Insights Into the Management of Acute Pulmonary Embolism

Ammar Safar, MD, FSCAI, FACC, FACP, RPVI

Interventional Cardiology & Endovascular Medicine
Disclosers

NONE
Pulmonary Embolism (PE)

---

**Annual incidence**
- United States: 69 per 100,000/year\(^1\)
- Over 600,000 cases annually\(^2\)
  - 1–2 PE episodes per 1000 people, up to 10 per 1000 in the elderly population\(^3-6\)

**Venous thromboembolism**\(^3\)
- PE commonly originates from lower limb deep vein thrombosis (DVT)
- 79% of patients presenting with PE have evidence of DVT
- PE occurs in up to 50% of patients with proximal DVT

---

5. Chunilal et al. JAMA 2003;290:2849-58
PE Mortality

- 100,000–180,000 PE-related deaths annually in the US
- PE is the most preventable cause of death among hospitalized patients

The Surgeon General’s Call to Action to Prevent Deep Vein Thrombosis and Pulmonary Embolism
2008

U.S. Department of Health and Human Services

AHA 2015 Statistics:
PE is the 3rd cause of CV death

# PE: A silent and fatal epidemic

Most patients who die from PE are not diagnosed at pre-mortem, and are not even suspected pre-mortem\(^1\)

<table>
<thead>
<tr>
<th>Study</th>
<th>Autopsies</th>
<th>PE present</th>
<th>PE suspected pre-mortem</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rubenstein(^2)</td>
<td>1,276</td>
<td>44</td>
<td>14 (32%)</td>
</tr>
<tr>
<td>Stein(^3)</td>
<td>404</td>
<td>59</td>
<td>6 (30%)</td>
</tr>
<tr>
<td>Lau(^4)</td>
<td>11,044</td>
<td>116</td>
<td>27 (23%)</td>
</tr>
<tr>
<td>Morgenthaler(^5)</td>
<td>2,427</td>
<td>92</td>
<td>45 (49%)</td>
</tr>
<tr>
<td>Pulido(^6)</td>
<td>1,032</td>
<td>231</td>
<td>42 (18%)</td>
</tr>
</tbody>
</table>

---

1. Tapson V. Emerging Management Options for PE: What the Vascular Specialist Must Know. VEITHsymposium 2012
High PE mortality
High re-admission rates

- Risk Adjusted 6-month Mortality Rate
- Risk Adjusted 30-day Readmission Rate
- Risk Adjusted 30-day Mortality Rate
- In-Hospital Mortality Rate
# PE risk stratification

## Patient risk stratification (per AHA Scientific Statement 2011)

<table>
<thead>
<tr>
<th>Massive PE</th>
<th>Submassive PE</th>
<th>Minor/Nonmassive PE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High risk</strong></td>
<td><strong>Moderate/intermediate risk</strong></td>
<td><strong>Low risk</strong></td>
</tr>
<tr>
<td>- Sustained hypotension (systolic BP &lt;90 mmHg for ≥ 15 min)</td>
<td>- Systemically normotensive (systolic BP ≥90 mmHg)</td>
<td>- Systemically normotensive (systolic BP ≥90 mmHg)</td>
</tr>
<tr>
<td>- Inotropic support</td>
<td>- <strong>RV dysfunction</strong></td>
<td>- No RV dysfunction</td>
</tr>
<tr>
<td>- Pulselessness</td>
<td>- Myocardial necrosis</td>
<td>- No myocardial necrosis</td>
</tr>
<tr>
<td>- Persistent profound bradycardia (HR &lt;40 bpm with signs or symptoms of shock)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**RV dysfunction**
- RV/LV ratio > 0.9 or RV systolic dysfunction on echo
- RV/LV ratio > 0.9 on CT
- Elevation of BNP (>90 pg/mL)
- Elevation of NTpro-BNP (>500 pg/mL)
- ECG changes
  - New complete or incomplete RBBB
  - Anteroseptal ST elevation or depression
  - Anteroseptal T-wave inversion

---


RV Dysfunction/ Tn Elevation Combo in PE: Prognosis (n=1,273)

Stein et al. Am J Cardiol 2010; 106: 558-563
PE patient population profile

MASSIVE PE
[High risk]
5% PE population
58%\(^1\) mortality @ 3 months

SUBMASSIVE PE
[Moderate/Intermediate risk]
40% PE population
2-3%\(^2,3\) mortality to
21%\(^1\) mortality @ 3 months

MINOR PE
[Low risk]
55% PE population
Good prognosis
Low mortality rate

Outcomes in Pulmonary Embolism

Mortality

- Sudden Death
- Cardiac Arrest
- Shock

Severity

- Embolism Size
- Cardiopulmonary Status

Stratification by RV dysfunction?
Outcomes in Pulmonary Embolism

Mortality

Emboli Size vs Severity vs Cardiopulmonary Status

- Sudden Death
- Cardiac Arrest
- Shock

Stratification by RV dysfunction?
Normotensive PE with RV dysfunction (ie Submassive) → up to 30% mortality!!!

thus

Relying soley on BP may fail to identify key prognostic features and delay more appropriate therapy

Chest 2002; 121: 878
Why submassive PE patients are at risk: Hemodynamic collapse in acute PE

Why treat intermediate risk PE patients aggressively?

Various studies report presence of right ventricular dysfunction (RVD) as a predictor of poor clinical outcomes

1. Mortality
2. Adverse events
3. VTE recurrence
Adverse outcomes associated with RVD
3x higher in-hospital mortality

Echocardiographic RV/LV ratio ≥ 0.9 shown to be independent predictive factor of hospital mortality

- Registry of 1,416 patients
- Mortality rate:
  - 1.9% if RV/LV ratio < 0.9
  - 6.6% if RV/LV ratio ≥ 0.9
Adverse outcomes associated with RVD

Increased mortality at 3 months

- PE-related mortality risk increases with stepwise increase in RV/LV Ratio

  - Retrospective analysis of 120 patients with hemodynamically stable PE based on chest CT

  - PE-related mortality at 3 months:
    - 17% if RV/LV ≥ 1.5
    - 8% if 1.0 ≤ RV/LV < 1.5
    - 0% if RV/LV < 1.0
Adverse outcomes associated with RVD

Presence of RV hypokinesis associated with increase in mortality rate at 3 months

- Prospective study of 2,454 consecutive PE patients at 52 hospitals in 7 countries

Mortality rate at 3 months
- 21% with hypokinesis
- 15% with no hypokinesis

Goldhaber, SZ et al, Acute pulmonary embolism: clinical outcomes in the International Cooperative Pulmonary Embolism Registry (ICOPER), Lancet 1999; 353: 1386-89,
Adverse outcomes with unresolved RVD

8 x incidence of *recurrent VTE*

---

PE patients with RVD unresolved exhibit 8x increased incidence of recurrent VTE compared to those with RVD resolved at discharge

- Retrospective analysis of 301 patients with first episode PE with mean f/u at 3.1 years

**Incidence of VTE at 4 years**

- 0.4 if RVD unresolved
- 0.05 if RVD resolved

Figure: Cumulative incidence of recurrent venous thromboembolism. RVD indicated right ventricular dysfunction.

Grifoni S et al. Association of Persistent Right Ventricular Dysfunction at Hospital Discharge After Acute Pulmonary Embolism with Recurrent Thromboembolic Events. Arch Intern Med 2006; 166:2151-2156
Standard PE therapy

Anticoagulation (ac)—Heparin

- AC therapy prevents further clot growth
- Studies\textsuperscript{1,2,3} found
  - LMWH as effective as UFH in reducing recurrent PE
  - LMWH carries reduced bleeding risk compared to UFH

Standard Of Care: usually UFH or LMWH, followed by oral warfarin

- However, AC therapy relies on endogenous tPA to dissolve occluding clot\textsuperscript{4}
  - a process that typically occurs over several weeks or months
  - endogenous fibrinolysis may often be incomplete at the end

Rationale for thrombolysis in acute PE

- Reduce Thrombus Burden (not achievable by AC alone)
  - Reverse RV afterload/failure toward prevention of hemodynamic collapse
  - Improve pulmonary reperfusion/capillary blood flow/gas exchange
  - Restore systemic arterial perfusion pressure
  - Decrease the risk of developing chronic pulmonary hypertension

IV thrombolysis with tPA

- 100 mg tPA infused over 2 hours
- Indicated for management of acute **massive** PE in adults
  - For the lysis of acute pulmonary emboli, defined as obstruction of blood flow to a lobe or multiple segments of the lungs
  - For the lysis of pulmonary emboli accompanied by unstable hemodynamics, e.g., failure to maintain blood pressure without supportive measures
Meta-analysis suggests reduced risk of recurrent PE or death from thrombolysis compared with heparin.

- Meta analysis of randomized clinical trials for PE comparing thrombolytic therapy with heparin
- Total of 11 trials, 748 patients included
- Data from trials that included massive PE

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Thrombolysis n/N(%)</th>
<th>Heparin n/N(%)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent PE or death</td>
<td>12/128 (9.4)</td>
<td>24/126 (19.0)</td>
<td>0.45 (0.22–0.92)</td>
</tr>
<tr>
<td>Recurrent PE</td>
<td>5/128 (3.9)</td>
<td>9/126 (7.1)</td>
<td>0.61 (0.23–1.62)</td>
</tr>
<tr>
<td>Death</td>
<td>8/128 (6.2)</td>
<td>16/126 (12.7)</td>
<td>0.47 (0.20–1.10)</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>28/128 (21.9)</td>
<td>15/126 (11.9)</td>
<td>1.98 (1.00–3.92)</td>
</tr>
</tbody>
</table>

PE Indicated Pulmonary embolism

Meta-analysis suggested thrombolysis was associated with lower mortality for intermediate-risk PE, recurrent PE.

Major bleeding was also significantly increased, but not for patients 65 years and younger.

<table>
<thead>
<tr>
<th>Outcome of Interest (No. of Studies Reporting)</th>
<th>No. of Events/No. of Patients, Absolute Event Rate (%)</th>
<th>No. Needed to Treat or harm</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Thrombolytic Group</td>
<td>Anticoagulant Group</td>
<td></td>
</tr>
<tr>
<td>All-cause mortality (16)</td>
<td>23/1061 (2.17)</td>
<td>41/1054 (3.89)</td>
<td>NNT = 59</td>
</tr>
<tr>
<td>Major bleeding (16)a</td>
<td>98/1061 (9.24)</td>
<td>36/1054 (3.42)</td>
<td>NNH = 18</td>
</tr>
<tr>
<td>ICH (15)</td>
<td>15/1024 (1.46)</td>
<td>2/1019 (.19)</td>
<td>NNH = 78</td>
</tr>
<tr>
<td>Recurrent PE (15)</td>
<td>12/1024 (1.17)</td>
<td>31/1019 (3.04)</td>
<td>NNT = 54</td>
</tr>
</tbody>
</table>

| Age > 65 y                                    |                        |                                |         |
| All-cause mortality (5)                       | 14/673 (2.08)          | 24/658 (3.65)                   | NNT = 64 | .07    |
| Major bleeding (5)a                           | 87/673 (12.93)         | 27/658 (4.10)                   | NNH = 11 | <.001  |

| Age ≤ 65 y                                    | 9/388 (2.32)          | 17/396 (4.29)                   | NNT = 51 | .09    |

| Intermediate-risk PE                          | 11/388 (2.84)         | 9/396 (2.27)                    | NNH = 176 | .89    |
| All-cause mortality (8)                       | 12/866 (1.39)         | 26/889 (2.92)                   | NNT = 65 | .03    |
| Major bleeding (8)a                           | 67/866 (7.74)         | 20/889 (2.25)                   | NNH = 18 | <.001  |

# Lysis in submassive PE

## Mortality meta-analysis

<table>
<thead>
<tr>
<th>Source</th>
<th># of Events</th>
<th># of Patients</th>
<th># of Events</th>
<th># of Patients</th>
<th>OR (95% CI)</th>
<th>Favors Thrombolitics</th>
<th>Favors Anticoagulants</th>
<th>Weight, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goldhaber et al, 2 1993</td>
<td>0</td>
<td>46</td>
<td>2</td>
<td>55</td>
<td>0.16 (0.01-2.57)</td>
<td></td>
<td></td>
<td>5.3</td>
</tr>
<tr>
<td>Konstantinides et al, 3 2002</td>
<td>4</td>
<td>118</td>
<td>3</td>
<td>138</td>
<td>1.58 (0.35-7.09)</td>
<td></td>
<td></td>
<td>18.4</td>
</tr>
<tr>
<td>TIPES, 29 2010</td>
<td>0</td>
<td>28</td>
<td>1</td>
<td>30</td>
<td>0.14 (0.00-7.31)</td>
<td></td>
<td></td>
<td>2.7</td>
</tr>
<tr>
<td>Fasullo et al, 11 2011</td>
<td>0</td>
<td>37</td>
<td>6</td>
<td>35</td>
<td>0.11 (0.02-0.58)</td>
<td></td>
<td></td>
<td>15.1</td>
</tr>
<tr>
<td>MOPETT, 10 2012</td>
<td>1</td>
<td>61</td>
<td>3</td>
<td>60</td>
<td>0.35 (0.05-2.57)</td>
<td></td>
<td></td>
<td>10.5</td>
</tr>
<tr>
<td>ULTIMA, 30 2013</td>
<td>0</td>
<td>30</td>
<td>1</td>
<td>29</td>
<td>0.13 (0.00-6.59)</td>
<td></td>
<td></td>
<td>2.7</td>
</tr>
<tr>
<td>TOPCOAT, 9 2014</td>
<td>1</td>
<td>40</td>
<td>1</td>
<td>43</td>
<td>1.08 (0.07-17.53)</td>
<td></td>
<td></td>
<td>5.3</td>
</tr>
<tr>
<td>PEITHO, 11 2014</td>
<td>6</td>
<td>506</td>
<td>9</td>
<td>499</td>
<td>0.66 (0.24-1.82)</td>
<td></td>
<td></td>
<td>40.0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>12</strong></td>
<td><strong>866</strong></td>
<td><strong>26</strong></td>
<td><strong>889</strong></td>
<td><strong>.48 (0.25-0.92)</strong></td>
<td></td>
<td></td>
<td><strong>100.0</strong></td>
</tr>
</tbody>
</table>

Heterogeneity: $\chi^2 = 7.63$; $P = .37$; $I^2 = 8%$

Overall effect: $z = 2.22$; $P = .03$

## Intermediate-risk PE

<table>
<thead>
<tr>
<th></th>
<th>Event Rate</th>
<th>OR (95% CI)</th>
<th>NNT</th>
<th>NNH</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality (8)</td>
<td>12/866 (1.39)</td>
<td>26/889 (2.92)</td>
<td>NNT = 65</td>
<td>.03</td>
</tr>
<tr>
<td>Major bleeding (8)</td>
<td>67/866 (7.74)</td>
<td>20/889 (2.25)</td>
<td>NNH = 18</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

For acute PE patients, thrombolytic therapy

- Reduced total mortality, PE recurrence, and PE-related mortality
- Decrease in overall mortality not significant in intermediate-risk PE patients
- Associated with an increase in major, fatal or ICH

RCT examined benefit of IV thrombolysis in intermediate-risk PE

**PEITHO Trial**

**Primary Objective**
- Investigate clinical benefits (efficacy) of thrombolysis with tenecteplase over placebo in normotensive patients with acute intermediate-risk PE (both treatment arms receive standard heparin anticoagulation)

**Secondary Objective**
- To assess the safety of tenecteplase in patients with intermediate-risk PE
IV thrombolysis reduced the risk of hemodynamic collapse

<table>
<thead>
<tr>
<th></th>
<th>Tenecteplase (n=506)</th>
<th>Placebo (n=499)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All cause mortality within 7 days</td>
<td>6 (1.2%)</td>
<td>9 (1.8%)</td>
<td>0.42</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>
<tr>
<td>– Need for CPR</td>
<td>1</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>– Hypotension/BP drop</td>
<td>8</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>– Catecholamines needed</td>
<td>3</td>
<td>14</td>
<td></td>
</tr>
</tbody>
</table>

But the benefit of lysis came at the cost of major bleeds (including ICH)

<table>
<thead>
<tr>
<th></th>
<th>Tenecteplase (n=506)</th>
<th>Placebo (n=499)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bleeding by day 7</strong></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>&lt;0.001</td>
</tr>
<tr>
<td>Major bleeding as defined by ISTH</td>
<td>58 (11.5%)</td>
<td>12 (2.4%)</td>
<td></td>
</tr>
<tr>
<td><strong>All Strokes by day 7</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemorrhagic</td>
<td>10</td>
<td>1</td>
<td>0.003</td>
</tr>
<tr>
<td>Ischemic</td>
<td>2</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td><strong>Serious adverse events (SAE) by day 30</strong></td>
<td>55 (10.9%)</td>
<td>59 (11.8%)</td>
<td>0.63</td>
</tr>
</tbody>
</table>

Adoption of IV thrombolysis hampered by elevated risk of severe bleeds

- In randomized trials, systemic PE thrombolysis is associated with a 11.5% risk of major bleeding and a 6.3% risk of intracranial hemorrhage\(^1\)

- In clinical practice, systemic PE thrombolysis is associated with a 19.2% risk of major bleeding and a 5% risk of intracranial hemorrhage\(^2\)

- In clinical practice, systemic thrombolysis is withheld in up to two thirds of patients with high-risk (massive) PE\(^3\)

---

2. Fiumara, K et al. Predictors of Major Hemorrhage Following Fibrinolysis for Acute PE. Am J Cardiol 2006;97:127-9
IV thrombolysis—limited drug delivery to thrombus

In vitro model of obstruction in the right main Pulmonary Artery
High-speed photo of systemically injected glass beads demonstrates how a vortex forms proximal to the obstruction and alters systemic drug delivery away from target embolus

Catheter Techniques: “Pharmaco-mechanical” Therapy

- Mechanical Fragmentation
- Hydrodynamic (AngioJet®)
- Ultrasound-Accelerated Fibrinolysis (EKOS®)
- Suction Embolectomy (AngioVac®)
Catheter-based thrombolysis

- Local administration of lytic agent
- Higher local drug concentration results in more rapid and complete thrombolysis
- Even distribution results in faster treatment of thrombus
EkoSonic® Endovascular System

Placement in the left and right pulmonary arteries for the treatment of bilateral PE
Ultrasound Accelerated Thrombolysis

The premise: Low-power ultrasound energy loosens fibrin strands, increases thrombus surface area, enhances lytic penetration, speeding thrombolysis, and facilitates reduction in fibrinolytic drug dose.
Review of the clinical evidence for EKOS® for the treatment of PE

- ULTIMA trial
- SEATTLE II trial
- Meta-analysis of historical published data
ULTIMA study
Comparing EKOS® to heparin in intermediate risk PE therapy

The first RCT for an advanced catheter-based modality

Primary Objective

- Determine whether fixed low-dose catheter-directed ultrasound accelerated thrombolysis is superior to heparin alone in reversal of RV dilatation in submassive/intermediate risk PE

ULTIMA study
Comparing EKOS® to heparin in intermediate risk PE therapy
Patients: Acute PE with RV/LV ≥ 1.0

Randomization

**30 Patients**
Unfractionated heparin + Ultrasound-assisted CDT using EKOS®
Infusion Protocol
- rtPA 1mg/h; saline coolant 35ml/h
- Patients monitored in the intermediate or ICU
- After five hours, rtPA reduced to 0.5 mg/h
- At 15(+-) hours, rtPA infusion, saline coolant and ultrasound discontinued
- EkoSonic® devices removed in the intermediate or ICU

**29 Patients**
Unfractionated heparin
- IV bolus: 80 IU/kg
- Infusion: 18 IU/kg/hour

Greater RVD reduction with EKOS® with tPA + heparin than with heparin alone

More improved echo findings from EKOS® with tPA + heparin than heparin alone

SYSTOLIC RV DYSFUNCTION SIGNIFICANTLY IMPROVED

*Two-sided exact Mantel-Haenzel test | **Wilcoxon rank sum test

No statistical difference in safety outcomes
No Deaths Or Significant Bleeding Complications

<table>
<thead>
<tr>
<th>Clinical outcomes at 90 days</th>
<th>EKOS® with tPA + Heparin N= 30</th>
<th>Heparin N= 29</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>0</td>
<td>1*</td>
<td>0.49</td>
</tr>
<tr>
<td>Recurrent venous thromboembolism</td>
<td>0</td>
<td>0</td>
<td>1.00</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>0</td>
<td>0</td>
<td>1.00</td>
</tr>
<tr>
<td>Minor bleeding</td>
<td>3**</td>
<td>1</td>
<td>0.61</td>
</tr>
</tbody>
</table>

*Rehospitalization and death from advanced pancreatic cancer
**Two patients with transient mild hemoptysis without medical intervention, one patient with groin hematoma requiring manual compression
***One patient with transient bleeding following endoscopic removal of colon polyp

Kucher N et al. Randomized, controlled trial of ultrasound-assisted catheter-directed thrombolysis for acute intermediate-risk pulmonary embolism.
ULTIMA study

CONCLUSION

ULTIMA confirmed that a fixed-dose, ultrasound-assisted catheter-directed thrombolysis EKOS® regimen was superior to anticoagulation alone in improving RV dysfunction at 24 hours without an increase in bleeding complications.

SEATTLE II Study
Examined EKOS® benefit in a clinical trial setting in the US

Evaluate ultrasound-facilitated fibrinolysis using EKOS® for massive and submassive PE (n=150; 22 centers):

- Efficacy – as measured by reduction in RV/LV ratio
- Safety – as measured by major bleeding within 72 hours

Ultrasound-facilitated fibrinolysis using EKOS®

- If unilateral PE: tPA 1 mg/hr using one device for 24 hours
- If bilateral PE: tPA 1 mg/hr per device (using two simultaneously) for 12 hours

Follow up at 48 +/- 6 hours

- CT measurement of RV/LV ratio
- Echocardiogram to estimate PA systolic pressure

## SEATTLE II Study
Patient characteristics and treatment details

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total enrollment</td>
<td>150*</td>
<td>100%</td>
</tr>
<tr>
<td>Massive/Submassive PE</td>
<td>31/119</td>
<td>21%/79%</td>
</tr>
<tr>
<td>History of previous DVT</td>
<td>30</td>
<td>20%</td>
</tr>
<tr>
<td>History of previous PE</td>
<td>15</td>
<td>10%</td>
</tr>
<tr>
<td>Concomitant use of antiplatelet agents</td>
<td>51</td>
<td>34%</td>
</tr>
<tr>
<td>Unilateral/Bilateral PE</td>
<td>20/130</td>
<td>13%/87%</td>
</tr>
</tbody>
</table>

* Denotes 1 patient died prior to treatment

Reduced RV/LV ratio and Modified Miller Score at 48 hours post-EKOS®

25% DECREASE IN RV/LV OVER 48 HOURS

<table>
<thead>
<tr>
<th></th>
<th>Pre-Procedure</th>
<th>48 Hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>RV/LV Ratio</td>
<td>1.55</td>
<td>1.13</td>
</tr>
</tbody>
</table>

P<0.0001

RAPIDLY RELIEVED PULMONARY ARTERY OBSTRUCTION

<table>
<thead>
<tr>
<th></th>
<th>Pre-Procedure</th>
<th>48 Hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Modified Miller Score</td>
<td>22.5</td>
<td>15.8</td>
</tr>
</tbody>
</table>

P<0.0001

Reduced pulmonary artery pressure immediately post-procedure

REDUCED PULMONARY HYPERTENSION

Mean PA Systolic Pressure (mmHg)

- Pre-Procedural: 51.4
- Post-Procedural: 37.5
- 48 Hours: 36.9

P<0.0001
Zero cases of intracranial hemorrhage reported in the study

<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)

## Zero cases of intracranial hemorrhage reported in the study

Minimized Risk of Intracranial hemorrhage

<table>
<thead>
<tr>
<th>Study</th>
<th>Intracranial hemorrhage (Fibrinolysis Group)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICOPER</td>
<td></td>
</tr>
<tr>
<td>Goldhaber SZ, et al. 1999</td>
<td>9/304 (3%)</td>
</tr>
<tr>
<td>PEITHO</td>
<td></td>
</tr>
<tr>
<td>Meyer G, et al. 2014</td>
<td>10/506 (2%)</td>
</tr>
<tr>
<td>SEATTLE II</td>
<td></td>
</tr>
<tr>
<td>Piazza G, et al. 2015</td>
<td>0/150 (0%)</td>
</tr>
</tbody>
</table>

CONCLUSION

Ultrasound-facilitated, catheter-directed, low-dose fibrinolysis for acute PE improves RV function and decreases pulmonary hypertension and angiographic obstruction. By minimizing the risk of intracranial bleed, it represents a potential “game-changer” in the treatment of high-risk PE patients.
Metanalysis showed consistent recovery of hemodynamics among patients treated using EKOS®

### Summary of published studies on ultrasound-assisted thrombolysis for acute pulmonary embolism

<table>
<thead>
<tr>
<th>First author and year of publication</th>
<th>No. of patients</th>
<th>Patients with high-risk PE</th>
<th>Total rt-PA dose (mg)</th>
<th>Total thrombolysis duration (h)</th>
<th>RV/LV ratio</th>
<th>Mean pulmonary artery pressure (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chamsuddin et al. (2008)²⁶</td>
<td>10</td>
<td>NA</td>
<td>21.8</td>
<td>24.8 ± 8.4</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Lin et al. (2009)²⁵</td>
<td>11</td>
<td>2 (18)</td>
<td>17.2 ± 2.4</td>
<td>17.4 ± 5.2</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Engelhardt et al. (2011)²⁹</td>
<td>24</td>
<td>5 (21)</td>
<td>33.5 ± 15.5</td>
<td>19.7 ± 8.1</td>
<td>1.33 ± 0.24d</td>
<td>1.0 ± 0.13d</td>
</tr>
<tr>
<td>Quintana et al. (2013)²⁸</td>
<td>10</td>
<td>2 (20)</td>
<td>18 (7-28)⁸</td>
<td>20.8 (12-49)⁸</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Kennedy et al. (2103)²¹</td>
<td>60</td>
<td>12 (20)</td>
<td>35.1 ± 11.1</td>
<td>19.6 ± 6.0</td>
<td>NA</td>
<td>27 ± 9</td>
</tr>
<tr>
<td>Engelberger et al. (2013)²¹</td>
<td>52</td>
<td>14 (27)</td>
<td>21.0 ± 5.7</td>
<td>15.2 ± 1.7</td>
<td>1.42 ± 0.21j</td>
<td>1.06 ± 0.23j</td>
</tr>
<tr>
<td>Kucher et al. (2013)³⁰</td>
<td>30</td>
<td>0 (0)</td>
<td>20.8 ± 3.0</td>
<td>15.0 ± 1.0</td>
<td>1.28 ± 0.19j</td>
<td>.99 ± 0.17l</td>
</tr>
<tr>
<td>Total ¹</td>
<td>197</td>
<td>35 (18)</td>
<td>26.9m</td>
<td>17.8m</td>
<td>1.36 ± 0.21</td>
<td>1.03 ± 0.20</td>
</tr>
</tbody>
</table>

Metaanalysis demonstrated a favorable safety profile among patients treated using EKOS®

Summary of published studies on ultrasound-assisted thrombolysis for acute pulmonary embolism

<table>
<thead>
<tr>
<th>First author and year of publication</th>
<th>No. of patients</th>
<th>Patients with high-risk PE</th>
<th>Total rt-PA dose (mg)</th>
<th>Total thrombolysis duration (h)</th>
<th>Bleeding Complications</th>
<th>Mortality at 3 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chamsuddin et al. (2008)²⁶</td>
<td>10</td>
<td>NA</td>
<td>21.8</td>
<td>24.8 ± 8.4</td>
<td>2 (20)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Lin et al. (2009)²⁵</td>
<td>11</td>
<td>2 (18)</td>
<td>17.2 ± 2.4</td>
<td>17.4 ± 5.2</td>
<td>0 (0)</td>
<td>0 (0)²⁶</td>
</tr>
<tr>
<td>Engelhardt et al. (2011)²⁹</td>
<td>24</td>
<td>5 (21)</td>
<td>33.5 ± 15.5</td>
<td>19.7 ± 8.1</td>
<td>2 (8)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Quintana et al. (2013)²⁸</td>
<td>10</td>
<td>2 (20)</td>
<td>18 (7-28)²⁸</td>
<td>20.8 (12-49)²⁸</td>
<td>2 (20)</td>
<td>0 (0)²⁸</td>
</tr>
<tr>
<td>Kennedy et al. (2103)²¹</td>
<td>60</td>
<td>12 (20)</td>
<td>35.1 ± 11.1</td>
<td>19.6 ± 6.0</td>
<td>1 (2)</td>
<td>4 (7)</td>
</tr>
<tr>
<td>Engelberger et al. (2013)²¹</td>
<td>52</td>
<td>14 (27)</td>
<td>21.0 ± 5.7</td>
<td>15.2 ± 1.7</td>
<td>11 (21)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Kucher et al. (2013)³⁰</td>
<td>30</td>
<td>0 (0)</td>
<td>20.8 ± 3.0</td>
<td>15.0 ± 1.0</td>
<td>3 (10)</td>
<td>0 (0)³⁰</td>
</tr>
<tr>
<td>Total ¹</td>
<td>197</td>
<td>35 (18)</td>
<td>26.9ᵐ</td>
<td>17.8ᵐ</td>
<td>21 (10.7)</td>
<td>7 (3.6)</td>
</tr>
</tbody>
</table>

PE diagnosis confirmed

Stable Patient

Unstable Patient, Massive PE (BP < 90 mm Hg for ≥ 15 min, significant clinical concern)

Suspicion for submassive PE (+ Troponin/BNP, tachycardic, RV dilation on CT, clinical)
1. Start UFH

Suspicion for submassive PE

1. Start UFH
2. Discuss IV Lytics vs. EKOS versus Surgical embolectomy with PERT leader
3. If Lytics chosen – consider beginning therapy in ED

No Suspicion for submassive PE

1. Low Molecular weight Heparin or Unfractionated Heparin (UFH) – Medicine floor admit

ECHO

ECHO (-) for RV dysfunction

1. Start UFH
2. Discuss IV Lytics vs. EKOS versus Surgical embolectomy with PERT leader
3. If Lytics chosen – consider beginning therapy in ED
4. Admit to CVICU

Admit to ICU

ECHO (+) for RV dysfunction

Admit to ICU

Provoked vs Unprovoked

<table>
<thead>
<tr>
<th>Condition</th>
<th>Recurrence Risk (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgically Provoked</td>
<td>0.7</td>
</tr>
<tr>
<td>Non-surgically Provoked</td>
<td>4.2</td>
</tr>
<tr>
<td>Unprovoked</td>
<td>7.4</td>
</tr>
<tr>
<td>Cancer-related</td>
<td>20.7</td>
</tr>
</tbody>
</table>

Arch Int Med 2010;170:1710-1716
Blood 2002; 100:3484-8
How Long to take AC?

- VTE due to transient risk factor
- Man with PE
- Man with DVT
- Woman with PE
- Woman with DVT, not hormones
- Woman with DVT or PE, hormones

**Other considerations:** Bleeding, fluctuating INRs, lifestyle impact, pt preference

**Other risk factors for recurrence:** Obesity?; age?
Antithrombotic Therapy for VTE

CHEST Guidelines 2016
Duration of Therapy

Proximal DVT or PE
- Provoked
  - 3 months
- Unprovoked
  - Low to moderate bleeding risk
  - Extended therapy
  - High bleeding risk
  - 3 months

Isolated Distal DVT
- Mild symptoms or high bleeding risk
  - Anticoagulate
  - Serial imaging x2 weeks
- Severe symptoms or risk for extension
  - Anticoagulate
  - Extending thrombus
  - Anticoagulate

Cancer-associated
- Extended therapy

Upper extremity DVT
- Anticoagulate
Conclusions

• Pulmonary embolism carries high morbidity and mortality.

• Quick recognition of massive PE allows for application of rapid effective treatment to prevent complications and reduce mortality.

• RV dysfunction on echo/CT and the presence of a DVT are a “high risk” groups within the submassive category
Conclusions

• To date, thrombolysis of any kind has yet to prove mortality benefit in submassive PE in RCT.

• Ultrasound accelerated thrombolysis appear to have less bleeding risks with improvement in hemodynamic parameters.

• Ultrasound accelerated thrombolysis uses less lytic, *may* reduce mortality, and thus may have a role in the “high risk” submassive PE patients.
Thank You

Ammar Safar, MD
Cell: 937-765-2330