Critical Review Form
Therapy

Heparin plus alteplase compared with heparin alone in patients with submassive pulmonary embolism, *NEJM* 2002; 347:1143-1150

Objective: **"To compare the effects of treatment with heparin plus alteplase with the effects of heparin plus placebo on the outcome of patients with acute submassive pulmonary embolism". (p. 1143)**

Methods: **Prospective industry-sponsored randomized, double-blind, placebo-controlled trial at 49 centers in Germany between September 1997 and August 2001. To be eligible subjects had to have PE (confirmed by V/Q, CT, or pulmonary angiogram) in conjunction with one of the following:**

- **echocardiographically confirmed RV dysfunction (RV enlargement with loss of inspiratory IVC collapse without left ventricular or mitral valve disease);**
- **echocardiographically confirmed PA hypertension (tricuspid regurgitant jet > 2.8 meters per second);**
- **right heart cath PA pressure > 20 mmHg with wedge pressure < 18mmHg;**
- **new ECG evidence of right heart strain (complete or incomplete right-heart strain, $S_1Q_3T_3$ with inverted T-waves in V_1, V_2, or V_3).**

Exclusion criteria were extensive and included the following:

Exclusion Criteria:

- **Age > 80 years;**
- **Hemodynamic instability, (systolic BP < 90 mm Hg with or without cardiogenic shock)**
- **Symptoms onset > 96 hours prior**
- **Thrombolytic therapy, major surgery, or biopsy within 7-days**
- **Major trauma within 10-days**
- **TIA/CVA craniocerebral trauma, neurologic surgery within 6-months**
- **GI bleeding within 3-months**
- **Uncontrolled hypertension**
- **Known bleeding diathesis**
- **Pregnant or breast-feeding**
- **Diabetic retinpathy**

- **Taking oral anticoagulant**
- **Life expectancy < 6 months because of underlying disease**
- **Planned use of thrombolytic therapy for DVT's**

Patients were evaluated at the end of their hospital stay or at 30-days (whichever came first). The primary endpoint was in-hospital death or clinical deterioration requiring treatment escalation after alteplase/placebo infusion. Treatment escalation was defined as catecholamine infusion, rescue thrombolysis (for worsening dyspnea/respiratory failure, arterial hypotension/shock, persistent or worsening RV dysfunction), CPR, intubation, surgical thrombectomy or catheter thrombus fragmentation. Secondary endpoints included recurrent PE, major bleeding, and ischemic stroke. Imaging confirmed all recurrent PE and strokes. Major bleeding was defined by a Hg decrease of at least 4g/dL.

Intention-to-treat analysis was conducted by "an independent clinical research organization". A sample size of 217 patients/group would be required to detect a 13% absolute reduction (39% to 26%) in the primary outcome with 80% power and (two-sided) $\alpha = 0.05$. An *a priori* interim analysis was planned to test these assumptions after the first 250 patients were recruited. Time-to-event analysis was conducted with Kaplan-Meier survival curves and to assess the prognostic importance of other baseline and treatment variables a Cox proportional hazards model was conducted for the primary endpoint.

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. Randomization was performed on a 1:1 basis with a fixed block size of six patients at each center, according to a standard randomization program.
2.	Was randomization concealed (blinded)?	Yes, although the investigators do not clearly state who was blinded (patient, clinician, investigator, outcome assessors, etc.) Also "the trial protocol permitted breaking of the randomization code if additional therapy had to be provided on an emergency basis to a patient whose condition was deteriorating". (p. 1144)

3.	Were patients analyzed in the groups to which they were randomized?	Yes. "Statistical analysis was performed according to the intention-to-treat principle". (p. 1114)
4.	Were patients in the treatment and control groups similar with respect to known prognostic factors?	Yes. "The two groups were well matched with regard to major clinical characteristics at baseline (Table 1). There were no significant differences in systolic or diastolic blood pressure, heart rate, or the severity of dyspnea or arterial hypoxemia". (p. 1144). A higher proportion of placebo groups had S_1Q_3 (55% vs. 35%, p = 0.002)
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?	No
2.	Were clinicians aware of group allocation?	No
3.	Were outcome assessors aware of group allocation?	Uncertain. Who, how and when assessed outcomes? Investigators should clearly state who was blinded to allocation (CONSORT).
4.	Was follow-up complete?	No loss to follow-up is reported.
II.	**What are the results (answer the questions posed below)?**	

1. How large was the treatment effect?

TABLE 2. In-Hospital Clinical Events.*

Event	Heparin Plus Alteplase (N=118)	Heparin Plus Placebo (N=138)	P-Value†
Primary end point	13 (11.0)	34 (24.6)	0.006
Death from all causes	4 (3.4)	3 (2.2)	0.71
Escalation of treatment	12 (10.2)	34 (24.6)	0.004
Catecholamine infusion (for persistent hypotension or shock)	3 (2.5)	8 (5.8)	0.33
Secondary thrombolysis	9 (7.6)	32 (23.2)	0.001
Endotracheal intubation	3 (2.5)	3 (2.2)	0.85
Cardiopulmonary resuscitation	0	1 (0.7)	1.0
Embolectomy or thrombus fragmentation	0	1 (0.7)	1.0
Secondary end points			
Recurrent pulmonary embolism‡	4 (3.4)	4 (2.9)	0.89
Major bleeding§	1 (0.8)	5 (3.6)	0.29
Fatal bleeding	0	1 (0.7)	1.0
Hemorrhagic stroke¶	0	0	—
Ischemic stroke¶	0	1 (0.7)	1.0

*The numbers shown are based on calculations for the intention-to-treat population.

†P values were calculated with the use of Fisher's exact test (two-sided).

‡Recurrence of pulmonary embolism had to be confirmed by ventilation–perfusion lung scanning, spiral computed tomography, or pulmonary angiography.

§Major bleeding was defined as fatal bleeding, hemorrhagic stroke, or a drop in the hemoglobin concentration by at least 4 g per deciliter, with or without the need for red-cell transfusion.

¶Hemorrhagic or ischemic stroke had to be confirmed by computed tomography or magnetic resonance imaging.

- 256 were randomized (118 heparin + alteplase, 138 heparin + placebo) with equal proportions having right heart cath and echo (90% vs. 94%)
- The primary outcome was dominated by secondary thrombolysis (76% in alteplase, 23.2% in placebo group, p = 0.001) mostly for worsening respiratory symptoms. As a result there was a statistically significant difference between alteplase (13/118 = 11%) and placebo (34/138 = 24.6%) [NNT = 8 (95% CI 5-24)] primary endpoint rates (p = 0.006) at the interim analysis so the trial was stopped prematurely.
- The probability of event free survival was higher for alteplase subjects on Kaplan-Meier analysis (p = 0.005 by the log-rank test) – Fig 1, (p.1147)
- Proportional hazards analysis identified several variables independently associated with the primary outcome:

Variable	Relative Risk (95% CI)	P-value
Placebo (vs. alteplase)	2.63 (1.32-5.26)	0.006
Age > 70	2.29 (1.14-4.60)	0.02
Female	2.68 (1.34-5.36)	0.005
Pa_{02} <70mmHg or severe dyspnea	3.57 (1.55-8.20)	0.003

- The incidence of recurrent PE was low in both groups and unaffected by alteplase therapy (3.4% vs. 2.9%, p=0.89)
- Alteplase did not alter the incidence of strokes, major bleeding, CPR embolectomy, or intubations (Table 2 at left from p 1146)
- No bleeding episodes or deterioration required treatment discontinuation or breaking of the randomization code.

2.	How precise was the estimate of the treatment effect?	See 95% CI above.
III.	**How can I apply the results to patient care (answer the questions posed below)?**	
1.	Were the study patients similar to my patient?	No. Although the authors do not elaborate upon the hospital locale for recruitment of patients (ED? Wards? ICU?), it is unlikely that most ED's could replicate their inclusion criteria (cardiac, echo, or PA catheter defined RV dysfunction). Future RCT's will need to assess the role of EM sonography to define RV dysfunction or deferring thrombolytic decisions until ICU echo which is when most of these occur.
2.	Were all clinically important outcomes considered?	Yes. Benefits (deterioration, death) and risks (bleeding).
3.	Are the likely treatment benefits worth the potential harm and costs?	Uncertain – see III-1 above. If highly select patients with RV dysfunction have outcomes similar to this trial when either EM sonography defines RV problems or later (12 hours?) formal cardiac echo identifies the RV dysfunction after the ED diagnosis of PE than the benefits probably outweigh the risks.

Limitations

1) **Industry-sponsored trial with premature closure and no *post-hoc* power calculation or *a priori* criteria for stopping this trial early. Though this is the largest controlled trial to date, the investigators lack power to detect differences in death or other important outcomes.**

2) **No CONSORT reference or flow diagram.**

3) **No discussion of protocol violations.**

4) **Limited external validity to ED without ready access to formal Echo.**

Bottom Line

In select hemodynamically stable PE patients (see exclusion criteria above) with RV dysfunction or pulmonary hypertension, alteplase plus heparin improves outcomes compared with heparin alone by reducing the need for secondary thrombolysis up to 30-days after presentation with NNT =8. The external validity of these findings must be tested in EDs without ready access to echocardiography 24/7.