Diagnosis and Management of Pulmonary Embolism
A Focus on Catheter Directed Thrombolysis and Pulmonary Embolism Response Team

Saurabh Malhotra, MD MPH FACC FASNC
Assistant Professor of Medicine (Cardiology) and Nuclear Medicine
Jacobs School of Medicine and Biomedical Sciences
DISCLOSURES

Research Support

• Becker Fund for Heart Research, Community Foundation of Greater Buffalo

• Intersocietal Accreditation Commission (IAC)

Application Reviewer

• Intersocietal Accreditation Commission (IAC)
Clinical Case

53 y/o female with HTN presents to ED with worsening dyspnea and chest pain

Diaphoretic and severely short of breath

HR 120s, SBP 100s

Hypoxemic correcting with O2 via NC

Elevated Tn and BNP
Chest CTA Shows Large Thrombus Burden
Right Ventricular Dysfunction on Echocardiography
Undefiled, Hyperdynamic Left Ventricle
Clinical Case

Patient with large pulmonary embolism with tachycardia, hypotension and RV dysfunction.

- Anticoagulation alone
- IV thrombolysis
- Catheter directed treatment
- Surgical thromboembolectomy
Pulmonary Embolism

Annual incidence

• United States: 69 per 100,000/year
  • Over 600,000 cases annually
  • 1-2 PE episodes per 1000 people, up to 10 per 1000 in the elderly population

Venous thromboembolism

• 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

4. Geering et al. CMAJ 2012
5. Chunilal et al. JAMA 2003
Pulmonary Embolism
A Silent and Fatal Epidemic

- 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>

\textsuperscript{1}Kasper et al. J Am Coll Cardiol. 1997;30:1165-1171
\textsuperscript{2}According to http://www.sirweb.org/patients/deep-vein-thrombosis/
\textsuperscript{5}Silverstein et al. Arch Internal Med. 1998;158:585-593.
More than 1/3rd of the Pulmonary Embolism are Submassive: ICOPER

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

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

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

Goldhaber et al, Lancet, 1999
### Evidence of Right Ventricular Dysfunction Needed for Submassive PE

#### 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

*Jaff et al, Circulation, 2011*

*Quiroz, Circulation, 2004*
## Pulmonary Embolism Severity Index (PESI)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Original version\textsuperscript{21,4}</th>
<th>Simplified version\textsuperscript{21,8}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Age in years</td>
<td>1 point (if age &gt;80 years)</td>
</tr>
<tr>
<td>Male sex</td>
<td>+10 points</td>
<td>-</td>
</tr>
<tr>
<td>Cancer</td>
<td>+30 points</td>
<td>1 point</td>
</tr>
<tr>
<td>Chronic heart failure</td>
<td>+10 points</td>
<td>1 point</td>
</tr>
<tr>
<td>Chronic pulmonary disease</td>
<td>+10 points</td>
<td>1 point</td>
</tr>
<tr>
<td>Pulse rate $\geq 110$ b.p.m.</td>
<td>+20 points</td>
<td>1 point</td>
</tr>
<tr>
<td>Systolic blood pressure $&lt;100$ mm Hg</td>
<td>+30 points</td>
<td>1 point</td>
</tr>
<tr>
<td>Respiratory rate $&gt;30$ breaths per minute</td>
<td>+20 points</td>
<td>-</td>
</tr>
<tr>
<td>Temperature $&lt;36$ °C</td>
<td>+20 points</td>
<td>-</td>
</tr>
<tr>
<td>Altered mental status</td>
<td>+60 points</td>
<td>-</td>
</tr>
<tr>
<td>Arterial oxyhaemoglobin saturation $&lt;90%$</td>
<td>+20 points</td>
<td>1 point</td>
</tr>
</tbody>
</table>

**Risk strata**\textsuperscript{a}

- **Class I:** $\leq 65$ points  
  very low 30-day mortality risk (0–1.6%)
- **Class II:** 66–85 points  
  low mortality risk (1.7–3.5%)
- **Class III:** 86–105 points  
  moderate mortality risk (3.2–7.1%)
- **Class IV:** 106–125 points  
  high mortality risk (4.0–11.4%)
- **Class V:** $>125$ points  
  very high mortality risk (10.0–24.5%)

$0$ points = 30-day mortality risk 1.0%  
(95% CI 0.0%–2.1%)

$\geq 1$ point(s) = 30-day mortality risk 10.9%  
(95% CI 8.5%–13.1%)
## Risk Stratification in PE

Adapted from ESC 2014 Guidelines: Diagnosis and Management of PE

<table>
<thead>
<tr>
<th>Early Mortality Risk</th>
<th>Risk Parameters and Scores</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Shock or Hypotension</td>
</tr>
<tr>
<td>High</td>
<td>+</td>
</tr>
<tr>
<td>Intermediate</td>
<td></td>
</tr>
<tr>
<td>Intermediate-high</td>
<td>−</td>
</tr>
<tr>
<td>Intermediate-low</td>
<td>−</td>
</tr>
<tr>
<td>Low</td>
<td>−</td>
</tr>
</tbody>
</table>
Contemporary Therapy for PE

ANTICOAGULATION (AC) – HEPARIN

- AC therapy prevents further clot growth
- 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
  - a process that typically occurs over several weeks or months
  - endogenous fibrinolysis may often be incomplete at the end

Simonneau et al. NEJM, 1997
Buller et al. NEJM, 2003
Meyer et al. Thromb Heamost 1995
Greater Clinical Improvement with Lytics Compared to Heparin Alone for Submassive PE

Kline et al., Chest, 2009
Advanced Treatment of Pulmonary Embolism

Reperfusion Therapies

Hemodynamic Support
Surgical Thromboembolectomy
Right ventricular dysfunction (RVD) is a predictor of poor clinical outcomes:

1. Mortality
2. Adverse events
3. VTE recurrence
Right Ventricular Dilatation Predicts Hospital Mortality

- 950 patients from ICOPER.
- All had RV/LV ratios on echocardiography.

Table 3—Multivariate Analysis for Risk Factors of In-hospital Mortality in the Study Population

<table>
<thead>
<tr>
<th>Variables</th>
<th>OR</th>
<th>95% CI</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RV/LV ratio ≥ 0.9</td>
<td>2.66</td>
<td>1.68–5.99</td>
<td>0.01*</td>
</tr>
<tr>
<td>History of left-heart failure</td>
<td>8.99</td>
<td>3.06–26.33</td>
<td>&lt; 0.0001*</td>
</tr>
<tr>
<td>Systolic arterial pressure &lt; 90 mm Hg</td>
<td>10.73</td>
<td>3.50–32.81</td>
<td>&lt; 0.0001*</td>
</tr>
<tr>
<td>Thrombolysis</td>
<td>1.33</td>
<td>0.58–3.05</td>
<td>0.49</td>
</tr>
</tbody>
</table>

Mortality rate:
- 1.9% if RV/LV ratio < 0.9
- 6.6% if RV/LV ratio ≥ 0.9

Fremont et al., Chest, 2008
Hypokinetic Right Ventricle Predicts Short-term Mortality

- 2454 patients from ICOPER (52 hospitals in 7 countries).
- All-cause mortality:
  - 11% in first 2 weeks
  - 17% at 3 months

Mortality rate at 3 months:

- 21% with hypokinesis
- 15% with no hypokinesis

Goldhaber et al., Chest, 2008
Persistence of Right Ventricular Dysfunction Predicts Mortality

- PE patients with RVD unresolved exhibit 2x 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:
  - Persistent RVD: 24% (10% PE related deaths)
  - Resolved RVD: 13% (0 PE related deaths)

Grifoni et al., Arch Int Med, 2006
Persistence of Right Ventricular Dysfunction Predicts Recurrent VTE

- Incidence of VTE at 4 years:
  - 0.4% with persistent RVD
  - 0.05% with no RVD

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

Grifoni et al., Arch Int Med, 2006
Thrombolysis in Acute Pulmonary Embolism

REDUCE THROMBUS BURDEN (not achievable by AC alone)

• Reverse RV afterload / failure; 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

Piazza and Goldhaber, Vascular Medicine, 2010
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.
Lower Risk of Recurrent PE or Death with Thrombolysis Compared with Heparin

- Metaanalysis 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 indicates pulmonary embolism.

Wan et al., Circulation, 2004
Comparison of Thrombolysis with Heparin in Intermediate-risk PE

PEITHO Trial (n=1005)

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

Meyer et al., NEJM, 2014
IV Thrombolysis Reduces the Risk of Acute Hemodynamic Compromise (≤ 7 days)

Table 3. Efficacy Outcomes.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Tenecteplase (N=506)</th>
<th>Placebo (N=499)</th>
<th>Odds Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcome — no. (%)</td>
<td>13 (2.6)</td>
<td>28 (5.6)</td>
<td>0.44 (0.23–0.87)</td>
<td>0.02</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>6 (1.2)</td>
<td>9 (1.8)</td>
<td>0.65 (0.23–1.85)</td>
<td>0.42</td>
</tr>
<tr>
<td>Hemodynamic decompensation</td>
<td>8 (1.6)</td>
<td>25 (5.0)</td>
<td>0.30 (0.14–0.68)</td>
<td>0.002</td>
</tr>
<tr>
<td>Time between randomization and primary efficacy outcome — days</td>
<td>1.54±1.71</td>
<td>1.79±1.60</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recurrent pulmonary embolism between randomization and day 7 — no. (%)</td>
<td>1 (0.2)</td>
<td>5 (1.0)</td>
<td>0.20 (0.02–1.68)</td>
<td>0.12</td>
</tr>
<tr>
<td>Fatal</td>
<td>0</td>
<td>3 (0.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonfatal</td>
<td>1 (0.2)</td>
<td>2 (0.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other in-hospital complications and procedures — no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>8 (1.6)</td>
<td>15 (3.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgical embolectomy</td>
<td>1 (0.2)</td>
<td>2 (0.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Catheter thrombus fragmentation</td>
<td>1 (0.2)</td>
<td>0 (0.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vena cava interruption</td>
<td>5 (1.0)</td>
<td>1 (0.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombolytic treatment other than study medication</td>
<td>4 (0.8)</td>
<td>23 (4.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death from any cause between randomization and day 30 — no. (%)</td>
<td>12 (2.4)</td>
<td>16 (3.2)</td>
<td>0.73 (0.34–1.57)</td>
<td>0.42</td>
</tr>
<tr>
<td>Patient still hospitalized at day 30 — no. (%)</td>
<td>59 (11.7)</td>
<td>50 (10.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rehospitalization between randomization and day 30 — no. (%)</td>
<td>22 (4.4)</td>
<td>15 (3.0)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Meyer et al., NEJM, 2014
Benefit from Thrombolysis was offset by a Greater Incidence of Acute Major Bleeds

**Table 4. Safety Outcomes in the Intention-to-Treat Population.**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Tenecteplase (N = 506)</th>
<th>Placebo (N = 499)</th>
<th>Odds Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bleeding between randomization and day 7</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major extracranial bleeding</td>
<td>32 (6.3)</td>
<td>6 (1.2)</td>
<td>5.55 (2.3–13.39)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Minor bleeding</td>
<td>165 (32.6)</td>
<td>43 (8.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major bleeding†</td>
<td>58 (11.5)</td>
<td>12 (2.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Stroke between randomization and day 7</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major extracranial bleeding</td>
<td>12 (2.4)</td>
<td>1 (0.2)</td>
<td>12.10 (1.57–93.39)</td>
<td>0.003</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>2 (0.4)</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemorrhagic stroke‡</td>
<td>10 (2.0)</td>
<td>1 (0.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serious adverse events between randomization and day 30</td>
<td>55 (10.9)</td>
<td>59 (11.8)</td>
<td>0.91 (0.62–1.34)</td>
<td>0.63</td>
</tr>
</tbody>
</table>

Meyer et al., NEJM, 2014
Adoption of IV thrombolysis hampered by elevated risk of severe bleeds

- In randomized trials, systemic PE thrombolysis is associated with a 13% risk of major bleeding and a 1.8% risk of intracranial hemorrhage

- In clinical practice, systemic PE thrombolysis is associated with a 20% risk of major bleeding and a 3% risk of intracranial hemorrhage

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

1Eur Heart J 2008; 29:2276-2315; 2Am J Cardiol. 2006;97:127-9
3Circulation 2006;113:577-82
**“Safe Dose” IV Thrombolitics for Moderate PE**

**MOPETT Trial**
- Single center prospective trial of 120 patients
- tPA dose: 50mg or 0.5 mg/kg if body weight < 50 kg
- RV dysfunction was not a pre-requisite for inclusion
- Primary endpoint: PHTN at 28 months
  - Lytic: 16%
  - Heparin: 57%
- Bleeding: 0%
- No difference in death or recurrent PE

**Moderate Pulmonary Embolism Treated With Thrombolysis (from the “MOPETT” Trial)**

Mohsen Sharifi, MD\(^a\,b\,c\), Curt Bay, PhD\(^b\), Laura Skrocki, DO\(^b\), Farnoosh Rahimi, MD\(^b\), and Mahshid Mehdipour, DMD\(^a\,b\), “MOPETT” Investigators

The role of low-dose thrombolysis in the reduction of pulmonary artery pressure in moderate pulmonary embolism (PE) has not been investigated. Because the lungs are very sensitive to thrombolysis, we postulated that effective and safe thrombolysis might be achieved by a lower dose of tissue plasminogen activator. The purpose of the present study was to evaluate the role of this “safe dose” thrombolysis in the reduction of pulmonary artery pressure in moderate PE. During a 22-month period, 121 patients with moderate PE were randomized to receive a “safe dose” of tissue plasminogen activator plus anticoagulation (thrombolysis group [TG], n = 61 patients) or anticoagulation alone (control group [CG], n = 60). The primary end points consisted of pulmonary hypertension and the composite end point of pulmonary hypertension and recurrent PE at 28 months. Pulmonary hypertension and the composite end point developed in 9 of 58 patients (16%) in the TG and 32 of 56 patients (57%) in the CG (p < .0001) and 9 of 58 patients (16%) in the TG and 35 of 56 patients (63%) in the CG (p < .0001), respectively. The secondary end points were total mortality, the duration of hospital stay, bleeding at the index hospitalization, recurrent PE, and the combination of mortality and recurrent PE. The duration of hospitalization was 2.2 ± 0.5 days in the TG and 4.9 ± 0.8 days in the CG (p < .0001). The combination of death plus recurrent PE was 1 (1.6%) in TG and 6 (10%) in the CG (p = .0489). No bleeding occurred in any group, and despite a positive trend in favor of a “safe dose” thrombolysis, no significant difference was noted in the rate of individual outcomes of death and recurrent PE when assessed independently. In conclusion, the results from the present prospective randomized trial suggest that “safe dose” thrombolysis is safe and effective in the treatment of moderate PE, with a significant immediate reduction in the pulmonary artery pressure that was maintained at 28 months. © 2013 Elsevier Inc. All rights reserved. (Am J Cardiol 2013;111:273–277)

Sharifi et al. AJC, 2013
Catheter Directed Thrombolysis (CDT)

Placement in the left and right pulmonary arteries for the treatment of bilateral PE
EkoSonic Endovascular System for CDT

Features
- 5.4 Fr catheter
- 106 and 135 cm working length
- 6, 12, 18, 24, 30, 40 and 50 cm treatment zones
EkoSonic Endovascular System for CDT
Mechanism of Action

How ultrasonic energy unlocks the clot

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

Braatan et al. Thromb Haemost 1997
Francis et al. Ultrasound in Medicine and Biology, 1995
Soltani et al. Physics in Medicine and Biology, 2008
RCT of EKOS vs Heparin in Intermediate Risk PE
The ULTIMA Trial

**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

**Diagram:**
- **Patients:** Acute PE with RV/LV ratio ≥ 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

Kucher et al. Circulation, 2014
Greater Reduction in RV Dilatation with EKOS with tPA and Heparin

Kucher et al. Circulation, 2014
Greater Improvement in RV Systolic Function from EKOS with t-PA and Heparin

Kucher et al. Circulation, 2014
Similar Safety Outcomes from EKOS with t-PA and Heparin vs. 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>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 anal bleeding following endoscopic removal of colon polyp

Kucher et al. Circulation, 2014
CDT with EKOS is Safe and Efficacious
SEATTLE II Study

**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

Piazza et al., JACC Interventions, 2015
CDT with EKOS is Safe and Efficacious

SEATTLE II Study

Piazza et al., JACC Interventions, 2015
# CDT with EKOS is Safe and Efficacious

## SEATTLE II Study

<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</td>
<td>21%</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</td>
<td>13%</td>
</tr>
<tr>
<td>Total rtPA dose</td>
<td>23.7 ± 2.9 mg</td>
<td></td>
</tr>
</tbody>
</table>
CDT with EKOS is Safe and Efficacious
SEATTLE II Study

**Figure 2** Efficacy Outcomes

**TABLE 5 Safety Outcomes (N = 150)**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Length of stay, SD, days</td>
<td>8.8 ± 5</td>
</tr>
<tr>
<td>In-hospital death</td>
<td>3 (2)</td>
</tr>
<tr>
<td>30-day mortality*</td>
<td>4 (2.7)</td>
</tr>
<tr>
<td>Serious and severe adverse events potentially related to device</td>
<td>3 (2)</td>
</tr>
<tr>
<td>Serious and severe adverse events potentially related to t-PA</td>
<td>2 (1.3)</td>
</tr>
<tr>
<td>IVC filter placed</td>
<td>24 (16)</td>
</tr>
<tr>
<td>Major bleeding within 30 days*</td>
<td>15 (10)</td>
</tr>
<tr>
<td>GUSTO moderate*</td>
<td>14 (9.3)</td>
</tr>
<tr>
<td>GUSTO severe*</td>
<td>1 (0.7)</td>
</tr>
<tr>
<td>Intracranial hemorrhage</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

Piazza et al., JACC Interventions, 2015
Reduced Risk of Intracranial Hemorrhage with CDT

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

<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></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Minor</td>
<td>Major</td>
</tr>
<tr>
<td>Chamsuddin et al. (2008)\textsuperscript{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)\textsuperscript{a}</td>
</tr>
<tr>
<td>Lin et al. (2009)\textsuperscript{25}</td>
<td>11</td>
<td>2 (18)</td>
<td>17.2 ± 2.4</td>
<td>17.4 ± 5.2</td>
<td>0 (0)\textsuperscript{c}</td>
<td>0 (0)\textsuperscript{c}</td>
</tr>
<tr>
<td>Engelhardt et al. (2011)\textsuperscript{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>4 (17)\textsuperscript{f}</td>
</tr>
<tr>
<td>Quintana et al. (2013)\textsuperscript{27}</td>
<td>10</td>
<td>2 (20)</td>
<td>18 (7–38)\textsuperscript{d}</td>
<td>20.8 (12–49)\textsuperscript{d}</td>
<td>2 (20)</td>
<td>0 (0)\textsuperscript{j}</td>
</tr>
<tr>
<td>Kennedy et al. (2013)\textsuperscript{28}</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>1 (2)\textsuperscript{a}</td>
</tr>
<tr>
<td>Engelberger et al. (2013)\textsuperscript{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)\textsuperscript{k}</td>
</tr>
<tr>
<td>Kucher et al. (2013)\textsuperscript{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)\textsuperscript{k}</td>
</tr>
<tr>
<td>Total\textsuperscript{f}</td>
<td>197</td>
<td>35 (18)</td>
<td>26.9\textsuperscript{m}</td>
<td>17.8\textsuperscript{m}</td>
<td>21 (10.7)</td>
<td>7 (3.6)</td>
</tr>
</tbody>
</table>

Engelberger and Kucher. Eur Heart J. 2014
Minimal Risk of Adverse Events from EKOS Registry

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

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

**Total rtPA dose**  35.1±1.1 mg

**Total infusion time**  19.6±6.0 hrs

### Outcomes

<table>
<thead>
<tr>
<th></th>
<th>N=57 (95%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survival to discharge</td>
<td></td>
</tr>
<tr>
<td>ICU stay (median)</td>
<td>1 day</td>
</tr>
<tr>
<td>Hospital stay (median)</td>
<td>9 days</td>
</tr>
</tbody>
</table>

**90-day survival:**
- Overall  N=56 (93%)
- Submassive PE  N=47 (98%)
- Massive PE  N=9 (75%)

**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%)
Better Outcomes but Higher Cost with CDT
Nationwide Comparison of CDT with Systemic Lysis

- Large observational comparative analysis
  - Lysis: 1521 patients
  - CDT: 352 patients
- Primary endpoint: in-hospital mortality
- Secondary endpoint: in-hospital mortality and ICH

### Table II. Study Outcomes in Systemic vs. Catheter-Directed Thrombolytic Groups in Unmatched and Propensity Score-Matched Groups

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Unmatched cohort</th>
<th>Propensity Score-Matched Cohort (1:3 Matching)</th>
<th>Odds ratio/coefficient (95% CI)</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Systemic</td>
<td>Catheter-directed</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>thrombolysis</td>
<td>thrombolysis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary outcome</td>
<td>20.02</td>
<td>10.23</td>
<td>0.45 (0.31–0.66)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Secondary outcome</td>
<td>21.04</td>
<td>10.51</td>
<td>0.44 (0.30–0.64)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ICH</td>
<td>1.37</td>
<td>0.28</td>
<td>0.21 (0.03–1.35)</td>
<td>0.09</td>
</tr>
<tr>
<td>Hemorrhage requiring transfusion</td>
<td>4.45</td>
<td>3.41</td>
<td>0.76 (0.4–1.44)</td>
<td>0.39</td>
</tr>
<tr>
<td>Acute renal failure requiring dialysis</td>
<td>0.34</td>
<td>1.42</td>
<td>4.20 (1.12–15.71)</td>
<td>0.02</td>
</tr>
<tr>
<td>LOS</td>
<td>7 (5–10)</td>
<td>7 (5–10)</td>
<td>0.84 (0.14–4.33)(^a)</td>
<td>0.02</td>
</tr>
<tr>
<td>Cost (Median, Quartile1 to Quartile3)</td>
<td>17,914 (12,806–26,764)</td>
<td>24,722(18,542–36,068)</td>
<td>8,213 (5,232–11,195)(^a)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

\(^a\): no odds ratio calculated because of one cell has zero value; ICH: intracranial hemorrhage; LOS: length of stay; CI: confidence interval.

Patel et al. CCI 2015
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

– CDT with EKOS for the treatment of massive/submassive pulmonary embolism
  – Loosens the fibrin structure
  – Increases drug penetration into the fibrin matrix
  – Ultimately reduces drug dose, treatment time and risk of complications

– Goals of CDT:
  – 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)
  – No reports of intracranial hemorrhage in published clinical studies
Clinical Case

53 y/o female with HTN presents to ED with worsening dyspnea and chest pain

Diaphoretic and severely short of breath

HR 120s, SBP 100s

Hypoxemic correcting with O2 via NC

Elevated Tn and BNP
Pulmonary Angiogram

PA pressure: 80/48 (56)
Pulmonary Angiogram
Echocardiograms
14 hours after CDT
Echocardiograms

At discharge: day 4
Echocardiograms
6 weeks post discharge
Clinical Case 2

– 59 y/o female with ovarian cancer currently undergoing treatment at RPCI presents to the ED with shortness of breath

– Tachycardic, elevated D-dimer and cardiac biomarkers

– CTA: saddle pulmonary embolism
Clinical Case 2
What to do?
Clinical Case 2
Surgical Thromboembolectomy
Buffalo General Medical Center/Gates Vascular Institute
PERT Program

• PERT: Collaborative multi-disciplinary team to assist primary providers in the evaluation and management of patients with intermediate and high-risk pulmonary embolism

• National PERT Consortium:
  • Advance the science of PE care by performing research
  • Develop advanced treatment protocols
  • Educating clinicians and community members

- Interventional cardiologists
- Imaging cardiologists
- Pulmonary and Critical Care Fellows
- Sonographers
Buffalo General Medical Center/Gates Vascular Institute
PERT Algorithm

Pulmonary Embolism Response Team (PERT)

Outpatient Algorithm

- Call from outside facility
  - Transfer Center will conference call with ED provider, PERT team and referring facility
    - Low risk
    - Intermediate risk
    - High risk
      - Contraindication or unable to give thrombolytics
        - Systemic thrombolytics at referring facility
          - Transfer to MICU
          - Patient transferred to ED
          - Patient diagnosed with PE in the ED