Hemostasis and Thrombosis for Primary Care Providers: An Update

43rd Annual Advances in Internal Medicine

Andrew D. Leavitt, MD

June 25, 2015

**Topic Outline**

- **Direct Oral Anti-Coagulants – DOACs**
  - Update and Review – Focus on Venous Thromboembolic Disorders
  - Drug Interactions – Spinach is not the issue, but there are issues...
  - Laboratory Monitoring
  - Reversal?
  - My patient needs a procedure
  - Specific patient populations

- **Prothrombin Complex Concentrates**

- **Superficial VT**

- **Act Wisely**

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### DOACs – 5 Years Young* (old?)

<table>
<thead>
<tr>
<th>Year</th>
<th>FDA Approved</th>
</tr>
</thead>
<tbody>
<tr>
<td>2009-2014</td>
<td>30 Phase III studies</td>
</tr>
<tr>
<td>Involving &gt;170,000 patients</td>
<td></td>
</tr>
<tr>
<td>For 6 different indications</td>
<td></td>
</tr>
<tr>
<td>➔ 4 DOACs FDA approved</td>
<td></td>
</tr>
</tbody>
</table>

Table & numbers from: Schulman, Thromb and Haemost (2014)111:575-82; and thanks to Ken Bauer, MD

*vs. Coumadin: 60+ years old

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### DOACs – A Few Summary Points to Start

- All have a black box warning with two key points:
  - Premature discontinuation increases risk of thrombotic events
  - These findings are from the **Atrial Fibrillation trials**
    - Therefore: Parenteral bridging if DOAC to Warfarin
  - Spinal/Epidural Hematoma
    - Need protocols for stopping/starting around procedures

- Decline in renal function leads to increased bleeding risk
  - Think Elderly, NSAIDs, Dehydration/vomiting (END)

- Be sure proceduralist is aware your patient is taking the medication

- Do not use with mechanical heart valves

- Patients need follow up but you lack the INR clinic connection
### Coagulation Cascade in Patients

![Diagram of the coagulation cascade in patients](image)

### DOACs – some important characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bioavailability</td>
<td>5%</td>
<td>Almost 100%</td>
<td>50%</td>
<td>62%</td>
</tr>
<tr>
<td>Time to maximum effect (tmax)</td>
<td>1.5-2 h</td>
<td>2 h</td>
<td>3-4 h</td>
<td>1-2 h</td>
</tr>
<tr>
<td>Half-life (t1/2)</td>
<td>17-17 h</td>
<td>5-9 h</td>
<td>8-15 h</td>
<td>9-10 h</td>
</tr>
<tr>
<td>Plasma protein binding</td>
<td>31%</td>
<td>92-99%</td>
<td>37%</td>
<td>80-90%</td>
</tr>
<tr>
<td>Renal elimination of active drug</td>
<td>80%</td>
<td>66%</td>
<td>75%</td>
<td>35-39%</td>
</tr>
<tr>
<td>Interactions mediated by P-gp</td>
<td>P-gp, CYP3A4</td>
<td>P-gp, CYP3A4</td>
<td>P-gp, CYP3A4</td>
<td>P-gp (CYP3A4)</td>
</tr>
<tr>
<td>Food effect</td>
<td>Absorption delayed, not reduced</td>
<td>Required for absorption of doses &gt;10 mg</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

Table from: Schulman, Thromb and Haemost (2014) 111: 575-82

### VTE Prophylaxis – Orthopedic Setting

**DOSING**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Dosing Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hip Replacement</td>
<td>10 mg qD x 35D&lt;sup&gt;1&lt;/sup&gt; Start 6-10 hrs post-op&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Knee Replacement</td>
<td>10 mg qD x 12D&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>10 mg qD x 35D&lt;sup&gt;1&lt;/sup&gt; Start 6-10 hrs post-op&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Apixaban</td>
<td>2.5 mg BID x 35D&lt;sup&gt;1&lt;/sup&gt; Start 12-24 hrs post-op&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

* Provided that adequate hemostasis has been achieved

**RESULTS:** Reduction in VTE; No increased bleeding

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*Compared to 40 mg subQ qDay or 30mg subQ q2 enoxaparin started 12 hours before surgery.*

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### VTE Treatment - Primary

**DOSES**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>DOSING</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Traditional</strong></td>
<td>LMWH</td>
</tr>
<tr>
<td>Vitamin K Antagonist</td>
<td>Day 1 → Day 7-10** “BRIDGING” 3-6 months</td>
</tr>
<tr>
<td><strong>Dabigatran</strong></td>
<td>LMWH</td>
</tr>
<tr>
<td>2,539 pts w/DVT PE</td>
<td>Day 1 – Day 7-10 “SWITCHING” 6 months</td>
</tr>
<tr>
<td>Dabigatran 150 mg BID</td>
<td></td>
</tr>
<tr>
<td><strong>Rivaroxaban</strong></td>
<td>LMWH</td>
</tr>
<tr>
<td>3,449 pts w/DVT PE</td>
<td>Day 1 – Day 3 weeks + &amp; then 20 mg qDay</td>
</tr>
<tr>
<td>Rivaroxaban 15 mg BID X 3 weeks &amp; then 20 mg qDay</td>
<td></td>
</tr>
<tr>
<td><strong>Apixaban</strong></td>
<td>LMWH</td>
</tr>
<tr>
<td>5,395 pts w/DVT PE</td>
<td>Day 1 – Day 1 week &amp; then 5 mg BID</td>
</tr>
<tr>
<td>Apixaban 10 mg BID X 1 week &amp; then 5 mg BID</td>
<td></td>
</tr>
<tr>
<td><strong>Edoxaban</strong></td>
<td>LMWH</td>
</tr>
<tr>
<td>8,290 pts w/DVT PE</td>
<td>Day 1 – Day 7 “SWITCHING” 3, 6, 12 months</td>
</tr>
<tr>
<td>Edoxaban 60 or 30mg (CrCl 30-50, &lt;60kg) qD</td>
<td></td>
</tr>
</tbody>
</table>

*All compared to ‘traditional’ approach; not tested in CrCl <30 ** Until INR >2 for 2 days
**VTE Treatment - Outcomes**

### Initial Treatment Phase

<table>
<thead>
<tr>
<th>Drug, trial</th>
<th>Primary efficacy outcome</th>
<th>Major bleeding</th>
<th>Major + CRNMB</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hazard ratio (95% CI)</td>
<td>Absolute difference in risk</td>
<td>Hazard ratio (95% CI)</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>1.10</td>
<td>0.4%</td>
<td>0.82</td>
</tr>
<tr>
<td>RE-DOSE</td>
<td>(0.66-1.84)</td>
<td>(0.69-1.84)</td>
<td>(0.68-1.84)</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>1.08</td>
<td>0.2%</td>
<td>0.69</td>
</tr>
<tr>
<td>RE-COVER II</td>
<td>(0.64-1.8)</td>
<td>(0.36-1.32)</td>
<td>(0.45-1.84)</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>1.12</td>
<td>0.1%</td>
<td>0.80</td>
</tr>
<tr>
<td>ENOXETIN PE</td>
<td>(0.75-1.68)</td>
<td>(0.31-0.97)</td>
<td>(0.76-1.68)</td>
</tr>
<tr>
<td>Apixaban</td>
<td>0.84</td>
<td>0.4%</td>
<td>0.84</td>
</tr>
<tr>
<td>(0.66-1.10)</td>
<td>(0.17-0.55)</td>
<td>(0.71-0.90)</td>
<td>(0.71-0.90)</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>0.81</td>
<td>0.4%</td>
<td>0.81</td>
</tr>
<tr>
<td>(0.70-1.1-1-3)</td>
<td>(0.36-0.55)</td>
<td>(0.71-0.90)</td>
<td>(0.71-0.90)</td>
</tr>
</tbody>
</table>

CRNMB: clinically relevant non-major bleeding; CI: confidence interval

*Recurrent symptomatic VTE or related death; *P value for non inferiority for Primary efficacy outcome is <0.001 for all agents

Table from: Schulman, Thromb and Haemost (2014) 111: 575-82

### Extended (Prevent Recurrence) Treatment Phase

<table>
<thead>
<tr>
<th>Drug, trial</th>
<th>Primary efficacy outcome</th>
<th>Major bleeding</th>
<th>Major + CRNMB</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hazard ratio (95% CI)</td>
<td>Absolute difference in risk</td>
<td>Hazard ratio (95% CI)</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>1.04</td>
<td>0.5%</td>
<td>0.84</td>
</tr>
<tr>
<td>vs warfarin</td>
<td>(0.79-1.50)</td>
<td>(0.52-1.50)</td>
<td>(0.64-1.26)</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>0.68</td>
<td>0.3%</td>
<td>0.80</td>
</tr>
<tr>
<td>vs RE-DOSE</td>
<td>(0.32-0.95)</td>
<td>(0.27-0.95)</td>
<td>(0.45-0.95)</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>0.50</td>
<td>0.1%</td>
<td>0.80</td>
</tr>
<tr>
<td>ENOXETIN</td>
<td>(0.50-0.90)</td>
<td>(0.40-0.90)</td>
<td>(0.70-0.90)</td>
</tr>
<tr>
<td>Apixaban</td>
<td>0.30</td>
<td>0.3%</td>
<td>0.80</td>
</tr>
<tr>
<td>5 mg vs P</td>
<td>(0.19-0.49)</td>
<td>(0.22-0.49)</td>
<td>(0.60-0.90)</td>
</tr>
<tr>
<td>Apixaban</td>
<td>0.33</td>
<td>0.3%</td>
<td>0.80</td>
</tr>
<tr>
<td>2.5 mg vs P</td>
<td>(0.22-0.49)</td>
<td>(0.25-0.49)</td>
<td>(0.60-0.90)</td>
</tr>
</tbody>
</table>

CRNMB: clinically relevant non-major bleeding; CI: confidence interval; P=placebo

Table from: Schulman, Thromb and Haemost (2014) 111: 575-82

### Drug Interactions

- **Permeability Glycoprotein (P-gp):** Efflux transporter
  - Locations: GI Tract (Enterocytes), Liver, Kidneys
  - Stimulation: Decreases Drug Levels
  - Inhibition: Increases Drug Levels

- **Cytochrome P450 System:** Involved in Drug Metabolism
  - CYP3A4: Most prevalent of all CYP in liver
  - Oxidizes a wide range of chemically diverse drugs
  - Stimulation: Decreases Drug Levels
  - Inhibition: Increases Drug Levels

**Common Drugs with Strong Effect on P-glycoprotein and/or CYP3A4**

- Azole antifungals
  - Ketoconazole
  - Itraconazole
  - Fluconazole
  - Voriconazole
- Protease inhibitors
  - Atazanavir/ritonavir
  - Indinavir/ritonavir
- Immunosuppressive drugs
  - Cyclosporine
  - Tacrolimus
- Other
  - Clarithromycin
  - Conivaptan
  - Aminoglycosides
  - Erythromycin
  - Valsartan
  - Quinidine

**Stimulators (Inducers)**

- Anti-epileptic drugs
  - Carbamazepine
- Other
  - Rifampin
  - St. John’s wort

**Fig. 1.** List compiled from US FDA-approved package inserts and European Medicines Agency (EMA)-approved package leaflets.

*EMA recommends against concomitant use of dabigatran with cyclosporine and tacrolimus, both strong P-gp inhibitors. No published recommendations against their use with rivaroxaban or apixaban.

**Chemotherapy?**

Short, Connors Oncologist 2013 Dec 6
Drugs That Affect P-glycoprotein and/or CYP3A4

<table>
<thead>
<tr>
<th>CYP3A Inhibitors</th>
<th>P-gp Stimulators</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Strong</strong></td>
<td><strong>Amiodarone</strong></td>
</tr>
<tr>
<td>Bosentan, efavirenz, etravirine, indinavir, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole</td>
<td></td>
</tr>
<tr>
<td><strong>Moderate</strong></td>
<td><strong>Ipratropium</strong>, nizatidine, ranitidine, rivastigmine, saquinavir, telithromycin, voriconazole</td>
</tr>
<tr>
<td><strong>Weak</strong></td>
<td><strong>Cimetidine</strong>, erythromycin, fluconazole, itraconazole, ketoconazole, miconazole, niacinamide, nizatidine <strong>Combined strong CYP3A and P-gp inhibitors</strong></td>
</tr>
<tr>
<td>Itraconazole, ketoconazole, rifampin, ritonavir, telithromycin, voriconazole</td>
<td></td>
</tr>
</tbody>
</table>

**DOACs & Laboratory Testing**

**No Published Data Correlating Drug Level and Efficacy/Hemorrhage**

- **aPTT and PT**: too insensitive, too sensitive, no clear dose response
  - Direct Thrombin Inhibitor – Dabigatran:
    - aPTT more sensitive than PT
    - But, not standardized and prolongation not predictable
    - And, normal aPTT does not rule out ‘on therapy’ drug level
  - Thrombin Time is exquisitely sensitive
    - If normal, then essentially no clinically significant drug in system

- **Xa Inhibitors – Rivaroxaban, Apixaban & Edoxaban**:
  - Need chromogenic Factor Xa activity assay standardized to the Rx
  - PT is more sensitive than the aPTT
  - But a normal PT does not rule out ‘on therapy’ drug level
  - No effect on Thrombin Time

**DOAC and Bleeding Management**

- **What Might Work**
- **Reported Experiences (anecdotes…)**
- **Reversal Agents**

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**Anti-Xa Activity Assay**

1. Add Patient Plasma
2. Add Factor Xa Reagent
3. Add Factor Xa Chromogenic Substrate
4. **Add anti-Xa Reagent**
5. **Color Change**

*Shannon M. Bates, and Jeffrey I. Weitz* Circulation. 2005;112:e53-e60

**More Blue = Less Inhibitor**
### DOAC Bleeding… Nothing Proven, but Options to Consider

- **Charcoal gavage** if within ~2-3 hours of ingestion
- **Dialysis** for Dabigatran, which is only ~1/3 protein bound
  - Rivaroxaban and Apixaban >90% protein bound
  - Edoxaban 40-60% ??
- **Prothrombinase Complex Concentrates**: 4-factor now available in US.
  - Case reports, but no clear demonstrated benefit
- rF7a
- **Activated Prothrombinase Complex Concentrates**: FEIBA – case reports, but no clear demonstrated benefit

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### Active Bleeding – Apixaban *

- Local hemostatic measures
- Consider activated charcoal if <6 hrs from last dose
- Volume and Blood products as clinically indicated
- Tranexamic acid for mucosal or superficial
  - Minor: 1gm PO QID is minor
  - Major: 15mg/kg IV bolus & 1mg/kg/hr continuous infusion
- 4-factor Prothrombin Complex Concentrate (PCC) 25-50 U/Kg IV
- If still bleeding – consider Activated Factor 7

**NOTE:** Check PT, PTT but NOT predictable for drug ‘on board.’


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### DOAC Bleeding NOW! - The Italian Experience

- **9/2013 – 2/2014**: 4 women; 4 men 84+/- 6.6 years of age
- 7 Dabigatran; 1 Rivaroxaban; All for A Fib
- 4 were prior warfarin users; 4 were new to anticoagulation
- All spontaneous & Gastrointestinal
- Hgb drop: 6 @ 2-4 g/dl; 2 @ >4 g/dl
- **CrCl <30 in 4**: others 43, 57, 58, 63
- 4 received P-RBC (4 or 5)
- 3 received tranexamic acid (not the transfused patients)
- 1 received 4-factor PCC
- Median time to normalized PT, aPTT = 3 days (range 1-6)
- All recovered


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### DOAC Bleeding NOW! - The Italian Experience

1 patient was hypotensive/hypovolemic shock:
- Fluid
- Tranexamic acid
- 4-factor PCC - 25 IU/Kg and bleeding stopped
- PT and aPTT remained abnormal so repeated PCC in 6 hours.
- No P-RBCs given because bleeding stopped with 4-PCC

DOAC Bleeding Now!
The New Zealand Experience

- First ~7,000 patients with Dabigatran starting late 2011
- 78 bleeds; 44 in the group that was monitoring
- 12/44 = major
  - 55% GI
  - 14% GU
  - 9% Mucosal
  - 2% Spontaneous ICH
  - 20% Other sites, trauma, post-op
- 48% Impaired Renal Function: moderate (30-50) or severe (<30)
- Age: 2/3 were >80 years old

Rates, management, and outcome of rivaroxaban bleeding in daily care: results from the Dresden NOAC registry

Jan Beyer-Westendorf,1 Karl Förster,1 Sven Ponnach,2 Franziska Ebertz,1 Veronika Gebrich,1 Christoph Thieme,1

230+ Dresden area MDs; Prospective; >18 yo; expected >90 days of therapy


1,775 Patients on Rivaroxaban

1,200 (67.5%) A Fib
388 days (median)
575 (32.5%) VTE
274 days (median)

<table>
<thead>
<tr>
<th>Table 1. Patient characteristics of 1,775 patients and subgroups of patients with and without major bleeding during rivaroxaban therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
</tr>
<tr>
<td>---------------</td>
</tr>
<tr>
<td>No. (%)</td>
</tr>
<tr>
<td>Mass BMI (kg/m²)</td>
</tr>
<tr>
<td>Coronal artery disease, n (%)</td>
</tr>
<tr>
<td>Prior stroke or transient ischemic attack, n (%)</td>
</tr>
<tr>
<td>Concomitant antiplatelet therapy or NSAID use, n (%)</td>
</tr>
<tr>
<td>Improved renal function, n (%)</td>
</tr>
</tbody>
</table>

Prothrombin Complex Concentrate (PCC)

- Contain Factors 2, 7, 9, 10 (Vit K-dep. factors) in variable amounts
- Activated – FEIBA (Factor Eight Inhibitor Bypassing Agent)
- Activated Factor 7 plus a 3-factor product
- Not activated: Bebulin - 3 factor (~no Factor 7)
- Kcentra* - 4 factor

Kcentra:

<table>
<thead>
<tr>
<th>Pre-treatment INR</th>
<th>2&lt;4</th>
<th>4-6</th>
<th>&gt;6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kcentra dose (F9 units/Kg)</td>
<td>25</td>
<td>35</td>
<td>50</td>
</tr>
<tr>
<td>Max dose (F9 units/Kg)</td>
<td>≤2,500</td>
<td>≤3,500</td>
<td>≤5,000</td>
</tr>
</tbody>
</table>

*FDA approved to reverse coumadin-induced intracranial bleeds
DOAC Reversal – Coming Soon

**Antidotes or Reversal Agents = NONE**

**BUT, IN DEVELOPMENT…**

**Dabigatran:** Antibody

**Xa inhibitors:** Decoy, crippled Factor Xa
- Catalytically inactive as a protease
- Lacks the membrane binding γ-carboxylase domain

**RETKNS:**
- Ability to bind Xa inhibitors
- Ability to bind & reverse Antithrombin-dependent anticoagulation by enoxaparin or fondaparinux
- Reverses lab tests and bleeding in animals

**PER977:** Small, synthetic, Water-soluble, cationic molecule
Binds UFH, LMWH, Rivarox, Apix, Edox, Dabig
Binds via noncovalent H-bonding & charge interactions

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Local Guidelines: Things to Consider*

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Thank you! to Steve Kayser and Margaret Fang, UCSF

**DOACs and VTE – some thoughts**

Patients with thrombophilia:
- No data but no a priori reason that they will not work
- Could they have a role for AT deficiency or Protein C deficiency?

Heparin-induced thrombocytopenia:
- No data – will be interesting to see how this evolves

I do not use at this time for:
- Cancer-associated or Pregnancy-associated VTE:
  - Massive PE: hemodynamic instability/considering thrombolysis
  - Massive DVT with phlegmasia cerulea dolens
  - “Extremes” of weight: <110 or >250 pounds
- If happy and stable on coumadin – do not switch
- Be very aware of renal function and ‘other’ medications
Veins of the Leg – A Brief Overview

*The confusing "superficial femoral vein" segment of the deep vein system.

Superficial Vein Thrombosis & American College of Chest Physicians*

- Recommends: Fondaparinux 2.5 mg sQ daily for 45 days for a new diagnosis of isolated SVT ≥5 cm in length in the lower extremity.
  - Grade 2B recommendation
- Recommends: Fondaparinux over LMWH
  - Grade 3B recommendation

- Not all patients will agree due to cost and inconvenience.
- In particular, anticoagulant treatment favored if:
  (i) extensive
  (ii) above knee
  (iii) greater saphenous vein
  (iv) near saphenofemoral jxn
  (v) severe symptoms
  (vi) History of VTE or SVT
  (vii) active cancer
  (viii) recent surgery

Superficial Vein Thrombosis: 2 Studies of Note


Cumulative Risk (%)

<table>
<thead>
<tr>
<th>Years since SVT Diagnosis</th>
<th>PE</th>
<th>DVT</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR @ 3 mo: 87 (70-108)</td>
<td>45 (34-61)</td>
<td>2.9 (2.5-3.5)</td>
</tr>
<tr>
<td>HR @ 5 Yr: 6.3 (5.6-7)</td>
<td>2.9 (2.5-3.5)</td>
<td></td>
</tr>
</tbody>
</table>


Treatment: 2.5mg qD fondaparinux vs placebo

Events: 13/1502 (0.9%) vs 88/1500 (5.9%)
(Sx PE, DVT, Extension to Jxn, Recurrence)
Rel Risk Red: 85% (95% CI: 74-92)
DVT & PE (0.2% vs 1.3%): Rel Risk Red: 85% (50-95)
Rel Risk Red maintained at day 77.

CALISTO Study

Danish National Registry Study

10,973 patients with SVT vs. 515,067 in comparison cohort
Again found DVT and PE risk.
Increased risk of MI and CVA
Suggests 'systemic disorder'

Thank you for your attention!

Questions?
UCSF Non-malignant Hematology Clinic

For Referrals:

415-353-2051 (phone line)

415-353-7765 (fax line)

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