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## Accelerated Thrombolysis for Pulmonary Embolism Will Clinical Benefit Be ULTIMately Realized?

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Over the past 25 years, thrombolytic therapy has consistently demonstrated improvement in hemodynamic parameters in patients with pulmonary embolism (PE).<sup>1</sup> Clinically, although it results in reduced mortality in patients with massive PE,<sup>2</sup> thrombolytic therapy is not beneficial in unselected patients with PE.<sup>3</sup> Major societal guidelines support systemic thrombolysis for massive PE and recommend catheter-based interventions for rescue therapy in centers with appropriate expertise.<sup>4-6</sup> For patients with submassive PE, selected guidelines suggest considering systemic thrombolysis in a limited population of patients with PE,<sup>4,5</sup> whereas others recommend against its use in these patients.<sup>6</sup> Recently, several studies have addressed thrombolytic therapy in patients with submassive PE. The Pulmonary Embolism International Thrombolysis (PEITHO) trial reported a substantial reduction in the combined endpoint of early mortality or hemodynamic collapse in patients receiving systemic thrombolysis (compared with heparin alone) at the expense of a significant increase in major hemorrhage (including intracranial hemorrhage). This was particularly evident among elderly patients aged >75 years.<sup>7</sup> In the much smaller Tenecteplase or Placebo: Cardiopulmonary Outcomes At Three Months (TOPCOAT) study, which was terminated prematurely, the composite primary outcome (5-day survival to hospital discharge without shock, intubation, or major hemorrhage; 90-day rate of normal right ventricular function, 6-minute walk distance >330 m, no dyspnea at rest, and no recurrent PE or deep vein thrombosis) was positive in the patients randomized to thrombolysis compared with the low-molecular-weight heparin patients.<sup>8</sup> Another small study comparing thrombolytic therapy with heparin alone demonstrated a decrease in the composite endpoint of death, recurrent venous thromboembolism, right ventricular dysfunction, and major hemorrhage at 6 months in the group randomized to thrombolytic therapy.<sup>9</sup> In the Moderate Pulmonary Embolism Treated with Thrombolysis (MOPETT) trial, half-dose systemic thrombolytic therapy resulted in long-term reduction in the incidence of pulmonary hypertension compared with anticoagulation alone without excess bleeding.<sup>10</sup>

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In this issue of *Circulation*, Kucher et al<sup>11</sup> compared the use of heparin and ultrasound accelerated thrombolysis (USAT) using the EkoSonic (EKOS, Bothell, WA) catheter with heparin alone in patients presenting with submassive PE. The primary outcome was change in the ratio of right ventricle/left ventricle size 24 hours after treatment, whereas the primary safety outcome was a composite of death, major and minor bleeding, recurrent venous thromboembolism, and serious adverse events at 90 days. The authors report a significant reduction in the primary outcome in the USAT group compared with the heparin group. This was coupled with a significant reduction in surrogates of pulmonary artery hypertension. At 90 days, the majority of patients in both groups had no or mild right ventricular dysfunction, representing an improvement from baseline, and although there was a difference between groups favoring USAT (overall 100% versus 93% in the USAT and heparin groups, respectively,  $P=0.003$ ), important clinical correlates (such as exertional dyspnea) were not reported. The authors also acknowledge a late “catch-up” by the heparin group that may result in less difference after additional follow-up. It is for this reason that some guidelines suggest following patients with PE for 6 months before reassessing measures of right ventricular function and pulmonary arterial pressure.<sup>12</sup>

Catheter-directed thrombolysis has the potential to offer benefits of systemic thrombolysis while minimizing bleeding risk attributable to a lower dose of the thrombolytic agent. More information about the safety of USAT may come from the EkoSonic Endovascular System (EKOS Corporation, Bothell, WA) and Activase for Treatment of Acute Pulmonary Embolism II (SEATTLE II) study, a single-arm prospective trial examining the safety of USAT in 150 patients with massive and submassive PE, which has completed enrollment but has not yet reported results.<sup>13</sup> Further complicating clinical decision making is the lack of reliable and well-validated bleeding-risk assessment tools in patients with PE. It is often that bleeding risk is inferred from scoring systems developed for other indications.<sup>14</sup>

Results from the Ultrasound Accelerated Thrombolysis of Pulmonary Embolism (ULTIMA) trial must be considered with the understanding that most patients with PE treated with anticoagulation alone will achieve embolus resolution at 4 weeks.<sup>15</sup> Although clot resolution can be accelerated with the use of thrombolytic therapy, the volume of residual thrombosis does not seem to differ between patients treated with thrombolytic therapy or anticoagulation. Mortality after submassive PE is uncommon. The number of patients with massive PE to receive thrombolytic therapy to demonstrate a mortality benefit has been estimated to be as low as 10.<sup>3</sup> To demonstrate a mortality benefit in patients with submassive PE would require a much larger sample size, suggesting that an appropriately powered prospective study may never be completed. Furthermore, the feared consequence of resultant chronic thromboembolic pulmonary hypertension<sup>16,17</sup> occurs in

only 0.1% to 3.8% of patients with PE,<sup>16,18</sup> and mechanisms to identify this subset of patients a priori are not available. It is unfortunate that clinical outcomes were not reported in the ULTIMA trial, but mean hospital length of stay was >8 days in both groups, suggesting limited clinically apparent benefit in the short term.

Realistically, thrombolytic therapy is not considered an option for many patients. Estimated bleeding risk is the main concern before administering thrombolytic therapy, especially in older patients and those with active malignancy. These are the exact populations that have the greatest potential to benefit from thrombolytic therapy. In the ULTIMA trial, many patients with submassive PE failed randomization (84%) for a multitude of reasons, most commonly increased bleeding risk, prolonged symptom duration, advanced age, and inadequate PE distribution on imaging. The authors also cite a potential selection bias, acknowledging that not all eligible patients were subject to randomization. This suggests limited applicability in a real-world setting.

Although USAT is appealing, there are other catheter-based PE treatments, including thrombus fragmentation, suction thrombectomy, and rotational thrombectomy.<sup>19</sup> As noted by the authors, direct comparison with varying techniques was not available in the current study. In the interim, as more information about various treatment options is being gathered, registry data may be useful. Applicable information may soon become available by PE response teams, which are becoming more commonplace in major clinical centers.<sup>20</sup>

The ULTIMA trial is extremely valuable in that it represents the first randomized trial to test a standardized, commonly used catheter-based intervention in patients with acute PE. For supporters of thrombolytic therapy in submassive PE, the ULTIMA trial proves that interventional treatments for submassive PE offer objective improvement in important hemodynamic parameters with very low risk of major and mortal hemorrhage. Until meaningful clinical outcomes are reported for patients receiving advanced therapy in randomized clinical trials against standard anticoagulation, clinicians may pursue interventional thrombolytic therapies for patients with high-risk PE but avoid them in low-risk patients. Patients felt to be at intermediate risk must be individually stratified by multispecialty “teams” while understanding the current literature gap.

## Disclosures

Dr Jaff is a noncompensated member of the Data Safety and Monitoring Board, EKOS Corporation and a board member of VIVA Physicians, a 501(c)3 nonprofit education and research organization. Dr Weinberg reports no conflicts.

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