Evolution of Acute Pulmonary Embolism Management: Review Article

Mohammed Faluk, MD, Syed Mustajab Hasan, MD, Jay J. Chacko, MD, Ramy Abdelmaseih, MD, and Jigar Patel, MD

Abstract: Acute pulmonary emboli are a major cause of morbidity and mortality and require prompt evaluation, diagnosis, and treatment. To date, anticoagulation using low molecular weight heparin or non-Vitamin K oral anticoagulants has been the mainstay of treatment in the subset of patients in whom pulmonary embolism does not compromise hemodynamics. On the other hand however, patients with massive pulmonary embolism and shock, thrombolytic therapy is necessary. This raises the question whether ultrasound-assisted catheter directed thrombolytic delivery might be superior to systemic administration. This review article aims to consolidate recent literature to help achieve a better understanding toward the utility of catheter directed therapy. (Curr Probl Cardiol 2021;46:100551.)

Introduction

Pulmonary embolism (PE) is a form of venous thromboembolism that is common, and sometimes fatal despite advances in diagnosis and treatment. The signs and symptoms of PE are often nonspecific making the diagnosis very challenging. Clinical presentation ranges from shock or sustained hypotension to mild dyspnea. Sometimes it may even be asymptomatic and diagnosed with imaging procedures performed for other purposes.[1] Depending on the clinical presentation

Curr Probl Cardiol 2021;46:100551
0146-2806/$ – see front matter
https://doi.org/10.1016/j.cpcardiol.2020.100551

and patient characteristics, outcomes in acute PE substantially vary with a case fatality rate ranging from about 60% to less than 1%. In the United States alone, 100,000 individuals die from PE annually.[2–4] With such diverse presentations and worrisome outcomes, it is important to know the different subgroups of PE, presentations, risk factors, and different treatment modalities. For instance death from hemodynamically unstable patient often occurs within the first 2 hours, and the risk remains elevated for up to 72 hours after presentation.[5,6] PE can be classified into different subgroups based on the temporal pattern of presentation (acute, subacute, or chronic), the presence or absence of hemodynamic instability (massive PE, submassive PE, or low-risk PE), the anatomic location (saddle, lobar, segmented, or subsegmental), and the presence or absence of symptoms. This review article will discuss the utilization of thrombolytic therapy within the various PE subgroups identified by the presence or absence of hemodynamic instability. The American Heart Association defined different subgroups of PE as follows: massive, submassive, and low-risk.[7] A massive PE is an acute PE with sustained hypotension (systolic blood pressure <90 mm Hg for at least 15 minutes or requiring inotropic support, which is not due to another medical condition such as arrhythmia, hypovolemia, sepsis, or left ventricular [LV] dysfunction), pulselessness, or persistent profound bradycardia (heart rate <40 bpm with signs or symptoms of shock). Submassive PE is an acute PE without systemic hypotension (systolic blood pressure ≥90 mm Hg), but with either right ventricular (RV) dysfunction or myocardial necrosis. Low-risk PE is an acute PE and the absence of the clinical markers of adverse prognosis that define massive or submassive PE. This review article focuses on the evolution of PE treatment modalities (especially submassive PE), and the potential complications that arises as a result of different treatment modalities. Epidemiology, predisposing factors, natural history, and the pathophysiology of PE have been described more extensively elsewhere.[8–10]

Different Treatment Modalities of Pulmonary Embolism

Hemodynamic and Respiratory Support

The initial approach to patients with suspected PE should focus on stabilizing the patient while clinical evaluation and diagnostic testing are in process as right ventricle failure with low systemic output is the leading cause of death in patients with massive PE. Resuscitations and medical therapy are described elsewhere.[11]

Anticoagulation Therapy

Historically, there have been 2 main treatment modalities for acute PE – anticoagulant or systemic thrombolytic therapy or combination of the 2. Anticoagulation still remains the first-line treatment of acute pulmonary embolism. The American College of Chest Physicians Evidence – based clinical practice guidelines (8th Edition) and American Heart Association recommend that patients with confirmed PE with no anticoagulant contraindications should receive prompt anticoagulant therapy with subcutaneous (SC) low molecular weight heparin (LMWH), monitored intravenous or SC unfractionated heparin (UFH), unmonitored weight-based SC UFH or SC Fondaparinux (all Grade 1A Recommendations). Patients with intermediate or high pretest probability of PE should receive anticoagulant while awaiting diagnostic test results (Grade 1C). Patient with suspected or confirmed heparin-induced thrombocytopenia, a nonheparin anticoagulant like Danaparoid, Lepirudin, Argatroban, or Bivalirudin should be used. Anticoagulation of choice and duration of the therapy is reviewed elsewhere.[7,11,12,13]

Thrombolysis

Although anticoagulants remain the first-line of PE treatment, some patients may benefit from additional therapy like fibrinolysis if they fulfill one of these 2 criteria: (A) Evidence of present or developing circulatory or respiratory insufficiency; or (B) evidence of moderate to severe right ventricle injury. Circulatory failure is defined as any episode of hypotension or a persistent shock index >1. The definition of respiratory failure may include hypoxemia, defined as a pulse oximetry reading <95% when the patient is breathing ambient room air and clinical judgment that the patient appears to be in respiratory distress.[7,14,15] The most popular randomized controlled trial that compared systemic thrombolytic plus heparin vs heparin alone was the PEITHO trial that has been published in 2014.[16] PEITHO trial investigators recruited 1006 patients with intermediate-risk for submassive PE with evidence of right ventricle strain and myocardial injury from 76 sites in 13 European countries and randomized to a double-blind trial of full-dose systemically administered tenecteplase (TNKase) plus heparin vs. heparin alone. 1,005 patients were included in the intention-to-treat analysis. The primary outcome was death or hemodynamic decompensation (or collapse) and main safety outcomes were major extra cranial bleeding and ischemic or hemorrhagic stroke within 7 days after randomization. Systemic thrombolysis halved the number of patients who died or who had hemodynamic collapse (5.6% with heparin

vs. 2.6% with TNKase) but there was 10-fold increase in hemorrhagic stroke (0.2% with heparin vs. 2.0% with TNKase) primarily in patients' ≥75 years of age. Extracranial bleeding occurred (6.3% with TNKase vs 1.2% with heparin). Stroke occurred in 12 patients (2.4%) in the TNKase group and was hemorrhagic in 10 patients; 1 patient (0.2%) in placebo group had stroke, which was hemorrhagic. This result raised too many questions. For instance, was the dose of TNKase too high? Would decreasing the dose eliminate the bad outcome and maintain the efficacy? Since higher number of bleeding complications occurred in older patients, should older folks be given smaller dose of thrombolytics? Would the use of catheter directed therapy (CDT) with low dose of thrombolytics maintain the efficacy but reduce the bleeding complications? In general, thrombolytic therapy irrespective of doses was associated with lower rates of all-cause mortality, PE-related mortality, and PE recurrence but with increased risks of major bleeding and fatal bleeding or intracranial hemorrhage compared with anticoagulation (Figure).[17–19]

Catheter-Based Therapy

Major hemorrhage following thrombolytic therapy for acute PE is a common complication that warrants specific evaluation of patient risk factors prior to determining appropriate candidacy for thrombolytic therapy. For patients considered to be at high risk of major bleeding, strategies to minimize risk should be considered, which include weight-adjusted thrombolytic doses or CDT.[20] There are 3 main categories of catheter directed intervention for pulmonary emboli removal and thrombus burden reduction: (A) aspiration thrombectomy, (B) thrombus fragmentation, and (C) rheolytic thrombectomy. In order to treat patients with thrombolytic contraindications, failed thrombolysis treatment, or to reduce the systemic bleeding complications while maintaining the efficacy of thrombolytic therapy, 4 CDT trials with or without ultrasounds were conducted. The trials were as follows: The ULTIMA (Ultrasound Accelerated Thrombolysis of Pulmonary Embolism), SEATTLE II, PERFECT (Pulmonary Embolism Response to Fragmentation, Embolectomy, and Catheter Thrombolysis), and OPTALYSE PE (Optimum Dose and Duration of acoustic Pulse Thrombolysis Procedure in Acute Intermediate-Risk Pulmonary Embolism). The trials will be individually assessed and evaluated based on the outcome, efficacy, and utility of CDT therapy for PE management as compared to the established primary treatment modality of anticoagulation and systemic thrombolysis.

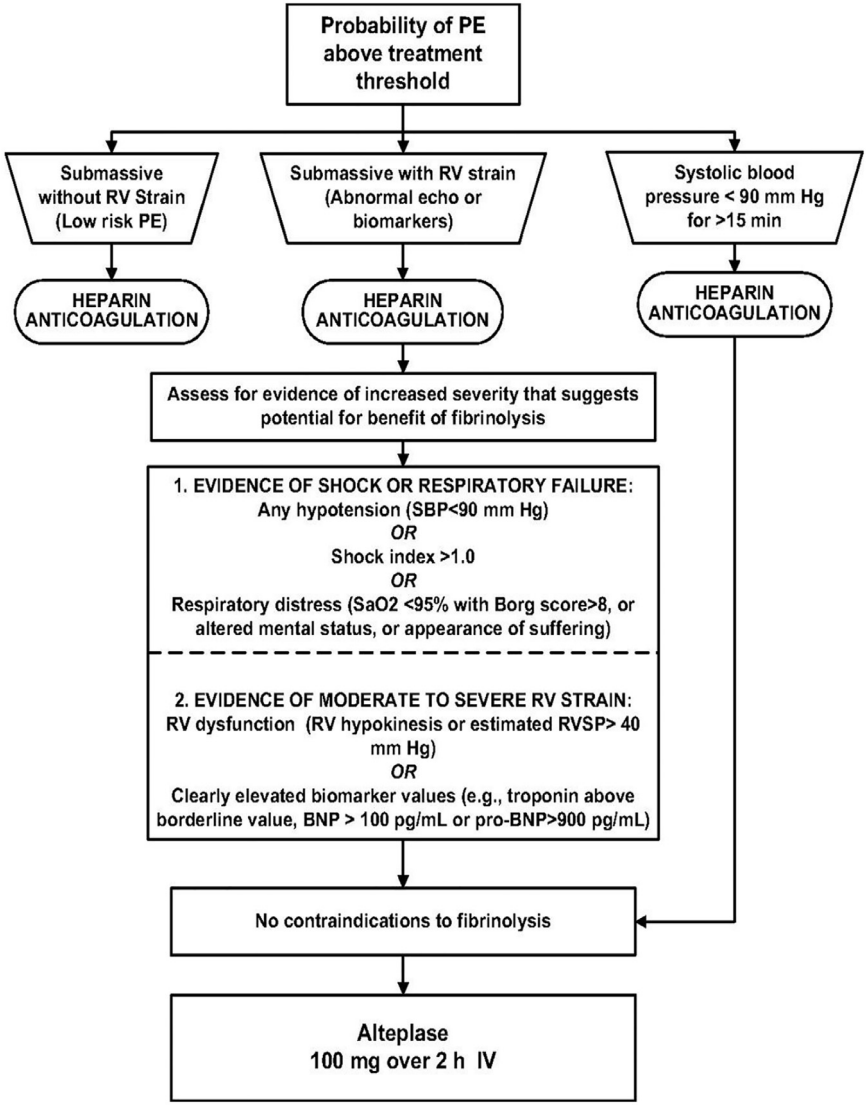

Figure. Suggested treatment algorithm for use of fibrinolytics to treat acute pulmonary embolism. PE indicates pulmonary embolism; RV, right ventricular; SBP, systolic blood pressure; RVSP, right ventricular systolic pressure; BNP, brain natriuretic peptide; and IV, intravenously.[7]

The ULTIMA trial investigated whether a standardized fixed-dose ultrasound-assisted catheter directed thrombolysis (USAT) regimen is superior to anticoagulation alone in the reversal of RV dilatation in intermediate-risk PE patients in 24 hours.[21] This multicenter randomized controlled trial (RCT), randomized 59 patients (63 ± 14 years) with acute

submassive PE and echocardiographic RV to LV ratio ≥1 to receive UFH alone (29 patients) or USAT regimen of 10-20 mg tissue-plasminogen activator (tPA) over 15 hours (30 patients). The difference of the RV/LV ratio from baseline to 24 hours was the primary outcome. Additionally, safety outcomes at 90 days included minor and major bleeding, death, and recurrent venous thromboembolism. This trial[21] revealed that the standardized USAT regimen was superior to anticoagulation with heparin alone in reversing RV dilatation at 24 hours, without an increase in major bleeding complications. There was almost no improvement at 24 hours in patients who were randomized to the heparin group, and the difference in improvement of RV dilatation between the USAT group and anticoagulant alone group was statistically significant. Furthermore, with regards to safety outcomes in 90 days, there were 4 minor bleeding events (One in the heparin arm and 3 in the USAT arm, $P = 0.61$), one death in the heparin but there was not a major bleeding in both arms.

The SEATTLE II trial is a single-arm prospective, multicenter (22 sites) trial to evaluate the safety and efficacy of ultrasound-facilitated, catheter-directed, low-dose fibrinolysis, using the EkoSonic Endovascular System (EKOS).[22] This study included 150 patients with proximal PE − massive (hemodynamically unstable; 31 patients) and submassive (normotensive; 119 patients) and RV/LV diameter ratio ≥0.9 on computed tmography (CT) pulmonary angiography. The patients were treated with 24 mg of tPA administered either as 1 mg/h for 24 hours with a unilateral catheter or 1 mg/h/catheter for 12 hours with bilateral catheters. The primary efficacy outcome was the change in the chest CT-measured RV/LV diameter ratio within 48 hours ± 6 hours of procedure initiation. Secondary outcomes observed were change in pulmonary artery pressure and assessment of change in thrombus burden via Modified Miller score. Repeat CT pulmonary angiogram after 48 hours ± 6 hours revealed 27% decrease of RV/LV diameter ratio and pulmonary artery pressure plus thrombus burden reduction by 30%. Each of these 3 improvements was statistically significant. The primary safety outcome was major bleeding within 72 hours of procedure initiation, and the bleeding events were assessed via the GUSTO (Global Utilization of Streptokinase and Tissue Plasminogen Activator of Occluded Coronary Arteries) bleeding criteria. There were 17 reported major bleeding events in 15 patients (10%) of which only one was considered to be severe and all others moderate as per the GUSTO bleeding criteria. There were no intracranial bleeds, and none were fatal. The study showed similar reduction of the RV/LV diameter ratio and pulmonary artery pressure in both submassive and massive PE, with the latter more likely to experience major bleeding events (23%

vs 7%, $\underline{P} = 0.02$). Noted limitations to the SEATTLE II trial were as follows: no comparison group (single arm); did not assess whether USCDT was more effective than standard CDT; and only short-term outcomes were assessed for efficacy not long-term outcomes such as quality of life or exercise capacity. Overall, the trial illustrated that US-facilitated, catheter-directed, low-dose fibrinolytic therapy decreased RV dilatation thereby improving RV function, reduced pulmonary arterial pressure and thrombus burden, while minimizing risk of ICH in patients with acute PE. Based partly on the findings of this study, ultrasound assisted, catheter-directed therapy was approved by the US Food and Drug Administration for treatment acute PE in May 2014 ("FDA Clears EKOS EkoSonic Endovascular System," n.d.)

The PERFECT Trial is a prospective, observational study to evaluate the safety and effectiveness of CDT including percutaneous mechanical thrombectomy as an alternative treatment of acute PE.[23] The study was initiated in 2010 and still ongoing, projected to be completed in 2020 with current data/results available via registry. The study included patients with contraindications of systemic thrombolysis, had an acute PE and presented within 14 days of diagnosis and underwent CDT to treat acute PE. One hundred one consecutive patients receiving CDT for acute PE were prospectively enrolled a multicenter, single-arm study in 6 sites of United States and one site in Europe. Of which, 28 patients had massive PE and 73 patients had submassive PE. These patients were immediately treated with pharmacomechanical or catheter-directed mechanical thrombectomy and/or CDT with small dose hourly drug infusion with tPA or urokinase. Meeting all the following criteria were defined as a clinical success rate: improvement of hemodynamics; right-sided heart strain or pulmonary hypertension improvement or both; and survival to hospital discharge. Major bleeding events and major complications from the procedure were the primary safety outcomes. Minor bleeding complications were the secondary outcomes. Beyond anticoagulation, CDT was the first-line therapy in 97% patients with acute pulmonary embolism. Among patients receiving with CDT infusion (100), 64% were managed with using standard infusion catheters, and 36% were managed with US-assisted thrombolysis; between these 2 arms no significance difference was noted. This study show 71 of 73 patients with submassive pulmonary embolism (97.3; 95% confidence interval, 90.5%-99.7%) and 24 of 28 patients with massive pulmonary embolism (85.7%; 95% confidence interval, 67.3%-96%) achieved clinical success. Furthermore, there is statistically significant improvement of mean pulmonary artery pressure and right-sided heart strain. There were no major bleeding events,

intracerebral hemorrhage/hemorrhagic strokes, or major procedure related complications noted in the registry for 30 days, although follow up may not have been as standardized as the follow up for the studies like ULTIMA and SEATTLE II studies. It was noted that 12 patients had minor bleedings and 6 patients died (4 with massive PE and 2 with submassive PE). The PERFECT trial illustrated that CDT improved clinical outcomes while minimizing the risk of major bleeding that is often associated with systemic thrombolysis. Additionally, CDT can be successfully used without the need of high-cost USAT catheters in patient with massive or submassive PE, while avoiding the use of Angiojet device to minimize procedure related complications. Although trial data for systemic thrombolysis supports that thrombolytic therapy may reduce long-term sequelae from PE, further studies examining the impact of low-dose CDT on long-term quality of life are needed. Based on this study, CDT can be utilized as a safe and effective alternative treatment for acute PE.[18]

The OPTALYSE PE trial is a multicenter, randomized control, parallel group study to determine the lowest optimum tPA dose and delivery duration using USCDT for the treatment of acute intermediate-risk pulmonary embolism as previous trials of USDCT used high tPA doses with longer duration (20-24 mg over 12-24 hours).[24] The investigators randomized 101 hemodynamically stable patients with submassive PE into prospective multicenter, parallel-group trial to varying alteplase doses and infusion times using USCDT. The patients were randomized into 4 different treatment groups (low to high) that varied by dosages (4-24 mg) and duration (2-6 hours) and received treatment via USCDT. The primary efficacy endpoint was reduction in RV to LV diameter ratio by computed tomographic angiography at 48 hours; and major secondary endpoint was embolic burden by refined Modified Miller Score, measured on computed tomographic angiography 48 hours after initiation of USCDT.[24] There were significant reductions in the RV/LV ratio at 48 hours post initiation of therapy in all treatment groups, with no significant variation in reduction regardless of dose/duration. Additionally, there was significant reduction in embolic burden in all 4 treatment groups with an inverse correlation of embolic burden reduction with increased dosages of tPA (from group 1 [lower dose] to group 4 [higher dose]). Predictably, the study confirmed higher risk of major bleeding events in the treatment group with high dose tPA (12-24 mg). No major bleeding event was noted in the lowest dose group. Group 2 (dose 4-8 mg, duration 4 hours) and group 3 (dose 6-12 mg, duration 6 hours) resulted in a singular major bleeding event, but it was noted only after receiving additional tPA due to hemodynamic instability. The limitations of this study are the lack of a control

group, limited number of patients in each treatment arm, primary outcome was not patient centered, and sponsors of trial were involved in study design. However, while reduction of RV/LV ratio at 48 hours cannot imply clinical improvement, this study does illustrate that low dose of tPA at shorter duration via USCDT is capable of reducing RV/LV ratio (indicative of improvement of RV function), thrombus burden, and minimizing major bleeding risk. Additionally, the OPTALYSE PE trial compared to the SEATTLE II trial showed lower bleeding rate of 3% vs the 10% noted in the SEATTLE II trial where tPA was administered at higher doses and longer duration (24 mg of tPA over 12 or 24 hours).

Conclusion

Anticoagulation still remains the first-line treatment of PE. High dose systemic thrombolysis is as effective as low dose but with higher major bleeding rates. More data to compare the long-term clinical and mortality outcomes of high-dose and low-dose thrombolytics is needed. CDT and low dose systemic thrombolysis both improve symptoms, RV/LV size, hemodynamics, pulmonary artery pressures, however, long-term clinical correlates are still lacking. Depending on local expertise, either catheter embolectomy/fragmentation or surgical embolectomy is reasonable for patients with massive acute PE and contraindications to fibrinolysis or those who remain unstable after receiving fibrinolysis.[11] It is still unknown whether addition of ultrasound to an infusion catheter adds any benefits to CDT alone, as there is no study that compared standard CDT to USCDT catheters in PE management. There is no data that defines the expected RV/LV ratio after 48 hours in patients with submassive pulmonary embolism that was treated anticoagulant alone. Until investigators conduct RCT that compares CDT with or without ultrasound versus non-CDT and assess both short- and long-term clinical outcomes, we cannot suggest CDT is superior to other treatment modalities.

Disclaimer

This research was supported (in whole or in part) by HCA and/or an HCA affiliated entity. The views expressed in this publication represent those of the authors and do not necessarily represent the official views of HCA or any of its affiliated entities.

REFERENCES

1. Agnelli G, Becattini C. Acute Pulmonary Embolism. *N Engl J Med* 2010;363:266–74. https://doi.org/10.1056/NEJMra0907731.

2. Goldhaber SZ, Visani L, De Rosa M. Acute pulmonary embolism: clinical outcomes in the International Cooperative Pulmonary Embolism Registry (ICOPER). *Lancet* 1999;353:1386–9. https://doi.org/10.1016/S0140-6736(98)07534-5.
3. Stefano G, Iacopo O, Paolo C, et al. Short-Term clinical outcome of patients with acute pulmonary embolism, normal blood pressure, and echocardiographic right ventricular dysfunction. *Circulation* 2000;101:2817–22. https://doi.org/10.1161/01.CIR.101.24.2817.
4. Horlander KT, Mannino DM, Leeper KV. Pulmonary embolism mortality in the United States, 1979-1998: an analysis using multiple-cause mortality data. *Arch Intern Med* 2003;163:1711–7. https://doi.org/10.1001/archinte.163.14.1711.
5. Coon WW, Willis PW. Deep venous thrombosis and pulmonary embolism: prediction, prevention and treatment. *Am J Cardiol* 1959;4:611–21. https://doi.org/10.1016/0002-9149(59)90145-6.
6. Soloff LA, Rodman T. Acute pulmonary embolism: II. Clinical. *Am Heart J* 1967;74:829–47. https://doi.org/10.1016/0002-8703(67)90102-0.
7. Jaff Michael R, McMurtry MSean, Archer Stephen L, et al. Management of massive and submassive pulmonary embolism, iliofemoral deep vein thrombosis, and chronic thromboembolic pulmonary hypertension. *Circulation* 2011;123:1788–830. https://doi.org/10.1161/CIR.0b013e318214914f.
8. Anderson Frederick A, Spencer Frederick A. Risk Factors for Venous Thromboembolism. *Circulation* 2003;107(23_suppl_1). https://doi.org/10.1161/01.CIR.0000078469.07362.E6. I–9.
9. Dalen JE. Pulmonary embolism: what have we learned since virchow?: natural history, pathophysiology, and diagnosis. *CHEST* 2002;122:1440–56. https://doi.org/10.1378/chest.122.4.1440.
10. White Richard H. The epidemiology of venous thromboembolism. *Circulation* 2003;107(23_suppl_1). https://doi.org/10.1161/01.CIR.0000078468.11849.66. I–4.
11. Torbicki A, Perrier A, Konstantinides S. 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). *Eur Heart J* 2008;29:2276–315. https://doi.org/10.1093/eurheartj/ehn310.
12. Kearon C, Kahn SR, Agnelli G, Goldhaber S, Raskob GE, Comerota AJ. Antithrombotic therapy for venous thromboembolic disease: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *CHEST* 2008;133:454S–545S. https://doi.org/10.1378/chest.08-0658.
13. Warkentin TE, Greinacher A, Koster A, Lincoff AM. Treatment and prevention of heparin-induced thrombocytopenia: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *CHEST* 2008;133:340S–80S. https://doi.org/10.1378/chest.08-0677.
14. Kline JA, Hernandez-Nino J, Newgard CD, Cowles DN, Jackson RE, Courtney DM. Use of pulse oximetry to predict in-hospital complications in normotensive patients with pulmonary embolism. *Am J Med* 2003;115:203–8. https://doi.org/10.1016/S0002-9343(03)00328-0.

15. Otero R, Trujillo-Santos J, Cayuela A, et al. Haemodynamically unstable pulmonary embolism in the RIETE Registry: Systolic blood pressure or shock index? *Eur Respir J* 2007;30:1111–6. https://doi.org/10.1183/09031936.00071007.
16. Meyer G, Vicaut E, Danays T, et al. Fibrinolysis for patients with intermediate-risk pulmonary embolism. *N Engl J Med* 2014;370:1402–11. https://doi.org/10.1056/NEJMoa1302097.
17. 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;311:2414–21. https://doi.org/10.1001/jama.2014.5990.
18. 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;12:459–68. https://doi.org/10.1111/jth.12521.
19. Marti C, John G, Konstantinides S, et al. Systemic thrombolytic therapy for acute pulmonary embolism: a systematic review and meta-analysis. *Eur Heart J* 2015;36:605–14. https://doi.org/10.1093/eurheartj/ehu218.
20. Daley MJ, Murthy MS, Peterson EJ. Bleeding risk with systemic thrombolytic therapy for pulmonary embolism: scope of the problem. *Ther Adv Drug Safety* 2015;6:57–66. https://doi.org/10.1177/2042098615572333.
21. Nils K, Peter B, Müller Oliver J, et al. Randomized, controlled trial of ultrasound-assisted catheter-directed thrombolysis for acute intermediate-risk pulmonary embolism. *Circulation* 2014;129:479–86. https://doi.org/10.1161/CIRCULATIONAHA.113.005544.
22. Piazza G, Hohlfelder B, Jaff MR, Ouriel K, Engelhardt TC, Sterling KM, . . ., Goldhaber SZ. A prospective, single-arm, multicenter trial of ultrasound-facilitated, catheter-directed, low-dose fibrinolysis for acute massive and submassive pulmonary embolism: the SEATTLE II study. *JACC Cardiovasc Interv* 2015;8:1382–92. https://doi.org/10.1016/j.jcin.2015.04.020.
23. 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;148:667–73. https://doi.org/10.1378/chest.15-0119.
24. 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;11:1401–10. https://doi.org/10.1016/j.jcin.2018.04.008.