

### EVIDENCE SUMMARY

Peter F. Lawrence, MD, Section Editor

# Catheter-directed interventions for acute pulmonary embolism

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Acute pulmonary embolism (PE) is a leading cause of cardiovascular mortality. Systemic anticoagulation is the standard of care, and treatment can be escalated in the setting of massive or submassive PE, given the high mortality risk. A secondary consideration for intervention is the prevention of late-onset chronic thromboembolic pulmonary hypertension. Treatment options include systemic thrombolysis, catheter-directed interventions, and surgical thromboembolectomy. Whereas systemic thrombolysis seems to be beneficial in the setting of massive PE, it appears to be associated with a higher rate of major complications compared with catheter-directed thrombolysis as shown in recent randomized trials for submassive PE. The hemodynamic and clinical outcomes continue to be defined to determine the indications for and benefits of intervention. The current review summarizes contemporary evidence on the role and outcomes of catheter-directed thrompies in the treatment of acute massive and submassive PE. (J Vasc Surg 2015;61:559-65.)

Acute pulmonary embolism (PE) is the third leading cause of cardiovascular mortality, accounting for 5% to 10% of in-hospital deaths in the Western world.<sup>1</sup> Recent registries and cohort studies suggest that approximately 10% of all patients with diagnosed acute PE will die within 3 months after diagnosis.<sup>2,3</sup> Management is mainly guided by the acuity and severity of clinical presentation. Initial systemic anticoagulation is the standard of care, and treatment is escalated on the basis of the clinical presentation and characteristics of patients that may stratify them at high risk of mortality. Massive PE is defined as PE associated with sustained hemodynamic instability, whereas submassive PE is defined as PE without hemodynamic instability but with abnormal right ventricular (RV) function or evidence of myocardial necrosis.<sup>4</sup> Treatment options include systemic thrombolysis, catheter-directed interventions (CDIs) with or without local thrombolysis, and surgical thromboembolectomy. The goals of therapy are primarily to prevent mortality and secondarily to prevent late-onset chronic thromboembolic pulmonary hypertension and to improve quality of life. The current review summarizes contemporary evidence emerging from recent systematic reviews and randomized trials on the role and outcomes of CDIs for the treatment of acute PE.

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## THROMBOLYSIS FOR MASSIVE AND SUBMASSIVE PE

Systemic intravenous thrombolysis is universally recommended by all guideline bodies for massive PE but remains controversial for submassive PE.<sup>4-7</sup> The most widely suggested regimen is 100 mg of alteplase during 2 hours.<sup>7</sup>

**Massive PE.** A meta-analysis of 11 historical (1973-2002; n = 748) randomized trials comparing heparin vs heparin and thrombolysis in massive and submassive PE showed no difference in PE recurrence and death.<sup>8</sup> However, subgroup analysis for massive PE showed significantly better outcomes for thrombolysis vs heparin alone in combined PE recurrence and death (19% vs 9.4%), accompanied, though, by significantly higher major bleeding rates (11.9% vs 21.9%).<sup>8</sup> A more recent analysis of a U.S. Nationwide Inpatient Sample (1999-2008; n = 72,230) demonstrated an all-cause (47% vs 15%) and PE-related (42% vs 8.4%) mortality benefit for thrombolysis in massive PEs.<sup>9</sup>

Submassive PE. It is difficult to demonstrate a survival benefit between either treatment (heparin vs heparin and thrombolysis), given that mortality is infrequent in patients with submassive PE. Quality of life measures such as lateonset chronic thromboembolic pulmonary hypertension and functional disability may be more relevant outcomes. In the most recent meta-analysis of randomized controlled trials comparing treatment alternatives, the subgroup analysis of eight submassive PE trials (1993-2014; n = 1775) showed that thrombolytic therapy was associated with a mortality reduction (1.39% vs 2.92%) and an increase in major bleeding (7.74% vs 2.25%).<sup>10</sup> These results were mainly driven by the largest randomized trial (PEI-THO; 1006 patients) that compared a single, weightadapted intravenous bolus of tenecteplase (not Food and Drug Administration [FDA] approved) with standard anticoagulation.<sup>11</sup> PEITHO showed a significant reduction

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	Level of supporting studies	Comments
Massive PE	One systematic review (594 patients) <sup>19</sup>	Noncontrolled, nonhomogeneous studies including various CDIs with and without lytics Publication and selection bias Survival 86.5% (range, 40%-100%)
	One comparative study of USAT + AC (15 patients) vs CDI + AC (18 patients) <sup>29</sup>	Major complications 2.4% Small sample Selection bias No mortality difference Fewer treatment-related complications for USAT
	Prospective and retrospective case series of various	No controls
Submassive PE	CDIs with and without lytics One randomized controlled trial comparing USAT + AC (30 patients) vs AC alone (29 patients) <sup>18</sup>	Majority with <20 patients and selection bias RV/LV ratio significantly improved within 24 hours in favor of USAT
		No difference in RV/LV ratio improvement at 90 days [trend ( $P = .07$ ) in favor of USAT] RV systolic function significantly improved at both 24 hours and 90 days in favor of USAT
	Sustaination particular of USAT $(107 \text{ participate})^{20}$	No major bleeding for either group
	Systematic review of USAT (197 patients)	RV/LV ratio decrease 24% within 24 hours
		Relative reduction in the pulmonary occlusion score 32%-69%
		Major bleeding 3.6%
		No intracranial or fatal bleed
	Retrospective case series of various CDIs	Unclear survival or long-term benefits Majority with <20 patients and selection bias
Areas of uncertain	ty or areas in need of higher quality evidence	
Anticoagulation vs	s CDI in massive PE with contraindications to systemic lysis	
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Table. Summary of current evidence for catheter-directed interventions (CDIs)

Low-dose systemic lysis protocols vs CDIs in massive and submassive PE Risk stratification and selection of patients with submassive PE who would benefit from CDIs

Long-term outcomes (pulmonary hypertension and quality of life) after CDI in submassive PE

AC, Anticoagulation; PE, pulmonary embolism; RV/LV, right ventricle/left ventricle; USAT, ultrasound-assisted thrombolysis.

in the combined primary end point of all-cause mortality and hemodynamic decompensation at 7 days in favor of tenecteplase (5.6% vs 2.6%). The main driver for the efficacy difference, however, was not mortality but a reduction in hemodynamic collapse. The benefits of thrombolysis came at the cost of a significant risk increase of extracranial major bleeding complications (1.2% vs 6.3%) and hemorrhagic stroke (0.2% vs 2.0%), particularly evident in the elderly (>75 years old).<sup>11</sup> Of note, only 3.4% of patients in the anticoagulation group had clinical deterioration that required thrombolysis, suggesting that a strategy of anticoagulation with thrombolysis reserved for patients who do not respond to standard therapy may be acceptable, particularly for older patients.<sup>11</sup> Five smaller randomized trials have investigated the efficacy and side effects of low-dose alteplase (50 mg) in predominantly submassive PE, and a recent meta-analysis (1990-2013; 440 patients) suggested that it has similar efficacy but is safer than the standard 100-mg dose. In addition, compared with heparin, low-dose protocols do not increase the risk of major bleeding complications for eligible PE patients.<sup>12</sup> As for later onset pulmonary hypertension, there is some recent evidence from three small randomized studies and a prospective uncontrolled trial that pulmonary artery pressures rise in the majority of patients with submassive PE but decline in those who are treated with thrombolysis, potentially altering exercise tolerance and quality of life.<sup>7,13-16</sup>

#### CDI

Despite the lack of sufficient direct evidence through controlled studies (CDIs vs anticoagulation or vs high- or low-dose systemic lysis), the beneficial effects, the limitations, and the anticipated complications of systemic thrombolysis in both massive and submassive PE drive contemporary practice toward CDIs as a first-line treatment in the appropriate clinical setting<sup>17-20</sup> (Table).

#### Massive PE

A systematic review of 35 noncontrolled studies (1998-2008; 594 patients) reporting on various CDIs for massive PE showed a pooled survival rate of 86.5% (range, 40%-100%).<sup>19</sup> In 95% of these patients, CDIs were initiated without prior intravenous thrombolysis, and only 60% to 67% received a thrombolytic agent. The success was higher in studies in which at least 80% of participants received local thrombolytic therapy during the procedure (91.2% vs 82.8%). Pooled risks of minor and major procedural complications were 7.9% and 2.4%, respectively. Twenty-five major complications were reported and included bleeding complications requiring transfusion, renal failure requiring



**Fig 1.** Suggested algorithm for the management of acute pulmonary embolism (*PE*). *RV*, Right ventricle; *SBP*, systolic blood pressure. \*Hypokinesis on echocardiography or elevated troponin I or T with local thresholds (values exceeding the 99th percentile with coefficient of variability <10%) or brain natriuretic peptide >90 pg mL<sup>-1</sup> or amino-terminal pro-B-type natriuretic peptide >900 pg mL<sup>-1</sup>. <sup>‡</sup>Absolute contraindications: any prior intracranial hemorrhage; known structural intracranial cerebrovascular disease or neoplasm; ischemic stroke within 3 months; suspected aortic dissection; active bleeding or bleeding diathesis; recent spinal or cranial/brain surgery; recent closed head or facial trauma with bone fracture or brain injury. Relative contraindications: age  $\geq$ 75 years; current use of anticoagulation; pregnancy; noncompressible vascular punctures; traumatic or prolonged cardiopulmonary resuscitation; recent internal bleeding (2-4 weeks); history of chronic, severe, and poorly controlled hypertension; severe uncontrolled hypertension on presentation; dementia; remote (3 months) ischemic stroke; major surgery within 3 weeks.

hemodialysis, cardiopulmonary events, cerebrovascular events, and death.<sup>19</sup>

#### Submassive PE

The first randomized controlled trial to include CDIs for submassive PE was recently published.<sup>18</sup> The Ultrasound Accelerated Thrombolysis of Pulmonary Embolism (ULTIMA) trial compared standardized fixed-dose ultrasound-assisted catheter-directed thrombolysis (USAT) (10 mg of recombinant tissue-type plasminogen activator per lung during 15 hours) and anticoagulation with anticoagulation alone. The primary outcome was reversal of RV dilation in intermediate-risk PE patients (2010-2013; 59 patients). In the USAT group but not in the heparin group, the mean right ventricle/left ventricle ratio was significantly reduced at 24 hours but became comparable between the two groups at 90 days, with a trend in favor of USAT (P = .07). The RV systolic function was significantly improved in the USAT group vs the heparin group at both 24 hours and 90 days. The ULTIMA trial was not designed to show long-term superiority of USAT to anticoagulation alone, however, nor was it powered to

show any difference in survival. In both study groups, bleeding complications were rare, with three (10%) minor bleedings in the interventional group and one (3%) in the control group. There were no major bleeding complications. At 90 days, there were no episodes of hemodynamic decompensation or recurrent PE in any group.<sup>18</sup>

A systematic review including seven USAT studies (2008-2013; 197 patients; 18% massive PE) followed the publication of the ULTIMA trial, reinforcing its findings.<sup>20</sup> Notably, these studies primarily included patients with intermediate risk or submassive PE; thus, it remains unclear if USAT acts fast enough to prevent hemodynamic deterioration and death in unstable patients with massive PE. However, the proven benefit of CDI in this population of patients had been established in the aforementioned systematic review on non-USAT catheter techniques for massive PE.<sup>19</sup>

There is no clinical trial comparing CDIs with systemic thrombolysis for PE and no randomized controlled trial comparing CDIs vs anticoagulation alone specifically for massive PE. However, in light of all the recently published data, mainly the PEITHO and the ULTIMA trials for



Fig 2. A 60-year-old otherwise healthy man presented with severe chest tightness, dyspnea, and near-syncope. Computed tomography angiography showed saddle pulmonary embolism (PE) with a large thrombus burden in the main segmental branches (R > L). He had worsening respiratory function and right-sided heart strain but no hemodynamic decompensation. Catheter-directed thrombolysis was performed. **a**, Pulmonary angiogram showing bilateral segmental thrombus (*arrows*). **b**, EKOS catheters were placed within the thrombus, and a lytic infusion was initiated (the *arrows* indicate the multiside hole infusion segments of the catheters and the inner wire segments with ultrasound microtransducers). **c**, Lysis check at 16 hours showed thrombus resolution, along with decreased oxygen requirements and normalization of right ventricular function.

submassive PE, it can be extrapolated that CDIs do not necessarily improve mortality rates, can improve RV function, and may prevent hemodynamic decompensation. They are also associated with a better safety profile, with decreased complication rates compared with systemic thrombolysis, shifting the harm-benefit ratio in favor of CDI. Whenever thrombolysis is considered beneficial in the setting of massive PE and in selected cases of submassive PE, CDI is the only alternative for patients at higher bleeding risk and can be considered a reasonable alternative in patients at low risk for bleeding, provided there is local expertise and around-the-clock availability. In addition, catheter techniques should be considered an escalation therapy when systemic thrombolysis has failed.<sup>21</sup> Given the lack of defined treatment algorithms and clear superiority of one therapy over the other, individualized patient decisions are best made as part of a multidisciplinary discussion among the different members of a PE team (Fig 1).

#### Technical considerations

Contemporary CDIs are variable and can be performed with or without thrombolysis. The latter include thrombus fragmentation or aspiration techniques, with no lytic agents, for patients with absolute contraindications to thrombolysis; their efficacy, however, remains controversial.<sup>7,19,20</sup>

The standard technique involves administration of local thrombolytics through a multiside hole catheter placed unilaterally or bilaterally into the pulmonary artery thrombus. Several adjuncts and technical alternatives have been described in various combinations, targeting rapid clot debulking. The majority of these technical adjuncts and devices lack background evidence and are not approved by the U.S. FDA for treatment of PE. As such, no standardized technical algorithm yet exists.

A clinically relevant reduction in thrombus burden rather than complete thrombus removal guides therapy. Invasive pressure tracings (right atrium, right ventricle, main pulmonary artery) before and after each treatment session or cardiac echocardiographic parameters can be used as adjuncts to monitor the progress of therapy. In massive PE, reversal of hemodynamic instability should primarily guide the termination of treatment. In patients with massive PE that was "downstaged" to submassive, or in submassive PE, continuation of catheter-directed thrombolysis should be guided by improved pulmonary artery pressures and reversal of right-sided heart strain, barring any complications that necessitate discontinuation of therapy or surgical conversion.<sup>19,22,23</sup>

Thrombus fragmentation. Rotating pigtail catheter fragmentation has been widely reported and used<sup>22</sup>; it is easily available and comes at a low cost. As it leads to distal clot embolization, adjunctive aspiration thrombectomy may be needed. Unless the thrombus is fragmented to allow a greater embolic surface area to the lytic drug's effect, thrombolytic infusion into the pulmonary artery proximal to the embolus will be no more efficacious than systemic delivery as it tends to rapidly wash into non-occluded arteries.<sup>19,22,24,25</sup>

The AngioJet Rheolytic Thrombectomy System (Bayer HealthCare, Medrad Inc, Indianola, Pa) provides pharmacomechanical thrombolysis and has been used in the past for PE, with several adverse events reported. Despite a recent study advocating its use in the setting of massive PE, it should probably by avoided.<sup>19,22,26-28</sup>

The use of ultrasound to enhance thrombolytic permeation of large emboli holds currently the highest level of evidence in both efficacy and safety (see previous section).<sup>18,20</sup> However, the clinical superiority of ultrasound-assisted thrombolysis over conventional catheter-directed thrombolysis has not been proved.<sup>29</sup> The EkoSonic Endovascular System (EKOS Corporation, Bothell, Wash) combines a multi–side hole drug infusion catheter with a multielement ultrasound core wire and was recently approved by the FDA for use in patients with PE (Fig 2).

Thrombus aspiration. Thrombus aspiration can be performed either as an adjunct to any CDI or as a stand-alone



**Fig 3.** Massive pulmonary embolism (PE; right ventricular strain and hemodynamic decompensation) in a patient with recent surgery and with intrapulmonary bleed due to the pulmonary infarct. **a**, Intraoperative pulmonary angiogram indicating bilateral thrombus (*arrows*) (L > R). **b**, Pigtail rotation within the major clot burden. **c**, Aspiration thrombectomy with a 10F Pronto catheter (Vascular Solutions, Minneapolis, Minn). **d**, Extracted thromboembolic material.



**Fig 4.** Submassive pulmonary embolism (PE; right ventricular strain without hemodynamic decompensation) with increasing oxygen requirement, in a young patient, after brain abscess evacuation. **a**, Pulmonary angiogram showing bilateral thrombus (R > L) (the *arrow* points to the occluded right main pulmonary artery). **b**, AngioVac (AngioDynamics, Latham, NY) aspiration from a jugular approach. **c**, Extracted thromboembolic material. Cardiopulmonary parameters subsequently normalized.

technique with dedicated large-bore suction devices. The simplest aspiration technique is by using any 5F to 9F end-hole catheter or dedicated steerable aspiration catheters 10F to 14F in size<sup>22,30</sup> (Fig 3).

A novel device but with limited evidence in the PE setting is the Vortex AngioVac aspiration system (AngioDynamics, Latham, NY), which is composed of an extracorporeal bypass circuit that facilitates drainage, filtration, and reinfusion of blood cleared from clot.<sup>31</sup> A funnelshaped distal tip facilitates en bloc removal of the embolus. The technique is FDA approved, and successful outcomes in the setting of PE have been reported in small case series. The device requires a 26F delivery sheath and can be used from the femoral or jugular approach and allows embolectomy without the use of lytic agents (Fig 4).

#### CONCLUSIONS

There is increasing evidence that percutaneous CDIs are an essential, effective, and safe alternative to systemic thrombolysis or anticoagulation in the contemporary management of massive and submassive PE. Robust, adequately powered studies comparing systemic vs catheter-directed thrombolysis for massive and submassive PE as well as different catheter-based techniques are still needed to determine the effect on survival, bleeding complications, and quality of life outcomes.

#### AUTHOR CONTRIBUTIONS

Conception and design: RC Analysis and interpretation: EA, RC Data collection: EA Writing the article: EA, RC Critical revision of the article: RC Final approval of the article: RC Statistical analysis: Not applicable Obtained funding: Not applicable Overall responsibility: RC

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