Burden of Venous Thromboembolism

- Pulmonary hypertension
- Pulmonary embolism
- Post-thrombotic syndrome
- Symptomatic DVT
- Asymptomatic DVT

Am Journal of Therapeutics 2009;16: 300-303

PE is the 3rd Leading Cause of CV Death
AHA - 2015 Statistics

© 2015 by the American College of Cardiology Foundation and the American Heart Association, Inc. Published by American Heart Association.

PE
MI
Stroke

Venous Thromboembolism
The Incidence is Increasing

- MI: #1 - rate is trending downward
- Stroke: #2 - rate has plateaued
- PE/DVT: #3 - rate is increasing in men and women

Management of Acute Pulmonary Embolism
Risk Stratification
**Classification of Acute PE**

**Risk Stratification**

- **Massive PE (~5%)**
  - Hypotension (< 90 mmHg), syncope, cardiac arrest
  - Respiratory failure
  - Often fatal if more aggressive treatment not initiated

- **Submassive PE (~25%)**
  - Normotensive
  - RV dysfunction
  - Increased risk of adverse outcomes

- **Low Risk PE (~70%)**
  - Normotensive
  - Normal RV function
  - Excellent prognosis with anticoagulation alone

**Most Patients with PE do well, but some do not!**

- Predictors of Mortality from PE and their Influence on Clinical Management

**Treatment Options for Acute Pulmonary Embolism**

- Monotherapy: Heparin, LMWH, Fondaparinux, Rivaroxaban, Apixaban
- Transition Therapy: Dabigatran, Edoxaban, Warfarin
- Thrombolytic Therapy (including catheter directed)
- IVC filter
- Surgery/Interventional approaches

**Antithrombotic Therapy for VTE Disease**

**CHST Guideline and Expert Panel Report**

- Monotherapy: Heparin, LMWH, Fondaparinux, Rivaroxaban, Apixaban
- Transition Therapy: Dabigatran, Edoxaban, Warfarin
- Thrombolytic Therapy (including catheter directed)
- IVC filter
- Surgery/Interventional approaches

**Thrombolytic Therapy in Unstable Patients with Acute Pulmonary Embolism: Saves Lives but Underused**

- Data from 1999 to 2008
- 2,110,320 patients discharged from short stay hospital in US with a diagnosis of PE
- 72,230 (3.4%) were unstable (in shock or ventilator dependent)

**Thrombolytic therapy in unstable patients with acute PE saves lives**

- All-cause case fatality rate in unstable patients with thrombolytic therapy was 15% vs. 47% without thrombolytic therapy. (p < .0001)
**MOPETT:** Half-Dose Fibrinolysis for Anatomically Large PE

**Variable**  | Low dose fibrinolysis (n=429)  | Standard Anticoagulation  | P value
---|---|---|---
Recurrent PE  | 0  | 3(5)  | 0.08
Total mortality  | 1(1.6)  | 3(5)  | 0.30

In patients with intermediate-risk pulmonary embolism, fibrinolysis therapy prevented hemodynamic decompensation but increased the risk of major hemorrhage and stroke.

**Fibrinolysis for PE Meta-Analysis: Mortality Reduction**

- 16 RCT comparing thrombolysis to standard anticoagulation (n=2115)
- 71% (1449) had intermediate risk PE (RV dysfunction)

Among patients with PE (including those who were hemodynamically stable with RV dysfunction), thrombolytic therapy was associated with lower rates of all-cause mortality and increased risks of major bleeding and ICH. Major bleeding was not significantly increased in patients 65 years or younger.

**Potential Advantages of US-Facilitated Catheter-Directed Low-Dose Fibrinolysis**

- Avoids the high risk of major bleeding associated with systemic fibrinolysis
  - Including intracranial hemorrhage
  - Dose-related: 25 mg vs. 100 mg
- More complete thrombus resolution
  - Catheter-directed fibrinolysis targets the area of highest thrombotic burden
- More effective for subacute thrombus
  - Pharmacomechanical therapy enhances fibrinolytic surface area by conditioning the thrombus
**SEATTLE II: RV/LV Ratio (Reduction)**

- **Pre-Procedure**
- **48 Hours**

- **RV/LV Ratio**
  - Pre-Procedure: 1.55
  - 48 Hours: 1.13

**p < 0.0001**

150 patients with massive (31) or submassive (119) PE received low dose (24 mg) of tPA with unilateral (24 hours) or bilateral (12 hours) catheter, NO ICH or fatal bleed.

(JACC Cardiovasc Interv 2015;8(10):1382-1392)

---

**Other Therapies**

- **VORTEX AngioVac®** - thrombus vacuum
- **Inari** - large bore percutaneous thrombus extraction
- **Penumbra** - thrombus aspiration
- **Argon Cleaner** - clot macerator
- **ECMO** – hemodynamic support as bridge to definitive treatment

---

**Surgical Embolectomy or Catheter-Based Interventions**

- **Patients with absolute contraindications to thrombolysis or (thrombolysis has failed) surgical embolectomy is preferred therapy (Grade 2C)**
- **If not immediately available, catheter embolectomy or thrombus fragmentation may be considered (Grade 2C)**

Grade 2C: weak recommendation, low or very low quality evidence

---

**PREPIC2: Anticoagulation ± IVC Filter for High-Risk PE**

<table>
<thead>
<tr>
<th>Group</th>
<th>No VC Filter</th>
<th>VC Filter</th>
<th>Relative Risk (95% CI)</th>
<th>Pvalue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormal clot lysis sensitivity (intravenous filter)</td>
<td>0.35 (0.25-0.49)</td>
<td>0.51 (0.37-0.71)</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>Nonsurgical</td>
<td>0.38 (0.26-0.56)</td>
<td>0.50 (0.36-0.69)</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>Nonsurgical, IPI &gt; 200</td>
<td>0.31 (0.22-0.44)</td>
<td>0.49 (0.34-0.71)</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>Nonsurgical, IPI &gt; 200, IVC filter</td>
<td>0.31 (0.22-0.44)</td>
<td>0.38 (0.27-0.55)</td>
<td>0.001</td>
<td></td>
</tr>
</tbody>
</table>

**Am J Med 2012; 125:478-484**

- **Among hospitalized patients with severe PE, the use of a ALN retrievable filter plus anticoagulation compared with anticoagulation alone did not reduce the risk of symptomatic recurrent PE at 3 months.**
- **Findings do not support the use of ALN filter in patients who can be treated with anticoagulation.**

(JAMA 2015;313:1627-1635)
Case Report

- 69 year old female
- PMH - HTN, diabetes mellitus, asthma
- Previous PE after surgery in 2010
- Left total knee replacement on 6/24/14
- LMWH for DVT prophylaxis

Case Report

- Developed shortness of breath, chest pain and syncope (7/2/14)
- 911 called, BP < 90 mmHg (responded to IV fluids)
- Required O₂
- ER - CTPA positive for an acute saddle PE
- Started on IV heparin
- Thrombocytopenia noted (heparin stopped)
- Argatroban initiated

Case Report

- Hemoglobin 12, platelets 18,000
- BUN 18, creatinine 1.21
- INR 1.1
- aPTT 57 seconds (target 46-84)
- PF4 strongly positive

Case Report

- Transferred – Cleveland Clinic Medical ICU (BP 105/63, HR 108, RR 22)
  - Pulse oximetry - 94% on 4 liters of oxygen
- Mild distress
- Echo: moderate RV dilation and moderate to severe RV dysfunction
- Duplex US: acute left femoral-popliteal DVT

CTPA

Case Report - PERT Call

- Develops atrial fibrillation with RVR 148
  - oxygen requirements increasing
  - More short of breath
  - Hypotensive again (BP < 90 mmHg)
- Troponin positive
- Platelet count 24,000, hemoglobin stable
- PERT TEAM CALLED
What to do Next?
What do the Guidelines Tell Us?

AHA Scientific Statement

Management of Massive and Submassive Pulmonary Embolism, Bil Omar Dop Embolism, and Chronic Thromboembolic Pulmonary Hypertension

A Scientific Statement From the American Heart Association

Recommendations for Fibrinolysis for Acute PE
1. Fibrinolysis is reasonable for patients with massive acute PE and acceptable risk of bleeding complications (Class IIa; Level of Evidence B).

Interpreting 3 Sets of Guidelines: Who Should Get Advanced Therapy?

Massive PE

- AHA (“reasonable”)
- ACCP (“suggested”)
- ESC (“recommended”)

Factors Associated with Clinical Deterioration Shortly after PE (in our patient)

- Hypotension
- Hypoxia
- Coronary artery disease
- Residual deep vein thrombosis
- Right heart strain on echocardiogram
- Elevated biomarkers
- RV enlargement on CT
What did we Do?

Case Report - PERT CALL
- 50 mg tissue plasminogen activator infused over 2 hours
- At the end of the infusion
  - HR low 70's (NSR)
  - Blood pressure normalized
  - Oxygen requirements decreased
  - Clinically significantly improved
- Discharged home 10 days later on warfarin

Case Report
- 24 year old female develops acute onset SOB, chest pain and a swollen left leg.
- PMH unremarkable
- Recently started on OCP's
- ER - hemodynamically stable
- Left common femoral/femoral vein DVT
- CT - submassive PE
- Elevated biomarkers and echo reveals moderate RV dysfunction
- What are your treatment options?

Interpreting 3 Sets of Guidelines: Who Should Get Advanced Therapy?

Submassive PE
(Normotensive, Right Ventricular Dysfunction, Elevated Biomarkers)

PE without shock or hypotension
Intermediate or Low Risk

*22. In most patients with acute PE not associated with hypotension, we recommend against systemically administered thrombolytic therapy (Grade 1B).

Grade 1B: strong recommendation, moderated quality evidence
AHA Scientific Statement

Management of Massive and Submassive Pulmonary Embolism, Iliofemoral Deep Vein Thrombosis, and Chronic Thromboembolic Pulmonary Hypertension

A Scientific Statement From the American Heart Association

Fibrinolysis may be considered for patients with submassive acute PE judged to have clinical evidence of adverse prognosis (new hemodynamic instability, worsening respiratory insufficiency, severe RV dysfunction, or major myocardial necrosis) and low risk of bleeding complications (Class IIb; Level of Evidence C).

Case Report - PERT Call

- 100 mg tissue plasminogen activator infused over two hours
- Patient converted to Rivaroxaban at discharge

PE Therapeutic Options: All Over the Map

Anticoagulation

IV Thrombolysis

Catheter Directed Thrombolysis

Pharmaco-Mechanical Catheter Treatment

Surgical Embolectomy

ECMO

Which Therapy to Use?

- Best treatment unknown
  - No standard approach
  - No “appropriate use criteria” for intervention
  - Practice varies by medical service, location, size
  - No standard algorithm or consistency in decision-making
  - No single team
  - No centralized locations for care or “centers of excellence”
  - No systematic evaluation of results

How do we decide whether to “intervene” and by what modality? Who decides? What is the endpoint?

Treatment Gap in Pulmonary Embolism

- <5% of patients with PE receive “advanced therapy”, including those with clear indications (hypotension, RV dysfunction, biomarkers, etc.)
- Many more are eligible than receive
- Reasons:
  - Failure to recognize potential benefit and integrate data in “real time”
  - Fear of complications
  - Inability to respond rapidly (systems issues)
  - “Paralysis in decision-making”

Multidisciplinary Pulmonary Embolism Response Teams:

Making Order out of Chaos
The Perks of PERTs

- PERTs provide rapid bedside evaluation and risk stratification of patients with acute PE.
- PERTs help interpret recommendations from 3 sets of guidelines in the context of the individual patient.
- PERTs facilitate access to advanced therapies such as systemic fibrinolysis, catheter-directed therapy, surgical pulmonary embolectomy, and IVC filter insertion.
- PERTs guide the utilization of advanced techniques such as ECMO for critically-ill PE patients.

PERT Program Flow Map

Expeditious input and clinical judgment from multiple specialties to optimize therapy

Cleveland Clinic – PERT Team

A Multidisciplinary Team

Outcomes - 82 patients

(July 2014 – Present)

- Average age - 57 years (22 to 89)
- 4 surgical embolectomy
- 20 IVC filters placed
- 13 catheter directed tPA
- 11 half dose tPA (50 mg)
- 2 full dose tPA (100 mg)
- 20 bleeding complications
- 6 deaths (2 CDT and 4 standard heparin)

Summary

- The best methods for risk stratification (ACCP, AHA, ESC) remains to be determined.
- The optimal strategy for selection of advanced therapies for moderate and high-risk PE patients is unclear.
- The role of advanced circulatory support for PE has yet to be defined.
- Multidisciplinary PE Response Teams provide real-time individualized bedside evaluation and recommendations until definitive management algorithms are established.
PE and DVT: A National Crisis
The Incidence is Increasing!

- Severely under-recognized and undertreated
- Significant immediate and long-term sequelae
- High recurrence rate
- Treatments available that reduce mortality, morbidity and sequelae