Treating Acute Pulmonary Embolism with Catheter Thrombolysis

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Vascular and Endovascular Surgeon

Imagine where we can go.
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;290:2849–68
High incidence

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

- **Coronary Heart Disease**: 47.7%
- **Stroke**: 16.4%
- **Heart Failure**: 7.4%
- **High Blood Pressure**: 8.3%
- **Disease of the Arteries**: 3.3%
- **Other**: 16.9%

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.

<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>• RV dysfunction</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

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PE patient population profile

MASSIVE PE
[High risk]
5% PE population
58% mortality @ 3 months

SUBMASSIVE PE
[Moderate/Intermediate risk]
40% PE population
2-3% mortality to
21% mortality @ 3 months

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

Current Treatments

- Anticoagulation (UFH, LMWH, Fondaparinux)
- Systemic thrombolysis
- Catheter-directed thrombolysis
- Pharmaco-mechanical interventions
- Surgical embolectomy
Treatment of Massive PE

ACCP 2012 Guidelines

- Urgent treatment with systemic thrombolytic therapy if low risk for bleeding.
- 100mg TPA over 2 hr via peripheral vein
- If treatment fails or patient is in extremis will need more invasive intervention

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</tr>
<tr>
<td>- Persistent profound bradycardia (HR &lt;40 bpm with signs or symptoms of shock)</td>
</tr>
</tbody>
</table>
Massive PE Treatment:
Catheter Assisted Thrombectomy
Figure 4. Pronto XL extraction device. Digital subtraction angiography is performed through a pigtail catheter positioned in the right interlobar artery (A). Note the numerous filling defects within the segmental branches. A Pronto straight catheter is positioned in the left lower lobar artery (B). Note the segmental filling defects. An embolus that was removed by manual aspiration through a Pronto catheter (C).
Massive PE Treatment: Catheter Assisted Thrombectomy

Figure 3. The Indigo CAT8 device was advanced into the patient’s right subclavian vein (B).
Catheter Directed Aspiration for Massive PE

- These methods can be life saving:
  - Can cause distal embolization
  - May cause PA damage.
  - Can be complicated by arrhythmias
  - No significant literature available due to rarity of use.
Massive PE Treatment

- Pulmonary Embolectomy
- Requires Cardiothoracic Surgery Team
- Chronic PE
Submassive PE

Should we treat patient with RV dysfunction aggressively?

Patient risk stratification (per AHA 2011 guidelines)

Submassive PE

Moderate risk

- Systemically normotensive (systolic BP $\geq$ 90 mmHg)
- RV dysfunction
- Myocardial necrosis
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
Key factors contributing to hemodynamic collapse in acute PE

INCREASED RV AFTERLOAD

RV wall tension ▲
Neurohormonal activation

RV ischaemia
RV contractility ▼

Low CO
Systemic BP ▼

RV O₂ delivery ▼

CARDIOGENIC SHOCK

DEATH

RV dilation
TV insufficiency

Myocardial inflammation
RV O₂ demand ▲

RV output ▼
LV pre-load ▼

RV coronary perfusion ▼

BP = blood pressure
CO = cardiac output
LV = left ventricular
RV = right ventricular
TV = tricuspid valve

Adverse outcomes associated with RVD – 3x higher mortality if RV/LV ≥ 0.9

- 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

Fremont B et al. Prognostic value of echocardiographic right/left ventricular end-diastolic diameter ratio in patients with acute pulmonary embolism. CHEST 2008;133:358-362
Adverse outcomes associated with RVD – increased mortality risk

- 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

Patients with RVD defined as RV/LV >0.9 have a greater chance of adverse events within 30 days

• Retrospective analysis of 63 patients with chest CT
• Adverse event rate at 30 days:
  – 80.3% if RV/LV ratio > 0.9
  – 51.3% if RV/LV ratio ≤ 0.9

Adverse outcomes associated with RVD

Presence of RV hypokinesis associated with 57% 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

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Adverse outcomes with unresolved RVD – 8x 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\(^1,2,3\) 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\(^4\)
  - 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

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)</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>
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<tr>
<td>Age &gt; 65 y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-cause mortality (5)</td>
<td>14/673 (2.08)</td>
<td>24/658 (3.65)</td>
<td>NNT = 64</td>
</tr>
<tr>
<td>Major bleeding (5)</td>
<td>87/673 (12.93)</td>
<td>27/658 (4.10)</td>
<td>NNH = 11</td>
</tr>
<tr>
<td>Age ≤ 65 y</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>All-cause mortality (11)</td>
<td>9/388 (2.32)</td>
<td>17/396 (4.29)</td>
<td>NNT = 51</td>
</tr>
<tr>
<td>Major bleeding (11)</td>
<td>11/388 (2.84)</td>
<td>9/396 (2.27)</td>
<td>NNH = 176</td>
</tr>
<tr>
<td>Intermediate-risk PE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-cause mortality (8)</td>
<td>12/866 (1.39)</td>
<td>26/889 (2.92)</td>
<td>NNT = 65</td>
</tr>
<tr>
<td>Major bleeding (8)</td>
<td>67/866 (7.74)</td>
<td>20/889 (2.25)</td>
<td>NNH = 18</td>
</tr>
</tbody>
</table>

## 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</th>
<th>Favors</th>
<th>Weight, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goldhaber et al, 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, 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, 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, 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, 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, 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, 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, 2014</td>
<td>6</td>
<td>506</td>
<td>9</td>
<td>499</td>
<td>.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>100.0</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># of Patients</th>
<th># of Patients</th>
<th>OR (95% CI)</th>
<th>NNT</th>
<th>P</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>
<td></td>
</tr>
<tr>
<td>Major bleeding (8)$^a$</td>
<td>67/866 (7.74)</td>
<td>20/889 (2.25)</td>
<td>NNH = 18</td>
<td>&lt;.001</td>
<td></td>
</tr>
</tbody>
</table>

Review and meta-analysis on systemic thrombolysis for PE weighed risks and benefits

Systemic thrombolytic therapy for acute pulmonary embolism: a systematic review and meta-analysis

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Received 19 February 2014; revised 10 April 2014; accepted 7 May 2014.

Aim
Thrombolytic therapy induces faster clot dissolution than anticoagulation in patients with acute pulmonary embolism (PE) but is associated with an increased risk of haemorrhage. We reviewed the risks and benefits of thrombolytic therapy in the management of patients with acute PE.

Methods and results
We systematically reviewed randomized controlled studies comparing systemic thrombolytic therapy plus anticoagulation alone in patients with acute PE. Fifteen trials involving 2017 patients were included in our meta-analysis. Compared with heparin, thrombolytic therapy was associated with a significant reduction of overall mortality (OR: 0.59, 95% CI: 0.36–0.94). This reduction was not statistically significant after exclusion of studies including high-risk PE (OR: 0.64, 95% CI: 0.33–1.17). Thrombolytic therapy was associated with a significant reduction in the combined endpoint of death or treatment escalation (OR: 0.34, 95% CI: 0.22–0.53), PE-related mortality (OR: 0.29, 95% CI: 0.14–0.60), and PE recurrence (OR: 0.50, 95% CI: 0.27–0.94). Major haemorrhage (OR: 2.91, 95% CI: 1.95–4.36) and fatal or intracranial bleeding (OR: 3.18, 95% CI: 1.25–8.11) were significantly more frequent among patients receiving thrombolysis.

Conclusions
Thrombolytic therapy reduces total mortality, PE recurrence, and PE-related mortality in patients with acute PE. The decrease in overall mortality is, however, not significant in hemodynamically stable patients with acute PE. Thrombolytic therapy is associated with an increase of major and fatal or intracranial haemorrhage.

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>
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<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>12 (2.4%)</td>
<td>1 (0.2%)</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>Serious adverse events (SAE) by day 30</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 hemorrhage¹

- In clinical practice, systemic PE thrombolysis is associated with a 19.2% risk of major bleeding and a 5% risk of intracranial hemorrhage²

- In clinical practice, systemic thrombolysis is withheld in up to two thirds of patients with high-risk (massive) PE³

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-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
EkoSonic® Endovascular System

Mechanism of action

HOW ULTRASONIC ENERGY UNLOCKS THE CLOT

- Ultrasonic energy causes fibrin strands to thin, exposing plasminogen receptor sites and fibrin strands to loosen
- Thrombus permeability and lytic penetration are dramatically increased
- Ultrasound pressure waves force lytic agent deep into the clot and keep it there

Acoustic Pulse Thrombolysis™ treatment
Mechanism of action

Fibrin Separation
Ultrasound separates fibrin without fragmentation of emboli

Active Drug Delivery
Drug is actively driven into clot by “Acoustic Streaming”

Fibrin without Ultrasound
Fibrin With Ultrasound

Acoustic streaming drives lytic into clot

EKOS® Acoustic Pulse Thrombolysis™ treatment is a minimally invasive system for accelerating thrombus dissolution.

EkoSonic® Endovascular System

Features

- 5.4 Fr catheter
- 106 and 135 cm working length
- 6, 12, 18, 24, 30, 40 and 50 cm treatment zones
Review of the clinical evidence for EKOS® for the treatment of PE

- ULTIMA trial
- SEATTLE II trial
- Meta-analysis of historical published data
- Recent single-center studies
ULTIMA study compared 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

RCT compared EKOS® to heparin for the treatment of intermediate risk PE
Patients: Acute PE with RV/LV ≥ 1.0

<table>
<thead>
<tr>
<th>Randomization</th>
</tr>
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</table>

<table>
<thead>
<tr>
<th>30 Patients</th>
<th>29 Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Unfractionated heparin + Ultrasound-assisted CDT using EKOS®</strong> Infusion Protocol</td>
<td></td>
</tr>
<tr>
<td>rtPA 1mg/h; saline coolant 35ml/h</td>
<td></td>
</tr>
<tr>
<td>Patients monitored in the intermediate or ICU</td>
<td></td>
</tr>
<tr>
<td>After five hours, rtPA reduced to 0.5 mg/h</td>
<td></td>
</tr>
<tr>
<td>At 15(+/-) hours, rtPA infusion, saline coolant and ultrasound discontinued</td>
<td></td>
</tr>
<tr>
<td>EkoSonic® devices removed in the intermediate or ICU</td>
<td></td>
</tr>
<tr>
<td><strong>Unfractionated heparin</strong></td>
<td></td>
</tr>
<tr>
<td>IV bolus: 80 IU/kg</td>
<td></td>
</tr>
<tr>
<td>Infusion: 18 IU/kg/hour</td>
<td></td>
</tr>
</tbody>
</table>

ULTIMA Trial
Measuring RV/LV Ratio

- Apical 4-Chamber view
- End diastolic image
- Center line through interventricular septum
- Obtain tricuspid annular line
- Obtain subannular line 1cm above annular line
- Obtain RV and LV dimensions using endocardial borders

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

**RV/LV Ratio Significantly Improved at 24 Hours**

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>24 Hours</th>
<th>Baseline</th>
<th>24 Hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>EKOS® with tPA + Heparin</td>
<td>1.28</td>
<td>0.99</td>
<td>1.20</td>
<td>1.17</td>
</tr>
<tr>
<td>Heparin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Reduction in RV/LV Ratio Significantly Greater at 24 Hours and Improved at 90 Days**

<table>
<thead>
<tr>
<th>Reduction in RV/LV Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline to 24 hrs.</td>
</tr>
<tr>
<td>Baseline to 90 days</td>
</tr>
<tr>
<td>Baseline to 24 hrs.</td>
</tr>
<tr>
<td>Baseline to 90 days</td>
</tr>
</tbody>
</table>

P-values: P<0.001, P=0.31, P= 0.07, P= 0.001

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

SYSTOLIC RV DYSFUNCTION SIGNIFICALLY IMPROVED

- **P<0.001**
- **P<0.001**
- **P=0.003***

*Two-sided exact Mantel-Haenzel test | **Wilcoxon rank sum test
No statistical difference in safety outcomes with EKOS® with tPA + Heparin than Heparin alone

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, 0%</td>
<td>1* 0%</td>
<td>0.49</td>
</tr>
<tr>
<td>Recurrent venous thromboembolism</td>
<td>0, 0%</td>
<td>0 0%</td>
<td>1.00</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>0, 0%</td>
<td>0 0%</td>
<td>1.00</td>
</tr>
<tr>
<td>Minor bleeding</td>
<td>3**, 10%</td>
<td>1 3%***</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

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 examined EKOS® benefit in a clinical trial setting in the US

Evaluate ultrasound-facilitated tibrinolysis 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

The SEATTLE II Study
Endpoints

- Primary Efficacy
  - Change in core lab-measured RV/LV ratio from baseline to 48 hours as assessed by chest CT

- Secondary Efficacy
  - Change in invasively measured PA systolic pressure from baseline to device removal and as estimated on 48-hour echocardiogram

- Primary Safety
  - Adjudicated major bleeding within 72 hours of the start of the procedure

The SEATTLE II Study
Patient characteristics and treatment details

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total enrollment</strong></td>
<td>150*</td>
<td>100%</td>
</tr>
<tr>
<td><strong>Massive/Submassive PE</strong></td>
<td>31/119</td>
<td>21%/79%</td>
</tr>
<tr>
<td><strong>History of previous DVT</strong></td>
<td>30</td>
<td>20%</td>
</tr>
<tr>
<td><strong>History of previous PE</strong></td>
<td>15</td>
<td>10%</td>
</tr>
<tr>
<td><strong>Concomitant use of antiplatelet agents</strong></td>
<td>51</td>
<td>34%</td>
</tr>
<tr>
<td><strong>Unilateral/Bilateral PE</strong></td>
<td>20/130</td>
<td>13%/87%</td>
</tr>
<tr>
<td><strong>Total rtPA dose</strong></td>
<td></td>
<td>23.7 ± 2.9 mg</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

Rapidly relieved pulmonary artery obstruction

P<0.0001

Reduced pulmonary artery pressure immediately post-procedure

REDUCED PULMONARY HYPERTENSION

<table>
<thead>
<tr>
<th></th>
<th>Mean PA Systolic Pressure (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-Proced</td>
<td>51.4</td>
</tr>
<tr>
<td>Post-Proced</td>
<td>37.5</td>
</tr>
<tr>
<td>48 Hours</td>
<td>36.9</td>
</tr>
</tbody>
</table>

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>9/304 (3%)</td>
</tr>
<tr>
<td>Goldhaber SZ, et al. 1999</td>
<td></td>
</tr>
<tr>
<td>PEITHO</td>
<td>10/506 (2%)</td>
</tr>
<tr>
<td>SEATTLE II</td>
<td>0/150 (0%)</td>
</tr>
<tr>
<td>Piazza G, et al. 2015</td>
<td></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.

Metaanalysis 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></td>
<td>Before NA After 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></td>
<td>Before NA After 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)³</td>
<td>20.8 (12-49)³</td>
<td></td>
<td>Before NA After 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></td>
<td>Before NA After NA</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 ± 0.21l</td>
<td>1.06 ± 0.23l</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 ± 0.19l</td>
<td>0.99 ± 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 ± 0.21l</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**

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<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>
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<td>2 (18)</td>
<td>17.2 ± 2.4</td>
<td>17.4 ± 5.2</td>
<td>0 (0)</td>
<td>1 (9)</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)</td>
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<td>2 (20)</td>
<td>0 (0)</td>
</tr>
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<td>60</td>
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<td>19.6 ± 6.0</td>
<td>1 (2)</td>
<td>4 (7)</td>
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<td>52</td>
<td>14 (27)</td>
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<td>2 (4)</td>
</tr>
<tr>
<td>Kucher et al. (2013)²⁰</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)</td>
</tr>
<tr>
<td>Total</td>
<td>197</td>
<td>35 (18)</td>
<td>26.9</td>
<td>17.8</td>
<td>21 (10.7)</td>
<td>7 (3.6)</td>
</tr>
</tbody>
</table>

Early study showed safer and more effective lysis with EKOS® than CDT

- Single center retrospective comparative study
- 25 patients with massive pulmonary embolism (PE) were treated with either EKOS® or catheter directed thrombolysis (CDT) without ultrasound.
- 11 patients received EKOS® therapy for 15 PE lesions
- 14 patients received CDT therapy for 18 PE lesions

<table>
<thead>
<tr>
<th></th>
<th>EKOS® (n=11)</th>
<th>CDT (n=14)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete thrombolysis</td>
<td>100%</td>
<td>50%</td>
<td>0.01</td>
</tr>
<tr>
<td>Thrombolytic dose (tPA, mg)</td>
<td>17.2 ± 2.36</td>
<td>25.43 ± 5.27</td>
<td>0.03</td>
</tr>
<tr>
<td>Bleeding complications</td>
<td>0%</td>
<td>21.4%</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Single center experience showed CTA evidence of RVD resolution with EKOS®

- Single center retrospective single arm study
- 24 patients with high risk (n=5) or intermediate risk (n=19) PE treated with EKOS®
- Mean rtPA dose was 33.5±15.5 mg over 19.7 hours

<table>
<thead>
<tr>
<th></th>
<th>Pre-EKOS®</th>
<th>Post-EKOS®</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RV/LV ratio</td>
<td>1.33 ± 0.24</td>
<td>1.00 ± 0.13</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Modified Miller Score</td>
<td>17.8 ± 5.3</td>
<td>8.7 ± 5.1</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

No deaths or systemic bleeding complications, including intracranial hemorrhage; 4 access site bleeds requiring transfusion

Single center experience showed CTA evidence of RVD resolution

Case Study 1

Pre-treatment:
RV/LV = 1.64

Post-treatment
RV/LV = 1.10
Single-center experience showed CTA evidence of RVD resolution
Case Study 2

Pre-treatment
RV/LV = 1.40

RV = 55.3 mm
LV = 39.6 mm

Post-treatment
RV/LV = 0.91

RV = 50.9 mm
LV = 55.7 mm
Largest US single-center EKOS® registry reported minimal risk of adverse events

- Single-center retrospective observational study
- 60 consecutive patients with either massive or submassive PE
- No intracranial hemorrhage, one intra-abdominal hemorrhage leading to hypovolemic shock and death, and one puncture site hematoma

### Treatment details

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilateral PE</td>
<td>53</td>
<td>88%</td>
</tr>
<tr>
<td>Unilateral PE</td>
<td>7</td>
<td>12%</td>
</tr>
<tr>
<td>Massive PE</td>
<td>12</td>
<td>20%</td>
</tr>
<tr>
<td>Submassive PE</td>
<td>48</td>
<td>80%</td>
</tr>
</tbody>
</table>

### Thrombus clearance:

- Complete (>90%)
  - N=33 (57%)
- Near complete (50-90%)
  - N=24 (41%)
- Partial (<50%)
  - N=1 (2%)

### Outcomes

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survival to discharge</td>
<td>57</td>
<td>95%</td>
</tr>
<tr>
<td>ICU stay (median)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospital stay (median)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>90-day survival:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Overall</td>
<td>56</td>
<td>93%</td>
</tr>
<tr>
<td>- Submassive PE</td>
<td>47</td>
<td>98%</td>
</tr>
<tr>
<td>- Massive PE</td>
<td>9</td>
<td>75%</td>
</tr>
</tbody>
</table>

### Adverse events:

- Major bleeding
  - N=1 (1.7%)
- Minor bleeding
  - N=1 (1.7%)
- Cardiopulmonary arrest
  - N=1 (1.7%)
- Acute renal injury
  - N=1 (1.7%)
- Recurrent PE
  - N=0 (0%)
EKOS® PE treatment showed shorter length of stay, more favorable long-term mortality compared to anti-coagulation alone.

- Single-center retrospective study to evaluate safety and efficacy of EKOS® therapy
  - n=45
- Comparison to separate control group (n=45) of intermediate to high-risk PE patients treated with systemic heparin or anticoagulation alone
- Average LoS: EKOS® treated = 3.2 days versus AC = 6.7 days

24-month survival rates favored EKOS® treated patients.

Single-center study showed significant reduction in PA pressure, RV/LV ratio using EKOS®

- Single-center study of 45 consecutive acute submassive PE patients (30 retrospective, 15 prospective)
- SEATTLE II protocol used and described
- Results
  - Decrease in average PA pressure from 49.8 mmHg to 31.1 mmHg (p<.0001)
  - Decrease in average RV:LV ratio from 1.59 to 0.93 (p<.0001)
  - 0 deaths, 0 re-admissions for PE in 30-day follow up
  - 4 minor bleeds at access sites, 2 major bleeds
    (1 pt. 3 days post-lysis; 1 pt. from a previous puncture site)

EKOS® treatment is a safe and effective method to treat submassive PE to reduce acute pulmonary hypertension and RVD

Multi-disciplinary PERT protocol facilitated rapid identification and optimal treatment

Study at Vanderbilt University Medical Center (tertiary referral center)
- Reduce delays in patient care and interhospital transfers for a time-sensitive illness
- Drive consistency in diagnostic testing to expedite decision-making

Protocol treatment strategies
- CDT (including EKOS® therapy)
- Surgical Embolectomy
- Medical Therapy

Vanderbilt Medical Center
Pulmonary Embolism critical pathway

- Identify PE via CT scan, other biomarkers
- Incorporate key diagnostic information and personnel with each subsequent step
RV dysfunction in PE patients predicts poor outcomes
  • Mortality
  • Adverse events
  • VTE recurrence

Anticoagulant therapy does not actively resolve the existing thrombus

IV thrombolysis is not used broadly
  • Clinical data show improvement in hemodynamics,
  • but it carries an elevated risk of severe bleeding, including ICH

Use of EKOS® enhances thrombolytic therapy by an intra-catheter ultrasound technology, which
  • Loosens the fibrin structure
  • Increases drug penetration into the fibrin matrix
  • Ultimately reduces drug dose, treatment time and risk of complications

Clinical data establish the evidence for EKOS® in massive and submassive (intermediate risk) PE

- ULTIMA—prospective, randomized, controlled, multicenter trial
- SEATTLE II—prospective, 1-arm, multicenter trial
- Single-center studies

Consistent EKOS® results among the various published studies

- Restoration of hemodynamics as evidenced by a reduced RV/LV ratio and decreased PA pressure
- Resolution of pulmonary artery obstruction
- Favorable outcomes with low dose thrombolysis (20-24 mg tPA based on the clinical trials)
- No reports of intracranial hemorrhage in published clinical studies