Society of Interventional Radiology Position Statement on Catheter-Directed Therapy for Acute Pulmonary Embolism

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ABBREVIATIONS

CDT = catheter-directed therapy, CTEPH = chronic thromboembolic pulmonary hypertension, LV = left ventricle, PE = pulmonary embolism, PERFECT = Pulmonary Embolism Response to Fragmentation, Embolectomy, and Catheter Thrombolysis: Initial Results from a Prospective Multicenter Registry, PPS = post–pulmonary embolism syndrome, RCT = randomized controlled trial, RV = right ventricle, SEATTLE II = A Prospective, Single-Arm, Multicenter Trial of Ultrasound-Facilitated, Catheter-Directed, Low-Dose Fibrinolysis for Acute Massive and Submassive Pulmonary Embolism, TPA = tissue plasminogen activator, ULTIMA = Randomized, Controlled Trial of Ultrasound-Assisted Catheter-Directed Thrombolysis for Acute Intermediate-Risk Pulmonary Embolism

STATEMENT

The Society of Interventional Radiology (SIR) considers the use of catheter-directed therapy (CDT) or thrombolysis to be an acceptable treatment option for carefully selected patients with massive (ie, high-risk) pulmonary embolism (PE) involving the proximal pulmonary arterial vasculature, in accordance with multidisciplinary guidelines (1–4). SIR defines acute proximal PE as new main or lobar emboli identified on radiographic imaging within 14 days of PE symptoms. In addition, SIR encourages the investigative use of CDT and new endovascular techniques in prospective outcomes studies and clinical trials, with particular attention to patients with acute submassive (ie, intermediate-risk) PE.

BACKGROUND

Acute PE is a common life-threatening condition that represents a severe manifestation along the spectrum of venous thromboembolic disease, and PE is the third leading cause of cardiovascular mortality in the United States (1). Acute PE is currently classified into three categories: low-risk, submassive (ie, intermediate-risk), and massive (ie, high-risk) (2).

Low-risk PE is defined by the absence of right heart strain and systemic arterial hypotension. The majority of patients diagnosed with PE present to the hospital without hypotension or heart strain, and these patients with low-risk PE (< 1% short-term mortality rate) can be successfully managed with prompt initiation of therapeutic anticoagulation (3).

Submassive or intermediate-risk PE is defined by the presence of right heart dysfunction in the setting of normal blood pressure, and this represents as many as 25% of all cases of acute PE. Currently, the greatest uncertainty in the PE treatment algorithm concerns the risk stratification and management of submassive PE. A recent randomized controlled trial (RCT) (4) in patients with submassive PE demonstrated a 5.6% rate of clinical deterioration (ie, death or hemodynamic decompensation) within 7 days and a 3% 30-day mortality rate with anticoagulation alone. In interpreting these findings against the background of previous studies, it should be noted that, for conventional and aggressive PE therapies, contemporary studies report lower mortality rates than older studies. In addition, RCTs have tended to report lower mortality rates than observational studies, which may result in part from selection of healthier populations (ie, strict inclusion/exclusion criteria) and closer subject monitoring in the RCTs. As such, earlier observational studies reported higher rates of mortality and rapid clinical deterioration in submassive PE populations treated with anticoagulation alone (5,6). Nevertheless, considering all the studies to date, it is clear that the estimated mortality risk from submassive PE is substantially higher than that associated with low-risk PE, but that the vast majority of patients survive, perhaps as a result of contemporary advances in medical care (5–7).

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Massive or high-risk PE is characterized by the presence of sustained systemic arterial hypotension defined by a systolic blood pressure < 90 mm Hg for at least 15 minutes or requiring inotropic support (2), and these patients carry a mortality risk of 25%–65% (8). As a result of the critical nature of high-risk PE, there is a current consensus that aggressive clot removal strategies be considered including systemic thrombolysis, CDT, and/or surgical embolectomy in select patients depending on risk/benefit assessment, presence of contraindications to such therapies, and available local expertise (2,3,9).

RATIONALE OF CDT FOR MASSIVE PE

Although systemic thrombolysis is currently indicated for the treatment of acute massive PE, many patients cannot receive systemic thrombolytic therapy because of contraindications. Even when patients with acute PE are prescreened for absolute contraindications, the rate of major hemorrhage associated with systemic thrombolysis has been estimated at 9.2%, with a 1.5% risk of intracranial hemorrhage reported in a metaanalysis of RCTs (7), and observational studies (4,5,10,11) have shown that these bleeding risks may be higher among real-world populations. Although systemic thrombolysis can be initiated in a shorter time frame than CDT, the full dose generally takes 2 hours to deliver, and possible advantages of CDT could include the ability to use a lower thrombolytic drug dose and obtain faster lysis as a result of the targeted intrathrombus drug delivery and the addition of mechanical treatment (ie, pharmacomechanical CDT) (3,12).

In a meta-analysis of 594 patients with acute massive PE treated with modern CDT (ie, use of low-profile devices < 10 F, mechanical fragmentation, and/or aspiration of emboli with or without the use of thrombolytic drugs) (12), clinical success was achieved in 86.5%, with success defined as the stabilization of hemodynamic parameters, resolution of hypoxia, and survival to hospital discharge. The analysis was limited because most of the identified studies were retrospective in design, most were small with heterogenous methods, and there were no randomized trials (although RCTs might pose an ethical challenge in patients with massive PE); nevertheless, there was no significant difference in clinical success rates between the prospective and retrospective study groups. In the same study (12), 96% of patients received CDT as the first adjunct to heparin with no previous systemic tissue plasminogen activator (TPA) infusion, and 33% of cases were initiated with mechanical treatment alone (ie, fragmentation and/or aspiration of emboli) without local thrombolytic agent infusion. In addition, the estimated rate of major complications associated with modern CDT was 2.4%, and most complications were attributed to the use of rheolytic thrombectomy with the use of an AngioJet (Possis Medical, Minneapolis, Minnesota) device (12). The highest complication rates occurred in the 68 patients who underwent CDT with the AngioJet rheolytic thrombectomy device, including 27 minor complications (40%) and 19 major complications (28%), with 5 procedure-related deaths (12); 76% of all major complications recorded in the study (19 of 25) were directly attributed to AngioJet rheolytic thrombectomy despite the fact that it was used in only a small percentage (11%) of the 594 patients studied (12). In this meta-analysis (12), use of the AngioJet device was the only catheter-based treatment associated with procedure-related deaths, and the device currently carries a black-label warning from the Food and Drug Administration (13), stating "There are reports of serious adverse events, including death, associated with cases where the [AngioJet] catheter was used in treatment of pulmonary embolism."

RATIONALE OF CDT FOR SUBMASSIVE PE

Among patients with submassive PE, the initial goal of treatment escalation with thrombolysis is to reduce mortality from PE without increasing the risk of treatment-related complications. Although a recent meta-analysis of randomized trials (7) demonstrated a survival benefit with use of systemic thrombolytic therapy in submassive PE, these data also revealed a much higher risk of major bleeding complications compared with anticoagulation alone. Therefore, the risk-to-benefit ratio of systemic thrombolysis in the submassive PE population is uncertain with regard to clinical decision-making. It is reasonable to hypothesize that delivering a lower overall thrombolytic agent dose via catheter could mitigate the risk of major bleeding complications (14). Interestingly, a previous study on flow dynamics (15) demonstrated that a systemically administered drug makes little contact with an obstructing embolus, and most of the drug flows away from the obstructing clot (ie, Venturi effect) toward the open nontarget vessels. Pharmacologic CDT overrides the Venturi effect because a soft, flexible catheter with multiple side holes is directly inserted under image guidance into the thrombosed target vessel to provide direct intraclot drug infusion. A potential advantage with CDT is targeted drug delivery into the clot to achieve low-dose thrombolysis, which may reduce bleeding risk (14). Therefore, relative to systemic drug therapy, local CDT may improve drug effectiveness, allow a lower drug dose to be used, and result in fewer bleeding complications.

DISCUSSION

Despite some limitations of available evidence (12), CDT is currently considered an acceptable treatment option (as are systemic thrombolysis and surgical embolectomy) for highly selected patients with massive PE (2,3,9). This largely reflects the imminent risk of death and the juxtaposition of a large degree of uncertainty with the estimates of safety and efficacy of CDT and surgical therapy versus the bleeding risk associated with systemic thrombolysis. However, the optimal treatment strategy for submassive PE is still evolving. The 2011 American Heart Association guidelines (2) state that "[systemic] Fibrinolysis may be considered for patients with submassive acute PE judged to have clinical evidence of adverse prognosis (new hemodynamic instability, worsening respiratory insufficiency, severe [right ventricular] RV dysfunction, or major myocardial necrosis) and low risk of bleeding complications… Either catheter embolectomy or surgical embolectomy may be considered for patients with submassive acute PE judged to have clinical evidence of adverse prognosis (new hemodynamic instability, worsening respiratory failure, severe RV dysfunction, or major myocardial necrosis)." The 2014 European Society of Cardiology guidelines (9) state that "Surgical pulmonary embolectomy or percutaneous catheter-directed treatment may be considered as alternative, 'rescue' procedures for patients with intermediate/high-risk PE, in whom hemodynamic decompensation appears imminent and the anticipated bleeding risk under systemic thrombolysis is high." The 2016 American College of Chest Physicians guidelines (3) state: "In selected patients with acute PE who deteriorate after starting anticoagulant therapy but have yet to develop hypotension and who have a low bleeding risk, we suggest systemically administered thrombolytic therapy over no such therapy… Patients who have a higher risk of bleeding with systemic thrombolytic therapy and who have access to the expertise and resources required to do CDT are likely to choose CDT over systemic thrombolytic therapy." A complete summary of these guidelines is included in the **Appendix**.

Because systemic thrombolysis carries a significant risk of major hemorrhage, current guidelines have tempered the indication for use of systemic thrombolysis for intermediate-risk PE, suggesting that it be used only when there is cardiac enzyme leak and/or impending hemodynamic collapse (2,3,9). This causes a dilemma because patients with moderate to severe RV strain are still at risk of sudden cardiac collapse and death before the development of cardiac enzyme leak and impending life-threatening shock (5,6); by then, it may be too late to escalate treatment. Other patients with submassive PE may have severe and persistent pulmonary symptoms (eg, severe hypoxia, tachypnea, and dyspnea on exertion) that is not relieved by therapeutic anticoagulation. In such scenarios, the availability of a treatment option with a more favorable risk-to-benefit profile than systemic thrombolysis would be optimal. It is possible that CDT meets this criterion; however, current estimates of the safety and efficacy of CDT are based on exceedingly limited data and therefore carry major uncertainty. For this reason, even though it is reasonable to target escalation of care to individual patient circumstances (especially for cases bordering on massive PE physiology that are associated with a low risk of bleeding), CDT cannot be firmly recommended for these patient groups at present. Further prospective studies are needed to address these issues, following the lead of three early prospective studies (16–18).

ULTIMA RCT

The ULTIMA RCT (16) enrolled 59 patients with submassive acute main or lower-lobe PE presenting within 14 days and an RV-to-left ventricle (LV) diameter ratio ≥ 1.0 on echocardiography. The study randomized patients to receive unfractionated heparin versus unfractionated heparin plus CDT with the use of an ultrasound (US)-assisted thrombolysis regimen and a maximum TPA dose of 10–20 mg over 15 hours. The ULTIMA trial showed that US-assisted CDT was superior to anticoagulation alone in reversing RV dilation at 24 hours, with no increase in bleeding complications. The trial was limited by selection of a small, idealized trial population, as 84% of screened patients were excluded and only 30 patients were enrolled in the treatment arm. The study was not designed to assess long-term outcomes of CDT and the risk of development of post-PE syndrome (PPS) or chronic thromboembolic pulmonary hypertension (CTEPH). The ULTIMA trial was also an industry-sponsored trial that did not compare US-assisted catheters versus standard CDT; therefore, the contribution of US was unclear. Nevertheless, the ULTIMA trial was the first RCT to test a standardized catheter intervention in patients with acute submassive PE and confirm that a low-dose CDT regimen is superior to anticoagulation alone in improving RV dilation at 24 hours (16).

SEATTLE II Multicenter Trial

The SEATTLE II trial (17) (a prospective, single-arm, multicenter trial of ultrasound-facilitated, catheter-directed, low-dose fibrinolysis for acute massive and submassive pulmonary embolism) enrolled 119 patients with submassive PE and 31 patients with massive PE. Eligible patients had proven proximal PE and an RV:LV diameter ratio ≥ 0.9 confirmed on contrast-enhanced chest computed tomography (CT). The maximum dose of TPA was 24 mg infused via US-assisted catheter over 12–24 hours. During CDT, unfractionated heparin was infused at intermediate intensity (ie, subtherapeutic) with a target activated partial thromboplastin time of 40–60 seconds. The study concluded that low-dose CDT fibrinolysis improves RV function in acute PE, decreases angiographic pulmonary artery obstruction, and reduces systolic pulmonary artery pressure. There was an 11% major bleeding rate in the SEATTLE II trial (17), which, despite the lack of catastrophic bleeding events, adds to the uncertainty concerning whether CDT is truly safer than systemic thrombolysis. In addition, the risk of major bleeding was associated with multiple venous access attempts (ie, access site complications) (19). The trial (17) was limited by a nonrandomized design, even though this allowed more types of patients to be included compared with the ULTIMA trial (16). The SEATTLE II trial (17) was not designed to assess long-term outcomes of CDT, and, similar to ULTIMA (16), SEATTLE II (17) was an industry-sponsored trial that did not compare the use of high-cost US-assisted catheters versus standard CDT; therefore, the contribution of US was unclear. While recognizing that the absence of a randomized control group precludes any inference to be drawn about CDT specifically, the SEATTLE II trial (17) suggests that the combination of medical therapy (including anticoagulation), close patient monitoring, and low-dose CDT fibrinolysis may improve RV function, decrease pulmonary artery angiographic obstruction, and reduce pulmonary artery systolic pressure in acute PE.

PERFECT Multicenter Registry

The PERFECT registry (18) (Pulmonary Embolism Response to Fragmentation, Embolectomy, and Catheter Thrombolysis) was a multicenter PE registry that enrolled 73 patients with submassive PE and 28 patients with massive PE. There were very few exclusion criteria, and the study included patients with contraindications to systemic thrombolysis. Eligible patients had acute PE presenting within 14 days and CT evidence of proximal PE defined as a filling defect in at least one main or lobar pulmonary artery. Submassive PE was defined as acute PE causing right ventricular dilation and hypokinesis confirmed on echocardiography, chest CT, or both without systemic hypotension. The average thrombolytic agent doses infused via catheter were 28 mg ± 11 TPA (n = 76) and 2,697,101 IU ± 936,287 urokinase (n = 23), with an average infusion time of less than 24 hours. One patient with submassive PE (1%) did not receive any thrombolytic drug and was treated with only mechanical CDT. During CDT thrombolysis with TPA, subtherapeutic low-dose intravenous heparin was infused at 300–500 U/h. The study (18) concluded that CDT improves clinical outcomes (RV strain, pulmonary artery pressure) in patients with acute submassive and massive PE. There were no major procedure-related complications, no major hemorrhages, and no intracranial hemorrhages following CDT. The registry included patients treated with either US-assisted catheters or standard CDT catheters, and found no advantage in those treated with high-cost US-assisted catheters versus standard CDT infusion catheters. Similar to the SEATTLE II trial (17), the PERFECT registry (18) was not randomized and did not assess long-term outcomes, and therefore cannot confidently support inferences about the efficacy of CDT versus other therapies. Nevertheless, the registry enrolled many patients who would have been excluded in earlier RCTs and provides useful data to support the design of additional prospective studies and future CDT protocols (18).

Although there is still some uncertainty in regard to estimates of the safety of CDT because of the paucity of large-scale data, it is encouraging that no intracranial bleeding events were observed in the latest prospective studies. Although various thrombolytic infusion catheters exist, the available evidence to date has not revealed any advantage with use of higher-cost US-assisted thrombolysis catheters versus standard infusion catheters (18,20).

SIR recognizes the methodologic limitations of existing studies supporting CDT for submassive PE, especially with regard to the prevention of long-term PE sequelae (21). Although the impact of CDT on long-term outcomes has yet to be adequately studied, the concept of early thrombolytic treatment to prevent long-term PE sequelae has been demonstrated. Data from earlier systemic thrombolysis studies suggest that treatment with early thrombolysis may decrease the long-term risk of developing CTEPH and diminish the long-term risk of exercise intolerance, RV dysfunction, decreased quality of life, and breathlessness, collectively referred to as PPS (22,23). However, the impact of early CDT (vs systemic therapy) in the aforementioned groups to reduce the long-term risk of PPS and CTEPH remains unclear. A research consensus panel (sponsored by the SIR Foundation) (21) including a multidisciplinary group of 19 experts discussed key questions and data gaps surrounding submassive PE. The research consensus panel concluded that a randomized trial of CDT versus anticoagulation alone is a primary research priority to determine if early use of CDT can reduce the long-term risk of PPS and CTEPH (21). Based on all the concepts above, SIR holds the following positions:

1. SIR supports the use of CDT in carefully selected patients with proximal acute massive PE, especially in highly-compromised or rapidly-deteriorating PE patients who have failed systemic thrombolysis.
2. At present, the available data are insufficient to support the routine use of CDT for patients with submassive PE. Recognizing that clinical progression to massive PE physiology can occur rapidly and may be signaled by findings on serial clinical assessments, patients with submassive PE should be closely monitored for deterioration, with notification of a multidisciplinary team if this occurs (including an interventional radiologist if reperfusion therapies are being considered). Although it is acknowledged that CDT may have advantages over other modalities for specific patients, in centers that use CDT for treatment of submassive PE, SIR encourages data collection with institutional review board oversight and strongly recommends that local practices and treatment outcomes be reviewed periodically for quality-improvement purposes. Before undertaking CDT, a careful assessment should be performed to detect clinical factors that might increase the risk of bleeding or diminish the importance of any clinical benefit achieved.
3. For patients who undergo CDT for PE, SIR suggests the following precautions: (*i*) patients should be closely monitored in an advanced care unit; (*ii*) US guidance for venous puncture should be routinely used to reduce bleeding risk; (*iii*) because of its suspected association with severe adverse events, use of the AngioJet Rheolytic Thrombectomy System should probably be avoided except in the context of a prospective study; (*iv*) to minimize the risk of compromising the condition of patients in stable condition, mechanical interventions should usually

be avoided in patients with submassive PE unless as part of a prospective study; and (*v*) if heparin is given during thrombolytic infusion, subtherapeutic dosing (eg, 300–500 U/h or less than 2× normal partial thromboplastin time) is suggested to reduce bleeding risk.

4. SIR strongly supports the conduct of new RCTs and other prospective studies on the use of CDT for acute PE, in particular for submassive PE, with a focus on studying long-term outcomes and possible prevention of PPS and CTEPH.

APPENDIX. SUMMARY OF GUIDELINES ON THROMBOLYTIC THERAPY FOR ACUTE PE

AMERICAN HEART ASSOCIATION, 2011 (2)

Recommendations for Systemic Fibrinolysis for Acute PE.

1. Fibrinolysis is reasonable for patients with massive acute PE and acceptable risk of bleeding complications (class IIa; level of evidence B).
2. Fibrinolysis may be considered for patients with submassive acute PE judged to have clinical evidence of adverse prognosis (ie, new hemodynamic instability, worsening respiratory insufficiency, severe RV dysfunction, or major myocardial necrosis) and low risk of bleeding complications (class IIb; level of evidence C).
3. Fibrinolysis is not recommended for patients with low-risk PE (class III; level of evidence B) or submassive acute PE with minor RV dysfunction, minor myocardial necrosis, and no clinical worsening (class III; level of evidence B).

Fibrinolysis is not recommended for undifferentiated cardiac arrest (class III; level of evidence B) (2).

Recommendations for Catheter Embolectomy and Fragmentation.

4. Depending on local expertise, catheter embolectomy and fragmentation or surgical embolectomy is reasonable for patients with massive PE and contraindications to fibrinolysis (class IIa; level of evidence C).
5. Catheter embolectomy and fragmentation or surgical embolectomy is reasonable for patients with massive PE who remain in unstable condition after receiving fibrinolysis (class IIa; level of evidence C).
6. For patients with massive PE who cannot receive fibrinolysis or who remain in unstable condition after fibrinolysis, it is reasonable to consider transfer to an institution experienced in catheter embolectomy or surgical embolectomy if these procedures are not available locally and safe transfer can be achieved (class IIa; level of evidence C).
7. Catheter embolectomy or surgical embolectomy may be considered for patients with submassive acute PE judged to have clinical evidence of adverse prognosis (ie, new hemodynamic instability, worsening respiratory failure, severe RV dysfunction, or major myocardial necrosis; class IIb; level of evidence C).

Catheter embolectomy and surgical thrombectomy are not recommended for patients with low-risk PE or submassive acute PE with minor RV dysfunction, minor myocardial necrosis, and no clinical worsening (class III; level of evidence C) (2).

EUROPEAN SOCIETY OF CARDIOLOGY, 2014 (9)

1. PE with shock or hypotension (ie, high-risk PE):

Patients with PE presenting with shock or hypotension are at high risk of in-hospital death, particularly during the first few hours after admission. In addition to hemodynamic and respiratory support, intravenous unfractionated heparin should be administered to these patients as the preferred mode of initial anticoagulation, as low-molecular-weight heparin or fondaparinux have not been tested in the setting of hypotension and shock. Primary reperfusion treatment, particularly systemic thrombolysis, is the treatment of choice for patients with high-risk PE. In patients with contraindications to thrombolysis—and in those in whom thrombolysis has failed to improve hemodynamic status—surgical embolectomy is recommended if surgical expertise and resources are available. As an alternative to surgery, percutaneous CDT should be considered if expertise with this method and the appropriate resources are available on site (9).

2. PE without shock or hypotension (ie, intermediate- or low-risk PE):

The European Society of Cardiology subclassifies intermediate-risk PE into high- and low-risk categories, and treatment escalation is recommended for the intermediate (high)-risk category defined by the presence of RV dysfunction (on echocardiography or CT)[a] and abnormal cardiac enzyme levels.[b] According to the European Society of Cardiology, such patients are candidates for rescue reperfusion[c]:

a. If echocardiography has already been performed during diagnostic workup for PE and detected RV dysfunction, or if the CT scan already performed for diagnostic workup has shown RV enlargement (ie, RV/LV diameter ratio $\geq$ 0.9), a cardiac troponin test should be performed except in cases in which primary reperfusion is not a therapeutic option (eg, as a result of severe comorbidity or limited life expectancy of the patient).
b. Markers of myocardial injury (eg, elevated cardiac troponin I or T concentrations in plasma) or of heart failure as a result of (right) ventricular dysfunction (eg, elevated natriuretic peptide concentrations in plasma). If a laboratory test for a cardiac biomarker has already been performed during initial diagnostic workup (eg, in the chest pain unit) and had positive findings, an echocardiogram should be considered to assess RV function or RV size should be (re) assessed on CT.
c. Rescue reperfusion with thrombolysis if (and as soon as) clinical signs of hemodynamic decompensation appear, surgical pulmonary embolectomy, or percutaneous CDT may be considered as alternative options to systemic thrombolysis, particularly if the bleeding risk is high.

Surgical pulmonary embolectomy or percutaneous CDT may be considered as alternative rescue procedures for patients with intermediate/high-risk PE in whom hemodynamic decompensation appears imminent and the anticipated bleeding risk under systemic thrombolysis is high (9).

AMERICAN COLLEGE OF CHEST PHYSICIANS, 2016 (3)

Systemic Thrombolytic Therapy for PE

1. In patients with acute PE associated with hypotension (eg, systolic blood pressure < 90 mm Hg) who do not have a high bleeding risk, systemically administered thrombolytic therapy is recommended over no such therapy (grade 2B).
2. In most patients with acute PE not associated with hypotension, the American College of Chest Physicians recommends against systemically administered thrombolytic therapy (grade 1B).
3. In selected patients with acute PE whose condition deteriorates after starting anticoagulant therapy but who have yet to develop hypotension and who have a low bleeding risk, systemically administered thrombolytic therapy is suggested over no such therapy (grade 2C).

Remarks: Patients with PE and without hypotension who have severe symptoms or marked cardiopulmonary impairment should be monitored closely for deterioration. Development of hypotension suggests that thrombolytic therapy has become indicated. Cardiopulmonary deterioration (eg, symptoms, vital signs, tissue perfusion, gas exchange, cardiac

biomarkers) that has not progressed to hypotension may also alter the risk/benefit assessment in favor of thrombolytic therapy in patients initially treated with anticoagulation alone (3).

Catheter-Based Thrombus Removal for the Initial Treatment of PE

4. In patients with acute PE who are treated with a thrombolytic agent, systemic thrombolytic therapy via a peripheral vein is suggested over CDT (grade 2C).

Remarks: Patients who have a higher risk of bleeding with systemic thrombolytic therapy and who have access to the expertise and resources required to perform CDT are likely to choose CDT over systemic thrombolytic therapy.

5. In patients with acute PE associated with hypotension and who have (*i*) a high bleeding risk (16), (*ii*) undergone failed systemic thrombolysis, or (*iii*) shock that is likely to cause death before systemic thrombolysis can take effect (ie, within hours), if appropriate expertise and resources are available, catheter-assisted thrombus removal is suggested over no such intervention (grade 2C).

Remarks: Catheter-assisted thrombus removal refers to mechanical interventions with or without catheter directed thrombolysis (3).

REFERENCES

1. Mozaffarian D, Benjamin EJ, Go AS, et al. Heart disease and stroke statistics–2015 update: a report from the American Heart Association. Circulation 2015; 131:e29–e322.
2. Jaff MR, McMurtry 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.
3. Kearon C, Akl EA, Ornelas J, et al. Antithrombotic therapy for VTE disease: CHEST guideline and expert panel report. Chest 2016; 149:315–352.
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.
5. Goldhaber SZ, Visani L, De Rosa M. Acute pulmonary embolism: clinical outcomes in the International Cooperative Pulmonary Embolism Registry (ICOPER). Lancet 1999; 353:1386–1389.
6. Fremont B, Pacouret G, Jacobi D, Puglisi R, Charbonnier B, de Labriolle A. 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.
7. Chatterjee S, Chakraborty A, Weinberg I, 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.
8. Kasper W, Konstantinides S, Geibel A, et al. Management strategies and determinants of outcome in acute major pulmonary embolism: results of a multicenter registry. J Am Coll Cardiol 1997; 30:1165–1171.
9. Konstantinides SV, Torbicki A, Agnelli G, et al. 2014 ESC Guidelines on the diagnosis and management of acute pulmonary embolism: the task force for the diagnosis and management of acute pulmonary embolism of the European Society of Cardiology (ESC) endorsed by the European Respiratory Society (ERS). Eur Heart J 2014; 35:3033–3073.
10. Fiumara K, Kucher N, Fanikos J, Goldhaber SZ. Predictors of major hemorrhage following fibrinolysis for acute pulmonary embolism. Am J Cardiol 2006; 97:127–129.
11. Goldhaber SZ. Integration of catheter thrombectomy into our armamentarium to treat pulmonary embolism. Chest 1998; 114:1237–1238.
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; 20:1431–1440.
13. AngioJet Xpeedior [product insert]. Minneapolis: Possis Medical, 2008.
14. Kuo WT. Endovascular therapy for acute pulmonary embolism. J Vasc Interv Radiol 2012; 23:167–179.
15. Schmitz-Rode T, Kilbinger M, Günther RW. Simulated flow pattern in massive pulmonary embolism: significance for selective intrapulmonary thrombolysis. Cardiovasc Intervent Radiol 1998; 21:199–204.
16. 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.
17. 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 (SEATTLE II). JACC Cardiovasc Interv 2015; 8:1382–1392.
18. Kuo WT, 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.
19. Sadiq I, Goldhaber SZ, Liu PY, Piazza G, for the SEATTLE II investigators. Risk factors for major bleeding in the SEATTLE II trial. Vasc Med 2017; 22:44–50.
20. Tafur AJ, Shamoun FE, Patel SI, Tafur D, Donna F, Murad MH. Catheter-directed treatment of pulmonary embolism: a systematic review and meta-analysis of modern literature. Clin Appl Thromb Hemost 2017; 23:821–829.
21. Sista AK, Goldhaber SZ, Vedantham S, et al. Research priorities in submassive pulmonary embolism: proceedings from a multidisciplinary research consensus panel. J Vasc Interv Radiol 2016; 27:787–794.
22. 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; 136:1202–1210.
23. 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.