Catheter-directed Thrombolysis for Pulmonary Embolism

*Is It Good Advice to Lyse?*

Texas Society of Health-System Pharmacists

April 7, 2018

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Adjunct Assistant Professor, UT Health San Antonio, Department of Medicine, Division of Pulmonary Diseases and Critical Care Medicine
Financial Disclosures

• I have no conflicts of interest to disclose.
**Pharmacist Learning Objectives:**

1. Classify a patient with pulmonary embolism into the appropriate risk category using the PESI or simplified PESI score.
2. Evaluate the current guideline recommendations for the role of thrombolysis for treatment of pulmonary embolism.
3. Compare efficacy of systemic versus catheter-directed thrombolysis.

**Technician Learning Objectives:**

1. Determine the appropriate risk category for a patient with pulmonary embolism.
2. State the current guideline recommendations for the role of thrombolysis for treatment of pulmonary embolism.
3. Describe how ultrasound-assisted catheter-directed thrombolysis works.
4. Evaluate efficacy and the risk of bleeding with systemic versus catheter-directed thrombolysis.
Acute pulmonary embolism (PE)
- Symptoms begin immediately after obstruction of pulmonary arteries
- 3rd most common cause of cardiovascular related death
- Incidence
  - 112 cases per 100,000
  - Male > female
  - Older age
- 200,000 deaths each year in US

Definitions

Low Risk
• No evidence of right ventricular strain

Intermediate Risk
• Evidence of right ventricular strain

High Risk
• Hypotension due to PE (SBP<90 mmHg)

75% 20-25% 5%

PE: pulmonary embolism
SBP: systolic blood pressure

Complications

- Recurrent VTE
- CTEPH
- Hemodynamic compromise
- Death

VTE: venous thromboembolism
CTEPH: chronic thromboembolic pulmonary hypertension

CC: “I can’t breathe”
HPI: MH is a 54-year-old female who presents to the emergency room with shortness of breath and pleuritic chest pain. The shortness of breath began yesterday and has continued to progressively worsen.
PMH: none
PSH: none
Medications: Excedrin 2 tabs PRN headaches
Vital Signs: T 100.2°F, HR 118 bpm, RR 22 bpm, BP 128/72 mmHg, SaO₂ 88%
Height: 64 inches; Weight 123 kg
Patient Case

**Labs:**

- 142
- 102
- 9
- 8.3
- TnI 0.528 → 1.24
- 105
- 6.1
- 245
- BNP 82 → 186
- 3.7
- 25
- 0.8
- 29.2
- D Dimer >7360

**Imaging:**

- **Doppler Ultrasound:** (+) occlusive left popliteal deep vein thrombosis

- **CT PE Protocol:** extensive pulmonary emboli in bilateral upper, middle, and lower lobar, segmental, and subsegmental arteries with mild dilation of right ventricle

- **Echocardiogram:** left ventricular ejection fraction >70%, estimated pulmonary artery systolic pressure 31 mmHg, right ventricular dilation and bowing

- **Pulmonary angiogram:** extensive PE with pulmonary artery pressures 48/18 mmHg
### Pulmonary Severity Index Score (PESI)

#### Clinical Feature Points

<table>
<thead>
<tr>
<th>Clinical Feature</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (X e.g., 65)</td>
<td></td>
</tr>
<tr>
<td>Male gender</td>
<td>10</td>
</tr>
<tr>
<td>History of cancer</td>
<td>30</td>
</tr>
<tr>
<td>Heart failure</td>
<td>10</td>
</tr>
<tr>
<td>Chronic lung disease</td>
<td>10</td>
</tr>
<tr>
<td>Pulse ≥100 bpm</td>
<td>20</td>
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<td>Systolic blood pressure &lt;100mmHg</td>
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<tr>
<td>Respiratory rate ≥30/min</td>
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<tr>
<td>Temperature &lt;36°C</td>
<td>20</td>
</tr>
<tr>
<td>Altered mental status</td>
<td>60</td>
</tr>
<tr>
<td>Arterial oxygen saturation &lt;90%</td>
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</tr>
</tbody>
</table>

#### Class Risk Points

<table>
<thead>
<tr>
<th>Class</th>
<th>Risk</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Low risk</td>
<td>&lt;66</td>
</tr>
<tr>
<td>II</td>
<td>Low risk</td>
<td>66 to 85</td>
</tr>
<tr>
<td>III</td>
<td>High risk</td>
<td>86 to 105</td>
</tr>
<tr>
<td>IV</td>
<td>High risk</td>
<td>106 to 125</td>
</tr>
<tr>
<td>V</td>
<td>≥125</td>
<td></td>
</tr>
</tbody>
</table>

### Simplified Pulmonary Embolism Severity Index (sPESI)

<table>
<thead>
<tr>
<th>Clinical Feature</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt; 80 years</td>
<td>1</td>
</tr>
<tr>
<td>History of cancer</td>
<td>1</td>
</tr>
<tr>
<td>Chronic cardiopulmonary disease</td>
<td>1</td>
</tr>
<tr>
<td>Pulse ≥ 110 bpm</td>
<td>1</td>
</tr>
<tr>
<td>Systolic blood pressure &lt; 100 mmHg</td>
<td>1</td>
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<tr>
<td>Arterial oxygen saturation &lt; 90% on room air</td>
<td>1</td>
</tr>
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<table>
<thead>
<tr>
<th>Risk</th>
<th>Points</th>
</tr>
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<tbody>
<tr>
<td>Low</td>
<td>0</td>
</tr>
<tr>
<td>High</td>
<td>&gt;1</td>
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</tbody>
</table>

1. Using the Pulmonary Severity Index Score (PESI) or Simplified Pulmonary Severity Index Score (sPESI), determine MH’s risk category.

   a. Low risk

   b. High risk
CC: “I can’t breathe”

HPI: MH is a 54-year-old female who presents to the emergency room with shortness of breath and pleuritic chest pain. The shortness of breath began yesterday and has continued to progressively worsen.

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### Class Risk Points

- **I** (Low risk)  | <66
- **II** (66 to 85) | 66 to 85
- **III** (High risk) | 86 to 105
- **IV**              | 106 to 125
- **V**               | ≥125

## Simplified Pulmonary Embolism Severity Index (sPESI)

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Treatment

Low Risk
- Establish peripheral IV access
- Oxygen supplementation
- Parenteral anticoagulation

Intermediate Risk
- Establish peripheral IV access
- Oxygen supplementation
- Fluid resuscitation
- Parenteral anticoagulation

High Risk
- Establish peripheral IV access
- Oxygen supplementation
- Fluid resuscitation
- Vasopressor support
- Parenteral anticoagulation

No thrombolysis

Consider thrombolysis if:
- Large clot burden, severe RV enlargement, high oxygen requirement, severe tachycardia

Systemic or catheter-directed thrombolysis if no contraindication
Mechanism of Action of Thrombolytics

1. Recombinant tPA binds to fibrin in thrombus
2. Converts entrapped plasminogen to plasmin
3. Plasmin initiates local fibrinolysis

Plasminogen
Activation
Plasmin
Dissolves fibrin
Fibrin degradation products

Thrombus
Fibrin threads

<table>
<thead>
<tr>
<th>Population</th>
<th>Recommendation</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute PE associated with hypotension (SBP 90&lt;mmHg)</td>
<td>FOR systemic thrombolysis</td>
<td>Grade 2B</td>
</tr>
<tr>
<td>Acute PE NOT associated with hypotension</td>
<td>AGAINST systemic thrombolysis</td>
<td>Grade 1B</td>
</tr>
<tr>
<td>Acute PE who deteriorate after starting anticoagulation but have yet to develop hypotension and who have a low bleeding risk</td>
<td>FOR systemic thrombolysis</td>
<td>Grade 2C</td>
</tr>
<tr>
<td>Acute PE who are treated with thrombolytic agent</td>
<td>FOR systemic administration in peripheral vein over catheter-directed therapy</td>
<td>Grade 2C</td>
</tr>
</tbody>
</table>
## Antithrombotic Therapy for VTE Disease

**CHEST Guideline and Expert Panel Report**

### Systemic Thrombolytic Therapy vs Anticoagulation Alone for Acute PE

<table>
<thead>
<tr>
<th>Outcomes</th>
<th># of participants</th>
<th>Relative Effect (95%CI)</th>
<th>Risk with Anticoagulation Alone</th>
<th>Risk Difference with Systemic Thrombolytic Therapy (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>2,115 (17 studies)</td>
<td>OR 0.53 (0.32-0.88)</td>
<td>39 per 1,000</td>
<td>18 fewer per 1,000 (from 5-26 fewer)</td>
</tr>
<tr>
<td>Recurrent PE</td>
<td>2,043 (15 studies)</td>
<td>OR 0.40 (0.22-0.74)</td>
<td>30 per 1,000</td>
<td>18 fewer per 1,000 (from 8-24 fewer)</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>2,115 (16 studies)</td>
<td>OR 2.73 (1.91-3.91)</td>
<td>34 per 1,000</td>
<td>54 more per 1,000 (from 29-87 more)</td>
</tr>
<tr>
<td>Intracranial hemorrhage</td>
<td>2,043 (15 studies)</td>
<td>OR 4.63 (1.78-12.04)</td>
<td>2 per 1,000</td>
<td>7 more per 1,000 (from 2 to 21 more)</td>
</tr>
</tbody>
</table>

Assessment of Efficacy vs Safety

• Meta-analysis of 16 trials with 2,115 patients, including 8 trials of 1775 patients with intermediate risk pulmonary embolism

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Thrombolysis</th>
<th>Anticoagulation Alone</th>
<th>Odds Ratio and 95% Confidence Interval</th>
<th>Number Needed to Treat or Harm</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>OVERALL</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-Cause Mortality</td>
<td>2.17% (23/1061)</td>
<td>3.89% (41/1054)</td>
<td>0.53 (0.32-0.88)</td>
<td>NNT 59</td>
</tr>
<tr>
<td>Risk of Major Bleeding</td>
<td>9.24% (98/1061)</td>
<td>3.42% (36/1054)</td>
<td>2.73 (1.91-3.91)</td>
<td>NNH 18</td>
</tr>
<tr>
<td>Age ≤65 years</td>
<td>2.84% (11/288)</td>
<td>2.27% (9/396)</td>
<td>1.25 (0.50-3.14)</td>
<td>--</td>
</tr>
<tr>
<td>Age &gt;65 years</td>
<td>12.93% (87/673)</td>
<td>4.10% (27/658)</td>
<td>3.10 (2.10-4.56)</td>
<td>NNH 11</td>
</tr>
<tr>
<td><strong>INTERMEDIATE RISK PE</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-Cause Mortality</td>
<td>1.39% (12/866)</td>
<td>2.92% (26/889)</td>
<td>0.48 (0.25-0.92)</td>
<td>NNT 65</td>
</tr>
<tr>
<td>Risk of Major Bleeding</td>
<td>7.74% (67/866)</td>
<td>2.25% (20/889)</td>
<td>3.19 (2.07-4.92)</td>
<td>NNH 18</td>
</tr>
</tbody>
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Actual Use of Thrombolysis

- Database study of 72,230 patients from Nationwide Inpatient Sample (1999-2008) with acute PE who were in shock or ventilator dependent.
2. Based on the 2016 ACCP Chest Guideline and Expert Panel Report on Antithrombotic Therapy for VTE Disease, which treatment regimen is most appropriate for MH at this time?

   a. Unfractionated heparin infusion
   b. Alteplase
   c. Catheter-directed alteplase
MH has become more symptomatic than on presentation. Her current oxygen saturation is 84% on room air and her current blood pressure has decreased to 102/60 mmHg.

3. Based on the 2016 ACCP Chest Guideline and Expert Panel Report on Antithrombotic Therapy for VTE Disease, which treatment regimen is most appropriate for MH at this time?

   a. Unfractionated heparin infusion
   b. Alteplase
   c. Catheter-directed alteplase
Contraindications to Thrombolysis

Absolute

- Structural intracranial disease
- Previous intracranial hemorrhage
- Recent brain or spinal surgery
- Recent head trauma with fracture or brain injury
- Active bleeding or bleeding diathesis
- Ischemic stroke in previous 3 months

Relative

- Severe uncontrolled hypertension
- Ischemic stroke >3 months ago
- Surgery within previous 10 days
- Pregnancy
- Trauma or prolonged CPR in previous 3 weeks
- Recent bleeding
- Active peptic ulcer
- Pericarditis or pericardial fluid
- Age > 75 years
- Diabetic retinopathy
- Anticoagulated

Safety of Systemic Thrombolysis

Comparison of 100 vs 50 mg Alteplase for Massive PE

- Overall: 10% for 100 mg, 3% for 50 mg
- <65 kg BMI: 41.20% for 100 mg, 14.80% for 50 mg
- BMI <24 kg/m²: 42.90% for 100 mg, 8.70% for 50 mg


Fibrinolysis with Tenecteplase in Submassive PE

- Minor Bleeding: 32.6% for Tenecteplase, 8.6% for Placebo
- Major Bleeding: 11.5% for Tenecteplase, 2.4% for Placebo
- Hemorrhagic Stroke: 2.0% for Tenecteplase, 0.2% for Placebo

Safety of Systemic Thrombolysis

Major Extracranial Bleeding

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Tenecteplase (N=506)</th>
<th>Placebo (N=499)</th>
<th>Odds Ratio (95% CI)</th>
<th>P Value for Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;75 yr</td>
<td>14/244 (5.8)</td>
<td>5/225 (2.2)</td>
<td>2.80 (1.00–7.86)</td>
<td>0.09</td>
</tr>
<tr>
<td>&gt;75 yr</td>
<td>18/162 (11.1)</td>
<td>1/164 (0.6)</td>
<td>20.38 (2.69–154.53)</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>11/242 (4.5)</td>
<td>4/231 (1.7)</td>
<td>2.70 (0.85–8.61)</td>
<td>0.13</td>
</tr>
<tr>
<td>Female</td>
<td>21/264 (8.0)</td>
<td>2/268 (0.7)</td>
<td>11.49 (2.67–49.53)</td>
<td></td>
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</table>

Overall Bleeding Rate: ≈10-20%
Intracranial Hemorrhage: up to 3%

More likely to bleed if:
- Older (>65 years)
- Lower weight (<65 kg or BMI<24kg/m²)
- Female

Catheter-Directed Thrombolysis

- Alternative option to systemic thrombolysis
  - Types:
    - Ultrasound assisted techniques may aid clot dissolution
    - Mechanical clot removal
  - Lower dose of thrombolytic $\rightarrow$ ↓ bleeding?
  - Rationale for use
    - Achieves a high local concentration by infusing thrombolytic directly into PE
    - ↑ thrombus fragmentation
    - ↑ thrombus permeability from ultrasound
  - Limitations
    - Availability
    - Faster delivery with systemic thrombolysis

Consider in:

- Persistent hemodynamic instability despite systemic thrombolysis
- Clinical deterioration despite anticoagulation
- High risk of bleeding
Ultrasound-Assisted, Catheter-Directed Thrombolysis

https://www.btg-im.com/en-GB/EKOS/Disease-states/Pulmonary-Embolism
Ultrasound-Assisted Catheter-Directed Thrombolysis

How Does It Work?

• Delivers low energy, high frequency (2.2 MHz) ultrasound and drug

• Drug is actively delivered into clot by acoustic streaming
  - Helps to unwind fibrin strands
  - ↑ transport of alteplase into fibrin bundles
  - ↑ clot dissolution

Drug Administration in Ultrasound-Assisted, Catheter-Directed Thrombolysis

- **Drug lumen**
  - Alteplase (10 mg/100 mL)
    - Unilateral PE: 1 mg/hour x 24 hours
    - Bilateral PE: 0.5-1 mg/hour x 12-24 hours
    - Maximum dose: 24 mg
  - Maximum flow 35 mL/hour

- **Coolant**
  - Heparinized or normal saline at room temperature
  - Rate: 35 to 120 mL/hour

- **Heparin**: therapeutic or subtherapeutic
  - Goals studied:
    - Factor Xa inhibition: 0.3-0.7 IU/mL
    - During procedure: target aPTT 40-60 seconds; after procedure: target aPTT 60-80 seconds

Ultrasound-Assisted Catheter-Directed Thrombolysis

https://www.btg-im.com/en-GB/EKOS/Learning-Center/EKOS-sup-trade;-sup-Inservice
EkoSonic™ Catheter In place

Follow up Angiogram demonstrating complete lysis.
Right Ventricular Effects of CDT

Before:
- RV:LV ratio 2.1
- Septal bowing (arrow)

After:
- RV:LV ratio < 0.9

4. MH is initiated on ultrasound-assisted, catheter directed thrombolysis. Which of the following drug and rate pair is NOT correct for this technique?

a. Unfractionated heparin infusion: 18 units/kg/hour

b. Alteplase: 50 mg/hour x 2 hours

c. Alteplase: 1 mg/hour x 24 hours

d. Normal saline: 150 mL/hour
# Efficacy of Catheter-Directed Thrombolysis

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<tr>
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<th>ULTIMA Study 2014</th>
<th>SEATTLE II Study 2015</th>
<th>PERFECT Registry 2015</th>
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<tr>
<td><strong>Design</strong></td>
<td>Prospective</td>
<td>Prospective, single-arm study</td>
<td>Prospective registry study USAT and standard CDT</td>
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<td></td>
<td>USAT vs. UFH alone</td>
<td></td>
<td>USAT and standard CDT</td>
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<tr>
<td><strong>Sample Size</strong></td>
<td>59 (30 USAT, 29 UFH alone)</td>
<td>150</td>
<td>101</td>
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<tr>
<td><strong>Intervention</strong></td>
<td></td>
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<tr>
<td>Alteplase</td>
<td>1 mg/h x 5 h, 0.5 mg/h x 10 h</td>
<td>24 mg total, either as 1 mg/h x 24h (unilateral) or 1 mg/h each x 12 h (bilateral)</td>
<td>0.5-1 mg/h or urokinase 100,000 units/h</td>
</tr>
<tr>
<td>Heparin</td>
<td>80 IU/kg, 18 units/kg/h Target: Anti-Xa 0.3-0.7 IU/mL</td>
<td>UFH with target aPTT 40-60s during tPA infusion, 60-80 s after tPA infusion</td>
<td>300-500 units/h</td>
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USAT: ultrasound-assisted thrombolysis
UFH: unfractionated heparin
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<td><strong>Average thrombolytic dose</strong></td>
<td>Bilateral: 20.8 ± 3 mg</td>
<td>23.7 ± 2.9 mg</td>
<td>28.0 ± 11 mg (n=76)</td>
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<td></td>
<td>Unilateral: 10.5 ± 0.6 mg</td>
<td></td>
<td>USAT: 30.27 ± 9.07 mg (over 23 h)</td>
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<td>Standard CDT: 25.63 ± 11.71 mg over 21 h</td>
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<tr>
<td><strong>Efficacy</strong></td>
<td>↓ mean RV/LV ratio</td>
<td>↓25% RV:LV ratio</td>
<td>Clinical Success</td>
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<td>• 0.30 (sd 0.20) vs 0.03 (sd 0.16), p &lt; 0.0001</td>
<td>↓30% pulmonary artery systolic pressure</td>
<td>Massive PE: 24/28 patients (85.7%, 67.3%-96.0%)</td>
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<td>• ↓ pulmonary pressures</td>
<td>↓30% in anatomical clot burden</td>
<td>Submassive PE: 71/73 patients (97.3%, 90.5%-99.7%)</td>
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<td></td>
<td>• No recurrent PE</td>
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<td>84.8% showed improvement in PAP</td>
</tr>
<tr>
<td></td>
<td>• No hemodynamic decompensation</td>
<td></td>
<td>89% had improvement in right-sided heart strain</td>
</tr>
<tr>
<td><strong>Bleeding</strong></td>
<td>Major bleeding: 0</td>
<td>Major bleeding: 15 (10%)</td>
<td>Major bleeding: 0</td>
</tr>
<tr>
<td></td>
<td>Minor bleeding: 4 (3 USAT, 1 UFH)</td>
<td>• 94% GUSTO moderate bleeds</td>
<td>Minor bleeding: 12.9%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• 1 severe bleed</td>
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<tr>
<td></td>
<td></td>
<td>• More likely if older, massive PE, or multiple access attempts</td>
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</tbody>
</table>
Efficacy of Catheter-Directed Thrombolysis

Efficacy & Safety of Systemic vs Catheter-Directed Thrombolysis

• High bleeding risk
  • PERFECT Registry
    • 9 patients with absolute contraindication to systemic alteplase
      - 1 received mechanical CDT only (no thrombolytic)
      - 8 received catheter-directed tPA infusion (average dose, 24.0 ± 13.2 mg) with no major bleeding events
    • 8/9 survived; 1 died of massive PE
  • Risk factors for bleeding:
    • Massive PE
    • Age ≥ 70 years
    • Major contraindication to thrombolysis

• Use in patients who failed thrombolysis
  • PERFECT Registry
    • 3 patients had a prior failure to systemic tPA
    • All 3 were successfully rescued with CDT
  • Prospective study of 13 patients with massive PE who failed thrombolysis
    • EKOS catheter with alteplase (1 mg/hour/catheter + UFH)
    • Improved RV:LV ratio, mPAP, and CO in 12 patients
    • No bleeding complications

Efficacy & Safety of Systemic vs Catheter-Directed Thrombolysis

Propensity Matched Study of 4,426 Patients
- In-hospital mortality:
  - Systemic (n=3,107): 14.94%
  - Catheter-directed (n=1,319): 6.12%
- In-hospital mortality + GI Bleed + ICH:
  - Systemic (n=3,107): 18.13%
  - Catheter-directed (n=1,319): 8.42%
- 30-day readmission:
  - Systemic (n=3,107): 10.58%
  - Catheter-directed (n=1,319): 7.65%

Propensity Matched Study of 1,521 Patients
- In-hospital mortality:
  - Systemic (n=1,169): 0.00%
  - Catheter-Directed (n=352): 13.36%
- In-hospital mortality + ICH:
  - Systemic (n=1,169): 21.81%
  - Catheter-Directed (n=352): 22.89%

GI: gastrointestinal
ICH: intracranial hemorrhage
Summary

Current Guidelines
• Massive versus submassive PE

Assess Risk
• PESI and sPESI score
• Clinical deterioration

Systemic vs CDT
• Massive: systemic
• Submassive: CDT?
Summary

- Older age?
- Low weight?
- Long-term outcomes?
- High Risk of Bleeding?
- Low BMI?

Contraindications to systemic thrombolysis?
Catheter-directed Thrombolysis for Pulmonary Embolism

Is It Good Advice to Lyse?

ACPE Continuing Education Credit

Pharmacist Code: shKi
Technician Code: WZ3d