Thrombolysis 2016 - Which Patient, Which Technique?

Matt Rondian, MD
Associate Professor of Medicine, University of Utah Molecular Medicine Program, Director of Precision Medicine, Center for Clinical and Translational Science, Investigator, Geriatric Research and Education Center, George E. Wahlene VAMC; Salt Lake City, Utah

Objectives:
• Describe the pharmacologic strategies available for thrombolysis for acute pulmonary embolism
• Describe the pharmacologic strategies available for thrombolysis for acute deep vein thrombosis
• Identify indications and contraindications for use of thrombolysis in patients with acute venous thromboembolism
Thrombolysis 2016 – Which Patient, Which Technique?

Matthew T. Rondina, M.D.
University of Utah Health Sciences Center
GRECC, George E. Wahlen VAMC

April 22, 2016
Learning Objectives

• Describe the pharmacologic strategies available for thrombolysis for acute pulmonary embolism.

• Describe the pharmacologic strategies available for thrombolysis for acute deep vein thrombosis.

• Recall indications and contraindications for use of thrombolysis in patients with acute venous thromboembolism.
Overview: Potential Benefits and Harms of Thrombolytic Therapy in PE and DVT

- **Potential Benefits**
  - More rapid symptom resolution
  - Cardiorespiratory stabilization without need for mechanical ventilation or vasopressor support
  - Reduction of RV damage
  - Improved exercise tolerance and QOL
  - Reduced risk of post-thrombotic syndrome
  - Prevention of recurrent VTE
  - Reduced mortality risk

- **Potential Harms**
  - Disabling or fatal hemorrhage (e.g. ICH, etc)
  - Increased risk of minor bleeding
    - May prolong hospitalization
    - May increase need for blood product replacement

# Contraindications to Thrombolytic Therapy

## Major Contraindications
- Structural intracranial disease
- Previous ICH
- Ischemic stroke ≤ 3 months
- Active bleeding
- Recent brain or spinal surgery
- Recent head trauma with fracture or brain injury
- Bleeding diathesis

## Relative Contraindications
- SBP > 180 or DBP > 110
- Recent bleeding (not ICH)
- Recent surgery / procedure
- Ischemic stroke > 3 months
- Anticoagulated
- Traumatic CPR
- Pericarditis / pericardial fluid
- Diabetic retinopathy
- Pregnancy
- Age > 75 years
- Low body weight (e.g. < 60kg)
- Female
- Black race

PE Pathophysiology: Role of the Right Ventricle

Piazza G and Goldhaber SZ. Circulation 2010;122:1124
Spectrum of Pulmonary Embolism

Massive PE (~5%)
- Hypotension (SBP < 90 mmHg)
- Cardiogenic shock or cardiac arrest
- Often fatal if aggressive care not instituted

Submassive PE (~25%)
- SBP > 90 mmHg
- Evidence of right ventricular (RV) dysfunction
- Increased risk of adverse outcomes

PE with normal BP and RV function (~70%)
- Normotensive
- No evidence of RV dysfunction
- Excellent prognosis with anticoagulation alone

Adapted, courtesy of Dr. Greg Piazza
Algorithm to Risk Stratify Patients with PE and Consider Advanced Therapies

- **Hemodynamically stable patient with acute PE**
  - Non-elevated cardiac biomarkers **AND** normal RV size on CT
    - Echocardiography
      - Normal RV size and function
        - Therapeutic anticoagulation alone
      - RV dysfunction
  - Elevated cardiac biomarkers
    - RV enlargement on CT
    - Echocardiography
      - Consider advanced therapies: fibrinolysis **OR** embolectomy **OR** IVC filter

- **Hemodynamically unstable patient with acute PE**
  - Elevated cardiac biomarkers
  - RV enlargement on CT
    - Consider advanced therapies: fibrinolysis **OR** embolectomy **OR** IVC filter
Massive PE Increases Mortality Risk

**Prospective RIETE Registry Data in Confirmed PE**

**Table 1. Patient Characteristics (N=15 520)**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Count (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men, n (%)</td>
<td>7720 (49.7)</td>
</tr>
<tr>
<td>Age, mean±SD, y</td>
<td>66.3±16.9</td>
</tr>
<tr>
<td>Age &gt;75 years, n (%)</td>
<td>5800 (37.4)</td>
</tr>
<tr>
<td>Body-mass index &gt;30 kg/m², n (%)*</td>
<td>2739 (27.2)</td>
</tr>
<tr>
<td>History of venous thromboembolism, n (%)</td>
<td>2471 (15.9)</td>
</tr>
<tr>
<td>Varicose veins, n (%)†</td>
<td>2304 (20.2)</td>
</tr>
<tr>
<td>Cancer, n (%)</td>
<td>3172 (20.4)</td>
</tr>
<tr>
<td>Cardiac or respiratory disease, n (%)</td>
<td>2611 (16.8)</td>
</tr>
<tr>
<td>Recent surgery, n (%)</td>
<td>2006 (12.9)</td>
</tr>
<tr>
<td>Immobilisation &gt;4 days for neurological disease, n (%)</td>
<td>567 (3.6)</td>
</tr>
<tr>
<td>Type of index venous thromboembolism, n (%)</td>
<td></td>
</tr>
<tr>
<td>Symptomatic distal deep-vein thrombosis</td>
<td>2109 (13.6)</td>
</tr>
<tr>
<td>Symptomatic proximal deep-vein thrombosis</td>
<td>6899 (44.4)</td>
</tr>
<tr>
<td>Symptomatic non-massive pulmonary embolism</td>
<td>6264 (40.4)</td>
</tr>
<tr>
<td>Symptomatic massive pulmonary embolism‡</td>
<td>248 (1.6)</td>
</tr>
</tbody>
</table>

*5444 missing values; †456 missing values.
‡Massive pulmonary embolism was defined as pulmonary embolism with systolic blood pressure <90 mm Hg.

Massive PE is a Significant Predictor of Mortality

Prospective RIETE Registry Data in Confirmed PE

Table 3. Clinical Predictors for Fatal Pulmonary Embolism Within 3 Months (Multivariable Analysis, Training and Validation Models)*

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Training Model (n=10,345)</th>
<th>Validation Model (n=5174)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds Ratio</td>
<td>95% Confidence Interval</td>
</tr>
<tr>
<td>Index venous thromboembolism</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Distal/proximal deep-vein thrombosis</td>
<td>1</td>
<td>...</td>
</tr>
<tr>
<td>Symptomatic nonmassive pulmonary embolism</td>
<td>5.66</td>
<td>3.79–8.44</td>
</tr>
<tr>
<td>Symptomatic massive pulmonary embolism</td>
<td>16.3</td>
<td>8.50–31.4</td>
</tr>
<tr>
<td>Immobilisation &gt;4 days for neurological disease</td>
<td>2.80</td>
<td>1.61–4.86</td>
</tr>
<tr>
<td>Age &gt;75 years</td>
<td>2.31</td>
<td>1.67–3.21</td>
</tr>
<tr>
<td>Cancer</td>
<td>2.40</td>
<td>1.72–3.26</td>
</tr>
<tr>
<td>Cardiac or respiratory disease†</td>
<td>1.89</td>
<td>1.35–2.65</td>
</tr>
<tr>
<td>Recent surgery†</td>
<td>0.53</td>
<td>0.29–0.96</td>
</tr>
</tbody>
</table>

Laporte S, et al.  *Circ* 2008 (RIETE Investigators)
Massive PE Carries a Higher Risk of Mortality than Non-Massive PE

2,392 patients from the International Cooperative PE Registry

Pharmacologic Strategies Available for Thrombolysis for Acute Pulmonary Embolism

• FDA approved systemic fibrinolytic agents for PE
  – Alteplase (recombinant tissue type plasminogen activator (tPA))
  – Streptokinase (SK)
  – Recombinant human urokinase (UK)

• Non FDA approved systemic fibrinolytic agents for PE
  – Lanoteplase
  – Tenecteplase
  – Reteplase (tPA)

• Catheter-directed therapies (CDT)
  – Aspiration thrombectomy
  – Thrombus fragmentation
  – Rheolytic thrombectomy
  – Rotational embolectomy
  – Catheter-directed thrombolysis

Sista AK & Kearon C. JACC Cardiovasc Interv 2015
Alteplase

Properties
• Naturally occurring enzyme
• Produced by many tissues, including endothelial cells
• Binds to fibrin, increasing fibrin’s affinity for plasminogen
• Catalyzes conversion of plasminogen to plasmin
• Plasmin is the major enzyme responsible for fibrinolysis
• Dosing varies:
  – 100mg IV infusion over 2 hours (systemic)
  – 10-20mg infused over 15 hours (CDT)
  – Single bolus of 0.6mg/kg over 2 min.*

*Tbolus dose has not been directly compared to a 2-hour infusion.
See PI for full dosing information.
Streptokinase (SK)

- Derived from *Streptococci*
  - Gram positive bacteria
  - Discovered by US bacteriologist William Tillet in 1930s
  - Observed that haemolytic *Streptococcus* bacteria did not agglutinate in serum
  - Purified in the 1950s by Lederle Laboratories (now part of Pfizer)
  - First became known as “fibrinolysin”
- Binds to and activates human plasminogen
- Catalyzes plasmin production
- Least expensive of the thrombolytics
  - On WHO List of Essential Medicines
- Commonly associated with allergic reactions and hypotension
  - Immunosensitization with repeated dosing especially
  - Hypotension can be reversed by stopping infusion
- Dosing:
  - 250,000U IV over 30 minutes, followed by 100,000 U/hr x 12-24h

See PI for full dosing information
Urokinase (urokinase-type plasminogen activator, uPA)

- Normally present in urine
- Physiologically active in blood stream and extracellular matrix
- Activates plasminogen
- Dosing:
  - 4,400 U/kg x 10 min. and then 4,400U/k per hour x 12-24 hours (systemic)

See PI for full dosing information
Summary of 5 Randomized Trials of Systemic Thrombolysis that Included Patients with Massive PE

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Thrombolysis</th>
<th>Heparin Alone</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>%</td>
<td>n/N</td>
</tr>
<tr>
<td>Recurrent PE or death</td>
<td>12/128</td>
<td>9.4</td>
<td>24/126</td>
</tr>
<tr>
<td>Recurrent PE</td>
<td>5/128</td>
<td>3.9</td>
<td>9/126</td>
</tr>
<tr>
<td>Death</td>
<td>8/128</td>
<td>6.2</td>
<td>16/126</td>
</tr>
<tr>
<td>Major Bleeding</td>
<td>28/128</td>
<td>21.9</td>
<td>15/126</td>
</tr>
</tbody>
</table>

Table adapted from Wan et al, Circ 2004
UPET Trial, Circ 1973
Tibbutt et al, BMJ 1974
Dotter et al, Vasc Surg 1979
Jerjes-Sanchez et al, J Thromb Thrombolysisi 1995

*Inclusive of 1980-2003; (excludes trials of surgical or percutaneous mechanical thrombolysis)
Summary of Randomized Trials of Systemic Thrombolysis that Excluded Patients with Massive PE

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Thrombolysis</th>
<th>Heparin Alone</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n/N</td>
<td>%</td>
<td>n/N</td>
<td>%</td>
</tr>
<tr>
<td>Recurrent PE or death</td>
<td>13/246</td>
<td>12/248</td>
<td>1.07 (0.50-2.30)</td>
</tr>
<tr>
<td>Recurrent PE</td>
<td>5/246</td>
<td>7/248</td>
<td>0.76 (0.28-2.08)</td>
</tr>
<tr>
<td>Death</td>
<td>8/246</td>
<td>6/248</td>
<td>1.16 (0.44-3.05)</td>
</tr>
<tr>
<td>Major Bleeding</td>
<td>6/246</td>
<td>8/248</td>
<td>0.67 (0.24-1.86)</td>
</tr>
</tbody>
</table>

Table adapted from Wan et al, *Circ* 2004

*Inclusive of 1980-2003; (excludes trials of surgical or percutaneous mechanical thrombolysis)*
## Systemic Fibrinolysis with Tenectaplaste and Heparin versus Heparin Alone in Intermediate Risk PE

**Efficacy and Safety Outcomes within 7 Days After Randomization**

### A Death or Hemodynamic Decompensation

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Tenectaplaste (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>≤75 yr</td>
<td>6/344 (1.7)</td>
<td>17/335 (5.1)</td>
<td>0.33 (0.13–0.85)</td>
<td>0.36</td>
</tr>
<tr>
<td>&gt;75 yr</td>
<td>7/162 (4.3)</td>
<td>11/164 (6.7)</td>
<td>0.63 (0.24–1.66)</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>7/242 (2.9)</td>
<td>14/231 (6.1)</td>
<td>0.46 (0.18–1.16)</td>
<td>0.90</td>
</tr>
<tr>
<td>Female</td>
<td>6/264 (2.3)</td>
<td>14/268 (5.2)</td>
<td>0.42 (0.16–1.12)</td>
<td></td>
</tr>
</tbody>
</table>

### B Major Extracranial Bleeding

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Tenectaplaste (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>≤75 yr</td>
<td>14/344 (4.1)</td>
<td>5/335 (1.5)</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>
</tr>
</tbody>
</table>
Mechanical Thrombectomy Devices

Mostafa et al, Am J Card 2016
Catheter-Directed Thrombolysis and Ultrasound-Assisted Technologies for PE

- Requires positioning of an infusion catheter within the embolus
- Provides intrapulmonary injection of fibrinolytics
- Local delivery of fibrinolytic helps prevent deactivation from circulating inhibitors
- May achieve higher drug concentrations at site of thrombus
- May be combined with other methods of thrombus fragmentation or aspiration
  - Ultrasound (high-frequency, low-power) to enhance fibrinolysis via disaggregation of uncrosslinked fibrin fibers

Mostafa et al, Am J Card 2016
PE Complicated by Right Ventricular (RV) Enlargement

Example of Reduction in Obstruction with Thrombolysis

Courtesy of Drs. Keith Sterling & Greg Piazza
Example of Reduction (Improvement) in RV/LV Ratio with Thrombolysis

**Pre**

RV/LV = 2.5

**Post**

RV/LV = 0.7

Courtesy of Drs. Keith Sterling & Greg Piazza
CDT in Massive and Submassive PE: Results from PERFECT (Prospective Multicenter Registry of n=101 Patients)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>n,/N</th>
<th>%</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Success</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Massive PE</td>
<td>24/28</td>
<td>85.7</td>
<td>67.3-96.0</td>
</tr>
<tr>
<td>Submassive PE</td>
<td>71/73</td>
<td>97.3</td>
<td>90.5-99.7</td>
</tr>
<tr>
<td>In-Hospital Mortality</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Massive PE</td>
<td>4/28</td>
<td>14.3</td>
<td>NR</td>
</tr>
<tr>
<td>Submassive PE</td>
<td>2/73</td>
<td>2.7</td>
<td>NR</td>
</tr>
<tr>
<td>Major Bleeding within 30 days</td>
<td>0</td>
<td>0</td>
<td>--</td>
</tr>
<tr>
<td>ICH</td>
<td>0</td>
<td>0</td>
<td>--</td>
</tr>
<tr>
<td>Minor Bleeding</td>
<td>13/101</td>
<td>12.9</td>
<td>7.0-21.0</td>
</tr>
</tbody>
</table>

Clinical success defined as meeting all 3 endpoints:
1. Stabilization of hemodynamics
2. Improvement in pulmonary hypertension, right-sided heart strain, or both
3. Survival to hospital discharge

ULTIMA: Randomized, Controlled Trial of Ultrasound-Assisted Catheter-Directed Thrombolysis (EKOS) for Acute Intermediate-Risk PE
ULTIMA: Efficacy Endpoints of ΔRV/LV Ratio

(1° Endpoint of BL to 24 hours)

Reduction in RV/LV Ratio

p < 0.001

p = 0.07

SEATTLE II: Prospective, Single-Arm Trial of Ultrasound-Facilitated (EKOS) CDT in Massive and Submassive PE

- Symptoms ≤14 days AND
- Massive or submassive PE AND
- RV/LV diameter ratio ≥0.9

Ultrasound-facilitated, catheter-directed, low-dose fibrinolysis
- tPA 1 mg/h for 24 h (1 device) OR
- tPA 1 mg/h for 12 h (2 devices)

TOTAL tPA Dose = 24 mg

Primary Efficacy Outcome: RV/LV Diameter Ratio

- 25% decrease in CT-measured RV/LV diameter ratio over 48 h
- 30% decrease in pulmonary arterial systolic pressure by the end of the procedure
- 30% decrease in pulmonary artery angiographic obstruction over 48 h
- No intracranial hemorrhage

SEATTLE II: Prospective, Single-Arm Trial of Ultrasound-Facilitated (EKOS) CDT in Massive and Submassive PE

Mean RV/LV Diameter Ratio

Mean PA Systolic Pressure (mm Hg)

* p<0.001

Odds of Mortality in Patients with Submassive Risk PE Treated with Thrombolytics versus Anticoagulation Alone *(Includes Systemic and CDT)*

<table>
<thead>
<tr>
<th>Source</th>
<th>No. of Events</th>
<th>No. of Patients</th>
<th>No. of Events</th>
<th>No. of Patients</th>
<th>OR (95% CI)</th>
<th>Favors Thrombolytics</th>
<th>Favors Anticoagulants</th>
<th>Weight, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goldhaber et al, 1993</td>
<td>0</td>
<td>46</td>
<td>2</td>
<td>55</td>
<td>0.16 (0.01-2.57)</td>
<td></td>
<td></td>
<td>5.3</td>
</tr>
<tr>
<td>Konstantinides et al, 2002</td>
<td>4</td>
<td>118</td>
<td>3</td>
<td>138</td>
<td>1.58 (0.35-7.09)</td>
<td></td>
<td></td>
<td>18.4</td>
</tr>
<tr>
<td>TIPES, 2010</td>
<td>0</td>
<td>28</td>
<td>1</td>
<td>30</td>
<td>0.14 (0.00-7.31)</td>
<td></td>
<td></td>
<td>2.7</td>
</tr>
<tr>
<td>Fasullo et al, 2011</td>
<td>0</td>
<td>37</td>
<td>6</td>
<td>35</td>
<td>0.11 (0.02-0.58)</td>
<td></td>
<td></td>
<td>15.1</td>
</tr>
<tr>
<td>MOPETT, 2012</td>
<td>1</td>
<td>61</td>
<td>3</td>
<td>60</td>
<td>0.35 (0.05-2.57)</td>
<td></td>
<td></td>
<td>10.5</td>
</tr>
<tr>
<td>ULTIMA, 2013</td>
<td>0</td>
<td>30</td>
<td>1</td>
<td>29</td>
<td>0.13 (0.00-6.59)</td>
<td></td>
<td></td>
<td>2.7</td>
</tr>
<tr>
<td>TOPCOAT, 2014</td>
<td>1</td>
<td>40</td>
<td>1</td>
<td>43</td>
<td>1.08 (0.07-17.53)</td>
<td></td>
<td></td>
<td>5.3</td>
</tr>
<tr>
<td>PEITHO, 2014</td>
<td>6</td>
<td>506</td>
<td>9</td>
<td>499</td>
<td>0.66 (0.24-1.82)</td>
<td></td>
<td></td>
<td>40.0</td>
</tr>
<tr>
<td>Total</td>
<td>12</td>
<td>866</td>
<td>26</td>
<td>889</td>
<td>0.48 (0.25-0.92)</td>
<td></td>
<td></td>
<td>100.0</td>
</tr>
</tbody>
</table>

Heterogeneity: $\chi^2 = 7.63; P = .37; I^2 = 8%$

Overall effect: $z = 2.22; P = .03$
# Meta-Analysis of Major Bleeding in Patients with Massive or Submassive PE Treated with CDT

<table>
<thead>
<tr>
<th>Studies</th>
<th>Estimate (95% C.I.)</th>
<th>Major Bleeding/Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>PERFECT 2015</td>
<td>0.005 (0.000, 0.019)</td>
<td>0/100</td>
</tr>
<tr>
<td>SEATTLE II 2014</td>
<td>0.007 (0.000, 0.020)</td>
<td>1/150</td>
</tr>
<tr>
<td>ULTIMA 2014</td>
<td>0.016 (0.000, 0.060)</td>
<td>0/30</td>
</tr>
<tr>
<td>Dumantepe et al 2014</td>
<td>0.022 (0.000, 0.081)</td>
<td>0/22</td>
</tr>
<tr>
<td>Engelberger et al 2013</td>
<td>0.038 (0.000, 0.091)</td>
<td>2/52</td>
</tr>
<tr>
<td>Kennedy et al 2013</td>
<td>0.017 (0.000, 0.049)</td>
<td>1/60</td>
</tr>
<tr>
<td>Quintana et al 2013</td>
<td>0.045 (0.000, 0.169)</td>
<td>0/10</td>
</tr>
<tr>
<td>Engelhardt et al 2011</td>
<td>0.167 (0.018, 0.316)</td>
<td>4/24</td>
</tr>
<tr>
<td>Lin et al 2009</td>
<td>0.042 (0.000, 0.155)</td>
<td>0/11</td>
</tr>
<tr>
<td>Chamsuddin et al 2008</td>
<td>0.045 (0.000, 0.169)</td>
<td>0/10</td>
</tr>
<tr>
<td><strong>Overall (I^2=0%, P=0.590)</strong></td>
<td><strong>0.009 (0.001, 0.018)</strong></td>
<td><strong>8/469</strong></td>
</tr>
</tbody>
</table>
# Absolute Risk Metrics of Outcomes of Major Interest

*Includes both Major and Intermediate Risk PE*

## Table 2. Absolute Risk Metrics of Outcomes of Major Interest

<table>
<thead>
<tr>
<th>Outcome of Interest (No. of Studies Reporting)</th>
<th>No. of Events/No. of Patients, Absolute Event Rate (%)</th>
<th>No. Needed to Treat or Harm</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Thrombolytic Group</td>
<td>Anticoagulant Group</td>
<td></td>
</tr>
<tr>
<td>All-cause mortality (16)</td>
<td>23/1061 (2.17)</td>
<td>41/1054 (3.89)</td>
<td>NNT = 59</td>
</tr>
<tr>
<td>Major bleeding (16)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>98/1061 (9.24)</td>
<td>36/1054 (3.42)</td>
<td>NNH = 18</td>
</tr>
<tr>
<td>ICH (15)</td>
<td>15/1024 (1.46)</td>
<td>2/1019 (0.19)</td>
<td>NNH = 78</td>
</tr>
<tr>
<td>Recurrent PE (15)</td>
<td>12/1024 (1.17)</td>
<td>31/1019 (3.04)</td>
<td>NNT = 54</td>
</tr>
<tr>
<td>Age &gt;65 y</td>
<td>asaki mortality (5)</td>
<td>14/673 (2.08)</td>
<td>NNT = 64</td>
</tr>
<tr>
<td>Major bleeding (5)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>87/673 (12.93)</td>
<td>27/658 (4.10)</td>
<td>NNH = 11</td>
</tr>
<tr>
<td>Age ≤65 y</td>
<td>All-cause mortality (11)</td>
<td>9/388 (2.32)</td>
<td>17/396 (4.29)</td>
</tr>
<tr>
<td>Major bleeding (11)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>11/388 (2.84)</td>
<td>9/396 (2.27)</td>
<td>NNH = 176</td>
</tr>
<tr>
<td>Intermediate-risk PE</td>
<td>All-cause mortality (8)</td>
<td>12/866 (1.39)</td>
<td>26/889 (2.92)</td>
</tr>
<tr>
<td>Major bleeding (8)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>67/866 (7.74)</td>
<td>20/889 (2.25)</td>
<td>NNH = 18</td>
</tr>
</tbody>
</table>
Role of CDT in Patients with PE?

“…current evidence suggests that CDT is preferred to systemic thrombolytic therapy in patients with acute PE who require active thrombus removal and have risk factors for bleeding.”
AT10 Guidelines: Thrombolysis for Pulmonary Embolism

“We suggest thrombolytic therapy for pulmonary embolism with hypotension (Grade 2B) and systemic therapy over catheter-directed thrombolysis (Grade 2C)”

“Patients who have a higher risk of bleeding with systemic thrombolytic therapy and who have access to the expertise and resources required to do CDT are likely to choose CDT over systemic thrombolytic therapy.”
Algorithm for Treatment of Massive and Submassive PE

Hemodynamically unstable or massive PE:
1. Syncope
2. Persistent Hypotension
3. Cardiogenic Shock
4. Resuscitated Cardiac Arrest

Hemodynamically stable or submassive PE with:
1. RV dysfunction with RV/LV diameter ratio > 1
2. Elevated cardiac biomarkers
3. Severe hypoxemia
4. RA or RV thrombus
5. Large clot burden on V/Q scan or CT

Anticoagulation

Contraindications to Thrombolysis?

Yes
- Surgical Embolectomy
- Catheter intervention
+/- low dose local Thrombolysis

No
- Systemic Thrombolysis
- Catheter directed/Ultrasound assisted local Thrombolysis

If no improvement: Surgical Embolectomy or Transcatheter Aspiration Thrombectomy

Mostafa et al, Am J Card 2016
Thrombolysis in Deep Vein Thrombosis

from Johnson SA, Eleazor P, Rondina MT. JAGS 2016
Post-Thrombotic Syndrome

A) Normal Vein Function
B) Damage to Venous Valves
C) Venous Valve Insufficiency
D) Venous Hypertension

Postulated Pathophysiology of PTS

Venous thrombosis

Recanalization

Venous valve damage

Venous valvular reflux

Inflammatory response

Persistent Outflow obstruction

Collateral venous circulation

Venous hypertension

Telangiectasiae
Venous ectasia

Capillary leakage

Edema
Hyperpigmentation
Lipodermatosclerosis
Ulceration

Clinical Manifestations of Post-Thrombotic Syndrome

- Edema
- Venous ectasia
- Hyperpigmentation
- Venous ulcer
- Skin induration
- Venous ectasia

## Villalta Scale for PTS

<table>
<thead>
<tr>
<th>Symptoms</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cramps</td>
</tr>
<tr>
<td></td>
<td>Itching</td>
</tr>
<tr>
<td></td>
<td>Pins and Needles</td>
</tr>
<tr>
<td></td>
<td>Leg Heaviness</td>
</tr>
<tr>
<td></td>
<td>Pain</td>
</tr>
<tr>
<td>Signs</td>
<td>Pretibial Edema</td>
</tr>
<tr>
<td></td>
<td>Skin Induration</td>
</tr>
<tr>
<td></td>
<td>Hyperpigmentation</td>
</tr>
<tr>
<td></td>
<td>Venous Ectasia</td>
</tr>
<tr>
<td></td>
<td>Redness</td>
</tr>
<tr>
<td></td>
<td>Pain during Calf Compression</td>
</tr>
<tr>
<td></td>
<td>Ulcer Present?</td>
</tr>
</tbody>
</table>

Each Graded As:
- None/Minimal – 0
- Mild – 1
- Moderate – 2
- Severe – 3

- Score > 5 is diagnostic of PTS
- Presence of an ulcer confers severe PTS
CDT for Acute Ileofemoral Deep Vein Thrombosis: The CaVenT Study

209 patients included

101 allocated additional CDT
- 4 withdrew from study before CDT
- 4 did not meet eligibility criteria
  - 2 with exclusion criteria
  - 2 without inclusion criteria
  - 93 started additional CDT procedure
    - 2 technical failures
    - 1 distal femoral DVT at start of CDT did not receive alteplase
  - 1 withdrew from study follow-up
    - 2 deceased
    - 1 from cancer

108 allocated standard treatment
- 1 received additional systemic thrombolysis due to acute PE
- 4 withdrew from study follow-up
  - 4 from cancer

90 included in ITT analysis

99 included in ITT analysis

### CDT for Acute Ileofemoral Deep Vein Thrombosis: The CaVenT Study

#### Table 2: Short-term and long-term outcomes

<table>
<thead>
<tr>
<th></th>
<th>Additional catheter-directed thrombolysis (n=90)</th>
<th>Standard treatment only (n=99)</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>% (95% Cl)</td>
<td>n</td>
</tr>
<tr>
<td>Post-thrombotic syndrome at 24 months†</td>
<td>37</td>
<td>41.1% (31.5–51.4)</td>
<td>55</td>
</tr>
<tr>
<td>Iliofemoral patency at 6 months† ‡</td>
<td>58</td>
<td>65.9% (55.5–75.0)</td>
<td>45</td>
</tr>
<tr>
<td>Post-thrombotic syndrome at 6 months§</td>
<td>27</td>
<td>30.3% (21.8–40.5)</td>
<td>32</td>
</tr>
</tbody>
</table>

Post-thrombotic syndrome defined as Villalta score of 5 points or higher. *χ² test. †Co-primary outcomes. ‡Five patients had inconclusive patency assessments and one was lost to follow-up at 6 months. §Secondary outcome.

ARR = 14.4% (NNT of 7)

N=20 bleeding complications (Major – 3; Clinically relevant – 5; Minor – 12)

Enden T et al, Lancet 2012
The ATTRACT Trial

- Ongoing investigator-initiated, Phase III, open-label RCT sponsored by NHLBI
  - 1:1 randomization to either standard therapy + pharmacomechanical CDT (PCDT) or standard therapy alone

- Support from Bayer, BSN Medical, Covidien, Genentech

- Symptomatic ileofemoral DVT (n=692)

- Primary efficacy objective is to determine if PCDT reduces PTS during 24 months of follow-up vs. standard therapy alone

- Primary safety outcome is major bleeding within 10 days of randomization

- Study is closed to enrollment (Dec 2014), results expected in 2016

Vedantham S, et al Am Heart J 2013
http://attract.wustl.edu
Proposed Decision Model to Perform CDT Based on Presentation and Bleeding Risk

<table>
<thead>
<tr>
<th>Presentation</th>
<th>Low BR</th>
<th>Moderate BR</th>
<th>High BR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute limb threat</td>
<td>✔</td>
<td>✔</td>
<td>Surgery</td>
</tr>
<tr>
<td>Extensive IVC thrombosis</td>
<td>✔</td>
<td>✔</td>
<td>No</td>
</tr>
<tr>
<td>Progression of symptoms or anatomic extent despite anticoagulation</td>
<td>✔</td>
<td>Usually No</td>
<td>No</td>
</tr>
<tr>
<td>Ileofemoral DVT to prevent PTS</td>
<td>✔</td>
<td>Usually No</td>
<td>No</td>
</tr>
<tr>
<td>Femoropopliteal DVT to prevent PTS</td>
<td>Usually No</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

AT10 Guidelines: Thrombolysis for Acute DVT

“In patients with acute proximal DVT of the leg, we suggest anticoagulant therapy alone over CDT (Grade 2C)”

“Patients who are most likely to benefit from CDT, who attach a high value to prevention of PTS, and a lower value to the initial complexity, cost, and risk of bleeding with CDT, are likely to choose CDT over anticoagulation alone.”

Conclusions

• Systemic thrombolysis is recommended in patients with massive PE without contraindications

• CDT may be considered in patients with PE who require thrombus removal and have contraindications to systemic fibrinolytics

• Thrombolysis in patients with DVT may prevent PTS and improve QOL

• Ongoing prospective trials will help inform selection of patients with PE/DVT who may benefit from thrombolysis as well as evolving role of CDT