Thrombolytic Therapy for Pulmonary Embolism

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**Pulmonary embolism** (PE) accounts for nearly 200,000 hospital discharges and contributes to nearly 30,000 deaths in the United States each year. Treatment of PE requires balancing the benefits of anticoagulation with the risk of bleeding. Determining the value of a therapy, incorporating both therapeutic and adverse effects, requires understanding net clinical benefit, the weighing of net benefit (or harm) for a specific therapy. Currently, anticoagulation is standard therapy for patients with PE because the risk of fatal bleeding is low compared with the benefit of reduced mortality and recurrent PE. In contrast, more than 40 years after the first trial of thrombolysis was published, the role of thrombolytic therapy in PE remains unclear, because no single clinical trial has provided a definitive answer about its benefit. Furthermore, because of the increased risk of major bleeding, there is uncertainty about which patients may benefit from thrombolysis.

Currently, the classification of patients into risk groups guides clinical decisions about whether to use thrombolysis. Patients presenting with right ventricular failure and hemodynamic compromise are classified as having a “massive” PE in North America and a high-risk PE in Europe. High-risk PE represents a minority of all patients presenting with PE but is associated with an in-hospital mortality of 15% or more, with death occurring commonly within the first 24 hours. For these patients, both European and North American guidelines recommend thrombolytic therapy despite limited available evidence.

For patients with stable blood pressure, further risk stratification is necessary because significant heterogeneity in outcomes is observed, resulting in distinct optimal treatment strategies based on the presence vs absence of right ventricular dysfunction. For example, low-risk patients with stable blood pressure and normal right ventricular function may be treated in the outpatient setting. In contrast, patients with stable blood pressure and right ventricular dysfunction have substantially higher mortality than low-risk patients and are classified as “intermediate risk.” The value of thrombolytic therapy in patients with intermediate-risk PE, in particular, has been unclear.

Intermediate risk is defined by the presence of subclinical cardiovascular compromise in the setting of PE. Patients with intermediate-risk PE have an increased risk of mortality or recurrent PE, compared with patients with low-risk PE, and are considered likely to benefit from thrombolytic therapy. However, when RV dysfunction was used as a criterion for entry into clinical trials of PE and thrombolytic therapy, mortality rates were low, raising questions about the value of thrombolytic therapy in this population. Recent studies examining biomarkers of elevated right heart pressures and myocardial injury, including brain natriuretic peptide (BNP) and cardiac troponins, have demonstrated that elevated blood levels of BNP or troponin occur in approximately half of all patients with PE. However, meta-analyses conclude that neither biomarker is associated with higher rates of adverse events in patients with intermediate risk. Currently, studies are under way to determine whether predicting adverse outcomes may be improved with combinations of clinical assessment, imaging parameters, and laboratory analysis. In a recent trial of thrombolysis in PE that required both right ventricular dysfunction and an elevated troponin level to define intermediate risk, this combination of adverse characteristics was still associated with low rates of short-term mortality, less than 2% in both study groups, without significant difference in outcomes between treatment groups.

In this issue of *JAMA*, Chatterjee et al report the results of a meta-analysis of thrombolysis for PE. The authors evaluated 16 trials performed over the last 45 years comprising 2115 patients and performed subset analyses in the 1775 patients with intermediate risk. The authors report several important findings. First, overall, thrombolysis was associated with lower mortality risk compared with standard anticoagulation (3.89% vs 2.17%, relative reduction of 47%). However, thrombolysis was associated with higher rates of major bleeding (9.24% vs 3.42%) and intracranial hemorrhage (1.46% vs 0.19%) compared with anticoagulation. Second, in a subset of 1331 patients older than 65 years, thrombolysis was associated with a higher rate of major bleeding (12.93% vs 4.10%). This association was not observed in patients 65 years or younger. Third, in 8 recent trials in intermediate-risk patients, thrombolytic therapy was associated with a mortality reduction (1.39% vs 2.92%, relative reduction of 52%) and an increase in major bleeding compared with standard anticoagulation (7.74% vs 2.25%). The authors calculated the net clinical benefit of lives saved compared with intracranial hemorrhagic events (weighted at 0.75 events per death event) and reported a net clinical benefit in intermediate-risk patients of 0.62%.

For the clinician, do these results require change in the standard of care, particularly for patients with intermediate-risk PE? The calculated net clinical benefit provides important information to help in this assessment. For perspective, the net clinical benefit of warfarin anticoagulation for patients with atrial fibrillation is a significant annual 0.97% absolute reduction of stroke, systemic embolism, and intracranial hemorrhage (weighted at 1.5 events per embolic event) for patients with a CHADS2 score of 2. Thus, the net clinical benefit of thrombolysis suggests evidence of modest efficacy for...
thrombolysis in intermediate-risk PE, rendering the need for decision making on a patient-by-patient basis.

The meta-analysis provides direction for additional research. The accrual of 2000 patients over 45 years for a problem associated with 200,000 hospitalizations and 30,000 deaths per year suggests need for a large definitive trial, perhaps stratifying patients by age, using lower doses of thrombolytic agents, or applying a catheter-based strategy to reduce the potentially lethal bleeding risk. In the meantime, thrombolytic therapy should be individualized based on clinical presentation, comorbid conditions, and patient and physician risk tolerance.

The relevance of the meta-analysis including trials conducted over many years must be considered in the context of PE therapy in 2014. In the largest study, the Pulmonary Embolism Thrombolysis (PEITHO) trial, published this year, the mortality rate was 1.2% in the thrombolytic group and 1.8% in the control group, whereas the hemorrhagic stroke rate was 2% in the thrombolytic group and 0.2% in the control group. Only 3.4% of patients (17/500) in the anticoagulation group had clinical worsening with anticoagulation alone that required thrombolysis. This suggests that a management strategy of anticoagulation with thrombolysis reserved for patients who do not respond to standard therapy may be acceptable, particularly for older patients with intermediate risk. The rate of patients requiring thrombolysis after standard therapy fails in this trial was significantly reduced from 24.6% of patients in a trial performed by the same principal investigator a decade earlier and suggests outcomes are improving significantly over time.

The meta-analysis by Chatterjee et al raises new questions. For example, should thrombolytic therapy in intermediate-risk patients older than 65 years be avoided? While the risk of bleeding is increased in older patients, the point estimate for mortality is similar to that in younger patients. Risk stratification for bleeding may favor use of thrombolysis in patients older than 65 years. Second, would the net clinical benefit be better with consistent use of catheter-based thrombolysis using lower doses of fibrinolytic agents for significant pulmonary artery thrombus reduction? Additional clinical trials are needed to guide optimal use of thrombolytic therapy in patients with PE.

ARTICLE INFORMATION
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