Review of Pharmacology and Management of Bleeding Complications of Novel Oral Anticoagulants
<table>
<thead>
<tr>
<th>External Industry Relationships *</th>
<th>Company Name</th>
<th>Role</th>
</tr>
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<tbody>
<tr>
<td>Equity, stock, or options in biomedical industry companies or publishers</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Board of Directors or officer</td>
<td>None</td>
<td></td>
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<tr>
<td>Royalties from Emory or from external entity</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Industry funds to Emory for my research</td>
<td>None</td>
<td></td>
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<tr>
<td>Consulting</td>
<td>ECN/Various Law Firms</td>
<td>Reviewer</td>
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Case Report

- 70 yo male with a history of a. fib suffers a CHI from falling down 4 steps.
- Per Wife, Medications: Metoprolol, Simvastatin, Dabigatran
- GCS 12, HR 70 RR 14 BP 138/70
- Exam normal except for scalp hematoma
- Head CT reveals an Epidural Hematoma
- Next Steps?
The Ideal Anticoagulant

- 1. High efficacy-to-safety index
- 2. Predictable dose response that allows dosing without the need for laboratory monitoring
- 3. Administration by parenteral and oral routes
- 4. Rapid onset of action
- 5. Availability of a safe antidote
- 6. Freedom from non-anticoagulant side effects
- 7. Minimal interaction with other drugs
Contact activation (intrinsic) pathway

Damaged surface → XII → Xla → XI → IXa → VIIIa → Xa → Va → Prothrombin (II)

Protein C + Thrombomodulin

Tissue factor (extrinsic) pathway

Trauma → VIIa → VII → Tissue factor → Fibrinogen (I) → Fibrin (Ia)

Antithrombin

Common pathway

Cross-linked fibrin clot → XIII → XIIIa
Novel Anticoagulants

- Thrombin Inhibitors
  - Dabigatran
  - Argatroban (IV)
- Activated factor X (Xa) inhibitor
  - Rivaroxaban
- Hirudin: Thrombin Inhibitors
  - Bivalrudin
  - Lepirudin
Dabigatran

- Competitive direct thrombin inhibitor
- Approved for stroke prevention
  - Non Valvular Afib
- Predictable anticoagulation response
  - No cyp 450 metabolism
  - Few drug/drug
  - Does not require frequent monitoring

……but no way to reliably reverse hemorrhagic complications, YET
Pharmacology

- Reversible, potent competitive direct thrombin inhibitor
- Heparin binds only free thrombin
- Dabigatran can inhibit both free and clot bound thrombin
Pharmacokinetics

- Administered as a prodrug
- Immediate anticoagulation after hydrolysis into active drug
- Peak plasma level within 2 h (higher peak if pill is cut or chewed, delayed if take with food)
- 35% protein bound
- Metabolized by glucuronidation
  - 10% loss of potency per glucuronide
- $\frac{1}{2}$ life 12-17 hours, renal excretion (dose based on creatinine clearance)
- INR < 2.0 when transitioning from warfarin to dabigatran
Rivaroxaban

- Xarelto
- Competitively inhibits free and prothrombinase/clot-associated factor Xa via reversible interactions with active site
- Approved for VTE Prophylaxis in patients after hip and knee replacement
- Approved for stroke prevention
  - Non Valvular Afib
Pharmacology: Rivaroxaban

- Highly protein bound
- Renal (40%) and Hepatic metabolism CYP3A4,2J2
- Predictable effects; does not require frequent monitoring
- Drug/drug interactions
- Peak plasma 2 to 4 hrs
- T½ 9-13 hrs
## Effects of Coagulation Tests

<table>
<thead>
<tr>
<th></th>
<th>PT</th>
<th>aPTT</th>
<th>TCT</th>
<th>Ecarin</th>
<th>Hemoclot assay</th>
<th>Anti-factor Xa Activity</th>
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<tbody>
<tr>
<td>Dabigatran</td>
<td>↑ or no Δ (Linear but not precise)</td>
<td>↑ (non-linear)</td>
<td>↑</td>
<td>↑</td>
<td>↑*</td>
<td>_</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>↑ or no Δ</td>
<td>↑ or no Δ</td>
<td>_</td>
<td>_</td>
<td>_</td>
<td>↑*</td>
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Available Coagulation Test

- Despite their limitations, conventional coagulation assays may provide qualitative information regarding the presence of drug.
- A normal TCT in patients receiving dabigatran, normal PT in patients receiving rivaroxaban suggest very low drug levels and intact haemostatic function.
Dabigatran Clinical Trials

• RE-LY study
  • Vs warfarin in 18113 patients within afib
    • 110 mg bid- same rates of stroke and emboli, lower rate of bleeding
    • 150 mg bid- lower rate of stroke and emboli, similar rate of bleeding
    • Older or renal impaired more likely to bleed

• RE-COVER
  • Vs Warfarin for acute VTE
    • 150 mg BID, no difference in VTE or bleeding

• 5 trials for post orthopedic surgery show non-inferiority vs LMWH
Management of Bleeding Complications: Factor Replacement

- Current recommendations are not based on evidence or clinical experience
- FFP- theoretical basis
  - Contains prothrombin- ? overcome dabigatran inhibition
  - May replace other factors that may be deficient
- Prothrombin Complex Concentrates (PCC)
  - USA 3-factor II, IX, X
  - Improved clotting times in animal and human IN VITRO studies
  - Thrombogenic- can lead to ischemia
Prothrombin Complex Concentrate (PCC)

- Three Factor PCC: Non activated II, IX and X small amounts of VII (Profilnine or Bebulin)
- Activated PCC: Activated VII, II, IX and X (Feiba), during manufacture.
Prohemostatic agents: aPCC

- Activated PCC: Activated VII, II, IX and X (Feiba).
- aPCC has been shown to correct the anticoagulant effect of high dose rivaroxaban in animal models.
- In human plasma incubated with dabigatran, aPCC reduced clot initiation time in vitro.
- aPCC corrected thrombin generation parameters in vitro in plasma from healthy volunteers receiving single doses of rivaroxaban or dabigatran and in blood from healthy volunteers following the addition of apixaban
Prohemostatic agents

- rFVIIa- development to treat hemophilia patients with inhibitors to factors VIII and IX
- Has FDA blackbox warning: arterial thromboembolic events
- No demonstrated efficacy
Figure 1. Clotting cascade and location of activity of new oral anticoagulants and hemostatic agents. Proteins are depicted by their zymogen symbols. The new oral anticoagulants are depicted in dark gray boxes with bold inhibition lines. Hemostatic agents are in light gray boxes with dashed lines in the area of activity. The PCC is depicted as containing nonactivated proteins for simplicity but can contain activated proteins and factor VII also depending on the product.
Hemodialysis

- Closed space bleeding
  - GI bleed lasting 12-17 hours (1 x ½ life) may be tolerated with supportive care
  - Protracted bleeding into intracranial, spinal or pericardial space can be devastating

- No current human data- pharmacokinetic evidence suggests the HD would help
  - Healthy volunteers with ESRD
    - Dialysis removes 62% at 2 H and 68% at 4 h.

- HD can cause fluid shifts, decreased serum osmolality and cerebral edema-problem with ICH
<table>
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<tr>
<th></th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FDA Indications</strong></td>
<td>Nonvavular a.fib</td>
<td>Nonvavular a.fib; Ortho Replacement VTE prophylaxis</td>
</tr>
<tr>
<td><strong>Mechanism</strong></td>
<td>Inhibits free and clot bound Thrombin (IIa)</td>
<td>Inhibits Factor Xa</td>
</tr>
<tr>
<td><strong>Dose</strong></td>
<td>150 mg BID; 75 mg BID</td>
<td>20mg QD; 15 mg QD; 10 mg QD</td>
</tr>
<tr>
<td><strong>Onset &amp; ½ Life</strong></td>
<td>1.5-3hrs; 14-17 hrs</td>
<td>2-4 hrs; 5-9 hrs</td>
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<tr>
<td><strong>Lab Monitoring</strong></td>
<td>ECT; TT</td>
<td>Anti-Xa assay</td>
</tr>
<tr>
<td><strong>Interactions</strong></td>
<td>P-Glycoprotein</td>
<td>P-Glycoprotein &amp; CYP 3A4 inhibitors</td>
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P-Glycoproteins

- Efflux transporters
- Using ATP as an energy source, they transport certain hydrophobic substances in the following directions:
  - Out of brain, gonads
  - Into the gut, urine, bile
- Substrates, Inhibitors, Inducers
Bleeding Management

• Assess severity of bleeding
• Assess severity of anticoagulation
• Additional Labs: CBC, Type and Cross, Creatnine, Transaminases
Mild to Moderate Bleeding

- Risk vs Benefit to hold anticoagulation
- Local Control of Bleeding
- Transfuse Blood Products
Severe Bleeding

- Hold anti-coagulant
- Transfuse blood products (PRBC’s, FFP)
- Surgery or Embolization?
- Activated Charcoal?
- Consider aPCC or PCC
- Dialysis for Dabigatran
- Consider antifibrinolytic therapy (tranexamic acid)
- Consider rFVIIa
On the Horizon

- Monoclonal antibody for Dabigatrin
- Plasma-derived and recombinant factor Xa
Overdose

- No current evidence
- AC absorbs (animal data)
- 2-3 fold elevations well tolerated, accidental ingestions unlikely to have bleeding complications
- In large overdose with severe uncontrolled bleeding, HD should be considered
Procedures

- Discontinue dabigatran & Rivaroxaban 24 hrs (CrCl 50 mL/min or greater) or 48 hrs (CrCl less than 50 mL/min) prior to invasive or surgical procedure if possible due to the increased risk of bleeding;
- Longer times should be considered in patients undergoing major surgery, spinal puncture, or placement of a spinal or epidural catheter or port.
- Anticoagulant therapy should be reinitiated as soon as possible after procedure
Antiplatelet Agents

- Irreversible cyclooxygenase inhibitors
  - Aspirin
- Adenosine diphosphate (ADP) receptor inhibitors
  - Clopidogrel, ticlopidine
- Phosphodiesterase inhibitors
  - Cilostazol (pletal)
- Glycoprotein IIB/IIA inhibitors (I.V. only)
  - Abciximab, eptifibatide, tirofiban
- Adenosine reuptake inhibitors
  - Dipyidamole (Persantine)
Antiplatelet Agents: Hemorrhage

- Management
  - Discontinuation of antithrombotic drugs
  - Resuscitation with intravenous fluid
  - Packed red cell transfusion
  - Surgical or other procedures to control the bleeding.
  - Platelets (in severe bleeding)
  - No known antidote