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

Risk Stratification in PE
Recommended by ACCP

“All PE patients should undergo rapid risk stratification”

Kearon C, et al CHEST suppl June 2008

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?

1. Yes
2. No
3. It depends, is he a lawyer?
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 (>100 pg/ml) or NT-proBNP (600ng/L)**
  - NPV 94-100% for short term mortality and complications

Becattini C, Circulation. 2007; Cavallazzi, Critical Care Med 2008; Pulm Eur Heart J 2007

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**Pulmonary Embolism Severity Index**

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Points</th>
<th>30 day mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>age</td>
<td>1-65 &lt;1.7%</td>
</tr>
<tr>
<td>Male</td>
<td>10</td>
<td>66.4-3.5%</td>
</tr>
<tr>
<td>Cancer</td>
<td>30</td>
<td>86.10-7.1%</td>
</tr>
<tr>
<td>Heart failure</td>
<td>10</td>
<td>106-125 4-11%</td>
</tr>
<tr>
<td>Chronic lung disease</td>
<td>10</td>
<td>&gt;125 10-25%</td>
</tr>
<tr>
<td>HR &gt; 110</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>SBP &lt; 100 mmHg</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>RR &gt; 30</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Temp &gt; 36</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>A mental status</td>
<td>60</td>
<td></td>
</tr>
<tr>
<td>O2 sat &lt;90%</td>
<td>20</td>
<td></td>
</tr>
</tbody>
</table>

Aujesky et al Eur Heart Journal 2006

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**Simplified Pulmonary Embolism Severity Index**

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Points</th>
<th>30 day mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (1 if &gt; 80)</td>
<td>1</td>
<td>1%</td>
</tr>
<tr>
<td>Cancer</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Heart failure lung disease</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>SBP &lt; 100 mmHg</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>O2 sat &lt;90%</td>
<td>1</td>
<td></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 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
Prognostic Significance of DVT in PE-Mortality

Jimenez D, Am J Respir Crit Care Med 2010

3 month mortality rate
Cohort 10.9%
DVT 16.2%
NO DVT 6.4%
HR of PE related death 4.5

Residual Vein Thrombosis & VTE Recurrence


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

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

**PREPIC Study**

<table>
<thead>
<tr>
<th>Filter</th>
<th>No Filter</th>
</tr>
</thead>
<tbody>
<tr>
<td>PE @ 12 days</td>
<td>1%</td>
</tr>
<tr>
<td>DVT @ 2 years</td>
<td>20%</td>
</tr>
<tr>
<td>PE @ 2 years</td>
<td>3.4%(ns)</td>
</tr>
</tbody>
</table>

**PREPIC Study Group, Circulation 2005; Decousus NEJM 1998**

**PREPIC Study 8 yr Follow Up**

- 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

**IVC 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

**Prevalence**
- Antithrombin deficiency
- Protein C/S deficiency
- Factor V Leiden
- Protein S deficiency
- APLS
- Factor V Leiden and Protein S deficiency
- Antiphospholipid antibodies

**Increased recurrence risk**
- Antithrombin deficiency 3x
- Protein C/S deficiency 1.5-3x
- Double defect 2-5x
- APLS 2-4x

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>No effect</td>
<td>Decreased</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

**BTS Guidelines for Duration of Anticoagulation for VTE**

<table>
<thead>
<tr>
<th>Indication</th>
<th>8th ACCP guidelines 2008</th>
<th>BTS guidelines 2003</th>
<th>BTS recommendations 2008</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>At least 6 months (Grade C)</td>
<td>Long term if APLS AT deficiency or recurrence</td>
<td></td>
</tr>
</tbody>
</table>


**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 ug/L on AC
  - BMI >30kg/m²
  - Age > 65
  - Female patients with 0-1 risk factor had recurrence risk of 1.6%: ≥2 = 14%

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

Duration of Anticoagulation Unprovoked VTE
- After 3 months of tx, assess bleeding risk. Consider indefinite tx (PE, male, thrombophilia). Discuss patient preference.
- Female: No RVO, stop anticoagulation.
- Male: No RVO, stop AC and measure D-dimer at 30days. If low ok, if elevated consider restarting tx.
- Evidence of RVO, continue anticoagulation and repeat US.

Rodgers et al CMAJ August 2008
Baglin T et al J Thromb Haemost. 2010
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

<table>
<thead>
<tr>
<th>MOA</th>
<th>DTI</th>
<th>Direct antiXa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advantages</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NMDA</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### New Oral Antithrombotics

| Drug       | Status   | Approved in:
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran (Pradax)</td>
<td>Approved in FDA in 2008</td>
<td></td>
</tr>
<tr>
<td>Rivaroxaban (Xarelto)</td>
<td>Approved in FDA in 2008</td>
<td></td>
</tr>
<tr>
<td>Apixaban (n/a)</td>
<td>Approved in FDA in 2008</td>
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</tbody>
</table>

### Oral agents

<table>
<thead>
<tr>
<th>Drug</th>
<th>CYP3A4*</th>
<th>pGP inhibitors</th>
<th>PPI</th>
<th>Food</th>
<th>Liver disease</th>
<th>Extremes of wt</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran (Pradax)</td>
<td>Yes</td>
<td>Yes</td>
<td>--</td>
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<td>--</td>
</tr>
<tr>
<td>Rivaroxaban (Xarelto)</td>
<td>Yes</td>
<td>Yes</td>
<td>--</td>
<td>--</td>
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<td>--</td>
</tr>
<tr>
<td>Apixaban (n/a)</td>
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</tbody>
</table>

###Drug Interaction

<table>
<thead>
<tr>
<th>Drug</th>
<th>CYP3A4*</th>
<th>pGP inhibitors</th>
<th>PPI</th>
<th>Food</th>
<th>Liver disease</th>
<th>Extremes of wt</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran (Pradax)</td>
<td>Yes</td>
<td>Yes</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Rivaroxaban (Xarelto)</td>
<td>Yes</td>
<td>Yes</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Apixaban (n/a)</td>
<td>--</td>
<td>--</td>
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<td>--</td>
</tr>
</tbody>
</table>

### Monitoring

<table>
<thead>
<tr>
<th>Drug</th>
<th>ECT, TT Anti Xa, PT Anti X1, hep test</th>
<th>Prodrug is dialyzable</th>
<th>PPI interferes with absorption</th>
<th>Better for renal impairment</th>
<th>Worse for hepatic impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran (Pradax)</td>
<td>--</td>
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</tr>
</tbody>
</table>
Dabigatran vs Warfarin: Cumulative Risk of Recurrent VTE or Related Death


Dabigatran vs Warfarin: Cumulative Risk of Bleeding


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?