Updates in the Management of Venous Thromboembolism

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Venous Thromboembolism (VTE)
- >350,000 hospitalizations and >100,000 deaths each year in the US
- Untreated VTE has a high recurrence rate (~50% within 3 months)
- Anticoagulation is the cornerstone of VTE treatment and prevention

Outline
- Clinical prediction of PE
- Predicting mortality after PE
- Duration of anticoagulation therapy
- D-dimer and residual venous occlusion
- Thrombophilia evaluation
- Newer anticoagulants

Case #1
A 67 y/o woman presents to your office with acute right sided chest pain and mild dyspnea. She denies recent immobility or other acute symptoms. Her only medical history is HTN.

Exam: BP = 135/70, HR = 88, O2 sat=98%
CV: regular, normal S1, S2, no murmurs
Lungs: clear bilaterally, normal lung exam
Extremities: no edema, erythema, or pain
What is this patient’s pre-test probability for PE?

1. Low risk (~10%)
2. Intermediate risk (~30%)
3. High risk (~60%)

Clinical Prediction Rules for Pulmonary Embolism (PE)

- Various prediction rules are available and seem to have similar accuracy
- Most extensively validated scores:
  - Wells (and Simplified Wells) Score
    - Depends in part on clinician judgment, and may therefore be subject to bias
  - Geneva Score (and related modifications)
    - Only validated for outpatients

Revised Geneva Score

<table>
<thead>
<tr>
<th>Clinical factor</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt; 65</td>
<td>1</td>
</tr>
<tr>
<td>Prior DVT or PE</td>
<td>3</td>
</tr>
<tr>
<td>Surgery or fracture within 1 month</td>
<td>2</td>
</tr>
<tr>
<td>Active malignancy</td>
<td>2</td>
</tr>
<tr>
<td>Heart rate 75-94</td>
<td>3</td>
</tr>
<tr>
<td>Heart rate ≥ 95</td>
<td>5</td>
</tr>
<tr>
<td>Pain with leg palpation + unilateral edema</td>
<td>3</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>2</td>
</tr>
</tbody>
</table>

Low Risk 0 – 3 (10% PE)  Intermediate Risk 4 – 10 (30% PE)  High Risk ≥ 11 (65% PE)

Wells Criteria

<table>
<thead>
<tr>
<th>Clinical factor</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Signs of DVT</td>
<td>3</td>
</tr>
<tr>
<td>Recent surgery or immobilization</td>
<td>1.5</td>
</tr>
<tr>
<td>Heart rate &gt; 100 bpm</td>
<td>1.5</td>
</tr>
<tr>
<td>Prior DVT or PE</td>
<td>1.5</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>1</td>
</tr>
<tr>
<td>Malignancy</td>
<td>1</td>
</tr>
<tr>
<td>Alternative diagnosis less likely than PE</td>
<td>3</td>
</tr>
</tbody>
</table>

Low <2 (10% PE)  Med 2-6 (30% PE)  High > 6 (65% PE)

OR  ≤ 4: PE unlikely (12% PE)  > 4: PE likely (37% PE)
What is this patient’s pre-test probability for PE?

1. Low risk (10%)
2. Intermediate risk (30%)
3. High risk (>60%)

What would be your next diagnostic step?

1. Obtain chest CT angiogram
2. Obtain a D-dimer blood test
3. Obtain lower extremity ultrasounds
4. Do not obtain further work-up for pulmonary embolism

D-Dimer Testing for PE

- Quantitative ELISA D-dimer
  - High sensitivity (can “rule out”) but poor specificity (cannot “rule in” because of false positives due to infection, malignancy, older age)
  - Most useful when the probability of PE is low or intermediate

<table>
<thead>
<tr>
<th>Pre-test probability</th>
<th>Post-test probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low (~10%)</td>
<td>0.5 – 2%</td>
</tr>
<tr>
<td>Intermediate (~30%)</td>
<td>5 – 6%</td>
</tr>
<tr>
<td>High (~65%)</td>
<td>20 – 35%</td>
</tr>
</tbody>
</table>

D-Dimer for DVT

- A negative D-dimer also has a high negative predictive value for DVT
  - … IF the patient has a low pre-test probability for DVT
  - May be less useful in patients with cancer or are acutely ill
- An elevated D-dimer doesn’t rule-in DVT → it should prompt further testing
**PE Diagnostic Algorithm**

- Suspected PE
  - Wells Score ≤ 4
    - Obtain D-dimer
      - ≤ 500 ng/mL: PE unlikely (0.5%), no further diagnostic tests
      - > 500 ng/mL: PE possible (23%), obtain further imaging (e.g., CT)
  - Wells Score > 4
    - Obtain D-dimer
      - ≤ 500 ng/mL: PE unlikely (0.5%), no further diagnostic tests
      - > 500 ng/mL: PE possible (23%), obtain further imaging (e.g., CT)

The Christopher Writing Group, JAMA 2006

**What would be your next diagnostic step?**

1. Obtain chest CT angiogram
2. Obtain a D-dimer blood test
3. Obtain lower extremity ultrasounds
4. Do not obtain further work-up for pulmonary embolism

**Case #2**

A 65 y/o man with a history of COPD presents with an unprovoked PE. He is hemodynamically stable. Past medical history is only significant for COPD.

**Which of the following might help you estimate his short-term prognosis?**

1. Serum troponin
2. Echocardiography
3. History and physical exam
4. BNP
5. All of the above
Predicting Outcomes After PE

- 3 month mortality rate varies: 1%–17%

Factors Associated with Worse PE Outcomes

- Right ventricular dysfunction
  - Occurs in ~25% of patients with PE
  - Doubles the risk of PE-associated mortality
  - Can identify using Echo, RV measurements on CT, elevated serum BNP

- Troponin I or T elevation
  - Associated with 3-4x increased risk of 3-month mortality

Torbicki, ESC Guidelines, EHJ 2008, Jimenez BJH 2010

Factors Associated with Worse PE Outcomes

- Note: lack of RV dysfunction and troponin elevation might help you identify patients with good outcomes (high negative predictive value) but poor at predicting patients with bad outcomes
- Compared to clinical factors, may not provide much additional information on short-term prognosis

Simplified Pulmonary Embolism Severity Index (PESI)

<table>
<thead>
<tr>
<th>Clinical factor</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt; 80 years</td>
<td>1</td>
</tr>
<tr>
<td>History of cancer</td>
<td>1</td>
</tr>
<tr>
<td>Chronic cardiopulmonary disease</td>
<td>1</td>
</tr>
<tr>
<td>Heart rate ≥ 110 bpm</td>
<td>1</td>
</tr>
<tr>
<td>Systolic blood pressure &lt; 100 mm Hg</td>
<td>1</td>
</tr>
<tr>
<td>Arterial O₂ saturation &lt; 90%</td>
<td>1</td>
</tr>
</tbody>
</table>

0 points: 30 day mortality → 1%
≥1 points: 30 day mortality → 9–11%
Which of the following might help you estimate his short-term prognosis?

1. Serum troponin
2. Echocardiography
3. History and physical exam
4. BNP
5. All of the above

Duration of Anticoagulation

How long would you anticoagulate this patient with PE?

1. 3 months
2. 6 months
3. 12 months
4. Lifelong

Duration of Therapy

- Depends on
  - Risk of VTE recurrence
  - Risk of major bleeding with anticoagulants
  - Patient preference

Kearon et al. 8th ACCP Guidelines, Chest 2008
Risk Factors for Recurrent VTE

- Unprovoked VTE
  - High recurrence rate; might be considered a chronic disease process
  - ~10% recurrence at 1 year
  - ~25% recurrence at 5 years
  - ~50% recurrence rate at 10yrs
- Men with unprovoked VTE
  - ~Twice the risk compared to women

VTE in Patients with Cancer

- Patients with cancer have higher VTE recurrence rates (14% per year) but also higher hemorrhage rates on anticoagulation (10 - 17%)
- Low molecular weight heparins (LMWH) appear to be more effective than warfarin in patients with cancer
  - Probably supports using ≥ 3 months LMWH for the initial treatment of VTE in cancer

Duration of Therapy

- Diagnosed VTE
  - Unprovoked
    - Cancer?
      - No: ≥ 3 months anticoagulation; then consider further risk stratification
      - Yes: Indefinite anticoagulation
  - Provoked: 3 months anticoagulation

Risk Stratification for Unprovoked VTE

- Count number of risk factors:
  - BMI >30
  - Age >65
  - D-dimer on warfarin ≥250 ng/mL
  - Post-thrombotic syndrome

- Male
  - ≥ 2: ≥ 3 months anticoagulation; Consider indefinite therapy
  - 0 – 1: Risk of recurrent VTE < 3% per yr; Consider discontinuation of anticoagulation after 3 months

- Female
  - ≥ 2: Consider indefinite anticoagulation
  - 0 – 1: Risk of recurrent VTE ≥ 10% per yr; Consider indefinite anticoagulation

Kearon et al, 8th ACCP Guidelines, Chest 2008


Rodger et al, CMAJ 2008
Duration of Therapy

- Provoked DVT/PE: 3 months
- Unprovoked DVT/PE: treat for ≥ 3 months and consider lifelong therapy
  - Men have a higher risk for recurrence and should consider lifelong therapy
  - Consider further risk stratification in women
- Decision strongly depends on individualized risks vs. benefits

How long would you anticoagulate this patient with PE?

1. 3 months
2. 6 months
3. 12 months
4. Lifelong

Risk Stratification for Recurrent VTE

- D-dimer testing?
- Residual venous occlusion?
- Thrombophilia testing?

Utility of D-Dimer Testing to Predict VTE Recurrence after Unprovoked VTE

- Abnormal D-dimer* after completing 3 months of therapy associated with ~2.2 times increased risk of recurrence
  - Normal D-dimer → 3.5% per year
  - Abnormal D-dimer → 8.9% per year
- D-dimers that are initially normal become abnormal 10-15% of the time when rechecked
- Should probably not be used as the sole test to determine cessation of anticoagulant therapy

* Normal D-dimer range varied across studies: generally, < 250 - 500 ng/mL
Residual Venous Occlusion (RVO)

- AESOPUS trial compared fixed-duration anticoagulation* to RVO-guided duration
  - Ultrasounds obtained at 3 months, then q6 months
  - If no RVO, anticoagulation was discontinued
  - Assessing for RVO resulted in a mean ~4 – 5 months additional anticoagulation and lower recurrent VTE rate (11.9% RVO-guided vs. 17.2% in fixed-duration)
  - Substantial rate of RVO at 21 months: 20% – 30%
- RVO may be helpful in identifying patients who benefit from additional anticoagulation after DVT

*R3 months for provoked VTE, 6 months for unprovoked VTE
Prandoni et al, Ann Intern Med 2009

Risk Stratification for Recurrent VTE

- Serial D-dimer testing and assessing for residual venous occlusion (for DVTs) may have some utility in estimating a person’s risk for recurrent events
  - Benefit may come from prolonging course of anticoagulation
  - Still needs to be validated in the setting of clinical prediction rules and outcomes

Thrombophilia Testing

- A number of inherited factors are commonly found in patients with VTE
  - ~20-30% of patients will have 1 factor
  - Only 2.7% will have ≥ 2 factors
- Association is often weak and does not consistently predict recurrence of VTE
  - Only anticardiolipin antibodies or ≥ 2 concurrent thrombophilias predict recurrence

Who of the following would you test for a hereditary thrombophilia?

1. A 55 y/o man who presents with unprovoked PE
2. A 35 y/o woman who presents with unprovoked DVT
3. A 27 y/o asymptomatic woman whose 55 y/o father just developed an unprovoked PE
4. None of the above
5. All of the above

Kearon et al, 8th ACCP Guidelines, Chest 2008
Thrombophilia Testing

- Many tests are not accurate in setting of acute VTE and/or anticoagulation therapy
  - E.g., Activated protein C resistance, Protein C, S, and antithrombin functional assays, Factor VIII assay, antiphospholipid antibody testing
  - Factor V Leiden mutation, homocysteine, and Prothrombin gene mutation not affected
- If testing, should test 2 - 3 weeks after discontinuation of anticoagulation

When to Test?

- Test if it will change your duration decision
  - Decide on what your management decision will be prior to testing for thrombophilias
  - May affect recommendations for higher-risk situations (e.g., extended flights, hormone contraception, pregnancy)
- If results will change management, consider testing:
  - Young patients with unexplained thromboembolism
  - If there is a strong family history of VTE (first degree relatives who developed idiopathic VTE at age ≤ 50 years)
  - VTE that is unusually extensive or in an unusual location (e.g., portal vein thrombosis)

Who of the following would you test for a hereditary thrombophilia?

1. A 55 y/o man who presents with unprovoked PE
2. A 35 y/o woman who presents with unprovoked DVT
3. A 27 y/o asymptomatic woman whose 55 y/o father just developed an unprovoked PE
4. None of the above
5. All of the above

Newer Anticoagulants

- Direct thrombin inhibitors (e.g., dabigatran)
- Factor Xa inhibitors (e.g., rivaroxaban, apixaban)
**New and Investigational Agents**

**Mechanisms**

- **Intrinsic pathway**
  - XI
  - IX
  - VIII
  - VII
  
- **Extrinsic pathway**
  - Tissue factor

- **Direct FXa inhibitors**
  - (rivaroxaban, apixaban)

- **Direct thrombin inhibitors**
  - (dabigatran)

**Dabigatran for VTE**

- Dabigatran (150mg po bid) compared to adjusted-dose warfarin for acute VTE
  - Patients were first treated with parenteral agents and then oral agents for 6 months
  - Because dabigatran is renally excreted, patients with renal insufficiency (creatinine clearance < 30 ml/min) were excluded

**Dabigatran vs. Warfarin: Outcomes at 6 months after VTE**

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran (n = 1274)</th>
<th>Warfarin (n = 1265)</th>
<th>Dabigatran vs. Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>% patients</td>
<td>2.4</td>
<td>2.1</td>
<td>1.10 (0.65-1.84)</td>
</tr>
<tr>
<td>VTE or related death</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All cause death</td>
<td>1.6</td>
<td>1.7</td>
<td>0.98 (0.53-1.79)</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>1.6</td>
<td>1.9</td>
<td>0.82 (0.45-1.48)</td>
</tr>
<tr>
<td>Any bleeding</td>
<td>16.1</td>
<td>21.9</td>
<td>0.71 (0.59-0.85)</td>
</tr>
</tbody>
</table>

**Rivaroxaban for DVT**

- **Rivaroxaban**
  - 15mg po bid for first 3 weeks after initial DVT followed by 20mg once daily
  - Compared to enoxaparin 1 mg/kg bid + vitamin K antagonist (warfarin or acenocoumarol)
  - Standard lengths of treatment (3, 6, or 12 months)

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The EINSTEIN Investigators, N Engl J Med, 2010
Rivaroxaban vs. Enoxaparin-VKA

<table>
<thead>
<tr>
<th></th>
<th>Rivaroxaban</th>
<th>Enox--VKA</th>
<th>Rivaroxaban vs. Enox--VKA</th>
</tr>
</thead>
<tbody>
<tr>
<td>% patients</td>
<td>% patients</td>
<td>HR (95%CI)</td>
<td></td>
</tr>
<tr>
<td>Recurrent VTE</td>
<td>2.1</td>
<td>3.0</td>
<td>0.68 (0.44-1.04)</td>
</tr>
<tr>
<td>All cause death</td>
<td>2.2</td>
<td>2.9</td>
<td>0.67 (0.44-1.02)</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>0.8</td>
<td>1.2</td>
<td>0.65 (0.33-1.30)</td>
</tr>
<tr>
<td>Any bleeding</td>
<td>8.1</td>
<td>8.1</td>
<td>0.97 (0.76-1.22)</td>
</tr>
</tbody>
</table>

The EINSTEIN Investigators, N Engl J Med, 2010

Newer Anticoagulants

- May eventually become alternatives to warfarin
- Most costly than warfarin
- Dabigatran nor rivaroxaban have not been approved by the FDA for use in VTE
  - May require additional safety data

Summary

- Use clinical prediction rules followed by D-dimer testing to help guide further diagnostic testing
- PE severity index may be useful to identify low risk individuals
  - But does not give clear guidance on duration of hospitalization or optimal management

Duration of Therapy

- Several factors are associated with high recurrence rates of VTE
  - Underlying cancer
  - Unprovoked VTE
- Men with unprovoked VTE have a high recurrence risk → consider lifelong therapy
- Women may benefit from additional risk stratification
Risk Stratification

- Serial D-dimer testing and ultrasounds for residual venous occlusion might become useful in estimating recurrence risk, but more studies on how to use them are still needed.
- Thrombophilia testing usually recommended only for selected individuals and only if management will change based on the results.

Newer Anticoagulants

- Direct thrombin inhibitors and Factor Xa inhibitors may become viable alternatives to warfarin in the future.

Bibliography

Bibliography


