Evolving Strategies in Venous Thromboembolism

Thrombolysis in PE

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Thrombolyis in PE

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Massachusetts General Hospital
Disclosures

• Nothing to disclose
Objectives

• Identify patients that may benefit from thrombolytic therapy for VTE
The consequences of acute PE are primarily *hemodynamic* and become manifest when 30–50% of the pulmonary arterial bed is obstructed.

Secondary and less important mechanisms: *Inflammatory mediator release* with pulmonary vasoconstriction, atelectasis, shunting, surfactant dysfunction.
Why Give Thrombolytics? Only 2 possible reasons

• Save lives

• Reduce morbidity (and costs), short or long term, including the sequelae of VTE: CTEPH and post-phlebitic syndrome
PE: Pathophysiology

- When the pulmonary vascular bed is obstructed by ~75%, the RV must generate a systolic pressure > 50 mmHg (mean PAP ~ 40 mmHg) to maintain perfusion. A normal RV cannot typically attain this pressure and fails.
ARS Question

What defines “submassive” PE?

A. Size of the embolus, i.e. main/lobar vs. segmental
B. Comorbidities
C. Blood pressure
D. The effect the PE is having on the right ventricle
PE: Clinical Presentation

**Non Massive**
- Low Risk
- NL RV & Biomarkers

**Submassive**
- Intermediate Risk
+/- RV dysfunction
+/- Biomarkers

**Massive**
- High Risk
## Massive vs. Submassive PE

**Massive PE**
- SBP < 90 mmHg or decrease ≥ 40 mmHg from baseline for > 15 min
- Inotropic support
- Pulselessness
- Persistent bradycardia (HR < 40 bpm)

**Submassive PE**
- SBP ≥ 90 mmHg
- RV dysfunction
- RV dilatation ECHO or CT (RV/LV diameter > 0.9)
- BNP > 90 pg/mL
- EKG changes
- Myocardial necrosis:
  - Troponin I > 0.4 ng/mL
  - Troponin T > 0.1 ng/mL

*Circulation 2011;123:1788*
PE Mortality (ICOPER)


*62.5% from recurrent PE
PE patients with right ventricle dysfunction (RVD) unresolved prior to discharge suffered 3X mortality rate than patients whose RVD resolved

PE related mortality rate at 3 years:
- 13.3% if RVD unresolved at discharge
- 4.4% if RVD resolved at discharge
Patients with right heart dysfunction defined as \( \text{RVD/LVD} > 0.9 \) have a significantly higher chance of adverse events within 30 days.

**Adverse event rate:**
- 54% if \( \text{RVD/LVD} \) ratio < 0.9
- 82% if \( \text{RVD/LVD} \) ratio \( \geq 0.9 \)
- OR: 4.02 (\( p=0.041 \))
Guidance in the Literature for Treatment of Massive/Submassive PE: Very Little

Management of Massive and Submassive Pulmonary Embolism, Iliofemoral Deep Vein Thrombosis, and Chronic Thromboembolic Pulmonary Hypertension: A Scientific Statement From the American Heart Association


Circulation published online Mar 21, 2011;
Acute Massive/Submassive PE Therapy

1. **EVIDENCE OF SHOCK OR RESPIRATORY FAILURE:**
   - Any hypotension (SBP < 90 mm Hg)
   - Shock index > 1.0
   - Respiratory distress (SaO2 < 95% with Borg score > 8, or altered mental status, or appearance of suffering)

2. **EVIDENCE OF MODERATE TO SEVERE RV STRAIN:**
   - RV dysfunction (RV hypokinesis or estimated RVSP > 40 mm Hg)
   - Clearly elevated biomarker values (e.g., troponin above borderline value, BNP > 100 pg/mL or pro-BNP > 900 pg/mL)

   No contraindications to fibrinolysis

**Alteplase**
- 100 mg over 2 h IV
Thrombolysis for PE: Recent Trials

Full dose systemic lysis:
- PEITHO
- TOPCOAT

Reduced dose lysis:
- MOPPET: half dose systemic lysis
- ULTIMA, SEATTLE II: Ultrasound enhanced lysis
What was the primary conclusion of the PEITHO trial?

A. tPA reduces mortality in submassive PE
B. Tenectaplastase reduces the likelihood of death or hemodynamic collapse at day 7
C. Thrombolysis has a more favorable risk/benefit ratio in older patients with submassive PE
D. Tenectaplastase is the treatment of choice in patients with large PEs, provided RV function is normal
PEITHO: A 10 Year Trial to Finally Answer the Question

• **Purpose:**
  - To investigate the benefit and safety of thrombolysis (Tenecteplase) versus placebo for normotensive patients with intermediate risk PE.

• **Randomized Trial**
  - double blind
  - placebo controlled
  - 1006 patients

<table>
<thead>
<tr>
<th>PE-related early MORTALITY RISK</th>
<th>RISK MARKERS</th>
<th>Potential treatment implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIGH &gt; 15%</td>
<td>+</td>
<td>(+)*</td>
</tr>
<tr>
<td>CLINICAL (Shock or hypotension)</td>
<td>(+)*</td>
<td>Thrombolysis or Embolectomy</td>
</tr>
<tr>
<td>RV Dysfunction</td>
<td>(+)</td>
<td></td>
</tr>
<tr>
<td>Myocardial Injury</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

PEITHO

<table>
<thead>
<tr>
<th></th>
<th>Tenecteplase (n=506)</th>
<th>Placebo (n=499)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%</td>
<td>13 (2.6)</td>
<td>28 (5.6)</td>
<td>0.015</td>
</tr>
<tr>
<td>All-cause mortality or hemodynamic collapse within 7 days of randomization</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

![Graph showing odds ratio and comparison between age groups]

## Intravenous Thrombolysis

**PEITHO**

<table>
<thead>
<tr>
<th></th>
<th>Tenecteplase (n=506)</th>
<th>Placebo (n=499)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>(%)</td>
<td>n</td>
</tr>
<tr>
<td>Non-intracranial major bleeding</td>
<td>32  (6.3)</td>
<td>6 (1.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Severe</td>
<td>16</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Moderate</td>
<td>16</td>
<td></td>
<td>4</td>
</tr>
</tbody>
</table>

### Death or hemodynamic collapse (primary EP)

- Stroke *without* primary EP (*not* leading to death or hemodynamic collapse)

### ≤ 75 years

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>TNK</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>335</td>
<td>344</td>
</tr>
</tbody>
</table>

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**CHEST 2014**

**MORNING EDUCATIONAL SYMPOSIA**
TOPCOAT

- Investigator-initiated, Industry-funded
- Double blind RCT
- Novel composite endpoint: favorable composite patient-oriented outcome at 90 days
- 8 U.S. centers
- Ended early due to principal investigator changing jobs (!)

Intravenous Thrombolysis TOPCOAT

5 Days

<table>
<thead>
<tr>
<th>Adverse outcome</th>
<th>PLACEBO</th>
<th>TENECTEPLASE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TOTAL</strong></td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td><em>Death</em></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td><em>Circ shock + thrombectomy</em></td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td><em>Intubation + thrombectomy</em></td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>7%</th>
<th>3%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Death</strong></td>
<td>2%</td>
<td>3%</td>
</tr>
<tr>
<td><strong>Circ shock + thrombectomy</strong></td>
<td>2%</td>
<td>0%</td>
</tr>
<tr>
<td><strong>Intubation + thrombectomy</strong></td>
<td>7%</td>
<td>0%</td>
</tr>
</tbody>
</table>
### Intravenous Thrombolysis TOPCOAT

#### 90 Days

<table>
<thead>
<tr>
<th>Adverse outcome</th>
<th>PLACEBO</th>
<th>TENECTEPLASE</th>
</tr>
</thead>
<tbody>
<tr>
<td>TOTAL UNIQUE PATIENTS</td>
<td>13</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>30%</td>
<td>12.5%</td>
</tr>
<tr>
<td>Poor functional capacity</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>5%</td>
<td>7.5%</td>
</tr>
<tr>
<td>Recurrent VTE</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>2%</td>
<td>2.5%</td>
</tr>
<tr>
<td>Low perception of wellness</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>5%</td>
<td>0%</td>
</tr>
<tr>
<td>Two of the above</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>16%</td>
<td>2.5%</td>
</tr>
<tr>
<td>All three of the above</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>2%</td>
<td>0%</td>
</tr>
</tbody>
</table>

Kline et al J Thromb Haemost. 2014

### Proportion free of any adverse outcome:

63% (Placebo) vs 85% (Tenecteplase), p=0.017
TOPCOAT

Hospital Resource Utilization

Kline et al J Thromb Haemost. 2014
TOPCOAT
Conclusion

Patients with submassive pulmonary embolism who were treated with tenecteplase were more likely to have a good health related quality of life at three months.
Reduced dose systemic thrombolysis: MOPETT Trial

Moderate Pulmonary Embolism Treated With Thrombolysis (from the “MOPETT” Trial)

Mohsen Sharifi, MD\textsuperscript{a,b,*}, Curt Bay, PhD\textsuperscript{b}, Laura Skrocki, DO\textsuperscript{a}, Farnoosh Rahimi, MD\textsuperscript{a}, and Mahshid Mehdipour, DMD\textsuperscript{a,b}, “MOPETT” Investigators

Am J Cardiol 2013;11:273-277
MOPETT: Definition of Moderate PE

• Involvement of >70% in either at least 2 lobar arteries or left or right main PA

• At least 2 new signs or symptoms (chest pain, tachypnea, tachycardia, cough, dyspnea, O2 dsat (<95%) or elevated JVP.

• Echo measured but not element of inclusion or exclusion
MOPETT: 121 patients randomized

**TG:** Enoxaparin 1 mg/kg q 12 with initial dose not to exceed 80 mg. UF 70 U/kg bolus not to exceed 6000, dose adjustment to keep PTT 1.5-2. No higher than 10 U/kg/hour. After tPA, 18 U/kg/Hr.

**CG:** LMWH 1 mg/kg bid. UFH 80 U/kg then 18 U/kg/hr.

tPA dose: For patients > 50 kg, dose 50 mg given as 10 mg push Over 1 minute followed by 40 mg over 2 hours
MOPETT: Primary Endpoint

<table>
<thead>
<tr>
<th>Variable</th>
<th>TG</th>
<th>CG</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary hypertension*</td>
<td>9 (16%)</td>
<td>32 (57%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pulmonary hypertension plus recurrent pulmonary embolism</td>
<td>9 (16%)</td>
<td>35 (63%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

* Pulmonary artery systolic pressure ≥40 mm Hg.
RV enlargement in 20% of TG and 23% CG at baseline
RV hypokinesis in 4.4% of TG and 6.6% CG at baseline

<table>
<thead>
<tr>
<th>Timing</th>
<th>Pulmonary Artery Systolic Pressure (mm Hg)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TG</td>
<td>CG</td>
</tr>
<tr>
<td>On admission</td>
<td>50 ± 6</td>
<td>51 ± 7</td>
</tr>
<tr>
<td>Within 48 h</td>
<td>34 ± 7</td>
<td>41 ± 4</td>
</tr>
<tr>
<td>6 mo</td>
<td>31 ± 6</td>
<td>49 ± 8</td>
</tr>
<tr>
<td>28 ± 5 mo</td>
<td>28 ± 7</td>
<td>43 ± 6</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD.
Reduced dose thrombolysis via catheter

- Direct infusion of lytic agent into clot
- Higher local concentration by lower doses of lytic agent
- PA pressure monitoring
- Direct clot fragmentation
EKOS Thrombolysis

- Ultrasonic pressure waves emitted along the catheter
- Lower drug dose (16-24 mg rt-PA) delivered at 1-2 mg/hour
ULTIMA: Randomized, Controlled Trial:
Ultrasound Accelerated Thrombolysis with $\leq 20$ mg TPA: Rx of Acute Submassive PE

ULTIMA: 59 patients randomized RV/LV ratio (echo)

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>24 hrs</th>
<th>90 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>EKOS+Heparin</td>
<td>1.28</td>
<td>0.99</td>
<td>0.95</td>
</tr>
<tr>
<td>Heparin</td>
<td>1.20</td>
<td>1.17</td>
<td>0.98</td>
</tr>
</tbody>
</table>

- P<0.0001
- P=0.31
- P<0.0001
SEATTLE II

A Prospective, Single-Arm, Multicenter Trial of Ultrasound-Facilitated, Low-Dose Fibrinolysis for Acute Massive and Submassive Pulmonary Embolism (SEATTLE II)

Gregory Piazza, MD, MS
on behalf of the SEATTLE II Investigators
ACC: March 30, 2014

Sponsored by the EKOS Corporation
SEATTLE II: 150 patients treated
Outcomes: RV/LV Ratio

RV/LV Ratio

1.55

1.13

Pre-Procedure

48 Hours

p < 0.0001
SEATTLE II Outcomes: PA Systolic Pressure

Mean PA Systolic Pressure (mmHg)

<table>
<thead>
<tr>
<th>Pre-Procedure</th>
<th>Post-Procedure</th>
<th>48 Hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>51.4</td>
<td>37.5</td>
<td>36.9</td>
</tr>
</tbody>
</table>

p < 0.0001
# Clinical Outcomes

<table>
<thead>
<tr>
<th>Clinical outcomes</th>
<th>N = 150</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean length of stay ± SD, days</td>
<td>8.8 ± 5</td>
</tr>
<tr>
<td>In-hospital death, n (%)</td>
<td>3 (2)</td>
</tr>
<tr>
<td>30-day mortality**, n (%)</td>
<td>4 (2.7)</td>
</tr>
<tr>
<td>Serious adverse events due to device, n (%)</td>
<td>2 (1.3)</td>
</tr>
<tr>
<td>Serious adverse events due to t-PA, n (%)</td>
<td>2 (1.3)</td>
</tr>
<tr>
<td>IVC filter placed, n (%)</td>
<td>24 (16)</td>
</tr>
<tr>
<td>Major bleeding within 30 days**, n (%)</td>
<td>17 (11.4)</td>
</tr>
<tr>
<td>GUSTO moderate**</td>
<td>16 (10.7)</td>
</tr>
<tr>
<td>GUSTO severe**</td>
<td>1 (0.7)</td>
</tr>
<tr>
<td>Intracranial hemorrhage, n (%)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

*All death, serious adverse, and bleeding events were adjudicated by an independent safety monitor.

**N = 149 (1 patient lost to follow-up)