

Submassive Pulmonary Embolism: Opportunity Emerging From a Challenging Disease

A presentation of key questions and a discussion of potential next steps in clinical trial development.

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The last few years have seen a surge in interest in submassive pulmonary embolism (PE), fueled by publication of a large randomized trial, several meta-analyses, and prospective studies of catheter-directed thrombolysis (CDT).¹⁻⁷ There is no other PE category that carries the clinical equipoise than that of submassive PE. Nearly every aspect of submassive PE lends itself to controversy, including its definition, gravity, treatment, and contribution to long-term morbidity. Therefore, it is not surprising that societal guidelines do not offer strong recommendations outside of anticoagulation for the treatment of submassive PE.^{8,9}

This article presents the key questions surrounding submassive PE and discusses what the next submassive PE trial might look like.

What is the best definition of a submassive PE, and are all submassive PEs the same?

Submassive PE is defined in the American Heart Association guidelines as right ventricular (RV) dysfunction without hypotension. RV dysfunction can be identified with dynamic (echocardiography) or static (computed tomography [CT]) imaging, biomarkers of RV strain and/or ischemia (brain natriuretic peptide [BNP] or troponin), and/or certain changes seen on

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electrocardiography.⁸ However, within this definition there is a range of clinical presentations. Although some patients look uncomfortable, acutely dyspneic, and on the verge of hemodynamic instability, others appear comfortable, maintain normal oxygen saturation on room air, and do not have an elevated respiratory rate. However, data generated thus far are not granular enough to determine which patients with submassive PE are at higher risk for short-term, poor outcomes.

The European Society of Cardiology (ESC) guidelines divide submassive (intermediate) PE into high risk and low risk, and they suggest treatment escalation for patients in the high-risk category and conservative management for patients in the low-risk category.¹⁰ High risk is defined as a simplified Pulmonary Embolism Severity Index (PESI) score ≥ 1 , evidence of RV dysfunction as seen on CT or echocardiography, and an

elevated RV biomarker (ie, troponin, BNP). Low risk is defined as a simplified PESI score ≥ 1 and either (1) no evidence of RV dysfunction or (2) RV dysfunction on imaging without an elevated biomarker or (3) an elevated biomarker without RV dysfunction. The justification given for this scheme is the results of the recently completed PEITHO trial,⁵ the largest randomized trial of systemic thrombolysis versus anticoagulation alone for treatment of submassive PE, which enrolled only high-risk patients with intermediate (submassive) PE. There was a 5.6% rate of death or clinical deterioration in patients treated with anticoagulation alone, a sufficiently high incidence for the ESC authors to define intermediate high-risk PE by the PEITHO inclusion criteria.

How common is submassive PE, and what is the mortality rate?

Approximately 300,000 to 600,000 PEs are diagnosed in the United States per year. It is difficult to accurately estimate the overall mortality rate, because many patients have comorbid conditions or die before presenting to the hospital. However, the range between 60,000 and 150,000 deaths per year.

Some studies note that RV dysfunction or strain is present in up to 50% of patients presenting with acute PE,¹¹ but the likely range is between 25% and 35%. Even this number indicates that a significant number of patients have RV dysfunction on presentation. Registry data from the late 1990s imply a high mortality rate from submassive PE, ranging from 10% to 15%.^{12,13} Each marker of RV dysfunction is associated with an elevated 30-day mortality risk, ranging from two- to eightfold depending on the study and the marker examined.¹⁴⁻¹⁶

In contrast, the combined mortality rate in the anticoagulation arms of the two largest randomized trials of submassive PE is 3% (19 deaths in 637 patients).^{5,17} It is hypothesized that patients in these trials were monitored more closely for signs of clinical deterioration than those in the registry and were thus more rapidly resuscitated.

Is clinical deterioration an important endpoint?

Clinical deterioration, defined in essence by the PEITHO trial as transitioning from submassive to massive PE, has been used as part of a composite primary endpoint along with mortality in several randomized trials of systemic lytics. Although mortality was not significantly different between the patients treated with systemic thrombolysis and those treated with anticoagulation alone, the composite endpoint of death and clinical deterioration was met significantly more often

in the anticoagulation-only arms. The implication is that early thrombolysis reduces the incidence of clinical deterioration later in the hospital course. Systemic meta-analyses have confirmed that systemic thrombolysis reduces the rate of clinical deterioration.⁶

Some clinicians argue that a slight but significant increase in clinical deterioration (5% vs 1.6% for anticoagulation and thrombolysis, respectively)⁵ is not a compelling enough reason to treat with systemic thrombolysis given the major bleeding risk (6% extracranial and 2% intracranial in PEITHO). These practitioners argue that the benefits outweigh the risks only if the patient deteriorates. Others argue that the risk of bleeding in patients without risk factors is low and that clinical deterioration is volatile and precarious to manage and therefore worth avoiding.

What is the best option when treatment escalation beyond anticoagulation is being considered?

Most data have been collected for systemic thrombolysis, which has been studied for over 3 decades. The past year has seen three meta-analyses published as well as the PEITHO trial, which was the largest randomized trial evaluating systemic lytics conducted thus far. Although PEITHO found no mortality benefit with the use of systemically administered tenecteplase for submassive PE, a meta-analysis by Chatterjee et al found a small but statistically significant reduction in mortality in patients with submassive PE who were treated with systemic thrombolysis (any drug).¹ It is also clear that major and intracranial bleeding are significantly increased in patients who receive systemic thrombolysis. It appears that this risk is particularly high for elderly patients.

Surgical embolectomy used to be reserved for patients with massive PE who failed systemic thrombolysis and were progressing to or in cardiogenic shock. Mortality rates were therefore extremely high, and the procedure fell out of favor. However, in the past decade, it has been revived in specialty centers due to improved patient selection. The largest series of 46 patients, which included a significant number of patients with submassive PE, showed a high survival rate (94%) at 30 days.¹⁸

CDT delivers thrombolytic drug directly into the clot, thus achieving effective thrombolysis with an overall lower dose. Three prospective studies analyzed the short-term safety and efficacy of CDT in the setting of submassive PE and confirmed that CDT effectively lyses thrombi and rapidly restores RV function.^{2,3,7} The ULTIMA trial randomized 59 patients to either ultrasound-assisted CDT with heparin or heparin alone. CDT

more effectively normalized the RV/left ventricular (LV) ratio at 24 hours postrandomization than heparin alone. No major bleeding was observed in either arm.² SEATTLE II enrolled 150 patients with either submassive or massive PE into a single-arm, ultrasound-assisted CDT study. At 48 hours, there was a significant reduction in the RV/LV ratio and pulmonary arterial pressure. Moderate bleeding was recorded in 16 patients, and severe bleeding was recorded in one patient; all of these bleeds required blood transfusion.⁷ The PERFECT prospective global registry enrolled > 100 patients with massive and submassive PE and showed a > 80% “clinical success” rate with no major bleeds and a significant reduction in pulmonary arterial pressure.³ No patients had intracranial bleeding in any of these studies. Absent from all three studies were rigorous analyses of long-term clinical outcomes. Overall, they demonstrated the short-term efficacy rather than the long-term effectiveness of CDT.

Thus, it is difficult to identify the best treatment beyond anticoagulation for submassive PE. Certainly, the most data have been generated for systemic thrombolysis, and meta-analyses show a slight mortality benefit. It is by far the most convenient and rapid method—and for the patient who is progressing toward massive physiology without immediate access to the operating room or endovascular suite, it may be the best option, especially if the bleeding risk is low. However, the risk of bleeding is real, especially in elderly patients. CDT may be theoretically safer, but the studies thus far are not sufficiently powered to definitively make this conclusion. Although embolectomy is a powerful and important tool when used in appropriate patients, there is still considerable morbidity, and a limited number of centers are willing to perform surgery for submassive PE. Multidisciplinary teams (sometimes referred to as PE response teams, or PERTs) have emerged in some centers to determine the most appropriate therapy for a given patient through consensus and algorithms.¹⁹

Should inferior vena cava (IVC) filters be placed in patients with submassive PE?

The clinical equipoise extends to the use of IVC filters in submassive PE. On the one hand, RV dysfunction implies that further increases in pulmonary vascular resistance due to continued thromboembolism would be highly detrimental, especially in patients with poor cardiopulmonary reserve. However, data from randomized trials appear to refute the idea that IVC filters should be routinely placed for patients with submassive PE. The recently published PREPIC2 study,²⁰ which randomized 399 patients with symptomatic PE and “high-risk” features to receive either

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anticoagulation plus an IVC filter or anticoagulation alone, showed no reduction in mortality or recurrent PE in the adjunctive filter arm compared with the anticoagulation-only arm; 66% of patients in each group had submassive PEs. The PEITHO trial had a very low rate of IVC filter placement in either arm, and yet the rates of recurrent venous thromboembolism were low during the study period (30 days). Therefore, immediate anticoagulation alone appears to be very effective in preventing recurrent PE. The well-documented, long-term risks of ongoing IVC filtration must be considered as well.

Should we be paying attention to long-term outcomes in patients with submassive PE?

This question is probably the most intriguing aspect of PE care. The medical community has considered PE to be an acute disease, so guiding a patient through the precarious first days and weeks has been the primary therapeutic focus. However, data have emerged in the past 10 years suggesting that quality of life and exercise tolerance may be negatively affected in patients who had a prior PE. Some clinicians have called this phenomenon the “post-PE syndrome,”²¹ analogous to the postthrombotic syndrome (PTS) following deep vein thrombosis. Like PTS, post-PE syndrome has a spectrum of clinical manifestations, with the most severe being chronic thromboembolic pulmonary hypertension (4% incidence).²² The incidence of the post-PE syndrome, which is assessed via echocardiography, quality-of-life questionnaires, and/or exercise tests, may be > 20%, although additional studies will be useful in characterizing the severity of these cases.²³⁻²⁷

The potential for acute submassive PE to reduce quality of life and exercise tolerance in the long term cannot be ignored. Patients should be periodically followed and assessed for the development of dyspnea on exertion, with a low threshold for ordering diagnostic studies such as echocardiography, ventilation/perfusion scintigraphy, or exercise testing, and referral to the appropriate specialist.

What features of a clinical trial will address the equipoise surrounding submassive PE?

Randomized controlled trials (RCTs) are the gold standard for proving the benefit of one strategy over another. The main drawback of RCTs is generalizability, given difficulties with enrollment and restrictive inclusion and exclusion criteria. Accordingly, many observational studies of PE have been conducted that have made significant contributions to the literature. However, it should be acknowledged that consensus will not be achieved unless data from RCTs clarify how submassive PE should be treated.

Should one trial try to include surgery, systemic lysis, and CDT? Practically speaking, powering such a study would be exceedingly difficult. A significant amount of data has been gathered on systemic thrombolysis, although there may still be some data gaps regarding reduced lytic dosing. Surgical embolectomy for submassive PE is not prevalent enough to allow for a multicenter trial at present. CDT, on the other hand, is gaining significant traction across the United States, and the time is ripening for a rigorous RCT examining the safety and effectiveness of CDT for submassive PE.

Several groups have proven that an RCT investigating systemic thrombolysis for submassive PE is feasible given the ease of administration. Enrollment of patients into a trial evaluating surgical or interventional versus medical therapy would be much more challenging. This fact must be taken into account given that > 1,700 patients had to be analyzed to show a slight mortality benefit in the meta-analysis by Chatterjee et al. Enrolling that many patients into an RCT evaluating CDT plus anticoagulation versus anticoagulation alone would be impractical.

A composite endpoint of death or clinical deterioration, as used in PEITHO, could be used as the primary outcome, but again, it would be exceedingly challenging to enroll the number of patients required to show a meaningful clinical difference in a trial evaluating interventional versus medical therapy.

So what is the ideal endpoint? Long-term outcomes that are important to patients should be considered. The primary endpoint could be quality of life or exercise tolerance, with secondary endpoints assessing short-term morbidity, safety, and recurrent venous thromboembolism.

SUMMARY

This is an exciting time for providers who manage submassive PE, and there are many opportunities to clarify how these patients should be triaged, treated, and followed. If these opportunities are seized, there

may be a real change in the tenor and language of societal guidelines in the next decade. ■

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