Current treatment of DVT and PE: an interventionist's perspective

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Approximately 600,000 new cases of DVT in the U.S. each year, 1/3 of whom develop PE
DVT in Upper and Lower extremities: Symptoms

- Sudden swelling in affected limb
- Limb pain/tenderness
- Pain on dorsiflexion of the foot
- Dilated superficial collateral veins
- Warm skin over area of thrombosis
- Lack of distal pulses
DVT: Complications

- Pulmonary embolism
- Chronic venous insufficiency, venous ulcers and valvular incompetence comprising of Post-thrombotic syndrome (PTS)
- Critical limb ischemia
DVT: Treatment options

- Anticoagulation: Heparin, Warfarin, Enoxaparin

- Thrombus containment: IVC filter placement

- Thrombus removal:
  - Surgical removal
  - Catheter-directed thrombolysis (CDT)
  - PharmacoMechanical Thrombectomy (PMT)
Indications for CDT and PMT

- Phlegmasia cerulea dolens:
- Subacute and chronic Iliofemoral DVT:
- Acute iliofemoral or femoropopliteal DVT:
Mechanism of action of CDT

- Acceleration of the body’s natural thrombolytic pathway.
- Activation of fibrin-bound plasminogen, which in turn promotes thrombus resolution.
- Early lysis results in preserved valve function, reduced incidence of Post-Thrombotic Syndrome (PTS).
Local vs. systemic

Catheter-directed Thrombolysis (CDT) vs Systemic Intravenous Thrombolytic Therapy:

- Direct intra-thrombus injection of the thrombolytic agent protects the medication from deactivation by circulating inhibitors
- Achieves higher drug concentration at the site of thrombosis with a lower total dose
- Lower incidence of systemic and intracranial hemorrhagic complications.
Benefits of CDT

Catheter-directed Thrombolysis (CDT) vs Conventional Anticoagulant Therapy:

- Prompt resolution of symptoms
- Decreased incidence of PE
- Restoration of normal venous circulation
- Preservation of venous valvular function
- Reduced incidence of PTS.

However, CDT does not prevent clot propagation, rethrombosis, or subsequent embolization. Heparin therapy and oral anticoagulant therapy must always follow a course of thrombolysis.
Success rates of CDT: The Data

- In acute iliofemoral venous thrombosis, reported to be 80–85%, with 1 year patency at 60–65%.
- Major bleeding complication rates vary from 5–11% with most bleeding occurring at the puncture site.

- A prospective registry of 287 patients treated with a mean 53-hour infusion of urokinase type plasminogen activator (uPA) showed anatomic success in 83%. Major bleeding and rethrombosis were observed in 11% and 25% of patients, respectively, at 30 day followup.

- The transcatheter approach facilitates the diagnosis of predisposing anatomic lesions or anomalies. In patients with iliofemoral DVT, catheter-directed thrombolysis was successful for recanalization in 92–100% of patients, and it revealed an underlying lesion in 50–66%.
  - Treatment of these stenoses with angioplasty and stent placement reestablished unobstructed flow and achieved a prompt clinical response. Studies with 2 year followup documented a 5–11% incidence of valvular incompetence.
CDT: Contraindications

Absolute contraindications:
- Active internal bleeding or DIC
- CVA,
- Trauma to the head
- Neurosurgery within 3 months.

Relative contraindications:
- Major surgery within 10 days
- Intracranial or spinal cord tumor
- Uncontrolled hypertension
- Major GI bleed (within 3 mo)
CDT: Complications

- The hemorrhagic complications are about 3 times higher than that of anticoagulant therapy.
- Small, but potentially fatal, risk of intracerebral hemorrhage.

- Currently, the American College of Chest Physicians (ACCP) recommend CDT only for selected patients with extensive acute proximal DVT (e.g., those with iliofemoral DVT, symptoms for less than 14 days, good functional status, and life expectancy of >1 year) who are at low risk of bleeding.
Summary

- DVT associated with significant morbidity.
- Anticoagulation is still the mainstay of DVT therapy.
- Current options include CDT with EKOS catheter and PMT with AngioJet.
- Important indications include Phlegmasia Cerulea Dolens, DVT in IVC, Ileofemoral and Femoropopliteal DVTs.
- Efficacy is comparable to Systemic thrombolytic therapy.
- Benefits include prompt resolution of symptoms, lower incidence of PTS and intracranial bleed.
Acute, massive and submassive pulmonary embolism
Pulmonary Embolism (PE)

Annual incidence

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

Venous thromboembolism\(^3\)

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

5. Chunilal et al. JAMA 2003;290:2849–58
Patient risk stratification (per AHA Scientific Statement 2011*)

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

**PE patient population profile**

- **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
  - 2-3% mortality to 21% mortality @ 3 months

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3. Casazza et al. Thrombosis Research 2012; 130:847-852
Why treat intermediate risk PE patients aggressively?

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

- Mortality
- VTE recurrence
- Adverse cardiovascular events.
Adverse outcomes associated with RVD: Mortality

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

Echocardiographic RV/LV ratio ≥ 0.9 shown to be independent predictive factor of hospital mortality
Adverse outcomes associated with RVD: Bigger is not always better!

- 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

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

Adverse outcomes associated with RVD: MACE

- 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

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

Adverse outcomes associated with RVD: the international cooperative registry

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

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: VTE Recurrence

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

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

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
Standard PE therapy

ANTICOAGULATION (AC) – HEPARIN

- AC therapy prevents further clot growth
- Studies\(^1-3\) 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

Rationale for thrombolysis in acute PE

REDUCE THROMBUS BURDEN (not achievable by AC alone):

1. Reverse RV afterload / failure toward prevention of hemodynamic collapse.
2. Improve pulmonary reperfusion/capillary blood flow / gas exchange
3. Restore systemic arterial perfusion pressure

B. Decrease the risk of developing chronic pulmonary hypertension

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.
Meta-analysis suggests reduced risk of recurrent PE or death from 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:

Recent 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>0.43</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</td>
<td>3</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Resulted in death</td>
<td>1</td>
<td>6</td>
<td></td>
</tr>
</tbody>
</table>

http://clinicaltrialresults.org/Slides/ACC%202013/Konstantinides_PEITHO_ACC%202013.pdf
But the benefit of lysis came at the cost of major bleeds (including ICH)

<table>
<thead>
<tr>
<th></th>
<th>Tenecteplase (n=506)</th>
<th>Placebo (n=499)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All strokes by day 7</td>
<td>12 (2.4%)</td>
<td>1 (0.2%)</td>
<td>0.003</td>
</tr>
<tr>
<td>- Hemorrhagic</td>
<td>10</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>- Ischemic</td>
<td>2</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Serious adverse events (SAE)</td>
<td>29 (5.7%)</td>
<td>39 (7.8%)</td>
<td>0.19</td>
</tr>
</tbody>
</table>

http://clinicaltrialresults.org/Slides/ACC%202013/Konstantinides_PEITHO_ACC%202013.pdf
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

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1 Torbicki A et al. Guidelines on the diagnosis and management of acute PE. Eur Heart J 2008; ;29:2276-2315
2 Fiumara, K et al. Predictors of Major Hemorrhage Following Fibrinolysis for Acute PE. Am J Cardiol 2006;97:127-9
3 Kucher, N et al. Massive PE. Circulation 2006;113:577-82
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
- **No clinical trial for the treatment of PE using catheter-based thrombolysis has been completed to-date**
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
Fibrin Separation
Ultrasound separates fibrin without fragmentation of emboli

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

Acoustic Pulse Thrombolysis™

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: 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

EkoSonic® Endovascular System

Placement in the left and right pulmonary arteries for the treatment of bilateral PE
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 ratio ≥ 1.0**

- Randomization
  - 30 patients
    - Unfractionated heparin + Ultrasound-assisted CDT using EKOS®
  - 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.
More improved echo findings from EKOS® with tPA + heparin than heparin alone

*Systolic RV dysfunction significantly improved*

- P<0.001*
- P<0.001

*Kucher et al. Circulation. 2014;129:479-486*

* Two-sided exact Mantel-Haenszel test
† Wilcoxon rank sum test
No statistical difference in safety outcomes with EKOS® with tPA + heparin than heparin alone

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.
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

Primary Efficacy

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

Secondary Efficacy

- Change in noninvasively 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>Description</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

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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

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>(Meyer G, et al. 2014)</td>
<td></td>
</tr>
<tr>
<td>SEATTLE II</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.

Meta-analysis showed consistent recovery of hemodynamics among patients treated using EKOS®.

<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></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Before After</td>
<td>Before After</td>
</tr>
<tr>
<td>Chamsuddin et al. (2008)</td>
<td>10</td>
<td>NA</td>
<td>21.8</td>
<td>24.8 ± 8.4</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Lin et al. (2009)</td>
<td>11</td>
<td>2 (18)</td>
<td>17.4 ± 2.4</td>
<td>17.4 ± 5.2</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Engelhardt et al. (2011)</td>
<td>24</td>
<td>5 (21)</td>
<td>33.5 ± 15.5</td>
<td>19.7 ± 8.1</td>
<td>1.33 ± 0.24</td>
<td>1.0 ± 0.13</td>
</tr>
<tr>
<td>Quintana et al. (2013)</td>
<td>10</td>
<td>2 (20)</td>
<td>18.7 (38)</td>
<td>20.8 (12–49)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Kennedy et al. (2013)</td>
<td>60</td>
<td>12 (20)</td>
<td>35.1 ± 11.1</td>
<td>19.6 ± 6.0</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Engelberger et al. (2013)</td>
<td>52</td>
<td>14 (27)</td>
<td>21.0 ± 5.7</td>
<td>15.2 ± 1.7</td>
<td>1.42 ± 0.21</td>
<td>1.06 ± 0.23</td>
</tr>
<tr>
<td>Kucher et al. (2013)</td>
<td>30</td>
<td>0 (0)</td>
<td>20.8 ± 3.0</td>
<td>15.0 ± 1.0</td>
<td>1.28 ± 0.19</td>
<td>0.99 ± 0.17</td>
</tr>
<tr>
<td>Total</td>
<td>197</td>
<td>35 (18)</td>
<td>26.9m</td>
<td>17.8m</td>
<td>1.36 ± 0.21</td>
<td>1.03 ± 0.20</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Treatment details</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilateral PE</td>
<td>Survival to discharge</td>
</tr>
<tr>
<td>Unilateral PE</td>
<td>N=57 (95%)</td>
</tr>
<tr>
<td>Massive PE</td>
<td>ICU stay (median)</td>
</tr>
<tr>
<td>Submassive PE</td>
<td>1 day</td>
</tr>
<tr>
<td>Thrombus clearance:</td>
<td>Hospital stay (median)</td>
</tr>
<tr>
<td>- Complete (&gt;90%)</td>
<td>9 days</td>
</tr>
<tr>
<td>- Near complete (50-90%)</td>
<td></td>
</tr>
<tr>
<td>- Partial (&lt;50%)</td>
<td></td>
</tr>
<tr>
<td>Total rtPA dose</td>
<td>90-day survival</td>
</tr>
<tr>
<td>35.1±1.1 mg</td>
<td>- Overall</td>
</tr>
<tr>
<td>Total infusion time</td>
<td>- Submassive PE</td>
</tr>
<tr>
<td>19.6±6.0 hrs</td>
<td>- Massive PE</td>
</tr>
</tbody>
</table>

Adverse events:
- Major bleeding
- Minor bleeding
- Cardiopulmonary arrest
- Acute renal injury
- Recurrent PE

N=1 (1.7%)
N=1 (1.7%)
N=1 (1.7%)
N=1 (1.7%)
N=0 (0%)
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
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
- One metaanalysis
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
Case Study

- 45 y/o female with pmhx of DVT/PE on Coumadin for 5 years but recently discontinued who presented with shortness of breath and tachycardia. Was noted to be hypoxic with an 85% O2.
ER course

- BP 105/80 HR: 120’s
- Started on O2 5L and heparin drip.
- No systemic Lytics since patient is “hemodynamically stable”
- Cardio consulted for EKOS
- 2D echo is obtained.
In the cath lab

- Pt has a seizure episode without losing pulse.
- RHC reveals:
  - RA sat of 24%
  - PA sat of 19%
  - CI of 1.5 L/min/m²
  - Mean PA of 48 mmHg
  - PVR of 12.8 woods units

- Diagnosis: severe acute on chronic cor pulmonale with RV shock!
EKOS
24 hrs later:

- **Hemodynamics:**
  - RA sat: 60%
  - PA sat: 59%
  - Mean PA: 38 mmHg
  - CI: 2.4 L/min/m²!
48 HR echo
The St. John PE Experience (database)

- 10 cases to date
- No major bleeding complications (no GIB, no intracranial bleeding, no retroperitoneal hematoma)
- 1/10 patients needed transfusion (Platelets of 70K prior to procedure due to chronic thrombocytopenia)
- 1/10 patients with a puncture site hematoma due to anomalous anatomy and difficulty with access.
- 0/10 accidental arterial sticks!
- 0/10 patients went home on portable O2!
Mean Pulmonary arterial pressures

PA Systolic Pressures

Patient 1  Category 2  Category 3  Category 4  Patient 5  Patient 6  Patient 7  Patient 8  Patient 9

Baseline  At procedure completion
RA pressures (mmHg) (If > 20 or if > PCWP signifies severe RV dysfunction/failure)

Patient 1  Patient 2  Patient 3  Patient 4  Patient 5  Patient 6  Patient 7  Patient 8  Patient 9
Baseline  At procedure completion

Graph showing RA pressures for different patients.
Transpulmonary gradient (Mean PA-Mean wedge) (normal < 12)
Cardiac output in L/min

Cardiac Output L/min

- Patient 1: 7.6 at baseline, 7.8 at procedure completion
- Patient 2: 5.6, 7.0
- Patient 3: 4.3, 6.2
- Patient 4: 7.3, 4.3
- Patient 5: 6.3, 6.2
- Patient 6: 4.9
- Patient 7: 4.3
- Patient 8: 6.5
- Patient 9: 6.7

Baseline vs At procedure completion
Cardiac index in L/min/m²

Cardiac Index

Baseline
At procedure completion

0 1 2 3 4 5 6 7 8
Patient 1   Patient 2   Patient 3   Patient 4   Patient 5   Patient 6   Patient 7   Patient 8   Patient 9

Cardiac index values for different patients at baseline and at procedure completion.
Pulmonary vascular resistance

![Graph showing pulmonary vascular resistance over time for different patients. The x-axis represents patients, and the y-axis represents pulmonary vascular resistance in Woods units. The graph shows baseline and at procedure completion values for each patient.](image-url)