

Advanced Endovascular Interventions With Ultrasound-Accelerated Thrombolysis in Intermediate-Risk Pulmonary Embolism

An overview of management of intermediate-risk patients with ultrasound-accelerated thrombolysis and key considerations in treating those in the “gray zone.”

By Michael R. Jaff, DO

Pulmonary embolism (PE) is the leading cause of preventable hospital deaths in the United States.¹ A major challenge in the diagnosis and treatment of PE is heterogeneous patient presentation and prognosis. For patients with intermediate-risk PE, there is no clear consensus on first-line therapy. The short-term concern is the early relief of right heart strain. Clinicians may treat these patients with anticoagulant medications, surgical embolectomy, systemic parenteral thrombolytic therapy, or advanced endovascular intervention.² Recent research has focused on long-term outcomes including diminished physical function. This article reviews current stratification schemes for PE patients, provides an overview of current medical and endovascular interventions, and evaluates the use of advanced interventions for certain patients to assist clinicians in their decision process, with a focus on appropriate use of ultrasound-accelerated thrombolysis.

DEFINING PE SEVERITY AND RISK

Several algorithms exist for stratifying PE patients into “risk levels.” Risk stratification is based on clinical characteristics (vital signs), laboratory test results (brain natriuretic peptide, troponin levels, electrocardiogram changes), and imaging to assess right ventricular dysfunction (RVD).³⁻⁵ These categories are used to guide treatment.

One system divides patients into “minor,” “submassive,” and “massive” PE (Figure 1A).³⁻⁵ Individuals with submassive PE, also known as intermediate-risk PE, present with a variety of symptoms and prognoses. To better acknowledge the entire disease spectrum, a newer algorithm stratifies patients into “low,” “intermediate-low,” “intermediate-high,” and “high” risk (Figure 1B).⁶ Although intermediate-

risk patients may still not fit squarely into one of the two intermediate categories, this subcategorization is an effort to determine which intermediate-risk patients are at higher risk of clinical decompensation and would potentially benefit from invasive treatment.^{7,8}

RVD in acute PE is often defined using the ratio of the size of the right ventricle compared with that of the left ventricle on echocardiography or CT. An RV/left ventricular (LV) ratio > 0.9 has been shown to be a predictor of poor clinical outcomes, including venous thromboembolism recurrence, adverse events, and mortality.⁹ In a study of 2,454 PE patients, RV dysfunction was associated with 40% higher mortality rate at 3 months, even in the absence of hemodynamic instability; the overall mortality rate for these patients was 17.4% at 3 months.³ A retrospective analysis of 120 patients with hemodynamically stable PE found that those with an RVD ≤ 1 had a 0% mortality rate. The mortality rate increased with stepwise increases in RVD (ie, patients with an RVD > 1.0-1.5 had a mortality rate of 8% and those with an RVD > 1.5 had a rate of 17%).¹⁰ Another retrospective study of 301 PE patients experiencing their first acute episode found that patients with unresolved RVD at the time of hospital discharge were eight times more likely to have recurrent PE than patients whose RVD was resolved prior to discharge.¹¹

Most of the evidence to date for PE has been limited to short-term surrogate outcomes data with evaluation of change in RV/LV ratio. Although this serves an important role in acute PE, additional metrics are needed to determine the benefit of advanced interventional therapies in patients with intermediate-risk PE.^{9,11,12} Potential advantages of advanced treatment in patients with intermediate-risk disease include the reduction in risk

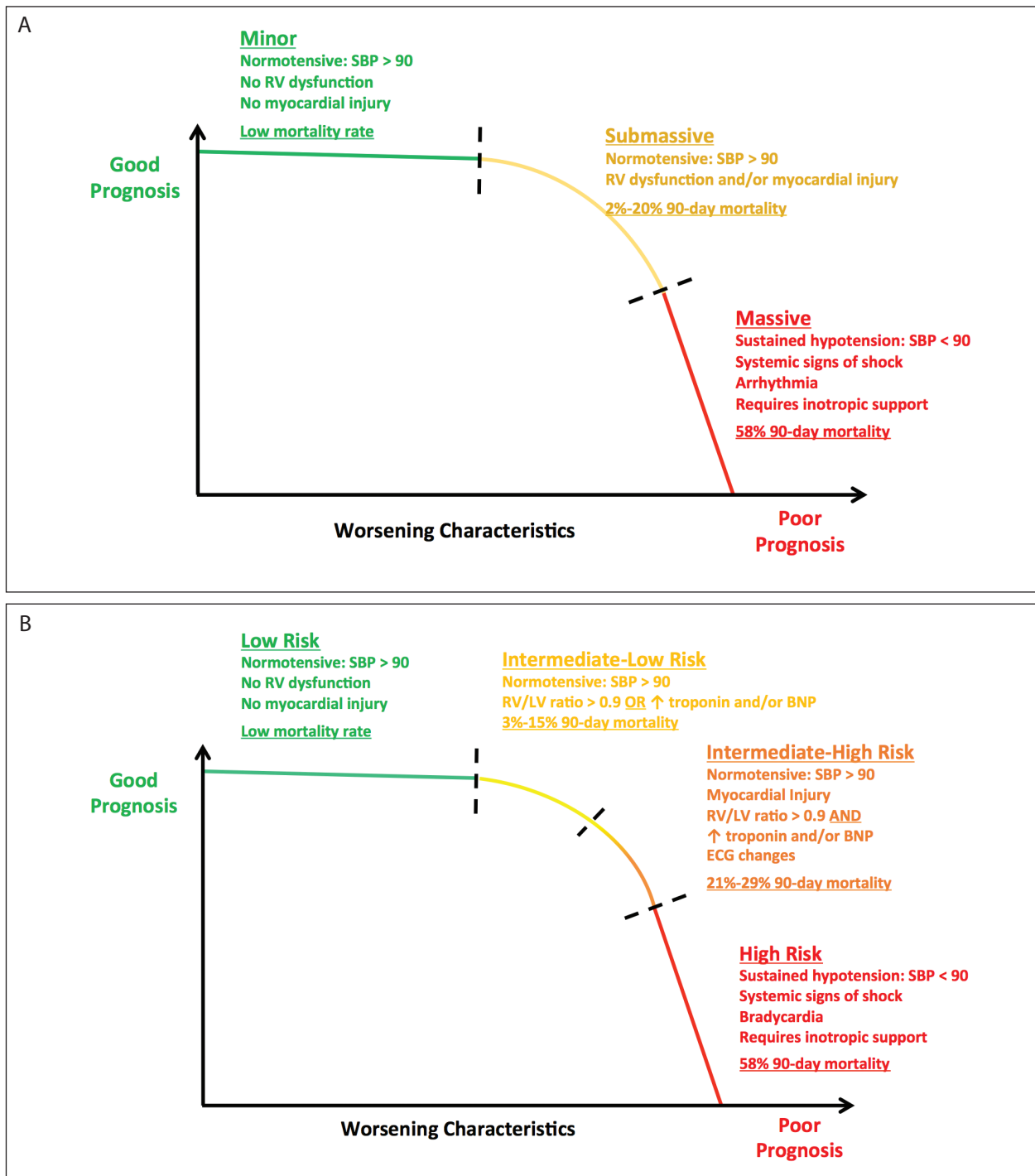


Figure 1. Stratification of prognosis of patients with PE under a three-group risk paradigm (A) and a four-group risk paradigm (B). BNP, brain natriuretic peptide; ECG, electrocardiogram; SBP, systolic blood pressure.

of hemodynamic collapse or death due to acute right-sided heart failure; reduction in the risk of PE recurrence; and minimizing the risk of post-PE syndrome and chronic thromboembolic pulmonary hypertension with

maintenance in exercise capacity in the mid and long term.¹³⁻¹⁵ However, there is conflicting evidence whether more invasive therapies for acute PE result in these advantages.¹³⁻¹⁵

CONVENTIONAL THERAPY FOR INTERMEDIATE-RISK PE

Anticoagulant therapy is often used as first-line treatment for patients with intermediate-risk PE. These include vitamin K antagonists (warfarin), unfractionated heparin, low-molecular-weight heparin, and direct oral anticoagulants (including dabigatran, apixaban, edoxaban, and betrixaban). Anticoagulants do not dissolve existing thromboemboli but rather prevent propagation and embolization.¹⁶ Anticoagulants have many advantages, including ease of administration, relatively low cost, and acceptance as standard of care. Limitations include that they do not resolve existing thromboemboli, prevent venous hypertension, or rapidly resolve symptoms.^{17,18} Although generally accepted as safe, anticoagulants do carry a bleeding risk of approximately 4%.¹⁶ Despite the newer PE classification, many providers continue to treat all intermediate-risk patients alike, prescribing anticoagulant treatment without consideration of more advanced intervention. Studies of patient outcomes indicate that this may not provide adequate treatment for some intermediate–high-risk PE patients.^{13,19,20}

Although anticoagulation is sufficient for some lower-risk PE patients, those who have high-risk PE may require more aggressive reperfusion strategies, such as systemic parenteral thrombolytic therapy.²¹ Thrombolytic agents work directly on the existing thrombus, initiating degradation of fibrin in the thromboemboli and causing dissolution. Thrombolytic therapy has been shown to resolve thromboemboli faster than anticoagulants alone.²¹ Traditionally reserved for patients with high-risk PE, standard- or low-dose parenteral systemic thrombolysis may be appropriate for select intermediate-risk patients who have a low bleeding risk.^{21,22} Systemic thrombolysis has been shown to provide a significant early improvement of RVD at 24 hours posttreatment, with sustained improvement at 6 months. A prospective study of 40 patients, 23 of whom were followed long term, found that patients who were treated with systemic thrombolysis had significantly lower mean pulmonary artery pressure over the long term (median follow-up, 7.4 years) compared with those who received heparin (22 vs 17 mm Hg; $P < .05$). Similarly, lower mean pulmonary vascular resistance was observed long term among those treated with thrombolysis compared with those receiving heparin (351 vs 171 dynes $s^{-1}cm^{-5}$; $P < .02$).¹⁴ In the PEITHO study of 1,005 intermediate-risk PE patients, parenteral systemic thrombolysis with tenecteplase (TNK) was associated with a reduction in the composite endpoint of all-cause mortality or hemodynamic decompensation at 7 days when compared to standard anticoagulation. However, TNK was also associated with significantly higher rates of major bleeding as compared to anticoagulation alone (11.5% vs 2.4%),

including higher rates of intracranial hemorrhage (2% vs 0.2%).⁴ This led to the recommendation against the use of systemic thrombolysis for patients with intermediate–high-risk PE in the 2019 European Society of Cardiology guidelines.⁶

ADVANCED ENDOVASCULAR INTERVENTIONS

Pharmacomechanical catheter-directed therapies are often used for high-risk PE but may be underutilized in intermediate-risk PE cases. Strategies include catheter-directed thrombolysis (CDT), ultrasound-accelerated thrombolysis (USAT), and pharmacomechanical catheter thrombectomy (PMCT). The role of thrombolysis in PE treatment is discussed herein.

CDT has been shown to be highly effective compared with anticoagulant treatment alone, as has USAT.²³ CDT delivers medications such as alteplase (recombinant tissue plasminogen activator) and TNK. Advantages of CDT include technically straightforward administration via minimally invasive procedures that partially resolves the existing thrombus with low device expense. Thrombolytic agents should not be administered if the patient has an absolute contraindication, such as active bleeding, recent major surgery, or serious trauma (particularly closed head trauma). Considerations to the risk-benefit ratio is required when faced with a relative contraindication to thrombolysis (ie, remote ischemic stroke, organ biopsy > 14 days). Prolonged exposure to lytic agents is a particular concern in some patients who have known intracranial processes (ie, malignant neoplasm), because such exposure may further increase the risk of intracranial hemorrhage.^{20,24} However, the PERFECT study found that in 73 patients with intermediate-risk PE treated with CDT, USAT, and/or PMCT, 71 achieved clinical success, with no major procedure-related complications, major hemorrhage, or hemorrhagic stroke.²⁴

A promising option for the delivery of thrombolytic agents is USAT. In USAT (EKOS, Boston Scientific Corporation), the device contains an ultrasonic core encased within a drug delivery catheter. Ultrasonic energy is used to cause the fibrin strands to thin, exposing plasminogen receptor sites and loosening the fibrin strands, which is thought to increase thrombus permeability for thrombolytic medications. As the thrombolytic drugs are administered, the ultrasound waves drive the thrombolytic agents deeper into the clot. Although the drug delivery system and USAT procedure are similar to that of CDT, the addition of ultrasound enhances the thrombolytic agent's ability to penetrate the clot, which translates to clot dissolution with shorter infusion time and reduced drug dose.²⁵⁻²⁸ In a study by Kucher et al, a 66% increase

	American Heart Association ⁷	European Society of Cardiology ⁶	PERT Consortium ³¹	Society of Interventional Radiology ³⁰
Intermediate High	<ul style="list-style-type: none"> Consider systemic thrombolysis or CDL if there is an elevated risk of decompensation Consider PMCT: <ul style="list-style-type: none"> If patient has an elevated bleeding risk, but balance with risk of intraprocedural respiratory hemodynamic/decompensation - or - If patient deteriorates 	<ul style="list-style-type: none"> Anticoagulation alone <ul style="list-style-type: none"> Consider rescue thrombolysis if patient deteriorates - Routine use not advised Consider PCDT or surgical thrombectomy: <ul style="list-style-type: none"> If patient develop signs of hemodynamic instability - or - As an alternative to rescue thrombolysis 	<ul style="list-style-type: none"> Consider CDL if patient has an elevated risk of decompensation but without contraindication to thrombolysis Consider PMCT: <ul style="list-style-type: none"> If patient has elevated risk of decompensation with contraindications to lytics - or - After failed systemic thrombolysis or CDL 	<ul style="list-style-type: none"> Routine PCDT not recommended If patient considered at risk of decompensation or deteriorates, notify multidisciplinary team to assess clinical factors: <ul style="list-style-type: none"> Risk-benefit of intervention Bleeding risk of thrombolysis Suggest PMCT generally be avoided, unless enrolled in a prospective study, to limit risk of decompensation in stable submassive PE patients
Intermediate Low	<ul style="list-style-type: none"> Anticoagulation alone 	<ul style="list-style-type: none"> Anticoagulation alone 	<ul style="list-style-type: none"> Anticoagulation alone 	

Figure 2. Society recommendations for catheter-directed therapies in submassive PE. CDL, catheter-directed lysis; PCDT, pharmacomechanical catheter-directed therapy. Note: All acronyms have been standardized to match nomenclature in this manuscript; terminology may vary across guidances.

in D-dimer was found, along with a 23% reduction in clot weight for USAT as compared with CDT.²³

Until randomized head-to-head trials are completed, decisions regarding the choice of advanced endovascular therapy should be based on the level of evidence, the clinical presentation of the patient, the experience of the operator, and associated costs.

ADVANCED INTERVENTION FOR INTERMEDIATE-RISK PE

Conventional therapy for intermediate-risk patients historically relied on anticoagulation alone.²⁹ Recent guideline updates from the American Heart Association,⁷ the Society of Interventional Radiology,³⁰ the European Society of Cardiology,⁶ and the Pulmonary Embolism Response Team (PERT) Consortium³¹ have emphasized the use of CDT in select intermediate-risk patients who have progressed or are at high risk of progression (Figure 2). Goals of advanced interventions in intermediate-risk PE patients are to provide acute stabilization of hemodynamics and a reduction in symptoms, including decreased pulmonary resistance, decreased pulmonary artery pressure, minimized bleeding, acute recovery of RV function, and increased systemic arterial pressure.^{32,33}

Short-Term Outcomes

Although there is debate regarding which metrics should be used to select patients for catheter-directed therapies (ie, hemodynamic compensation, size and location of the

thromboembolism), research has shown that careful application of catheter-directed therapies can lead to improved patient outcomes. Additionally, use of PERTs to guide catheter-directed therapy use in select intermediate-risk patients is associated with a trend toward shorter lengths of stay in both the hospital and the intensive care unit.³⁴⁻³⁶ Major concerns associated with using advanced catheter-directed therapies in intermediate-risk PE patients are focused on bleeding, particularly intracranial hemorrhage; however, studies have shown that this risk is comparable to or lower than rates with anticoagulation alone.³⁷

Several clinical trials have demonstrated that USAT provides significant therapeutic benefits for some intermediate-risk patients. This partly may be due to the fact that USAT requires shorter infusion times and, in turn, exposure to lower doses of the lytic drug.^{28,38-40} In a single-arm, multicenter, prospective clinical trial of the EKOS USAT system, 79.3% of the 150 patients enrolled were classified as having intermediate-risk PE, with the remainder found to have massive PE.²⁷ In the overall cohort, a 25% decrease in RVD was observed 48 hours after USAT, along with a 30% decrease in pulmonary artery systolic pressure and obstruction.²⁷ Additionally, 10% experienced bleeding events, most of which occurred in the subgroup of patients with massive PE and were found to be attributable to operator inexperience.²⁷ A randomized controlled trial comparing USAT to anticoagulation alone found that using USAT yielded significantly better clinical outcomes in intermediate-risk PE patients, with no statistically significant increase in bleeding

risk. Specifically, the bleeding rate associated with USAT in these trials was approximately 3%, with a rate of intracranial hemorrhage of approximately 0.9%.^{23,26} The OPTALYSE PE study specifically found that use of USAT in intermediate-risk patients had the additional benefit of an associated reduction in length of hospital stay.⁴¹

Long-Term Outcomes

Although most patients treated for acute PE show improvement in quality of life (QOL) and physical function within a year, some patients have chronic conditions including chronic thromboembolic pulmonary hypertension and post-PE syndrome.⁴² Risk factors for developing these chronic conditions include female sex, higher body mass index, and exercise limitations 1 month after treatment.⁴²

Despite the use of advanced endovascular technologies, unresolved thrombus persists in some patients, resulting in these chronic syndromes. Persistent obstruction does not correlate well with PE severity or location of the embolic material. Patients with distal thrombus can develop chronic conditions as well as those with central thromboemboli.⁴³ One concern that has yet to be proven is the risk of distal embolization of proximal PE into secondary and tertiary branches of the pulmonary vasculature. Although acutely this may not pose a clinical threat, there is concern that this will result in “no reflow” and limitations in physical functioning after the procedure. This is the likely mechanism for the post-PE syndrome as described by Kahn et al, whereby patients who had no or limited physical disabilities before the PE are left with marked impairment in performance on cardiopulmonary exercise testing after the PE.⁴²

In patients with distal obstruction, USAT has been shown in a small study to improve RV dilatation and increase distal blood volume after treatment.⁴⁴ Although the underlying biology of this phenomenon is not fully understood, one hypothesis is that distal pulmonary arteries may play a role in pulmonary vascular resistance and, in turn, RV size. This is supported by a recently published murine study that demonstrated that ultrasonic energy produced by the endovascular catheters used for USAT is associated with reduced vascular resistance and increased blood flow in the absence of lytic drug.⁴⁵ Additionally, the OPTALYSE PE study demonstrated that USAT was associated with continued reduction in RVD at 365 days post-treatment ($P < .0001$).⁴⁶ This is the first prospective interventional study of long-term outcomes to show improved QOL for PE patients at 1 year posttreatment, as measured by the Pulmonary Embolism QOL (PEmb-QoL) instrument and the Patient-Reported Outcomes Measurement Information System (PROMIS) physical function short form.⁴⁶ No other study has performed a similarly rigorous

and extensive echocardiographic evaluation and assessment after therapy for PE thus far. USAT may be uniquely suited to benefit intermediate-risk patients given improved QOL a year after the therapy. However, this study did not have a placebo arm, and the results cannot be compared to those who were treated with anticoagulation alone.

CONCLUSION

Although intermediate-risk PE patients are often treated with anticoagulation alone, there is a body of evidence that demonstrates that some patients may benefit from the addition of advanced endovascular interventions. Several studies, including randomized controlled trials, have specifically shown improved patient outcomes among those who received CDT, particularly in patients with acute PE and compromised RV function. Furthermore, most of these studies found no significant difference in bleeding risk between CDT and anticoagulation. The introduction of nonlytic-based mechanical thrombectomy devices has offered an alternate strategy for the management of select patients with serious PE. These data have led several major professional bodies to shift recommendations to emphasize the use of catheter-directed therapies in selected intermediate-risk PE patients. To improve the efficiency of conventional CDT, USAT has been shown to improve clinical outcomes, both in the acute and long-term phases, while maintaining a reasonable safety profile. The EKOS USAT system is the most studied advanced endovascular intervention for PE treatment. Additional investigation is needed to evaluate longer-term outcomes of low-dose CDT in patients with intermediate-risk disease. ■

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1. Smith SB, Geske JB, Kathuria P, et al. Analysis of national trends in admissions for pulmonary embolism. *Chest*. 2016;150:35-45. doi: 10.1016/j.chest.2016.02.638
2. Jaff MR, McMurry MS, Archer SL, 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;123:1788-1830. doi: 10.1161/CIR.0b013e318214914f
3. Goldhaber SZ, Visani L, De Rosa M. Acute pulmonary embolism: clinical outcomes in the International Cooperative Pulmonary Embolism Registry (ICOPE). *Lancet*. 1999;353:1386-1389. doi: 10.1016/S0140-6736(98)07534-5
4. Meyer G, Vicaut E, Danays T, et al. Fibrinolysis for patients with intermediate-risk pulmonary embolism. *N Engl J Med*. 2014;370:1402-1411. doi: 10.1056/NEJMoa1302097
5. Casazza F, Becattini C, Bongarzone A, et al. Clinical features and short term outcomes of patients with acute pulmonary embolism. The Italian Pulmonary Embolism Registry (IPER). *Thromb Res*. 2012;130:847-852. doi: 10.1016/j.thromres.2012.08.292
6. Konstantinides SV, Meyer G, Becattini C, et al. 2019 ESC guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS). *Eur Heart J*. 2020;41:543-603. doi: 10.1093/eurheartj/ehz405
7. Giri J, Sista AK, Weinberg I, et al. Interventional therapies for acute pulmonary embolism: current status and principles for the development of novel evidence: a scientific statement from the American Heart Association. *Circulation*. 2019;140:e774-e801. doi: 10.1161/CIR.0000000000000707
8. Edla S, Rosman H, Neupane S, et al. Early versus delayed use of ultrasound-assisted catheter-directed thrombolysis in patients with acute submassive pulmonary embolism. *J Invasive Cardiol*. 2018;30:157-162.
9. Frémont B, Pacouret G, Jacobi D, et al. Prognostic value of echocardiographic right/left ventricular end-diastolic diameter ratio in patients with acute pulmonary embolism: results from a monocenter registry of 1,416 patients. *Chest*. 2008;133:358-362. doi: 10.1378/chest.07-1231

10. van der Meer RW, Pattinama PM, van Strijen MJ, et al. Right ventricular dysfunction and pulmonary obstruction index at helical CT: prediction of clinical outcome during 3-month follow-up in patients with acute pulmonary embolism. *Radiology*. 2005;235:798-803. doi: 10.1148/radiol.2353040593
11. Grifoni S, Vanni S, Magazzini S, et al. Association of persistent right ventricular dysfunction at hospital discharge after acute pulmonary embolism with recurrent thromboembolic events. *Arch Intern Med*. 2006;166:2151-2156. doi: 10.1001/archinte.166.16.2151
12. Kline JA, Steuwerwald MT, Marchick MR, et al. 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;136:1202-1210. doi: 10.1378/chest.08-2988
13. Sharifi M, Bay C, Skrocki L, et al. Moderate pulmonary embolism treated with thrombolysis (from the "MOPET" Trial). *Am J Cardiol*. 2013;111:273-277. doi: 10.1016/j.amjcard.2012.09.027
14. Sharma GV, Folland ED, McIntyre KM, Sasahara AA. Long-term benefit of thrombolytic therapy in patients with pulmonary embolism. *Vasc Med*. 2000;5:91-95. doi: 10.1177/1358863X0000500205
15. Fasullo S, Scalzo S, Maringhini G, 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;341:33-39. doi: 10.1097/MAJ.0b013e3181f1f3e
16. Kearon C, Akl EA, Omelas J, et al. Antithrombotic therapy for VTE disease: CHEST guideline and expert panel report. *Chest*. 2016;149:315-352. doi: 10.1016/j.chest.2015.11.026
17. Streiff MB, Agnelli G, Connors JM, et al. Guidance for the treatment of deep vein thrombosis and pulmonary embolism. *J Thromb Thrombolysis*. 2016;41:32-67. doi: 10.1007/s11239-015-1317-0
18. Parker CS, Chen Z, Price M, et al. Adherence to warfarin assessed by electronic pill caps, clinician assessment, and patient reports: results from the IN-RANGE study. *J Gen Intern Med*. 2007;22:1254-1259. doi: 10.1007/s11606-007-0233-1
19. Kline JA, Nordenholz KE, Courtney DM, 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;12:459-468.
20. Chatterjee S, Chakraborty A, Weinberg J, et al. Thrombolysis for pulmonary embolism and risk of all-cause mortality, major bleeding, and intracranial hemorrhage: a meta-analysis. *JAMA*. 2014;311:2414-2421. doi: 10.1001/jama.2014.5990
21. Tapson VF, Friedman O. Systemic thrombolysis for pulmonary embolism: who and how. *Tech Vasc Interv Radiol*. 2017;20:162-174. doi: 10.1053/j.tvir.2017.07.005
22. Martin C, Sobolewski K, Bridgeman P, Boutsikaris D. Systemic thrombolysis for pulmonary embolism: a review. *P T*. 2016;41:770-775.
23. Kucher N, Boekstegers P, Müller OJ, et al. Randomized, controlled trial of ultrasound-assisted catheter-directed thrombolysis for acute intermediate-risk pulmonary embolism. *Circulation*. 2014;129:479-486. doi: 10.1161/CIRCULATIONAHA.113.005544
24. Kuo VT, Banerjee A, Kim PS, et al. Pulmonary embolism response to fragmentation, embolectomy, and catheter thrombolysis (PERFECT): initial results from a prospective multicenter registry. *Chest*. 2015;148:667-673. doi: 10.1378/chest.15-0119
25. Francis CW, Blinc A, Lee S, Cox C. Ultrasound accelerates transport of recombinant tissue plasminogen activator into clots. *Ultrasound Med Biol*. 1995;21:419-424. doi: 10.1016/0301-5629(94)00119-x
26. Tapson VF, Sterling K, Jones N, et al. A randomized trial of the optimum duration of acoustic pulse thrombolysis procedure in acute intermediate-risk pulmonary embolism: the OPTALYSE PE trial. *JACC Cardiovasc Interv*. 2018;11:1401-1410. doi: 10.1016/j.jcin.2018.04.008
27. Piazza G, Hohlfelder B, Jaff MR, 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;8:1382-1392. doi: 10.1016/j.jcin.2015.04.020
28. Sag S, Nas OF, Kaderli AA, et al. Catheter-directed ultrasound-accelerated thrombolysis may be life-saving in patients with massive pulmonary embolism after failed systemic thrombolysis. *J Thromb Thrombolysis*. 2016;42:322-328. doi: 10.1007/s11239-016-1370-3
29. de Winter MA, Vlachojannis GJ, Ruigrok D, et al. Rationale for catheter-based therapies in acute pulmonary embolism. *Eur Heart J Suppl*. 2019;21(suppl 1):116-122. doi: 10.1093/eurheartj/suz223
30. Kuo VT, Sista AK, Faintuch S, et al. Society of Interventional Radiology position statement on catheter-directed therapy for acute pulmonary embolism. *J Vasc Interv Radiol*. 2018;29:293-297. doi: 10.1016/j.jvir.2017.10.024
31. Rivera-Lebron B, McDaniel M, Ahrar K, et al. Diagnosis, treatment and follow up of acute pulmonary embolism: consensus practice from the PERT Consortium. *Clin Appl Thromb Hemost*. 2019;25:1076029619853037. doi: 10.1177/1076029619853037
32. Kucher N, Goldhaber SZ. Management of massive pulmonary embolism. *Circulation*. 2005;112:e28-32. doi: 10.1161/CIRCULATIONAHA.105.551374
33. Piazza G, Goldhaber SZ. Fibrinolysis for acute pulmonary embolism. *Vasc Med*. 2010;15:419-428. doi: 10.1177/1358863X10380304
34. Khaing P, Paruchuri A, Eisenbrey JR, et al. First year experience of a pulmonary embolism response team with comparisons of outcomes between catheter directed therapy versus standard anticoagulation. *Hosp Pract (1995)*. 2020;48:23-28. doi: 10.1080/21548331.2020.1706315
35. Rosovsky R, Chang Y, Rosenfield K, et al. Changes in treatment and outcomes after creation of a pulmonary embolism response team (PERT), a 10-year analysis. *J Thromb Thrombolysis*. 2019;47:31-40. doi: 10.1007/s11239-018-1737-8
36. Xenos ES, Davis GA, He Q, et al. The implementation of a pulmonary embolism response team in the management of intermediate- or high-risk pulmonary embolism. *J Vasc Surg Venous Lymphat Disord*. 2019;7:493-500. doi: 10.1016/j.jvs.2018.11.014
37. Rojo MR, Chauhan YM, Peden EK, IP279. Catheter interventions improve outcomes in patients with intermediate-risk pulmonary embolism. *J Vasc Surg*. 2019;69:e186. doi: 10.1016/j.jvs.2019.04.263
38. Graif A, Grilli CJ, Kimbiris G, et al. Comparison of ultrasound-accelerated versus pigtail catheter-directed thrombolysis for the treatment of acute massive and submassive pulmonary embolism. *J Vasc Interv Radiol*. 2017;28:1339-1347. doi: 10.1016/j.jvir.2017.07.004
39. Bagla S, Smimiotopoulos JB, van Breda A, et al. Ultrasound-accelerated catheter-directed thrombolysis for acute submassive pulmonary embolism. *J Vasc Interv Radiol*. 2015;26:1001-1006. doi: 10.1016/j.jvir.2014.12.017
40. Makary MS, Fogler BD, Dube PP, et al. Ultrasound-accelerated, catheter-directed thrombolysis for submassive pulmonary embolism: single-center retrospective review with intermediate-term outcomes. *J Vasc Interv Radiol*. 2020;31:438-443. doi: 10.1016/j.jvir.2019.11.008
41. Wayne NB, Davis GA, Macaulay TE, et al. Reduced dose thrombolysis with ultrasound-facilitated catheter-directed administration for acute pulmonary embolism reduces length of stay. *J Thromb Thrombolysis*. 2020;49:540-544. doi: 10.1007/s11239-019-02009-2
42. Kahn SR, Akaberi A, Granton JT, et al. Quality of life, dyspnea, and functional exercise capacity following a first episode of pulmonary embolism: results of the ELOPE cohort study. *Am J Med*. 2017;130(8):990.e999-990.e921. doi: 10.1016/j.amjmed.2017.03.033
43. Lerche M, Bailis N, Akritidou M, et al. Pulmonary vessel obstruction does not correlate with severity of pulmonary embolism. *J Clin Med*. 2019;8:584. doi: 10.3390/jcm8050584
44. Rahaghi FN, San José Estépar R, Goldhaber SZ, et al. Quantification and significance of pulmonary vascular volume in predicting response to ultrasound-facilitated, catheter-directed fibrinolysis in acute pulmonary embolism (SEATTLE-3D). *Circ Cardiovasc Imaging*. 2019;12:e009903. doi: 10.1161/CIRCIMAGING.119.009903
45. Muller MA, Xie A, Zhao Y, et al. 1170-260 Direct vascular effects of catheter-based ultrasound devices used for facilitated clot lysis. Presented at: ACC.20 World Congress of Cardiology virtual conference; March 28-30, 2020.
46. Piazza G, Sterling KM, Tapson VF, et al. One-year echocardiographic, functional, and quality of life outcomes after ultrasound-facilitated catheter-based fibrinolysis for pulmonary embolism. *Circ Cardiovasc Interv*. 2020;13:e009012. doi: 10.1161/CIRCINTERVENTIONS.120.009012



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