SUBMASSIVE PULMONARY EMBOLISM

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According to the 2012 ACCP Concensus Statement, in the absence of a high risk of bleeding, thrombolysis is suggested for a PE in which of the following circumstances?

1. Massive PE with hypotension
2. Submassive PE with hypoxemia
3. Submassive PE with severe RV strain on echo
4. Submassive PE with elevated Troponin
5. All of the above circumstances

Answer: Massive PE with hypotension (Persistent SBP < 90) (Grade 2C)

- In addition, thrombolysis can be considered in selected patients at "high-risk" for developing hypotension who are at low risk of bleeding (2C)
- Thrombolysis (Full 100 mg dose) should be given IV, not catheter directed (2C). It is as effective when given by IV as by CDT, with no increased risk of bleeding, and with a lower risk for mechanical complications. CDT can be considered if systemic fails.
- 2 hr infusion time recommended (2C).

Treatment of PE with Thrombolytics

- Metanalysis of 748 patients from 11 randomized controlled trials of AC plus Lytic vs AC alone.
- Lytic with trend toward reduction in recurrent PE, all-cause mortality, increase in major bleeding.
- 5 of these trials with more severe PE: significant decrease in mortality (6.2% vs 12.7%) and increase in major bleeding (21.9% vs 11.9%).

Treatment of PE with Lytics

- Positive Effects of Lytics: accelerated clot lysis, decrease in PA pressures, normalization of RV function.

Treatment of PE with Thrombolytics

- JAMA 2014;311:2414
- Metanalysis of 16 trials totaling 2115 patients given thrombolytic plus AC vs AC alone.
- 15 % of patients at high risk (low BP), 71% at intermediate risk (normal BP but RV dysfunction on echo), 10% low risk.

Treatment of PE with Thrombolytics

- Pimary Outcome: All cause mortality lower in lytic group (2.2 vs 3.9%, OR 0.53) with NNT=59.
- Primary Outcome: Major bleeding higher in lytic group (9.2 vs 3.4%, OR 2.73) with NNH=18. However, increased bleeding only in the 1331 patients >65 yo (12.9 vs 4.1%). Under age 65 OR 1.25 (NS).

Treatment of PE with thrombolytics

- Secondary Outcome: less recurrent PE with lytics with OR=0.40.
- Secondary Outcome: more ICH with OR=4.63 with NNH=78.

Treatment of PE with Thrombolytics: JAMA 2014

- Pre-specified subgroup analysis of the 8 trials with only RV dysfunction (no hypotension): 1775 patients with Mortality benefit maintained (1.4 vs 2.9%, OR=0.48), but increased major bleeding (OR=3.19).
- Overall mortality benefit not significant in patients over 65 yo (2.1 vs 3.6%, OR 0.55, CI 0.29-1.05)

Treatment of PE with Thrombolytics: JAMA 2014

- Overall NNT to prevent one death was 59, while NNH with major bleed was 18.
- Other limitations: different thrombolytic agents used and at varying doses, different definitions of hemodynamic instability, no differentiation between systemic and CDT lytic delivery.
- Still need large randomized trials to definitively prove efficacy of lytics.

Other Possible Uses for Lytics in Pulmonary Embolism

- RV Dysfunction: probably the most clinically meaningful definition of submassive PE
- Extensive clot burden on CT or VQ Scan
- Severe Hypoxemia
- Elevated Troponin
- Free-floating RA or RV thrombus

Other Possible Uses of Lytics in Pulmonary Embolism

- Patent Foramen Ovale
- CPR with high suspicion of PE as cause of arrest

Lytics in Submassive PE: PLEITHO Trial

NEJM April 2014: 370;1402-1411

- Multicentered, randomized, placebo controlled trial of 1006 patients with, given low dose tenecteplace (recombinant TPA) plus heparin vs placebo plus heparin.
- Primary Outcome: Less death or further hemodynamic compromise within 7 days in treatment group (2.6% vs 5.6%, p=0.02). The difference, however, was predominantly in hemodynamics, not in death rate.

PLEITHO Trial

- TPA doses (all low dose) 30 mg < 60 kgm, 35 mg 61-69 kgm, 40 mg 70-79 kgm, 45 mg 80-89 kgm, 50 mg over 90 kgm
- Complications:

--Extracranial hemorrhage: 6.3% treatment group vs 1.2% placebo group ($p<0.001$).

--CVA: 2.4% treatment group (10/12 hemorrhagic) vs 0.2% placebo group (1/1 hemorrhagic).

Efficacy Outcomes.

Table 3. Efficacy Outcomes.*

Outcome	Tenecteplase (N=506)	Placebo (N=499)	Odds Ratio (95% CI)	P Value
Primary outcome — no. (%)	13 (2.6)	28 (5.6)	0.44 (0.23–0.87)	0.02
Death from any cause	6 (1.2)	9 (1.8)	0.65 (0.23–1.85)	0.42
Hemodynamic decompensation	8 (1.6)	25 (5.0)	0.30 (0.14–0.68)	0.002
Time between randomization and primary efficacy outcome — days	1.54±1.71	1.79±1.60		
Recurrent pulmonary embolism between randomization and day 7 — no. (%)	1 (0.2)	5 (1.0)	0.20 (0.02–1.68)	0.12
Fatal	0	3 (0.6)		
Nonfatal	1 (0.2)	2 (0.4)		
Other in-hospital complications and procedures — no. (%)				
Mechanical ventilation	8 (1.6)	15 (3.0)		
Surgical embolectomy	1 (0.2)	2 (0.4)		
Catheter thrombus fragmentation	1 (0.2)	0 (0.0)		
Vena cava interruption	5 (1.0)	1 (0.2)		
Thrombolytic treatment other than study medication	4 (0.8)	23 (4.6)		
Death from any cause between randomization and day 30 — no. (%)	12 (2.4)	16 (3.2)	0.73 (0.34–1.57)	0.42
Patient still hospitalized at day 30 — no. (%)	59 (11.7)	50 (10.0)		
Rehospitalization between randomization and day 30 — no. (%)	22 (4.4)	15 (3.0)		

* Plus–minus values are means ±SD. Odds ratios and P values are provided for efficacy outcomes that were prespecified in the trial protocol.

Meyer G et al. N Engl J Med 2014;370:1402-1411.

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Safety Outcomes in the Intention-to-Treat Population.

Table 4. Safety Outcomes in the Intention-to-Treat Population.*

Outcome	Tenecteplase (N = 506)	Placebo (N = 499)	Odds Ratio (95% CI)	P Value
	no. (%)			
Bleeding between randomization and day 7				
Major extracranial bleeding	32 (6.3)	6 (1.2)	5.55 (2.3–13.39)	<0.001
Minor bleeding	165 (32.6)	43 (8.6)		
Major bleeding†	58 (11.5)	12 (2.4)		
Stroke between randomization and day 7	12 (2.4)	1 (0.2)	12.10 (1.57–93.39)	0.003
Ischemic stroke	2 (0.4)	0		
Hemorrhagic stroke‡	10 (2.0)	1 (0.2)		
Serious adverse events between randomization and day 30	55 (10.9)	59 (11.8)	0.91 (0.62–1.34)	0.63

* Odds ratios and P values are provided for efficacy and safety outcomes that were prespecified in the trial protocol.
† Major bleeding was defined according to the criteria of the International Society on Thrombosis and Haemostasis.
‡ Hemorrhagic stroke included hemorrhagic conversion of ischemic stroke.

Meyer G et al. N Engl J Med 2014;370:1402-1411.

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Summary of PLEITHO Trial

- Submassive PE with low dose TPA led to less hemodynamic compromise, but more intracranial and extracranial bleeding.
- No change in mortality

MOPETT Trial: Am J. Cardiol 2013:111(2):273

- 121 Patients with extensive clot burden on CT (>70% embolism with emboli in at least 2 lobar arteries) or High Prob VQ with mismatch in at least 2 lobar arteries
- No patients were hypotensive and only 25% had RV dysfunction
- Heparin plus low dose TPA (<=50 mg) vs Heparin plus placebo

MOPETT TRIAL RESULTS

- Lower rate of Pulmonary Hypertension: 16% vs 57%
- Lower PAS pressure at 28 months: 28 vs 43 mmHG
- Faster resolution of PH by 28 months
- Similar rates of bleeding (0 vs 0%)
- Similar recurrent PE (0 vs 5%)
- Similar mortality (1.6 vs 5%)

Persistence of Thrombolytic Effect

- NEJM 1980;303:842 and J Am Coll Cardiol 1990;15:65A.
- 40 patients randomized to Lytic plus AC or AC alone. At 2 weeks and one year Lytic group had more complete resolution of emboli. At 7 years Lytic group had lower PA pressures.

Persistence of Thrombolytic Effects

- Am J Cardiol 1998;82:966
- 40 non-randomized patients with Acute PE getting Lytic or not. Lytic group had improved RV function at 12 hrs, but no difference at 1 week.

Summary of Thrombolytic Effects in PE

- Proven to accelerate clot lysis and to lead to early hemodynamic improvement (improved PA pressures and RV function)
- Proven to increase major bleeding
- Not yet convincing evidence that it improves mortality or that it reduces the frequency of recurrent pulmonary emboli

Catheter Directed Therapy

- Consider for persistent hemodynamic instabilty despite systemic thrombolysis (Scondary CDT)
- Primary CDT is investigational at present
- Potential advantages: Can use lower dose of lytic to reduce risk of bleeding (may make risk:benefit ratio more reasonable in submassive PE) and can add mechanical interventions at same time.

Catheter Directed Therapy

- Circulation 1988: 100 mg TPA in 34 patients with massive PE (low BP) given IV vs IPA. No difference in PAP, amount of residual clot, or bleeding

Catheter Directed Thrombolysis

- ULTIMA Study: Circulation 2014;129:479.
- 59 patients with RVE (RV:LV>=1) randomized to US-assisted CDT with 10-20 mg TPA infused over 15 hours followed by heparin, or heparin alone
- At 24 hours improved RV:LV ratio (by 0.3 vs 0.03).
- At 90 days: no change in mortality or major bleeding

Which of the following is an indication for IVC Filter Placement in a patient with an acute DVT or PE?

1. Contraindication to Anticoagulation (AC)
2. Failure of Anticoagulation
3. Massive DVT
4. Massive PE
5. All of the above

Answer: Contraindication to AC

- Contraindication to AC has a Grade 1B recommendation.
- The other potential indications are commonly employed, but w/o EBM to support them.
- Often placed for contraindication of AC, failure of AC, and for massive or submassive PE in whom TPA is not being given.
- Give conventional AC when possible (2B).
- Do not need AC solely because of the presence of the filter.

IVC Filter Placement in patients with High Risk PE or DVT

- JAMA April 2015;313(16):1627-1635.
- Multi-center controlled trial in 17 French centers. 399 patients with acute symptomatic PE or DVT and at least one high risk criterion were randomized open label to > 6 months AC or > 6 months AC plus filter placement for 3 months.
- Severity Criteria: age > 75, active CA, Chronic Cardiac or Pulmonary insufficiency, large proximal DVT, RVE or PH on echo, elevated BNP or Troponin.

IVC Filter placement in patients with severe PE

Primary Outcome: no difference in incidence of severe symptomatic recurrent PE at 3 months.

Secondary Outcomes: no difference in PE at 6 months or in DVT at 3 or 6 months.

Question: How about same study but just with patients who have evidence of RVE, PH, or RV dysfunction echo?

THANK YOU!