Breaking Up Is Hard To Do: The Role of Thrombolytics in Intermediate Risk Pulmonary Embolism

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Breaking Up Is Hard to Do: The Role of Thrombolytics in Intermediate Risk Pulmonary Embolism

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Objectives
1. Determine the category of pulmonary embolism risk using stratification tools.
2. Evaluate current literature related to treatment of intermediate risk pulmonary embolism using systemic thrombolysis.
3. Analyze the utility of alternative dosing strategies, such as low dose and catheter directed thrombolysis.

Patient Case
HP is a 82 year old Hispanic male with PMH of diabetes admitted 4 days ago with a hip fracture. He is now POD#3 from surgery, and complains of increasing dyspnea for the past 24 hours. Vitals: HR 83 bpm, BP 102/68 mmHg, RR 20 rpm, O₂ sat 98% Troponin-I: 1.7 ng/mL CT angiography is positive for pulmonary embolism. The team starts heparin using an 80 units/kg bolus with 18 units/kg/hr infusion. Should you recommend using a thrombolytic for HP?

Background

• Venous thromboembolism (VTE)
  – Deep vein thrombosis (DVT)
  – Pulmonary embolism (PE)
• Incidence of 60-70 PE cases per 100,000 people
• Risk factors
  – Hypercoagulability: genetic disorder, oral contraception, cancer
  – Venous stasis: immobility, obesity
  – Vascular injury: surgery, trauma
• Underdiagnosed
  – Silent PE present in up to 50% of patients with DVT
  – Often not diagnosed until autopsy

Presentation

• Symptoms
  – Dyspnea
  – Chest pain
  – Hemoptysis
  – Syncope
• Leg pain or swelling due to DVT
• Heterogeneous disease
  – Asymptomatic
  – Sudden death in 25% of patients
• Diagnosis: CT angiography is gold standard
Pathophysiology

- Arterial occlusion
  - Increased pulmonary artery pressure
  - Thromboxane A2 and serotonin release
  - Increased vascular resistance
- Right ventricle (RV) dilation
  - Initially adaptive function
  - Increased oxygen demand and decreased oxygen delivery leads to heart failure
- Dependent on physical reserves and comorbidities

Complications of PE

- Hemodynamic collapse
  - Often leads to death
  - 30 day all-cause mortality rates of up to 11%
- Recurrence of VTE
  - 13% recurrence at one year
  - 30% recurrence at ten years
- Chronic thromboembolic pulmonary hypertension (CTEPH)
  - Incidence of up to 9.1% at two years
  - Causes progressive dyspnea on exertion and right sided heart failure

Factors Associated with Poor Outcomes

- Right ventricular dysfunction
  - Independent predictor of poor in-hospital outcomes
  - Hazard Ratio (HR) 3.5 in overall population
- Elevated brain natriuretic protein (BNP)
  - 10% risk of early death
  - 23% risk of adverse clinical outcome
- Elevated troponins associated with higher mortality
  - HR 9.4 in overall population
  - HR 5.9 in hemodynamically stable patients

Risk Stratification of PE

- Hypotension
  - Sustained systolic blood pressure (SBP) <90 mmHg
- Dilated RV
  - Imaging via echocardiogram or computed tomography (CT) scan
  - 4-chamber right ventricular diameter divided by left ventricular diameter (RV/LV ratio) >0.9
- Elevated Cardiac Biomarkers
  - BNP >90 pg/mL
  - Pro-BNP >500 pg/mL
  - Troponin I >0.4 ng/mL or troponin T >0.1 ng/mL

Risk Stratification - HP

HP is a 82 year old Hispanic male with PMH of diabetes admitted 4 days ago with a hip fracture. He is now POD#3 from surgery, and complains of increasing dyspnea for the past 24 hours.

Vitals: HR 83 bpm, BP 102/68 mmHg, RR 20 rpm, O₂ sat 98%

Troponin-I: 1.7 ng/mL

CT angiography is positive for pulmonary embolism.

Should you recommend using a thrombolytic for HP?

1. Which risk category does HP fall into?
Acute PE treatment

- Parenteral anticoagulation
  - Low molecular weight heparin (LMWH) preferred in most patients
  - Unfractionated heparin (UFH) used if contraindications exist, or short half-life is desired

- Thrombolysis
  - Quickly dissolve clot
  - Not indicated in all patients

Mechanism of Action

- Thrombus forms when the clotting cascade is activated
  - Fibrinogen converted to fibrin
  - Fibrin holds the clot together

- Thrombolytics convert plasminogen to plasmin
  - Plasmin degrades fibrin links
  - Allows the thrombus to dissolve

Thrombolytic agents

<table>
<thead>
<tr>
<th>Generic</th>
<th>FDA Dosing</th>
<th>FDA Indication?</th>
<th>Half-life (minutes)</th>
<th>Fibrin Selective?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alteplase (tPA)</td>
<td>100 mg IV Over 2 hours</td>
<td>Yes</td>
<td>5</td>
<td>Yes</td>
</tr>
<tr>
<td>Reteplose (tPA)</td>
<td>10 units x 2 IV Given 30 minutes apart</td>
<td>No</td>
<td>13</td>
<td>Yes</td>
</tr>
<tr>
<td>Tenecteplase (tPA)</td>
<td>Weight based IV push</td>
<td>No</td>
<td>90</td>
<td>Yes</td>
</tr>
<tr>
<td>Streptokinase</td>
<td>250,000 unit bolus IV Then 100,000 units over 12-24 hours</td>
<td>Yes</td>
<td>23</td>
<td>No</td>
</tr>
<tr>
<td>Urokinase</td>
<td>4,400 unit/kg bolus IV Then 4,400 units/kg/hour over 12-24 hours</td>
<td>Yes</td>
<td>20</td>
<td>No</td>
</tr>
</tbody>
</table>

Risk of Bleeding

Package Inserts

- Alteplase
  - Intracranial hemorrhage (ICH) in 0.4% of patients

- Tenecteplase
  - Major bleeding in 4.7% of patients
  - ICH in 0.9% of patients

Registry Data

- International Cooperative PE Registry (ICOPER)
  - 21.7% major bleeding
  - ICH in 3.0% of patients
- Polish Registry (ZATPOL)
  - 19% major bleeding
  - Major bleeding was an independent predictor of 90 day mortality

Contraindications to Thrombolysis

**Absolute**

- Previous ICH at any time
- Ischemic stroke in past 3 months
- Active bleeding
- Recent neurosurgical procedure
- Recent head trauma with fracture or brain injury
- Bleeding diathesis
- Structural intracranial disease

**Relative**

- Blood pressure >180/110
- Recent bleeding, surgery, or invasive procedure
- Ischemic stroke >3 months prior
- Anticoagulation therapy
- Traumatic cardiopulmonary resuscitation
- Pericarditis or pericardial fluid
- Diabetic retinopathy
- Pregnancy
- Age >75 years old
- Low body weight (<60 kg)
- Female
- African American

Guideline Summary

<table>
<thead>
<tr>
<th></th>
<th>CHEST Guidelines</th>
<th>European Society of Cardiology</th>
<th>American Heart Association</th>
</tr>
</thead>
<tbody>
<tr>
<td>Last Update</td>
<td>2016</td>
<td>2014</td>
<td>2011</td>
</tr>
<tr>
<td>Factors Used for Risk Classification</td>
<td>Hypotension</td>
<td>Hypotension RV imaging</td>
<td>Hypotension RV imaging</td>
</tr>
<tr>
<td>Use in High Risk</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Use in Intermediate Risk</td>
<td>Consider if deteriorating after anticoagulation</td>
<td>Consider if intermediate-high risk</td>
<td>Consider if RV strain or deteriorating</td>
</tr>
<tr>
<td>Use in Low Risk</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>
Systemic Thrombolysis

**PEITHO - 2014**

<table>
<thead>
<tr>
<th>Design</th>
<th>Study Population</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multicenter, Prospective,</td>
<td>Inclusion</td>
<td>Primary</td>
</tr>
<tr>
<td>Double-blind, Randomized</td>
<td>Confirmed PE</td>
<td>Death from any cause or hemodynamic decapsulation or collapse within 7 days</td>
</tr>
<tr>
<td>Controlled Trial</td>
<td>RV dysfunction</td>
<td>Safety</td>
</tr>
<tr>
<td>n = 1006</td>
<td>Positive troponins</td>
<td>Ischemic or hemorrhagic stroke and extracranial bleeding within 7 days</td>
</tr>
<tr>
<td><strong>Treatment Group (n = 506)</strong></td>
<td></td>
<td>Follow-up</td>
</tr>
<tr>
<td>Tenecteplase IV push + UFH</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;60 kg: 30 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>60-69 kg: 35 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>70-79 kg: 40 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥80 kg: 45 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Control Group (n = 499)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo IV push + UFH</td>
<td></td>
<td></td>
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</tbody>
</table>

**PEITHO: Outcomes**

<table>
<thead>
<tr>
<th></th>
<th>TG n = 506</th>
<th>CG n = 499</th>
<th>p value</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Outcome at 7 days, n (%)</td>
<td>13 (2.6)</td>
<td>28 (5.6)</td>
<td>0.02</td>
<td>0.44</td>
</tr>
<tr>
<td>Death from any cause, n (%)</td>
<td>6 (1.2)</td>
<td>9 (1.8)</td>
<td>0.42</td>
<td>0.65</td>
</tr>
<tr>
<td>Hemodynamic decompensation, n (%)</td>
<td>8 (1.6)</td>
<td>25 (5.0)</td>
<td>0.002</td>
<td>0.30</td>
</tr>
<tr>
<td>Rescue Fibrinolysis, n (%)</td>
<td>4 (0.8%)</td>
<td>23 (4.6%)</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Mechanical Ventilation, n (%)</td>
<td>8 (1.6%)</td>
<td>15 (3.0%)</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Death from any cause at 30 days, n (%)</td>
<td>12 (2.4%)</td>
<td>16 (3.2%)</td>
<td>0.42</td>
<td>0.73</td>
</tr>
</tbody>
</table>

**PEITHO: Subgroups**

<table>
<thead>
<tr>
<th>Subgroup Analysis</th>
<th>Odds Ratio</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender Male</td>
<td>0.06 (0.96-1.06)</td>
<td>0.90</td>
</tr>
<tr>
<td>Age &gt;75 years</td>
<td>0.50 (0.37-0.68)</td>
<td>0.06</td>
</tr>
<tr>
<td>History of VTE no</td>
<td>0.39 (0.25-0.61)</td>
<td>0.002</td>
</tr>
<tr>
<td>Symptom Onset &lt;24 hours</td>
<td>0.79 (0.32-1.97)</td>
<td>0.69</td>
</tr>
<tr>
<td>Heart Rate &lt;100 bpm</td>
<td>0.80 (0.69-0.91)</td>
<td>0.003</td>
</tr>
<tr>
<td>Respiratory rate &lt;24 bpm</td>
<td>0.79 (0.70-2.19)</td>
<td>0.91</td>
</tr>
</tbody>
</table>

**PEITHO: Safety Outcomes**

<table>
<thead>
<tr>
<th></th>
<th>TG n = 506</th>
<th>CG n = 499</th>
<th>p value</th>
<th>Odds Ratio</th>
<th>NNH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bleeding within 7 days, n (%)</td>
<td>32 (6.3)</td>
<td>58 (11.5)</td>
<td>&lt;0.001</td>
<td>5.55</td>
<td>19</td>
</tr>
<tr>
<td>Major extracranial bleeding</td>
<td>165 (32.6)</td>
<td>6 (1.2)</td>
<td>12 (2.4)</td>
<td>43 (8.6)</td>
<td></td>
</tr>
<tr>
<td>Minor bleeding</td>
<td>32 (6.3)</td>
<td>58 (11.5)</td>
<td>&lt;0.001</td>
<td>5.55</td>
<td>19</td>
</tr>
<tr>
<td>Stroke within 7 days, n (%)</td>
<td>12 (2.4)</td>
<td>10 (2.0)</td>
<td>0.003</td>
<td>12.10</td>
<td>45</td>
</tr>
<tr>
<td>Composite stroke</td>
<td>12 (2.4)</td>
<td>10 (2.0)</td>
<td>0.003</td>
<td>12.10</td>
<td>45</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>12 (2.4)</td>
<td>10 (2.0)</td>
<td>0.003</td>
<td>12.10</td>
<td>45</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Serious adverse events within 30 days, n (%)</td>
<td>55 (10.9)</td>
<td>59 (11.8)</td>
<td>0.63</td>
<td>0.91</td>
<td>--</td>
</tr>
</tbody>
</table>

**PEITHO: Hemorrhagic Stroke**

- 60% female
- Age range 65-80 years old
- Four deceased at 30 days
- TG patients with hemorrhagic stroke (n = 10)
- One with moderate disability
- Four with no to slight disability
PEITHO: Author’s Conclusions

• Use of tenecteplase in intermediate risk PE
  – Reduced hemodynamic decomposition
  – Non-significant decrease in early death
• Significantly increased the risk of bleeding
  – Risk of hemorrhagic stroke consistent with other reports
  – Thrombolysis may be associated with a lower risk of bleeding in patients younger than 75 years old
• Caution is warranted when considering thrombolytic therapy in this patient population

PEITHO: Implications

Strengths
• Randomized controlled trial
• Large sample size
• Multicenter

Weaknesses
• Short duration of follow-up
• No central lab to interpret CT and echo results
• Not powered to detect mortality difference
• Clinical significance of decompensation outcomes is unclear

Conclusions about Systemic Thrombolysis

NNT from PEITHO:
• 28 for death and hemodynamic decompensation at 7 days
• 45 for composite stroke
• 19 for extracranial bleeding

Patient Case

HP is a 82 year old Hispanic male with PMH of diabetes admitted 4 days ago with a hip fracture. He is now POD#3 from surgery, and complains of increasing dyspnea for the past 24 hours.
Vitals: HR 83 bpm, BP 102/68 mmHg, RR 20 rpm, O₂ sat 98%
Troponin-I: 1.7 ng/mL
CT angiography is positive for pulmonary embolism. Should you recommend using a thrombolytic for HP?
1. Which risk category does HP fall into?
2. What are HP’s risk factors for bleeding?

Conclusions about Systemic Thrombolysis

NNT from PEITHO:
• 28 for death and hemodynamic decompensation at 7 days
• 45 for composite stroke
• 19 for extracranial bleeding

Watchful Waiting
• Low mortality rates in PEITHO
• Ability to monitor patients
• Wait to see if signs of decompensation develop prior to using systemic thrombolytics

Patient Case

HP is a 82 year old Hispanic male with PMH of diabetes admitted 4 days ago with a hip fracture. He is now POD#3 from surgery, and complains of increasing dyspnea for the past 24 hours.
Vitals: HR 83 bpm, BP 102/68 mmHg, RR 20 rpm, O₂ sat 98%
Troponin-I: 1.7 ng/mL
CT angiography is positive for pulmonary embolism. Should you recommend using a thrombolytic for HP?
1. Which risk category does HP fall into?
2. What are HP’s risk factors for bleeding?
3. Should systemic thrombolytics be used?
Patient Case: HP

A few hours later, HP's blood pressure reading is 94/54 mmHg, and he is still complaining of dyspnea.

The team orders an echocardiogram. Results show RV dilation with an RV/LV ratio of 1.1.

1. Which risk category does HP fall into?
2. What are HP's risk factors for bleeding?
3. Should systemic thrombolytics be used?
4. Now that HP is deteriorating, let's consider some alternative options.

MOPPET - 2013

<table>
<thead>
<tr>
<th>Study Population</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Primary</td>
</tr>
<tr>
<td></td>
<td>Safety</td>
</tr>
<tr>
<td></td>
<td>Follow-up</td>
</tr>
<tr>
<td></td>
<td>Hospital stay, mean days ± SD</td>
</tr>
<tr>
<td></td>
<td>Bleeding, n (%)</td>
</tr>
<tr>
<td>Single Center, Prospective, Open-label, Randomized Controlled Trial: n = 121</td>
<td></td>
</tr>
<tr>
<td>Treatment Group (n = 58): IV alteplase 10 mg bolus with remainder over one hour + LMWH or UFH ≥50 kg 50 mg ≤50 kg 0.5 mg/kg</td>
<td></td>
</tr>
<tr>
<td>Control Group (n = 56): LMWH or UFH only</td>
<td></td>
</tr>
<tr>
<td>LMWH: low molecular weight heparin (enoxaparin)</td>
<td></td>
</tr>
<tr>
<td>UFH: unfractionated heparin infusion</td>
<td></td>
</tr>
</tbody>
</table>

MOPPET: Results

<table>
<thead>
<tr>
<th>Primary Outcome</th>
<th>TG n = 58</th>
<th>CG n = 56</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary HTN, n (%)</td>
<td>9 (16%)</td>
<td>32 (57%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Recurrent PE, n (%)</td>
<td>9 (16%)</td>
<td>35 (63%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total mortality, n (%)</td>
<td>1 (1.6%)</td>
<td>3 (5%)</td>
<td>0.30</td>
</tr>
<tr>
<td>Total mortality plus recurrent PE, n (%)</td>
<td>1 (1.6%)</td>
<td>6 (10%)</td>
<td>0.49</td>
</tr>
<tr>
<td>Hospital stay, mean days ± SD</td>
<td>2.2 ± 0.5</td>
<td>4.9 ± 0.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Bleeding, n (%)</td>
<td>0</td>
<td>0</td>
<td>---</td>
</tr>
</tbody>
</table>

MOPPET: Author's Conclusions

• Low dose tPA is safe and effective in intermediate risk PE
  – Significant and maintainable decrease in pulmonary artery systolic pressure
  – No major or minor bleeding events
• Possible mechanism
  – Lungs receive 100% of cardiac output
  – Other organs receive only a fraction of cardiac output
  – Lower tPA doses result in equivalent or higher concentrations
• Future studies may examine even lower doses of tPA

MOPPET: Implications

Strengths

- Randomized controlled trial
- Extended follow-up period

Weaknesses

- Small sample size, single center, open-label
- Did not require RV dysfunction or elevated cardiac biomarkers
- Excluded patients eligible for full dose thrombolysis
- No definition provided for bleeding events
- Unusually high incidence of pulmonary HTN at 28 months
- Pulmonary HTN diagnosed by echo, not catheterization

Low dose thrombolysis = hypothesis generating, but not yet recommended
Catheter Directed Thrombolysis (CDT)

Types of CDT

- Mechanical CDT
- Pharmacologic CDT
  - Alone
  - Plus mechanical CDT
  - Plus ultrasound to enhance fibrinolysis
- Experience and equipment required

Major CDT Trials: Design

<table>
<thead>
<tr>
<th>Trial</th>
<th>Design</th>
<th>n</th>
<th>PE Type</th>
<th>Protocol</th>
</tr>
</thead>
<tbody>
<tr>
<td>ULTIMA</td>
<td>Randomized controlled, open label</td>
<td>59</td>
<td>Intermediate Risk</td>
<td>USAT with 10 mg tPA over 15 hours + UFH vs UFH alone</td>
</tr>
<tr>
<td>SEATTLE II</td>
<td>Prospective, single-arm</td>
<td>150</td>
<td>High and Intermediate Risk</td>
<td>USAT plus 24 mg tPA at 1 mg/hour + UFH</td>
</tr>
<tr>
<td>PERFECT</td>
<td>Prospective, registry</td>
<td>101</td>
<td>High and Intermediate Risk</td>
<td>Various types of CDT + low dose UFH 36% USAT 64% thrombolytic only</td>
</tr>
</tbody>
</table>

USAT: ultrasound assisted thrombolysis
UFH: unfractionated heparin infusion

Major CDT Trials: Results

<table>
<thead>
<tr>
<th>Trial</th>
<th>Primary Outcome</th>
<th>Major Bleeding</th>
<th>Additional Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>ULTIMA</td>
<td>Change in RV/LV ratio at 24 hours</td>
<td>No events</td>
<td>Change in RV/LV ratio at 90 days was significant in both arms, with no difference between arms (p = 0.36)</td>
</tr>
<tr>
<td>SEATTLE II</td>
<td>Change in RV/LV ratio at 48 hours</td>
<td>10% of patients</td>
<td>No intracranial hemorrhage, significant change in PA pressure (change -14 mmHg, p&lt;0.001)</td>
</tr>
<tr>
<td>PERFECT</td>
<td>Clinical success and survival to discharge</td>
<td>No events</td>
<td>No difference in PA pressure change between USAT and traditional CDT (p=0.90)</td>
</tr>
</tbody>
</table>

RV/LV ratio: right ventricular to left ventricular ratio (>0.9 indicates RV strain)
PA: pulmonary artery

CDT Conclusions

Strengths
- Localized therapy
- Improved hemodynamics
- Smaller doses
- Low bleed rates

Weaknesses
- No long term data
- No outcomes data
- Complications
- Equipment and expertise required

Current Guideline Recommendations
- ESC: alternative to surgical thrombectomy for patients in whom full dose thrombolysis is contraindicated or has failed (IIa, C)
- Chest: alternative in patients who have high bleed risk or failed systemic thrombolysis (2C)
- Both recommend systemic thrombolysis over CDT when thrombolysis is indicated
Conclusions

• Empiric systemic thrombolysis in intermediate risk PE
  – Decreased risk of hemodynamic decompensation
  – No mortality benefit
  – Increased risk of bleeding
  – No long term data
• Alternative options for patients with high bleed risk
  – CDT is promising, dependent on cost and availability
  – Low dose thrombolysis is another option if CDT is not possible
• More studies are needed
  – Determine the most appropriate dosing strategy
  – Long term clinical outcomes

Patient Case: HP

A few hours later, HP’s blood pressure reading is 94/54 mmHg, and he is still complaining of dyspnea. Echocardiogram shows RV dilation with an RV/LV ratio of 1.1.

1. Which risk category does HP fall into?
2. What are HP’s risk factors for bleeding?
3. Should systemic thrombolytics be used?
4. Now that HP is deteriorating, let’s consider some alternative options – low dose thrombolysis and CDT.
5. Considering all risks and benefits, what is your plan for HP?

Recommendations

After Risk Stratification:

Intermediate Risk PE
Watch and Wait

Decompensation?

Evaluate

NO

YES

Systemic Thrombolysis

High Bleed Risk?

NO

YES

CDT if available; consider low dose thrombolysis

Appendix D

Acknowledgements

Mitch Daley, PharmD, BCPS
Emily Hodge, PharmD, BCCCP
Manasa Murthy, PharmD, BCPS

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Appendices

Appendix A: Risk Stratification of PE
Appendix B: Thrombolytic Agents
Appendix C: PEITHO Subgroups
Appendix D: Recommendations
Appendix E: Pulmonary Embolism Severity Index (PESI)
Appendix F: Abbreviations
Appendix A: Risk Stratification of PE

- **High Risk**
  - YES: Shock or Hypotension?
  - NO: Dilated RV or Elevated Biomarkers?\(^1\)

- **Intermediate Risk\(^2\)**
  - YES: Dilated RV or Elevated Biomarkers?\(^1\)
  - NO: Low Risk

- **Low Risk**

\(^1\)CHEST uses deterioration after anticoagulation instead of tests. ESC also allows use of PESI score (appendix E)
\(^2\)ESC differentiates intermediate-high risk if both are present, intermediate-low risk if only one present
## Appendix B: Thrombolytic agents

<table>
<thead>
<tr>
<th>Generic</th>
<th>FDA Dosing</th>
<th>FDA Indication?</th>
<th>Half-life (minutes)</th>
<th>Fibrin Selective?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alteplase (tPA)</td>
<td>100 mg IV Over 2 hours</td>
<td>Yes</td>
<td>5</td>
<td>Yes</td>
</tr>
<tr>
<td>Reteplase (tPA)</td>
<td>10 units x 2 IV Given 30 minutes apart</td>
<td>No</td>
<td>13</td>
<td>Yes</td>
</tr>
<tr>
<td>Tenecteplase (tPA)</td>
<td>Weight based IV push &lt;60 kg: 30 mg 60-69 kg: 35 mg 70-79 kg: 40 mg 80-89 kg: 45 mg ≥90 kg: 50 mg</td>
<td>No</td>
<td>90</td>
<td>Yes</td>
</tr>
<tr>
<td>Streptokinase</td>
<td>250,000 unit bolus IV Then 100,000 units over 12-24 hours</td>
<td>Yes</td>
<td>23</td>
<td>No</td>
</tr>
<tr>
<td>Urokinase</td>
<td>4,400 unit/kg bolus IV Then 4,400 units/kg/hour over 12-24 hours</td>
<td>Yes</td>
<td>20</td>
<td>No</td>
</tr>
</tbody>
</table>

* tPA: tissue plasminogen activator

Circulation 2011; 123: 1788-1830
## Appendix C: PEITHO Subgroups

### Subgroup Analysis

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Odds Ratio</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>0.46 (0.16-1.18)</td>
<td>0.90</td>
</tr>
<tr>
<td>Female</td>
<td>0.42 (0.16-1.12)</td>
<td></td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤75 years</td>
<td>0.33 (0.13-0.85)</td>
<td>0.36</td>
</tr>
<tr>
<td>&gt;75 years</td>
<td>0.63 (0.24-1.66)</td>
<td></td>
</tr>
<tr>
<td><strong>History of VTE</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>0.394 (0.177-0.877)</td>
<td>0.502</td>
</tr>
<tr>
<td>Yes</td>
<td>0.656 (0.187-2.294)</td>
<td></td>
</tr>
<tr>
<td><strong>Symptom Onset</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤24 hours</td>
<td>0.484 (0.211-1.107)</td>
<td>0.690</td>
</tr>
<tr>
<td>&gt;24 hours</td>
<td>0.362 (0.114-1.153)</td>
<td></td>
</tr>
<tr>
<td><strong>Heart Rate</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤100 bpm</td>
<td>0.488 (0.216-1.102)</td>
<td>0.799</td>
</tr>
<tr>
<td>&gt;100 bpm</td>
<td>0.404 (0.122-1.341)</td>
<td></td>
</tr>
<tr>
<td><strong>Respiratory Rate</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤24 rpm</td>
<td>0.789 (0.307-2.028)</td>
<td>0.028</td>
</tr>
<tr>
<td>&gt;24 rpm</td>
<td>0.062 (0.008-0.489)</td>
<td></td>
</tr>
</tbody>
</table>

*Note: The odds ratios and p-values are derived from the study published in N Engl J Med 2014; 370: 1402-11.*
Appendix D: Recommendations

After Risk Stratification:
- Intermediate Risk PE: Watch and Wait

Decompensation?
- NO: EVALUATE
- YES:
  - YES: CDT if available; consider low dose thrombolysis
  - NO: High Bleed Risk?
    - NO: Systemic thrombolysis
    - YES:
      - NO: Systemic thrombolysis
      - YES: CDT if available; consider low dose thrombolysis
## Appendix E: Pulmonary Embolism Severity Index (PESI)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Original PESI</th>
<th>Simplified PESI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>Age in years</td>
<td>1 point if &gt;80 years</td>
</tr>
<tr>
<td><strong>Male sex</strong></td>
<td>10 points</td>
<td>--</td>
</tr>
<tr>
<td><strong>Cancer</strong></td>
<td>30 points</td>
<td>1 point</td>
</tr>
<tr>
<td><strong>Chronic heart failure</strong></td>
<td>10 points</td>
<td>1 point total</td>
</tr>
<tr>
<td><strong>Chronic pulmonary disease</strong></td>
<td>10 points</td>
<td></td>
</tr>
<tr>
<td><strong>Pulse ≥ 110 bpm</strong></td>
<td>20 points</td>
<td>1 point</td>
</tr>
<tr>
<td><strong>Systolic BP &lt;100 mmHg</strong></td>
<td>30 points</td>
<td>1 point</td>
</tr>
<tr>
<td><strong>Respiratory rate &gt;30 breaths/min</strong></td>
<td>20 points</td>
<td>--</td>
</tr>
<tr>
<td><strong>Temperature &lt;36 °C</strong></td>
<td>20 points</td>
<td>--</td>
</tr>
<tr>
<td><strong>Altered mental status</strong></td>
<td>60 points</td>
<td>--</td>
</tr>
<tr>
<td><strong>Oxyhemoglobin saturation &lt;90%</strong></td>
<td>20 points</td>
<td>1 point</td>
</tr>
</tbody>
</table>
# Appendix E: Pulmonary Embolism Severity Index (PESI)

<table>
<thead>
<tr>
<th>Original PESI</th>
<th>Simplified PESI</th>
<th>Risk Stratification</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Class I: ≤65 points</strong>&lt;br&gt;0-1.6% mortality risk</td>
<td>0 points&lt;br&gt;1.0% mortality risk (CI 0-2.1%)</td>
<td>Low risk</td>
</tr>
<tr>
<td><strong>Class II: 66-85 points</strong>&lt;br&gt;1.7-3.5% mortality risk</td>
<td>≥1 point&lt;br&gt;10.9% mortality risk (CI 8.5-13.2%)</td>
<td>Intermediate risk if normotensive&lt;br&gt;High risk if hypotensive</td>
</tr>
</tbody>
</table>
Appendix F: Abbreviations

BNP: brain natriuretic protein
BP: blood pressure
CDT: catheter directed thrombolysis
CG: control group
CT: computed tomography
CTEPH: chronic thromboembolic pulmonary hypertension
DVT: deep vein thrombosis
ESC: European Society of Cardiology
HR: hazard ratio
HR: heart rate
HTN: hypertension
ICH: intracranial hemorrhage
IV: intravenous
LMWH: low molecular weight heparin
NNH: number needed to harm
NNT: number needed to treat
O₂ sat: oxygen saturation
PE: pulmonary embolism
RR: respiratory rate
RV: right ventricle
RV/LV ratio: right ventricle to left ventricle ratio
SBP: systolic blood pressure
TG: treatment group
tPA: tissue plasminogen activator
UFH: unfractionated heparin
USAT: ultrasound assisted thrombolysis
VTE: venous thromboembolism