Pulmonary Embolism: New Ideas About An Old Problem

Belinda Rivera-Lebron, MD MS
Assistant Professor of Medicine
Division of Pulmonary, Allergy & Critical Care
University of Pittsburgh
PE is a Serious Problem

VTE (PE + DVT) 900,000/yr in US

PE Hospitalizations 150,000-250,000/yr

PE Deaths 100,000-200,000/yr

PE sequela 50%

CTEPH 4%
VTE INCIDENCE: INCREASING

First-Time Occurrence

Annual Event Rate, per 100,000

VTE

DVT

PE

PE is the #3 cause of CV death

PE Natural History

Adapted from Fedullo

30% recurrence within 10 yrs

>90% complete resolution

4% CTEPH

Full recovery
Partial recovery
American Classifications of PE

Low Risk
- Normotensive
- No RV dysfunction
- Normal biomarkers

Submassive (Intermediate Risk)
- Normotensive
- RV strain (CT/TTE)
  - RV dilation
  - RV dysfunction
- BNP > 90 pg/mL, pro-BNP > 500 pg/mL
- Myocardial necrosis
  - Trop I > 0.4 ng/mL, Trop T > 0.1 ng/mL

Massive (High Risk)
- Hypotension (SBP < 90 for > 15 min)
- Shock (on pressor)
- Pulselessness

Jaff. Circ 2011
## European Classifications of PE

<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></td>
<td>PESI class III-V or sPESI ≥1(^a)</td>
</tr>
<tr>
<td></td>
<td>Signs of RV dysfunction on an imaging test(^b)</td>
</tr>
<tr>
<td></td>
<td>Cardiac laboratory biomarkers(^c)</td>
</tr>
<tr>
<td>High</td>
<td>+</td>
</tr>
<tr>
<td>Intermediate</td>
<td>Intermediate–high</td>
</tr>
<tr>
<td></td>
<td>Intermediate–low</td>
</tr>
<tr>
<td>Low</td>
<td>–</td>
</tr>
</tbody>
</table>

\(^a\) PESI: Pulmonary Embolism Severity Index; \(^b\) RV: Right Ventricular; \(^c\) Cardiac biomarkers include troponins, NT-proBNP, etc.; \(^d\) The (+) symbol indicates a positive test result; \(^e\) The decision to proceed with further testing or treatment is based on clinical judgment.
Adapted from Dudziski
Integrated Prognostic Factors

PESI score

Imaging (Echo/CT)

Biomarkers (Trp/BNP)
## PE Severity Index (PESI)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Original version</th>
<th>Simplified version</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Age in years</td>
<td>1 point (if age &gt;80 years)</td>
</tr>
<tr>
<td>Male sex</td>
<td>+10 points</td>
<td>–</td>
</tr>
<tr>
<td>Cancer</td>
<td>+30 points</td>
<td>–</td>
</tr>
<tr>
<td>Chronic heart failure</td>
<td>+10 points</td>
<td>–</td>
</tr>
<tr>
<td>Chronic pulmonary disease</td>
<td>+10 points</td>
<td>–</td>
</tr>
<tr>
<td>Pulse rate ≥110 b.p.m.</td>
<td>+20 points</td>
<td>–</td>
</tr>
<tr>
<td>Systolic blood pressure &lt;100 mm Hg</td>
<td>+30 points</td>
<td>–</td>
</tr>
<tr>
<td>Respiratory rate &gt;30 breaths per minute</td>
<td>+20 points</td>
<td>–</td>
</tr>
<tr>
<td>Temperature &lt;36 °C</td>
<td>+20 points</td>
<td>–</td>
</tr>
<tr>
<td>Altered mental status</td>
<td>+60 points</td>
<td>–</td>
</tr>
<tr>
<td>Arterial oxyhaemoglobin saturation &lt;90%</td>
<td>+20 points</td>
<td>–</td>
</tr>
</tbody>
</table>

### Risk strata

- **Class I**: ≤65 points
  - very low 30-day mortality risk (0–1.6%)
  - low mortality risk (1.7–3.5%)

- **Class II**: 66–85 points
  - moderate mortality risk (3.2–7.1%)
  - high mortality risk (4.0–11.4%)

- **Class III**: >86–105 points
  - very high mortality risk (10.0–24.5%)

### Scores

- 0 points = 30-day mortality risk 1.0% (95% CI 0.0%–2.1%)
- ≥1 point(s) = 30-day mortality risk 10.9% (95% CI 8.5%–13.2%)

Aujesky. Am J Respir Crit Care Med 2005
Jimenez. Arch Intern Med 2010
Zamorano. European Heart J 2014
Imaging

**Echo**

- RV:LV > 0.9 or RV dysf
  - Sens 74%, Spec 54%
  - 7% in-hospital mortality
  - 41% worse outcomes (pressors, thrombolysis, CPR)

**CT scan**

- RV_D:LV_D > 0.9
  - Sens 84%, Spec 35%
  - 5-fold risk for PE-related mortality

- Thrombus load and central PE **not** associated with mortality

---

J Am Coll Cardiol 1997
Int J Cardiovasc Imaging 2015
Combined Approach to Risk Stratification

<table>
<thead>
<tr>
<th>Parameter</th>
<th>30-day complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>sPESI</td>
<td>10%</td>
</tr>
<tr>
<td>sPESI + BNP</td>
<td>14%</td>
</tr>
<tr>
<td>sPESI + BNP + Troponin</td>
<td>20%</td>
</tr>
<tr>
<td>sPESI + BNP + Troponin + DVT</td>
<td>26%</td>
</tr>
</tbody>
</table>

Handoko. Am J Respir Crit Care Med. 2014
Management Alternatives

- Anticoagulant
- IVC Filter
- Mechanical
  - MCS
  - Percutaneous Fragmentation & Aspiration
  - Pharmacomechanical
  - Surgical Embolectomy

~More likely with ↑ severity~
Acute PE Team (PERT)

• A multidisciplinary group with expertise in the diagnosis, medical, surgical and interventional management of PE who collaborate to improve patient care

• Goals
  • Improve patient care
  • Facilitate multidisciplinary consultation with rapid mobilization
  • Outpatient follow up: Post-PE clinic
  • Regular meetings to discuss cases
  • Facilitate research (PE registry, clinical trials)
  • National PERT consortium
Multidisciplinary Collaboration

PE Team

Pulmonary/Critical Care

Vascular Surgery

Interventional Cardiology

Cardiac Surgery

Emergency Medicine

Hematology
New ACCP Anticoagulation Guidelines 2016

- **VTE w/o cancer**: 1st line tx NOAC (dabigatran*, rivaroxaban, apixaban and endoxaban*)
  - * Bridging required
  - 39% lower major bleeding, 64% lower fatal bleeding, 63% lower ICH
  - Reversal agent for dabigatran: Idarucizumab (Praxbind ®). Dexanet alpha awaiting FDA approval

- **VTE w cancer**: 1st line tx LMWH

Antithrombotic Therapy for VTE Disease. CHEST. 2016
Blood 2014
New ACCP Anticoagulation Guidelines 2016

• **Provoked** VTE: treat x 3 mo

• **Unprovoked** VTE: treat *indefinitely* (until risk of bleeding>clotting)

• No **IVC Filter** unless unable to tolerate AC

Antithrombotic Therapy for VTE Disease. CHEST. 2016
## New ACCP Anticoagulation Guidelines 2016

### Out of Hospital
- Low-risk PE
- Clinically stable with good cardiopulmonary reserve
- No contraindications (recent bleeding, severe renal or liver disease, or low platelets)
- Compliant
- Patient feels well enough to be treated at home
- PESI score <85 or sPESI = 0

### Subsegmental PE
- No AC for indicated for:
  - Single PE
  - With low risk for recurrence
  - No DVT in LE dopplers
  - Asymptomatic

Antithrombotic Therapy for VTE Disease. CHEST. 2016
Systemic Thrombolysis in High Risk (Massive) PE

- Meta analysis of 11 RCT comparing lysis vs UFH
  - All PE (748 pts): OR 0.67 (CI 0.4-1.12)
  - Massive PE: 9.4% vs 19%, OR 0.45 (CI 0.22-0.92)

- Cohort study of 72,230 HD unstable patients 1999-2008
  - HD unstable = shock or ventilator
  - Mortality 15% vs 47%, RR 0.2 (p < 0.001)
Systemic Thrombolysis in Intermediate Risk (Submassive) PE

- **PEITHO Trial**: RCT lysis/heparin vs placebo/heparin
- 1006 patients w RV dysfunction (CT/TTE) and myocardial injury (Trop I or T)
- Primary endpoint: All cause mortality or Hemodynamic collapse within 7 days of randomization (CPR, SPB < 90 mmHg for 15 min or drop ≥ 40 mmHg with end organ hypoperfusion, pressor initiation)

NEJM 2014; 370: 1402-11
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></td>
<td>n</td>
<td>(%)</td>
<td>n</td>
</tr>
<tr>
<td>All-cause mortality or hemodynamic collapse within 7 days of randomization</td>
<td>13 (2.6)</td>
<td>28 (5.6)</td>
<td>0.015</td>
</tr>
</tbody>
</table>

Odds ratio

0.23 0.44 0.88

Thrombolysis superior
<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>Primary outcome — no. (%)</td>
<td>13 (2.6)</td>
<td>28 (5.6)</td>
<td>0.44 (0.23–0.87)</td>
<td>0.02</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>6 (1.2)</td>
<td>9 (1.8)</td>
<td>0.65 (0.23–1.85)</td>
<td>0.42</td>
</tr>
<tr>
<td>Hemodynamic decompensation</td>
<td>8 (1.6)</td>
<td>25 (5.0)</td>
<td>0.30 (0.14–0.68)</td>
<td>0.002</td>
</tr>
<tr>
<td>Time between randomization and primary efficacy outcome — days</td>
<td>1.54±1.71</td>
<td>1.79±1.60</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recurrent pulmonary embolism between randomization and day 7 — no. (%)</td>
<td>1 (0.2)</td>
<td>5 (1.0)</td>
<td>0.20 (0.02–1.68)</td>
<td>0.12</td>
</tr>
<tr>
<td>Fatal</td>
<td>0</td>
<td>3 (0.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonfatal</td>
<td>1 (0.2)</td>
<td>2 (0.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other in-hospital complications and procedures — no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>8 (1.6)</td>
<td>15 (3.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgical embolectomy</td>
<td>1 (0.2)</td>
<td>2 (0.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Catheter thrombus fragmentation</td>
<td>1 (0.2)</td>
<td>0 (0.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vena cava interruption</td>
<td>5 (1.0)</td>
<td>1 (0.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombolytic treatment other than study medication</td>
<td>4 (0.8)</td>
<td>23 (4.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death from any cause between randomization and day 30 — no. (%)</td>
<td>12 (2.4)</td>
<td>16 (3.2)</td>
<td>0.73 (0.34–1.57)</td>
<td>0.42</td>
</tr>
<tr>
<td>Patient still hospitalized at day 30 — no. (%)</td>
<td>59 (11.7)</td>
<td>50 (10.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rehospitalization between randomization and day 30 — no. (%)</td>
<td>22 (4.4)</td>
<td>15 (3.0)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Table 4. Safety Outcomes in the Intention-to-Treat Population.†

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Tenecteplase (N = 506) no. (%)</th>
<th>Placebo (N = 499) no. (%)</th>
<th>Odds Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bleeding</strong></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>43 (8.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major bleeding†</td>
<td>58 (11.5)</td>
<td>12 (2.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Stroke between randomization and day 7</strong></td>
<td>12 (2.4)</td>
<td>1 (0.2)</td>
<td>12.10 (1.37–93.39)</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><strong>Serious adverse events between randomization and day 30</strong></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>

#### B Major Extracranial Bleeding

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Tenecteplase (N=506) no. (%)</th>
<th>Placebo (N=499) no. (%)</th>
<th>Odds Ratio (95% CI)</th>
<th>P Value for Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></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>0.13</td>
</tr>
<tr>
<td><strong>Sex</strong></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 (0.83–8.61)</td>
<td></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>

Meyer. NEJM 2014
How about Low-dose Thrombolysis?

• Meta-analysis of 5 studies
• **Low-dose tPA** (50mg) vs. standard dose (100mg)
• No difference in all-cause mortality or recurrent PE
• Less major bleeding with low-dose tPA (OR 0.33, 95% CI 0.12-0.91)

Sharifi M et al. Am J Cardiol 2013
Zhang Z et al. Thromb Res. 2013
Armstrong PW et al. Am Heart J 2015
ACCP Antithrombotic Guidelines 2016:
Systemic Thrombolysis

- PE with hypotension and low bleeding risk
- PE with deterioration after starting AC, but yet to develop hypotension and with low bleeding risk
- PE w/o hypotension, with severe symptoms or marked cardiopulmonary impairment - may benefit from lytics

Antithrombotic Therapy for VTE Disease. CHEST. 2016
Catheter-directed tPA in Intermediate Risk (Submassive) PE

- **ULTIMA (ULTrasound accelerated thrombolysis of pulMonAry embolism with EKOS): Heparin/EKOS vs Heparin**
- 59 patients with submassive PE (RV:LV ratio >1)
- Primary outcome: Δ RV/LV at 24 hrs

Kucher. Circulation 2014
RV/LV ratio (echo)

- EKOS+Heparin
  - Baseline: 1.28
  - 24 hrs: 0.99
  - 90 days: 0.95

- Heparin
  - Baseline: 1.20
  - 24 hrs: 1.17
  - 90 days: 0.98

Statistical significances:
- EKOS+Heparin:
  - Baseline vs. 24 hrs: P<0.0001
  - Baseline vs. 90 days: P<0.0001

- Heparin:
  - Baseline vs. 24 hrs: P=0.31
  - Baseline vs. 90 days: P<0.0001
Does *catheter-based interventions* improve outcomes?

- **PERFECT trial**: prospective, multicenter registry
- 101 patients (Massive 28; Submassive 73)
- Primary outcome: clinical success (stabilization of HD + improvement in PH or RV strain) and survival to discharge

**Results:**
- Clinical success 24/28 Massive; 71/73 Submassive
- $\downarrow$mPA from 51 to 37 mmHg
- Improved RV strain in 89%
- No major complications related to procedure or bleeding
- No differences among various techniques/devices
What about **survival** benefit?

- National Inpatient Sample 2010-2012 identified 110,731 PE → 1,521 (1.4%) patients received thrombolysis
  - 77% systemic and 23% catheter-directed (CDL)
  - ↓ **in-hospital mortality** 22% vs. 13%, OR 0.55 (CI 0.36-0.85, p = 0.007)
  - Similar length of stay 7 days
  - ↑ cost of hospitalization $23,799 vs $17,218

Patel et al. Cath and Card Interv 2015
Catheter-based Embolectomy

- Thrombus fragmentation/aspiration
- Can be alone or in combination CDL
- Fragmentation may cause distal embolization and worsen obstruction
Surgical Embolectomy

- Requires median sternotomy with bypass
- Mortality rate 5%
- Preoperative thrombolysis increases risk of bleeding but is not absolute contraindication

RV assist devices

- Impella, ECMO
- Reserved for cardiac arrest or refractory shock
Life after PE: Post-PE Sequelae

Klok. Blood Reviews 2014
Take Home Points

• PE is the 3\textsuperscript{rd} most common cardiovascular disorder in the USA with a high mortality in Massive and Submassive PE

• Systemic thrombolysis – reserved for Massive PE - associated with increased bleeding and ICH

• Catheter-directed thrombolysis acutely decreases clot burden and may help in Massive and Submassives

• PE is associated with acute and long-term negative cardiopulmonary outcomes, including CTEPH
Thank you!

Belinda Rivera-Lebron
riveralebronbn@upmc.edu