Practical How-to: Treating Patients with New Anticoagulants — *case scenarios*

Robert Barcelona, PharmD, BCPS, Matthew Eisen, MD and Lindsey Federle, PharmD, BCPS
Objectives

Patient Case #1
- Discuss data using novel oral anticoagulants (NOACs) post cardioversion or ablation
- Describe metabolism and identify significant drug interactions with the NOACs

Patient Case #2
- To understand when to stop and start NOAC’s around invasive procedures

Patient Case #3
- Identify risk factors and frequency of bleeding with NOACs in clinical trials
- List laboratory monitoring and strategies to control bleeding episodes with NOACs
Patient Case #1

67 M seen after TEE & atrial fibrillation DCCV

PMH: afib, HTN, HIV

Vitals:
- BP: 125/76
- HR: 76 (in normal sinus rhythm)
- Temp: 98.6° F
- Height: 5’7
- Weight: 260 lbs (118.2 kg)

Home medications:
- Aspirin 325 mg PO daily
- Lisinopril/HCTZ 20 mg/25 mg PO daily
- Ritonavir 100 mg PO daily
- Atazanavir 300 mg PO daily
- Tenofovir/Emtricitabine 300 mg/200 mg PO daily

Medication Compliance: Fills a Mediset weekly to help him remember.

Labs: SCr 1.1, CBC & LFTs normal
After cardioversion, which oral anticoagulant will you discharge the patient home with?

A. Warfarin 5 mg PO daily with enoxaparin 120 mg SQ every 12 hours

B. Dabigatran 150 mg PO BID

C. Apixaban 2.5 mg PO BID

D. Rivaroxaban 20 mg PO daily with dinner
## Evidence for Using NOACs after Cardioversion

<table>
<thead>
<tr>
<th>Study</th>
<th>Enrollment</th>
<th>TEE performed</th>
<th>Stroke and Systemic Embolism</th>
<th>Major bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nagarakanti¹</td>
<td>1983 ECV and PCV:</td>
<td>25.5% D110 (1.8% positive)</td>
<td>At 30 days:</td>
<td>1.7% D110  0.6% D150  0.6% Warfarin</td>
</tr>
<tr>
<td></td>
<td>• 647 D110</td>
<td>24.1% D150 (1.2%)</td>
<td>• 0.8% D110</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• 672 D150</td>
<td>13.3% Warfarin (1.1%)</td>
<td>• 0.3% D150</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• 664 Warfarin</td>
<td></td>
<td>• 0.6% Warfarin</td>
<td></td>
</tr>
<tr>
<td>Piccini²</td>
<td>321 ECV, PCV, or ablation:</td>
<td>Not reported</td>
<td>1.88% Rivaroxaban</td>
<td>18.75% Rivaroxaban#  13.04% Warfarin#</td>
</tr>
<tr>
<td></td>
<td>• 160 Rivaroxaban</td>
<td></td>
<td>1.86% Warfarin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• 161 Warfarin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flaker³</td>
<td>743 ECV and PCV in 540 patients:</td>
<td>32.4% Apixaban (0.3%)</td>
<td>At 30 days:</td>
<td>0.3% Apixaban  0.2 % Warfarin</td>
</tr>
<tr>
<td></td>
<td>• 265 Apixaban</td>
<td>30.9% Warfarin (1.1%)</td>
<td>• No stroke or systemic emboli occurred</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• 275 Warfarin</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

TEE = transesophageal echocardiogram; ECV = electrical cardioversion; PCV = pharmacologic cardioversion; D110 = Dabigatran 110 mg BID; D150 = Dabigatran 150 mg BID

#Includes non major clinically relevant bleeding

NOAC Metabolism

# Potential Medication Interactions with NOACs

<table>
<thead>
<tr>
<th>CYP 3A4 Inhibitors</th>
<th>Strong</th>
<th>Moderate</th>
<th>Weak</th>
</tr>
</thead>
<tbody>
<tr>
<td>PGP Inhibitors</td>
<td>Amiodarone, azithromycin, captopril, carvedilol, clarithromycin, conivaptan, cyclosporine, diltiazem, dronedarone, erythromycin, felodipine, itraconazole, ketoconazole, lopinavir and ritonavir, quinidine, ranolazine, verapamil</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PGP Inducers</td>
<td>Carbamazepine, phenytoin, rifampin, St John’s wort, tipranavir/ritonavir</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CYP 3A4 Inducers</th>
<th>P-gp Inhibitor</th>
<th>Non-P-gp Inhibitor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strong CYP3A4 Inhibitor</td>
<td>Itraconazole, lopinavir/ritonavir, clarithromycin, ritonavir, ketoconazole, indinavir/ritonavir, conivaptan</td>
<td>Voriconazole, nefazodone</td>
</tr>
<tr>
<td>Moderate CYP3A4 Inhibitor</td>
<td>Verapamil, erythromycin, diltiazem, dronedarone</td>
<td>None identified</td>
</tr>
<tr>
<td>Weak CYP3A4 Inhibitor</td>
<td>Quinidine, ranolazine, amiodarone, felodipine, azithromycin</td>
<td>Cimetidine</td>
</tr>
</tbody>
</table>

**Table:**

- **PGP Inhibitors:**
  - Clarithromycin, telithromycin, conivaptan, grapefruit juice, itraconazole, posaconazole, ketoconazole, voriconazole, Nefazodone, boceprevir, indinavir, lopinavir/ritonavir, nelfinavir, ritonavir, saquinavir, telaprevir

- **PGP Inducers:**
  - Carbamazepine, phenytoin, rifampin, St John’s wort

- **Strong CYP3A4 Inhibitors:**
  - Clarithromycin, telithromycin, conivaptan, grapefruit juice, itraconazole, posaconazole, ketoconazole, voriconazole, Nefazodone, boceprevir, indinavir, lopinavir/ritonavir, nelfinavir, ritonavir, saquinavir, telaprevir

- **Moderate CYP3A4 Inhibitors:**
  - Carbamazepine, phenytoin, rifampin, St John’s wort

- **Weak CYP3A4 Inhibitors:**
  - Alprazolam, amiodarone, amlodipine, atorvastatin, bicalutamide, cilostazol, cimetidine, cyclosporine, fluoxetine, fluvoxamine, gingko, goldenseal, isoniazid, nitrofurantoin, oral contraceptives, ranitidine, ranolazine, tipranavir/ritonavir, zileuton

- **CYP3A4 Inducers:**
  - Bosentan, efavirenz, etravirine, modafinil, nafcillin

- **Amprenavir, aprepitant, atazanavir, ciprofloxacin, darunavir/ritonavir, diltiazem, erthyromycin, fluconazole, fosamprenavir, imatinib, verapamil

- **Alprazolam, amiodarone, amlodipine, atorvastatin, bicalutamide, cilostazol, cimetidine, cyclosporine, fluoxetine, fluvoxamine, gingko, goldenseal, isoniazid, nitrofurantoin, oral contraceptives, ranitidine, ranolazine, tipranavir/ritonavir, zileuton

- **Cimetidine**

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<table>
<thead>
<tr>
<th>Study Protocols: Exclusion Criteria</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>RELY</th>
<th>ROCKET-AF</th>
<th>ARISTOTLE</th>
</tr>
</thead>
</table>
| • Patients who have developed transaminase elevations upon exposure to ximelagatran | • Aspirin >100 mg daily  
• Aspirin in combination with thienopyridines  
• Chronic treatment with non-steroidal anti-inflammatory drug  
• **Strong inhibitor of CYP 3A4**  
• **Strong inducer of CYP 3A4** | • Aspirin > 165 mg/day  
• Treatment with both aspirin and thienopyridine  
• **Potent inhibitors of CYP3A4**  
• **Potent inducer of CYP3A4:**  
  • Investigator should carefully evaluate subject’s risk of thromboembolism, as the plasma concentration of apixaban may be lower |
In Vivo Data on Drug Interactions

**Dabigatran**

- **Dronedarone**: Increases exposure to dabigatran by 70 to 140% compared to dabigatran alone.

- **Verapamil**: If verapamil is present in the gut when dabigatran is taken, it will increase exposure to dabigatran with the greatest increase observed when a single dose of immediate-release verapamil is given one hour prior to dabigatran (AUC increased by a factor of 2.4).

- **Rifampin**: 600 mg once daily for 7 days followed by a single dose of dabigatran decreased its AUC and Cmax by 66% and 67%, respectively. By Day 7 after cessation of rifampin treatment, dabigatran exposure was close to normal.

**Rivaroxaban**

- Inhibition of cytochrome 3A4 by ketoconazole results in an increase in plasma concentrations by about 2.6-fold for AUC, whereas cosubstrates of cytochrome 3A4 (midazolam) have no influence.

- When combined with a potent inducer of cytochrome 3A4 (rifampicin), AUC, Cmax, and t1/2 were reduced by approximately 50% in normal volunteers.

**Apixaban**

Dose reduce to apixaban 2.5 mg BID

---

1. Pradaxa Package Insert  
3. Eliquis Package Insert
| **Ritonavir**  
Inhibitor of **CYP3A4** (strong), **PGP**, and CYP2D6  
Inducer of CYP2C19 (strong), CYP2C9, and CYP1A2 (moderate) | **Dabigatran** | **Rivaroxaban** | **Apixaban** | **Clinical Management** |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Possible ↑ AUC as a result of inhibition of PGP; unlikely to be clinically relevant if administration times are separated by 2 hours</td>
<td>Possible ↑ clinical effect as a result of inhibition of CYP3A4 metabolism</td>
<td>Possible ↑ clinical effect as a result of inhibition of CYP3A4 metabolism</td>
<td>Suggest use of Dabigatran with administration times separated or warfarin</td>
</tr>
</tbody>
</table>
Dabigatran Storage

Keep dabigatran in its original container...

*capsule not actual size

...never in a pill box or pill organizer.

1. Adapted from Pradaxa.com
After cardioversion, which oral anticoagulant will you discharge the patient home with?

A. Warfarin 5 mg PO daily with enoxaparin 120 mg SQ every 12 hours

B. Dabigatran 150 mg PO BID

C. Apixaban 2.5 mg PO BID

D. Rivaroxaban 20 mg PO daily with dinner
Take Home Points

- Drug interactions for dabigatran, rivaroxaban and apixaban are possible and may be clinically significant.
Objectives

Patient Case #1
- Discuss data using novel oral anticoagulants (NOACs) post cardioversion or ablation
- Describe metabolism and identify significant drug interactions with the NOACs

Patient Case #2
- To understand when to stop and start NOAC’s around invasive procedures

Patient Case #3
- Identify risk factors and frequency of bleeding with NOACs in clinical trials
- List laboratory monitoring and strategies to control bleeding episodes with NOACs
Case #2

- 76 year old man with A fib, HTN, CHF, OA – scheduled for THA
- On dabigatran 150 mg bid
- CHADS\(_2\) score = 3 (annual stroke risk 5.9%), CHA\(_2\)DS\(_2\)-VASc = 4 (annual stroke risk 4%)
- Pre-op labs notable for creatinine 1.6 (GFR = 42)
Case #2 - Questions

• When should last dose of dabigatran be taken prior to surgery?
  ◦ 1 day
  ◦ 2 days
  ◦ 3 days
  ◦ 4 days

• When should dabigatran be restarted after surgery?
  ◦ evening post-op
  ◦ POD 1
  ◦ POD 2
  ◦ POD 3
Timing of Preoperative Anticoagulant Interruption

• Should be based on:

1. Bleeding risk of procedure

2. Elimination half-life of drug – depends on renal/liver function
   ◦ 2-3 half-lives before minor procedure (12-25% residual AC effect)
   ◦ 4-5 half-lives before major procedure (3-6% residual AC effect)
Bleeding risk of procedure

**Very low bleeding risk**
Dental interventions (extraction of 1 to 3 teeth, periodontal surgery)  
Cataract or glaucoma surgery  
Diagnostic endoscopy  
Superficial surgery (abscess incision, minor dermatologic procedures)

**Low bleeding risk**
Endoscopy with biopsy  
Prostate or bladder biopsy  
EP study or RFA  
Angiography  
Pacemaker or ICD implantation

**High bleeding risk**
Spinal or epidural anesthesia, lumbar puncture  
Thoracic surgery  
Abdominal surgery  
Major orthopedic surgery  
Liver biopsy  
Transurethral prostate resection  
Kidney biopsy

Anticoagulant Pharmacokinetics

<table>
<thead>
<tr>
<th>Medication</th>
<th>Half-life (hours)</th>
<th>Renal Elimination (%)</th>
<th>Onset of Action (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heparin</td>
<td>1-2</td>
<td>minimal</td>
<td>immediate</td>
</tr>
<tr>
<td>Enoxaparin</td>
<td>4-5</td>
<td>high</td>
<td>3-5</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>7-11</td>
<td>35</td>
<td>2-4</td>
</tr>
<tr>
<td>Apixiban</td>
<td>9-14</td>
<td>27</td>
<td>3-4</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>12-17</td>
<td>80</td>
<td>1-3</td>
</tr>
<tr>
<td>Fondaparinux</td>
<td>17-21</td>
<td>77</td>
<td>2-3</td>
</tr>
<tr>
<td>Warfarin</td>
<td>20-60</td>
<td>minimal</td>
<td>36-72</td>
</tr>
</tbody>
</table>
Impact of Renal Impairment on Dabigatran Pharmacokinetics

<table>
<thead>
<tr>
<th>CrCl (mL/min)</th>
<th>Half-life (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 80</td>
<td>13</td>
</tr>
<tr>
<td>50-80</td>
<td>15</td>
</tr>
<tr>
<td>30-50</td>
<td>18</td>
</tr>
<tr>
<td>15-30</td>
<td>27</td>
</tr>
</tbody>
</table>

- Patients with severe renal impairment were not studied in RE-LY and RE-COVER
- Dosing recommendations in subjects with severe renal impairment are based on pharmacokinetic modeling
RE-LY Sub-study

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran 150 mg (N=1546) % (n)</th>
<th>Warfarin (N=1558) % (n)</th>
<th>Relative Risk (95% CI, P Value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major Bleeding</td>
<td>5.1 (78)</td>
<td>4.6 (72)</td>
<td>1.09 (0.80-1.49, 0.58)</td>
</tr>
<tr>
<td>Ischemic Stroke</td>
<td>0.5 (7)</td>
<td>0.5 (7)</td>
<td>1.01 (0.35-2.87, 0.99)</td>
</tr>
<tr>
<td>or Systemic Embolism</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Major bleeding in patients having urgent surgery: dabigatran 17.7%, warfarin 21.6% (RR 0.82; 0.50-1.35, 0.44)
Dresden NOAC Registry

• Ongoing, prospective, non-interventional registry
• 2179 patients
• 595 (27%) underwent 863 procedures: 16% minimal, 74% minor, 10% major
• NOAC not interrupted in 22%
• Major CV events (ACS, stroke, VTE) in 1.0% [0.5-2.0]
• Major bleeding in 1.2% [0.6-2.1]
• CV events and bleeding higher after major procedures: 4.6%, 8.0%
• Bridging used in 30% - did not reduce CV events but did increase major bleeding (2.7%, 1.1-5.5) compared with no bridging (0.5%, 0.1-1.4), $P = 0.010$

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran</th>
<th>Apixaban</th>
<th>Edoxaban</th>
<th>Rivaroxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low risk</td>
<td>High risk</td>
<td>Low risk</td>
<td>High risk</td>
</tr>
<tr>
<td>CrCl ≥ 80 ml/min</td>
<td>≥ 24 h</td>
<td>≥ 48 h</td>
<td>≥ 24 h</td>
<td>≥ 48 h</td>
</tr>
<tr>
<td>CrCl 50–80 ml/min</td>
<td>≥ 36 h</td>
<td>≥ 72 h</td>
<td>≥ 24 h</td>
<td>≥ 48 h</td>
</tr>
<tr>
<td>CrCl 30–50 ml/min</td>
<td>≥ 48 h</td>
<td>≥ 96 h</td>
<td>≥ 24 h</td>
<td>≥ 48 h</td>
</tr>
<tr>
<td>CrCl 15–30 ml/min</td>
<td>Not indicated</td>
<td>Not indicated</td>
<td>≥ 36 h</td>
<td>≥ 48 h</td>
</tr>
<tr>
<td>CrCl &lt; 15 ml/min</td>
<td>Not indicated</td>
<td>Not indicated</td>
<td>No data</td>
<td>No data</td>
</tr>
</tbody>
</table>

*Table 9 Last intake of drug before elective surgical intervention*
When to Restart Anticoagulant after Surgery

• In patients undergoing non-high-bleeding-risk surgery, we suggest resuming therapeutic-dose LMWH approximately 24 h after surgery

• In patients undergoing high-bleeding-risk surgery, we suggest resuming therapeutic-dose LMWH 48 to 72 h after surgery
Case #2 - Revisited

• When should last dose of dabigatran be taken prior to surgery?
  ◦ 1 day
  ◦ 2 days
  ◦ 3 days
  ◦ 4 days

• When should dabigatran be restarted after surgery?
  ◦ evening post-op
  ◦ POD 1
  ◦ POD 2
  ◦ POD 3
Case #2 - Continued

• POD 1 creatinine increases to 2.3 (GFR = 28)

• What is the best option now?
  ◦ decrease dose of dabigatran to 75 mg bid
  ◦ change to apixaban 5 mg bid (or 2.5 mg bid)
  ◦ change to warfarin (with or without UFH or LMWH “bridge”)
  ◦ defer therapeutic anticoagulation until renal function improves (use VTE prophylaxis)
Take Home Points

• Drug interactions for dabigatran, rivaroxaban and apixaban are possible and may be clinically significant.

• Anticoagulation interruption should be based on procedure bleeding risk, drug elimination half-life, and patient renal/liver function
Objectives

Patient Case #1
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- Describe metabolism and identify significant drug interactions with the NOACs

Patient Case #2
- To understand when to stop and start NOAC’s around invasive procedures

Patient Case #3
- Identify risk factors and frequency of bleeding with NOACs in clinical trials
- List laboratory monitoring and strategies to control bleeding episodes with NOACs
Patient Case

- 84 yo female presenting with hemoptysis, intubated in MICU and subsequently went into PEA arrest
- PMH: AFib on rivaroxaban 20 mg daily, last dose morning of admission
- Renal and hepatic function WNL
- Coagulation studies:
  - PT: 26.6 (9.3-12.8 sec)
  - INR: 2.4
Questions

1. What lab parameters would you draw to assess presence of rivaroxaban?
   a. Prothrombin time
   b. Thrombin time
   c. Dilute thrombin time
   d. Chromogenic Xa assay

2. Which agent would you choose to control bleeding caused by rivaroxaban?
   a. FFP
   b. Prothrombin Complex Concentrate
   c. Activated Prothrombin Complex Concentrate
   d. Factor VIIa
Risk Factors for Bleeding

- Intensity of anticoagulation
- Elderly patients
- Bleeding history
- Interacting medications
- Renal/hepatic impairment

<table>
<thead>
<tr>
<th>Drug, dose</th>
<th>Categories of renal function and major bleeding rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal</td>
</tr>
<tr>
<td>Dabigatran</td>
<td></td>
</tr>
<tr>
<td>• 150 mg  BID</td>
<td>2.09</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td></td>
</tr>
<tr>
<td>• 20 or 15 mg Daily</td>
<td>3.39</td>
</tr>
<tr>
<td>Apixaban</td>
<td></td>
</tr>
<tr>
<td>• 5 or 2.5 mg BID</td>
<td>1.5</td>
</tr>
</tbody>
</table>

# Intracranial Hemorrhage Incidence

<table>
<thead>
<tr>
<th>Drug, study</th>
<th>ICH, NOAC, %/patient-year</th>
<th>ICH, VKA, %/patient-year</th>
<th>Hazard ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stroke prevention in atrial fibrillation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dabigatran 150 mg, RE-LY</td>
<td>0.32</td>
<td>0.76</td>
<td>0.3 (0.19-0.45)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Rivaroxaban, ROCKET-AF</td>
<td>0.5</td>
<td>0.7</td>
<td>0.67 (0.47-0.93)</td>
<td>0.02</td>
</tr>
<tr>
<td>Apixaban, ARISTOTLE</td>
<td>0.33</td>
<td>0.8</td>
<td>0.42 (0.30-0.58)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>VTE Treatment</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dabigatran, RE-COVER + RE-COVER II + RE-MEDY</td>
<td>0.13</td>
<td>0.29</td>
<td>0.44 (0.10-1.59)</td>
<td>0.16</td>
</tr>
<tr>
<td>Rivaroxaban, EISTEIN-DVT + EINSTEIN-PE</td>
<td>0.21</td>
<td>0.58</td>
<td>0.36 (0.10-1.04)</td>
<td>0.038</td>
</tr>
<tr>
<td>Apixaban, AMPLIFY</td>
<td>0.22</td>
<td>0.45</td>
<td>0.50 (0.08-2.35)</td>
<td>0.51</td>
</tr>
</tbody>
</table>
Evaluating Patient with NOAC Related Bleeding

- Patient characteristics
  - Severity of bleeding
  - Overdose

- History needed
  - Which agent
  - Indication
  - Time of last dose

- Specific tests
  - SCr. and LFTs
  - CBC
  - Coagulation tests
# Lab Monitoring Specifics

<table>
<thead>
<tr>
<th>Drug</th>
<th>Monitoring Tests</th>
<th>Lab characteristics</th>
<th>Limitations</th>
</tr>
</thead>
</table>
| Dabigatran | • Activated partial thromboplastin time (aPTT)  
• Thrombin time (TT)  
• Dilute thrombin time  
• Ecarin clotting time (ECT) | • Prolongs aPTT  
• TT sensitive, if normal dabigatran absent or low concentrations  
• ECT sensitive | • aPTT provides nonlinear correlation and dabigatran levels, influenced by other factors  
• ECT, TT and dilute thrombin time not readily available |
| Apixaban  | • Prothrombin time (PT)  
• Chromogenic antifactor Xa assay | • Prolongs PT  
• Chromogenic assay provides quantitative effect | • PT not sensitive at low concentrations  
• Chromogenic assay not readily available |
| Rivaroxaban | • PT  
• aPTT  
• Chromogenic antifactor Xa assay | • Prolongs PT  
• Prolongs aPTT  
• Chromogenic assay provides quantitative effect | • PT results may differ with different thromboplastin reagents  
• Chromogenic assay not readily available |
<table>
<thead>
<tr>
<th>Agent</th>
<th>Components</th>
<th>Dosing Ranges</th>
<th>Duration of effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recombinant factor VIIa (Novoseven RT®)</td>
<td>Factor VIIa</td>
<td>90 mcg/kg</td>
<td>4-6 hours</td>
</tr>
<tr>
<td>Prothrombin Complex Concentrate (non-activated) 3-Factor (Profilnine®)</td>
<td>Factors II, IX, X (low levels of VII)</td>
<td>25 – 50 units/kg</td>
<td>6-8 hours</td>
</tr>
<tr>
<td>Prothrombin Complex Concentrate (non-activated) 4-Factor (KCentra®)</td>
<td>Factors II, VII, IX, X Protein C and S Heparin</td>
<td>25 – 50 units/kg</td>
<td>6-8 hours</td>
</tr>
<tr>
<td>Prothrombin Complex Concentrate (activated) 4-Factor (FEIBA™)</td>
<td>Factors II, IX, X, VIIa (activated)</td>
<td>50 – 100 units/kg</td>
<td>8-12 hours</td>
</tr>
</tbody>
</table>
Evidence of Clotting Factors and NOACs

- 10 healthy volunteers given single dose of 150 mg dabigatran or 20 mg rivaroxaban
- *In vitro* effect of different coagulation factors:
  - Activated prothrombin complex concentrate (corresponding to 80 units/kg)
  - Four factor prothrombin complex concentrate (corresponding to 25 units/kg)
  - Recombinant factor VIIa (corresponding to 120 mcg/kg)
- Samples taken before (H0) and 2 hours after (H2) drug administration
- Curves show *ex vivo* addition of non-specific reversal agents to obtained blood samples
Type of Bleed

Minor Bleeding
- Local Hemostatic Measures
- Consider anticoagulant withdrawal

Moderate Bleeding
- General Measures
  - Anticoagulant withdrawal
  - Mechanical compression
  - Volume replacement
- Blood Product Transfusion
  - RBC if anemia
  - Consider platelets for patients on antiplatelet agents/thrombocytopenia

Severe/Life-Threatening Bleeding
- (In addition to moderate bleeding recommendations)
- Severe/Life-Threatening Bleeding
  - Intensive care
  - Hemodynamic support
  - Hematology consult (if available)
- Dabigatran related:
  - Activated PCC 80 units/kg
- Rivaroxaban/apixaban related:
  - PCC 50 units/kg
- Adjunctive therapies
  - Oral charcoal if ingestion within 2 hours
  - Hemodialysis for dabigatran
  - Desmopressin
  - Antifibrinolytic agents

Idarucizimab: Dabigatran Antidote

- Humanized antibody fragment (Fab) against dabigatran
- Does not demonstrate prothrombotic activities
- 350 times greater affinity for dabigatran than thrombin

145 healthy male volunteers study
- Part I
  - Single IV escalating doses up to 8 grams
  - Doses safe and well tolerated
- Part II
  - 1, 2, and 4 grams as 5 minute IV infusion in presence of dabigatran 220 mg BID x 4 days
  - Reversed clotting times at end of 5 minute infusion
  - Reversal sustained in all subjects receiving 4 gram
  - Thrombin time reversed to < 2-fold

Glund S. AHA 2013 meeting;17765 (abstr).
Other Future Antidotes

- **Andexanet alfa**
  - Protein derived from human coagulation factor X
  - No procoagulant or anticoagulant activity
  - Acts as decoy for factor Xa inhibitor

- **Aripazine**
  - Reverses oral NOACs and parenteral agents (e.g., UFH, LMWH, fondaparinux) via hydrogen bond
  - Single bolus injection

<table>
<thead>
<tr>
<th>Factor Xa inhibitor</th>
<th>Andexanet alfa dose (IV bolus)</th>
<th>Anti-Xa activity after andexanet alfa</th>
<th>Anti-Xa activity after placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>(days 1-6)</td>
<td></td>
<td>(N=4)</td>
<td>(N=2)</td>
</tr>
<tr>
<td>Apixaban 5 mg BID</td>
<td>90 mg</td>
<td>2 min: -65%</td>
<td>2 min: +6%</td>
</tr>
<tr>
<td>Rivaroxaban 20 mg daily</td>
<td>210 mg</td>
<td>(N=6)</td>
<td>(N=3)</td>
</tr>
<tr>
<td></td>
<td>2 min: -20%</td>
<td>2 min: 0%</td>
<td></td>
</tr>
<tr>
<td>Rivaroxaban 20 mg daily</td>
<td>420 mg</td>
<td>(N=6)</td>
<td>(N=3)</td>
</tr>
<tr>
<td></td>
<td>2 min: -53%</td>
<td>2 min: 0%</td>
<td></td>
</tr>
</tbody>
</table>

Questions?

• What lab parameters would you draw to assess presence of rivaroxaban?
  • Prothrombin time
  • Thrombin time
  • Dilute thrombin time
  • Chromogenic Xa assay

• What would you do to reverse the effect of rivaroxaban?
  • FFP
  • Activated Prothrombin Complex Concentrate
  • Prothrombin Complex Concentrate
  • Factor VIIa
Take Home Points

• Drug interactions for dabigatran, rivaroxaban and apixaban are possible and may be clinically significant.

• Anticoagulation interruption should be based on procedure bleeding risk, drug elimination half-life, and patient renal/liver function

• For patients with NOAC related bleeding:
  • Limited laboratory tests available to accurately monitor NOACs and limited data available on clotting factors to control bleeding
  • Antidotes still in clinical trial phase
Questions?

Practical How-to: Treating Patients with New Anticoagulants – *case scenarios*

Robert Barcelona, PharmD, BCPS, Matthew Eisen, MD and Lindsey Federle, PharmD, BCPS