Controverse in management of Acute pulmonary embolism

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National Heart Institute

Introduction

• INTRODUCTION — Acute pulmonary embolism (PE) is common and often fatal, with a mortality rate of approximately 30 percent without treatment.
• Most deaths are due to recurrent PE within the first few hours of the initial event.
• Therapy with anticoagulants decreases the mortality rate to 3 to 8 percent, making it imperative that effective therapy be instituted as quickly as possible.
Why care?

- PE is the most common preventable cause of death in hospitalized patients
- ~600,000 deaths/year
- 80% of pulmonary emboli occur without prior warning signs or symptoms
- 2/3 of deaths due to pulmonary emboli occur within 30 minutes of embolization
- Death due to massive PE is often immediate
- Diagnosis can be difficult
- Early treatment is highly effective
- YOU WILL TAKE CARE OF PATIENTS WITH PE!

Pathology

At least 90% of pulmonary emboli originate from major leg veins.
National heart institute registry for PE

National heart institute registry for PE
Natural History of VTE

• 40-50% of pts with DVT develop PE, often “silent”
• PE presents 3-7 days after DVT
  – Fatal within 1 hour after onset of respiratory symptoms in 10%
  – Shock/persistent hypotension in 5-10% (up to 50% of patients with RV dysfunction)
• Most fatalities occur in untreated pts
• Perfusion defects completely resolve in 75% of all patients (who survive)
Clinical Diagnosis of PE

- In summary, clinical signs, symptoms and routine tests do not allow for the exclusion or confirmation of acute PE but may increase the index of its suspicion
- Consider PE in cases of unexplained tachycardia or syncope
Diagnosis-Probability Assessment

- Implicit clinical judgement is fairly accurate: “Do you think this patient has a PE?”
- Validated prediction rules standardize clinical judgement
  - Wells
  - Geneva

<table>
<thead>
<tr>
<th>Table 1: Predisposing factors for venous thromboembolisms (3, 9)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Strong predisposing factors (odds ratio &gt;10)</strong></td>
</tr>
<tr>
<td>-------------------------------------------------</td>
</tr>
<tr>
<td>Bone fractures (hip, leg)</td>
</tr>
<tr>
<td>Hip or knee replacement</td>
</tr>
<tr>
<td>Major general surgery</td>
</tr>
<tr>
<td>Major trauma</td>
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<tr>
<td>Spinal cord injury</td>
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</tr>
</tbody>
</table>
### Modified Wells criteria: clinical assessment for pulmonary embolism

<table>
<thead>
<tr>
<th>Clinical symptoms of DVT (leg swelling, pain with palpation)</th>
<th>3.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Other diagnosis less likely than pulmonary embolism</td>
<td>3.0</td>
</tr>
<tr>
<td>Heart rate &gt;100</td>
<td>1.5</td>
</tr>
<tr>
<td>Immobilization (23 days) or surgery in the previous four weeks</td>
<td>1.5</td>
</tr>
<tr>
<td>Previous DVT/PE</td>
<td>1.5</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>1.0</td>
</tr>
<tr>
<td>Malignancy</td>
<td>1.0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Probability</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>&gt;6.0</td>
</tr>
<tr>
<td>Moderate</td>
<td>2.0 to 6.0</td>
</tr>
<tr>
<td>Low</td>
<td>&lt;2.0</td>
</tr>
</tbody>
</table>

**Proportion with PE**

- 65%
- 30%
- 10%

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### Revised Geneva Score*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age older than 65 years</td>
<td>1</td>
</tr>
<tr>
<td>Previous deep venous thrombosis or pulmonary embolism</td>
<td>3</td>
</tr>
<tr>
<td>Surgery or fracture within 1 month</td>
<td>2</td>
</tr>
<tr>
<td>Active malignant condition</td>
<td>2</td>
</tr>
<tr>
<td>Unilateral lower limb pain</td>
<td>3</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>2</td>
</tr>
<tr>
<td>Heart rate 75–94 beats/minute</td>
<td>3</td>
</tr>
<tr>
<td>Heart rate 95 beats/minute or more</td>
<td>5</td>
</tr>
<tr>
<td>Pain in response to lower-limb deep venous palpation, unilateral edema</td>
<td>4</td>
</tr>
</tbody>
</table>

0–3 points indicates low clinical probability of pulmonary embolism (8% in the original validation study*)

4–10 points indicates intermediate clinical probability of pulmonary embolism (28% in the original validation study*)

≥11 points indicates high clinical probability of pulmonary embolism (74% in the original validation study*)

• The clinical severity of acute PE can be highly variable, ranging from asymptomatic to severe hypoxemia, right ventricular failure, shock, and death. As a result, therapy varies from patient to patient and requires considerable clinical judgment. Common questions asked by clinicians when a patient presents with PE include:
  • Which anticoagulant should I administer? How much? How long?
  • Should I administer thrombolytic therapy?
  • Should an inferior vena caval filter be placed?
  • Is embolectomy indicated?
  • Can the patient be treated as an outpatient?

### PE: Indicators of Poor Outcome

**ESC criteria** (based on consensus; lack of validation)

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High risk</strong></td>
<td>Cardiovascular shock or persistent hypotension</td>
</tr>
<tr>
<td><strong>Intermediate risk</strong></td>
<td>Lab (troponin, BNP) ↑ or RV dysfunction</td>
</tr>
<tr>
<td><strong>Low risk</strong></td>
<td>nl labs (troponin, BNP); nl RV function</td>
</tr>
</tbody>
</table>

[Toribio A et al. Eur Heart J 2008;2276-315]
Outpatient vs. Inpatient – HESTIA Criteria

1. Hemodynamically unstable?
2. Thrombolysis or embolectomy needed?
3. Active bleeding or high risk of bleeding?
4. Oxygen needed to keep $O_2$ saturation > 90 % for > 24 hrs?
5. PE dx’d during anticoagulant therapy?
6. iv pain meds for > 24 hrs?
7. Medical or social reason for admission?
8. GFR < 30 ml/min?
9. Severe liver impairment?
10. Pregnant?
11. Documented h/o HIT?

ACCP 2012

Acute Treatment

Recommend home treatment for DVT (1B) and •
early d/c for low-risk PE. (2B).
### Table 5: Risk stratification according to expected pulmonary embolism-related early mortality rate

<table>
<thead>
<tr>
<th>PE-related early mortality risk</th>
<th>Clinical markers</th>
<th>Risk markers</th>
<th>Potential treatment implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIGH &gt;15%</td>
<td>+</td>
<td>(+)</td>
<td>Thrombolysis or embolectomy</td>
</tr>
<tr>
<td>INTERMEDIATE 3-15%</td>
<td>-</td>
<td>+</td>
<td>Hospital admission</td>
</tr>
<tr>
<td>LOW &lt;1%</td>
<td>-</td>
<td>-</td>
<td>Early discharge or home treatment</td>
</tr>
</tbody>
</table>

In the presence of shock or hypotension it is not necessary to confirm RV dysfunction/injury to classify as high risk of PE-related early mortality.

PE = pulmonary embolism; RV = right ventricle.

### Summary-Elements of PE Risk Stratification

<table>
<thead>
<tr>
<th>Clinical markers</th>
<th>Shock</th>
<th>Hypotension&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Markers of RV dysfunction</td>
<td>RV dilatation, hypokinesis or pressure overload on echocardiography</td>
<td>RV dilatation on spiral computed tomography</td>
</tr>
<tr>
<td></td>
<td>BNP or NT-proBNP elevation</td>
<td>Elevated right heart pressure at RHC</td>
</tr>
<tr>
<td>Markers of myocardial injury</td>
<td>Cardiac troponin T or I positive&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>Defined as a systolic blood pressure < 90 mmHg or a pressure drop of ≥ 40 mmHg for > 15 min if not caused by new-onset arrhythmia, hypovolaemia or sepsis.

<sup>b</sup>Heart-type fatty acid binding protein (H-FABP) is an emerging marker in this category, but still requires confirmation.
Diagnostic Algorithm

Suspected high-risk PE

CT immediately available? (patient sufficiently stable?)

no

yes

Echocardiography (RV dysfunction)

no

yes

CT possible (patient stabilized)

MDCT

CT or other tests not possible, patient still unstable*1

positive

treat (thrombolysis or embolectomy if required)

negative

do not treat (other cause for instability)

do not treat (other cause for instability)
• Risk-adapted therapeutic strategies with acute PE
• Apart from hemodynamic stabilization and reversal of hypoxemia, the therapeutic goals for acute PE are—depending on the severity—prevention of appositional thrombus growth, restoration of pulmonary blood flow, and prevention of recurrences (8). If there is no contraindication, parenteral anticoagulation is therefore obligatory. The options available include unfractionated heparin (UFH), low-molecular-weight heparin (LMWH), or fondaparinux (3). Where suspicion of an acute PE is high (high or intermediate clinical probability), initial anticoagulation—with consideration of the bleeding risk—must be initiated before a definitive diagnosis is available (evidence level C)
• **Therapeutic strategies with high-risk PE**
  - As well as general circulatory support and therapeutic anticoagulation, hemodynamically unstable patients with confirmed PE require immediate thrombolysis to relieve the right ventricle (evidence level A) [3]. The following active substances and dosage regimens are recommended in the literature [5, 12]:
    - **Alteplase (rtPA):** 10 mg IV bolus over 1 to 2 minutes followed by 90 mg over 2 hours (with body weight <65 kg maximal 1.5 mg/kg)
    - **Urokinase:** 3 million IU over 2 hours
    - **Streptokinase:** 1.5 million IU over 2 hours.
  - In Germany, reteplase and tenecteplase are not approved for acute PE

• **Contraindications to fibrinolytic therapy**
  - **Absolute contraindications**
    - † Haemorrhagic stroke or stroke of unknown origin at any time
    - † Ischaemic stroke in preceding 6 months
    - † Central nervous system damage or neoplasms
    - † Recent major trauma/surgery/head injury (within preceding 3 weeks)
  - † Gastrointestinal bleeding within the last month
  - † Known bleeding
  - **Relative contraindications**
    - † Transient ischaemic attack in preceding 6 months
    - † Oral anticoagulant therapy
    - † Pregnancy or within 1 week post partum
    - † Non-compressible punctures
    - † Traumatic resuscitation
    - † Refractory hypertension (systolic blood pressure >180 mmHg)
    - † Advanced liver disease
    - † Infective endocarditis
    - † Active peptic ulcer
• Recommendations: acute treatment Classa Levelb
  • High-risk pulmonary embolism
  • † Anticoagulation with unfractionated heparin should be initiated without delay in patients with high-risk PE I A
  • † Systemic hypotension should be corrected to prevent progression of RV failure and death due to PE I C
  • † Vasopressive drugs are recommended for hypotensive patients with PE I C
  • † Dobutamine and dopamine may be used in patients with PE, low cardiac output and normal blood pressure Ila B
  • † Aggressive fluid challenge is not recommended III B
  • † Oxygen should be administered in patients with hypoxaemia I C
  • † Thrombolytic therapy should be used in patients with high-risk PE presenting with cardiogenic shock and/or persistent
  • arterial hypotension
  • I A
  • † Surgical pulmonary embolectomy is a recommended therapeutic alternative in patients with high-risk PE in whom thrombolysis
    • is absolutely contraindicated or has failed
  • I C
  • † Catheter embolectomy or fragmentation of proximal pulmonary arterial clots may be considered as an alternative to surgical
  • treatment in high-risk patients when thrombolysis is

Heparin plus Alteplase Compared with Heparin Alone in Patients with Submassive Pulmonary Embolism

Stavros Konstantinides, M.D., Annette Geibel, M.D., Gerhard Heusel, Ph.D., Fritz Heinrich, M.D., Wolfgang Kasper, M.D. and the Management Strategies and Prognosis of Pulmonary Embolism-3 Trial Investigators

N Engl J Med
Volume 347;15:1143-1150
October 10, 2002
Table 2. In-Hospital Clinical Events.*

<table>
<thead>
<tr>
<th>Event</th>
<th>Heparin Plus (N=118)</th>
<th>Placebo (N=138)</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary end point</td>
<td>13 (11.0)</td>
<td>34 (24.6)</td>
<td>0.006</td>
</tr>
<tr>
<td>Death from all causes</td>
<td>4 (3.4)</td>
<td>3 (2.2)</td>
<td>0.71</td>
</tr>
<tr>
<td>Escalation of treatment</td>
<td>12 (10.2)</td>
<td>34 (24.6)</td>
<td>0.604</td>
</tr>
<tr>
<td>Catecholamine infusion</td>
<td>3 (2.5)</td>
<td>8 (5.9)</td>
<td>0.63</td>
</tr>
<tr>
<td>(for persistent hypotension or shock)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Secondary thorobolvism</td>
<td>9 (7.6)</td>
<td>32 (23.2)</td>
<td>0.001</td>
</tr>
<tr>
<td>Endotracheal intubation</td>
<td>3 (2.5)</td>
<td>3 (2.2)</td>
<td>0.85</td>
</tr>
<tr>
<td>Cardiopulmonary resuscitation</td>
<td>0</td>
<td>1 (0.7)</td>
<td>1.0</td>
</tr>
<tr>
<td>Thrombolysis or thrombus fragmentation</td>
<td>0</td>
<td>1 (0.7)</td>
<td>1.0</td>
</tr>
<tr>
<td>Secondary end points</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recurrence pulmonary embolism‡</td>
<td>4 (3.4)</td>
<td>4 (2.9)</td>
<td>0.89</td>
</tr>
<tr>
<td>Major bleeding§</td>
<td>1 (0.8)</td>
<td>5 (3.6)</td>
<td>0.29</td>
</tr>
<tr>
<td>Final bleeding</td>
<td>0</td>
<td>1 (0.7)</td>
<td>1.0</td>
</tr>
<tr>
<td>Hemorrhagic stroke¶</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Ischemic stroke¶</td>
<td>0</td>
<td>1 (0.7)</td>
<td>1.0</td>
</tr>
</tbody>
</table>

*The numbers shown are based on calculations for the intention-to-treat population.
†P values were calculated with the use of Fisher’s exact test (two-sided).
‡Recurrence of pulmonary embolism had to be confirmed by ventilation-perfusion lung scanning, spiral computed tomography, or pulmonary angiography.
§Major bleeding was defined as fatal bleeding, hemorrhagic stroke, or a drop in the hemoglobin concentration by at least 4 g per deciliter, with or without the need for red cell transfusion.
¶Hemorrhagic or ischemic stroke had to be confirmed by computed tomography or magnetic resonance imaging.

The PEITHO (Pulmonary Embolism THrombolysis) Trial

- Haemodynamically stable patient with PE
- Meets inclusion criteria, no exclusion criteria

- Chest CT, VQ scan, or pulmonary angiogram: Positive
- Troponin I or T: Positive
- ECO: Right Ventricular Dysfunction

Informed Consent Obtained, Randomisation

- Placebo
- Tenecteplase

Primary Endpoint
- Death or haemodynamic collapse within 7 days

Secondary Endpoints
- Death within 7 days
- Haemodynamic collapse within 7 days
- Confirmed symptomatic pulmonary embolism recurrence within 7 days
- SAEs within 30 days
- Death within 30 days

Est. completion date November 2012
Conclusions:

• A combination of alteplase (100 mg given over a two-hour period) and heparin prevented the need for escalation of treatment (with open-label alteplase, catecholamine infusion, or mechanical ventilation) due to clinical deterioration more often than a combination of placebo and heparin. Clinical deterioration usually meant worsening symptoms, especially worsening respiratory failure.

Bottom line

• The decision to use thrombolytic therapy in the intermediate risk PE group should be made on a case-by-case basis after carefully weighing the strength of the indication, the potential benefits, the contraindications, and potential adverse effects.
ESC Guidelines: Non-High Risk PE

1. Anticoagulation should be initiated without delay in patients with high or intermediate clinical probability of PE while diagnostic workup is still ongoing
2. Use of LMWH or fondaparinux is the recommended form of initial treatment for most patients with non-high-risk PE
3. In patients at high risk of bleeding and in those with severe renal dysfunction, unfractionated heparin with an aPTT target range of 1.5–2.5 times normal is a recommended form of initial treatment

Guidelines on the diagnosis and management of acute pulmonary embolism

Non-High Risk PE

4. Initial treatment with unfractionated heparin, LMWH or fondaparinux should be continued for at least 5 days and may be replaced by vitamin K antagonists only after achieving target INR levels for at least 2 consecutive days
5. Routine use of thrombolysis in non–high-risk PE patients is not (yet) recommended, but it may be considered in selected patients with intermediate-risk PE (RV dysfunction, elevated troponin, BNP) and low bleeding risk

Guidelines on the diagnosis and management of acute pulmonary embolism
Treatment of Acute Pulmonary Embolism


Recurrent PE or PE and uncured cancer: Consider long term anticoagulation if benefits>risk

First unprovoked PE: rx for at least 3-6 months

IVC Filters

• May provide lifelong protection against PE
• Unclear effect on overall survival
• Complications:
  • DVT (20%)
  • Post thrombotic syndrome (40%)
  • IVC thrombosis (30%)
• Risk/benefit ratio difficult to determine since no RCT
• Use when there are absolute contraindications to anticoagulation and a high risk of VTE recurrence
• Consider in pregnant women with extensive thrombosis
• Optimal duration of retrievable filters is unclear
Prevalence of Fracture and Fragment Embolization of Bard Retrievable Vena Cava Filters and Clinical Implications Including Cardiac Perforation and Tamponade

William Nicholson, MD; W. Jay Nicholson, MD; Paul Torretto, MD; Bradley Taylor, MD; Samuel Solomon, MD; Thomas Schroyer, MD; Kevin McCullam, MD; Howard Goldberg, MD; James Mills, MS; Brian Schuler, MD; Larry Shears, MD; Kyle Siddleway, MD; Nikhilash Agarwal, MD; Christopher Twombly, MS, MPH

Background: Vena cava filters represent an alternative treatment option for patients with contraindications to anticoagulation, or they might serve as adjunctive treatment for continued emboli despite anticoagulation. The fracture of a filter strut with subsequent end-organ embolization is a rarely reported but potentially life-threatening occurrence.

Methods: We sought to determine the prevalence of fracture and embolization of the Bard Recovery (first generation) and the Bard G2 (second generation) vena cava filters. A retrospective, single-center, cross-sectional study was conducted by evaluating all patients who received either a Bard Recovery or Bard G2 filter from April 2008 until January 2009. A total of 189 patients had undergone implantation: 1 pregnant woman and 35 patients who died were excluded from this study. In addition, 10 patients who had the filter removed were also excluded. Ultimately, 80 patients participated in the trial. Subjects underwent fluoroscopy to assess the filter’s integrity. Embolized struts were localized by fluoroscopy, echocardiography, and computed tomography were performed in patients with fragment embolization to the heart.

Results: Thirteen of 80 patients had at least 1 strut fracture (16%). At least 1 strut in 7 of the 28 Bard Recovery filters fractured and embolized (25%). In 5 of those 7 cases, patients had at least 1 fragment embolize to the heart (71%). These patients experienced life-threatening symptoms of ventricular tachycardias and/or tamponade, including 1 patient who experienced sudden death at home. Six of 32 Bard G2 filters fractured (12%). In 2 of those 6 cases, the patients had asymptomatic end-organ fragment embolization.

Conclusion: The Bard Recovery and Bard G2 filters had high prevalences of fracture and embolization, with potentially life-threatening sequelae.

Arch Intern Med. Published online August 9, 2010. doi:10.1001/archinternmed.2010.316

2013 Update on Venous Thromboembolism

Stephan Moll, MD
University of North Carolina
Chapel Hill, NC
Advocate Lutheran General Hospital; Park Ride, IL,
March 2nd, 2013
The 3 Major Developments in 2012

- Publication of ACCP Guidelines
- Approval of Rivaroxaban for VTE
- Approval of Apixaban for atrial fibrillation

Question – Anticoagulant Choice

Outpatient management is chosen. CBC, PT, aPTT normal; Creatinine 0.95; liver enzymes normal. How would you treat?

- LMWH or fondaparinux / warfarin .A
- Rivaroxaban (Xarelto) .B
- Dabigatran (Pradaxa) .C
- Apixaban (Eliquis) .D
**Rivaroxaban**

In which patient do I consider rivaroxaban?

a) Acute DVT or PE
   - All patients treated as outpatients
   - Mild to moderate DVT; HESTIA criteria for PE

b) On long-term warfarin
   - I discuss it with all patients
   - Fluctuating INRs, high “warfarin hate factor”

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**VTE: Length of Anticoagulation**

Conglomerate decision of:

- Risk of recurrent VTE .1
  (a)...., (b)...., (c) ..... 
- Risk of Bleeding .2
  (a)...., (b)...., (c) ..... 
- Patient preference .3
  “Coumadin hate factor”
Treatment beyond Acute Period

- Surgery-associated DVT/PE: recommend 3 months. (1B)
- Non-surgical transient risk factor: recommend 3 months over 6 or more months. (1B)

- Unprovoked DVT/PE and low/intermediate risk for bleeding: suggest extended anticoagulation (2B). High bleeding risk: 3 months (1B).
- Cancer patient with DVT/PE: recommend/suggest extended therapy LMWH rather than VKA (2B).

Summary

1. Outpatient VTE management
   - Suitable for, may be, 50% of PE patients;
   - HESTIA criteria for PE risk can be useful for decision making.

2. Rivaroxaban for VTE (acute; previous): possible treatment option.

3. New oral anticoagulants
   - Starting the drugs;
   - D/c before surgery (24 h for standard risk; 2-4 d for high
**Takehome massage**

- Acute PE is one of the commonest cause of inhospital and outhospital mortality which reach up to 30% in untreated patients and decreased to less than 3% when diagnoosed and treated in early proper time
- You should suspect Acute PE in all patients esp cancer patients, presented with unexplained dyspnea &tachpnea esp postoperative bedridden pt with clinical or radiological evidence of DVT or RV dysfunction and /or elevated treponin or BNP

- We should follow WILLS or Geneva criteria to determine the exact propability of the diagnosis and then shift to the algorism of defint diagnosis
- The next step after definit diagnosis is to catagorise the patient between high risk or non high risk PE
- In high risk PE you should start thrombolytic therapy without delay unless containdicated
• If thrombolytic is contraindicated surgical or catheter embolectomy is strongly indicated
• Anticoagulant therapy together with Oxygen therapy, possitive intropic support when indicated
• In non high risk patients no need for thromb. Therapy except in patients with Rv dysfunction or elevated biomarkers treponin or BNP

• In low risk patients home therapy can be activated
• Fondaparinux is the preferred IV anticoagulant but in patients with renal impairment you should shift to UFH
• To prevent recurrence you should continue oral anticoagulant for at least 3m except patients with cancer or thrombophilia which need lifelong anticoagulant
• IVC filter only indicated if anticoag is contraindicated