Ultrasound-Assisted Pharmacomechanical Thrombectomy—Does This Really Work?

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- INTACT Vascular, Shockwave

Speakers Bureau:
- Boston Scientific, Penumbra, Medtronic, Cook, Endologix

Research Support:
- Philips Healthcare, Spectranetics, Terumo, BTG, Boston Scientific

Disclosures:
In the past 12 months, my spouse or myself have engaged in financial relationships as follows:

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  - Boston Scientific, Medtronic, Abbott Vascular

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EkoSonic™ Endovascular System

Features:
- 5.4 Fr catheter
- 50 and 135 cm working lengths
- 6, 12, 18, 24, 30, 40, and 50 cm treatment zones

Central coolant lumen
Drug lumen
Therapy optimization sensor
Ultrasonic cone

EkoSonic™ Endovascular System

Ultrasound Mechanism of Action

Fibrin Separation
Ultrasound separates fibrin without fragmentation of emboli


Active Drug Delivery
Lytic is actively driven into the clot with the help of the ultrasound

Fibrin separation
Without Ultrasound
With Ultrasound

Ultrasound energy drives lytic into the clot

ADD REFERENCE

Identical volumes of tPA (dark red) were infused into identical human plasma cultures (straw color)
Total exposure time: 15 minutes
17% increase in density and 38% increase in depth of tPA on EKOS™ treated side

Standard Infusion Catheter
EKOS™ Infusion Catheter

Spread of Stained tPA
Plasma Clot

ACTUAL PHOTOGRAPHS

Source: Internal company data

EkoSonic™ Endovascular System

Ultrasound Mechanism of Action

89% Greater Uptake at 4 Hours
84% Greater Uptake at 2 Hours
48% Greater Uptake at 1 Hour

53% Deeper Penetration of tPA into Clot at 2 Hours

89% Greater Uptake at 4 Hours
84% Greater Uptake at 2 Hours
48% Greater Uptake at 1 Hour

53% Deeper Penetration of tPA into Clot at 2 Hours
Goals of Catheter-Directed Thrombolysis

- Decrease pulmonary vascular resistance
- Decrease pulmonary arterial pressure
- Decrease the risk of developing chronic thromboembolic pulmonary hypertension (CTEPH)
- Minimize the risk of bleeding
- Recover right ventricular function
- Increase systemic arterial pressure

EKOS™ Key PE Studies

- ULTIMA
- SEATTLE II
- OPTALYSE PE

Key PE Studies

ULTIMA

Prospective Multi-centered Randomized

Primary Objective
Determine whether fixed-dose, catheter-directed ultrasound accelerated thrombolysis is superior to heparin alone in RV dilatation in patients with submassive/intermediate risk PE

Key Endpoints

Efficacy
- Reduction in RV/LV at 24 h and 90 days
- Systolic RV function

Safety
- Major and minor bleeding
- Recurrent VTE
- Death

Select Inclusion and Exclusion Criteria

Inclusion Criteria
- Acute symptomatic PE on CT (filling defect in ≥1 main, lobar, or segmental pulmonary artery)
- Age ≥ 18 years
- PE symptoms duration ≤14 days
- RV/LV diameter ratio ≥1 on echocardiographic apical 4-chamber view

Exclusion Criteria
- Stroke/TIA, head trauma, or intracranial or intraspinal disease within one year
- Major surgery within 10 days
- Active bleeding or known significant bleeding risk
- Hematocrit <30%, platelets <100,000/mm³, INR >2.5
- Pregnancy

Patient Demographics

<table>
<thead>
<tr>
<th></th>
<th>EKOS N=30</th>
<th>Heparin N=29</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>64 ± 15</td>
<td>62 ± 12</td>
</tr>
<tr>
<td>Female (n, %)</td>
<td>19 (63)</td>
<td>12 (41)</td>
</tr>
<tr>
<td>History of previous DVT (n, %)</td>
<td>4 (13)</td>
<td>9 (31)</td>
</tr>
<tr>
<td>History of previous PE (n, %)</td>
<td>4 (13)</td>
<td>2 (7)</td>
</tr>
<tr>
<td>Systolic arterial pressure (mmHg)</td>
<td>147 ± 18</td>
<td>151 ± 20</td>
</tr>
<tr>
<td>Troponin test positive (n, %)</td>
<td>16/20 (80)</td>
<td>17/22 (77)</td>
</tr>
<tr>
<td>Bilateral main PA embolism (n, %)</td>
<td>9 (31)</td>
<td>15 (52)</td>
</tr>
<tr>
<td>Bilateral lower-lobe PA embolism (n, %)</td>
<td>8 (27)</td>
<td>4 (14)</td>
</tr>
<tr>
<td>Bilateral lower-lobe PA embolism (n, %)</td>
<td>12 (40)</td>
<td>5 (17)</td>
</tr>
<tr>
<td>Bilateral main PA embolism (n, %)</td>
<td>3 (10)</td>
<td>5 (17)</td>
</tr>
</tbody>
</table>

ULTIMA Treatment Arms

- 29 patients
  - Unfractionated heparin 80 IU/kg bolus + 18 IU/kg/hr
  - EKOS 10 mg* or 20 mg** rtPA over 15 h

- 30 patients
  - Unfractionated heparin 80 IU/kg bolus + 18 IU/kg/hr
  - EKOS 10 mg* or 20 mg** rtPA over 15 h

Infusion Protocol:
- rtPA 1 mg/h; saline coolant 35 mL/h
- After 5 hours, ↓ to 0.5 mg/h
- At ~15 hours, discontinued rtPA, saline coolant, and ultrasound

*unilateral PE, **bilateral PE.
1. Apical 4-Chamber view
2. End diastolic image
3. Center line through interventricular septum
4. Obtain tricuspid annular line
5. Obtain sub-annular line 1 cm above annular line
6. Obtain RV and LV dimensions using endocardial borders

**ULTIMA**

**Measuring RV:LV with Echocardiography (ECHO)**

- RV:LV significantly reduced at 24 hours
- Reduction in RV:LV ratio significantly greater at 24 hours and improved at 90 days
- Systolic RV dysfunction significantly improved

**ULTIMA**

**Safety Outcomes**

<table>
<thead>
<tr>
<th>Clinical outcomes at 90 days</th>
<th>Death</th>
<th>Rehospitalization</th>
<th>Major bleeding</th>
<th>Minor bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>EKOS™ with tPA + Heparin</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>10%</td>
</tr>
<tr>
<td>Heparin</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>3%</td>
</tr>
</tbody>
</table>

*No deaths or significant bleeding complications*

**ULTIMA**

**Study Conclusions**

Fixed-dose, ultrasound-assisted catheter directed thrombolysis using EKOS™ was superior to heparin alone in:

- Improving RV:LV at 24 hours and 90 days
- Improving RV systolic function at 24 hours and 90 days
- With no increased risk of major or minor bleeding, recurrent venous thromboembolism, or death
**SEATTLE II Study**

**Prospective**
**Multi-centered**
**Single-arm**

**Primary Objective**
Evaluate ultrasound-facilitated, catheter directed fibrinolysis using EKOS™ for massive and submassive PE

**Key Endpoints**

**Efficacy**
- Reduction in RV/LV at 48 h
- Clot burden via modified miller score
- Change in pulmonary artery systolic pressures at 48 hours

**Safety**
- Major and minor bleeding within 72 hours
- Recurrent VTE
- Death

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**SEATTLE II Inclusion and Exclusion Criteria**

**Inclusion Criteria**
- Proximal PE (filling defect in at least 1 main or lobar artery)
- Age ≥ 18 years
- PE symptoms duration ≤ 14 days
- RV:LV diameter ratio ≥ 0.9 on chest CT

**Exclusion Criteria**
- Stroke/TIA, head trauma, or intracranial or intraspinal disease within one year
- Recent active bleeding or known significant bleeding risk
- Major surgery within 7 days
- Hematocrit < 30%, platelets < 100,000/mm³, INR > 3
- Pregnancy

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**SEATTLE II Treatment**

**Patients**

- n = 150
- 22 centers
- RV:LV ≥ 0.9

**Interventions**

- EKOS
  - rtPA 1 mg/hr x 24 h* or 1 mg/hr x 12 h**
- Unfractionated heparin
  - Target aPTT 40 to 60 seconds

**SAFETY**
- Major and minor bleeding within 72 hours
- Recurrent VTE
- Death

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**SEATTLE II Patient Demographics**

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

*Denotes 1 patient died prior to treatment

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**SEATTLE II Reduction in RV:LV and Modified Miller Score**

<table>
<thead>
<tr>
<th>Time</th>
<th>RV/LV Ratio</th>
<th>Modified Miller Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-Pro</td>
<td>22.5</td>
<td>22.5</td>
</tr>
<tr>
<td>Post-Pro</td>
<td>15.8</td>
<td>15.8</td>
</tr>
<tr>
<td>48 Hours</td>
<td>15.8</td>
<td>15.8</td>
</tr>
</tbody>
</table>

25% decrease in RV/LV over 48 hours
6.7% decrease in pulmonary artery obstruction

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**SEATTLE II Reduction in PA Pressures**

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

P = 0.0005

Pulmonary hypertension
**SEATTLE II**

**Safety Outcomes**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>N</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean length of stay ± SD, days</td>
<td>8.8 ± 5</td>
<td></td>
</tr>
<tr>
<td>In-hospital death, n (%)</td>
<td>3 (3)</td>
<td></td>
</tr>
<tr>
<td>30-day mortality*, n (%)</td>
<td>4 (2.7)</td>
<td></td>
</tr>
<tr>
<td>Serious adverse events due to device, n (%)</td>
<td>2 (2)</td>
<td></td>
</tr>
<tr>
<td>Serious adverse events due to tPA, n (%)</td>
<td>2 (2)</td>
<td></td>
</tr>
<tr>
<td>IVC filter placed, n (%)</td>
<td>24 (16)</td>
<td></td>
</tr>
<tr>
<td>Major bleeding within 30 days**, n (%)</td>
<td>15 (10)</td>
<td></td>
</tr>
<tr>
<td>GUSTO moderate**</td>
<td>14 (9.3)</td>
<td></td>
</tr>
<tr>
<td>GUSTO severe**</td>
<td>1 (0.7)</td>
<td></td>
</tr>
</tbody>
</table>

*All death, serious adverse and bleeding events were adjudicated by an independent safety monitor

**SEATTLE II**

**Study Conclusions**

Low-dose, ultrasound-assisted catheter directed thrombolysis using EKOS® for acute PE:

- Improved RV systolic function at 48 hours
- Improved pulmonary hypertension at 48 hours
- Reduced pulmonary clot burden
- With low risk of major or minor bleeding, recurrent venous thromboembolism, or death

**OPTALYSE PE**

**Prospective**

**Multi-centered**

**Four-arm**

**Primary Objective**

Determine the lowest optimal tPA dose and duration of EKOS® for the treatment of acute submassive PE

**Key Endpoints**

**Efficacy**
- Change in RV/LV by >0.2 on CTA at 48 hours after start of treatment

**Safety**
- Major bleeding within 72 hours (ISTH criteria)

**Key Secondary Endpoints**

**Efficacy**
- Technical success of procedure as assessed by adjudication committee
- Change in baseline echo parameters at 48, 48h, 30d, 90d, 365d post procedure
- RV/LV
- Estimated RVSP
- TAPSE
- Collapse of the IVC with respiration

**Safety**
- Technical procedural complications
- Symptomatic recurrent PE
- All-cause mortality

**Main Inclusion Criteria**

- 18-75 years old AND
- CTA evidence of proximal PE (unilateral or bilateral) AND
- Acute PE symptom duration ≤14 days AND
- Submassive PE (RV/LV diameter ≥0.9 and hemodynamically stable)

**Main Exclusion Criteria**

- No recent history of:
  - Stroke or TIA
  - Head trauma
  - Active bleeding from major organ
  - Major surgery
  - Catheter-based pharmaco-mechanical treatment for PE
  - No high-risk for catastrophic bleeding

**Eligible subjects received treatment with EKOS® within 48 h of diagnostic CTA**

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Patients</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>27</td>
<td>4* &amp; 8** mg</td>
</tr>
<tr>
<td>2</td>
<td>27</td>
<td>4* &amp; 8** mg</td>
</tr>
<tr>
<td>3</td>
<td>28</td>
<td>6* &amp; 12** mg</td>
</tr>
<tr>
<td>4</td>
<td>18</td>
<td>12* &amp; 24** mg</td>
</tr>
</tbody>
</table>
### Patient Demographics

<table>
<thead>
<tr>
<th>Demographics</th>
<th>2 hr (2 mg/hr/cath)</th>
<th>4 hr (1 mg/hr/cath)</th>
<th>6 hr (1 mg/hr/cath)</th>
<th>8 hr (2 mg/hr/cath)</th>
<th>All arms (mean)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>28</td>
<td>27</td>
<td>28</td>
<td>18</td>
<td>101</td>
</tr>
<tr>
<td>Age (y)</td>
<td>56</td>
<td>57</td>
<td>59</td>
<td>59</td>
<td>57.6</td>
</tr>
<tr>
<td>Female</td>
<td>43%</td>
<td>44%</td>
<td>61%</td>
<td>39%</td>
<td>48%</td>
</tr>
<tr>
<td>Caucasian</td>
<td>57%</td>
<td>52%</td>
<td>68%</td>
<td>61%</td>
<td>59%</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>36</td>
<td>36</td>
<td>40</td>
<td>29</td>
<td>35.8</td>
</tr>
<tr>
<td>DVT (US)</td>
<td>43%</td>
<td>41%</td>
<td>36%</td>
<td>56%</td>
<td>43%</td>
</tr>
</tbody>
</table>

**Results: RV:LV**

<table>
<thead>
<tr>
<th>Cohort</th>
<th>2 hr (2 mg/hr/cath)</th>
<th>4 hr (1 mg/hr/cath)</th>
<th>6 hr (1 mg/hr/cath)</th>
<th>8 hr (2 mg/hr/cath)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>26% reduction</td>
<td>24% reduction</td>
<td>23% reduction</td>
<td>26% reduction</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

All arms (mean) p<0.0001, p<0.0001, p=0.0001, p=0.0011

**Results: Modified Miller Score**

<table>
<thead>
<tr>
<th>Cohort</th>
<th>2 hr (2 mg/hr/cath)</th>
<th>4 hr (1 mg/hr/cath)</th>
<th>6 hr (1 mg/hr/cath)</th>
<th>8 hr (2 mg/hr/cath)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5.5% reduction</td>
<td>9.2% reduction</td>
<td>14% reduction</td>
<td>26% reduction</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

All arms (mean) p<0.0001, p<0.0001, p=0.0032

**Results: 6-Minute Walking Distance**

<table>
<thead>
<tr>
<th>Cohort</th>
<th>30 days</th>
<th>365 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>320</td>
<td>380</td>
</tr>
<tr>
<td>2</td>
<td>340</td>
<td>400</td>
</tr>
<tr>
<td>3</td>
<td>360</td>
<td>420</td>
</tr>
<tr>
<td>4</td>
<td>380</td>
<td>440</td>
</tr>
</tbody>
</table>

All arms (mean) 30 d, 365 d.
OPTALYSE PE
Results: Quality of Life

- PEmb-QoL contains six dimensions:
  1. Frequency of complaints
  2. ADL limitations
  3. Work related problems
  4. Social limitations
  5. Intensity of complaints
  6. Emotional complaints

- Lower score indicates better outcome

Cohort 1 Cohort 2 Cohort 3 Cohort 4

30d 365d

PEmb-QoL from 30 to 365 days post-procedure

OPTALYSE PE
Safety

<table>
<thead>
<tr>
<th>Safety Outcome</th>
<th>n</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major bleeding from day 30 to 365</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cohort 1</td>
<td>27</td>
<td>2 (7.4)</td>
</tr>
<tr>
<td>Cohort 2</td>
<td>27</td>
<td>5 (18.5)</td>
</tr>
<tr>
<td>Cohort 3</td>
<td>28</td>
<td>7 (25)</td>
</tr>
<tr>
<td>Cohort 4</td>
<td>18</td>
<td>4 (22.2)</td>
</tr>
<tr>
<td>Total</td>
<td>100</td>
<td>18 (18)</td>
</tr>
<tr>
<td>Recurrent PE from day 30 to 365</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Suspected and Confirmed</td>
<td>100</td>
<td>1 (1)</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>2</td>
<td>2 (2)</td>
</tr>
</tbody>
</table>

Safety population includes all patients who received access; numbers across are arithmetic; confidence intervals not reported

OPTALYSE PE
Study Conclusions

Lower doses and shorter infusions of ultrasound-assisted catheter directed thrombolysis using EKOS™ for acute PE resulted in:

- Reduction in RV:LV in all 4 treatment groups at 48 hours
- Reduced pulmonary clot burden at 48 hours
- Improved exercise tolerance and quality of life at 365 days for some patients
- With low incidence of major or minor bleeding, recurrent venous thromboembolism, or death