Novel Therapy for Acute Pulmonary Embolism

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Cardiology Associates of North Mississippi
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

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5. Chunilal et al. JAMA 2003;290:2849–58
– PE causes or contributes to 15% of all hospital deaths\textsuperscript{1,2}

– More people die each year from PE than highway fatalities, breast cancer and AIDS combined\textsuperscript{3}

<table>
<thead>
<tr>
<th>Cause of Death</th>
<th># of deaths/yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>PE\textsuperscript{4,5}</td>
<td>Up to 200,000</td>
</tr>
<tr>
<td>Highway fatalities\textsuperscript{6}</td>
<td>42,116</td>
</tr>
<tr>
<td>Breast Cancer\textsuperscript{7}</td>
<td>40,200</td>
</tr>
<tr>
<td>AIDS\textsuperscript{8}</td>
<td>14,499</td>
</tr>
</tbody>
</table>

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>Morganthaler(^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>

Impact of PE

- If not treated, there is 30 percent mortality with pulmonary embolism, usually within the first few hours after the episode.\textsuperscript{1,2}
- Patients with massive PE have a > 50% in hospital mortality rate.\textsuperscript{3}
- Patients with submassive PE have a 25% in hospital rate of death or significant clinical deterioration.\textsuperscript{4}

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

Submassive PE [Moderate / Intermediate risk]
40% PE population
21% mortality @ 3 months

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

### 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

RV dilation
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 et al. CHEST 2008;133:358-362
Adverse outcomes associated with RVD

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
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

Fremont et al. CHEST 2008;133:358-362
Adverse outcomes with unresolved RVD

PE patients with RVD unresolved exhibit 4x increased incidence of mortality 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

- Mortality rate at f/u:
  - 10.2% if RVD unresolved at d/c
  - 2.3% if RVD resolved at d/c

Grifoni et al. Arch Intern Med 2006; 166:2151-2156
Adverse outcomes with unresolved RVD

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

Grifoni 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
ANTICOAGULATION (AC) – HEPARIN

- AC therapy prevents further clot growth
- Studies\(^1\text{-3}\) 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 t-PA to dissolve occluding clot\(^4\)
  - a process that typically occurs over several weeks or months
  - endogenous fibrinolysis may often be incomplete at the end

IV thrombolysis with t-PA

100 mg t-PA 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.
Rationale for A New Therapy

- In randomized trials, systemic thrombolysis for PE is associated with a 13% risk of major bleeding and 1.8% risk of intracranial bleed.\(^1\)

- In clinical practice, these complications rise to 20% and 3%, respectively.\(^2\)

- In clinical practice, systemic thrombolysis is **NOT** given to up to 2/3 of patients who may qualify based on the PE itself.\(^3\)

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\(^1\) Eur Heart J 2008; 29:2276-2315
\(^2\) Am J Cardiol. 2006;97:127-9
\(^3\) Circulation 2006;113:577-82
**Features**
- 5.4 Fr catheter
- 106 and 135 cm working length
- 6, 12, 18, 24, 30, 40 and 50 cm treatment zones
The EkoSonic® Endovascular System is indicated for:

- controlled and selective infusion of physician-specified fluids, including thrombolytics, into the peripheral vasculature
- infusion of solutions into the pulmonary arteries
- the ultrasound facilitated, controlled and selective infusion of physician-specified fluids, including thrombolytics, into the vasculature for the treatment of pulmonary embolism

http://www.ekoscorp.com
Acoustic Pulse Thrombolysis™

Mechanism of action

**Fibrin Separation**

Non-cavitational 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

EKOS’ Acoustic Pulse Thrombolysis™ is a minimally invasive system for dissolving thrombus.

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

ULTIMA study compared EKOS® to standard care 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 flow chart

PE patients diagnosed by Chest CT (N = 363)

Screening failure: N = 304 (84%)
- No main pulmonary artery embolism at CT (N = 125)
- RV/LV ratio < 1 at CT or echocardiography (N = 82)
- Active bleeding or increased risk of bleeding (N = 19)
- High-risk PE (N = 16)
- Major surgery or trauma within 10 days (N = 13)
- Asymptomatic or symptom duration > 14 days (N = 13)
- No patient consent (N = 12)
- Age > 80 years (N = 11)
- Life expectancy < 3 months (N = 6)
- Other reasons (N = 7)

Randomization (N = 59)

Data Safety Monitoring Board:
Randomization terminated if at least 25 patients per group with evaluable primary endpoint (RV/LV ratio) identified

Echocardiography Core Lab:
Blind assessment of echocardiograms

Received USAT + Heparin (N = 30)
Primary endpoint evaluable (N = 25)
FU visit at 3 months (N = 30)

Received Heparin alone (N = 29)
Primary endpoint evaluable (N = 28)
FU visit at 3 months (N = 27)
RCT compared EKOS® to heparin for the treatment of intermediate risk PE

Patients: Acute PE with RV/LV ratio $\geq 1.0$

Randomization

- 30 patients
  - Unfractionated heparin + Ultrasound-assisted CDT using EKOS®

- 29 patients
  - Unfractionated heparin

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

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

**RV/LV ratio significantly improved at 24 hours**

- **EKOS® with tPA + Heparin**
  - Baseline: 1.28
  - 24 hrs: 0.99
  - **P<0.001**

- **Heparin**
  - Baseline: 1.20
  - 24 hrs: 1.17
  - **P=0.31**

**Reduction in RV/LV ratio significantly greater at 24 hours and improved at 90 days**

- **EKOS® with tPA + Heparin**
  - Baseline to 24 hrs: 0.30
  - Baseline to 90 days: 0.35
  - **P<0.001**

- **Heparin**
  - Baseline to 24 hrs: 0.03
  - Baseline to 90 days: 0.24
  - **P=0.07**

*Kucher et al. Circulation. 2014;129:479-486*
More improved echo findings from EKOS® with tPA + heparin than heparin alone

No statistical difference in safety outcomes with EKOS® with tPA + heparin than heparin alone.

<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>10%</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 anal bleeding following endoscopic removal of colon polyp

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

Patients
Acute Massive and Submassive PE with RV/LV ratio ≥ 0.9
(n = 150; 22 centers)

Objectives

Evaluate ultrasound-facilitated, catheter-directed low-dose fibrinolysis:

- **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>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>
<tr>
<td>Total rtPA dose</td>
<td>23.7 ± 2.9 mg</td>
<td></td>
</tr>
</tbody>
</table>

* Denotes 1 patient died prior to treatment

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

Reduced pulmonary artery pressure immediately post-procedure

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

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

Patient Selection

- Evidence of proximal PE on CTA
- Evidence of massive / submassive PE
  - RV enlargement
  - Elevated BNP
  - Elevated troponin
  - Hypotension
  - Large A/a gradient
- No evidence of active bleeding
Getting Started

- 12 French St. Jude Fast-Cath™ Duo Hemostasis Introducers Cath-Lock™ Locking Hub 12 cm Sheath  (Product Number 406301)

- Allows for a single venous puncture (femoral vein)
Getting Started
Getting Started

- Use an angled pigtail and exchange-length 0.035 J-wire to selectively engage each pulmonary artery.

- Then exchange over the J-wire for the EKOS® catheter.
EkoSonic® Endovascular System

Placement in the left and right pulmonary arteries for the treatment of bilateral PE
– I like to use a 12 cm treatment length EKOS® catheter placed into each lung (total 2 catheters).
  – EKOS® Mach 4 106 cm / 12 cm 500-55112

– Some docs place a 12 cm catheter into the left lung and an 18 cm catheter in the right lung
  – EKOS® Mach 4 106 cm / 12 cm 500-55112
  – EKOS® Mach 4 106 cm / 18 cm 500-55118
After both catheters are in place, insert ultrasound wires, and attach coolant and lytic infusion lines.
Infusion rates

- Single EKOS® catheter
  - 1 mg/hour infusion of tPA x **24 hours** (24 mg)
  - coolant infusion (NS) at 35 ml/hour

- Double EKOS® catheter
  - 1 mg/hour infusion of tPA into each catheter x **12 hours** (total 24 mg)
  - coolant infusion (NS) at 25 ml/hour into each catheter

- Heparin
  - 5000 unit bolus IV upon suspicion of PE
  - Infusion at 400 units/ hour via femoral sheaths
Post Infusion

- Remove sheaths at bedside
- Consider repeat echo to look at RV size
- After 4 hours to allow for hemostasis - begin Xarelto 15 mg po twice a day x 3 weeks, then change to 20 mg daily
- Usually can d/c on Day 3
Case Study

- 68 year old man who is two days post-CABG suddenly develops chest pain and shortness of breath.

- ECG shows new RBBB and there was concern for acute graft closure.

- Cath lab notified for “Code STEMI” and stat echo obtained.
Case Study

Cath cancelled and CTA lungs ordered
Case Study

EKOS® procedure performed
No bleeding!
Symptoms resolved
Summary

- 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
Summary

– 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, controlled, multicenter trial
  – Single-center studies
  – One metaanalysis
Summary

- 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
Acoustic Pulse Thrombolysis™ system

For Pulmonary Embolus

The New “Code Blue”