O

ver the past 25 years, thrombolytic therapy has consistently
demonstrated improvement in hemodynamic parameters in
patients with pulmonary embolism (PE). Clinically, although
it results in reduced mortality in patients with massive PE,
thrombolytic therapy is not beneficial in unselected patients
with PE. Major societal guidelines support systemic thromboly-

cosis for massive PE and recommend catheter-based interven-
tions for rescue therapy in centers with appropriate expertise.

For patients with submassive PE, selected guidelines suggest
considering systemic thrombolysis in a limited population of
patients with PE, whereas others recommend against its use
in these patients. 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 receiv-
ing systemic thrombolysis (compared with heparin alone) at the
expense of a significant increase in major hemorrhage (includ-
ing intracranial hemorrhage). This was particularly evident
among elderly patients aged >75 years. 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 dis-
charge without shock, intubation, or major hemorrhage; 90-day
rate of normal right ventricular function, 6-minute walk dis-
tance >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. 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 in 6 months in
the group randomized to thrombolytic therapy. In the Moderate
Pulmonary Embolism Treated with Thrombolysis (MOPPETT)
trial, half-dose systemic thrombolytic therapy resulted in long-
term reduction in the incidence of pulmonary hypertension com-
pared with anticoagulation alone without excess bleeding.

In this issue of Circulation, Kucher et al 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 differ-
ence 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 ven-
tricular function and pulmonary arterial pressure.

Catheter-directed thrombolysis has the potential to offer
benefits of systemic thrombolysis while minimizing bleed-


ing 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. 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.

Results from the Ultrasound Accelerated Thrombolysis
of Pulmonary Embolism (ULTIMA) trial must be considered with
the understanding that most patients with PE treated with anti-
coagulation alone will achieve embolus resolution at 4 weeks.
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 ther-


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only 0.1% to 3.8% of patients with PE, 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. 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.

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.

References


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