Risk Stratification of Patients With Acute PE: Identifying Which Patients Benefit from Thrombolysis

Ian Del Conde, MD, FACC
Vascular Medicine and Cardiology
Miami Cardiac and Vascular Institute
HeartWell
December 12, 2015

Disclosures

CONSULTANT
Merck; New Haven Pharmaceuticals

ADVISORY BOARD
Merck, IC Sciences

SPEAKER’S BUREAU
Johnson & Johnson, BMS, Pfizer
PE Presents in a Continuum of Severity

Incidentally discovered
Subsegmental PE
Mortality: <1%

Mortality: 3-15%

Massive PE
cardiogenic shock, death
Mortality: 50-65%

PE Presents in a Continuum of Severity

Incidentally discovered
Subsegmental PE
Mortality: <1%

Mortality: 3-15%

Massive PE
cardiogenic shock, death
Mortality: 50-65%

Treatment:
Anticoagulation
Interventional Anticoagulation
Thrombolysis Embolectomy
Standard Definitions

• **Massive PE:**
  Persistent hypotension (SBP<90mmHg for over 15 min),
  vasopressor requirement, or in profound bradycardia (hr < 40 bpm)

• **Submassive PE:**
  Normal blood pressure, but:
  – RV dysfunction
    • Echo: showing RV dilatation and/or hypokinesis
    • RV:LV diameter ratio > 0.9
    • Elevated plasma BNP, pro-BNP
  – Elevated cardiac biomarkers (troponin T or I).
  – Less validated: EKG, symptoms and vital signs at rest.

• **Low-Risk PE**

Revascularization in Acute Pulmonary Embolism:

*Selecting the Patient Who Will Benefit*

• Identify the patient who is at high risk of dying without thrombolysis
• Identify the patient likely to develop chronic thromboembolic pulmonary hypertension
Thrombolysis vs Heparin in the Treatment of Pulmonary Embolism

A Clinical Outcome-Based Meta-analysis

Giancarlo Agenlot, MD; Cecilia Becattini, MD; Time Kirschstein, MD

In conclusion, the present meta-analysis of comparative studies in pulmonary embolism showed that death and recurrences are less frequent with thrombolysis than with heparin treatment. The excessive bleeding

The Uncertain Role of Thrombolytic Therapy in the Treatment of Pulmonary Embolism

Once available, I believe that thrombolytic therapy should only be considered in patients with massive PE complicated by shock.

ARCH INTERN MED/VOL 162, DEC 9/23, 2002
International Cooperative Pulmonary Embolism Registry (ICOPER) (n=2454)

<table>
<thead>
<tr>
<th>Mortality</th>
<th>Hospital</th>
<th>2 Weeks</th>
<th>3 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Mortality</td>
<td>...</td>
<td>11.4%</td>
<td>17.4%</td>
</tr>
<tr>
<td>Hemodynamically unstable</td>
<td>...</td>
<td>...</td>
<td>58.3</td>
</tr>
<tr>
<td>Hemodynamically stable</td>
<td>...</td>
<td>...</td>
<td>15.1%</td>
</tr>
<tr>
<td>No RV dysfunction (N=263)</td>
<td>10%</td>
<td>11%</td>
<td>15%</td>
</tr>
<tr>
<td>RV dysfunction (N=428)</td>
<td>19%</td>
<td>21%</td>
<td>23%</td>
</tr>
</tbody>
</table>


Right Ventricular Enlargement on CT

431 consecutive patients with PE

30d mortality
- RV dilatation = 15.5%
- No RV dilatation = 7.7%

Pro-Brain Natriuretic Peptide and Outcome in Acute Pulmonary Embolism


What do the Guidelines Say?
Thrombolysis

<table>
<thead>
<tr>
<th>ACCP</th>
<th>AHA/ACC</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Consider in patients with acute <strong>Massive PE</strong> associated with hypotension (SBP &lt; 90 mm Hg) and acceptable bleeding risk.</td>
<td>Class IIa / LOE B</td>
</tr>
<tr>
<td>Grade 2C</td>
<td></td>
</tr>
<tr>
<td>• Consider in patients with <strong>Submassive PE</strong>, judged to have evidence of adverse prognosis and low bleeding risk.</td>
<td></td>
</tr>
<tr>
<td>Grade 2C</td>
<td>“High risk for developing hypotension despite AC”</td>
</tr>
<tr>
<td>“Without associated hypotension.”</td>
<td>“Hemodynamic and/or Respiratory instability, severe RV dysfunction, or major myocardial necrosis”</td>
</tr>
<tr>
<td>Grade 3C</td>
<td>“Low-risk PE, or minor RV dysfunction, minor myocardial necrosis and no clinical worsening.”</td>
</tr>
<tr>
<td>• Recommendation against thrombolysis in <strong>Low-Risk</strong> patients.</td>
<td></td>
</tr>
<tr>
<td>Grade 2C</td>
<td>“Consider Catheter-assisted if contraindication or failed systemic lysis, shock likely to cause death. Suck out if failed catheter-assisted approach.”</td>
</tr>
<tr>
<td>Class IIa / LOE C</td>
<td>“Consider Catheter OR Surgery if contraindication or failed systemic lysis in massive PE, may be considered in submassive with evidence of adverse prognosis.”</td>
</tr>
</tbody>
</table>
MAPPET Registry

Right heart failure and/or pulmonary hypertension

<table>
<thead>
<tr>
<th>In Hospital event</th>
<th>Thrombolysis (n=169)</th>
<th>Heparin (n=550)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>4.7%</td>
<td>11%</td>
<td>.016</td>
</tr>
<tr>
<td>Death from PE</td>
<td>4.1%</td>
<td>10%</td>
<td></td>
</tr>
<tr>
<td>Recurrent PE</td>
<td>7.7%</td>
<td>19%</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Major Bleeding</td>
<td>22%</td>
<td>7.8%</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>IC Bleed</td>
<td>1.2%</td>
<td>0.4%</td>
<td></td>
</tr>
</tbody>
</table>


Thrombolysis in Massive Pulmonary Embolism:
(Hypotension and Heart Failure)

- Randomized trial of thrombolysis and anticoagulation vs. anticoagulation alone.
- The trial was stopped after the first 8 patients were enrolled:
  - All 4 patients in the anticoagulation group died from right heart failure.
  - All 4 patients in the thrombolysis group survived.

Thrombolysis for Submassive Pulmonary Embolism
(In-Hospital Clinical Events)

<table>
<thead>
<tr>
<th>Event</th>
<th>Heparin Plus Alteplase (N=118)</th>
<th>Heparin Plus Placebo (N=138)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary end point</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death from all causes</td>
<td>13 (11%)</td>
<td>34 (24.6%)</td>
<td>0.006</td>
</tr>
<tr>
<td>Escalation of treatment</td>
<td>4 (3.4%)</td>
<td>3 (2.2%)</td>
<td>0.71</td>
</tr>
<tr>
<td></td>
<td>12 (10.2%)</td>
<td>34 (24.6%)</td>
<td>0.004</td>
</tr>
<tr>
<td>Secondary end points</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recurrent PE</td>
<td>4 (3.4%)</td>
<td>4 (2.9%)</td>
<td>NS</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>1 (0.8%)</td>
<td>5 (3.6%)</td>
<td>NS</td>
</tr>
<tr>
<td>Fatal bleeding</td>
<td>0</td>
<td>1 (0.7%)</td>
<td>NS</td>
</tr>
<tr>
<td>CNS bleed</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>


---

**Thrombolysis for Submassive Pulmonary Embolism**

- Event free survival
  - In-hospital death or
  - Escalation of therapy
- Escalation of therapy
  - Catacholamine infusion
  - Secondary thrombolysis
  - Endotrachial intubation
  - CPR
  - Surgical or catheter thrombectomy

Fibrinolysis for Patients with Intermediate-Risk Pulmonary Embolism

Guy Meyer, M.D., Eric Vicaut, M.D., Thierry Denays, M.D., Giancarlo Agnelli, M.D., Cecilia Becattini, M.D., Jan Beyer-Westendorf, M.D., Erich Bluhmki, M.D., Ph.D., Helene Bouvaist, M.D., Benjamin Brenner, M.D., Francis Couturaud, M.D., Ph.D., Claudia Delfas, M.D., Klaus Emgen, M.D., Ana Fracca, M.D., Nazareno Galié, M.D., Annette Gebel, M.D., Samuel Z. Goldhaber, M.D., David Jimenez, M.D., Ph.D., Matija Kozak, M.D., Christian Kujat, M.D., Nils Kucher, M.D., Irene M. Lang, M.D., Marek Lenkei, M.D., Nicolas Menewess, M.D., Ph.D., Gerard Proust, M.D., Massimiliano Palazzini, M.D., Antoniu Petris, M.D., Ph.D., Piotr Pszczolkowski, M.D., Matteo Rugolo, M.D., Aldo Salvi, M.D., Sebastian Schellong, M.D., Mustapha Sebbane, M.D., Bozena Sobkowicz, M.D., Branislav S. Stefanovic, M.D., Ph.D., Holger Tiele, M.D., Adam Torbicki, M.D., Franck Verversen, M.D., Ph.D., and Stavros V. Konstantinides, M.D., for the PEITHO Investigators*
PEITHO: Primary efficacy outcome

<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>
</tbody>
</table>

All-cause mortality or hemodynamic collapse within 7 days of randomization

Risk reduction = 66%

Thrombolysis superior

Heparin alone superior

---

Clinical outcomes (within 7 days)

<table>
<thead>
<tr>
<th></th>
<th>Tenecteplase (n=506)</th>
<th>Placebo (n=499)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PE recurrence</td>
<td>1 (0.2)</td>
<td>5 (1.0)</td>
<td>0.12</td>
</tr>
<tr>
<td>Intubation / mechanical ventilation</td>
<td>8 (1.6)</td>
<td>15 (3.0)</td>
<td>0.13</td>
</tr>
<tr>
<td>Open-label thrombolysis</td>
<td>4 (0.8)</td>
<td>23 (4.6)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Bleeding Risk of Thrombolysis

Table 4. Safety Outcomes in the Intention-to-Treat Population.6

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Tenecteplase (N=506)</th>
<th>Placebo (N=499)</th>
<th>Odds Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bleeding between randomization and day 7</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major extracranial bleeding</td>
<td>32 (6.3)</td>
<td>6 (1.2)</td>
<td>5.55 (2.3–13.39)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Minor bleeding</td>
<td>165 (32.6)</td>
<td>48 (9.6)</td>
<td>3.48 (2.0–6.1)</td>
<td>0.001</td>
</tr>
<tr>
<td>Major bleeding†</td>
<td>58 (11.5)</td>
<td>12 (2.4)</td>
<td>2.83 (1.6–5.0)</td>
<td>0.001</td>
</tr>
<tr>
<td>Stroke between randomization and day 7</td>
<td>12 (2.4)</td>
<td>1 (0.2)</td>
<td>12.10 (1.57–93.39)</td>
<td>0.003</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>2 (0.4)</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemorrhagic stroke‡</td>
<td>10 (2.0)</td>
<td>1 (0.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serious adverse events between randomization and day 30</td>
<td>55 (10.9)</td>
<td>59 (11.8)</td>
<td>0.91 (0.62–1.34)</td>
<td>0.63</td>
</tr>
</tbody>
</table>

PEITHO: Primary end point according to age

Age ≤ 75 years

Age >75 years
Catheter-directed thrombolysis

EkoSonic Catheter

SEATTLE-II Outcomes: RV/LV Ratio

Pre-Procedural RV/LV Ratio: 1.55
48 Hour RV/LV Ratio: 1.13

p < 0.0001

Courtesy of Greg Piazza, MD (BWH)
Outcomes: PA Systolic Pressure

<table>
<thead>
<tr>
<th>Time</th>
<th>Mean PA Systolic Pressure (mmHg)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-Procedure</td>
<td>51.4</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Post-Procedure</td>
<td>37.5</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>48 Hours</td>
<td>36.9</td>
<td></td>
</tr>
</tbody>
</table>

SEATTLE II

Zero cases of Intracranial hemorrhage

Courtesy of Greg Piazza, MD (BWH)
Summary

- Risk-stratify ALL patients with PE, even if blood pressure is normal.
  - RV/LV ratio
  - proBNP, troponin T or I
  - RV systolic function by echo
  - Clinical assessment

- Massive PE
  - IV thrombolysis or surgical embolectomy
  - Consider catheter-based in patients at higher risk for bleeding.

- Submassive PE
  consider thrombolysis if:
  - Patients less than 75 yrs, the younger the better
  - Significant RV dilatation and myonecrosis
  - Low risk of bleeding

Thanks

Ian del Conde, MD, FACC

Vascular Medicine and Cardiology
Miami Cardiac and Vascular Institute
HeartWell
Miami, FL

iand@baptisthealth.net