EVIDENCE SUMMARY

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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 therapies 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.[1] Recent registries and cohort studies suggest that approximately 10% of all patients with diagnosed acute PE will die within 3 months after diagnosis.[2,3] 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.[4] 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.[4-7] The most widely suggested regimen is 100 mg of alteplase during 2 hours.[7]

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.[8] 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%).[8] 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.[9]

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 late-onset 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%).[10] These results were mainly driven by the largest randomized trial (PEITHO; 1006 patients) that compared a single, weight-adapted intravenous bolus of tenecteplase (not Food and Drug Administration [FDA] approved) with standard anticoagulation.[11] PEITHO showed a significant reduction

Table. Summary of current evidence for catheter-directed interventions (*CDIs*)

	Level of supporting studies	*Comments*
Massive PE	One systematic review (594 patients)[19]	Noncontrolled, nonhomogeneous studies including various CDIs with and without lytics Publication and selection bias Survival 86.5% (range, 40%-100%) Major complications 2.4%
	One comparative study of USAT + AC (15 patients) vs CDI + AC (18 patients)[29]	Small sample Selection bias No mortality difference Fewer treatment-related complications for USAT
	Prospective and retrospective case series of various CDIs with and without lytics	No controls Majority with <20 patients and selection bias
Submassive PE	One randomized controlled trial comparing USAT + AC (30 patients) vs AC alone (29 patients)[18]	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 No major bleeding for either group
	Systematic review of USAT (197 patients)[20]	18% had massive PE 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 Unclear survival or long-term benefits
	Retrospective case series of various CDIs	Majority with <20 patients and selection bias
Areas of uncertainty or areas in need of higher quality evidence		
Anticoagulation vs CDI in massive PE with contraindications to systemic lysis 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).[11] 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.[11] 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.[12] 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.[7,13-16]

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[17-20] (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%).[19] 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