Thrombolysis of “Submassive” Pulmonary Embolism

“Short Snappers” CSIM 2015
Elizabeth Zed, MD, FRCPC
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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

<table>
<thead>
<tr>
<th>PE-related early MORTALITY RISK</th>
<th>CLINICAL (shock or hypotension)</th>
<th>RV dysfunction</th>
<th>Myocardial injury</th>
<th>Potential treatment implications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HIGH</strong> 15%</td>
<td>+</td>
<td>(+)(^a)</td>
<td>(+)(^a)</td>
<td>Thrombolysis or embolectomy</td>
</tr>
<tr>
<td><strong>NON HIGH</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermediate 3–15%</td>
<td></td>
<td>+</td>
<td>–</td>
<td>Hospital admission</td>
</tr>
<tr>
<td>Low &lt;1%</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Early discharge or home treatment</td>
</tr>
</tbody>
</table>

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
Treatment Options For PE

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  - Systemic anticoagulation
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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

Fibrinolysis for Patients with Intermediate-Risk Pulmonary Embolism

Evidence for Thrombolitics: 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 Thrombolitics: 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 thrombolitics
    - 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

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

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Thrombolytics</th>
<th>Anticoagulants</th>
<th>Risk Ratio M-H, Fixed, 95% CI Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goldhaber et al, 1993</td>
<td>0</td>
<td>2</td>
<td>0.24 [0.01, 4.84] 1993</td>
</tr>
<tr>
<td>Konstantinides et al, 2002</td>
<td>4</td>
<td>3</td>
<td>1.56 [0.36, 6.83] 2002</td>
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<tr>
<td>TIPES, 2010</td>
<td>0</td>
<td>1</td>
<td>0.36 [0.02, 8.40] 2010</td>
</tr>
<tr>
<td>Fasullo et al, 2011</td>
<td>0</td>
<td>6</td>
<td>0.07 [0.00, 1.25] 2011</td>
</tr>
<tr>
<td>MOPETT, 2012</td>
<td>1</td>
<td>3</td>
<td>0.33 [0.04, 3.06] 2012</td>
</tr>
<tr>
<td>Kucher et al, 2013</td>
<td>0</td>
<td>1</td>
<td>0.32 [0.01, 7.61] 2013</td>
</tr>
<tr>
<td>Kline et al, 2014</td>
<td>1</td>
<td>1</td>
<td>1.07 [0.07, 16.62] 2014</td>
</tr>
<tr>
<td>PEITHO, 2014</td>
<td>6</td>
<td>9</td>
<td>0.66 [0.24, 1.83] 2014</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>866</td>
<td>889</td>
<td>0.52 [0.28, 0.97]</td>
</tr>
<tr>
<td>Total events</td>
<td>12</td>
<td>26</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Chi² = 5.01, df = 7 (P = 0.66); I² = 0%
Test for overall effect: Z = 2.06 (P = 0.04)
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<tr>
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<tr>
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<td>0</td>
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<td>1</td>
<td>118</td>
<td>5</td>
<td>138</td>
</tr>
<tr>
<td>TIPES, 2010</td>
<td>2</td>
<td>28</td>
<td>1</td>
<td>30</td>
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<td>2</td>
<td>37</td>
<td>1</td>
<td>35</td>
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<tr>
<td>MOPETT, 2012</td>
<td>0</td>
<td>61</td>
<td>0</td>
<td>60</td>
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<td>Kucher et al, 2013</td>
<td>0</td>
<td>30</td>
<td>0</td>
<td>29</td>
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<td>Kline et al, 2014</td>
<td>1</td>
<td>40</td>
<td>0</td>
<td>43</td>
</tr>
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<td>PEITHO, 2014</td>
<td>58</td>
<td>506</td>
<td>12</td>
<td>499</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>820</strong></td>
<td></td>
<td><strong>834</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td><strong>64</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Chi² = 7.64, df = 4 (P = 0.11); I² = 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

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

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


- www.thrombosiscanada.ca
Questions?