Percutaneous Pharmacomechanical Intervention For PE: Do We Really Know About The Hows And Whens

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Conflict of interest
• Speaker and consultant honoraria from BTG

Do We Really Know About The Whens?
• Not really, because we do not have results from RCTs powered for clinical endpoints
• What do the guidelines suggest?

2014 ESC Guidelines
Risk-adjusted PE management algorithm (I)

<table>
<thead>
<tr>
<th>Early mortality risk</th>
<th>Risk parameters and scores</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Shock or hypotension</td>
</tr>
<tr>
<td>High</td>
<td>+</td>
</tr>
<tr>
<td>Intermediate-high</td>
<td>−</td>
</tr>
<tr>
<td>Intermediate-low</td>
<td>−</td>
</tr>
<tr>
<td>Low</td>
<td>−</td>
</tr>
</tbody>
</table>

2014 ESC Guidelines
Risk-adjusted PE management algorithm (II)

2014 ESC Guidelines
Recommendations for acute phase treatment (I)

<table>
<thead>
<tr>
<th>PE with shock or hypotension (high-risk)</th>
<th>II</th>
<th>C</th>
</tr>
</thead>
<tbody>
<tr>
<td>It is recommended to initiate intravenous anticoagulation with UFH without delay in patients with high-risk PE.</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>Thrombolytic therapy is recommended.</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>Surgical pulmonary embolectomy is recommended for patients in whom thrombolysis is contraindicated or has failed.</td>
<td>IIa</td>
<td>C</td>
</tr>
</tbody>
</table>

The Problems with Systemic PE Thrombolysis

- In clinical practice, systemic thrombolysis is withheld in up to three quarters of patients with massive PE.
- The proportion of unstable PE patients receiving thrombolytic therapy in the United States decreased from 40% in 1999 to 23% in 2008.

PE mortality reduction from thrombolysis???

Meta-analysis (16 RCT, 2115 patients)

Mortality: RRR 47%; NNT 59

PE thrombolysis: major bleeding...

OR 2.7!

PE thrombolysis: Intracranial hemorrhage...

OR 4.6!
Do We Really Know About The Hows?

- There is no evidence that mechanical PE interventions without adjunctive lytics work
- We have some data and protocols for ultrasound-assisted catheter-directed thrombolysis

The evidence for mechanical interventions is poor

Meta-analysis on PE catheter interventions (35 studies)

<table>
<thead>
<tr>
<th></th>
<th>Clinical success*</th>
<th>Clinical success in studies with &gt;80% patients receiving thrombolysis</th>
<th>Clinical success in studies with &lt;80% patients receiving thrombolysis</th>
<th>Major complications</th>
<th>Minor complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 594</td>
<td>86%</td>
<td>91%</td>
<td>83%</td>
<td>2%</td>
<td>8%</td>
</tr>
</tbody>
</table>

*Defined as stabilization of hemodynamic parameters, resolution of hypoxia, and survival to discharge


Combined Mechanical Techniques: Fragmentation and Thrombectomy

Pharmacomechanical Thrombolysis

= Local thrombolysis + mechanical intervention

AngioJet: Power Pulse thrombolysis + thrombectomy (Venturi effect)

EKOS: Ultrasound-assisted thrombolysis

Ultrasound accelerated thrombolysis

Mechanism of Action

- Ultrasound pulses
- Fibrin separation
- Active drug delivery by acoustic streaming

EKOS EkoSonic® Mach 4e Endovascular System

- Infusion side-hole catheter with a multielement ultrasound core
- 12 cm nominal treatment zone length typically used for PE therapy
**ULTrasound Accelerated Thrombolysis of PulMonAry Embolism**

- **Phase II, multicenter, open-label, randomized, controlled clinical trial**
- **Aim:** determine whether fixed low-dose, catheter-directed ultrasound-accelerated thrombolysis is superior to anticoagulation alone in the reversal of RV dilatation in intermediate-risk PE patients

**ULTIMA Investigators**

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- Ulrich Tebbe, MD Klinikum Lippe-Detmold, Detmold, Germany
- Klaus Empen, MD Universitätsmedizin Greifswald der Ernst-Moritz-Arndt-Universität, Greifswald, Germany

- Hemodynamically stable patients with acute symptomatic PE
- UFH 80 U/kg Bolus IV, UFH continuous infusion of 18 U/kg/min IV (max 1800 U/h)
- Contrast-Enhanced Chest CT: Filling defect in at least one main or proximal lower lobe pulmonary artery
- Baseline ECHO: RV/LV ratio ≥1.0
- Secondary endpoints: Mortality, recurrent PE, major & minor bleeding at 90 days

**Primary endpoint assessed by blinded core-lab:**

- Reduction in RV/LV ratio from baseline to 24h

**Primary endpoint:**

- Reducing in RV/LV ratio

**SEATTLE II: Overview**

- CT-confirmed PE:
  - Symptoms ≤ 14 days
  - Massive or submassive
  - Meets all inclusion and no exclusion criteria
- RV enlargement as documented by initial CT
- RV:LV ratio ≥ 0.9
- Ultrasound-facilitated fibrinolysis:
  - t-PA 1 mg/hr for 24 hours (1 device)
  - t-PA 1 mg/hr for 12 hours (2 devices)
  - TOTAL t-PA Dose = 24 mg
- Follow-up at 48 hours after start of the procedure
- CT measurement of RV/LV ratio
- Echocardiograms to evaluate PE symptoms: pre-procedure

**Seattle II: Primary Efficacy Outcome: RV/LV Ratio**

- RV/LV Ratio: 1.55
- P = 0.0001

**U.S. Study Sites = 22**
**Total Trial Population = 150**
RV/LV Ratio: Pre- and Post-Procedure

Pre: RV/LV = 2.5
Post: RV/LV = 0.7

Courtesy of Keith M. Sterling, MD

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>3 (2)</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 (%) GUSTO moderate***</td>
<td>17 (11.4)</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)

Ultrasound-Assisted PE Thrombolysis

Dose Regimens

<table>
<thead>
<tr>
<th>Studies</th>
<th>N</th>
<th>Massive PE N (%)</th>
<th>Total r-tPA dose, mg (mean ± SD)</th>
<th>Thrombolysis duration, h (mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chamsuddin 2008</td>
<td>10</td>
<td>NA</td>
<td>21.8</td>
<td>24.8 ± 6.4</td>
</tr>
<tr>
<td>Lin 2009</td>
<td>11</td>
<td>2 (18%)</td>
<td>17.2 ± 2.4</td>
<td>17.4 ± 5.2</td>
</tr>
<tr>
<td>Engelhardt 2011</td>
<td>24</td>
<td>5 (21%)</td>
<td>33.5 ± 15.5</td>
<td>19.7 ± 8.1</td>
</tr>
<tr>
<td>Quintana 2013</td>
<td>10</td>
<td>2 (20%)</td>
<td>18 (7-38)*</td>
<td>20.8 (12-46)*</td>
</tr>
<tr>
<td>Kennedy 2013</td>
<td>60</td>
<td>12 (20%)</td>
<td>35.1 ± 11.1</td>
<td>19.6 ± 6.0</td>
</tr>
<tr>
<td>Engelberger 2013</td>
<td>92</td>
<td>14 (27%)</td>
<td>21.0 ± 6.7</td>
<td>15.2 ± 5.7</td>
</tr>
<tr>
<td>Kucher 2013</td>
<td>30</td>
<td>0 (0)</td>
<td>20.8 ± 3.0</td>
<td>15.0 ± 1.0</td>
</tr>
<tr>
<td>Total</td>
<td>197</td>
<td>35 (18%)</td>
<td>26.9</td>
<td>17.8</td>
</tr>
</tbody>
</table>

*p Median (ranges); §pooled mean without study by Quintana et al.

Conclusions

- Ultrasound-assisted, fixed-low dose catheter-directed thrombolysis is a promising treatment modality for patients with intermediate and high-risk PE
- Ultrasound-assisted catheter-directed PE thrombolysis rapidly reverses RV dysfunction and hemodynamic instability and is associated with a low risk of bleeding and mortality