HYPERCOAGULABLE STATES

CHIRAG J. AMIN, MD
Disclosures

- I have no personal or professional conflicts of interest to disclose
OVERVIEW

1. HYPERCOAGULABLE WORKUP
2. HOW TO DECIDE ON DURATION OF ANTICOAGULATION
3. NEW ORAL ANTICOAGULANTS
Virchow’s Triad

- **Stasis of Blood Flow**
  - \( \uparrow \) Procoagulants/cofactors
  - \( \downarrow \) Natural anticoagulants
  - Altered endothelial hemostatic interactions
  - Hypofibrinolysis

- **Vessel Injury**

- **Hypercoagulability**

Incidence

Adults

- 1 case per 1000 per year
- 2.5 - 5% of general population
- Venous thromboembolism third most common CV disease
  - ~10% are in hospitalized patients (50% preventable)
## Risk Factors For Venous Thrombosis

<table>
<thead>
<tr>
<th>Acquired</th>
<th>Inherited</th>
<th>Mixed/Unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advancing age</td>
<td>Factor V Leiden (FVL)</td>
<td>Homocysteine ↑</td>
</tr>
<tr>
<td>Obesity</td>
<td>Prothrombin G20210A</td>
<td>Factor Levels ↑</td>
</tr>
<tr>
<td>Prior thrombosis</td>
<td>Protein C deficiency</td>
<td>APC resistance</td>
</tr>
<tr>
<td>Immobilization</td>
<td>Protein S deficiency</td>
<td>May-Thurner Syndrome</td>
</tr>
<tr>
<td>Major surgery</td>
<td>Antithrombin deficiency</td>
<td>Paget-Schroetter Syndrome</td>
</tr>
<tr>
<td>Malignancy</td>
<td>Dysfibrinogenemias (rare)</td>
<td></td>
</tr>
<tr>
<td>Estrogens</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antiphospholipid antibody syndrome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myeloproliferative disorders, IBD, Nephrotic syndrome, Heparin induced thrombocytopenia, PNH</td>
<td></td>
<td>IDIOPATHIC</td>
</tr>
</tbody>
</table>
Who Do You Evaluate?

- < 60 years, 1st episode, idiopathic
- Risk factors?
  - Birth control pill
  - Estrogen replacement
  - Pregnancy
- Recurrent VTE even in setting of known risk factors
- VTE in unusual sites
  - Cerebral venous sinus, hepatic or mesenteric veins
- Recalcitrant superficial phlebitis
- Warfarin induced skin necrosis
- Strong family history
- ? Recurrent Miscarriages
The “Hypercoagulable Workup”

- Genetic test for Factor V Leiden Mutation or coagulation assay for Activated Protein C Resistance (if abnormal, confirm genetically)
- Genetic test for Prothrombin G20210 mutation
- Functional assay of Antithrombin*
- Functional assay of Protein C*
- Functional Protein S Assays*

- Tests for Antiphospholipid Antibody Syndrome
- Measurement of fasting plasma homocysteine (hcy) level?

* Can omit in patients with a first VTE at age >50 and a negative family history
<table>
<thead>
<tr>
<th>Thrombophilia Trait</th>
<th>Caucasian General Population (% Carriers)</th>
<th>Unselected Patients with VTE (% Carriers)</th>
<th>Selected Patients with VTE (% Carriers)</th>
<th>Relative Risk of VTE (Case-Control Studies)</th>
<th>Relative Risk of VTE (Family Studies)</th>
<th>Annual Incidence of VTE (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AT Deficiency</td>
<td>0.02-0.16</td>
<td>1.9</td>
<td>4.3</td>
<td>5</td>
<td>5-8</td>
<td>1-2</td>
</tr>
<tr>
<td>PC Deficiency</td>
<td>0.2-0.4</td>
<td>3.7</td>
<td>4.8</td>
<td>6.5</td>
<td>5-8</td>
<td>1-2</td>
</tr>
<tr>
<td>PS Deficiency</td>
<td>—</td>
<td>2.3</td>
<td>4.3</td>
<td>1.7</td>
<td>5-8</td>
<td>1-2</td>
</tr>
<tr>
<td>Factor V Leiden</td>
<td>4.8</td>
<td>18.8</td>
<td>18.1</td>
<td>7 (Heterozygotes) 40-80 (Homozygotes)</td>
<td>2-4</td>
<td>0.19-0.67</td>
</tr>
<tr>
<td>PT G20210A</td>
<td>2.0</td>
<td>7.1</td>
<td>7.3</td>
<td>2-3</td>
<td>2</td>
<td>0.13</td>
</tr>
<tr>
<td>FVL + PT G20210A</td>
<td>0.01 (Expected)</td>
<td>—</td>
<td>2.2</td>
<td>20</td>
<td>6</td>
<td>0.57</td>
</tr>
</tbody>
</table>

## Sites of Thrombosis

<table>
<thead>
<tr>
<th>ABNORMALITY</th>
<th>ARTERIAL</th>
<th>VENOUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factor V Leiden</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Prothrombin 20210A</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>AT Deficiency</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Protein C Deficiency</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Protein S Deficiency</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Hyperhomocysteinemia</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Antiphospholipid Syndrome</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>
Two Most Common Inherited Thrombophilias

- **Factor V Leiden Gene Mutation**
  - Less efficiently degraded by APC than normal factor Va

- **Prothrombin Gene Mutation**
  - Elevates baseline prothrombin level 30%
# First Episode of Deep Venous Thrombosis (Leiden Thrombophilia Study)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>1</td>
</tr>
<tr>
<td>P20210A heterozygote</td>
<td>2.8↑</td>
</tr>
<tr>
<td>Oral contraceptives</td>
<td>4 X↑</td>
</tr>
<tr>
<td>FVL heterozygote</td>
<td>7 X↑</td>
</tr>
<tr>
<td>Oral contraceptives + FVL</td>
<td>35 X↑</td>
</tr>
<tr>
<td>FVL homozygote</td>
<td>80 X↑</td>
</tr>
</tbody>
</table>
## First Episode of Deep Venous Thrombosis (Leiden Thrombophilia Study)

<table>
<thead>
<tr>
<th></th>
<th>Absolute Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>1 out of 12,000</td>
</tr>
<tr>
<td>Oral contraceptives</td>
<td>1 out of 3,500</td>
</tr>
<tr>
<td>FVL heterozygote</td>
<td>1 out of 1,700</td>
</tr>
<tr>
<td>Oral contraceptives + FVL</td>
<td>1 out of 500</td>
</tr>
<tr>
<td>FVL homozygote</td>
<td>1 out of 150</td>
</tr>
</tbody>
</table>
“Natural” anticoagulants

- Antithrombin
- Protein C
- Protein S
  - Screening test should always include Activity level

Confounders
- **Pregnancy, BCP**
- **Acute Thrombosis**
- Liver disease
- Anticoagulants
  - Warfarin (Protein C and S)
  - LMWH (Antithrombin)
Risk of Recurrent Venous Thrombosis in Patients with Hereditary Thrombophilia

- Heterozygosity for Factor V Leiden (FVL) or Prothrombin (PT) G20210A do not increase risk
- Higher in heterozygotes with both FVL and PT G20210A (retrospective studies); probably higher in homozygotes with FVL
- Antithrombin, Protein C, Protein S Deficiency
  - High in selected kindreds with strong clinical penetrance (retrospective studies)
  - Little data in unselected patients
Treatments for Protein C, S, and Antithrombin

- Initial treatment, heparin, low-molecular weight heparins, and coumadin

- Rare refractory cases
  - Antithrombin
    - Antithrombin Concentrate (Thrombate III®)
      - Also, used for prophylaxis in high risk procedures
  - Protein C and Protein S
    - Concentrates available in Europe but rarely used

- Fresh Frozen Plasma can be used for all three
Methylenetetrahydrofolate reductase [MTHFR] Mutation

Homocysteine’s intracellular metabolism occurs through remethylation to methionine or transulfation to cysteine

- Don’t order it
  - MTHFR genetic mutations (C677T and A1298C)
  - 12% are homozygous for the mutation

- HCY Lowering by B-vitamin Supplements Does Not Lower Risk of Recurrent Thrombosis (Multiple trials-arterial/venous)
  - HOPE 2
  - VITRO Study
  - NORVIT (trend to worse outcomes on B supplements)

De Stefano V et al. Blood Vol 87(9)1996:3531-3544. Pg 3534
Summary of Pros and Cons of Testing

**Pros**
- May help explain why an individual has had a thrombosis or why families have a tendency toward thrombosis
- Anticipatory advice (future risk avoidance)
- May help identify family members at risk
- Occasionally influences clinical management

**Cons**
- What to do with this information?
- Insurance/genetic discrimination
- Anxiety and family issues
- Risk of overtreatment?
- Expensive (doubtful cost benefit)
- Usually does not change clinical management
- High chance of false positives
Antiphospholipid Syndrome (APLS)

- One or more episodes of venous, arterial or small vessel thrombosis
- Pregnancy morbidity
  - One or more miscarriages after 10\textsuperscript{th} week
  - Three or more miscarriages before 10\textsuperscript{th} week
  - One or more morphologically normal pregnancies in setting pre-eclampsia or eclampsia with 34 or < gestational weeks
- APA on 2 or more occasions at least 12 weeks apart
  - Moderate or high titer IgG and/or IgM aCL
  - IgG or IgM to beta-2-GPI
  - Lupus anticoagulant
- Associated with SLE, cancer, infections, drugs, idiopathic
Manifestations

- Venous thrombosis
- Arterial thrombosis
- Pregnancy loss
- ITP
- Valvular Heart Disease (Libman-Sacks endocarditis)
- Catastrophic APLS
  - Widespread thrombotic disease
  - TTP-like syndrome
Retrospective studies indicated that patients with APLS require a target INR range of >3 to obtain adequate antithrombotic protection. Two randomized trials have shown that an INR of 2-3 is adequate in patients with venous thrombosis.

Turpie, A. G.G. *Eur Heart J* 2008 29:155-165
Thrombosis doggy bag

- Negative work-up does not rule out the presence of a hypercoagulable state nor does a positive workup confer a hypercoagulable state
- Superficial phlebitis may be a symptom of an underlying thrombophilia
- Patients with APLS and lupus anticoagulants may have discordant INRs
Evaluation for Malignancy in the Patient Presenting with Thrombosis

- Available data do not support an extensive search for occult malignancy

- However, recurrent idiopathic events should raise awareness for age appropriate malignancies
May-Thurner Syndrome

- Women
- 20-40’s
- Left leg edema with or without DVT
- Left common iliac vein compressed by right common iliac artery

Tx:
- Anticoagulation, Thrombolyis, Angioplasty, Stent, and/or Surgery
Compression of the left common iliac vein

Angioplasty of the left iliac vein

After Angioplasty
Catheter directed thrombolysis

- Consider catheter-directed thrombolysis in symptomatic proximal DVT
  - Currently no data to support that improves overall survival or outcome
  - Limited data for improvement of postthrombotic syndrome
- Massive PE - (SBP<90 mmHg sustained for at least 15 min or requiring inotropic support)
  - Improves OS
  - Submassive PE: Trials running if it improves mortality or morbidity (pulmonary HTN)
- Nationwide randomized study currently underway on benefits of thrombolysis (ATTRACT trial)
Paget-Schroetter Syndrome (or “effort-thrombosis” or thoracic outlet syndrome)

- Presentation as Upper Extremity DVT, swelling, and/or pain.
- Caused by compression of subclavian vein against the first rib
- Dx: Venogram
- Tx:
  - Anticoagulation, thrombolysis/angioplasty
  - Surgery early-on upfront leads to better outcomes
  - Surgeries performed at high volume centers lead to better outcomes

Images: ©http://thoracicoutletsyndromes.com/
DURATION OF ANTICOAGULATION

- Who should be on indefinite anticoagulation?
VTE 5 Year Recurrence Risk

- Surgical provocation: 3%
- Nonsurgical provocation: 15%
- Unprovoked: 30%

Erratum in: Chest. 2012 Dec;142(6):1698-1704
**Risk Factors for Bleeding with Anticoagulant Therapy & Estimated Risk of Major Bleeding in Low-, Moderate-, & High-Risk Categories**

**Risk Factors**
- Age > 65 years
- Age >75 years
- Previous bleeding
- Cancer
- Metastatic cancer
- Renal failure
- Liver failure
- Thrombocytopenia
- Previous stroke
- Diabetes
- Anemia
- Antiplatelet therapy
- Poor anticoagulant control
- Comorbidity & reduced functional capacity
- Recent surgery
- Frequent falls
- Alcohol use

<table>
<thead>
<tr>
<th>Categorization of Risk of Bleeding</th>
<th>Low Risk (0 Risk Factors)</th>
<th>Moderate Risk (1 Risk Factor)</th>
<th>High Risk (&gt; 2 Risk Factors)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anticoagulation 0-3 Months</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline risk (%)</td>
<td>0.6</td>
<td>1.2</td>
<td>4.8</td>
</tr>
<tr>
<td>Increased risk (%)</td>
<td>1.0</td>
<td>2.0</td>
<td>8.0</td>
</tr>
<tr>
<td>Total risk (%)</td>
<td>1.6</td>
<td>3.2</td>
<td>12.8</td>
</tr>
<tr>
<td><strong>Anticoagulation After First 3 Months</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline risk (% per year)</td>
<td>0.3</td>
<td>0.6</td>
<td>≥ 2.5</td>
</tr>
<tr>
<td>Increased risk (% per year)</td>
<td>0.5</td>
<td>1.0</td>
<td>≥ 4.0</td>
</tr>
<tr>
<td>Total risk (% per year)</td>
<td>0.8</td>
<td>1.6</td>
<td>≥ 6.5</td>
</tr>
</tbody>
</table>

Recurrence VTE: Length of Anticoagulant Therapy

Patients with VTE who should be treated for 3 months & who should be treated indefinitely

Treat for 3 Months & Reassess

- Isolated distal DVT
  - Stop at 3 Months

- Reversible provoking factor
  - Stop at 3 Months

- Unprovoked proximal DVT or PE

- Cancer
  - Indefinite therapy or until cancer inactive

1: Male would stop even if recurrence risk is 16% in 1st year
Female would stop even if recurrence risk 10% in 1st year

2: Male would stay on if recurrence risk 8% in 1st year
Female would stay on even if recurrence risk 5% in first year

Treat For 3 Months & Reassess

- High Bleeding Risk
  - OR
  - Prefers to stop even if D-dimer was positive
  - Stop at 3 Months

- Others
  - Stop & measure D-dimer after 1 month

- Not High Bleeding Risk
  - AND
  - Prefers to stay on even if D-dimer negative
  - Indefinite Therapy

- Second VTE
  - Indefinite Therapy

Negative D-dimer
- Stay off therapy
  - (Stop at 3 Months)

Positive D-dimer
- Restart therapy
  - (Indefinite therapy)

Use of D-dimer testing to guide treatment decisions in patients with a first unprovoked proximal DVT or PE is optional. If D-dimer not used, the decision is based on risk of bleeding & patient preference (estimated risk of recurrence in the first year of 12% for men and 8% for women).

Guidelines on Duration of Anticoagulant Therapy

- **First event with reversible or time limited risk factor**
  - 3-6 months at INR 2-3

- **Unprovoked VTE, first or second event**
  - 6 months at INR 2-3, then consider Indefinite anticoagulation at INR 2-3 weighing recurrence versus bleeding risk

- **Special Situation – Indefinite anticoagulation**
  - First event with
    - Cancer until resolved (consider chronic LMWH)
    - Antiphospholipid antibody syndrome
    - Antithrombin deficiency or multiple genetic defects, ? Deficiencies of protein C or protein S
    - Cardiovascular compromise or life-threatening event

- **Vigorous prophylaxis in high risk situations**

- **Think of bleeding if a patient with a therapeutic INR presents with new pain and swelling**
Criteria for Long-Term Oral Anticoagulation in Patients with Venous Thrombosis

- Resolution of triggering risk factor
- Sites and severity of thrombosis
- Bleeding risk
- Identification of a prothrombotic defect coupled with family’s thrombotic history
- PATIENT PREFERENCE (role of lifestyle and occupation)
- Aspirin provides mild benefit
New Oral Anticoagulants

Dabigatran, Apixaban, and Rivaroxaban approved for non-valvular atrial fibrillation
Rivaroxaban and Dabigatran* approved for treatment of DVT.
*Dabigatran requires parenteral treatment prior

Adapted from Weitz & Bates, J Thromb Haemost 2007
New oral anticoagulants

Table 1. Properties of warfarin and oral inhibitors of thrombin and factor Xa inhibitors approved for use in the United States

<table>
<thead>
<tr>
<th></th>
<th>Warfarin</th>
<th>Dabigatran etexilate</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Target</strong></td>
<td>Vitamin K epoxide reductase (VKORC1) lowers levels of vitamin K-dependent coagulation factors</td>
<td>Thrombin</td>
<td>Factor Xa</td>
<td>Factor Xa</td>
</tr>
<tr>
<td><strong>Prodrug</strong></td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>Bioavailability</strong></td>
<td>&gt; 95%</td>
<td>6.5%</td>
<td>80%</td>
<td>80%</td>
</tr>
<tr>
<td><strong>Tmax</strong></td>
<td>2 h</td>
<td>2.5-4 h</td>
<td>3 h</td>
<td>3 h</td>
</tr>
<tr>
<td><strong>Half-life</strong></td>
<td>40 h</td>
<td>12-14 h</td>
<td>7-13 h</td>
<td>8-13 h</td>
</tr>
<tr>
<td><strong>Routine coagulation monitoring</strong></td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>Dosing</strong></td>
<td>Once daily (INR-adjusted)</td>
<td>Fixed, BID</td>
<td>Fixed, BID</td>
<td>Fixed, BID</td>
</tr>
<tr>
<td><strong>Elimination</strong></td>
<td>Hepatically metabolized</td>
<td>80% renal</td>
<td>67% renal (half is inactive drug), 33% fecal</td>
<td>25% renal, 75% fecal</td>
</tr>
<tr>
<td><strong>Potential drug interactions</strong></td>
<td>CYP 2C9, 3A4, and 1A2</td>
<td>Potent P-gp inhibitors and P-gp inducers</td>
<td>Strong dual CYP 3A4 and P-gp inhibitors/inducers</td>
<td>Strong dual CYP 3A4 and P-gp inhibitors/inducers</td>
</tr>
</tbody>
</table>

Bauer K. ASH Educ Program. Hematology 2013
Apixaban (Xa)

<table>
<thead>
<tr>
<th>TRIALS</th>
<th>ADVANCE</th>
<th>AMPLIFY</th>
<th>ARISTOTLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>DVT prophylaxis</td>
<td>2.5mg BID</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Treatment of VTE</td>
<td>NA</td>
<td>10mg BIDx7 days</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5mg BID</td>
<td></td>
</tr>
<tr>
<td>Non-valvular Atrial Fibrillation (FDA)</td>
<td>NA</td>
<td>NSA</td>
<td>5mg BID</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2.5mg BID*</td>
</tr>
</tbody>
</table>

*2.5mg BID if any of the 2 of the following 3 characteristics: Age ≥80, weight ≤60kg, or serum creatinine ≥1.5mg/dl

- Only 25% eliminated by renal
- Noninferior
- Bleeding rates were lower at all endpoints
Rivaroxaban (Xa)

<table>
<thead>
<tr>
<th>TRIALS</th>
<th>RECORD</th>
<th>EINSTEIN</th>
<th>ROCKET</th>
</tr>
</thead>
<tbody>
<tr>
<td>DVT prophylaxis (FDA)</td>
<td>10 mg QD</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Treatment of VTE (FDA)</td>
<td>NA</td>
<td>15mg BIDx21 days, then 20mg QD</td>
<td>NA</td>
</tr>
<tr>
<td>Non-valvular Atrial Fibrillation (FDA)</td>
<td>NA</td>
<td>NA</td>
<td>20mg QD 15mg QD*</td>
</tr>
</tbody>
</table>

*15mg QD creatinine clearance of 15-30mL/min ≥1.5mg/dl

- Needs to be taken with food for absorption
- Noninferior
- Overall Bleeding rates similar
  - Higher rates of GI Bleeding
Dabigatran (IIa)

<table>
<thead>
<tr>
<th>TRIALS</th>
<th>RE-NOVATE RE-MODEL RE-MOBILE</th>
<th>RE-COVER</th>
<th>RE-LY</th>
</tr>
</thead>
<tbody>
<tr>
<td>DVT prophylaxis</td>
<td>150mg or 220mg qd</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Treatment of VTE</td>
<td>NA</td>
<td>150mg BID*</td>
<td>NA</td>
</tr>
<tr>
<td>Non-valvular Atrial Fibrillation (FDA)</td>
<td>NA</td>
<td>NA</td>
<td>150mg BID 75mg BID**</td>
</tr>
</tbody>
</table>

- *All patients initially treated with parenteral 7 days prior
- **75mg BID creatinine clearance 15-29m/min
- 150mg BID superior to warfarin. 110mg BID equivalent with less bleeding rates (latter dose not FDA approved)
  - Other trials noninferior
- Overall bleeding rates similar
  - GI Bleeding higher, particular >85yo
- Dyspepsia common side effect (10%)
- ? Mild increase risk for MI
Can you measure it?

- **Dabigatran**: Ecarin Clotting Time, Thrombin Time
- **Apixaban, Rivaroxaban**:
  - PT more sensitive than PTT but reagant specific
  - Anitxa levels can be measured but not standardized

---

**TABLE 5. Effects of the New Oral Anticoagulants on Routine and Special Coagulation Assays**

<table>
<thead>
<tr>
<th>Assay</th>
<th>VKA</th>
<th>Dabigatran</th>
<th>Rivaroxaban/apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>aPTT</td>
<td>Mild increase</td>
<td>Variable, normal or prolonged</td>
<td>Variable, normal or prolonged</td>
</tr>
<tr>
<td>PT/INR</td>
<td>Moderate increase</td>
<td>Variable, normal or prolonged</td>
<td>Variable, normal or prolonged</td>
</tr>
<tr>
<td>TCT</td>
<td>Unaffected</td>
<td>Marked increase</td>
<td>Unaffected</td>
</tr>
<tr>
<td>aPTT mixing study</td>
<td>Complete correction</td>
<td>Incomplete correction</td>
<td>Incomplete correction</td>
</tr>
<tr>
<td>PT mixing study</td>
<td>Incomplete correction</td>
<td>Incomplete correction</td>
<td>Incomplete correction</td>
</tr>
<tr>
<td>LA (screening and confirmatory)</td>
<td>Normal or false-positive</td>
<td>False-positive</td>
<td>False-positive</td>
</tr>
<tr>
<td>Activated protein C resistance ratio</td>
<td>Possible interference</td>
<td>False elevated</td>
<td>False elevated</td>
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<td>False elevated or decreased</td>
<td></td>
</tr>
<tr>
<td>aPTT-dependent clotting factor assays</td>
<td>Decreased factor IX</td>
<td>False decreased factors: VIII, IX, and IX</td>
<td>False decreased factors: VIII, IX, and XIa</td>
</tr>
<tr>
<td>Antithrombin activity</td>
<td>Factor Xa based</td>
<td>Unaffected</td>
<td>Unaffected</td>
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<td></td>
<td>Factor II based</td>
<td>Unaffected</td>
<td>False elevated</td>
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<td></td>
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<td>Unaffected</td>
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<td>False elevated</td>
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<td>Protein C activity</td>
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<td></td>
<td>Clot based</td>
<td>Decreased</td>
<td>False elevated</td>
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<tr>
<td></td>
<td>Chromogenic based</td>
<td>Decreased</td>
<td>False elevated</td>
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<tr>
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<td></td>
<td>Protein S activity, clot based</td>
<td>False elevated</td>
</tr>
</tbody>
</table>

*aPTT = activated partial thromboplastin time; INR = international normalized ratio; LA = lupus anticoagulant; PT = prothrombin time; TCT = thrombin clotting time; VKA = vitamin K antagonist.
*aOnly at supratherapeutic levels.
Adapted from Hematology Am Soc Hematol Educ Program.**

What do with bleeding?

- Short half-life so conservative therapy may help
- Fresh Frozen Plasma is not recommended due to lack of efficacy
- Dabigatran is dialyzable
- Activated and Unactivated (Prothrombin Complex Concentrates (PCCs))
  - Activated (FEIBA©)
  - Unactivated: 3 factor (2,9,10) - Profilnine© vs 4 factor (2,7,9,10) - Kcentra©
    - Suggestion that 4 factor is better
    - Suggestion of possible poorer efficacy in Dabigatran
- Recombinant VIIa (Novoseven©)
- Future:
  - Dabigatran Antibody
  - Factor Xa molecule which has a higher affinity to the inhibitors
- www.clotconnect.org (Personally think they relay good data/information)
Other Fun Facts

- **Drug Interactions limited but…**
  - Rifampin
  - Seizure medications (Phenytoin, Carbamazepine)
  - Ketoconazole (not Fluconazole)
  - Antiretrovirals (Ritonavir)
  - Herbal Medications: St. John’s Wart

- **Unknown populations**
  - Creatinine clearance <30
  - Age over 85
  - Extremes body weight (morbidly obese, malnourished)
  - Gastric Bypass surgery
  - Malignancy
**WHAT I DISCUSS WITH EVERY PATIENT**

1. These drugs seem to have similar/better efficacy when compared with warfarin with fewer intracranial hemorrhage.
2. Risk of major bleeding is reduced with apixaban, but equivalent with rivaroxaban and dabigatran.
3. Dabigatran and rivaroxaban seem to increase the rate of GI bleeding.
4. We cannot measure levels to adjust for drug interactions.
5. The recommendations for reversal of these drugs are based on experiments in lab animals and test tubes.
6. We have been using warfarin for 60 years compared with 3-5 years for the novel agents.
7. **COST!!!!!!**
QUESTIONS?