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EDITORIAL COMMENT

The OPTALYSE PE Trial

Another Step Toward Understanding the Truth About Catheter-Directed Thrombolysis for Submassive Pulmonary Embolism*

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"…Everyone says something true about the nature of things, and while individually they contribute little to … the truth, by the union of all a considerable amount is amassed."
—Aristotle, Metaphysics (1)

In this issue of *JACC: Cardiovascular Interventions*, Tapson et al. (2) report the results of the OPTALYSE PE (Optimum Dose and Duration of Acoustic Pulse Thrombolysis Procedure in Acute Intermediate-Risk Pulmonary Embolism) trial, which randomized 101 submassive PE patients to varying alteplase doses and infusion times using ultrasound-assisted catheter-directed thrombolysis (USCDT). Doses ranged in 4 groups from 4 to 24 mg, with infusion times between 2 and 6 h. There were reductions in the right ventricular/left ventricular (RV/LV) ratio at 48 h post-entry in all groups, a 4% major bleeding rate, and 2 intracranial hemorrhages, 1 of which was attributed to USCDT (resulting in death). The USCDT-attributed intracranial hemorrhage occurred in the highest-dose cohort, which was closed after the incident. Higher doses of alteplase were associated with lower thrombus burden at 48 h.

SEE PAGE 1401

The investigators should be commended for their effort to refine the "truth" about USCDT: they asked, "Is a 24-mg dose of alteplase necessary?" The OPTALYSE PE trial's predecessor, the SEATTLE II trial (A Prospective, Single-Arm, Multicenter Trial of EkoSonic Endovascular System and Activase for Treatment of Acute Pulmonary Embolism), required at least a 12-h infusion and 24-mg alteplase; the 10% major bleeding rate alarmed many who considered catheter-directed thrombolysis (CDT) to be safer than systemic thrombolysis (3). Thus, Tapson et al. (2) conducted a phase 1-type study to see whether lowering the dose and infusion time improves safety and maintains efficacy.

As Aristotle implies, the answers we receive from clinical investigation are more commonly incremental than groundbreaking, even in studies much larger than the OPTALYSE trial. Thus, our search to understand the value of CDT to treat submassive PE is far from over. That being said, there were some valuable truths that were uncovered or confirmed by the OPTALYSE PE trial:

Truth # 1: Alteplase dissolves pulmonary thrombus. We have decades of experience proving this for systemic thrombolysis, and 3 prospective CDT trials that directly or indirectly do the same, but a significant scientific contribution from the OPTALYSE PE trial is that higher USCDT alteplase doses result in better thrombus clearance at 48 h. A stepwise increase in thrombus clearance was seen from the lowest dose, arm 1 (mean: 5.5% [95% confidence interval: 1.7% to 9.3%] thrombus clearance) to the highest dose, arm 4 (mean: 25.7% [95% confidence interval: 12.8% to 38.6%] thrombus clearance). The clinical significance of this finding is unknown but important, especially given that PE survivors may be at risk for reduced exercise tolerance and dyspnea

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in the months to years following the acute event. Will better thrombus removal confer better exercise tolerance after 6 to 12 months? Sanchez et al. (4) correlated the presence of residual thrombus with shorter walk distances and higher dyspnea scores at 1 year, but whether short-term thrombus removal affects these outcomes has been incompletely investigated.

Truth #2: Alteplase is a potentially lethal drug. The investigators closed arm 4 after 1 subject died from an intracranial hemorrhage attributed to USCDT. The hourly alteplase dose in this arm was higher than any previous CDT study (2 to 4 mg/h). The SEATTLE II trial, with its 10% major bleeding rate, administered 2 mg/h to the majority of patients (3). These outcomes suggest that lower per-hour dosing may be safer (e.g., 1 mg/h).

Truth #3: Submassive PE disproportionately affects obese patients. The average body mass index in the OPTALYSE trial was 35.8. The average American has a body mass index of 26 (5). Rising obesity is one of several reasons that venous thromboembolism continues to increase in incidence. Thus, the need for therapies to improve short- and long-term outcomes will be ever present.

Truth #4: The OPTALYSE PE trial does *not* confirm that USCDT reduces the RV/LV ratio at 48 h. The investigators decided against a control arm. There are no data, historical or otherwise, that defines the expected RV/LV ratio after 48 h in submassive PE patients treated with anticoagulation (AC) alone. The PEITHO trial (Pulmonary Embolism Thrombolysis Study) taught us that the risk for clinical deterioration with AC alone is low (~5%) (6) implying that RV recovery happens within 72 h (though there are no imaging data to confirm). The ULTIMA (ULTrasound Accelerated ThrombolysIs of PulMonAry Embolism) trial did provide evidence that the RV is unloaded more quickly with USCDT than AC alone, but that assessment occurred at 24 h (7). An additional 24 h (48-h assessment) is a significant amount of time for the right heart to recover. Especially given the very low doses in arm 1, one has to wonder what the relative contributions of USCDT versus endogenous fibrinolysis were to the RV/LV ratio reduction.

Truth #5: We still have not settled on USCDT's bleeding risk. The OPTALYSE trial had a major bleeding rate that is closer to what has been anecdotally observed and seen in a recent meta-analysis (8). But the OPTALYSE trial was inadequately powered in each arm and in aggregate to give us a true understanding of USCDT's safety.

Truth #6: It is still unknown whether the addition of ultrasound to an infusion catheter adds value. No study has compared standard CDT catheters to USCDT catheters in PE to determine which is better. The OPTALYSE PE trial was not designed to answer this particular question, but if an implication of the work is that USCDT reduces hospital costs by shortening intensive care and hospital length of stay, physicians and payers need to know whether the technology is truly superior to standard CDT and is worth the much higher upfront cost of the USCDT catheter.

On the basis of the OPTALYSE PE trial results, should interventionalists begin shortening the dose and duration of USCDT? The trial, although provocative, did not prove that lower dose and duration USCDT reduces the RV/LV ratio at 48 h. It did not prove that reduced dosing is safe. It used imaging surrogates rather than clinical endpoints. Thus, reduced dose/duration USCDT infusion cannot be recommended as the standard of care at this time.

Like Aristotle, physicians who take care of submassive PE patients are in limbo (A.K.A Dante's first circle of hell); it is unknown whether and for whom we should routinely use CDT or USCDT. To be fair, no trial can answer all the truths about submassive PE. But PE clinical investigators need to take the next needed step by randomizing a large number of patients to CDT versus No-CDT and assessing both short- and long-term clinical outcomes. We cannot take the results of the ULTIMA, SEATTLE II, and now the OPTALYSE PE, trials and declare victory. Our current conclusions need to be measured, and the opportunities for future investigation must be clearly articulated. Only after such investigation can we look back and say that a "considerable amount of truth has been amassed."

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