Reversal Strategies for Novel Oral Anticoagulants

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• No conflicts of interest to disclose

Outline
• Overview of novel oral anticoagulants (NOACs)
• Management of bleeding
• Reversal strategies for NOACs
• Antidotes in the pipeline
• UCSF Guidelines

Warfarin
• Widely used oral anticoagulant

• Disadvantages
  – Narrow therapeutic range
  – Need for routine laboratory monitoring
  – Variable dose response in patients
  – Interactions with food and drug

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Overview of Novel Oral Anticoagulants

Novel Oral Anticoagulants (NOACs)

- Also known as target specific oral anticoagulants
- Direct thrombin inhibitors (DTI)
  - Dabigatran (Pradaxa®)
- Direct factor Xa inhibitors (FXa)
  - Rivaroxaban (Xarelto®)
  - Apixaban (Eliquis®)

Dabigatran

- FDA Approved Indications
  - Reduction of risk of stroke and systemic embolism in non-valvular atrial fibrillation (AF)
  - Treatment of deep venous thrombosis (DVT) and pulmonary embolism (PE)
  - Reduction in the risk of recurrence of DVT and PE
- Dose
  - 150mg twice daily
- Dose adjustment for renal impairment
  - CrCl < 30 ml/min: avoid use
Rivaroxaban and Apixaban

**Rivaroxaban**

- **FDA Approved Indications and Dose**
  - Non-valvular AF: 20mg daily
  - DVT/PE treatment: 15mg twice daily for 21 days, then 20mg daily
  - Prophylaxis of DVT following hip or knee replacement surgery: 10mg daily

- **Dose adjustment with renal impairment**
  - Non-valvular AF with CrCl 30-49ml/min: 15mg daily
  - CrCl < 30ml/min: avoid use

**Apixaban**

- **FDA Approved Indications**
  - To reduce the risk of stroke and systemic embolism in patients with non-valvular AF
  - Prophylaxis of DVT following hip or knee replacement surgery

- **Dose**
  - Non-valvular AF: 5mg twice daily
  - Prophylaxis of DVT/PE following hip or knee replacement surgery: 2.5mg twice daily

- **Dose adjustment in renal impairment**
  - CrCl < 25 ml/min: avoid use

**Pharmacokinetics of NOACs**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal elimination of unchanged drug (%)</td>
<td>80</td>
<td>36</td>
<td>27</td>
</tr>
<tr>
<td>Half-life (hr)</td>
<td>12-14</td>
<td>5-9</td>
<td>8-15</td>
</tr>
<tr>
<td>Protein binding (%)</td>
<td>35</td>
<td>92-95</td>
<td>87</td>
</tr>
<tr>
<td>Dialyzable?</td>
<td>Yes</td>
<td>Unlikely</td>
<td>Unlikely</td>
</tr>
</tbody>
</table>
Coagulation Assays

- Routine monitoring not required
- Indications
  - Major bleeding
  - Surgery
  - Reversal of anticoagulation
  - Suspicion of overdose

*Activated partial thromboplastin time (aPTT)
  - Intrinsic pathway

*Prothrombin time (PT) and International normalized ratio (INR)
  - Extrinsic and common pathway

*Thrombin clotting time (TT)
  - Directly assesses activity of thrombin

Ecarin clotting time (ECT)
  - Specific assay for thrombin generation
  - Direct measure of direct thrombin inhibitor activity

Chromogenic Anti-factor Xa
  - Functional test to assess plasma concentrations of factor Xa

*a available at UCSF Medical Center

Effect of Coagulation Assays

<table>
<thead>
<tr>
<th>Lab Test</th>
<th>Dabigatran</th>
<th>Rivaroxaban/Apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>aPTT</td>
<td>Sensitive</td>
<td>Sensitive</td>
</tr>
<tr>
<td></td>
<td>Curvilinear</td>
<td>Curvilinear</td>
</tr>
<tr>
<td></td>
<td>Response flattens at higher drug concentration</td>
<td>Response varies depending on reagent used</td>
</tr>
<tr>
<td>PT/INR</td>
<td>Not sensitive</td>
<td>Sensitive at higher drug concentration</td>
</tr>
<tr>
<td></td>
<td>Linear</td>
<td>Linear</td>
</tr>
<tr>
<td>TT</td>
<td>Sensitive at low concentration</td>
<td>Not effective</td>
</tr>
<tr>
<td></td>
<td>Linear</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Not useful at higher concentration</td>
<td></td>
</tr>
<tr>
<td>ECT</td>
<td>Sensitive</td>
<td>Not effective</td>
</tr>
<tr>
<td></td>
<td>Linear</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Potentially quantify amount of drug present</td>
<td></td>
</tr>
<tr>
<td>Anti-Xa</td>
<td>Not effective</td>
<td>Sensitive</td>
</tr>
<tr>
<td></td>
<td>Linear</td>
<td></td>
</tr>
</tbody>
</table>

Usefulness of lab test

- **strong**
  - ECT
- **weak**
  - PT/INR

- **ECT**
  - Chromogenic Antifactor Xa
- **TT**
- **aPTT**
- **PT/INR**

Advantages and Disadvantages of NOACs

**Advantages**
- Targeted mechanism
- Rapid and reliable onset of action
- Short half-life
- Low potential for food and drug interactions

**Disadvantages**
- Inability to titrate
- Cost
- Reversal strategies have not been established
- Absence of specific antidote

Management of Bleeding

**Summary of Bleeding Events**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Endpoint</th>
<th>Major bleeding</th>
<th>GI bleeding</th>
<th>Intracranial hemorrhage</th>
<th>Fatal bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran vs warfarin</td>
<td>Prevention of stroke or systemic embolism with AF</td>
<td>3.11% vs 3.06%</td>
<td>1.81% vs 1.02%</td>
<td>0.60% vs 0.54%</td>
<td>0.4% vs 0.36%</td>
</tr>
<tr>
<td>Dabigatran vs warfarin</td>
<td>Prevention of recurrent VTE in patients with acute VTE</td>
<td>1.6% vs 1.9%</td>
<td>4.2% vs 2.8%</td>
<td>0.5% vs 0.2%</td>
<td>0.08% vs 0.08%</td>
</tr>
<tr>
<td>Rivaroxaban vs warfarin</td>
<td>Prevention of stroke and systemic embolism in patients with AF</td>
<td>3.6% vs 3.4%</td>
<td>No Data</td>
<td>0.5% vs 0.7%</td>
<td>0.2% vs 0.5%</td>
</tr>
<tr>
<td>Rivaroxaban vs warfarin</td>
<td>Prevention of recurrent VTE in patients with PE</td>
<td>1.1% vs 2.2%</td>
<td>No Data</td>
<td>&lt; 0.1% vs 0.4%</td>
<td>&lt; 0.1% vs 0.1%</td>
</tr>
<tr>
<td>Apixaban vs warfarin</td>
<td>Prevention of stroke or systemic embolism in patients with AF</td>
<td>2.13% vs 3.06%</td>
<td>0.76% vs 0.80%</td>
<td>0.33% vs 0.6%</td>
<td>No Data</td>
</tr>
</tbody>
</table>


**Management of Bleeding**

- Discontinue the anticoagulant
- Attempt hemostasis of bleeding site
- Maintenance of adequate fluid resuscitation and hemodynamic support
- Transfusion
- Laboratory test results
  - Level of anticoagulation
  - Markers of blood loss
  - Organ function
Reversal Strategies for NOACs

Activated Charcoal

- **Indication**
  - To reduce absorption unless contraindicated in overdose or accidental ingestion

- **Recommendation**
  - Use within 2 hours of ingestion of dabigatran, rivaroxaban, apixaban

Hemodialysis

- **Recommendation**
  - Dabigatran is dialyzable due to low plasma binding
    - Plasma levels can be decreased by at least half after a 4 hour session
  - Rivaroxaban and apixaban are not expected to be dialyzable

Available Reversal Agents

- **Prothrombin Complex Concentrates (PCC)**
  - Three-factor PCC (PCC3)
  - Four-factor PCC (PCC4)

- **Activated PCC (aPCC)**

- **Recombinant Factor VIIa (rFVIIa)**
Comparison of Available Reversal Agents

<table>
<thead>
<tr>
<th>Brand name</th>
<th>PCC3</th>
<th>PCC4</th>
<th>wFVIIa</th>
<th>rtFVIIa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brand name</td>
<td>Bebulin® VH</td>
<td>Profilnine® SD</td>
<td>Kcentra®</td>
<td>NovoSeven® RT</td>
</tr>
<tr>
<td>Dose based on</td>
<td>Units of factor IX activity</td>
<td>Units of factor IX activity</td>
<td>Units of factor VIII inhibitor bypassing activity</td>
<td>Units of recombinant factor VIIa</td>
</tr>
<tr>
<td>Administration time</td>
<td>Max 2 ml/min</td>
<td>Max 10 ml/min</td>
<td>Max 8.4 ml/min</td>
<td>Max 2 units/kg/min</td>
</tr>
<tr>
<td>Factor II</td>
<td>24–38 IU/dL</td>
<td>150 IU/100 IU</td>
<td>0.76-1.6 units</td>
<td>1.3 IU/ML</td>
</tr>
<tr>
<td>Factor VII</td>
<td>≤ 5 IU/dL</td>
<td>≤35 IU/100 IU</td>
<td>0.6-1 units/unit</td>
<td>0.9 IU/ML activated</td>
</tr>
<tr>
<td>Factor IX</td>
<td>24–38 IU/dL</td>
<td>100 IU</td>
<td>0.6-1.24 units/unit</td>
<td>1.4 IU/ML</td>
</tr>
<tr>
<td>Factor X</td>
<td>24–38 IU/dL</td>
<td>100 IU</td>
<td>1-2.04 units/unit</td>
<td>1.1 IU/ML</td>
</tr>
<tr>
<td>Unfractionated Heparin</td>
<td>0.15 IU per 1 IU/ML</td>
<td>None</td>
<td>0.816-0.98 units/unit</td>
<td>None</td>
</tr>
<tr>
<td>Other components</td>
<td>Protein C/S, Antithrombin III</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

• Reversal of dabigatran
  – Limited to animal studies
  – Reduced excess bleeding and shortened time to hemostasis in a dose-dependent manner in rabbits following kidney incision
  – aPTT, PT, and ECT remained prolonged after administration of PCC3, despite reversal of bleeding time in a rat tail bleeding model

PCC3

Study

Comparison of three- and four-factor prothrombin complex concentrates on the anticoagulant effects of rivaroxaban in healthy volunteers

Study design

Open-label, single-center, parallel-group

Population

N = 35 healthy adults

Intervention

• Rivaroxaban 20mg BID x 4 days
• PCC3 (Profilnine® SD) vs PCC4 (Beriplex® P/N): 50 IU/kg

Results

• Variable effects on coagulation assays
  • PCC3 increased endogenous thrombin potential (ETP) faster
  • PCC4 had a greater effect in reversing PT
  • PCC and PCC4 did not affect aPTT and chromogenic anti-factor Xa
  • No signs/symptoms of thromboembolic effects after PCC administration

PCC4

Study

Reversal of rivaroxaban and dabigatran by prothrombin complex concentrate

Study design

Randomized, placebo-controlled, cross-over study

Population

N = 12 healthy males

Intervention

• Rivaroxaban 20mg BID or dabigatran 150mg BID x 2.5 days
• Treated with Cofact® 50 IU/kg or placebo
• 11-day wash out period, then switch

Endpoints

• Laboratory measurements
  • PT, aPTT, ECT, TT
  • Endogenous thrombin potential (ETP)
PCC4

**Effect on rivaroxaban**
- PT and ETP completely normalized after PCC4 infusion

**Effect on dabigatran**
- PCC4 infusion had no effect on aPTT, ETP, TT, ECT

Conclusion: PCC4 immediately and completely reverses effect of rivaroxaban on healthy subjects but have no effect on dabigatran

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**aPCC**

**Study**
- Reversing dabigatran in life-threatening bleeding occurring during cardiac ablation with factor eight inhibitor bypassing activity

**Study design**
- Case report

**Population**
- 67M with a history of symptomatic AF with rapid ventricular rate
- Bleeding and hemodynamic compromise occurred during repeat ablation
- Last dose of dabigatran was 7 hours prior to procedure

**Intervention**
- FEIBA 26 IU/kg actual body weight
- Second dose of FEIBA 16 IU/kg actual body weight 30 min later after concern for rebleeding

**Results**
- Hemostasis notable within 5 minutes of infusion
- TT and ECT did not normalize after FEIBA administration
- INR and APTT normalized following FEIBA administration

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**rFVIIa**

**Study**
- Effect of non-specific reversal agents on anticoagulant activity of dabigatran and rivaroxaban

**Study design**
- Randomized, crossover, ex vivo study

**Population**
- N = 10 healthy males
- Exclusion: personal family history of thrombosis or bleeding disorders, renal or liver impairment

**Intervention**
- Dabigatran 150mg x1 or Rivaroxaban 20mg x1
- 15-day wash out period, then switch
- Reversal agents:
  - rFVIIa 20-120 mcg/kg
  - aPCC 20-160 units/kg
  - PCC4 12.5-50 units/kg

**Results**
- PCC4 corrected ETP but not lag time
- rFVIIa corrected lag time but not ETP
- aPCC corrected both parameters
- Higher doses of PCC4 and aPCC were responsible for over-correction of ETP

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**Thrombogenicity**

- **Pathogenesis**
  - Uncertain which component of PCCs is the leading cause of thrombogenicity
  - Linear relationship between increasing levels of factor II and increased thrombin generation

- **PCC**
  - Improved safety profile
  - Inclusion of coagulation inhibitors (protein C, protein S, heparin, antithrombin III) to avoid excessive increase in thrombin generation

- **aPCC**
  - Comparable thrombosis risk to PCC

- **rFVIIa**
  - Increased rates of arterial thromboembolism in elderly
Antidotes in the Pipeline

Antidotes for NOACs

• **Idarucizumab**
  – Humanized antibody fragment that binds dabigatran with high affinity to prevent dabigatran inhibition of thrombin
  – Clinical studies:
    • Completed phase 1 and 2 study in 145 healthy volunteers¹
      o Prolongation of clotting times reversed to baseline after 5-minute infusion
      o Dose-dependent reversal
      o Well-tolerated
    • Phase 3 study in patients treated with dabigatran who have uncontrolled bleeding or require emergency surgery or procedures²
      o Open-label, single group study
      o Start date 2014 with an estimated completion in 2017
  – Advantages
    • Lacks off-target toxicity
    • Lacks pro-thrombotic activity

¹ Glund S, et al. AHA Scientific Sessions, Dallas, TX. November 2013, abstract 17765

• **Andexanet alfa**
  – Factor Xa decoy that targets and sequesters direct and indirect Factor Xa inhibitors with high specificity
  – Clinical studies:
    • Phase 2, double-blind, placebo-controlled, dose escalation studies in healthy subjects administered rivaroxaban or apixaban¹ ²
      o Administration of single IV bolus injection or bolus injection followed by a continuous infusion
      o Anti-fXa activity decreased immediately after bolus administration and was sustained after completion of IV infusion
      o Dose-dependent reversal
      o Well-tolerated with no thrombotic, serious or severe adverse events
  – Phase 3 trial anticipated to start 2014

¹ Crowther M, et al. ASH Annual Meeting and Exposition, New Orleans, LA. December 2012, abstract 332

UCSF Guideline
**Conclusion**

- NOACs that directly inhibit thrombin or factor Xa are an effective and more convenient alternative to warfarin
- Available evidence for reversal is limited to animal models, in vitro experiments, and healthy human volunteers
- Conventional laboratory assays do not correlate well with bleeding or reversal of anticoagulation
- Evidence to support hemodialysis and aPCC for dabigatran reversal
- Evidence to support PCC4 for rivaroxaban reversal
- Lowest effective dose of product should be given to balance risk of thrombosis
- Specific reversal agents are in the pipeline