Accelerated Thrombolysis for Pulmonary Embolism:
Will Clinical Benefit Be ULTIMAtely Realized?

Running title: Weinberg et al.; Accelerated Thrombolysis for Pulmonary Embolism

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Over the past 25 years, thrombolytic therapy has consistently demonstrated improvement in
hemodynamic parameters in patients with pulmonary embolism (PE)\(^1\). Clinically, while
resulting in reduced mortality in patients with massive PE\(^2\) thrombolytic therapy is not beneficial
in unselected PE patients\(^3\). Major societal guidelines support *systemic* thrombolysis for massive
PE, and recommend catheter-based interventions for rescue therapy in centers with appropriate
expertise\(^4\textit{-}^6\). For patients with submassive PE, selected guidelines suggest considering systemic
thrombolysis in a limited population of PE patients\(^4\textit{-}^5\), while others recommend against its use in
these patients\(^6\). 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 (as compared to heparin alone) at the expense of a
significant increase in major hemorrhage (including intracranial hemorrhage). This was
particularly evident among elderly patients over the age of 75\(^7\). In the much smaller TOPCOAT
study (Tenecteplase or Placebo: Cardiopulmonary Outcomes At Three Months), 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 (RV)
function, 6 minute walk distance>330 meters, no dyspnea at rest, and no recurrent PE or deep
vein thrombosis) was positive in the patients randomized to thrombolysis as compared to the low
molecular weight heparin patients\(^8\). Another small study comparing thrombolytic therapy to
heparin alone demonstrated a decrease in the composite endpoint of death, recurrent venous
thromboembolism, RV dysfunction and major hemorrhage at 6 months in the group randomized
to thrombolytic therapy\(^9\). In the MOPPETT trial, half-dose systemic thrombolytic therapy
resulted in long-term reduction in the incidence of pulmonary hypertension compared to
anticoagulation alone without excess bleeding\textsuperscript{10}.

In this issue of \textit{Circulation}, Kucher and colleagues compared the use of heparin and ultrasound accelerated thrombolysis (USAT) utilizing the EkoSonic (EKOS Corporation, Bothell, WA, USA) catheter to heparin alone in patients presenting with submassive PE\textsuperscript{11}. The primary outcome was change in the ratio of right ventricle to left ventricle size 24 hours following treatment, while 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 to 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 RV dysfunction, representing an improvement from baseline, and while there was a difference between groups favoring USAT (overall 100\% vs. 93\% in the USAT and heparin groups, respectively, \textit{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, which may result in less difference after further follow-up. It is for this reason that some guidelines suggest following PE patients for 6 months before re-assessing measures of RV function and pulmonary arterial pressure\textsuperscript{12}.

Catheter directed thrombolysis has the potential to offer benefits of systemic thrombolysis while minimizing bleeding risk due to a lower dose of the thrombolytic agent. More information about the safety of USAT may come from the 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\textsuperscript{13}. 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.\textsuperscript{14}

Results from the ULTIMA trial must be considered with the understanding that most PE patients treated with anticoagulation alone will achieve embolus resolution at 4 weeks.\textsuperscript{15} While 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 following submassive PE is uncommon. The number of patients with massive PE to receive thrombolytic therapy in order to demonstrate a mortality benefit has been estimated to be as low as 10\textsuperscript{3}. 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\textsuperscript{16,17} occurs in only 0.1\% to 3.8\% of patients with PE\textsuperscript{16,18} and mechanisms to identify this subset of patients \textit{a priori} are not available. It is unfortunate that clinical outcomes were not reported in ULTIMA, but mean hospital length of stay was more than 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 prior to 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 ULTIMA 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.

While USAT is appealing, there are other catheter-based PE treatments including thrombus fragmentation, suction thrombectomy and rotational thrombectomy. As noted by the authors, direct comparison to 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 pulmonary embolism response teams (PERT) which are becoming more commonplace in major clinical centers.

ULTIMA 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, ULTIMA 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 while avoiding 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.

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