Critical Review Form
Therapy

Moderate pulmonary embolism treated with thrombolysis (from the "MOPETT" Trial). Am J Cardiol. 2013 Jan.

Objectives: **"to assess the effects of low-dose tissue plasminogen activator (tPA) on pulmonary artery systolic pressure in patients with "moderate" PE [pulmonary embolism] at 28 months." (p. 273)**

Methods: **This prospective, randomized controlled trial was conducted on adult patients with "moderate" PE, defined as > 70% of involvement of thrombus in 2 or more lobar or left or right main pulmonary arteries on CT scan, or by a high probability V/Q scan with mismatch in 2 or more lobes. CT and V/Q imaging was interpreted by a radiologist not involved in the study.**

Eligibility required 2 or more of the following signs or symptoms: chest pain, tachypnea (RR ≥ 22 breaths/min), tachycardia (HR ≥ 90 beats/min), dyspnea, cough, oxygen desaturation (SpO_2 ≤ 95%), and elevated jugular venous pressure ≥ 12 cm H_2O. Exclusion criteria included symptom onset > 10 days prior to diagnosis; > 8 hours since initiation of anticoagulation; systolic blood pressure (SBP) < 95 or > 200 mm Hg; eligibility for full-dose thrombolysis; contraindication to anticoagulation; platelet count < 50K/mm^3; major bleeding within 2 months; surgery or major trauma within 2 weeks; brain mass; neurologic surgery, intracerebral hemorrhage, or subdural hemorrhage within one year; terminal illness with no plan for PE treatment; and inability to perform echocardiography (ECHO).

Patients were randomized to either receive thrombolysis with tPA (TG), or to the control group (CG). The dose of tPA was as follows: for weight < 50 kg a total of 50 mg was given (10-mg IV bolus followed by infusion of the remaining 40 mg over 2 hours); for weight <50 kg, 0.5 mg/kg was given (10-mg IV bolus followed by infusion of the remainder within 2 hours). All patients received either unfractionated heparin IV or enoxaparin SC. Warfarin was started at admission in all patients.

ECHO was performed within 2 hours of randomization but prior to administration of tPA, again 24 to 48 hours following tPA administration, and at 6-month intervals. A cardiologist who was blinded to treatment group interpreted the ECHOs. The primary outcomes were the development of pulmonary hypertension and the composite endpoint of pulmonary hypertension or recurrent PE. Over 22 months (beginning May 2008), 178 patients with PE were screened for enrollment, of which 121 were randomized. There were 61 patients randomized to tPA, of whom 48 (79%)

received enoxaparin, compared to 49 of 60 (81%) subjects randomized to the control group. The mean follow-up period was 28 ± 5 months.

Guide		Comments
I.	**Are the results valid?**	
A.	**Did experimental and control groups begin the study with a similar prognosis (answer the questions posed below)?**	
1.	Were patients randomized?	Yes. "After evaluation of the patient, the study investigator placed a telephone call to the study center, and, by opening of sealed envelopes, randomization to the TG or CG was made." (p. 276)
2.	Was randomization concealed (blinded)?	Yes. Off-site randomization was performed and envelope selection was instructed over the telephone.
3.	Were patients analyzed in the groups to which they were randomized?	Yes. He authors make no mention of crossover, and it is to be assumed that patients were analyzed by intention to treat.
4.	Were patients in the treatment and control groups similar with respect to known prognostic factors?	Yes. Patients were similar with respect to age, comorbidities, cancer history, prior thromboembolic disease, and concomitant DVT. Patients were also similar with respect to initial ECHO findings of RV enlargement and RV hypokinesis, as well as elevations of BNP or troponin I.
B.	**Did experimental and control groups retain a similar prognosis after the study started (answer the questions posed below)?**	
1.	Were patients aware of group allocation?	Yes. This was an open-label trial without the use of placebo. It seems unlikely that performance bias on the part of the patients would have affected outcomes.
2.	Were clinicians aware of group allocation?	Yes. This was an open-label trial without the use of placebo. It is possible that performance bias on the part of the clinicians could have affected outcomes.
3.	Were outcome assessors aware of group allocation?	Yes. "Interpretation of the echocardiographic findings was performed by a cardiologist who was unaware of the patients' treatment assignments" (p. 274)
4.	Was follow-up complete?	No. "Follow-up was obtained for 58 [of 61] patients in the TG and 56 [of 60] in the CG." (p. 276). There were therefore 3 patients in the treatment group lost to

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<tr><td></td><td></td><td>follow-up compared to 4 in the control group (attrition bias).</td></tr>
<tr><td>II.</td><td>What are the results (answer the questions posed below)?</td><td></td></tr>
<tr><td>1.</td><td>How large was the treatment effect?</td><td>

At follow-up, pulmonary hypertension was noted in 9 (16%) patients in the TG vs. 32 (57%) in the CG (p < 0.001): RR 0.27 (95% CI 0.14 to 0.52); ARR 42% (95% CI 26% to 58%); NNT 2.4 (95% CI 1.7 to 3.9).
Pulmonary hypertension or recurrent PE was noted in 9 (16%) patients in the TG vs. 35 (63%) in the CG (p < 0.001): RR 0.25 (95% CI 0.13 to 0.47); ARR 47% (31% to 63%); NNT 2.1 (95% CI 1.6 to 3.2).
Secondary endpoints are noted in Table 1.

Table 1. Secondary endpoints
<table>
<tr><td>End-point</td><td>TG (n = 61)</td><td>CG (n = 60)</td><td>p-value</td></tr>
<tr><td>Recurrent PE</td><td>0 (0%)</td><td>3 (5%)</td><td>0.08</td></tr>
<tr><td>Mortality</td><td>1 (1.6%)</td><td>3 (5%)</td><td>0.30</td></tr>
<tr><td>Mortality + recurrent PE</td><td>1 (1.6%)</td><td>6 (10%)</td><td>0.049</td></tr>
<tr><td>Hospital LOS (days)</td><td>2.2 ± 0.5</td><td>4.9 ± 0.8</td><td>< 0.001</td></tr>
<tr><td>Bleeding</td><td>0</td><td>0</td><td>N/A</td></tr>
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</td></tr>
<tr><td>2.</td><td>How precise was the estimate of the treatment effect?</td><td>See above.</td></tr>
<tr><td>III.</td><td>How can I apply the results to patient care (answer the questions posed below)?</td><td></td></tr>
<tr><td>1.</td><td>Were the study patients similar to my patient?</td><td>No. “Moderate” PE in this case was based on the involvement of 2 or more lung lobes on CT or V/Q, rather than on findings of right heart strain or myocardial injury. This is a different definition than other studies on this topic. The absence of any bleeding events suggest as well that this is a population at very low risk of bleeding compared to those seen in other cohorts (e.g. ICOPER, PEITHO).</td></tr>
<tr><td>2.</td><td>Were all clinically important outcomes considered?</td><td>No. The primary outcomes included evidence of pulmonary hypertension and recurrent PE at follow-up, both of which are of uncertain clinical significance. More patient-centered outcomes – such as quality of</td></tr>
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		life and functional ability – were not considered.
3.	Are the likely treatment benefits worth the potential harm and costs?	No. This was a small, open-label trial involving patients with "moderate" PE defined by the number of lobes involved on imaging, rather than RV dysfunction or elevated cardiac biomarkers. The primary outcomes were of uncertain clinical significance, and the absence of any bleeding (intracranial or extracranial) suggests either poor safety monitoring or a patient population at unusually low risk of hemorrhage.

Limitations:

1. **Patients and clinicians in the study were not blinded to treatment group, introducing the possibility of performance bias.**
2. **The specific method of follow-up was not well-defined.**
3. **The primary outcomes included evidence of pulmonary hypertension (a surrogate outcome of functional status) and recurrent PE rates, both of unclear clinical significance.**
4. **No major or minor bleeding episodes were reported. Despite the fact that low-dose thrombolytic was used, this is inconsistent with prior reports of bleeding rates when anticoagulation alone was used, and suggests a patient population of very low risk of hemorrhage (external validity).**

Bottom Line:

In this small, open-label trial of low-dose tPA vs. placebo, patients receiving thrombolysis had lower rates of recurrent PE and pulmonary hypertension (defined solely by ECHO findings) at follow-up. This was a cohort of patients with "moderate" PE, defined by the number of lobes involved rather than evidence of right heart strain. Moreover, the absence of bleeding complications suggests a different population from that usually treated in our practice.