Thrombolysis of "Submassive" Pulmonary Embolism

"Short Snappers" CSIM 2015
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Disclosures

- Off label use of tenecteplase will be discussed.

Objectives

- Define “submassive” pulmonary embolism
- Cite evidence for thrombolytics in this population
- Understand the risks and potential benefits of using thrombolytics in submassive pulmonary embolism

Outline

- Review risk stratification of pulmonary embolism
- Review evidence around use of thrombolytics in pulmonary embolism
- Discuss potential adverse events
- Take home points
- Questions

Risk stratification of PE

- Mortality in acute PE:
  - ~5% die of the initial PE or PE within 7 days
  - ~70% mortality if cardiopulmonary arrest occurs
  - ~ 30% mortality if shock requiring inotropic support
  - ~2% mortality in patients who are normotensive

Pathophysiology of PE

- Clinical consequences primarily hemodynamic
  - Clinically apparent with 30-50% of vascular bed occluded
  - Increased PVR leading to increased afterload (large or multiple emboli)
  - RV can't overcome pressure leading to RV failure
  - Results in: electromechanical dissociation/sudden death, syncope, shock

Table 5 Risk stratification according to expected pulmonary embolism-related early mortality rate

PE-related early MORTALITY RISK		RISK MARKERS			Potential treatment implications
		CLINICAL (shock or hypotension)	RV dysfunction	Myocardial injury	
HIGH >15%		+	(+)[a]	(+)[a]	Thrombolysis or embolectomy
NON HIGH	Intermediate 3–15%	–	+	+	Hospital admission
			+	–	
			–	+	
	Low <1%	–	–	–	Early discharge or home treatment

Torbicki et al. Eur Heart J, 2008;29:2276-315.

Risk Stratification of PE

- High risk = Massive:
  - PE with hypotension/shock
- Intermediate-risk = Submassive:
  - PE with acute myocardial injury or right ventricular dysfunction without hemodynamic compromise
- Low-risk:
  - Hemodynamically stable with no RV dysfunction or myocardial injury

Treatment Options For PE

- Low risk:
  - Systemic anticoagulation
    - UFH, LMWH, warfarin, DOAC (dabigatran, apixaban, rivaroxaban)
- Intermediate risk :
  - Systemic anticoagulation
  - ? thrombolytics
- High risk:
  - Systemic anticoagulation
  - Thrombolytics
  - Catheter-assisted thrombectomy

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Thrombolytics

- Thrombolytic agents:
  - Recombinant tissue type plasminogen activator (tPA): binds fibrin, increases its affinity for plasminogen and enhances plasminogen activation
  - Streptokinase (SK) : binds plasminogen, that activates plasmin
  - Recombinant urokinase (UK): activates plasminogen in the extravascular component
  - Tenecteplase (off label): binds fibrin and converts plasminogen to plasmin

Thrombolytics

- Administration
  - Administered peripherally through IV (bolus or infusion)
    - Duration depends on agent
      - tPA 2 hrs
    - Catheter directed techniques are available
  - Followed by full anticoagulation when aPTT is <2x ULN
    - Typically UFH initially

Thrombolytics

- Contraindications
  - Absolute
    - Intracranial neoplasm
    - Recent <2 mths intracranial or spinal surgery, trauma
    - Hx hemorrhagic stroke
    - Active bleeding or bleeding diathesis
  - Relative
    - Severe uncontrolled hypertension
    - Non-hemorrhagic stroke within 3 mths
    - Surgery within 10 days
    - Pregnancy

Review of the Evidence

- Data has been lacking
- In past 40 years, <1000 patients in RCT looking at thrombolytics versus heparin alone

Evidence for Thrombolytics

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Fibrinolysis for Patients with Intermediate-Risk Pulmonary Embolism

Meyer et al. NEJM 2014; 370(15):1402-11.

Evidence for Thrombolytics: PIETHO

- RCT: double blind, placebo controlled
- Eligible: 18 yo, confirmed PE with onset of symptoms within 15 days, RV dysfunction or myocardial injury
- Tenecteplase: single, weight based dose over 5 to 10 seconds
  - All patients started IV UFH at time of randomization
- F/U 30 days
- Primary outcome: composite endpoint of death (any cause) or hemodynamic decompensation within 7 days
- Secondary outcomes: death within 7 days, death within 30 days, major adverse events within 30 days
- Safety outcomes: ischemic or hemorrhagic stroke within 7 days, moderate or severe extracranial bleeding within 7 days and serious AE within 30 days

Evidence for Thromobolytics: PIETHO

- Total 1006 patients randomized
  - 1005 in ITT analysis
- Efficacy:
  - Primary: 2.6% in tenecteplase versus 5.6% in placebo
    - Driven by a decrease in hemodynamic compromise
      - 1.6% vs 5%
    - No significant decrease in death between the groups
      - 1.2% vs 1.8%
    - More patients in placebo required catecholamines or CPR
    - Patients could get open label rescue thrombolytics
      - 0.8% vs 4.6%

Evidence for Thrombolytics: PIETHO

- Secondary outcomes:
  - By day 30, no difference in death (2.4% vs 3.2%)
- Safety:
  - Major bleeding 11.5% vs 2.4%
    - Major extracranial bleeding 6.3% vs 1.2%
  - TNK: 12 patients stroke (10 hemorrhagic) versus 1 patient in placebo arm
    - Case fatality 40% in TNK arm with hemorrhagic stroke
    - Survivors: mild or moderate disability

Evidence for thrombolytics: PIETHO

- Overall:
  - Decreased hemodynamic compromise
  - No mortality difference at 30 days
  - Risk of ICH 2%
  - "…great caution is warranted when considering fibrinolytic therapy for hemodynamically stable patients with pulmonary embolism, right ventricular dysfunction and positive cardiac troponin test."

Evidence for thrombolytics: Meta-analysis

- Gao et al 2015:
  - 8 RCT, total 1755 patients with intermediate risk PE

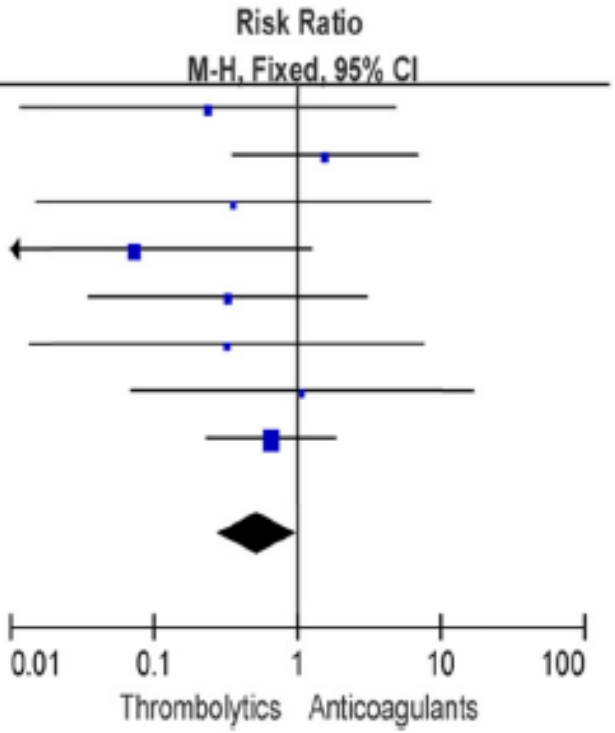
Source	No. of patients	Randomized treatment (No. of patients)	Compared treatment (No. of patients)	PE confirmation	RVD/MI confirmation	Major bleeding criteria	Follow-up, d	Male, No. (%)
[10]	101	Alteplase (100 mg) followed by heparin (46)	Heparin alone (55)	V/Q scan, PAng	Echocardiography	Not reported	14	44 (43.56)
[16]	256	Alteplase (100 mg) plus heparin (118)	heparin plus placebo (138)	spiral CT, V/Q scan, PAng	Echocardiography	Fatal, ICH, Hgb drop ≥4 g/dl	30	122 (47.66)
[3]	58	Tenecteplase (30–50 mg) plus heparin (28)	Heparin plus placebo (30)	CT, V/Q scan, PAng	Echocardiography	Fatal, ICH, need for transfusion or intervention	30	23 (39.66)
[8]	72	Tenecteplase (100 mg) plus heparin (37)	Heparin plus placebo (35)	spiral CT	Echocardiography	Fatal, ICH, need for transfusion or intervention	180	41 (56.94)
[22]	121	Tissue plasminogen activator (≤50 mg) (61)	Heparin or enoxaparin alone (60)	CTPA, V/Q scan	Echocardiography, cTn-I, BNP	Not pre-specified	840	55 (45.45)
[17]	59	Catheter-directed regimen of rt.-PA (10 mg) plus heparin (30)	Heparin alone (29)	CT, V/Q scan, PAng	Echocardiography	Hgb drop ≥2.0 g/l, need for transfusion, bleeding in a critical site	90	28 (47.46)
[15]	83	Tenecteplase (weight-based) followed by LMWH (40)	Placebo followed by LMWH (43)	CTPA	Echocardiography, cTn-I, cTn-T, BNP	ICH, Hgb drop >2.0 g/l with transfusion, need for invasive therapy	90	49 (59.03)
[19]	1005	Tenecteplase (30–50 mg) plus heparin (506)	Placebo plus heparin (499)	CTPA, V/Q scan, PAng	Echocardiography, CT, cTn-I, cTn-T	Fatal, bleeding in a critical site, need for transfusion	30	473 (47.06)

Gao et al: Mortality

Study or Subgroup	Thrombolytics Events	Total	Anticoagulants Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
Goldhaber et al, 1993	0	46	2	55	8.2%	0.24 [0.01, 4.84]	1993
Konstantinides et al, 2002	4	118	3	138	10.0%	1.56 [0.36, 6.83]	2002
TIPES, 2010	0	28	1	30	5.2%	0.36 [0.02, 8.40]	2010
Fasullo et al, 2011	0	37	6	35	24.1%	0.07 [0.00, 1.25]	2011
MOPETT, 2012	1	61	3	60	10.9%	0.33 [0.04, 3.06]	2012
Kucher et al, 2013	0	30	1	29	5.5%	0.32 [0.01, 7.61]	2013
Kline et al, 2014	1	40	1	43	3.5%	1.07 [0.07, 16.62]	2014
PEITHO, 2014	6	506	9	499	32.7%	0.66 [0.24, 1.83]	2014
Total (95% CI)		**866**		**889**	**100.0%**	**0.52 [0.28, 0.97]**	
Total events	12		26				

Heterogeneity: $Chi^2 = 5.01$, $df = 7$ ($P = 0.66$); $I^2 = 0\%$

Test for overall effect: $Z = 2.06$ ($P = 0.04$)

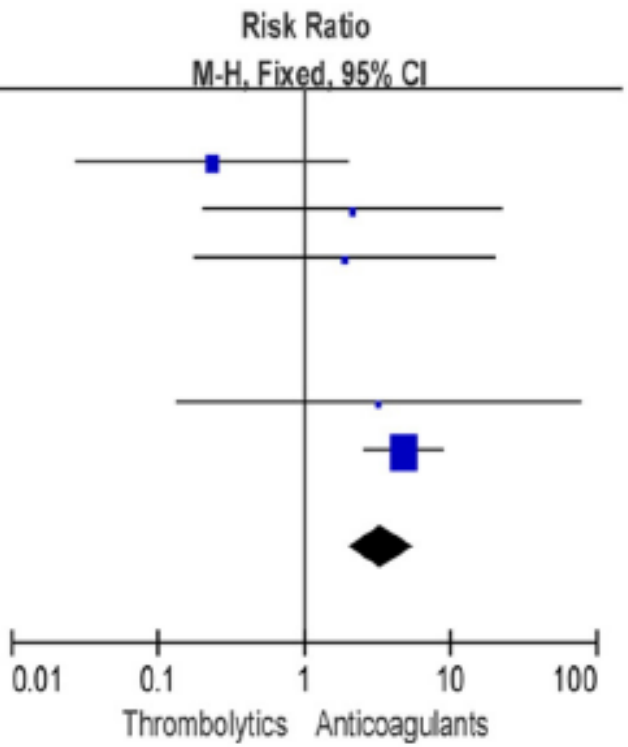


Gao et al: Bleeding

Study or Subgroup	Thrombolytics Events	Total	Anticoagulants Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
Goldhaber et al, 1993	0	0	0	0		Not estimable	1993
Konstantinides et al, 2002	1	118	5	138	24.0%	0.23 [0.03, 1.97]	2002
TIPES, 2010	2	28	1	30	5.0%	2.14 [0.21, 22.35]	2010
Fasullo et al, 2011	2	37	1	35	5.4%	1.89 [0.18, 19.95]	2011
MOPETT, 2012	0	61	0	60		Not estimable	2012
Kucher et al, 2013	0	30	0	29		Not estimable	2013
Kline et al, 2014	1	40	0	43	2.5%	3.22 [0.13, 76.82]	2014
PEITHO, 2014	58	506	12	499	63.0%	4.77 [2.59, 8.76]	2014
Total (95% CI)		**820**		**834**	**100.0%**	**3.35 [2.03, 5.54]**	
Total events	64		19				

Heterogeneity: $Chi^2 = 7.64$, $df = 4$ ($P = 0.11$); $I^2 = 48\%$

Test for overall effect: $Z = 4.72$ ($P < 0.00001$)



Evidence for thrombolytics: Meta-analysis

- Xu et al 2015:
  - 7 RCT
  - Early all cause mortality:
    - Decreased in thrombolytic group but not stat sig
  - Clinical deterioration events:
    - Stat sig lower rate in thrombolytic group 4.1% vs 14.1%
  - Recurrent PE:
    - Lower in thrombolytic group
  - Hemorrhagic events:
    - No stat sig difference in major bleeding between two groups
    - Thrombolytic arm higher rates minor bleeding

Xu et al. Journal thoracic disease 2015; 7(5): 810-821.

Adverse events

- Risk of major bleeding: 9.2%
  - Possibly higher in older patients
- Rates ICH: 1.5-2%
- Examples:
  - ICH with neuro symptoms: recovered at 6 mths
  - GI bleeding needing H-D support, transfusions, IVC filter
  - Hematuria requiring transfusion
  - GI bleeding needing transfusion
  - Intra-abdo hematoma compressing bladder
  - Abdo bleeding requiring transfusion
- Streptokinase:
  - Infusion reactions 10%:
    - Pyrexia, shivering, rash
    - Hypotension

Xu et al. Journal thoracic disease 2015; 7(5): 810-821.

Summary

- Data in the area is conflicting
- More recent meta-analyses main patient population from 1 large study
- Evidence suggests:
  - Will improve hemodynamics in the short term
  - Long term mortality benefit has not panned out
  - Any hemodynamic benefit seems to come at expense of increased bleeding complications

Take home points

- Massive PE with persistent hypotension or shock due to acute PE is the only widely accepted indication for systemic thrombolysis
  - Even in this population, patient selection must be considered carefully due to risk of major bleeding
- Thrombolytics can improve hemodynamic parameters, and in some analyses all cause mortality BUT this comes at the expense of increased risk of major and minor bleeding
- In most patients with acute PE and no hypotension, systemic anticoagulation is preferred over thrombolytics (CHEST grade 1C)
- Future directions:
  - Catheter-directed thrombolytics
  - Reduced-dosage thrombolytics
  - Rescue thrombolytics

References

- Torbicki et al. Eur Heart J, 2008;29:2276-315.
- Kearon et al. Antithrombotic Therapy for VTE Disease. Chest. 2012;141(2_suppl):e419S-e494S.
- Meyer et al. Fibrinolysis for intermediate-risk pulmonary embolism. NEJM 2014; 370(15):1402-11.
- Gao et al. Thrombolysis for acute intermediate-risk pulmonary embolism: A meta-analysis. Thrombosis Research (2015), http://dx.doi.org/10.1016/j.thromres.2015.09.012.
- Xu et al. Initial thrombolytsis treatment compared with anticoagulation for acute intermediate-risk pulmonary embolism : A meta-analysis. Journal of thoracic disease, 2015; 7(5):810-821.
- www.thrombosiscanada.ca

Questions?