Pulmonary Thromboembolism
Pulmonary Embolism

Pulmonary Embolus is a fragment of the thrombus that breaks off and travels in the blood until it lodges at the pulmonary vasculature.

Exogenous or endogenous material (usually a venous thrombus) travelling to lungs (via the venous circulation)
Introduction

- Acute PE is a relatively common cardiovascular emergency.
- High mortality rate if left untreated
- Clinical presentation is highly variable and non-specific
- Diagnosis requires appropriate and accurate imaging
- Prompt diagnosis and treatment can reduce mortality from 30% to 2-8%

• Highest incidence in hospitalized patients

• Autopsy reports suggest it is commonly "missed" diagnosed

• A Common disorder and potentially deadly

• Globally more people die from PE than MI
Incidence of Pulmonary Embolism Per Year in the United States*

Total Incidence 630,000

89% Survival > 1 hr
563,000

11% Death within 1 hr
67,000

71% Dx not made
400,000

29% Dx made, therapy instituted
163,000

70% Survival
280,000

30% Death
120,000

92% Survival
150,000

8% Death
120,000

*Progress in Cardiovascular Diseases, Vol. XVII, No. 4 (Jan/Feb 1975)
90-95% of pulmonary emboli originate in the deep venous system of the lower extremities

Other rare locations include

- Uterine and prostatic veins
- Upper extremities
- Renal veins
- Right side of the heart
Rudolf Virchow postulated more than a century ago that a triad of factors predisposed to venous thrombosis

Rudolph Virchow, 1858

**Triad:**
- Hypercoagulability
- Stasis to flow
- Vessel injury

Risk Factors

Hypercoagulability

- Malignancy
- Nonmalignant thrombophilia
  - Pregnancy
  - Postpartum status (<4wk)
  - Estrogen/ OCP’s
- Genetic mutations (Factor V Leiden, Protein C & S deficiency, Factor VIII, Prothrombin mutations, anti-thrombin III deficiency)

Venous Statis

- Bedrest > 24 hr
- Recent cast or external fixator
- Long-distance travel or prolong automobile travel

Venous Injury

- Recent surgery requiring endotracheal intubation
- Recent trauma (especially the lower extremities and pelvis)
VTE Risk Factors

- **Specific to women:**
  - Obesity BMI ≥ 29
  - Pregnancy
  - Hypertension
  - Heavy smoking (> 25cigs/day)
  - Hormone replacement therapy
  - OCP’s 10-30/100,000 users vs. 4-8/100,000 non-users.
Air travel & Risk of PE

- The risk of fatal PE in this setting is less than 1 in 1 million.
- Activation of the coagulation system during air travel.
- For each 2-hour increase in travel duration, there appears to be an 18% higher risk of VTE.

Non-thrombotic pulmonary embolism

- Septic embolism- drug addicts, catheters & pacemaker wires, septic thrombophlebitis
- Intravascular foreign bodies- broken catheters, guidewires, vena cava filters
- Fat embolism- trauma
- Venous air embolism
- Amniotic fluid embolism- occur in 1/8000 – 1/80,000, high maternal & fetal mortality
- Talc embolism
Pathophysiology

- Increased pulmonary vascular resistance
- Impaired gas exchange
- Alveolar hyperventilation
- Increased airway resistance
- Decreased pulmonary compliance
Pathophysiology

- More than 50% of the vascular bed has to be occluded before PAP becomes substantially elevated.

- When obstruction approaches 75%, the RV must generate systolic pressure in excess of 50mmHg to preserve pulmonary circulation.

- The normal RV is unable to accomplish this acutely and eventually fails.
Pulmonary embolism

- Anatomical obstruction
- Neurohumoral effects

↑ PA pressure  
↑ RV afterload

RV dilation/dysfunction

↓ RV output  
Interventricular septal shift to LV

↓ LV preload

↓ LV output

↓ Systemic perfusion

↑ RV wall tension

↑ RV O₂ demand

↓ RV O₂ supply

↓ Coronary perfusion

↓ Systemic perfusion

Hypotension
Clinical Presentation

- **The Classic Triad:** (Hemoptysis, Dyspnea, Pleuritic Pain)
  - Not very common!
  - Occurs in less than 20% of patients with documented PE

- **Three Clinical Presentations**
  - Pulmonary Infarction
  - Submassive Embolism
  - Massive Embolism
Clinical Features

Symptoms in Patients with Angio Proven PTE

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspnea</td>
<td>84</td>
</tr>
<tr>
<td>Chest Pain, pleuritic</td>
<td>74</td>
</tr>
<tr>
<td>Anxiety</td>
<td>59</td>
</tr>
<tr>
<td>Cough</td>
<td>53</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>30</td>
</tr>
<tr>
<td>Sweating</td>
<td>27</td>
</tr>
<tr>
<td>Chest Pain, nonpleuritic</td>
<td>14</td>
</tr>
<tr>
<td>Syncope</td>
<td>13</td>
</tr>
</tbody>
</table>

Stein, PD, et al. Am J Cardiol 1991; 68:1723-
## Clinical Features

### Signs with Angiographically Proven PE

<table>
<thead>
<tr>
<th>Sign</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tachypnea &gt; 20/min</td>
<td>92</td>
</tr>
<tr>
<td>Rales</td>
<td>58</td>
</tr>
<tr>
<td>Accentuated S2</td>
<td>53</td>
</tr>
<tr>
<td>Tachycardia &gt;100/min</td>
<td>44</td>
</tr>
<tr>
<td>Fever &gt; 37.8</td>
<td>43</td>
</tr>
<tr>
<td>Diaphoresis</td>
<td>36</td>
</tr>
<tr>
<td>S3 or S4 gallop</td>
<td>34</td>
</tr>
<tr>
<td>Thrombophlebitis</td>
<td>32</td>
</tr>
<tr>
<td>Lower extremity edema</td>
<td>24</td>
</tr>
</tbody>
</table>

Stein, PD, et al. Am J Cardiol 1991; 68:1723-
Broad Differential

- Pneumothorax
- Myocardial ischemia
- Pericarditis
- Asthma
- Pneumonia
- MI with cardiogenic shock
- Cardiac tamponade
- Aortic dissection
Diagnostic Test

- **Imaging Studies**
  - CXR
  - V/Q Scans
  - Spiral Chest CT
  - Pulmonary Angiography
  - Echocardiography

- **Laboratory Analysis**
  - CBC, ESR, Hgb/Hct,
  - D-Dimer
  - ABG’s

- **Ancillary Testing**
  - EKG
  - Pulse Oximetry
Chest X-Ray Myth:

“We have to do a chest x-ray so we can find Hampton’s hump or a Westermark sign.”

Reality:

Most chest x-rays in patients with PE are nonspecific and insensitive.
### Chest radiograph findings in patient with pulmonary embolism

<table>
<thead>
<tr>
<th>Result</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiomegaly</td>
<td>27%</td>
</tr>
<tr>
<td>Normal study</td>
<td>24%</td>
</tr>
<tr>
<td>Atelectasis</td>
<td>23%</td>
</tr>
<tr>
<td>Elevated Hemidiaphragm</td>
<td>20%</td>
</tr>
<tr>
<td>Pulmonary Artery Enlargement</td>
<td>19%</td>
</tr>
<tr>
<td>Pleural Effusion</td>
<td>18%</td>
</tr>
<tr>
<td>Parenchymal Pulmonary Infiltrate</td>
<td>17%</td>
</tr>
</tbody>
</table>

*Am Heart J 1997;134:479-87*
Chest X-ray Eponyms of PE

- Hampton’s Hump – consists of a pleura based shallow wedge-shaped consolidation in the lung periphery with the base against the pleural surface.
Chest X-ray Eponyms of PE

- **Westermark sign** – Dilatation of pulmonary vessels proximal to embolism along with collapse of distal vessels, often with a sharp cut off.
Radiographic Eponyms
- Hampton’s Hump, Westermark’s Sign
Palla’s Signs

Chest radiograph demonstrating focal oligemia in the right lung (area between white arrowheads) and a prominent right descending pulmonary artery (black arrow).
Ventilation/Perfusion Scan - “V/Q Scan”

- A common modality to image the lung and its use still stems.
- Relatively noninvasive and sadly most often nondiagnostic
- In many centers remains the initial test of choice
- Preferred test in pregnant patients
  - 50 mrem vs 800 mrem (with spiral CT)
**V/Q Scan**

- Technique

1. Radioactive compound inhaled into airspaces of lung. In a normal lung, this will distribute evenly to all regions.

2. Radioactive compound injected into vein. Travels to lung tissues in blood vessels.

3. No injected material reaches this region. "Mismatch" of inhaled and injected compounds on the lung scan images = pulmonary embolus.
V/Q Scan

**Advantages**
- Excellent negative predictive value (97%)
- Can be used in patients with contraindication to contrast medium

**Limitations**
- 30-50% of patients have non-diagnostic scan necessitating further investigation
**Spiral CT**

- Major advantage of Spiral CT is speed:
  - Often the patient can hold their breath for the entire study, reducing motion artifacts.
  - Allows for more optimal use of intravenous contrast enhancement.
  - Spiral CT is quicker than the equivalent conventional CT permitting the use of higher resolution acquisitions in the same study time.
  - Contraindicated in cases of renal disease.
  - Sensitive for PE in the proximal pulmonary arteries, but less so in the distal segments.
CT Angiogram

- Quickly becoming the test of choice for initial evaluation of a suspected PE.
- CT unlikely to miss any lesion.
- CT has better sensitivity, specificity and can be used directly to screen for PE.
- CT can be used to follow up "non diagnostic V/Q scans."
Chest computed tomography scanning demonstrating extensive embolization of the pulmonary arteries.
Multidetector helical CT pulmonary angiography

- Increasingly the first-line imaging modality
- PIOPED-II Study: 824 patients evaluated prospectively with multidetector CTA versus composite reference test
  - Sensitivity 83%
  - Specificity 96%
  - PPV = 96% with concordant clinical assessment

Multidetector helical CT pulmonary angiography – **Advantages**

- Diagnosis of alternative disease entities
- Coverage of entire chest with high spatial resolution in one breath hold
- High interobserver correlation
- Availability
- Improved depiction of small peripheral emboli

Multidetector helical CT pulmonary angiography – **Limitations**

- Reader expertise required
- Expense
- Requires precise timing of contrast bolus
- Radiation exposure
- Not portable
- Contraindications to contrast
  - Renal insufficiency
  - Contrast allergy

Multidetector-CT Findings

- Partial or complete filling defects in lumen of pulmonary arteries
  - Most reliable sign is filling defect forming acute angle with vessel wall with defect outlined by contrast material
  - “Tram-track sign”
    - Parallel lines of contrast surrounding thrombus in vessel that travels in transverse plane
  - “Rim sign”
    - Contrast surrounding thrombus in vessel that travels orthogonal to transverse plane

- RV strain indicated by straightening or leftward bowing of interventricular septum
**MRI**

Image: 59 y.o. male with severe dyspnea

MR angiogram depicts large amounts of embolic material (arrowheads) in right pulmonary artery, in right upper and lower lobes, and in left lingual pulmonary artery. Nonenhancing masses (arrow) are present in liver.

- **PIOPED III Trial**
  - Accuracy of gadolinium-enhanced MR angiography in combination with venous phase venography in diagnosing acute PE
  - Insufficient sensitivity
  - High rate of technically inadequate images

MRI

Advantages
- Lack of ionizing radiation

Limitations
- Respiratory and cardiac motion artifact
- Suboptimal resolution for peripheral pulmonary arteries
- Complicated blood flow patterns
- Experimental technology may have role in future
  - Real-time MR sequence without breath hold
  - Molecular MRI with fibrin-specific contrast agent

Pulmonary angiogram

- Gold Standard.
- Positive angiogram provides 100% certainty that an obstruction exists in the pulmonary artery.
- Negative angiogram provides > 90% certainty in the exclusion of PE.
- “Court of Last Resort”
Pulmonary angiogram

Left-sided pulmonary angiogram showing extensive filling defects within the left pulmonary artery and its branches.
Echocardiography

- This modality generally has limited accuracy in the diagnosis.
- The overall sensitivity and specificity for diagnosis of central and peripheral pulmonary embolism by ECHO is 59% and 77%.
- It may allow diagnosis of other conditions that may be confused with pulmonary embolism.
**ECHO signs of PE**

- RV enlargement or hypokinesis especially free wall hypokinesis, with sparing of the apex (the McConnell sign)
- **60/60 Sign** - Acceleration time of RV ejection <60ms in the presence of TR pressure gradient <\= 60mmHg.
- Interventricular septal flattening and paradoxical motion toward the LV, resulting in a “D-shaped” LV in cross section.
- Tricuspid regurgitation
Echocardiography

- Features include
  - RV dilation (apical 4-chamber RV diameter divided by LV diameter > 0.9)...25%
  - Decreased RV function
  - Tricuspid regurgitation
  - RV thrombus
  - Regional wall motion abnormalities that spare the right ventricular apex ("McConnell's sign")
  - Pulmonary hypertension with a tricuspid regurgitant jet velocity >2.6 m/sec
  - Dilated inferior vena cava without physiologic inspiratory collapse
  - Interventricular septal flattening and paradoxical motion toward the left

Only 30 to 40 percent of patients with PE have echocardiographic abnormalities suggestive of acute PE
Imaging in Pregnancy

- No validated clinical decision rules
- No consensus in evidence for diagnostic imaging algorithm
- Balance risk of radiation vs. risk of missed fatal diagnosis or unnecessary anticoagulation
- MDCT delivers higher radiation dose to mother but lower dose to fetus than V/Q scanning
- Consider low-dose CT-PA or reduced-dose lung scintigraphy

Imaging-nut shell

- Plain chest radiograph – Usually normal and non-specific signs.
- Radionuclide ventilation-perfusion lung scan – Excellent negative predictive value.
- CT Angiography of the pulmonary arteries – Quickly becoming method of choice.
- Pulmonary angiography – Gold standard but invasive.
Ancillary Test

- **WBC**
  - Poor sensitivity and nonspecific
  - Can be as high as 20,000 in some patients

- **Hgb/Hct**
  - PTE does not alter count but if extreme, consider polycythemia, a known risk factor

- **ESR**
  - Don’t get one, terrible test in regard to any predictive value
D-dimer Test

- Fibrin split product
- Circulating half-life of 4-6 hours
- Quantitative test have 80-85% sensitivity, and 93-100% negative predictive value

False Positives:

- Pregnant Patients
- Malignancy
- Advanced age > 80 years
- Hemorrhage
- AMI
- Hepatic Impairment
- Post-partum < 1 week
- Surgery within 1 week
- Sepsis
- CVA
- Collagen Vascular Diseases

Arch Intern Med 2004;140:589
Diagnostic Testing

- **D-dimer**
  - **Qualitative**
    - Bed side RBC agglutination test
      - “SimpliRED D-dimer”
  - **Quantitative**
    - Enzyme linked immunosorbent assay “Dimertest”
    - Positive assay is $> 500$ ng/ml
    - VIDAS D-dimer, 2$^{nd}$ generation ELISA test
ABG analysis

- ABG has a limited role.
- It usually reveal hypoxemia, hypocapnia and respiratory alkalosis.
- Alveolar arterial oxygen gradient, done at room air, a gradient > 15-20 is considered abnormal.
The electrocardiogram (ECG) helps exclude acute myocardial infarction.

T wave inversion in leads V1 to V4 has the greatest accuracy for identification of right ventricular dysfunction in patients with acute PE.

Electrocardiographic manifestations of right-sided heart strain, which is an ominous prognostic finding.
ECG Signs of PE

- Sinus tachycardia: 8-73%
- P Pulmonale: 6-33%
- Rightward axis shift: 3-66%
- Inverted T-waves in ≥ right chest leads: 50%
- S1Q3T3 pattern: 11-50% (S1-60%, Q3-53%, T3-20%)
- Clockwise rotation: 10-56%
- RBBB (complete/incomplete): 6-67%
- AF or A flutter: 0-35%
- No ECG changes: 20-24%
S1 Q3 T3 Pattern
T-wave inversion
Rt. Bundle Branch Block
Rt. Ventricular Strain
Electrocardiogram from a 33-year-old man who presented with a left main pulmonary artery embolism on chest CT scan. He was hemodynamically stable and had normal right ventricular function on echocardiography. His troponin and brain natriuretic peptide levels were normal. He was managed with anticoagulation alone. On the initial electrocardiogram, he has a heart rate of 90/min, S1Q3T3, and incomplete right bundle branch block, with inverted or flattened T waves in leads V1 through V4.
Prognostic Value of Troponins in Acute Pulmonary Embolism
Conclusion: Elevated troponin levels were associated with a high risk of (early) death resulting from pulmonary embolism (OR, 9.44; 95% CI, 4.14 to 21.49)

These findings identify troponin as a promising tool for rapid risk stratification of patients with pulmonary embolism.
BNP & pro-BNP

- Typically greater in patients with PE.
- Sensitivity of 60% and specificity of 62%.
- At a threshold of 500 pg/mL, the sensitivity of pro-BNP for predicting adverse events was 95%, and the specificity was 57%.

Doppler ultrasound of leg veins

Principle - Veins are normally compressible; Presence of DVT renders veins non-compressible
50% of patients with PE have positive ultrasound
(95% of PE are due to leg DVT)
## Diagnostic Tests for Suspected Pulmonary Embolism

<table>
<thead>
<tr>
<th>Test</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxygen saturation</td>
<td>Nonspecific, but suspect PE if there is a sudden, otherwise unexplained decrement</td>
</tr>
<tr>
<td>D-dimer</td>
<td>An excellent “rule-out” test if normal, especially if accompanied by non–high clinical probability</td>
</tr>
<tr>
<td>Electrocardiography</td>
<td>May suggest an alternative diagnosis, such as myocardial infarction or pericarditis</td>
</tr>
<tr>
<td>Lung scanning</td>
<td>Usually provides ambiguous result; used in lieu of chest CT for patients with anaphylaxis to contrast agent, renal insufficiency, or pregnancy</td>
</tr>
<tr>
<td>Chest CT</td>
<td>The most accurate diagnostic imaging test for PE; beware if CT result and clinical likelihood probability are discordant</td>
</tr>
<tr>
<td>Pulmonary angiography</td>
<td>Invasive, costly, uncomfortable; used primarily when local catheter intervention is planned</td>
</tr>
<tr>
<td>Echocardiography</td>
<td>Best used as a prognostic test in patients with established PE rather than as a diagnostic test; many patients with large PE will have normal echocardiograms</td>
</tr>
<tr>
<td>Venous ultrasonography</td>
<td>Excellent for diagnosis of acute symptomatic proximal DVT; a normal study does not rule out PE because a recent leg DVT may have embolized completely; calf vein imaging is operator dependent</td>
</tr>
<tr>
<td>Magnetic resonance</td>
<td>Reliable only for imaging of proximal segmental pulmonary arteries; requires gadolinium but does not require iodinated contrast agent</td>
</tr>
</tbody>
</table>
Approach to the patient of PE

- Stratify patients into high clinical likelihood or non–high clinical likelihood of PE.
- In low-risk group, only about 5% of patients were subsequently diagnosed with PE.
How do we work up?
- Pretest Probability

- Definition: “The probability of the target disorder (PE) before a diagnostic test result is known”.

- Used to decide how to proceed with diagnostic testing and final disposition
Classic Wells Criteria to Assess Clinical Likelihood of Pulmonary Embolism

<table>
<thead>
<tr>
<th>SCORE POINTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>DVT symptoms or signs</td>
</tr>
<tr>
<td>An alternative diagnosis is less likely than PE</td>
</tr>
<tr>
<td>Heart rate &gt;100/min</td>
</tr>
<tr>
<td>Immobilization or surgery within 4 weeks</td>
</tr>
<tr>
<td>Prior DVT or PE</td>
</tr>
<tr>
<td>Hemoptysis</td>
</tr>
<tr>
<td>Cancer treated within 6 months or metastatic</td>
</tr>
</tbody>
</table>

>4 score points = high probability
≤4 score points = non–high probability
## Simplified Wells Criteria to Assess Clinical Likelihood of Pulmonary Embolism

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>DVT symptoms or signs</td>
<td>1</td>
</tr>
<tr>
<td>An alternative diagnosis is less likely than PE</td>
<td>1</td>
</tr>
<tr>
<td>Heart rate &gt;100/min</td>
<td>1</td>
</tr>
<tr>
<td>Immobilization or surgery within 4 weeks</td>
<td>1</td>
</tr>
<tr>
<td>Prior DVT or PE</td>
<td>1</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>1</td>
</tr>
<tr>
<td>Cancer treated within 6 months or metastatic</td>
<td>1</td>
</tr>
</tbody>
</table>

>1 score point = high probability
≤1 score point = non–high probability
Original Geneva score

Variable and score

Age
- 60–79 yr — 1
- ≥80 yr — 2

Previous DVT or PE — 2
Recent surgery — 3
Heart rate >100 beats/min — 1

PaCO₂
- <36.2 mm Hg (<4.8 kPa) — 2
- 36.2–38.9 mm Hg (4.8–5.19 kPa) — 1

PaO₂
- <48.8 mm Hg (<6.5 kPa) — 4
- 48.8–59.9 mm Hg (6.5–7.99 kPa) — 3
- 60–71.2 mm Hg (8.0–9.49 kPa) — 2
- 71.3–82.4 mm Hg (9.5–10.99) — 1

Chest radiograph
- Platelike atelectasis — 1
- Elevation of hemidiaphragm — 1

• SCORE 0–16
  • Low clinical probability of PE
    • score, ≤4
  • Intermediate probability of PE
    • score, 5 to 8
  • High probability of PE
    • score, ≥9
Revised Geneva score

- Age >65 yr - 1
- Previous DVT or PE - 3
- Surgery or lower limb fracture in previous wk - 2
- Active cancer - 2
- Unilateral lower limb pain - 3
- Hemoptysis - 2
- Heart rate
  - 75–94 beats/min — 3
  - ≥95 beats/min — 5
- Pain on leg palpation or unilateral edema — 4

- low-probability
  - 0 to 3 points
- intermediate-probability
  - 4 to 10 points
- high-probability category
  - ≥11 points
ACC/AHA Classification

- Massive
- Submassive
- Low-Risk PE
- Pulmonary infarction syndrome
Massive PE

- Acute PE with sustained hypotension (systolic blood pressure 90 mm Hg for at least 15 minutes or requiring inotropic support, not due to a cause other than PE, such as
  - Arrhythmia
  - Hypovolemia
  - Sepsis
  - Left ventricular (LV) dysfunction
  - Pulselessness
  - Persistent profound bradycardia (heart rate 40 bpm with signs or symptoms of shock)
Submassive PE

- Acute PE without systemic hypotension (systolic blood pressure 90mm Hg) but with either RV dysfunction or myocardial necrosis
- RV dysfunction means the presence of at least 1 of the following
  - RV dilation (apical 4-chamber RV diameter divided by LV diameter 0.9) or RV systolic dysfunction on echocardiography
  - RV dilation (4-chamber RV diameter divided by LV diameter 0.9) on CT
  - Elevation of BNP (90 pg/mL)
  - Elevation of N-terminal pro-BNP (500 pg/mL)
  - Electrocardiographic changes (new complete or incomplete right bundle-branch block, anteroseptal ST elevation or depression, or anteroseptal T-wave inversion)

Low-Risk PE

- Acute PE and the absence of the clinical markers of adverse prognosis that define massive or submassive PE
Pulmonary Infarction Syndrome

- Caused by a tiny peripheral pulmonary embolism
  - Pleuritic chest pain, often not responsive to narcotics
  - Low-grade fever
  - Leukocytosis
  - Pleural rub
  - Occasional scant hemoptysis
Integrated diagnostic approach
Treatment:

Goals:
- Prevent death from a current embolic event
- Reduce the likelihood of recurrent embolic events
- Minimize the long-term morbidity of the event

Patient replies: “Uh-huh, when do I get to eat!”
Treatment options for pulmonary emboli

- Anticoagulation
- Inferior vena cava filter
- Additional options for massive PE
  - Thrombolytic agent
  - Catheter embolectomy
  - Surgical embolectomy
  - Haemodynamic support - inotropes
KEY STUDIES IN PE TREATMENT

- 1937 Murry: first use of heparin
- 1960 Barritt: “RCT” warfarin vs. placebo
- 1968 Sasahara: UPET
- 2003 Konstantinides: Alteplase
Treatment - Anticoagulation

- Begin treatment with either unfractionated heparin or LMWH, then switch to warfarin (Prevents additional thrombus formation and permits endogenous fibrinolytic mechanisms to lyse clot that has already been formed, Does NOT directly dissolve thrombus that already exists)

- It is important that a patient should be anticoagulated with heparin before initiating warfarin therapy

- Target INR is 2 – 3
Recommendations for Initial Anticoagulation for Acute PE (AHA/ASC 2011)

- Therapeutic anticoagulation with subcutaneous LMWH, intravenous or subcutaneous UFH with monitoring, unmonitored weight-based subcutaneous UFH, or subcutaneous fondaparinux should be given to patients with objectively confirmed PE and no contraindications to anticoagulation (Class I; Level of Evidence A)

- Therapeutic anticoagulation during the diagnostic workup should be given to patients with intermediate or high clinical probability of PE and no contraindications to anticoagulation (Class I; Level of Evidence C)
I/V UF Heparin

- 80 units/kg bolus (minimum, 5000 units; maximum, 10,000 units) followed by a continuous infusion of 18 units/kg/h
- aPTT monitoring is required
### Intravenous Unfractionated Heparin

**“Raschke Nomogram”**

<table>
<thead>
<tr>
<th>Activated partial thromboplastin time</th>
<th>Change of dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;35 s (&lt;1.2 times control)</td>
<td>80 U/kg bolus; increase infusion rate by 4 U/kg/h</td>
</tr>
<tr>
<td>35–45 s (1.2–1.5 times control)</td>
<td>40 U/kg bolus; increase infusion rate by 2 U/kg/h</td>
</tr>
<tr>
<td>46–70 s (1.5–2.3 times control)</td>
<td>No change</td>
</tr>
<tr>
<td>71–90 s (2.3–3.0 times control)</td>
<td>Reduce infusion rate by 2 U/kg/h</td>
</tr>
<tr>
<td>&gt;90 s (&gt;3.0 times control)</td>
<td>Stop infusion for 1 h, then reduce infusion rate by 3 U/kg/h</td>
</tr>
</tbody>
</table>
Subcutaneous UFH

- **Subcutaneous UFH: aPTT monitoring**
  - 15,000 units or 17,500 units every 12 h (initial dose for patients weighing 50–70 kg and >70 kg, respectively)

- **Subcutaneous UFH: no aPTT monitoring**
  - 330 units/kg bolus then 250 units/kg every 12 h
<table>
<thead>
<tr>
<th>NAME</th>
<th>STATUS</th>
<th>MOLECULAR WEIGHT</th>
<th>ANTI-Xa/ANTI-IIa RATIO</th>
<th>TREATMENT DOSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enoxaparin</td>
<td>FDA approved for DVT treatment</td>
<td>4800</td>
<td>3.9</td>
<td>1 mg/kg twice daily (approved as an inpatient or outpatient dose), or 1.5 mg/kg once daily (inpatient dose only)</td>
</tr>
<tr>
<td>Dalteparin</td>
<td>FDA approved for cancer-associated DVT</td>
<td>5000</td>
<td>2.2</td>
<td>100 units/kg twice daily, or 200 units/kg once daily</td>
</tr>
<tr>
<td>Nadroparin</td>
<td>Not available in the United States</td>
<td>4500</td>
<td>3.5</td>
<td>4100 units twice daily for patients weighing &lt;50 kg, 6150 units twice daily for 50-70 kg, and 9200 units twice daily for &gt;70 kg</td>
</tr>
<tr>
<td>Reviparin</td>
<td>Not available in the United States</td>
<td>3900</td>
<td>3.3</td>
<td>3500 units twice daily for patients weighing 35-45 kg, 4200 units twice daily for 46-60 kg, and 6300 units twice daily for &gt;60 kg</td>
</tr>
<tr>
<td>Tinzaparin</td>
<td>FDA approved for DVT treatment</td>
<td>4500</td>
<td>1.5</td>
<td>175 units/kg once daily</td>
</tr>
</tbody>
</table>
COLUMBUS

Trial Design: COLUMBUS was a multi-center randomized trial of low-molecular-weight heparin (LMWH; reviparin) compared with unfractionated heparin (UFH) in patients with venous thromboembolism. Patients were followed for 12 weeks. The primary endpoints were recurrent thromboembolic events and major bleeding at 12 weeks.

<table>
<thead>
<tr>
<th>Recurrent Thromboembolism</th>
<th>Major Bleeding</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>p=NS</td>
<td>p=NS</td>
<td>p=NS</td>
</tr>
</tbody>
</table>

Results

- There was no significant difference between LMWH and UFH in the occurrence of recurrent thromboembolic events, major bleeding, or mortality
- Met pre-specified criteria for non-inferiority in recurrent thromboembolism

Conclusions

- Among patients with venous thromboembolism, fixed-dose subcutaneous LMWH was as effective as intravenous UFH in the initial treatment of venous thromboembolism without a significant increase in the rate of major bleeding or mortality

1997;337(10):657-662

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Fondaparinux

- Anticoagulant pentasaccharide that specifically inhibits activated factor X
- By selectively binding to antithrombin, fondaparinux potentiates (about 300 times) the neutralization of factor Xa by antithrombin
- Fondaparinux does not cross-react with heparin-induced antibodies
- FDA has approved fondaparinux for initial treatment of acute PE and acute DVT as a bridge to oral anticoagulation with warfarin

<table>
<thead>
<tr>
<th>Patient weight</th>
<th>&lt;50 kg</th>
<th>50-100 kg</th>
<th>&gt;100 kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily dose of fondaparinux*</td>
<td>5 mg</td>
<td>7.5 mg</td>
<td>10 mg</td>
</tr>
</tbody>
</table>
Fondaparinux vs Unfractionated Heparin for Pulmonary Embolism

Trial Design: The trial was a randomized, open-label trial of fondaparinux (s.c. 5.0, 7.5, or 10.0 mg/day in patients weighing <50, 50-100, or >100 kg, respectively; n=1,103) or i.v. unfractionated heparin (aPTT 1.5-2.5 times control; n=1,110) in patients with acute symptomatic pulmonary embolism. The primary endpoint was composite of symptomatic, recurrent pulmonary embolism and new or recurrent deep-vein thrombosis at 3 month follow-up.

Results
- 14.5% of patients in fondaparinux arm received outpatient treatment
- Absolute difference in recurrent thromboembolic events −1.2% (95% CI −3.0 to 0.5), demonstrating noninferiority of fondaparinux to UFH
- No difference in major bleeding (Figure) or mortality between treatment arms (5.2% with fondaparinux vs 4.4% with UFH, absolute difference 0.8%, 95% CI −1.0 to 2.6)

Conclusions
- Among patients with acute symptomatic pulmonary embolism, treatment with fondaparinux was noninferior compared with unfractionated heparin for the primary endpoint of recurrent pulmonary embolism and new or recurrent deep-vein thrombosis
- Fondaparinux regimen allows for fixed-dose, once-daily subcutaneous injection without need for monitoring, unlike unfractionated heparin, which requires continuous IV infusion with laboratory monitoring and dose titration
- Further studies comparing fondaparinux with low-molecular weight heparins are warranted

Use of Heparin Before and After Thrombolysis

1. Discontinue the continuous infusion of intravenous UFH as soon as the decision has been made to administer thrombolysis.
2. Proceed to order thrombolysis. Use the U.S. Food and Drug Administration–approved regimen of alteplase 100 mg as a continuous infusion during 2 hours.
3. Do not delay the thrombolysis infusion by obtaining an activated partial thromboplastin time (aPTT).
4. Infuse thrombolysis as soon as it becomes available.
5. At the conclusion of the 2-hour infusion, obtain a stat aPTT.
6. If the aPTT is 80 seconds or less (which is almost always the case), resume UFH as a continuous infusion without a bolus.
7. If the aPTT exceeds 80 seconds, hold off from resuming heparin for 4 hours and repeat the aPTT. At this time, the aPTT has virtually always declined to <80 seconds. If this is the case, resume continuous infusion of intravenous UFH without a bolus.
Novel Anticoagulants

- Promise immediate onset of action and administration in fixed doses without routine laboratory coagulation monitoring
- These drugs have few drug-drug or drug-food interactions, making them more “user friendly”
- Dabigatran is a direct thrombin inhibitor
- Rivaroxaban is a factor Xa inhibitor
- Both are approved in Canada and Europe for VTE prevention after knee or hip arthroplasty
**RECORD3**

**Trial Design:** RECORD3 was a randomized, double-blind trial of rivaroxaban (10 mg orally per day; n = 1,254), a novel direct factor Xa inhibitor, vs. enoxaparin (40 mg subcutaneous per day; n = 1,277) for the prevention of venous thromboembolism (VTE) in patients undergoing elective total knee replacement surgery. Primary endpoint was deep vein thrombosis (DVT), pulmonary embolism (PE), or death by day 42.

**Results**
- Primary composite endpoint ↓ with rivaroxaban vs. enoxaparin (Figure), driven by reduction in DVT (9.6% vs. 18.2%, p < 0.001)
- PE was infrequent but ↓ with rivaroxaban (0 vs. 0.5%, p = 0.06)
- Symptomatic VTE ↓ in rivaroxaban group (0.7% vs. 2.0%, p = 0.005)
- In safety cohort, no difference in major bleeding (Figure) or any bleeding (4.9% vs. 4.8%)

**Conclusions**
- Among patients undergoing total knee replacement surgery, treatment with the novel anticoagulant rivaroxaban was associated with reductions in DVT and symptomatic VTE vs. enoxaparin, with no difference in bleeding
- Other studies with rivaroxaban are underway in settings of acute coronary syndrome and atrial fibrillation
- RECORD3 provided information on rivaroxaban in the venous system; ongoing trials will provide insight into rivaroxaban in the arterial system

RE-COVER

**Trial design:** Evaluated the safety and efficacy of dabigatran 150 mg twice daily vs. warfarin for the treatment of acute VTE. Patients were followed for 6 months.

**Results**
- Primary outcome (recurrent VTE or death due to VTE): 2.4% vs. 2.1%
- Mortality: 1.6% vs. 1.7% (p > 0.05)
- Major bleeding: 1.6% vs. 1.9%; Major + clinically relevant bleeding: 5.6% vs. 8.8% (p = 0.002)

**Conclusions**
- Dabigatran 150 mg twice daily is noninferior to warfarin for the treatment of acute VTE, with a slightly better bleeding profile
- Complements other studies showing safety and efficacy of dabigatran, as compared with warfarin in other settings, such as AF

ACC 2012: EINSTEIN PE: Oral rivaroxaban for the treatment of symptomatic PE

EINSTEIN–PE

Trial design: Patients with symptomatic PE were randomized to rivaroxaban 15 mg twice daily for 3 weeks, then 20 mg daily (n = 2,420) versus usual care with enoxaparin 1 mg/kg twice daily, then a vitamin K antagonist with goal INR 2-3 (n = 2,413).

Results

- Recurrent venous thromboembolism: 2.1% of the rivaroxaban group vs. 1.8% of the usual care group (p for noninferiority = 0.003)
- Major or clinically relevant nonmajor bleeding: 10.3% vs. 11.4% (p = 0.23)
- Major bleeding: 1.2% vs. 2.2% (p = 0.003)

Conclusions

- Among patients with acute symptomatic PE, the use of fixed-dose rivaroxaban was noninferior to usual care with enoxaparin/vitamin K antagonist in the prevention of recurrent venous thromboembolism
- Bleeding was similar or slightly reduced with rivaroxaban

## Optimal Duration of Anticoagulation

<table>
<thead>
<tr>
<th>CLINICAL SETTING</th>
<th>RECOMMENDATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>First provoked PE/proximal leg DVT</td>
<td>3 to 6 months</td>
</tr>
<tr>
<td>First provoked upper extremity DVT or isolated calf DVT</td>
<td>3 months</td>
</tr>
<tr>
<td>Second provoked VTE</td>
<td>Uncertain</td>
</tr>
<tr>
<td>Third VTE</td>
<td>Indefinite duration</td>
</tr>
<tr>
<td>Cancer and VTE</td>
<td>Consider indefinite duration or until cancer is resolved</td>
</tr>
<tr>
<td>Unprovoked PE/proximal leg DVT</td>
<td>Consider indefinite duration</td>
</tr>
<tr>
<td>First unprovoked calf DVT</td>
<td>3 months</td>
</tr>
<tr>
<td>Second unprovoked calf DVT</td>
<td>Uncertain</td>
</tr>
</tbody>
</table>
Treatment (cont)-- *Thrombolysis*

- Thrombolysis
  - 1. Hemodynamically compromised by PE – definitive indication
  - 2. Pulmonary hypertension or right ventricular dysfunction detected by echocardiography, pulmonary arterial catheterization.
Thrombolysis of a massive pulmonary embolism

A 52-year-old man with bilateral proximal deep venous thrombosis developed multiple episodes of arterial desaturation and increasing oxygen requirements despite anticoagulation with heparin. A computed tomographic angiogram shows a large saddle embolus at the bifurcation of the main pulmonary artery, with extension into the right and left pulmonary arteries (arrow in Panel A). Following treatment with intravenous tissue plasminogen activator, the patient's respiratory status dramatically improved over a period of several hours. Computed tomography obtained approximately 24 hours later demonstrates resolution of the saddle embolus (Panel B). Reproduced with permission from: Fam, NP, Verma, A. Thrombolysis of a massive pulmonary embolism. N Engl J Med, 2002; 347:1161. Copyright © 2002 Massachusetts Medical Society.
AGREEMENT AND CONTROVERSY

- Massive or major PE: Thrombolytic therapy is indicated
- Submassive (non-massive) PE: Thrombolytic therapy may be indicated in the presence of RV dysfunction
MAPPET-3

Trial Design: MAPPET-3 was a randomized, placebo-controlled trial (n=256) designed to compare the effects of treatment with heparin plus alteplase vs. heparin alone on the outcome of hemodynamically stable patients with acute submassive pulmonary embolism (PE) and pulmonary hypertension and/or right ventricular dysfunction. Primary Endpoint: In-hospital death or clinical deterioration that required an escalation of treatment.

Results
- Right ventricular dysfunction 31% in both arms, and PA pressures were similar
- Although rate of in-hospital death similar in both study arms, rate of escalation of treatment because of clinical deterioration ↑ in heparin alone group vs alteplase/heparin group (24.6% vs. 10.2%, p=0.004)
- This was primarily due to ↑ in secondary (rescue) thrombolysis performed in heparin alone group vs alteplase/heparin group (Figure)
- Bleeding complications generally infrequent, and occurred with similar frequency in both groups

Conclusions
- Among hemodynamically stable patients with acute submassive PE and pulmonary hypertension and/or right ventricular dysfunction, treatment with alteplase and heparin was associated with a reduction in death or escalation of therapy when compared to heparin alone
- Results driven almost entirely by reduction in escalation of treatment, with no difference in mortality or other endpoints

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NEJM 2002; 347: 1143-1150
ACC/AHA Recommendations

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

2. 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 \((\text{Class IIb; Level of Evidence C})\).

3. Fibrinolysis is not recommended for patients with low-risk PE \((\text{Class III; Level of Evidence B})\) or submassive acute PE with minor RV dysfunction, minor myocardial necrosis, and no clinical worsening \((\text{Class III; Level of Evidence B})\).

4. Fibrinolysis is not recommended for undifferentiated cardiac arrest \((\text{Class III; Level of Evidence B})\).
# Thrombolytic agents

<table>
<thead>
<tr>
<th>Fibrinolytic</th>
<th>FDA Indication for PE?</th>
<th>Direct Plasminogen Activator?</th>
<th>Fibrinolytic Dose</th>
<th>Fibrin Specificity (Relative to Fibrinogen)</th>
<th>PAI Resistance*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Streptokinase</td>
<td>Yes</td>
<td>No</td>
<td>250 000-IU IV bolus followed by 100 000-IU/h infusion for 12–24 h</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Urokinase</td>
<td>Yes</td>
<td>No</td>
<td>4400-IU/kg bolus, followed by 4400 IU·kg⁻¹·h⁻¹ for 12–24 h</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Alteplase</td>
<td>Yes</td>
<td>Yes</td>
<td>100-mg IV infusion over 2 h</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Reteplase</td>
<td>No</td>
<td>Yes</td>
<td>Double 10-U IV bolus† 30 min apart</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Tenecteplase</td>
<td>No</td>
<td>Yes</td>
<td>Weight-adjusted IV bolus over 5 s (30–50 mg with a 5-mg step every 10 kg from &lt;60 to &gt;90 kg)</td>
<td>+++</td>
<td>+++</td>
</tr>
</tbody>
</table>
At present, the alteplase regimen in which 100 mg is administered intravenously over two hours is the most rapidly administered protocol that is currently approved for use in the United States.
CONTRAINDICATIONS

These should be particularly scrutinized if lytic therapy is considered.

Contraindications to Thrombolytic Therapy in Pulmonary Embolism

**Absolute**
- Hemorrhagic stroke
- Active intracranial neoplasm
- Recent (< 2 months) intracranial surgery or trauma
- Active or recent internal bleeding in prior 6 months

**Relative**
- Bleeding diathesis
- Uncontrolled severe hypertension (systolic BP >200 mmHg or diastolic BP >110 mmHg)
- Cardiopulmonary resuscitation
- Nonhemorrhagic stroke within prior 2 months
- Surgery within the previous 10 days
- Thrombocytopenia (<100,000 platelets per mm$^3$)
General guidelines for administration

Guidelines for Thrombolytic Therapy in Venous Thromboembolism

- Clear documentation of PE (or DVT)†
- Potential contraindications carefully reviewed
- Delivery by peripheral intravenous infusion
- Initiate or continue other supportive therapy
- Discontinue heparin during thrombolytic infusion

†High-probability ventilation-perfusion scan or positive pulmonary arteriogram
About administration

- **Intravenous route**
  -- primary method of delivery

- **Rapid infusion**
  -- Shorter regimens may not only prove efficacious but also reduce the risk of hemorrhagic complications

- **Catheter-directed therapy**
  -- for massive PE, may induce major bleeding
Potential Benefits and Harm

- **Potential benefits include**
  - More rapid resolution of symptoms (e.g., dyspnea, chest pain, and psychological distress)
  - Stabilization of respiratory and cardiovascular function without need for mechanical ventilation or vasopressor support
  - Reduction of RV damage
  - Improved exercise tolerance
  - Prevention of PE recurrence
  - Increased probability of survival
● Potential harm includes

- Disabling or fatal hemorrhage including intracerebral hemorrhage
- Increased risk of minor hemorrhage, resulting in prolongation of hospitalization and need for blood product replacement
Catheter-Based Interventions

- Performed as an alternative to thrombolysis
  - When there are contraindications
  - When emergency surgical thrombectomy is unavailable or contraindicated
  - Hybrid therapy that includes both catheter-based clot fragmentation and local thrombolysis is an emerging strategy

- Goals of catheter-based therapy include
  - Rapidly reducing pulmonary artery pressure, RV strain, and pulmonary vascular resistance (PVR)
  - Increasing systemic perfusion
  - Facilitating RV recovery
3 general categories of percutaneous intervention
  - Aspiration thrombectomy
  - Thrombus fragmentation
  - Rheolytic thrombectomy
VARIOUS DEVICES

- The Greenfield embolectomy catheter
- Balloon angioplasty and stents
- Pigtail rotational catheter
- Amplatz thrombectomy device (ATD)
- Hydrodynamic thrombectomy catheter devices
- Aspirex pulmonary embolism thrombectomy catheter
Catheter-directed therapy

- **Local delivery of streptokinase**
  -- Extensive lysis (by perfusion scan and pulmonary arteriography at 12 to 24 hour follow-up)

- **Intrapulmonary versus peripheral alteplase**
  -- no advantage over the intravenous route

- **Direct delivery into clot**
  -- Enhanced thrombolysis, relatively low doses (in an animal model of PE)
  -- Could prove advantageous over the intravenous route
Recommendations (AHA 2011)

1. Depending on local expertise, either catheter embolectomy and fragmentation or surgical embolectomy is reasonable for patients with massive PE and contraindications to fibrinolysis (Class IIa; Level of Evidence C).

2. Catheter embolectomy and fragmentation or surgical embolectomy is reasonable for patients with massive PE who remain unstable after receiving fibrinolysis (Class IIa; Level of Evidence C).

3. For patients with massive PE who cannot receive fibrinolysis or who remain unstable after fibrinolysis, it is reasonable to consider transfer to an institution experienced in either catheter embolectomy or surgical embolectomy if these procedures are not available locally and safe transfer can be achieved (Class IIa; Level of Evidence C).
Surgical Embolectomy

- When contraindications preclude thrombolysis
- Surgical excision of a right atrial thrombus
- Rescue patients whose condition is refractory to thrombolysis
- Older case series suggest a mortality rate between 20% and 30%
- In a more recent study, 47 patients underwent surgical embolectomy in a 4-year period, with a 96% survival rate

Am Heart J 2011;134:479-87
4. Either catheter embolectomy or surgical embolectomy may be considered for patients with submassive acute PE judged to have clinical evidence of adverse prognosis (new hemodynamic instability, worsening respiratory failure, severe RV dysfunction, or major myocardial necrosis) \( (\text{Class IIb; Level of Evidence C}) \).

5. Catheter embolectomy and surgical thrombectomy are not recommended for patients with low-risk PE or submassive acute PE with minor RV dysfunction, minor myocardial necrosis, and no clinical worsening \( (\text{Class III; Level of Evidence C}) \).
Inferior Vena Cava Filters

- PREPIC Trial randomized 400 patients with proximal DVT at high risk for PE
- IVC filters significantly reduced the incidence of recurrent PE at 12 days (1.1% versus 4.8%, P = 0.03) and at 8 years (6.2% versus 15.1%, P = 0.008)
- IVC filters were associated with an increased incidence of recurrent DVT at 2 years (20.8% versus 11.6%, P = 0.02)
PREPIC

Trial Design: PREPIC was a multi-center randomized trial of the efficacy of venal caval filters, unfractionated heparin (UFH) and low-molecular weight heparin in preventing pulmonary embolus (PE) in patients with proximal deep-vein thrombosis (DVT). Patients were assessed at 12 days and at 2 years.

Results
- Rate of PE ↓ in filter group at 12 days (Figure)
- PE occurred in 1.6% of low-molecular weight heparin group vs 4.2% of UFH group (p=0.14)
- At 2 years, recurrent DVT ↑ in filter group (Figure)
- No major differences in death or major bleeding

Conclusions
- Among patients with proximal deep vein thrombosis, placement of a vena caval filter was associated with a decreased incidence of pulmonary embolism at 12 days but an increase in recurrent deep-vein thrombosis at 2 years

Limitations
- Follow-up was limited to symptomatic PE/DVT
Various inferior vena caval filters-
A Greenfield filter
B Titanium Greenfield filter
C Simon-Nitinol filter
D LGM or Vena Tech filter
E Amplatz filter
F Bird’s Nest filter
G Günther filter

(Adapted from Becker et al.)
Complications associated with IVC filter

Early complications
- Device malposition (1.3%)
- Pneumothorax (0.02%)
- Hematoma (0.6%)
- Air embolism (0.2%)
- Inadvertent carotid artery puncture (0.04%)
- Arteriovenous fistula (0.02%)

Late complications
- Recurrent DVT (21%)
- IVC thrombosis (2% to 10%)
- IVC penetration (0.3%)
- Filter migration (0.3%)
Recommendations on IVC Filters in the Setting of Acute PE

1. Adult patients with any confirmed acute PE (or proximal DVT) with contraindications to anticoagulation or with active bleeding complication should receive an IVC filter (Class I; Level of Evidence C).
2. Anticoagulation should be resumed in patients with an IVC filter once contraindications to anticoagulation or active bleeding complications have resolved (Class I; Level of Evidence B).
3. Patients who receive retrievable IVC filters should be evaluated periodically for filter retrieval within the specific filter’s retrieval window (Class I; Level of Evidence C).
4. For patients with recurrent acute PE despite therapeutic anticoagulation, it is reasonable to place an IVC filter (Class IIa; Level of Evidence C).
Recommendations on IVC Filters in the Setting of Acute PE

5. For DVT or PE patients who will require permanent IVC filtration (eg, those with a long-term contraindication to anticoagulation), it is reasonable to select a permanent IVC filter device (Class IIa; Level of Evidence C).

6. For DVT or PE patients with a time-limited indication for an IVC filter (eg, those with a short-term contraindication to anticoagulation therapy), it is reasonable to select a retrievable IVC filter device (Class IIa; Level of Evidence C).

7. Placement of an IVC filter may be considered for patients with acute PE and very poor cardiopulmonary reserve, including those with massive PE (Class IIb; Level of Evidence C).

8. An IVC filter should not be used routinely as an adjuvant to anticoagulation and systemic fibrinolysis in the treatment of acute PE (Class III; Level of Evidence C).
Table 12  Routinely available clinical predictors of 30-day all-cause mortality in patients with acute PE

<table>
<thead>
<tr>
<th>Variable</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1/year</td>
</tr>
<tr>
<td>Male sex</td>
<td>10</td>
</tr>
<tr>
<td>Cancer</td>
<td>30</td>
</tr>
<tr>
<td>Heart failure</td>
<td>10</td>
</tr>
<tr>
<td>Chronic lung disease</td>
<td>10</td>
</tr>
<tr>
<td>Heart rate $&gt;110$/min</td>
<td>20</td>
</tr>
<tr>
<td>Systolic blood pressure $&lt;100$ mmHg</td>
<td>30</td>
</tr>
<tr>
<td>Respiratory rate $\geq 30$/min</td>
<td>20</td>
</tr>
<tr>
<td>Body temperature $&lt;36^\circ$ C</td>
<td>20</td>
</tr>
<tr>
<td>Disorientation, lethargy, stupor, coma</td>
<td>60</td>
</tr>
<tr>
<td>$\text{SaO}_2$ $&lt;90%$</td>
<td>20</td>
</tr>
</tbody>
</table>

Data are from reference 214.
Risk categories (30-day all-cause mortality, %): class I, $<65$ points (0%); class II, 66–85 points (1%); class III, 86–105 points (3.1%); class IV, 106–125 points (10.4%); class V, $>125$ points (24.4%). Low risk = classes I and II (0–1%).  
$\text{SaO}_2$ = pulsoximetry.
**ICOPER DATA**

Figure 1: Cumulative mortality through 90 days in 108 patients with systolic blood pressure (SBP) < 90 mm Hg and in 2,284 patients with SBP ≥ 90 mm Hg at presentation.
## Prevention of PE

<table>
<thead>
<tr>
<th></th>
<th>Procedures</th>
<th>Medication Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Hospitalization with medical illness</td>
<td>Enoxaparin 40 mg SC qd or Dalteparin 5000 units SC qd or Fondaparinux 2.5 mg SC qd (in patients with a heparin allergy such as heparin-induced thrombocytopenia) or Graduated compression stockings or intermittent pneumatic compression</td>
</tr>
<tr>
<td>2</td>
<td>General surgery</td>
<td>Unfractionated heparin 5000 units SC bid or tid or Enoxaparin 40 mg SC qd or Dalteparin 2500 or 5000 units SC qd</td>
</tr>
<tr>
<td>3</td>
<td>Major orthopedic surgery</td>
<td>Warfarin (target INR 2 to 3) or Enoxaparin 30 mg SC bid or Enoxaparin 40 mg SC qd or Dalteparin 2500 or 5000 units SC qd or Fondaparinux 2.5 mg SC qd Rivaroxaban 10 mg qd (in Canada and Europe) Dabigatran 220 mg bid (in Canada and Europe)</td>
</tr>
</tbody>
</table>
## Prevention of PE

<table>
<thead>
<tr>
<th></th>
<th>Procedure</th>
<th>Prevention Measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>Oncologic surgery</td>
<td>Enoxaparin 40 mg SC qd</td>
</tr>
<tr>
<td>5</td>
<td>Neurosurgery</td>
<td>Unfractionated heparin 5000 units SC bid or</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Enoxaparin 40 mg SC qd and</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Graduated compression stockings or intermittent pneumatic compression</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Consider surveillance lower extremity ultrasonography</td>
</tr>
<tr>
<td>6</td>
<td>Thoracic surgery</td>
<td>Unfractionated heparin 5000 units SC tid and</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Graduated compression stockings or intermittent pneumatic compression</td>
</tr>
</tbody>
</table>
Few Indian literature on VTE
Thrombolytic Therapy in Acute and Subacute PTE

Dr. Rajendra Kumar Jain, Dr. P.A. Jiwani, Dr. D.S. Rao, Dr. T.N. C. Padmanabhan, Dr. G. Ravi Kanth, Dr. V.S. Srinath, Dr. Vasanth, Dr. Sidharth, Dr. Sachin, Dr. Sudhakar, Dr. Vinay B
Dept. of Cardiology, KIMS, Tumkur

Background: Thrombolytic therapy has benefits in patients with acute and subacute PTE.

Methods and Results: 27 cases of acute & subacute PTE presented to KIMS. The major presenting complaints were shortness of breath & patient had surgery (−30 days in 2, within 5 days in 2), syncope in 2 & 1 patient had past history of PTE. The diagnosis was established by echocardiography and pulmonary CT Angiography. 12 patients were received weight adjusted dose of tenecteplase, streptokinase (2.5 lakh bolus over 30 min followed by 1 lakh slow infusion for 2 hr), TPA & urokinase in one, three & two patients respectively. All patient tolerated tenecteplase, STK & urokinase well without any major bleeding complications except two patients (immediately post op) developed bleeding & there was significant improvement in breathlessness, reduction in HR, improvement in hemodynamic status & regression of RV pressure. 2 patients out of 3 who received TPA died, while one patient developed severe bleeding, IVC Filter was implanted in 2 patient. All the patients are under clinical follow up & on oral anticoagulation.

Conclusion: IV thrombolytic therapy (bolus tenecteplase, STK, Urokinase) in treatment of acute and subacute PTE is safe and associated with improvement in symptomatic and hemodynamic status. Improvement was early with tenecteplase, TPA was associated with increased mortality.

Keywords: Pulmonary Thromboembolism, Tenecteplase, Streptokinase.

PULMONARY THROMBOEMBOLISM IN A TERTIARY CARE HOSPITAL – A DESCRIPTIVE STUDY

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Background: Pulmonary thromboembolism (PTE) is an important cause of mortality in hospitalized patients. The aim of the current study was to analyze retrospectively the clinical presentation, therapy offered and outcome in patients with PTE.

Methods: The hospital records of patients diagnosed to have PTE based on Wells score, clinical features and echocardiography or computed tomography (CT) between September 2005 and June 2009 were analyzed.

Results: Twenty four patients (17 Male, 7 female) with pulmonary embolism were identified. The mean age was 40.9±14.2 years. The predisposing conditions were Deep Vein Thrombosis (n=14), prolonged immobilization (n=9), malignancy (n=4) and Prothrombotic states (n=3). The presenting symptoms and signs were dyspnea (n=23), angina (n=11), Leg swelling (n=15), Tachypnoea (n=20), Tachycardia (n=16), hypoxia (n=15), and palpitations (n=5). Hypotension was the presenting feature in three patients. Wells score was predictive of pulmonary embolism in non-cancer patients. Echocardiogram showed RA, RV dilatation in twenty one patients, and intra cardiac thrombi in two patients. The mean RVSP was 58.1±22.12 mm Hg. Mammomullar's sign was present in 13 cases. Contrast CT thorax was diagnostic in the 19 patients in which it was performed. Thrombolysis was done in 3 patients. Three patients died in spite of thrombolysis. Anticoagulation with heparin was given in twenty two patients. Of the twenty four patients treated eight patients (33.3%) died. Inferior Vena Cava (IVC) filter was deployed in one patient. The mean Geneva score in patients who survived was 1.8 and 3.37 in the group who died.

Conclusion: A high index of suspicion has to be maintained for diagnosing pulmonary embolism. Echocardiography is an important tool which helps in decision making in the appropriate clinical setting when emergency CT is not available. Prompt therapy is life saving in most cases.

Keywords: Pulmonary Thromboembolism, Inferior Vena Cava, Echocardiography.
A prospective study of risk factor profile & incidence of deep venous thrombosis among medically-ill hospitalized patients at a tertiary care hospital in northern India


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Background & objectives: Hospitalization for medical-illness is associated with an increased risk of deep venous thrombosis (DVT). However, there are no published data from India addressing at this issue. We sought to study the risk factor profile and the incidence of DVT among hospitalized medically-ill patients, a tertiary care hospital in northern India.

Methods: All adults admitted to the medical wards and intensive care unit with level 1 or 2 mobility over a period of two years (July 2006 to July 2008) at the All India Institute of Medical Sciences hospital, New Delhi, were prospectively studied. Patients having DVT at admission or an anticipated hospital stay less than 48 h were excluded. The presence of clinical risk factors for DVT was recorded and laboratory evaluation was done for hypercoagulable state. A routine surveillance venous compression Doppler ultrasonography was performed 12 ± 8 days after hospital admission.

Results: Of the 163 patients, 77 (47%) had more than one risk factor for DVT. Five (3%) patients developed DVT; none of them had symptomatic DVT. None of these patients received anticoagulation prior to the development of DVT. The mean age of those who developed DVT was 40 ± 13 (25-50) yr; two of five were male. The incidence rate of DVT was 2.7 per 1000 person-days of hospital stay [95% confidence interval (CI): 0.87 to 6.27]. None of the factors was found to be significantly associated with the risk of DVT.

Interpretation & conclusions: In our setting, although many hospitalized medically-ill patients had risk factors for DVT, the absolute risk of DVT was low compared to the western population but clearly elevated compared to non-hospitalized patients. Large studies from India are required to confirm our findings.

Key words Deep venous thrombosis - intensive care unit - medical illness - pulmonary embolism - venous compression ultrasonography
Is routine thromboprophylaxis justified among Indian patients sustaining major orthopedic trauma? A systematic review

Ramesh K Sen, Sujit K Tripathy, Amit K Singh

ABSTRACT
Venous thromboembolism (VTE) is one of the most common preventable cause of morbidity and mortality after trauma. Though most of the western countries have their guidelines for thromboprophylaxis in these patients, India still does not have these. The increasing detection of VTE among Indian population, lack of awareness, underestimation of the risk, and fear of bleeding complications after chemical prophylaxis have made deep vein thrombosis (DVT) a serious problem, hence a standard guideline for thromboprophylaxis after trauma is essential. The present review article discusses the incidence of DVT and role of thromboprophylaxis in Indian patients who have sustained major orthopedic trauma. A thorough search of ‘PubMed’ and ‘Google Scholar’ revealed 10 studies regarding venous thromboembolism in Indian patients after major orthopedic trauma surgery (hip or proximal femur fracture and spine injury). Most of these studies have evaluated venous thromboembolism in patients of arthroplasty and trauma. The incidence, risk factors, diagnosis and management of VTE in the subgroup of trauma patients (1049 patients) were separately evaluated after segregating them from the arthroplasty patients. Except two studies, which were based on spinal injury, all other studies recommended screening/thromboprophylaxis in posttraumatic conditions in the Indian population. Color Doppler was used as common diagnostic or screening tool in most of the studies (eight studies, 722 patients). The incidence of VTE among thromboprophylaxis-receiving group was found to be 8% (10/125), whereas it was much higher (14.49%, 40/276) in patients not receiving any form of prophylaxis. Indian patients have definite risk of venous thromboembolism after major orthopedic trauma (except spinal injury), and thromboprophylaxis either by chemical or mechanical methods seems to be justified in them.

Key words: Thromboprophylaxis, trauma, venous thromboembolism
Conclusion

Summary Points

- Pulmonary Emboli remain a potentially deadly and common event which may present in various ways
- Don't’ be fooled if your patient lacks the “classic” signs and symptoms!
- Consider PE in any patient with an unexplainable cause of dyspnea, pleuritic chest pain, or findings of tachycardia, tachpnea, or hypoxemia
- 2nd Generation Qualitative D-Dimers have NPV of 93-99%
- Heparin remains the mainstay of therapy with the initiation of Warfarin to follow
- Simplified Algorithm: (Pretest probability, D-Dimer, +/- CT angio), then disposition
Just wait only 4 more slides........

Know something about a great scientist who gave us a lot in VTE--------Rudolph Virchow
Rudolf Virchow

- Born in Pomerania 1821
- graduated in medicine 1843
- presented work on thrombosis 1845 but could not get it published
- founded own journal
This is the first page of the original manuscript, which consists of this narrative introduction entitled “Wichtigste Arbeiten” followed by the chronological outline. Ackerknecht in his biography of Virchow called the manuscript a curriculum vitae. The form of the manuscript however is more akin to a simple autobiographical piece of work. Virchow used one single sheet of 81/2” by 11” paper that was folded in half with the “Most Important Works” as the front cover and the inside right half of the page and the reverse of that right half of the page containing the chronological outline.
Rudolf Virchow

- Appointed Professor of Pathology in Wurzburg
- Described leukaemia, pulmonary embolism and much more
- 1856 appointed Professor of Pathology in Berlin despite government opposition
Rudolf Virchow

- 1858 published ‘Cellular Pathology’ one of the most influential medical books ever written
- Died aged 81 after fracturing his hip jumping from a moving tram
THANK YOU