreported causes of death, and different anticoagulation protocols can be possible explanations for the absence of bleeding events.²³

In a recent meta-analysis of USAT for acute PE, the major bleeding rate associated with CDI was reported around 0.9%.²⁴ However, a reanalysis of the same studies using defined homogeneous major bleeding criteria resulted in a major bleeding rate of 3.5%.²⁵ Other studies reporting similar or even higher bleeding rates were also excluded from this meta-analysis. A 2009 meta-analysis reported a CDI procedural complication rate of around 10% for massive PE. These complications include access site hematomas, pulmonary artery dissection, arrhythmias, tricuspid valve injury, renal insufficiency requiring hemodialysis, and cardiac tamponade.¹² Of note, several complications were attributable to the AngioJet device that is no longer recommended for use.

Yet, CDIs appear to be superior to systemic thrombolytics in terms of stroke reduction as the literature is consistent in showing a nearly 0% stroke rate.^{6,7,12–14} Our study had one (1.0%) hemorrhagic stroke event, although this patient had a major contraindication to thrombolytics (recent stroke). He had massive worsening PE and was not a surgical candidate; we were obliged to proceed with catheter thrombolysis as the only lifesaving option, given the unavailability of suction thrombectomy at that time.

A major contraindication to thrombolytics was associated with CDI failure and major bleeding. This suggests that whereas CDIs involve a low thrombolytic dose delivered at the local embolic site, systemic effects are still present, and therefore CDIs cannot be viewed as systemic thrombolytic substitutes in patients with absolute contraindications. However, among the patients with relative contraindications to thrombolytics, none experienced major bleeding events. This suggests that CDIs may play a role in the management of this subset of patients. Age ≥ 70 years was also correlated with major bleeding after CDI. The PEITHO trial did show a higher rate of major extracranial bleeding in elderly patients (>75 years old) compared with younger patients, although the difference was not significant ($P = .09$).⁸ High-risk PE was another predictor of CDI failure. This is due to the high mortality rate associated with high-risk PEs compared with intermediate-risk PEs.

High-risk PE is associated with an in-hospital mortality rate reaching 30% and up to 60% in patients with cardiopulmonary arrest.^{26,27} The current standard of care for high-risk PE is systemic thrombolysis; however, ineligibility of patients due to thrombolytic contraindications and the increased major bleeding rate have led to increased CDI use, which is presumed to be safer. Current guidelines suggest suction thrombectomy or surgical thrombectomy based on comorbidities, lytic contraindications, and local expertise.^{4,5} The optimal treatment modality for high-risk PE patients with contraindications remains controversial, and the jury is still out. PERT can help in controversial cases with no clear treatment indication.

A subsequent analysis of the SEATTLE II patients revealed that high-risk PE and multiple venous access attempts were independently associated with higher odds of major bleeding with respective odds ratios of 3.6 and 10.1 ($P < .05$).²⁸ Our analysis goes in parallel with that study in showing that high-risk PE patients have higher odds of major bleeding events.

Interestingly, CDI technique was not predictive of CDI failure. This is consistent with most of the literature, indicating no significant difference between USAT and standard CDI techniques for acute PE.^{14,29}

Thrombolytic dose used in CDI was not associated with CDI failure or major bleeding. Studies comparing thrombolytic doses used in CDI are sparse. However, a thrombolytic dose ranging between 20 and 30 mg is widely used in practice.^{22,29} We suggest that at this range of low thrombolytic doses, there is no dose-response relationship, and this might explain why the dose was not predictive of major bleeding.

Whereas this study is one of the few articles looking at the predictors of CDI failure and major bleeding, the results should be interpreted with caution, given the retrospective nature of the study and the lack of a control group. Also, the number of CDI failure events did not allow a comprehensive multivariate logistic regression model.¹⁸ Selection bias favoring a cohort of high-risk patients cannot be ruled out. In addition, CDI was used as rescue therapy in some patients who had received prior systemic thrombolytics. These factors may have overestimated our CDI failure rate. Finally, as there is no standardized CDI protocol within our institution, the ideal CDI technique, thrombolytic dose, and duration remain heterogeneous and unclear.

CONCLUSIONS

CDI is gaining more momentum in contemporary PE practice despite the scarcity of high-quality evidence supporting its use. However, we should understand that CDIs are not risk-free procedures as shown by several studies. CDI use with even a low dose of thrombolysis should be avoided in patients with absolute contraindications. Nonetheless, these interventions appear to decrease the risk of intracranial hemorrhage, given their almost 0% risk of intracranial hemorrhages. Careful selection of patients and appropriate center expertise employing a multidisciplinary team are important components for intervention success and for minimizing complications. Long-term studies investigating the role that CDIs play in the prevention of long-term morbidity, such as chronic thromboembolic pulmonary hypertension, and in the improvement of quality of life are needed.

REFERENCES

1. Kahn SR, Houweling AH, Granton J, Rudski L, Dennie C, Hirsch A. Long-term outcomes after pulmonary embolism: current knowledge and future research. *Blood Coagul Fibrinolysis* 2014;25:407–15. [PubMed: 24469387]
2. Huang W, Goldberg RJ, Anderson FA, Kiefe CI, Spencer FA. Secular trends in occurrence of acute venous thromboembolism: the Worcester VTE study (1985–2009). *Am J Med* 2014;127:829–39.e5. [PubMed: 24813864]
3. Jaff MR, McMurtry MS, Archer SL, Cushman M, Goldenberg N, Goldhaber SZ, et al. Management of massive and submassive pulmonary embolism, iliofemoral deep vein thrombosis, and chronic thromboembolic pulmonary hypertension: a scientific statement from the American Heart Association. *Circulation* 2011;123:1788–830. [PubMed: 21422387]
4. Kearon C, Akl EA, Ornelas J, Blaivas A, Jimenez D, Bounameaux H, et al. Antithrombotic Therapy for VTE Disease: CHEST Guideline and Expert Panel Report. *Chest* 2016;149:315–52. [PubMed: 26867832]
5. Konstantinides SV. 2014 ESC Guidelines on the diagnosis and management of acute pulmonary embolism. *Eur Heart J* 2014;35:3145–6. [PubMed: 25452462]
6. Patel N, Patel NJ, Agnihotri K, Panaich SS, Thakkar B, Patel A, et al. Utilization of catheter-directed thrombolysis in pulmonary embolism and outcome difference between systemic thrombolysis and catheter-directed thrombolysis. *Catheter Cardiovasc Interv* 2015;86:1219–27. [PubMed: 26308961]
7. Kucher N, Boekstegers P, Muller OJ, Kupatt C, Beyer-Westendorf J, Heitzer T, et al. Randomized, controlled trial of ultrasound-assisted catheter-directed thrombolysis for acute intermediate-risk pulmonary embolism. *Circulation* 2014;129: 479–86. [PubMed: 24226805]
8. Meyer G, Vicaut E, Danays T, Agnelli G, Becattini C, Beyer-Westendorf J, et al. Fibrinolysis for patients with intermediate-risk pulmonary embolism. *N Engl J Med* 2014;370:1402–11. [PubMed: 24716681]
9. Chatterjee S, Chakraborty A, Weinberg I, Kadakia M, Wilensky RL, Sardar P, et al. Thrombolysis for pulmonary embolism and risk of all-cause mortality, major bleeding, and intracranial hemorrhage: a meta-analysis. *JAMA* 2014;311: 2414–21. [PubMed: 24938564]
10. Engelberger RP, Moschovitis A, Fahrni J, Willenberg T, Baumann F, Diehm N, et al. Fixed low-dose ultrasound-assisted catheter-directed thrombolysis for intermediate and high-risk pulmonary embolism. *Eur Heart J* 2015;36: 597–604. [PubMed: 24334719]
11. Engelberger RP, Kucher N. Ultrasound-assisted thrombolysis for acute pulmonary embolism: a systematic review. *Eur Heart J* 2014;35:758–64. [PubMed: 24497337]
12. Kuo WT, Gould MK, Louie JD, Rosenberg JK, Sze DY, Hofmann LV. Catheter-directed therapy for the treatment of massive pulmonary embolism: systematic review and meta-analysis of modern techniques. *J Vasc Interv Radiol* 2009;20: 1431–40. [PubMed: 19875060]

13. Piazza G, Hohlfelder B, Jaff MR, Ouriel K, Engelhardt TC, Sterling KM, et al. 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. *JACC Cardiovasc Interv* 2015;8:1382–92. [PubMed: 26315743]
14. Kuo WT, Banerjee A, Kim PS, DeMarco FJ, Jr, Levy JR, Facchini FR, et al. Pulmonary embolism response to fragmentation, embolectomy, and catheter thrombolysis (PERFECT): initial results from a prospective multicenter registry. *Chest* 2015;148:667–73. [PubMed: 25856269]
15. Jimenez D, Aujesky D, Moores L, Gómez V, Lobo JL, Uresandi F, et al. Simplification of the pulmonary embolism severity index for prognostication in patients with acute symptomatic pulmonary embolism. *Arch Intern Med* 2010;170:1383–9. [PubMed: 20696966]
16. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. The GUSTO investigators. *N Engl J Med* 1993;329:673–82. [PubMed: 8204123]
17. Antman EM, Anbe DT, Armstrong PW, Bates ER, Green LA, Hand M, et al. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction; a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1999 Guidelines for the Management of Patients with Acute Myocardial Infarction). *J Am Coll Cardiol* 2004;44: E1–211. [PubMed: 15358047]
18. Babyak MA. What you see may not be what you get: a brief, nontechnical introduction to overfitting in regression-type models. *Psychosom Med* 2004;66:411–21. [PubMed: 15184705]
19. Kline JA, Steuerwald MT, Marchick MR, Hernandez-Nino J, Rose GA. Prospective evaluation of right ventricular function and functional status 6 months after acute submassive pulmonary embolism: frequency of persistent or subsequent elevation in estimated pulmonary artery pressure. *Chest* 2009;136:1202–10. [PubMed: 19542256]
20. Kline JA, Nordenholz KE, Courtney DM, Kabrhel C, Jones AE, Rondina MT, et al. Treatment of submassive pulmonary embolism with tenecteplase or placebo: cardiopulmonary outcomes at 3 months: multicenter double-blind, placebo-controlled randomized trial. *J Thromb Haemost* 2014;12: 459–68. [PubMed: 24484241]
21. Fasullo S, Scalzo S, Maringhini G, Ganci F, Cannizzaro S, Basile I, et al. Six-month echocardiographic study in patients with submassive pulmonary embolism and right ventricle dysfunction: comparison of thrombolysis with heparin. *Am J Med Sci* 2011;341:33–9. [PubMed: 20890176]
22. Avgerinos ED, Liang NL, El-Shazly OM, Toma C, Singh MJ, Makaroun MS, et al. Improved early right ventricular function recovery but increased complications with catheter-directed interventions compared with anticoagulation alone for submassive pulmonary embolism. *J Vasc Surg Venous Lymphat Disord* 2016;4:268–75. [PubMed: 27318043]
23. Liang NL, Chaer RA, Avgerinos ED. Catheter-directed interventions for acute pulmonary embolism: the jury is still out. *Chest* 2015;148:e93. [PubMed: 26324145]
24. Mostafa A, Briassoulis A, Telila T, Belgrave K, Grines C. Treatment of massive or submassive acute pulmonary embolism with catheter-directed thrombolysis. *Am J Cardiol* 2016;117: 1014–20. [PubMed: 26833207]
25. Abou Ali AN, Liang NL, Chaer RA, Avgerinos ED. Catheter interventions for pulmonary embolism: are they really that safe? *Am J Cardiol* 2016;118:307–8. [PubMed: 27108339]
26. Kucher N, Rossi E, De Rosa M, Goldhaber SZ. Massive pulmonary embolism. *Circulation* 2006;113:577–82. [PubMed: 16432055]
27. Goldhaber SZ, Visani L, De Rosa M. Acute pulmonary embolism: clinical outcomes in the International Cooperative Pulmonary Embolism Registry (ICOPER). *Lancet* 1999;353: 1386–9. [PubMed: 10227218]
28. Sadiq I, Goldhaber SZ, Liu PY, Piazza G. Risk factors for major bleeding in the SEATTLE II trial. *Vasc Med* 2016 [Epub ahead of print].
29. Liang NL, Avgerinos ED, Marone LK, Singh MJ, Makaroun MS, Chaer RA. Equivalent outcomes between ultrasound-assisted thrombolysis and standard catheter-directed thrombolysis for the treatment of acute pulmonary embolism. *J Vasc Surg Venous Lymphat Disord* 2015;3:120–1.

CME Activity

Purpose or Statement of Need

The purpose of this journal-based CME activity is to enhance the vascular specialist's ability to diagnose and care for patients with the entire spectrum of circulatory disease through a comprehensive review of contemporary vascular surgical and endovascular literature.

Learning Objectives

At the end of this activity, participants should

- Initiate catheter-directed thrombolysis for submassive pulmonary embolism and determine the likelihood for success, complications, and death.

Target Audience

This activity is designed for vascular surgeons and individuals in related specialties.

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ARTICLE HIGHLIGHTS

- **Type of Research:** Single-center retrospective study
- **Take Home Message:** Failure of catheter-directed thrombolysis to treat pulmonary embolism (PE) is associated with massive PE and contraindication to lysis. Bleeding is associated with age >70 years and contraindications.
- **Recommendation:** The authors suggest avoidance of catheter-directed thrombolysis to treat PE in patients with a contraindication to lysis and suggest caution in elderly (>70 years) and/or massive PE patients.

Table I.

Characteristics of study population

	CDI (N = 102)
Age, years	59.19 ± 15.92
Male gender	50 (49.0)
Acute DVT	59 (57.8)
Hypercoagulable state	6 (5.9)
Recent surgery (within 1 month)	26 (25.5)
Recent trauma (within 1 month)	3 (2.9)
Malignant disease	20 (19.6)
Contraceptives	6 (5.9)
Recent travel	16 (15.7)
Recurrent VTE	18 (17.6)
Hypertension	54 (52.9)
Coronary disease	15 (14.7)
Cardiac failure	6 (5.9)
Pulmonary disease	18 (17.6)
Current smoking	14 (13.7)
Glomerular filtration rate	81.66 ± 42.23
No lysis contraindication	82 (80.4)
Absolute contraindications	7 (6.9)
Relative contraindications	13 (12.7)
Inferior vena cava filter	46 (45.1)
Troponin, ng/mL	0.78 ± 1.28
Brain natriuretic peptide, pg/mL	364 ± 345
PESI high risk	85 (83.3)

CDI, Catheter-directed intervention; *DVT*, deep venous thrombosis; *PESI*, Pulmonary Embolism Severity Index; *VTE*, venous thromboembolism.

Categorical variables are presented as number (%). Continuous variables are presented as mean ± standard deviation.

Table II.

Catheter-directed intervention (*CDI*) failures and complications stratified per pulmonary embolism (PE) type

	Total, No. (%)	High risk, No. (%)	Intermediate risk, No. (%)
Total CDIs	102	14	88
CDI failures	15 (14.7)	7 (50)	8 (9.1)
Major bleed	7 (6.9)	3 (21.4)	4 (4.5)
GUSTO severe	2 (2.0)	1 (7.1)	1 (1.1)
Perioperative stroke	1 (1.0)	1 (7.1)	0 (0)
Decompensation	8 (7.8)	—	3 (3.4)
Persistent shock		5 (35.7)	—
Surgical thrombectomy	3 (2.9)	2 (14.3)	1 (1.1)
Other major adverse event	2 (2)	0 (0)	2 (2.3)
Tricuspid valve rupture			
Coronary sinus perforation			
Death	4 (3.9)	3 (21.4)	1 (1.1)

GUSTO, Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries.

Table III.

Univariate analysis of pulmonary embolism (PE)-associated factors by catheter-directed intervention (CDI) outcomes

Associated factors	CDI success (n = 87) ^a	CDI failure (n = 15) ^a	P value	No major bleed (n = 95) ^a	Major bleed (n = 7) ^a	P value
Age 70 years	22 (25.3)	7 (46.7)	.121	24 (25.3)	5 (71.4)	.019
Massive PE type	7 (8.0)	7 (46.7)	.001	11 (11.6)	3 (42.9)	.052
Absolute contraindication	2 (2.3)	5 (33.3)	.001	4 (4.2)	3 (42.9)	.006
Acute DVT	50 (57.5)	9 (60.0)	.855	54 (56.8)	5 (71.4)	.696
Hypercoagulable state	6 (6.9)	0 (0)	.588	6 (6.3)	0 (0)	1
Recent trauma	2 (2.3)	1 (6.7)	.383	2 (2.1)	1 (14.3)	.194
Contraceptives	5 (5.7)	1 (6.7)	1	6 (6.3)	0 (0)	1
Recent surgery	20 (23.0)	6 (40.0)	.163	23 (24.2)	3 (42.9)	.367
Malignant disease	15 (17.2)	5 (33.3)	.147	18 (18.9)	2 (28.6)	.621
Recurrent DVT or PE	16 (18.4)	2 (13.3)	.635	17 (17.9)	1 (14.3)	1
Coronary artery disease	13 (14.9)	2 (13.3)	.871	13 (13.7)	2 (28.6)	.273
Heart failure	5 (5.7)	1 (6.7)	1	6 (6.3)	0 (0)	1
Hypertension	46 (52.9)	8 (53.3)	.974	48 (50.5)	6 (85.7)	.117
Pulmonary disease	13 (14.9)	5 (33.3)	.084	15 (15.8)	3 (42.9)	.103
Current smoking	14 (16.1)	0 (0)	.094	14 (14.7)	0 (0)	.589
Intervention type (reference: standard CDI)	52 (61.2)	8 (61.5)	.980	55 (60.4)	5 (71.4)	.703
IVC filter	37 (42.5)	9 (60.0)	.209	41 (43.2)	5 (71.4)	.239
PESI high risk	71 (81.6)	14 (93.3)	.455	79 (83.2)	6 (85.7)	1
Glomerular filtration rate	84.50 ± 43.20	65.19 ± 32.59	.102	82.56 ± 42.69	69.38 ± 35.91	.428
Lysis dose, mg	27.97 ± 14.33	29.72 ± 30.23	.840	28.49 ± 19.22	24.63 ± 12.90	.603
Troponin, ng/mL	0.70 ± 1.11	1.21 ± 1.95	.154	0.79 ± 1.31	0.58 ± 0.74	.672
Brain natriuretic peptide, pg/mL	354 ± 357	416 ± 282	.517	355 ± 350	458 ± 282	.488

DVT; Deep venous thrombosis; IVC, inferior vena cava; PESI, Pulmonary Embolism Severity Index.

Categorical variables are presented as number (%). Continuous variables are presented as mean ± standard deviation. P values in bold indicate statistical significance (<.05).

^aTotal number may vary, depending on missing values.