A Venous Thromboembolism (VTE) Symposium

Answering Your Top Questions on Treatment and Secondary Prevention
Today’s Presenter:

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- **Title/Affiliation:** Assistant Professor, Director of Inpatient Hospitalist Services, University of Maryland Medical Center.
- **Co-chair VTE Prophylaxis Committee.**
- **Disclosure:** Nothing to disclose
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Medical Director for Professional Development and Research, Division of Hospital Medicine, Henry Ford Hospital

Disclosure:
Scott Kaatz, DO, MSc, FACP, SFHM, has disclosed the following relevant financial relationships:

- Served as an advisor or consultant for: Boehringer-Ingelheim, Bristol-Myers Squibb/Pfizer Partnership, CSL Behring, Daiichi Sankyo, and Janssen
- Served as a speaker or a member of a speakers bureau for: Boehringer-Ingelheim, Bristol-Myers Squibb/Pfizer Partnership, CSL Behring, Daiichi Sankyo, and Janssen
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  Disclosures: Listed on previous slide
Sponsors and support

- This activity has been developed as part of the work of the TEAM-A Partnership, a 10-organization collaboration seeking to improve the care of patients with AFib and VTE conditions.

- This initiative is supported by an unrestricted educational grant from Bristol-Meyers-Squibb/Pfizer.
TEAM-A Collaborative

TEAM-A is an innovative educational collaboration among ten organizations committed to improving patient outcomes through clinician education:

- American College of Cardiology Foundation
- American Heart Association
- School of Medicine and Public Health, University of Wisconsin-Madison
- Healthcare Performance Consulting
- University of Virginia School of Medicine
- California Academy of Family Physicians
- Forefront Collaborative
- IPMA
- Physicians' Institute
- Telligen
At the end of today you should be able to:

- Define the short-term and long-term goals of anticoagulation for VTE
- Determine the optimal length of therapy based on clinical factors
- Manage anticoagulation around medical procedures and special situations
Introduction – Video 1

Cushman M, Creager M. Improving Awareness and Outcomes related to Venous Thromboembolism. JAMA 314(18) 11.10.2015
Meet Allison

Allison is a 49-year-old woman

- She develops unilateral leg pain and swelling 4 days after completing a 10.5 hour air flight.
- No active cancer, paralysis, previous VTE, hemoptysis, being bedridden or other likely diagnosis.
- Her heart rate is 86 and her blood pressure is normal. Arterial oxygen saturation is 97 percent on room air (by pulse oximetry).
- Entire leg is swollen and 4 cm in diameter greater than non-effected leg. She has pitting edema and accentuated superficial veins.
### Wells’ Criteria for DVT

**Clinical Feature** | **Points**
--- | ---
Active cancer | 1
Leg paralysis | 1
Bedridden >3 days | 1
Local vein tenderness | 1
Entire leg swollen | 1
Unilateral swelling >3 cm | 1
Unilateral pitting edema | 1
Superficial veins | 1
Likely alternative | -2

<table>
<thead>
<tr>
<th><strong>Total Points</strong></th>
<th><strong>Risk</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>≥3</td>
<td>High</td>
</tr>
<tr>
<td>1-2</td>
<td>Moderate</td>
</tr>
<tr>
<td>0</td>
<td>Low</td>
</tr>
</tbody>
</table>

DVT = deep vein thrombosis.

www.mdcalc.com/wells-criteria-for-dvt/
Approach to Diagnosis of DVT

Calculate Risk: Allison’s risk is high: 3 to 4

- If HIGH: treat and order confirmatory testing
- If moderate: treat consider D-dimer
- If low: look for other cause of symptoms
When do they need something other than anticoagulation?

**IVC placement?**
- Recent DVT/PE with absolute contraindication to anticoagulants

**Thrombolysis in DVT?**
- Compromise of tissue perfusion (dusky, painful, swollen extremity)
- Ilio-femoral thrombosis?
  - long term follow-up data suggest reduction of post-thrombotic syndrome
- more data to come from the ‘ATTRACT’ trial

What laboratory testing in suspected/confirmed VTE?

- CBC
- Comprehensive metabolic panel, especially kidney function and liver function tests
- Coagulants (PT/INR and PTT)
Does she need to go into the hospital?

- DVT becoming an outpatient diagnosis/treatment
- Access to medications, ability to follow up, social support, pain management, ability for patient education, access to follow up appointments
- Guidelines (2016) support outpatient treatment

Antithrombotic Therapy for VTE Disease:CHEST Guideline and Expert Panel Report
Case – Mr. Smith

- Mr. Smith is a 69 year old that developed sudden shortness of breath and pleuritic chest pain 5 days after hospital discharge (4 day inpatient) for an exacerbation of COPD
- History of post operative DVT 3 years ago
- No cancer or hemoptysis
- Heart rate 110, swelling of entire right lower extremity with pitting edema
What is the likelihood Mr. Smith has PE?

<table>
<thead>
<tr>
<th>Present</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Signs and Symptoms of DVT?</td>
<td>3</td>
</tr>
<tr>
<td>PE is No. 1 Dx or Equally likely Dx</td>
<td>3</td>
</tr>
<tr>
<td>Heart Rate &gt; 100</td>
<td>1.5</td>
</tr>
<tr>
<td>Immobilization at least 3 days, or Surgery in the Previous 4 weeks</td>
<td>1.5</td>
</tr>
<tr>
<td>Previous, objectively diagnosed PE or DVT?</td>
<td>1.5</td>
</tr>
<tr>
<td>Hemoptysis?</td>
<td>1</td>
</tr>
<tr>
<td>Malignancy with treatment within 6 months, or palliative?</td>
<td>1</td>
</tr>
</tbody>
</table>

Wells Criteria for PE

<table>
<thead>
<tr>
<th>Score</th>
<th>Risk</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 4</td>
<td>PE likely</td>
<td>Consider diagnostic imaging</td>
</tr>
<tr>
<td>4 or less</td>
<td>PE unlikely</td>
<td>Consider D-dimer to rule out PE</td>
</tr>
</tbody>
</table>

http://www.emed.ie/Haematology/Wells.php#pe
Remember - if you think Mr. Smith has a PE:
These are your tools…

- For DIAGNOSIS:
  - Clinical probability using the Wells PE score on prior slide
  - D-dimer that is negative is very sensitive for ruling PE out
  - ultimately a CT-angiogram.

- For PROGNOSIS:
  - Your clinical suspicion of patient’s stability (PESI tool, blood pressure, etc);
  - an echocardiogram showing right heart strain or infarction,
  - an elevated BNP showing heart failure, or an elevated troponin showing infarction
### The Pulmonary Embolism Severity Index (PESI) Score

www.mdcalc.com/pulmonary-embolism-severity-index-pesi/

<table>
<thead>
<tr>
<th>Predictors</th>
<th>Points Assigned</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographic characteristics</strong></td>
<td></td>
</tr>
<tr>
<td>Age, per year</td>
<td>Age (Years)</td>
</tr>
<tr>
<td>Male</td>
<td>+10</td>
</tr>
<tr>
<td><strong>Comorbid conditions</strong></td>
<td></td>
</tr>
<tr>
<td>Cancer</td>
<td>+30</td>
</tr>
<tr>
<td>Heart failure</td>
<td>+10</td>
</tr>
<tr>
<td>Chronic lung disease</td>
<td>+10</td>
</tr>
<tr>
<td><strong>Clinical findings</strong></td>
<td></td>
</tr>
<tr>
<td>Pulse &gt;110/min</td>
<td>+20</td>
</tr>
<tr>
<td>Systolic blood pressure &lt;100 mm Hg</td>
<td>+30</td>
</tr>
<tr>
<td>Respiratory rate &gt;30/min</td>
<td>+20</td>
</tr>
<tr>
<td>Temperature &lt;36°C</td>
<td>+20</td>
</tr>
<tr>
<td>Altered mental status</td>
<td>+60</td>
</tr>
<tr>
<td>Arterial oxygen saturation &lt;90%</td>
<td>+20</td>
</tr>
<tr>
<td><strong>Point total and risk classes</strong></td>
<td></td>
</tr>
<tr>
<td>&lt;65=Class I, 66-85=Class II, 86-105=Class III, 106-125=Class IV, &gt;125=Class V.</td>
<td></td>
</tr>
</tbody>
</table>

**Class I:** Low risk

**Class V:** Jump on this right now!

Low-risk PE may be treated out of hospital

<table>
<thead>
<tr>
<th>Outcome</th>
<th>90-day Event Rate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent VTE</td>
<td>1.47% (0.47 to 3.0%)</td>
</tr>
<tr>
<td>Fatal PE</td>
<td>0.47% (0.16 to 1.0%)</td>
</tr>
<tr>
<td>Major Bleeding</td>
<td>0.81% (0.37 to 1.42%)</td>
</tr>
<tr>
<td>Fatal ICH</td>
<td>0.29% (0.06 to 0.68%)</td>
</tr>
<tr>
<td>Overall Mortality</td>
<td>1.58% (0.71 to 2.80%)</td>
</tr>
</tbody>
</table>

Pooled analysis of > 1,200 patients with acute low-risk PE

All were treated as outpatients; 11 studies.

You can treat PE at home when:

The patient is clinically stable with good cardiopulmonary reserve (low PESI score)

And they **DO NOT** have:
- Hypoxia
- BP <100 systolic
- Recent bleeding
- Severe CP
- Platelets < 70,000
- PE on anticoagulation medications
- Severe liver or kidney disease

Patients treated at home need:
- Good social support
- Ready access to medical care / phone access
- Well maintained living conditions
- To be compliant and willing to follow-up
- Feel well enough to manage

*Antithrombotic Therapy for VTE Disease: CHEST Guideline and Expert Panel Report*
3 Ways to Start Anticoagulation

- Heparin OVERLAP with warfarin
- Heparin for 5 days then d/c and START NOAC (Dabigatran and Edoxaban)
- NO Heparin, START NOAC (Rivaroxaban and Apixaban) at higher dose and then de-escalate
Traditional Outpatient Treatment Plan for Most Patients

- Begin a parenteral anticoagulant
  - LMWH (enoxaparin, dalteparin or tinzaparain)
- Overlap with warfarin for at LEAST 5 days and until the INR is $\geq 2.0$ for two **consecutive** days
- Arrange appropriate follow-up appointments, care and activities

*Long-term LMWH preferred for cancer-associated VTE*
## NOACs for Venous Thrombosis: Now Preferred

<table>
<thead>
<tr>
<th>Rivaroxaban XARELTO®</th>
<th>Dabigatran PRADAXA®</th>
<th>Apixaban ELIQUIS®</th>
<th>Edoxaban SAVAYSA®</th>
</tr>
</thead>
<tbody>
<tr>
<td>15 mg bid for 3 weeks then 20 mg once daily</td>
<td>150 mg bid (or 75mg for renal impairment)</td>
<td>10 mg bid for 7 days then 5 mg bid</td>
<td>Daily (60 mg; or 30 mg for renal impairment or low weight)</td>
</tr>
<tr>
<td>Can be used <strong>without</strong> parenteral heparin treatment first</td>
<td>5 days of parenteral treatment needed before dabigatran</td>
<td>Can be used <strong>without</strong> parenteral heparin treatment first</td>
<td>5 days parenteral (LMWH) treatment needed before edoxaban</td>
</tr>
</tbody>
</table>

### FDA Approval Status (for VTE)

<table>
<thead>
<tr>
<th>Rivaroxaban</th>
<th>Dabigatran</th>
<th>Apixaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Approved November 2012</td>
<td>Approved April 2014</td>
<td>Approved August 2014</td>
<td>Approved January 2015</td>
</tr>
</tbody>
</table>

NOAC=Non-vitamin K oral anticoagulant. LMWH=low molecular weight heparin. VTE=Venous thromboembolism.
Reasons **NOT** to treat acute PE/DVT with NOACs

- Severe renal insufficiency (Cr Cl < 30 mL/min)
- tPA (thrombolysis) use contemplated
- PATIENT CANNOT AFFORD MEDICATION
- Known “pro-thrombotic state”
  - Cancer, antiphospholipid syndrome
  - Abrupt cessation/non-adherence

Clinicians’ own discomfort using NOACs can also be a barrier to prescribing these agents to patients.
Reversal Agents

- **Praxbind (idarucizumab)** (reverses dabigatran)
  - [http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm467300.htm](http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm467300.htm)

- Delayed approval until late 2016: **Andexanet Alfa** (antidote to factor Xa inhibitors; rivaroxaban, apixaban, edoxaban)
Warfarin and the New Oral Anticoagulants: A Quick Comparison

<table>
<thead>
<tr>
<th></th>
<th>Warfarin COUMADIN®</th>
<th>Dabigatran(^1) PRADAXA®</th>
<th>Rivaroxaban(^2) XARELTO®</th>
<th>Apixaban(^3) ELIQUIS®</th>
<th>Edoxaban(^4) SAVAYSA®</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Target</strong></td>
<td>VKORC1 Factors II, VII, IX, X</td>
<td>Thrombin</td>
<td>Factor Xa</td>
<td>Factor Xa</td>
<td>Factor Xa</td>
</tr>
<tr>
<td><strong>T (max)</strong></td>
<td>72-96 hours</td>
<td>2 hours</td>
<td>2.5-4 hours</td>
<td>3 hours</td>
<td>2-3 hours</td>
</tr>
<tr>
<td><strong>Half-life</strong></td>
<td>40 hours</td>
<td>14-17 hours</td>
<td>5-9 hours healthy, 9-13 hours elderly</td>
<td>8-15 hours</td>
<td>8-10 hours</td>
</tr>
<tr>
<td><strong>Monitoring</strong></td>
<td>Yes, with INR</td>
<td>Not needed</td>
<td>Not needed</td>
<td>Not needed</td>
<td>Not needed</td>
</tr>
<tr>
<td><strong>Administration</strong></td>
<td>Once daily</td>
<td>Twice daily</td>
<td>Once daily</td>
<td>Twice daily</td>
<td>Once daily</td>
</tr>
<tr>
<td><strong>Metabolism</strong></td>
<td>Cytochrome P450</td>
<td>80% renal, 20% fecal</td>
<td>35% renal</td>
<td>25% renal</td>
<td>35% renal</td>
</tr>
<tr>
<td><strong>Assay</strong></td>
<td>PT/INR</td>
<td>No specific assay commercially available in US</td>
<td>No specific assay commercially available in US</td>
<td>No specific assay commercially available in US</td>
<td>No specific assay commercially available in US</td>
</tr>
</tbody>
</table>

In Summary

- ASSESS RISK
- ASSESS BLEEDING RISK
- TREAT AS OUTPATIENT?
- CHOOSE A REGIMEN
- PATIENT EDUCATION
Allison

- Her original clot was provoked by travel
- You’ve prescribed rivaroxaban
- She’s been under your care for 2 months
- She’s asked how long she has to remain on the medication
How Long Do I treat?

In terms of anticoagulation in VTE:

- **Long term treatment**: Anticoagulation up to 3 months;
- **Extended or indefinite treatment**: Anticoagulation “forever” or until something changes in patients' risk/benefit status
2016 ACCP guidelines

- VTE without cancer
  - NOAC instead of VKA for first 3 months
- VTE with cancer
  - LMWH instead of NOAC or VKA for first 3 months
- Provoked VTE
  - Treat for 3 months
- Unprovoked VTE
  - Low –mod bleeding risk: Extended therapy
  - High bleeding risk- stop at 3 months
  - With cancer: extended therapy regardless of bleeding risk
Clots: provoked or unprovoked

- Provoked blood clot
- Unprovoked clot
- Management and workup different because the RISK is different
- NO difference any more between treatment lengths for PE vs. DVT; NO difference based on size of clot
Provoked Clots Are Associated With

- Surgery
- Estrogen therapy
- Pregnancy
- Leg injury
- Flights of >8 hours

**Provoked clots**

- Better long-term limb health
- Little work-up or additional testing is needed
- Stop anticoagulation after the appropriate duration; usually this will be 3 months
Unprovoked Clots

- Fare poorly/limb threatening
- Commonly associated with an underlying condition
- Need work-up

Unprovoked clots are nearly 2x more likely to recur as provoked clots.¹

Males are at higher risk for recurrence than females.²

Thrombophilia testing

- Acquired and inherited factors
- Acute clot not the time to test
- Homocysteine level, prothrombin gene mutation, and Factor V Leiden okay to test acutely
- Organized approach when stopping antithrombotic agent or soon thereafter.
- Choosing Wisely
Thrombophilia summary

- Antiphospholipid antibody testing is probably appropriate for many patients with unprovoked VTE.
- More comprehensive testing may be indicated with strong family history.
- Testing may be indicated for selected patients with a high risk of recurrence.
  - For example, in some patients with prior VTE who are planning pregnancy.
Treat Proximal DVT or PE (unprovoked) at least 3 months

- Ensure the patient is up-to-date on age-appropriate cancer screening and perform careful physical exam and review of systems. More extensive testing is not helpful.

- Discuss risks/benefits of extended anticoagulant therapy with all patients.
Treat Proximal DVT or PE (unprovoked) at least 3 months

- Encourage extended anticoagulant therapy for patients who:
  - are male
  - have had previous VTE
  - had PE (rather than DVT) as their index event
  - have poor cardiopulmonary reserve
  - have low risk of AC-related bleeding
Treat Proximal DVT or PE (unprovoked) at least 3 months

- Test young patients for antiphospholipid syndrome before permanently discontinuing.
- Consider d-dimer testing if other factors equivocal, patient is female, etc.
Peri-Operative and Peri-Procedural Care
Allison

- She’s been under your care for 2.5 months
- She is still taking the AC medication as prescribed
- She recently had a gall bladder attack
- She is now scheduled to have the gallbladder removed
How to decide about surgery timing and anticoagulation management?

- Determine risk of recurrent VTE
- Determine the procedure related risk of bleeding
- Determine the need to bridge
- Individualize plan based on medication, procedure, renal function, and other factors
Risk for VTE

High Risk
- Recent VTE 0-3 months
- Severe thrombophilia

Moderate Risk
- VTE 3-12 months
- Non-severe thrombophilia
- Recurrent VTE
- Active cancer

Low Risk
VTE > 12 months and no other risk factors
Risk for VTE vs Afib – Video 4
# What is Allison’s bleed risk?

<table>
<thead>
<tr>
<th>Higher risk surgeries for bleed</th>
<th>Lower risk surgeries for bleed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urological</td>
<td>Minor dental</td>
</tr>
<tr>
<td>Large colonic polyps</td>
<td>Derm</td>
</tr>
<tr>
<td>Bowel</td>
<td>Cataract</td>
</tr>
<tr>
<td>Extensive tissue injury</td>
<td></td>
</tr>
<tr>
<td>Pericardial/intracerebral/epidural</td>
<td></td>
</tr>
</tbody>
</table>
## Bridging

<table>
<thead>
<tr>
<th></th>
<th>Warfarin (Coumadin)</th>
<th>Dabigatran (Pradaxa)</th>
<th>Rivaroxaban (Xarelto)</th>
<th>Apixaban (Eliquis)</th>
<th>Edoxaban (Savaysa)</th>
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</thead>
<tbody>
<tr>
<td><strong>Half-life</strong></td>
<td>40 hours</td>
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<td>8-10 hours</td>
</tr>
</tbody>
</table>
Summary of Peri-Procedural Management

- Not many procedures can likely be performed safely without NOAC interruption - Need more data to select patients and procedures
- For patients whose procedure requires interruption - 24 – 48 hours likely sufficient if renal function normal. Longer interruptions if renal impairment and/or high-risk procedure
Summary of Peri-Procedural Management

- More data anticipated from P.A.U.S.E. (Perioperative Anticoagulant Use for Surgery Evaluation)*
- Prospective cohort study- AF pts on Dabigatran, Rivaroxaban or Apixaban undergoing elective procedure
- Individualized decision making required!
Thank you!