Recent Advances in Thromboembolism and Anticoagulation

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Objectives

- Perform risk stratification in patients with PE to guide treatment and triage
- Understand role of IVC filters in patients with VTE
- Determine duration of anticoagulation for venous thromboembolic disease
- Appreciate shrinking role of thrombophilia work up
- Review new oral anticoagulants

A 69 yo man with history of COPD presents with acute pleuritic chest pain. A chest CT reveals multiple segmental PEs. His vitals are stable. Can he be treated as an outpatient?

1. Yes
2. No
3. It depends, is he a lawyer?
Risk Stratification in PE
Recommended by ACCP

"All PE patients should undergo rapid risk stratification"

Kearon C, et al CHEST suppl June 2008

Why Risk Stratify in PE?

- Treatment
  - Is thromblysis indicated
- Disposition
  - Inpatient vs. outpatient
- Triage
  - ICU vs. ward

Mortality Rates in Pulmonary Embolism

- High risk/massive-30%
  - persistent hemodynamic instability
- Int risk/submassive-15%
  - hemodynamically stable with RVD dysfunction
- Low risk/nonmassive PE-3%
  - Hemodynamically stable, no RVD
Length of Hospital Stay Related to Post-Discharge Mortality

- A statewide evaluation of post discharge mortality in PE patients
- Patients with LOS ≤ 4 days had significantly higher mortality rate
- Half of the patients discharged early were high risk

Aujesky D et al Arch Intern Med. 2008

Risk Stratification in Hemodynamically Stable PE

- ECHO
- CTA RV/LV ratio (<1.0)


Serum Biomarkers for Risk Stratification in PE

- Troponin
  - NPV varies
  - Poor positive predictive value
- BNP (>100pg/ml) or NT-proBNP (600ng/L)
  - NPV 94-100% for short term mortality and complications

Becattini C, Circulation. 2007; Cavallazzi, Critical Care Med 2006; Pulls Eur Heart J 2007
Clinical Management of Confirmed Acute Pulmonary Embolism.


Pulmonary Embolism Severity Index

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Points</th>
<th>Class</th>
<th>30 day mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1</td>
<td>A</td>
<td>3.9%</td>
</tr>
<tr>
<td>Male</td>
<td>1</td>
<td>B</td>
<td>6.6%</td>
</tr>
<tr>
<td>Cancer</td>
<td>2</td>
<td>C</td>
<td>10%</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>3</td>
<td>D</td>
<td>13%</td>
</tr>
<tr>
<td>Cerebral bleeding</td>
<td>7</td>
<td>E</td>
<td>16%</td>
</tr>
<tr>
<td>SBP &lt; 90 mmHg</td>
<td>2</td>
<td>F</td>
<td>20%</td>
</tr>
<tr>
<td>History of PE</td>
<td>2</td>
<td>G</td>
<td>20%</td>
</tr>
<tr>
<td>Oxygen saturation &lt;90%</td>
<td>2</td>
<td>H</td>
<td>20%</td>
</tr>
</tbody>
</table>

Aujesky et al Eur Heart Journal 2006

Simplified Pulmonary Embolism Severity Index

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Points</th>
<th>Severity class</th>
<th>30 day mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1</td>
<td>Clinically</td>
<td>0.2%</td>
</tr>
<tr>
<td>Male</td>
<td>1</td>
<td>Major</td>
<td>0.7%</td>
</tr>
<tr>
<td>Cancer</td>
<td>2</td>
<td>Major</td>
<td>0.5%</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>3</td>
<td>Major</td>
<td>1.2%</td>
</tr>
<tr>
<td>Cerebral bleeding</td>
<td>7</td>
<td>Major</td>
<td>0.7%</td>
</tr>
<tr>
<td>SBP &lt; 100 mmHg</td>
<td>2</td>
<td>Major</td>
<td>0.7%</td>
</tr>
<tr>
<td>History of PE</td>
<td>2</td>
<td>Major</td>
<td>0.7%</td>
</tr>
<tr>
<td>Oxygen saturation &lt;90%</td>
<td>2</td>
<td>Major</td>
<td>0.7%</td>
</tr>
</tbody>
</table>

A 69 yo man with history of COPD presents with acute pleuritic chest pain. A chest CT reveals right sided segmental PE. His vitals are stable. Can he be treated as an outpatient?

This patient has PESI score of 89 (severity level III) or HIGH and considered high risk by clinical algorithm—patient should be admitted.

Does this patient with a confirmed diagnosis of PE need doppler ultrasound of the lower extremity to look for DVT?

1. No, it will not change management
2. Yes, it may help with triage and treatment

Prognostic Algorithm for PE

jakobsson c et al. j thromb haemostasis jun 2010
Prognostic Significance of DVT in PE-Recurrence

- 3 month recurrence rate:
  - Cohort 4.5%
  - DVT 7.2%
  - NO DVT 1.7%

Jimenez D, Am J Respir Crit Care Med 2010

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Prognostic Significance of DVT in PE-Mortality

- 3 month mortality rate:
  - Cohort 10.9%
  - DVT 15.2%
  - NO DVT 6.4%
  - HR of PE related death: 4.5

Jimenez D, Am J Respir Crit Care Med 2010

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Residual Vein Thrombosis & VTE Recurrence

- Recurrence rate:
  - No RVO 1%
  - RVO+AC 19%
  - RVO-AC 27%


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Copyright ©2008 American Society of Hematology. Copyright restrictions may apply.
Does this patient with a confirmed diagnosis of PE need doppler ultrasound of the lower extremity to look for DVT?

Yes, findings may provide prognostic information and guide duration of therapy.

**Which of the following are an indication for IVC filter placement?**

- Free floating thrombus on u/s
- Cancer patient with recurrent pe despite anticoagulation
- Neurosurg pt with PE on post op day #2
- None of the above
- All of the above

**IVC Filters**

<table>
<thead>
<tr>
<th></th>
<th>PREPIC STUDY</th>
<th>PREPIC 8 yr FOLLOW UP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Filter</td>
<td>No Filter</td>
</tr>
<tr>
<td>PE @ 12 days</td>
<td>1%</td>
<td>5%</td>
</tr>
<tr>
<td>DVT @ 2 years</td>
<td>20%</td>
<td>11%</td>
</tr>
<tr>
<td>PE @ 2 years</td>
<td>3.4%</td>
<td>6.3%</td>
</tr>
</tbody>
</table>

PREPIC STUDY GROUP; Circulation 2005; Decousus NEJM 1998
**IVC Filters**

- Placement of IVC filters is on the rise since introduction of temporary devices
  - Up to 70% of these are never taken out
  - No randomized controlled studies have evaluated IVC filters without anticoagulation for acute DVT or PE

**Filter complications**

- IVC thrombosis
- Migration/tilt
- Insertion site thrombosis
- Filter thrombosis
- Delay in anticoagulation

**IVC filter guidelines-ACCP**

- Use IVC filter in patients with proximal DVT and contraindication to anticoagulation
- Begin anticoagulation as soon as bleeding risk resolves
- Recommend against routine use of IVC filter in patients with DVT/PE on anticoagulation and as prophylaxis in trauma or SCI

Kearon et al. CHEST 2008

**IVC filter guidelines-BCSH**

- Use IVC filter in proximal DVT with contraindication to anticoagulation
- Begin anticoagulation as soon as bleeding risk resolves (step up)
- Recommend against routine use of IVC filter in patients with DVT/PE on anticoagulation

Baglin, TP et al British J Haematology 2006
IVC filter guidelines-
- May use filter if anticoagulation failure after trial of increased anticoagulation intensity/parenteral agent
- Consider in any preop patient with recent VTE (1 month) in whom AC must be interrupted
- Removable filters should be used if contraindication to anticoagulation may be temporary

Baglin, TP et al British J Haematology 2006

Which of the following are an indication for IVC filter placement?
Only commonly agreed upon indication is patient with acute proximal dvt and contraindication to anticoagulation. Weigh risks and benefits carefully before IVC filter placement Use retrievable filters and remember to remove them Start anticoagulation as soon as bleeding risk resolves

A 48 year old woman with hypertension presents with an unprovoked PE. When should the work up for thrombophilia be sent?
1. Before initiation of anticoagulation
2. Before discharge
3. Anytime after my shift
4. At 3 months, after acute thrombosis resolved
Testing for Laboratory Thrombophilia in VTE

- Is condition sufficiently prevalent?
- Are results reliable in this setting?
- Will results impact management?

Thrombophilia: Prevalence & Impact on Recurrence

<table>
<thead>
<tr>
<th>Prevalence</th>
<th>Increased recurrence risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antithrombin deficiency</td>
<td>3x</td>
</tr>
<tr>
<td>Protein C/S deficiency</td>
<td>1.5-3x</td>
</tr>
<tr>
<td>Double defect</td>
<td>2-5x</td>
</tr>
<tr>
<td>APLS</td>
<td>2-4x</td>
</tr>
<tr>
<td>Factor V Leiden or Prothrombin gene mutation</td>
<td>no increase in absolute recurrence risk</td>
</tr>
</tbody>
</table>

Impact of Acute Thrombosis & Anticoagulation on Thrombophilia Testing

<table>
<thead>
<tr>
<th>Test</th>
<th>Acute VTE</th>
<th>Heparin</th>
<th>Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticardiolipin antibodies</td>
<td>May be elevated</td>
<td>no effect</td>
<td>no effect</td>
</tr>
<tr>
<td>Lupus anticoagulant</td>
<td>May be prolonged</td>
<td>prolonged</td>
<td>prolonged</td>
</tr>
<tr>
<td>Protein C, S</td>
<td>decreased</td>
<td>No effect</td>
<td>decreased</td>
</tr>
<tr>
<td>Antithrombin level</td>
<td>decreased</td>
<td>decreased</td>
<td>no effect</td>
</tr>
<tr>
<td>Factor VIII level</td>
<td>increased</td>
<td>no effect</td>
<td>no effect</td>
</tr>
</tbody>
</table>
A 48 year old woman with hypertension presents with an unprovoked PE. When should the work up for thrombophilia be sent?

Only if indicated, it should be sent after acute thrombosis resolved (3 months).

A 48 year old woman with hypertension presents with an unprovoked PE. How long would you continue anticoagulation?

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

Risk of VTE Recurrence After Cessation of VTE

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>1st yr</th>
<th>Next 5 yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distal DVT</td>
<td>3% (6%)</td>
<td>&lt;10%</td>
</tr>
<tr>
<td>Major-transient</td>
<td>3%</td>
<td>10%</td>
</tr>
<tr>
<td>Minor-transient</td>
<td>5-6%</td>
<td>15%</td>
</tr>
<tr>
<td>Unprovoked</td>
<td>At least 10%</td>
<td>30%</td>
</tr>
<tr>
<td>Recurrent</td>
<td>&gt; 10%</td>
<td>&gt; 30%</td>
</tr>
</tbody>
</table>

Kearon, Blood 2005
Provoked vs Unprovoked

- Provoked
  - Major risk factors: major surgery, major trauma, cancer
  - Minor risk factors: OCP, HRT, pregnancy, airline travel, non-major surgery, minor trauma
  - Associated medical diseases

Guidelines for Duration of Anticoagulation for VTE

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>First episode of VTE secondary to a transient risk factor</td>
<td>3 months (Grade 1A).</td>
<td>4–6 weeks (Grade A).</td>
<td>3 months</td>
</tr>
<tr>
<td>First episode of (idiopathic unprovoked) VTE</td>
<td>At least 3 months, prefer long-term treatment if risk/benefit ratio ok (Grade 1A).</td>
<td>3 months (Grade A).</td>
<td>6 months</td>
</tr>
<tr>
<td>Other (recurrent, active cancer, ...)</td>
<td>Long term (Grade 1A).</td>
<td>At least 6 months (Grade C).</td>
<td>Long term if APLS, AT deficiency or recurrence</td>
</tr>
</tbody>
</table>

BTS PE Guideline Thora2003; Kearon et al CHEST suppl June 2008; Bounisameaux H et al Hematology 2009

Predicting Individual Recurrence Risk

- Residual vein thrombosis
- D-dimer elevation 30 days after stopping anticoagulation
- Clinical decision rule
- Thrombophilia work up
- Clinical presentation of VTE
Management Trial Using D-dimer Results to Determine Duration of Anticoagulation

Clinical Decision Rule

- Clinical predictors
  - Leg red or swollen or hyperpigment 5-7 mos after event
  - D-dimer >250 μg/L on AC
  - BMI >30kg/m2
  - Age > 65
  - Female patients with 0-1 risk factor had recurrence risk of 1.6%: ≥ 2 = 14%

Rodgers et al. CMAJ August 2008

Clinical presentation predicts likelihood and type of recurrence

- Distal (calf vein thrombosis)
  - Low risk of recurrence/PE
- Proximal- nearly 5 fold increased recurrence risk over distal
- PE vs. DVT
  - Patients presenting with PE are 3x more likely to suffer recurrent PE than those presenting with DVT

Baglin T et al. Thromb Haemost. 2010
Duration of Anticoagulation
Unprovoked VTE

After 3 months of Rx, assess bleeding risk. Consider indefinite Rx if PE, male, thrombophilia. Discuss patient preference.

Female: No RVO. Clinical prediction rule < 1 = stop anticoagulation.

Male: No RVO. Stop AC and measure D-dimer at 30 days. If low, ok; if elevated, consider restarting Rx.

Evidence of RVO: Continue anticoagulation and repeat US.

A 48 year old woman with hypertension presents with an unprovoked PE. How long would you continue anticoagulation?

A minimum of 3 months; strongly consider indefinite therapy after risk benefit analysis.

New Oral Anticoagulants-
Mechanism of Action
New Oral Antithrombotics

<table>
<thead>
<tr>
<th>Drug</th>
<th>Oral Agent</th>
<th>Bioavailability</th>
<th>Metabolism</th>
<th>Half Life</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>Glibenclamide</td>
<td>Poor</td>
<td>Prolonged</td>
<td>12 h</td>
</tr>
<tr>
<td>Warfarin</td>
<td>Cimetidine</td>
<td>Good</td>
<td>Rapid</td>
<td>4 h</td>
</tr>
</tbody>
</table>

Dabigatran vs Warfarin: Cumulative Risk of Recurrent VTE or Related Death

How will this talk change your practice?

1. I will risk stratify all patients with PE to guide disposition and treatment
2. I will look for DVT in PE patients to aid in triage and treatment
3. I will no longer send the million dollar thrombophilia work up
4. I will think before placing an IVC filter
5. All of the above

Questions?