Updates in Management of Pulmonary Embolism (PE)

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Hilton Head, SC
Objectives

• Highlight clinical features and presentation of acute PE

• Analyze strategies for diagnosis of PE

• Analyze strategies for risk stratification of acute PE

• Describe treatment strategies for acute PE

• Describe long-term follow-up for patients with acute PE

• Identify future directions in study of acute PE
BACKGROUND
Pulmonary Embolism (PE): Why it Matters

• PE is **common**
  – 1-2 cases per 1000 people per year
    • Incidence rising
  – 200-300K hospitalizations annually
  – Annual economic burden in US = $7-10 billion

*J Am Coll Card 2016;67:976
Lancet 2016;388:3060*
Pulmonary Embolism (PE): Why it Matters

• **PE is **deadly
  – Estimated all-cause mortality rate: 9-20%
  – PE-specific mortality rate: 2%

• **PE is **treatable
  – Timely treatment saves lives
    • PE-specific mortality rate: <0.5% with treatment
  – Timely diagnosis essential to initiate treatment

Arch Intern Med 2003;163:1711
Circulation 2008;117:171
Lancet 2016; 388: 3060–73
NEJM 2016;366:1287
NEJM 1992;326:1240-1245
Cochrane Database of Syst Review 2015;12:CD010957
DIAGNOSIS

PRE-TEST CLINICAL ASSESSMENT
- Revised Geneva score
- Wells rule
- Empirical assessment

DIAGNOSIS
- (Age-adjusted) D-dimers
- CTPA
- V/Q scan
- Echocardiography
- CUS

ALGORITHM FOR HIGH-RISK PE
- CTPA
- Echocardiography (if CTPA not readily available or uncontrolled hypotension)

ALGORITHM FOR NON HIGH-RISK PE
- CTPA
- V/Q scan
- CUS-based algorithms

HIGH CLINICAL PROBABILITY
- Hemodynamic Instability

LOW OR INTERMEDIATE CLINICAL PROBABILITY
- Absence of hemodynamic instability
- Age-adjusted positive d-dimers
48 yo F presents with chest pain, productive cough, dyspnea

History of lupus and prior DVT 4 years ago
No recent surgery or hospitalization

BP 135/80; HR 90; RR 16; 100% RA; Temp 38
No signs of DVT on exam

What is the probability of PE?

a) Low
b) Intermediate
c) High
Case #1

48 yo F presents with chest pain, productive cough, dyspnea

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No recent surgery or hospitalization

BP 135/80; HR 90; RR 16; 100% RA; Temp 38
No signs of DVT on exam

What is the probability of PE?

a) Low
b) Intermediate
c) High

Adapted from JAMA 2003;290:2849
Clinical Presentation

• Symptoms
  – Dyspnea
  – Chest pain
  – Cough
  – Hemoptysis
  – Syncope

• Signs
  – Tachycardia
  – Tachypnea
  – Accentuated pulmonary component of S2
  – Signs of RV failure (JVD, hepatomegaly, S3/S4)
Clinical assessment alone is insufficient
- Clinical signs and symptoms are non-specific
  - Many patients suspected of PE don’t have it
- No single, reliable diagnostic lab test exists
- Over and under-diagnosis may cause harms

In patients suspected of PE, how can we safely **rule out** the diagnosis?

*Ann Intern Med. 2011;155:448*
*JAMA 2003;290:2849*
Clinical Decision Rules (CDR)

- Correlation between pre-test probability and PE prevalence (PIOPED, Wells studies)

- Multiple validated clinical decision rules exist
  - Simple to use
  - Accurate across range of clinician experience

JAMA 2003;290:2849
J Am Coll Card 2016;67:976
Statistics in Diagnosis

PRE-TEST PROBABILITY → POST-TEST PROBABILITY

DIAGNOSTIC TEST
(LIKELIHOOD RATIO)
Using Diagnostic Tests to Spur Action

Zone of Action

Probability of Diagnosis

Zone of Uncertainty

Zone of Action

LR

LR

0% Test Threshold

100% Treatment Threshold

Probability below test threshold: no testing warranted

Probability between test and treatment threshold: further testing required

Probability above treatment threshold; testing completed; treatment commences
LR Nomogram

- Plot patient’s pretest probability on left
- Draw straight line through LR for given test result
- Line points to posttest probability
### Table 4. The Simplified Wells Scoring System*

<table>
<thead>
<tr>
<th>Findings</th>
<th>Score†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical signs/symptoms of deep venous thrombosis (minimum of leg swelling and pain with palpation of the deep veins of the leg)</td>
<td>3.0</td>
</tr>
<tr>
<td>No alternate diagnosis likely or more likely than pulmonary emboli</td>
<td>3.0</td>
</tr>
<tr>
<td>Heart rate &gt;100/min</td>
<td>1.5</td>
</tr>
<tr>
<td>Immobilization or surgery in last 4 weeks</td>
<td>1.5</td>
</tr>
<tr>
<td>Previous history of deep venous thrombosis or pulmonary emboli</td>
<td>1.5</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>1.0</td>
</tr>
<tr>
<td>Cancer actively treated within last 6 months</td>
<td>1.0</td>
</tr>
</tbody>
</table>

*JAMA 2003;290:2849*
## Clinical Decision Rules (CDR)

<table>
<thead>
<tr>
<th>CDR</th>
<th>Probability of PE</th>
<th>Points</th>
<th>PE Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extended Wells</td>
<td>Low</td>
<td>&lt;2</td>
<td>10%</td>
</tr>
<tr>
<td></td>
<td>Intermediate</td>
<td>2-6</td>
<td>30%</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>&gt;6</td>
<td>65%</td>
</tr>
<tr>
<td>Simplified Wells</td>
<td>Low (PE Unlikely)</td>
<td>≤4</td>
<td>12%</td>
</tr>
<tr>
<td></td>
<td>High (PE Likely)</td>
<td>&gt;4</td>
<td>50%</td>
</tr>
</tbody>
</table>

*JAMA 2003;290:2849*
# Accuracy of Wells Criteria for Assessing PE Pre-Test Probability

<table>
<thead>
<tr>
<th>Pre-Test Category</th>
<th>Pre-Test Probability</th>
<th>(+) Likelihood Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low (&lt;2)</td>
<td>4%</td>
<td>0.15 (0.07-0.33)</td>
</tr>
<tr>
<td>Intermediate (2-6)</td>
<td>28%</td>
<td>1.5 (1.01-2.2)</td>
</tr>
<tr>
<td>High (&gt;6)</td>
<td>63%</td>
<td>5.85 (3.51-9.74)</td>
</tr>
</tbody>
</table>

- Best for ruling out (low prob) or ruling in (high prob)
- Intermediate probability requires additional testing
48 yo F presents with chest pain, productive cough, dyspnea

History of lupus and prior DVT 4 years ago
No recent surgery or hospitalization

BP 135/80; HR 90; RR 16; 100% RA; Temp 38
No signs of DVT on exam

What is the best next step in evaluation for PE?

a) D-dimer
b) VQ scan
c) Chest CTA
d) No further testing necessary
48 yo F presents with chest pain, productive cough, dyspnea

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a) D-dimer
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c) Chest CTA
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Adapted from JAMA 2003;290:2849
Clinically suspected deep vein thrombosis or pulmonary embolism

Clinical decision rule

Deep vein thrombosis or pulmonary embolism unlikely

D-dimer testing

Normal

Abnormal

CUS for deep vein thrombosis or CTPA for pulmonary embolism

Negative

Deep vein thrombosis or pulmonary embolism excluded

Positive

Deep vein thrombosis or pulmonary embolism confirmed
<table>
<thead>
<tr>
<th>D-Dimer Assay</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>(-) LR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Organon Teknika latex immunoassay</td>
<td>96</td>
<td>45</td>
<td>0.09</td>
</tr>
<tr>
<td>Vidas Rapid ELISA</td>
<td>90</td>
<td>45</td>
<td>0.22</td>
</tr>
<tr>
<td>SimpliRed D-dimer</td>
<td>85</td>
<td>68</td>
<td>0.22</td>
</tr>
</tbody>
</table>
**Diagnosis – CDR + D-Dimer**

- Negative D-dimer and low clinical pre-test probability can safely exclude PE

**Table 3. Venous Thromboembolic Events (VTEs) During 3-Month Follow-up (n = 3138)**

<table>
<thead>
<tr>
<th>Variable</th>
<th>No.</th>
<th>Total VTEs, No. (%) [95% CI]</th>
<th>Fatal Pulmonary Embolism, No. (%) [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary embolism unlikely and normal D-dimer test result</td>
<td>1028</td>
<td>5 (0.5) [0.2-1.1]</td>
<td>0 (0) [0.0-0.3]</td>
</tr>
<tr>
<td>Pulmonary embolism excluded by CT</td>
<td>1436</td>
<td>18 (1.3) [0.7-2.0]</td>
<td>7 (0.5) [0.2-1.0]</td>
</tr>
<tr>
<td>CT normal</td>
<td>764</td>
<td>9 (1.2) [0.5-2.2]</td>
<td>3 (0.4) [0.1-1.1]</td>
</tr>
<tr>
<td>CT alternative diagnosis</td>
<td>672</td>
<td>9 (1.3) [0.6-2.5]</td>
<td>4 (0.6) [0.1-1.5]</td>
</tr>
<tr>
<td>Pulmonary embolism diagnosed by CT</td>
<td>674</td>
<td>20 (3) [1.8-4.6]</td>
<td>11 (1.6) [0.8-2.9]</td>
</tr>
</tbody>
</table>

*JAMA. 2006;295:172-179*
Risk for false+ higher with advanced age
D-Dimer – Adjustment with Age

- Negative D-dimer: <500 μg/L

- Normal D-dimer range increases with age
  - Age adjust by multiplying age (years) x 10

- Age-adjusted D-dimer cutoff for low prob PE can safely exclude PE and avoid further imaging
  - Similar recurrent VTE rate with age adjusted D-dimer

JAMA 2014;311(11):1117
D-dimer = 400

What is the best next step in evaluation?

a) VQ scan
b) Echo
c) Chest CTA
d) No further testing necessary

Adapted from JAMA 2003;290:2849
D-dimer = 400

What is the best next step in evaluation?

a) VQ scan
b) Echo
c) Chest CTA
d) No further testing necessary

Adapted from JAMA 2003;290:2849
Clinically suspected deep vein thrombosis or pulmonary embolism

Clinical decision rule*️

Deep vein thrombosis or pulmonary embolism unlikely†

D-dimer testing‡

Normal

Deep vein thrombosis or pulmonary embolism excluded

Abnormal

CUS for deep vein thrombosis or CTPA for pulmonary embolism

Deep vein thrombosis or pulmonary embolism likely†

Negative

Deep vein thrombosis or pulmonary embolism confirmed

Positive
CT angiography is first-line imaging study for patients at intermediate or high prob for PE

Modern CT scanners are accurate
  – Inconclusive scans are rare (0.9%)

VQ scans useful when CT contraindicated
  – Accurate but often non-diagnostic (30-40%)
<table>
<thead>
<tr>
<th>Imaging Test</th>
<th>+Likelihood Ratio (LR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VQ Scan</td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>0.1</td>
</tr>
<tr>
<td>Low Prob</td>
<td>0.39</td>
</tr>
<tr>
<td>Intermediate Prob</td>
<td>1.1</td>
</tr>
<tr>
<td>High prob</td>
<td>17</td>
</tr>
<tr>
<td>CTA</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>19.7</td>
</tr>
<tr>
<td>Negative</td>
<td>0.18</td>
</tr>
</tbody>
</table>

*JAMA 1990;263:2753  
NEJM 2006;354:2317*
Case #2

67 yo M presents with pleuritic chest pain and dyspnea

History of HTN, DM, COPD, and past DVT

BP 135/80; HR 110; R 20; T 37; 96% RA
No signs of DVT on exam

What is the probability of PE?

a) Low
b) Intermediate
c) High

Adapted from JAMA 2003;290:2849
Case #2

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No signs of DVT on exam

What is the probability of PE?

a) Low

b) Intermediate

(c) High

Adapted from JAMA 2003;290:2849
CTA positive for PE

What is the best next step in management?

a) Anticoagulation
b) Risk stratification
c) Thrombolysis
d) IVC filter
CTA positive for PE

What is the best next step in management?

a) Anticoagulation
b) Risk stratification
c) Thrombolysis
d) IVC filter
ACUTE RISK STRATIFICATION

- PESI and sPESI
- Biochemical markers*
- RV dysfunction (echocardiography)
- RV enlargement (CTPA)

HIGH RISK
- Hemodynamic instability

INTERMEDIATE RISK
- INTERMEDIATE-HIGH
- INTERMEDIATE-LOW

LOW RISK
Risk Stratification - Tools

- Hemodynamic status
- Prognostic scoring tools
- Cardiac biomarkers
- Imaging
• Defined by hemodynamic instability
  – Shock
  – Sustained hypotension
    • SBP <90 mmHg
    • Pressure drop >40 mmHg for >15 minutes

• Aggressive, direct intervention (e.g., fibrinolysis) is warranted
• Acute RV failure/pressure overload is key determinant of risk for bad outcome

• >95% of acute PE are stable and not high risk

• Key questions:
  1. Which patients in this not-high risk group (i.e., low and intermediate risk) need hospitalization?

  2. Which patients are low risk and could qualify for early discharge?
Pulmonary Embolism Severity Index (PESI) and simplified PESI (sPESI) are most studied.

- Low-risk
  - Class I-II (PESI)
  - 0 point (sPESI)

- High-risk
  - Class III-IV (PESI)
  - ≥1 points (sPESI)

Table 1. Original and Simplified Pulmonary Embolism Severity Index (PESI)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Original PESI</th>
<th>Simplified PESI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt;80 y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male sex</td>
<td>+10</td>
<td></td>
</tr>
<tr>
<td>History of cancer</td>
<td>+30</td>
<td>1</td>
</tr>
<tr>
<td>History of heart failure</td>
<td>+10</td>
<td></td>
</tr>
<tr>
<td>History of chronic lung disease</td>
<td>+10</td>
<td></td>
</tr>
<tr>
<td>Pulse ≥110 beats/min</td>
<td>+20</td>
<td>1</td>
</tr>
<tr>
<td>Systolic blood pressure &lt;100 mm Hg</td>
<td>+30</td>
<td>1</td>
</tr>
<tr>
<td>Respiratory rate ≥30 breaths/min</td>
<td>+20</td>
<td></td>
</tr>
<tr>
<td>Temperature &lt;36°C</td>
<td>+20</td>
<td></td>
</tr>
<tr>
<td>Altered mental status</td>
<td>+60</td>
<td></td>
</tr>
<tr>
<td>Arterial oxyhemoglobin saturation level &lt;90%</td>
<td>+20</td>
<td>1</td>
</tr>
<tr>
<td>Risk Score</td>
<td>Cut-Off</td>
<td>Outcome</td>
</tr>
<tr>
<td>------------</td>
<td>--------------------</td>
<td>--------------------------</td>
</tr>
<tr>
<td>PESI</td>
<td>≥ Class III (high-risk)</td>
<td>30-day all-cause mortality</td>
</tr>
<tr>
<td></td>
<td>Class I-II (low-risk)</td>
<td>2.3%</td>
</tr>
<tr>
<td>sPESI</td>
<td>≥ 1 point (high-risk)</td>
<td>30-day all-cause mortality</td>
</tr>
<tr>
<td></td>
<td>0 points (low-risk)</td>
<td>1.5%</td>
</tr>
</tbody>
</table>

BMJ Open 2016 Apr 29;6(4):e010324
Randomized trial in 19 EDs in Europe
- Acute symptomatic PE + low-risk (PESI class I-II)
- Outpatient LMWH (n=171) vs inpatient LMWH followed by oral anticoagulation (n=168)

### Risk Stratification – Low Risk

<table>
<thead>
<tr>
<th></th>
<th>Outpatient group</th>
<th>Inpatient group</th>
<th>Difference in percentages (%outpatient-%inpatient)</th>
<th>Upper 95% CL for difference</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary analysis outcomes within 90 days†</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recurrent VTE</td>
<td>1 (0.6%)‡</td>
<td>0</td>
<td>0.6%</td>
<td>2.7%</td>
<td>0.011</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>3 (1.8%)</td>
<td>0</td>
<td>1.8%</td>
<td>4.5%</td>
<td>0.086</td>
</tr>
<tr>
<td>Intramuscular</td>
<td>2 (1.2%)</td>
<td>0</td>
<td>1.2%</td>
<td>3.6%</td>
<td>0.031</td>
</tr>
<tr>
<td>Menometrorrhagia</td>
<td>1 (0.6%)</td>
<td>0</td>
<td>0.6%</td>
<td>2.7%</td>
<td>0.011</td>
</tr>
<tr>
<td><strong>Overall mortality</strong></td>
<td>1 (0.6%)§</td>
<td>1 (0.6%)¶</td>
<td>0%</td>
<td>2.1%</td>
<td>0.005</td>
</tr>
<tr>
<td><strong>Primary analysis outcomes within 14 days†</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recurrent VTE</td>
<td>0</td>
<td>0</td>
<td>0%</td>
<td>1.7%</td>
<td>0.003</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>2 (1.2%)</td>
<td>0</td>
<td>1.2%</td>
<td>3.6%</td>
<td>0.031</td>
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<td>0</td>
<td>0%</td>
<td>1.7%</td>
<td>0.003</td>
</tr>
</tbody>
</table>

Lancet Jul 2011; 378:41
• Myocardial dysfunction and injury associated with worse clinical outcomes

• Lab tests/imaging to supplement PESI/sPESI risk stratification scores
  – Troponin
    • (+)Tn associated with higher overall mortality (OR 5.2) and higher PE-specific mortality (OR 9.4)

  – BNP
    • High BNP associated with adverse in-hospital outcomes

  – Imaging
    • RV dysfunction associated with higher 30-day mortality
<table>
<thead>
<tr>
<th>Early Mortality Risk</th>
<th>Shock or Hypotension</th>
<th>PESI Class III-V or sPESI ≥1</th>
<th>Signs of RV Dysfunction on an Imaging Test</th>
<th>Cardiac Laboratory Biomarkers*</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>+</td>
<td>(+)</td>
<td>+</td>
<td>(+)</td>
</tr>
<tr>
<td>Intermediate-high</td>
<td>−</td>
<td>+</td>
<td>Both positive</td>
<td></td>
</tr>
<tr>
<td>Intermediate-low</td>
<td>−</td>
<td>+</td>
<td>Either 1 (or none) positive</td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>−</td>
<td>−</td>
<td>Assessment optional: If assessed, both negative</td>
<td></td>
</tr>
</tbody>
</table>
67 yo M with h/o HTN, DM, COPD, and past DVT

BP 135/80; HR 110; R 20; T 37; 96% RA

What is the patient’s PESI and sPESI class?

PESI = class III
sPESI = 3 points

Arch Intern Med. 2010;170(15):1383-1389
• PESI/sPESI are best studied/validated tools
  – Originally developed as epidemiologic tools with limited prospective clinical trial data

• High risk patients should receive lytics

• Potential role for outpatient care (low risk)

• Unclear whether all low/intermediate risk patients should have biomarkers and/or echo
TREATMENT

- Parenteral anticoagulants
- Oral anticoagulants
- Fibrinolytics
- Catheter-directed techniques
- Surgical embolectomy
- Vena cava filters

- PRIMARY REPERFUSION
  plus
  ANTICOAGULANT THERAPY

- ANTICOAGULANT THERAPY
  (Rescue reperfusion)

- ANTICOAGULANT THERAPY
  (Early discharge)
Management – Traditional Approach

- Traditional approach: parenteral anticoagulation then vitamin K antagonist – 3 phases: acute, maintenance, extended

<table>
<thead>
<tr>
<th>Initial Treatment</th>
<th>Long-Term Treatment</th>
<th>Extended Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unfractionated heparin</td>
<td>Vitamin K antagonists (INR target, 2.0–3.0)</td>
<td>Vitamin K antagonists (INR target, 2.0–3.0 or 1.5–1.9)</td>
</tr>
<tr>
<td>Low-molecular-weight heparin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fondaparinux</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombolyis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percutaneous mechanical embolectomy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamin K antagonists</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

≥5 Days

≥3 Mo

Indefinite
Effect of warfarin on blood clotting proteins

- Prothrombin
- Factor X
- Factor IX
- Protein C
- Factor VII

Coagulant activity, percent, log scale vs. Days after warfarin ingestion
Management – Updated Approach

• Downsides of VKA
  – Frequent INR monitoring
  – Interactions with foods and medications
  – Therapeutic range adherence (~50-60%)

• Direct oral anticoagulants (DOACs)
  – Efficacy similar to VKAs
  – Lower risk for major and non-major bleeding
  – Efficacy and safety similar across higher-risk subgroups (elderly, obese, moderate CKD)
  – No need for regular lab monitoring
DOACs have comparable efficacy to VKAs

<table>
<thead>
<tr>
<th></th>
<th>DOAC (n/N)</th>
<th>VKA (n/N)</th>
<th>Risk ratio (95% CI)</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMPLIFY</td>
<td>59/2609 (2.3%)</td>
<td>71/2635 (2.7%)</td>
<td>.84 (0.60-1.18)</td>
<td></td>
</tr>
<tr>
<td>EINSTEIN-DVT</td>
<td>36/1731 (2.1%)</td>
<td>51/1718 (3.0%)</td>
<td>.70 (0.46-1.07)</td>
<td></td>
</tr>
<tr>
<td>EINSTEIN-PE</td>
<td>50/2419 (2.1%)</td>
<td>44/2413 (1.8%)</td>
<td>1.13 (0.76-1.69)</td>
<td></td>
</tr>
<tr>
<td>Hokusai-VTE</td>
<td>66/4118 (1.6%)</td>
<td>80/4122 (1.9%)</td>
<td>0.83 (0.60-1.14)</td>
<td></td>
</tr>
<tr>
<td>RE-COVER</td>
<td>30/1274 (2.4%)</td>
<td>27/1265 (2.1%)</td>
<td>1.10 (0.66-1.84)</td>
<td></td>
</tr>
<tr>
<td>RE-COVER II</td>
<td>30/1279 (2.3%)</td>
<td>28/1289 (2.2%)</td>
<td>1.08 (0.65-1.80)</td>
<td></td>
</tr>
<tr>
<td>Combined (random)</td>
<td>271/13430 (2.0%)</td>
<td>301/13442 (2.2%)</td>
<td>0.90 (0.77-1.06)</td>
<td></td>
</tr>
</tbody>
</table>

DOACs associated with less major bleeding

<table>
<thead>
<tr>
<th>Study</th>
<th>DOAC (n/N)</th>
<th>VKA (n/N)</th>
<th>Risk ratio (95% CI)</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMPLIFY</td>
<td>15/2676 (0.6%)</td>
<td>49/2689 (1.8%)</td>
<td>0.31 (0.17-0.55)</td>
<td></td>
</tr>
<tr>
<td>EINSTEIN-DVT</td>
<td>14/1718 (0.8%)</td>
<td>20/1711 (1.2%)</td>
<td>0.70 (0.35-1.38)</td>
<td></td>
</tr>
<tr>
<td>EINSTEIN-PE</td>
<td>26/2412 (1.1%)</td>
<td>52/2405 (2.2%)</td>
<td>0.50 (0.31-0.80)</td>
<td></td>
</tr>
<tr>
<td>Hokusai-VTE</td>
<td>56/4118 (1.4%)</td>
<td>66/4122 (1.6%)</td>
<td>0.85 (0.60-1.21)</td>
<td></td>
</tr>
<tr>
<td>RE-COVER</td>
<td>22/1273 (1.7%)</td>
<td>29/1266 (2.3%)</td>
<td>0.75 (0.44-1.31)</td>
<td></td>
</tr>
<tr>
<td>RE-COVER II</td>
<td>15/1280 (1.2%)</td>
<td>22/1288 (1.7%)</td>
<td>0.69 (0.36-1.32)</td>
<td></td>
</tr>
<tr>
<td><strong>Combined (random)</strong></td>
<td>148/13477 (1.1%)</td>
<td>238/13481 (1.8%)</td>
<td><strong>0.61 (0.45-0.83)</strong></td>
<td></td>
</tr>
</tbody>
</table>

DOACs associated with less non-major bleeding

<table>
<thead>
<tr>
<th></th>
<th>Pooled DOAC (n/N)</th>
<th>Pooled VKA (n/N)</th>
<th>Risk ratio (95% CI)</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intracranial bleeding</td>
<td>15/13477 (0.1%)</td>
<td>43/13841 (0.3%)</td>
<td></td>
<td>0.37 (0.21-0.68)</td>
</tr>
<tr>
<td>Fatal bleeding</td>
<td>7/13477 (0.1%)</td>
<td>22/13481 (0.2%)</td>
<td></td>
<td>0.36 (0.15-0.84)</td>
</tr>
<tr>
<td>Major GI bleeding</td>
<td>63/13477 (0.5%)</td>
<td>76/13481 (0.6%)</td>
<td></td>
<td>0.78 (0.47-1.31)</td>
</tr>
<tr>
<td>CRNM bleeding</td>
<td>854/13477 (6.3%)</td>
<td>1103/13481 (8.0%)</td>
<td></td>
<td>0.73 (0.58-0.93)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drug</th>
<th>Initial Phase</th>
<th>Long-Term Phase</th>
<th>Extended Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rivaroxaban†</td>
<td>15 mg twice daily with food for 21 days</td>
<td>20 mg once daily with food</td>
<td></td>
</tr>
<tr>
<td>Dabigatran etexilate‡</td>
<td>Initial therapy with parenteral anticoagulation for 5-10 days should precede administration of dabigatran etexilate</td>
<td>150 mg twice daily</td>
<td></td>
</tr>
<tr>
<td>Apixaban</td>
<td>10 mg twice daily for 7 days</td>
<td>5 mg twice daily</td>
<td>2.5 mg twice daily after at least 6 months of treatment</td>
</tr>
<tr>
<td>Edoxaban§</td>
<td>Initial therapy with parenteral anticoagulation for 5-10 days should precede administration of edoxaban</td>
<td>60 mg once daily</td>
<td>30 mg once daily can be considered in patients with $\geq 1$ of the following factors: CrCl 15-50 ml/min; body weight $\leq 60$ kg; concomitant use of P-gp inhibitors, cyclosporin, dronedarone, erythromycin, or ketoconazole</td>
</tr>
</tbody>
</table>
*2. In patients with DVT of the leg or PE and no cancer, as long-term (first 3 months) anticoagulant therapy, we suggest dabigatran, rivaroxaban, apixaban, or edoxaban over vitamin K antagonist (VKA) therapy (all Grade 2B).
DOAC – Rx Considerations

- Pharmacokinetics
  - Contraindicated with CrCl <15-30
  - Moderate/severe liver disease with coagulopathy

- Lack of direct reversal agent
  - Idarucizumab (reversal for dabigatran) and Andexanet (reversal for Xa inhibitors) are forthcoming

- Patient characteristics/preferences
  - Low anticipated adherence
  - If active cancer, choose LMWH over VKA or DOAC
  - Dabigatran, edoxaban, and VKA require initial parenteral overlap
  - No evidence that one DOAC better than others

- Costs/insurance
  - Varies across regions/circumstances

*CHEST* 2016; 149(2):315-352
*Lancet* 2016;388:3060
Management - Thrombolytics

- Indicated for massive PE (high risk)

- **Benefits** – associated with reduced:
  - Overall mortality (OR 0.53); NNT = 59
  - PE mortality (OR 0.29)
  - PE recurrence (OR 0.4); NNT = 54

- **Risks** – associated with higher:
  - Major bleeding (OR 2.73); NNH = 18
  - Intracranial bleeding (OR 4.63); NNH = 78

*JAMA. 2014;311(23):2414-2421*
• Hospital discharge criteria
  – Clinically stable
  – Therapeutically anticoagulated (DOAC or LMWH+VKA overlap)
  – Post-discharge anticoagulation follow-up and monitoring in place
LONG-TERM MANAGEMENT

LONG-TERM CLINICAL COURSE

- Assess bleeding risk
- Predict VTE recurrence
- Focused screening for CTEPH in symptomatic patients

BLEEDING
No validated prediction models for VTE patients

RECURRENT VTE
Standard-duration vs. extended ( indefinite) treatment

CTEPH
Individualized follow-up programs and intervals
• Minimum initial duration = 3 months

• Decision about longer (extended) AC based on several factors
  – Presence/absence of transient risk factors (e.g., surgery, pregnancy, long flight)
  – Bleeding risk
  – History of prior unprovoked VTEs

• Balance recurrence risk vs bleeding risk
• Anticoagulation reduces VTE recurrence by 80-90% compared to placebo

• VTE recurrence rates:
  – Post-surgery = 1-3%
  – Non-surgery provoked risk factors = 15%
  – Unprovoked = 10-30%
  – Cancer = 15% recurrence per year
## Risk Factors for Bleeding with AC

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Estimated Absolute Risk of Major Bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low Risk (0 Risk Factors)</td>
</tr>
<tr>
<td>Anticoagulation 0-3 mo</td>
<td>0.6</td>
</tr>
<tr>
<td>Baseline risk (%)</td>
<td>1.0</td>
</tr>
<tr>
<td>Increased risk (%)</td>
<td>1.6</td>
</tr>
<tr>
<td>Anticoagulation after first 3 mo</td>
<td>0.3</td>
</tr>
<tr>
<td>Baseline risk (%/y)</td>
<td>0.5</td>
</tr>
<tr>
<td>Increased risk (%/y)</td>
<td>0.8</td>
</tr>
</tbody>
</table>

- Age >65 y
- Age >75 y
- Previous bleeding
- Cancer
- Metastatic cancer
- Renal failure
- Liver failure
- Thrombocytopenia
- Previous stroke
- Diabetes
- Anaemia
- Antiplatelet therapy
- Poor anticoagulant control
- Comorbidity and reduced functional capacity
- Recent surgery
- Frequent falls
- Alcohol abuse
- Nonsteroidal anti-inflammatory drug

**References:**

Duration of Anticoagulation

*Second or more unprovoked VTE merits extended AC

*Individualized decision incorporating patient preferences and reassessed annually

- **Active cancer?**
  - Yes: Extended AC*
  - No

- **First VTE?**
  - Yes: Transient Risk Factor?
  - No

- **Transient Risk Factor?**
  - Yes: Bleeding Risk
  - No

- **Bleeding Risk**
  - High: 3 months AC
  - Low/Moderate: 3 months AC

Adapted from CHEST 2016; 149(2):315-352
67 yo M with h/o HTN, DM, COPD, and past DVT.

No problems with anticoagulation for past DVT. Takes ASA 81 mg chronically.

BP 135/80; HR 110; R 20; T 37; 96% RA

How long should this patient receive anticoagulation?

a) At least 3 months
b) At least 12 months
c) Indefinitely
67 yo M with h/o HTN, DM, COPD, and past DVT.

No problems with anticoagulation for past DVT. Takes ASA 81 mg chronically.

BP 135/80; HR 110; R 20; T 37; 96% RA

How long should this patient receive anticoagulation?

a) At least 3 months
b) At least 12 months
c) Indefinitely
• Outpatient treatment of low-risk PE
• Thrombolysis – submassive PE
• Subsegmental PE (SSPE)
• IVC filters
• Occult malignancy evaluation following unprovoked VTE/PE
Outpatient Management of PE

Confirmed acute pulmonary embolism

- Haemodynamically stable
  - Initiate anticoagulation
  - Assess 30 day mortality risk
    - Low risk
      - Consider home treatment
    - High risk

- Haemodynamically unstable*
  - Systemic thrombolysis
  - Initiate anticoagulation
  - Consider inpatient treatment

*Lancet 2016; 388: 3060–73
Outpatient Management of PE

20. In patients with low-risk PE and whose home circumstances are adequate, we suggest treatment at home or early discharge over standard discharge (e.g., after the first 5 days of treatment) (Grade 2B).

- Potential candidates for OP management
  - Clinically stable and good cardiopulmonary reserve
    - No RV dysfunction or myocardial injury
  - No contraindications to anticoagulation (e.g., CKD, cirrhosis)
  - Anticipated to be adherent to anticoagulation at home
  - Patient feels well enough to be at home

- Use PESI or sPESI to identify low-risk patients
• PEITHO trial (2014)
  – RCT comparing thrombolysis+heparin vs placebo+heparin
  – Intermediate risk PE (+RV dysfunction, +trop)
  – Lower risk for hemodynamic collapse, but no reduction in overall mortality
  – Significantly increased risk for major bleeding and hemorrhagic stroke

• No role for routine lytics for submassive PE

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Tenecteplase (N=506)</th>
<th>Placebo (N=499)</th>
<th>Odds Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcome — no. (%)</td>
<td>13 (2.6)</td>
<td>28 (5.6)</td>
<td>0.44 (0.23–0.87)</td>
<td>0.02</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>6 (1.2)</td>
<td>9 (1.8)</td>
<td>0.65 (0.23–1.85)</td>
<td>0.42</td>
</tr>
<tr>
<td>Hemodynamic decompensation</td>
<td>8 (1.6)</td>
<td>25 (5.0)</td>
<td>0.30 (0.14–0.68)</td>
<td>0.002</td>
</tr>
</tbody>
</table>

*N Engl J Med* 2014;370:1402-11
Subsegmental PE (SSPE)

- SSPE more common as CT has improved
  - 5-10% of PE seen on CTA are SSPE
- Limited estimates of risk for progression or recurrence off AC, and no RCT data to-date
- Need bilateral LE U/S to exclude proximal DVT

*19. In patients with subsegmental PE (no involvement of more proximal pulmonary arteries) and no proximal DVT in the legs who have a (i) low risk for recurrent VTE (see text), we suggest clinical surveillance over anticoagulation (Grade 2C), and (ii) high risk for recurrent VTE (see text), we suggest anticoagulation over clinical surveillance (Grade 2C).
**IVC Filters**

- Typically placed in infrarenal IVC for patients with acute VTE and contraindications to AC

- IVC filters placed 25x more often in US than in Europe

- Complications can occur – e.g., fracture, embolization, IVC thrombus, IVC perforation
  - Complication rates can vary by manufacturer

- Filter retrieval rates very low (2-40%)
• PREPIC 2 Trial (2015)
  – RCT comparing retrievable IVC filter + AC (n=200) vs AC alone (n=199)
  – Patients with acute symptomatic PE + at least 1 severity criterion
  – Very high filter retrieval rate (93%)
  – No reduction in recurrent VTE at 3, 6 months

• No role for IVC filter in addition to anticoagulation for acute DVT/PE
Unprovoked VTE may be earliest sign of cancer

- Nearly 10% will have cancer dx within 1 year

SOME Trial (2015)

- New unprovoked VTE at 9 coagulation clinics
- Randomized to limited occult malignancy screening (n=431) vs occult screening + CT A/P (n=423)
- No difference in rates of new cancers diagnosed at 1 year (3.2% vs 4.5%; p=0.28)
- No difference in time to cancer diagnosis or cancer-related mortality

# Road Map

## Pre-Test Clinical Assessment
- Revised Geneva score
- Wells rule
- Empirical assessment

## Diagnosis
- (Age-adjusted) D-dimers
- CTPA
- V/Q scan
- Echocardiography
- CUS

## Acute Risk Stratification
- PESI and sPESI
- Biochemical markers*
- RV dysfunction (echocardiography)
- RV enlargement (CTPA)

## Treatment
- Parenteral anticoagulants
- Oral anticoagulants
- Fibrinolytics
- Catheter-directed techniques
- Surgical embolectomy
- Vena cava filters

## Long-Term Clinical Course
- Assess bleeding risk
- Predict VTE recurrence
- Focused screening for CTEPH in symptomatic patients

### Algorithm for High-Risk PE
- CTPA
  - Echocardiography (if CTPA not readily available or uncontrolled hypotension)

### Algorithm for Non High-Risk PE
- CTPA
  - V/Q scan
- CUS-based algorithms

### Hemodynamic Instability
- High Clinical Probability
- Low or Intermediate Clinical Probability

### Absence of Hemodynamic Instability
- Age-adjusted positive D-dimers

### High Risk
- Hemodynamic instability

### Intermediate Risk
- Intermediate-High
- Intermediate-Low

### Low Risk
- ANTICOAGULANT THERAPY
  - (Rescue reperfusion)

### Anticoagulant Therapy
- Primary Reperfusion
  - (Early discharge)

### Primary Reperfusion
- No validated prediction models for VTE patients

### Bleeding
- Standard-duration vs. extended (indefinite) treatment

### Recurrent VTE
- Individualized follow-up programs and intervals

### CTEPH
- No validated prediction models for VTE patients
Take Home Points

• PE remains a challenging diagnosis and is associated with morbidity and mortality

• Low clinical probability and negative D-dimer can safely exclude PE

• Risk stratification with PESI or sPESI should be done after diagnosis made by imaging

• DOACs are now first-line recommended AC option

• Decision-making about duration of AC requires balance between recurrence risk and bleeding risk

• Multiple clinical controversies persist and will help drive future areas of research


