PULMONARY EMBOLISM: THROMBOLYSIS, NOVEL ANTICOAGULANTS, ASPIRIN

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DISCLOSURES

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BMS; Daiichi; EKOS; NHLBI; Thrombosis Research Institute

Consultant:
Boehringer-Ingelheim; BMS; Daiichi; Janssen; Merck; Pfizer; Portola; Sanofi-Aventis
INTRODUCTORY REMARKS

1. Jerusalem: 1966 compared with 2013 (47 years later on visit #7)

2. Dr. Braunwald: mentor since 1972, visionary thinker, and senior author on TPA for acute PE clinical trials

3. Boston Marathon: your support and emails are appreciated; expect twice as many spectators in 2014; resilience will prevail
FATAL SADDLE PE
ITALIAN PE REGISTRY: MORTALITY RATE
N=1,787 (6.7% in-hospital mortality)
(Thrombosis Research 2012; 130: 847-852)

32% Mortality: Massive
Unstable

3.4% Mortality: Non-massive
Stable
THE POTENTIAL OF PE LYSIS

Reduce mortality/
Reverse hemodynamic collapse:
Prevent RV failure

Reduce RV pressure overload
• Rapidly resolve PA obstruction
• Reduce pulmonary vasoconstrictors

Prevent recurrent PE
• Decrease thromboembolic burden in the lower extremities and pelvis

Improve gas-exchange
• Increase pulmonary capillary blood flow
PE THROMBOLYSIS

1. **Systemic** thrombolysis:
   a) 100 mg/2h TPA (FDA: 1990)
   b) Tenecteplase: (PEITHO: ACC 2013)
   c) 50 mg TPA
      (MOPPETT: AJC 2013; 111: 273)
      (CHEST 2010; 137: 254)

2. **Catheter-directed**, Low-Energy Ultrasound-facilitated thrombolysis
   [< 20 mg TPA] (ULTIMA: ACC 2013)
PEITHO* PE LYSIS TRIAL
13 countries, including Israel
(Tenecteplase vs. placebo) (N=1,006)

• Submassive PE (enlarged/hypokineti
  c RV, troponin leak)
• A 10-year trial: 2003-2013
• **Primary Outcome:**
  – All-cause mortality ≤ 7 days
  – Hemodynamic collapse ≤ 7 days

(* PEITHO is the Greek Goddess of Persuasion)
<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>Tenecteplase (n=506)</th>
<th>Placebo (n=499)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Age (y)</td>
<td>66</td>
<td>66</td>
</tr>
<tr>
<td>Median Age (y)</td>
<td>70</td>
<td>70</td>
</tr>
<tr>
<td>Sex (female/male)</td>
<td>264/242</td>
<td>268/231</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>82</td>
<td>83</td>
</tr>
<tr>
<td>BP (mm Hg)</td>
<td>130/79</td>
<td>131/79</td>
</tr>
<tr>
<td>Heart rate (beats per min)</td>
<td>94</td>
<td>92</td>
</tr>
<tr>
<td>Respiratory rate (per min)</td>
<td>22</td>
<td>22</td>
</tr>
<tr>
<td>COPD (%)</td>
<td>26 (5.1)</td>
<td>34 (6.8)</td>
</tr>
<tr>
<td>Chronic heart failure (%)</td>
<td>21 (4.2)</td>
<td>26 (5.2)</td>
</tr>
<tr>
<td>Previous VTE (%)</td>
<td>126 (24.9)</td>
<td>147 (29.5)</td>
</tr>
<tr>
<td>Cancer (%)</td>
<td>41 (8.1)</td>
<td>32 (6.4)</td>
</tr>
</tbody>
</table>
## Primary efficacy outcome

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

**Odds ratio**

- Thrombolysis superior

- 0.23
- 0.44
- 0.88
## Secondary Efficacy Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Tenecteplase (n=506)</th>
<th>Placebo (n=499)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>(%)</td>
<td>n</td>
</tr>
<tr>
<td>All-cause mortality within 7 days</td>
<td>6 (1.2)</td>
<td>9 (1.8)</td>
<td>0.43</td>
</tr>
<tr>
<td>Hemodynamic collapse within 7 days</td>
<td>8 (1.6)</td>
<td>25 (5.0)</td>
<td>0.002</td>
</tr>
</tbody>
</table>
PEITHO: Safety outcomes

<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>n (%)</td>
<td></td>
</tr>
<tr>
<td><strong>Non-ICH bleeding</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major</td>
<td>32 (6.3)</td>
<td>6 (1.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Minor</td>
<td>165 (32.6)</td>
<td>43 (8.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Strokes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemorrhagic</td>
<td>10</td>
<td>1 (0.2)</td>
<td>0.003</td>
</tr>
<tr>
<td>Ischemic</td>
<td>2</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>
Efficacy and Safety: Age

≤75 years  >75 years

Death or hemodynamic collapse

Stroke *without* death or hemodynamic collapse

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Placebo N</th>
<th>TNK N</th>
<th>Placebo N</th>
<th>TNK N</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤75 years</td>
<td>335</td>
<td>344</td>
<td>164</td>
<td>162</td>
</tr>
<tr>
<td>&gt;75 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
1. Tenecteplase reduces the rate of death/hemodynamic collapse but increases major bleeding and ICH.

2. Rapid revascularization prevents clinical deterioration.

3. Take age into account when deciding whether to use systemic thrombolysis.

4. Risk stratification, combining RV size/function with troponin elevation, predicts adverse outcomes.
SUBMASSIVE PE: 50 mg TPA versus heparin (MOPETT) (N=121)

- TPA 10mg/1 min followed by 40 mg/2 h
- No bleeding complications/ no ICH
- PA Pressure (ECHO) lower with TPA

<table>
<thead>
<tr>
<th></th>
<th>TPA PAsyst</th>
<th>Controls</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Admission</td>
<td>50</td>
<td>51</td>
<td>0.4</td>
</tr>
<tr>
<td>Within 48h</td>
<td>34</td>
<td>41</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>6 months</td>
<td>31</td>
<td>49</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>28 months</td>
<td>28</td>
<td>43</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

(Am J Cardiology 2013; 111: 273-277)
PE Rx’d with 50 mg TPA vs. 100 mg TPA (China) (N=118)

- Massive or submassive PE
- TPA 50mg/2h versus 100 mg/2 h
- Assessed with ECHO, lung scan, CT
- Same efficacy, fewer bleeds with 50 mg

<table>
<thead>
<tr>
<th></th>
<th>TPA 50 mg</th>
<th>TPA 100 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improved 24h</td>
<td>84%</td>
<td>83%</td>
</tr>
<tr>
<td>Major bleed 14d</td>
<td>3%</td>
<td>10%</td>
</tr>
</tbody>
</table>

(CHEST 2010; 137: 254-262)
Catheter Techniques:
“Pharmacomechanical” Therapy

- Mechanical Fragmentation
- Hydrodynamic (AngioJet®)
- Ultrasound-Accelerated Fibrinolysis (EKOS®)
- Suction Embolectomy (AngioVac®)
EKOS® DRUG DELIVERY CATHETER

ULTRASOUND TRANSUDUCERS
The ULTIMA Trial (N=59)

Randomized, Controlled Trial: Ultrasound Accelerated Thrombolysis with ≤ 20 mg TPA: Rx of Acute Submassive PE

Nils Kucher, M.D.
University Hospital Bern
Bern, Switzerland

American College of Cardiology, March 9, 2013
ULTIMA: Primary Outcomes

Reduction in RV/LV Ratio

- $p < 0.0001$
- $p = 0.03$

Kucher N. Presented at ACC 2013
CONCLUSIONS: EKOS® TPA

• In submassive PE, low-dose, catheter-directed ultrasound-accelerated thrombolysis (up to 20 mg TPA/15h): superior to anticoagulation alone in reversing RV dilatation at 24 hours, without increased bleeding complications.

• More frequent improvement in RV systolic function at 90 days.
Evolving Anticoagulation Strategies

Overlapping
- LMWH/Warfarin Bridge
- UFH/Warfarin Bridge

Switching
- LMWH to Dabigatran (RE-COVER)
- LMWH to Edoxaban (HOKUSAI) (n=8,250)

Oral Monotherapy
- Rivaroxaban (3 week loading dose) (EINSTEIN)
- Apixaban (1 week load) (AMPLIFY)
1. Dabigatran: an oral DTI—twice daily (renal clearance)
2. Rivaroxaban: direct factor Xa inhibitor (renal clearance)—once daily
3. Apixaban: direct factor Xa inhibitor (hepatic clearance)—twice daily
4. Edoxaban: direct factor Xa inhibitor (hepatic clearance)—once daily
5. Betrixaban: direct factor Xa inhibitor (hepatic clearance)—once daily
EINSTEIN DVT/PE PROGRAM

EINSTEIN-DVT
(Confirmed DVT without PE)
Rivaroxaban 15 mg BID for 3 weeks; then 20 mg once daily

EINSTEIN-PE
(Confirmed PE without DVT)
Enoxaparin BID > 5 Days + VKA to target INR = 2.5 (range 2-3)

Primary Outcome:
Symptomatic recurrent VTE
EINSTEIN-PE

Symptomatic Recurrent VTE (Efficacy)

(N=4,832)

Clinically Significant Bleeding

Major Bleeding

(The EINSTEIN–PE Investigators. NEJM 2012; 366: 1287-1297)
“clinical equipoise”; 1 of 4: provoked DVT. (N=1,196)
AMPLIFY-EXT
N=2,482

Testing
Continuation
Of Anticoag
After 6-12 mos
Of therapy:

Apixaban 5 mg
Apixaban 2.5 mg
Placebo
(NEJM 2013; 368: 699=708)
RE-SONATE: Dabigatran 150 mg BID Vs. placebo

92% Less VTE

(NEJM; 2013 368: 709-718)
ROLE OF ASPIRIN

Inflammation & Thrombosis: The clot thickens

Libby & Simon
Circulation 2001
human PE:
CD11b (PMNs)
CD42b (platelets)
Inflammation and Thrombosis


(Becker RC. NEJM 2012; 366: 2028)
ASPIRE & WARFASA: Hazard Ratios for VTE, Major Vascular Events, Clinically Relevant Bleeding

(Brighton TA et al. NEJM 2012; 367: 1979-1987)
### Long-term Rx After 6-12 Months

**Standard Anticoagulation**

<table>
<thead>
<tr>
<th>Drug/Dose</th>
<th>Reduction vs Placebo</th>
<th>Citation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin (INR 2-3)</td>
<td>95%</td>
<td>NEJM 1999</td>
</tr>
<tr>
<td>Warfarin (INR 1.5-2)</td>
<td>64%</td>
<td>NEJM 2003: Ridker “PREVENT”</td>
</tr>
<tr>
<td>Aspirin 100 mg</td>
<td>32%</td>
<td>NEJM 2012; “WARFASA”/ “ASPIRE”</td>
</tr>
<tr>
<td>Rivaroxaban 20 mg</td>
<td>82%</td>
<td>NEJM 2010; “EINSTEIN-EXT”</td>
</tr>
<tr>
<td>Apixaban 2.5 mg</td>
<td>80%</td>
<td>NEJM 2013; “AMPLIFY-EXT”</td>
</tr>
<tr>
<td>Dabigatran 150 mg</td>
<td>92%</td>
<td>NEJM 2013; “RE-SONATE”</td>
</tr>
</tbody>
</table>
TAKE HOME MESSAGES

1. PE remains a major CV killer.
2. High risk PE: Consider systemic or pharmacomechanical catheter lysis.
4. PEITHO enrolled more patients than all lysis trials in past 40 years combined.
5. Will peripheral (catheter-based) venous intervention overtake systemic lysis because of a lower bleeding rate?
TAKE HOME MESSAGES


8. Low-dose aspirin reduces recurrent VTE rate after initial anticoagulation.

9. Warfarin, rivaroxaban, apixaban, and dabigatran are more effective than aspirin for preventing recurrent VTE.