DVT and Pulmonary Embolism
Overview

- Historical Perspective
- Risk Stratification and Pathway
- Diagnostic Tools
- Treatment Tools
- Prophylaxis
- Special Situations
  - Pregnancy
  - Thrombolysis
  - Vena Cava Filters
**Heparin Treatment of Thrombosis and Pulmonary Embolism at the Mariestad Hospital, Sweden, 1940–1946**

<table>
<thead>
<tr>
<th></th>
<th>No Treatment 1929–1938</th>
<th>Heparin Treatment October 1, 1940–September 30, 1946</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients admitted</td>
<td>25,628</td>
<td>20,002</td>
</tr>
<tr>
<td>Number of thrombosis cases</td>
<td>264</td>
<td>258*</td>
</tr>
<tr>
<td>Fatal embolism</td>
<td>47</td>
<td>3</td>
</tr>
<tr>
<td>Mortality in thrombosis cases</td>
<td>18 p.c.</td>
<td>1.1 p.c.</td>
</tr>
<tr>
<td>Average duration of stay in bed</td>
<td>40 days</td>
<td>4.6 days</td>
</tr>
<tr>
<td>Disabling after-effects</td>
<td>Serious</td>
<td>None or very slight</td>
</tr>
</tbody>
</table>

*104 patients were admitted to the Mariestad Hospital on account of thrombosis.

Look--no P value! This is not science!
Evidence Based Medicine

ANTICOAGULANT DRUGS IN THE TREATMENT OF PULMONARY EMBOLISM
A CONTROLLED TRIAL

D. W. Barritt
M.D. Lond., M.R.C.P.

S. C. Jordan
M.B. Brist.

From the Departments of Medicine and Cardiology,
United Bristol Hospitals

The diagnosis of pulmonary embolism is rarely proved before death. The diagnosis in life rests on a combination of symptoms and signs in the chest and legs and changes in the radiogram and electrocardiogram; and in the less severe cases the diagnosis is more uncertain. For this reason it is unsatisfactory to compare results in series reported by different workers.
The Cult of the $p$ Value

Bringing the Technology of Yesterday...to the Patients of Tomorrow!

TABLE II—RESULTS IN FIRST 35 CASES

<table>
<thead>
<tr>
<th>Group</th>
<th>Total</th>
<th>Deaths from pulmonary embolism</th>
<th>Non-fatal recurrences</th>
<th>Other deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Untreated</td>
<td>19</td>
<td>5</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Treated</td>
<td>16</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

First Stage of Trial (35 cases)

An analysis of the results (table II) showed that the difference in deaths in the two groups from pulmonary embolism was unlikely to be due to chance: $p = 0.036$ (1 in 28). When deaths from pulmonary embolism and non-fatal recurrences were taken together the result was convincing: $p = 0.0005$ (1 in 1987).
The Clotting Cascade

Extrinsic Pathway
- Tissue Factor
- VII
- IX
- X
- V
- II
- I
- Fibrin
- Thrombin

Intrinsic Pathway
- VIII
- XII

Initiation
- Green arrows

Amplification
- Red arrows
Anticoagulants

Tissue Factor

+ + +

IX VII VIII XII

Initiation

Amplification

Blockade

Low Molecular Wt Heparin

Unfractionated Heparin
Anticoagulants

- Factor Xa Inhibitors
  - Rivaroxiban
  - Apixiban
  - Fondaparinux
  - Idraparinux

- Direct Thrombin Inhibitors
  - Argatroban
  - Dabigatran
  - Hirudin
  - Bilivalirudin

- Tissue Factor

- VII

- IX

- VIII

- XII

- Factor Xa Inhibitors

- Direct Thrombin Inhibitors

Initiation

Amplification

Blockade
Inactivation of clotting enzymes by heparin. Top, ATIII is a slow inhibitor without heparin. Middle, Heparin binds to ATIII through a high-affinity pentasaccharide and induces a conformational change in ATIII, thereby converting ATIII from a slow inhibitor to a very rapid inhibitor. Bottom, ATIII binds covalently to the clotting enzyme, and the heparin dissociates from the complex and can be reused. AT = antithrombin. (Reprinted with permission from Hirsh et al.7)
### EFFECTS ON HEART
- Increased RV afterload
  - Decreased stroke volume
  - Hypotension, tachycardia
- Increased RV pressure and dilatation
  - RV infarction
- Reduced cardiac output
  - Shock
  - Hypoxemia

Shock and hypoxemia are direct effects of the embolus on the heart.

### EFFECTS ON LUNG
- Increased dead space
  - Hyperventilation
- Pulmonary infarction
  - Hemoptysis
  - Chest pain
- Low V/Q ratio in non-obstructed areas, bronchospasm (?)
  - Hypoxemia

Hypoxemia is an indirect effect of the embolus on the lung.
Approach to Diagnosis/Treatment

- Assess Risk
  - Make treatment decision
- Assess Physiologic Stability
  - Make disposition decision
- Diagnostic Testing
  - If positive, continue treatment
- Assess Residual Risk

Diagram:
- Risk Factors
- Physiologic Stability
- Disposition Treatment
- Chest film EKG
- Residual Risk
- Initial Imaging
- Final Imaging
Clinical Decision Making

- 500--mostly hospitalized--patients
- Patients clinically classified into low (10%), medium (50%), and high (90%) probability of PE
- Historical risk factors, symptoms, signs, EKG/X-ray data
- Relative weights assigned
- Validated on additional 250 patients

# Historical Risk Factors

## TABLE 1

<table>
<thead>
<tr>
<th>Preexisting Disease</th>
<th>PE Present $(n = 202)$</th>
<th>PE Absent $(n = 298)$</th>
<th><strong>p</strong> Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PE Present $(n = 202)$</td>
<td>PE Absent $(n = 298)$</td>
<td><strong>p</strong> Value</td>
</tr>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td></td>
</tr>
<tr>
<td>Preexisting disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>53 (26)</td>
<td>96 (32)</td>
<td>0.18</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>14 (7)</td>
<td>72 (24)</td>
<td>&lt; 0.000001</td>
</tr>
<tr>
<td>Neoplastic*</td>
<td>36 (18)</td>
<td>43 (14)</td>
<td>0.37</td>
</tr>
<tr>
<td>Endocrine</td>
<td>21 (10)</td>
<td>32 (11)</td>
<td>0.98</td>
</tr>
<tr>
<td>Risk factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immobilization $&gt; 3$ d $^\dagger$</td>
<td>119 (59)</td>
<td>138 (46)</td>
<td>0.007</td>
</tr>
<tr>
<td>Surgery $^\dagger$</td>
<td>81 (40)</td>
<td>116 (39)</td>
<td>0.72</td>
</tr>
<tr>
<td>Thrombophlebitis (ever)</td>
<td>69 (34)</td>
<td>57 (19)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Bone fractures (lower limb) $^\dagger$</td>
<td>46 (23)</td>
<td>36 (12)</td>
<td>0.002</td>
</tr>
<tr>
<td>Estrogen use</td>
<td>1 (0.5)</td>
<td>1 (0.3)</td>
<td>1.0</td>
</tr>
<tr>
<td>Pregnancy/postpartum</td>
<td>1 (0.5)</td>
<td>4 (1)</td>
<td>0.34</td>
</tr>
</tbody>
</table>

* Clinically active malignancy with pathologic diagnosis within 3 mo of study entry.

$^\dagger$ Within 4 wk of study entry.
## TABLE 2

### SYMPTOMS AND SIGNS IN 500 PATIENTS WITH CLINICALLY SUSPECTED PULMONARY EMBOLISM (PE)

<table>
<thead>
<tr>
<th></th>
<th>PE Present (n = 202)</th>
<th>PE Absent (n = 298)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>(%)</td>
<td>n</td>
</tr>
<tr>
<td>Symptoms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnea (sudden onset)</td>
<td>158</td>
<td>(78)</td>
<td>87</td>
</tr>
<tr>
<td>Dyspnea (gradual onset)</td>
<td>12</td>
<td>(6)</td>
<td>59</td>
</tr>
<tr>
<td>Orthopnea</td>
<td>2</td>
<td>(1)</td>
<td>27</td>
</tr>
<tr>
<td>Chest pain (pleuritic)</td>
<td>89</td>
<td>(44)</td>
<td>89</td>
</tr>
<tr>
<td>Chest pain (substernal)</td>
<td>33</td>
<td>(16)</td>
<td>29</td>
</tr>
<tr>
<td>Fainting</td>
<td>53</td>
<td>(26)</td>
<td>38</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>19</td>
<td>(9)</td>
<td>16</td>
</tr>
<tr>
<td>Cough</td>
<td>22</td>
<td>(11)</td>
<td>45</td>
</tr>
<tr>
<td>Palpitations</td>
<td>36</td>
<td>(18)</td>
<td>46</td>
</tr>
<tr>
<td>Signs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tachycardia &gt; 100/min</td>
<td>48</td>
<td>(24)</td>
<td>69</td>
</tr>
<tr>
<td>Cyanosis</td>
<td>33</td>
<td>(16)</td>
<td>44</td>
</tr>
<tr>
<td>Hypotension &lt; 90 mm Hg</td>
<td>6</td>
<td>(3)</td>
<td>5</td>
</tr>
<tr>
<td>Neck vein distention</td>
<td>25</td>
<td>(12)</td>
<td>28</td>
</tr>
<tr>
<td>Leg swelling (unilateral)</td>
<td>35</td>
<td>(17)</td>
<td>27</td>
</tr>
<tr>
<td>Fever &gt; 38 °C</td>
<td>14</td>
<td>(7)</td>
<td>63</td>
</tr>
<tr>
<td>Crackles</td>
<td>37</td>
<td>(18)</td>
<td>76</td>
</tr>
<tr>
<td>Wheezes</td>
<td>8</td>
<td>(4)</td>
<td>39</td>
</tr>
<tr>
<td>Pleural friction rub</td>
<td>8</td>
<td>(4)</td>
<td>11</td>
</tr>
</tbody>
</table>
## Risk Factors in Retrospect

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age $\geq$ 40 years</td>
<td>88.5</td>
</tr>
<tr>
<td>Obesity</td>
<td>37.8</td>
</tr>
<tr>
<td>History of venous thromboembolism</td>
<td>26.0</td>
</tr>
<tr>
<td>Cancer</td>
<td>22.3</td>
</tr>
<tr>
<td>Bed rest $\geq$ 5 days</td>
<td>12.0</td>
</tr>
<tr>
<td>Major surgery</td>
<td>11.2</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>8.2</td>
</tr>
<tr>
<td>Varicose veins</td>
<td>5.8</td>
</tr>
<tr>
<td>Fracture (hip or leg)</td>
<td>3.7</td>
</tr>
<tr>
<td>Estrogen treatment</td>
<td>2.0</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.8</td>
</tr>
<tr>
<td>Multiple trauma</td>
<td>1.1</td>
</tr>
<tr>
<td>Childbirth</td>
<td>1.1</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>0.7</td>
</tr>
<tr>
<td>One or more risk factors</td>
<td>96.3</td>
</tr>
<tr>
<td>Two or more risk factors</td>
<td>76.0</td>
</tr>
<tr>
<td>Three or more risk factors</td>
<td>39.0</td>
</tr>
</tbody>
</table>

Risk Factors—Mayo Clinic

Odds ratios (and 95% confidence intervals) of risk factors for definite deep vein thrombosis or pulmonary embolism among Olmsted County, Minnesota, residents with a first lifetime venous thromboembolism (VTE) diagnosed from 1976 through 1990. CHF indicates congestive heart failure.
# Wells Criteria for Predicting PE

**Clinical Characteristic** | **Score**
--- | ---
Previous PE or DVT | +1.5
Heart rate >100 beats per minute | +1.5
Recent surgery or immobilization (within the last 30 d) | +1.5
Clinical signs of DVT | +3
Alternative diagnosis less likely than PE | +3
Hemoptysis | +1
Cancer (treated within the last 6 mo) | +1

**Clinical Probability of Pulmonary Embolism** | **Score**
--- | ---
Low | 0-1
Intermediate | 2-6
High | ≥7

Summary of Risk Assessment

- Wells is a good start
- Refine your assessment with:
  - Age
  - Obesity
  - Vascular interventions
  - Remote leg fractures
  - Suddenness of onset
  - Other pulmonary diseases (weigh against Dx)
Most common: atelectasis

Hampton’s Hump
- Triangular pleural based opacity
- Pulmonary Infarct

Westermark’s Sign
- Absence of visible blood vessels in embolized area
Westermark’s Sign, 37 yo F
Findings:
- low lung volumes, cardiomegaly, shift to left,
- mediastinal widening (hematoma), retrocardiac atelectasis
Regrettably…not often present.

The main benefit of chest film and EKG in the diagnosis of pulmonary embolism is excluding other diagnoses.
### Physiologic Stability

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>Cardiac Output</th>
<th>Oxygenation</th>
<th>Disposition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High</strong></td>
<td>HR &gt;110</td>
<td>Pulse ox:</td>
<td>ICU</td>
</tr>
<tr>
<td></td>
<td>Cap refill &gt;3 secs</td>
<td>&lt;80% on RA</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cool, clammy skin</td>
<td>&lt;90% on 3L NC</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Urine output &lt;0.5 cc/kg/hr</td>
<td>&lt;45 on RA</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hypotension</td>
<td>&lt;65 on 3L NC</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Elevated neck veins</td>
<td>pO2: &gt;65 on RA</td>
<td></td>
</tr>
<tr>
<td><strong>Medium</strong></td>
<td>HR 90-110 at rest</td>
<td>Pulse ox:</td>
<td>Ward</td>
</tr>
<tr>
<td></td>
<td>Tachycardia with exertion</td>
<td>&lt;92% on RA</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hypotension responsive to small fluid bolus (1 L)</td>
<td>&gt;90% on 3L NC</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No oxygen requirement</td>
<td>pO2: &lt;65 on RA</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rise &lt;20 bpm with ambulation</td>
<td>&gt;65 on 3L NC</td>
<td></td>
</tr>
<tr>
<td><strong>Low</strong></td>
<td>HR 60-90 at rest</td>
<td>No oxygen requirement</td>
<td>Outpatient</td>
</tr>
</tbody>
</table>
TREATMENT AND DISPOSITION

TREAT

All patients except:
- where contraindicated
- both low risk and physiologically stable

Use:
- Low molecular weight heparin
- Unfractionated heparin 80 units/kg bolus
  - timely dose titration
- Factor Xa inhibitor

DISPOSITION

High risk: ICU
Moderate: Ward
Low risk: Observation
TREATMENT

- Unfractionated heparin
- LMWH
- Factor Xa Inhibitors
- Warfarin
- Aspirin
## Dosing Unfractionated Heparin

**Initial Bolus:** 80 U/Kg  
**Initial Maintenance:** 18 U/Kg/hr

<table>
<thead>
<tr>
<th>APTT</th>
<th>Bolus, U/kg</th>
<th>Hold, min</th>
<th>Rate change, U/kg/hr</th>
<th>Repeat APTT</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;45</td>
<td>80</td>
<td>0</td>
<td>+4</td>
<td>6 hr</td>
</tr>
<tr>
<td>45-75</td>
<td>40</td>
<td>0</td>
<td>+2</td>
<td>6 hr</td>
</tr>
<tr>
<td>76-100</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>6 hr</td>
</tr>
<tr>
<td>101-125</td>
<td>0</td>
<td>0</td>
<td>-2</td>
<td>6 hr</td>
</tr>
<tr>
<td>&gt;125</td>
<td>0</td>
<td>60</td>
<td>-3</td>
<td>6 hr</td>
</tr>
</tbody>
</table>

“The most common mistake with heparin dosing is the choice of an inadequate maintenance dose.”

For stroke patients, recommended bolus is 70U/kg and maintenance 15U/kg/hr

Chest 1998; 114:561S-578S
Low Molecular Wt. Heparins

Table 1. Heparin and LMWH Preparations Evaluated in Clinical Trials as Prophylaxis or Treatment for DVT*

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Trade Name</th>
<th>Mean Molecular Weight (daltons)</th>
<th>Anti-Xa:Anti-IIa Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heparin</td>
<td>—</td>
<td>15,000</td>
<td>1:1</td>
</tr>
<tr>
<td>Enoxaparin†</td>
<td>Lovenox</td>
<td>4500</td>
<td>2.7:1</td>
</tr>
<tr>
<td></td>
<td>Clexane</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dalteparin</td>
<td>Fragmin</td>
<td>5000</td>
<td>2:1</td>
</tr>
<tr>
<td>Nadroparin</td>
<td>Fraxiparine</td>
<td>4500</td>
<td>3.2:1</td>
</tr>
<tr>
<td>Tinzaparin</td>
<td>Logiparin</td>
<td>4500</td>
<td>1.9:1</td>
</tr>
<tr>
<td>Danaparoid‡</td>
<td>Orgaran</td>
<td>6500</td>
<td>2:1</td>
</tr>
</tbody>
</table>

*The majority of large clinical trials have been with these agents.
†Approved for use in the United States.
‡Low-molecular-weight heparinoid (ORG 10172).
Low Molecular Weight Heparin

- Simplified dosing
- Eliminates monitoring (for most patients)
- Proven safe and effective in DVT patients
- May reduce mortality (in DVT)

- Slow onset of action
- Not reversible
- Expensive
Enoxaparin Dosing

- 1 mg/kg actual body weight SQ BID
- Little literature on morbidly obese patients
  - ? Adequate absorption/effectiveness
  - Dose adjustments now exist--rely on lower water content of fatty tissue
- Caution in renal failure—reduce dose
The optimist

- 233 patients, Canada
- University-based hospitals
- Exclusions:
  - Other illness requiring hosp. >48 hrs: 20
  - Refused to pay for LMWH: 6
  - Other (bleeding, massive PE, etc.): 13
- Still eligible for outpatient Rx: 194 (83%)
Feasibility of Outpatient Rx

The pessimist

- 107 patients, inner-city hospital
- 38% transferred from long term care facilities
- Exclusions:
  - Other illness requiring hosp. >48 hrs: 42
  - Likely poor compliance: 14
  - Other (bleeding, etc.): 14
- Still eligible for outpatient Rx: 37 (35%)
Feasibility of Outpatient Rx

The historian

Heparin has been given in three or four daily intravenous injections, 100 to 125 or 150 mg. each time. Usually 350 to 450 mg. of a sodium salt with 80 Toronto units per milligram are given a day. The effect is not controlled by any blood analyses except for special cases, e.g. elderly persons with impaired renal function. Consequently heparin treatment can be given at any hospital, even the smallest ones, and if necessary, at the home of the patient. The bleeding tendency is not very pronounced.

Beyond Heparin

- Direct Thrombin Inhibitors
  - Dabigatran—effective but excess bleeding
  - Hirudin, Bilivalirudin, Argatroban—parenteral; indicated for HIT
- Factor Xa Inhibitors
  - Fondaparinux—parenteral
  - Rivaroxaban
  - Apixiban
STUDY DESIGN

- Patients with acute DVT or PE
- Randomized to
  - Unfractionated, adjusted IV heparin
  - SC Fondaparinux 5, 7.5, or 10 mg daily (by body weight)
- Converted to Warfarin once INR > 2.0
- Followed for three months

MAIN POINTS

Outcomes about equal

**Table 3. Clinical Outcomes during the Study Period.**

<table>
<thead>
<tr>
<th>Population</th>
<th>Fondaparinux</th>
<th>Unfractionated Heparin</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients randomly assigned to a study group</td>
<td>1103</td>
<td>1110</td>
</tr>
<tr>
<td>Recurrent venous thromboembolism — no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Initial treatment</td>
<td>14 (1.3)</td>
<td>19 (1.7)</td>
</tr>
<tr>
<td>- Entire study</td>
<td>42 (3.8)</td>
<td>56 (5.0)</td>
</tr>
<tr>
<td>Type of recurrence — no.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Fatal pulmonary embolism</td>
<td>16</td>
<td>15</td>
</tr>
<tr>
<td>- Nonfatal pulmonary embolism</td>
<td>14</td>
<td>24</td>
</tr>
<tr>
<td>- Deep-vein thrombosis only</td>
<td>12</td>
<td>17</td>
</tr>
<tr>
<td>Patients as treated</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of patients</td>
<td>1092</td>
<td>1092</td>
</tr>
<tr>
<td>Major bleeding — no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Initial treatment</td>
<td>14 (1.3)</td>
<td>12 (1.1)</td>
</tr>
<tr>
<td>- Entire study</td>
<td>22 (2.0)</td>
<td>26 (2.4)</td>
</tr>
<tr>
<td>Clinically relevant nonmajor bleeding only — no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Initial treatment</td>
<td>35 (3.2)</td>
<td>57 (5.2)</td>
</tr>
<tr>
<td>- Entire study</td>
<td>62 (5.7)</td>
<td>92 (8.4)</td>
</tr>
<tr>
<td>Death — no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Initial treatment</td>
<td>9 (0.8)</td>
<td>12 (1.1)</td>
</tr>
<tr>
<td>- Entire study</td>
<td>57 (5.2)</td>
<td>48 (4.4)</td>
</tr>
</tbody>
</table>

NEJM 349;18 Oct 30, 2003
Apixiban (AMPLIFY Study)

**STUDY DESIGN**
- Double blind, randomized controlled trial
- Sponsored by manufacturer
- 5400 patients
- Randomized to adjusted-dose warfarin vs. fixed dose apixiban
- Duration: 6 months

**MAIN POINTS**
- Apixiban:
  - 2.3% recurrence (vs 2.7%)
  - 0.8% major bleeding (vs 1.8%)

NEJM 369:9 August 29, 2013
It looks like no dropout, but we never see the number of patients screened and excluded.

So what do you do for the first five days?
Apixiban Summary

- Not inferior to warfarin
- May reduce bleeding
- 10 mg po bid x 7 days, then 5 mg po bid

- Cancer patients excluded from study
- Patients with Cr > 2.5 excluded from study
- Cytochrome P450 3A4 interactions
- Not for acute crisis
Aspirin as Add-On: WARFASA

- 400 patients
  - Completed warfarin for DVT/PE
- Randomized:
  - ASA 100 mg/day
  - Placebo
- Duration: two years
- Reduced recurrent VTE by about 40%

NEJM 366;21, May 24, 2012
## Table 2. Outcome Events According to Study Group.*

<table>
<thead>
<tr>
<th>Event</th>
<th>Aspirin (N= 205)</th>
<th>Placebo (N=197)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent VTE</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total episodes</td>
<td>28</td>
<td>43</td>
<td>0.58 (0.36–0.93)</td>
<td>0.02</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>11</td>
<td>14</td>
<td>0.70 (0.32–1.54)</td>
<td>0.37</td>
</tr>
<tr>
<td>Fatal pulmonary embolism</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deep-vein thrombosis</td>
<td>16</td>
<td>28</td>
<td>0.51 (0.27–0.94)</td>
<td>0.03</td>
</tr>
<tr>
<td>Episodes during treatment</td>
<td>23</td>
<td>39</td>
<td>0.55 (0.33–0.92)</td>
<td>0.02</td>
</tr>
<tr>
<td>Bleeding</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major bleeding or clinically relevant nonmajor bleeding</td>
<td>4</td>
<td>4</td>
<td>0.98 (0.24–3.96)</td>
<td>0.97</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>1</td>
<td>1</td>
<td>0.98 (0.24–3.96)</td>
<td>0.97</td>
</tr>
<tr>
<td>Clinically relevant nonmajor bleeding</td>
<td>3</td>
<td>3</td>
<td>0.98 (0.24–3.96)</td>
<td>0.97</td>
</tr>
<tr>
<td>Death</td>
<td>6</td>
<td>5</td>
<td>1.04 (0.32–3.42)</td>
<td>0.95</td>
</tr>
<tr>
<td>Recurrent VTE or death</td>
<td>33</td>
<td>47</td>
<td>0.62 (0.40–0.97)</td>
<td>0.04</td>
</tr>
<tr>
<td>Arterial event</td>
<td>8†</td>
<td>5‡</td>
<td>1.43 (0.47–4.37)</td>
<td>0.53</td>
</tr>
<tr>
<td>Recurrent VTE or arterial event</td>
<td>36</td>
<td>48</td>
<td>0.67 (0.43–1.03)</td>
<td>0.06</td>
</tr>
</tbody>
</table>

* CI denotes confidence interval, and VTE venous thromboembolism.
† These events included two acute myocardial infarctions (after discontinuation of the study drug), two episodes of unstable angina, two ischemic strokes, one transient ischemic attack, and one episode of acute lower-limb ischemia.
‡ These events included two acute myocardial infarctions (after discontinuation of the study drug), one ischemic stroke, and two episodes of acute lower-limb ischemia.
DIAGNOSTICS

- Ultrasound
- D-dimer
- CT-angiogram
- V/Q scan
- Echocardiogram
Many patients with PE have detectable DVT and vice versa
Not the initial study of choice (not enough overlap, does not assess severity of pulmonary embolism); need a pulmonary imaging study first
Does not assess pelvic veins
Two negative studies one week apart: risk of DVT in next 90 days < 1%
Not safe to withhold heparin on single doppler alone

The Low-Risk Patient: D-Dimers

- A degradation product of crosslinked fibrin
- Non-specific—many causes of elevation
  - +D-dimer does not make the Dx of PE!
- ELISA test performs well in excluding PE in outpatients (Swiss study, 1997)
- Focus use on:
  - Outpatients, no recent history of surgery, delivery; no cancer Dx, normal BUN.
D-Dimer in Outpatient Screening

- 671 consecutive patients in Emergency Center of Geneva University Hospital
- Patients with negative workup followed without anticoagulation for three months.
- Not all patients underwent PA gram
- Prevalence of PE 29%
- 198 negative D-dimers
- 1 false negative, 1 lost to follow up.
Sensitivity Training

![Graph showing Sensitivity and Specificity (%) across different age groups.

Age groups: < 30, 30-39, 40-49, 50-59, 60-69, 70-79, ≥ 80.

- Sensitivity (%):
  - < 30: 70%
  - 30-39: 60%
  - 40-49: 50%
  - 50-59: 40%
  - 60-69: 30%
  - 70-79: 20%
  - ≥ 80: 10%

- Specificity (%):
  - < 30: 80%
  - 30-39: 70%
  - 40-49: 60%
  - 50-59: 50%
  - 60-69: 40%
  - 70-79: 30%
  - ≥ 80: 20%

Number of patients:

- < 30: 63
- 30-39: 52
- 40-49: 92
- 50-59: 88
- 60-69: 112
- 70-79: 155
- ≥ 80: 109

Number of patients with PE:

- < 30: 11
- 30-39: 5
- 40-49: 17
- 50-59: 15
- 60-69: 46
- 70-79: 60
- ≥ 80: 42


D-Dimer: Choosing a Cutoff
D-Dimer and Uremia

![Graph showing D-dimer levels in different conditions: healthy, hypertension, angina pectoris, and uremia. The levels are compared with statistical significance (P-values: 0.0001, 0.0001, 0.0001).](image-url)
• D-dimer mandated at Brigham/Women’s as initial eval for pts suspected of PE
• 1100 tests: 559 elevated, 547 normal
• Only two false negatives
• 24% of patients with negative D-dimers got imaging tests…

JACC 40(8): 1475-8, 2002 Oct 16
The Moderate-Risk Patient

V/Q scan vs. CT angiogram

**V/Q scan**
- Long track record
- Excellent outcome studies (PIOPED)
- Only decisive if high-prob or normal
- Large number of indeterminate tests (60-80%)
- No contrast load

**CT Angiogram**
- Now the default study
- Does not show subsegmental emboli well
- May make other diagnoses
- Home of the nodule clinic
CT-A of Massive Embolism

37-year-old F
Sudden onset dyspnea
Chest pain
Pulse ox 88% RA
28 yo AD soldier
Cross-country travel
Chest pain
Normal CXR
+ D-dimer

Hounsfield unit
measurement
much lower than
similarly sized
nearby vessel.
23 year old F
Myasthenia Gravis
s/p redo thymectomy
c/b by phrenic nerve injury
To ER with:
Shortness of breath
Chest pain

CT-A of a complex case
23 year old F

Myasthenia Gravis

s/p redo thymectomy

c/b by phrenic nerve injury

To ER with:

- Shortness of breath
- Chest pain

CT-A of a complex case

Non-con CT

CT Angio
• 1015 patients: 285 underwent CT, 527 underwent V/Q scan
• 3 month follow up on patients with negative scans (including autopsy records and death records in neighboring counties)
• Subsequent PE in:
  • 2/198 patients with negative CT-A
  • 0/188 patients with negative V/Q
  • 5/162 patients with low-prob V/Q

Radiology 2000; 215:535-542
CT Venogram

- Keep the patient in the scanner 3-5 minutes longer
- Image from IVC to popliteal veins
- Overall 10% incidence of DVT detected
- Sensitivity good; must have adequate opacification of veins
Pulmonary Arteriogram

- The default “gold standard”
- Interobserver variability in subsegmental vessels
- Modest risk: requires central venous puncture and sheath placement
- Selective preferable to non-selective (use V/Q or CT-A to find area of interest)
- PERMITS INVASIVE THERAPIES

The High-Risk Patient

- Known risk factors, compatible symptoms, and physiologic instability
- Bedside echocardiogram
  - Exclude other diagnoses (tamponade, acute MI)
  - Assess RV distension and pressure
- Consider thrombolysis without definitive diagnosis by CT angiogram
Fig. 2. Echocardiographic 4-chamber views of a patient with massive PE and RV dysfunction in end-diastole (A) and in end-systole (B). Arrows indicate normally contracting apical segments in a globally hypokinetic right ventricle (McConnell sign). LA, left atrium; LV, left ventricle; RA, right atrium, and RV, right ventricle. (From Casazza F, Bongarzoni A, Capozi A, et al. Regional right ventricular dysfunction in acute pulmonary embolism and right ventricular infarction. Eur J Echocardiogr 2005;6[1]:11–4; with permission.)
Thrombolysis

Acute Pulmonary Embolism

Persistent hypotension or shock?

High-risk (massive) PE

Thrombolysis (if contraindicated: surgical or interventional embolectomy)
Unfractionated heparin

Non-high-risk PE

RV dysfunction (echocardiography, MDCT, natriuretic peptides) and/or

Myocardial injury (cardiac troponins, H-FABP)

Intermediate-risk PE

LMWH or fondaparinux
No routine thrombolysis (can be given in selected cases)
Hemodynamic monitoring

Low-risk PE

LMWH or fondaparinux
No thrombolysis (Home treatment at present not indicated)
Best current choice in US is Alteplase. This can be given with unfractionated heparin.

Tenecteplase reasonable alternative.
Thrombolysis: Serial Echo

Lancet 341:507-511, 1993 (Goldhaber first author)
Case series: 13 patients with angiographically proven PE

- CI < 2.5 L/m²
- Intervention: 500 cc dextran over 20 mins

<table>
<thead>
<tr>
<th></th>
<th>pre</th>
<th>post</th>
</tr>
</thead>
<tbody>
<tr>
<td>CI</td>
<td>1.6</td>
<td>2.0</td>
</tr>
<tr>
<td>RAP</td>
<td>9</td>
<td>17</td>
</tr>
<tr>
<td>RVvol</td>
<td>123</td>
<td>150</td>
</tr>
</tbody>
</table>

Crit Care Medicine
1999 Mar
27(3): 540-4
106 consecutive patients with confirmed acute PE
Troponin I elevated in 41%
TnI associated with echocardiographic evidence of RV dysfunction
Elevated mortality and greater risk of recurrent PE in patients with TnI > 1.5

Circulation 106 (10): 1263-8  2002 Sep 3
Both hormonal and mechanical causes

Leading cause of maternal death in developed world

1.1 – 1.5 deaths per 100,000 deliveries

C-section raises risks

DVT in left leg 70-80% of time

May—Thurner Syndrome

Treatment data are observational series

Avoid warfarin (birth defects)

NEJM 359;19 2008
## Risk Factors for VTE in Pregnancy

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Prevalence (%)</th>
<th>Odds Ratio for VTE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt; 35</td>
<td>19</td>
<td>1.5</td>
</tr>
<tr>
<td>Nulliparity</td>
<td>56</td>
<td>1.7</td>
</tr>
<tr>
<td>Gestational DM</td>
<td>2.3</td>
<td>4.1</td>
</tr>
<tr>
<td>Multiple Pregnancy</td>
<td>6.6</td>
<td>2.4</td>
</tr>
<tr>
<td>Assisted Reproduction</td>
<td>6.6</td>
<td>4.4</td>
</tr>
<tr>
<td>C- Section</td>
<td>25 (?)</td>
<td>2.5--20</td>
</tr>
<tr>
<td>Factor V Leiden</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Homozygous</td>
<td>2.0—7.0</td>
<td>9</td>
</tr>
<tr>
<td>Heterozygous</td>
<td>0.2—0.5</td>
<td>34</td>
</tr>
<tr>
<td>Prothrombin G20210A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Homozygous</td>
<td>2.0</td>
<td>7</td>
</tr>
<tr>
<td>Heterozygous</td>
<td>Rare</td>
<td>26</td>
</tr>
<tr>
<td>AT III deficiency</td>
<td>&lt;0.1—0.6</td>
<td>5</td>
</tr>
<tr>
<td>Prot S deficiency</td>
<td>0.2—0.3</td>
<td>5</td>
</tr>
<tr>
<td>Prot C deficiency</td>
<td>&lt;0.1—0.1</td>
<td>3</td>
</tr>
</tbody>
</table>

Data are combined from the two articles cited in lecture.
May-Thurner Syndrome

Formation of Collaterals

Compression of left iliac vein by right iliac artery
Case-control registry study from Norway.

615 cases
613,000 pregnancies

Am J OBGYN
198(2), Feb 2008
Prophylaxis for C-section

- Risk Assessment for all
- Treatment for at least six weeks post-partum
- LMWH is probably best

Table 4. Risk Assessment for Thromboembolism in Patients Who Undergo Cesarean Section.*

<table>
<thead>
<tr>
<th>Low risk: early ambulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cesarean delivery for uncomplicated pregnancy with no other risk factors</td>
</tr>
<tr>
<td>Moderate risk: low-molecular-weight heparin or compression stockings</td>
</tr>
<tr>
<td>Age &gt;35 yr</td>
</tr>
<tr>
<td>Obesity (BMI &gt;30)</td>
</tr>
<tr>
<td>Parity &gt;3</td>
</tr>
<tr>
<td>Gross varicose veins</td>
</tr>
<tr>
<td>Current infection</td>
</tr>
<tr>
<td>Preeclampsia</td>
</tr>
<tr>
<td>Immobility for &gt;4 days before operation</td>
</tr>
<tr>
<td>Major current illness</td>
</tr>
<tr>
<td>Emergency cesarean section during labor</td>
</tr>
<tr>
<td>High risk: low-molecular-weight heparin and compression stockings</td>
</tr>
<tr>
<td>Presence of more than two risk factors from the moderate-risk section</td>
</tr>
<tr>
<td>Cesarean hysterectomy</td>
</tr>
<tr>
<td>Previous deep-vein thrombosis or known thrombophilia</td>
</tr>
</tbody>
</table>

* BMI denotes body-mass index (the weight in kilograms divided by the square of the height in meters).
ACCP Guidelines recognize three categories:

- **Hospitalized non-surgical patients**
  - Few risk factors—no prophylaxis
  - Risk factors present—mechanical or pharmacological prophylaxis

- **General surgical patients**
  - Mechanical prophylaxis in low risk
  - Mechanical plus pharmacological prophylaxis otherwise

- **Orthopedic surgical patients**
  - Mechanical plus pharmacological prophylaxis

Guidelines are very detailed. This is a broad overview.
• DVT incidence about 5% in flights over 10 hours (high risk patients)
• LONFLIT 3: 300 patients, mean age 47
  • Control: 4.8% DVT
  • Aspirin prophylaxis: 3.6% DVT
  • Enoxaparin: 0 DVT, 1 superficial thrombosis
• Get the aisle seat. . .

Angiology 53(1):1-6, 2002 Jan-Feb
Directed Thrombolysis

- 51 patient series--assigned by patient choice to standard Rx of iliofemoral DVT or thrombolysis/stenting
- Usual contraindications to lytics; also no lytics in patients with clot >14 days old or chronic DVT

Usual caveats about selection bias apply. No mortality difference. No increased intracranial bleeds.

### Directed Thrombolysis: DVT

**Table 2. CLINICAL OUTCOME**

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (n = 33)</th>
<th>Group 2 (n = 18)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-day patency</td>
<td>1 (3%)</td>
<td>15 (83%)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>6-month patency</td>
<td>8 (24%)</td>
<td>15 (83%)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Long-term symptom resolution</td>
<td>10 (30%)</td>
<td>14 (78%)</td>
<td>.0015</td>
</tr>
</tbody>
</table>
Directed Thrombolysis: PE

Figure 4. Schematic drawing demonstrating the effect of mechanical fragmentation of a total occlusive central thrombus in the pulmonary artery, before (a) and after (b) mechanical fragmentation and dispersion of the smaller clots into the peripheral branches of the pulmonary artery. Fragmentation and distal dispersion is likely to reduce pulmonary artery pressure and increase total pulmonary perfusion. Note that a number of peripheral branches of the pulmonary artery are open after fragmentation of the thrombus.
Directed Thrombolysis: PE

- 57 year old F: syncope, 88% sat on 15 L
- HR 120, BP 92/50
- CT-PA: saddle emboli
- PA gram: pressures 73/18
- TNK total 20 mg directly into clots
  - (usual dose for MI ca. 50 mg)
- Final PA pressures 36/16
Vena Cava Filters

• Twenty year experience reported by L J Greenfield--642 patients; 140 lost to followup
  • Recurrent PE--4%
  • Vena Cava patency--96%
  • Movement of filter--8% (usually minimal)
  • Lower extremity ulceration--6%
• Filter can be placed from jugular or femoral position
• No procedural deaths
• Median survival after placement: 72 months

Cardiovascular Surgery Vol. 3: 199-205, 1995
Trauma & Prophylactic VCF

- 110 patients at a trauma center, 0.7% of “admissions” for 1991-1995
- Usual indications:
  - pelvic fx
  - multiple long bone fx
  - spinal cord injury with deficit
  - head injury (GCS <8) with immobilization
- Minimal acute complications
- No recurrent emboli
- No benefit for phlebitis

Vena Cava Filters and Mortality

- Retrospective study
- Chart review only
- Data source: “National Inpatient Sample”
- “Unstable” defined as a chart containing a code for shock or ventilator dependence

Figure 1  In-hospital all-cause case fatality rate in patients with pulmonary embolism who received a vena cava filter and those who did not. Patients are shown according to whether they were stable or unstable, and whether they received thrombolytic (lytic) therapy. Case fatality rate was lower with a vena cava filter in each group (P < .0001). PE = pulmonary embolism; VC = vena cava.

The American Journal of Medicine (2012) 125, 478-484
Heparin/Coumadin Overlap

- The INR isn’t everything.
- Must inactivate thrombin in the clot
  - Heparin does this; Factor Xa inhibitors do help
  - Coumadin simply reduces the factors available to form clot
  - INR would probably be different if a big chunk of clot were sent to the lab in the test tube.

- New ACCP guidelines: start with 10 mg Coumadin for first two days
- Five days overlap
Summary

- Assess Risk
  - History
  - Symptoms
- Assess physiologic stability
  - Oxygen
  - Cardiac Output
- Heparin unless low risk or contraindicated
  - 53% recurrence rate and 26% mortality if not treated*
- CT PA best initial test
- Lytics controversial—but better to employ early than late
- New respect for vena cava filters in unstable patients

*Lancet 1960; 1: 1309-1312