Perioperative Management of Novel Oral Anticoagulants (NOACs)

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Disclosures

• Presenter has no actual or potential conflicts of interest in relation to this program


Question

• What is the correct interval for neuraxial procedure after last dose of Rivaroxaban in a patient with PMH of AF and normal renal function?

A. 24 hours
B. 48 hours
C. 72 hours
D. 96 hours
Question

• Which of the following medications does not increase the risk of GI bleeding in patients when compared to warfarin?

A. Dabigatran
B. Rivaroxaban
C. Apixaban
D. Edoxaban
Question

A patient is scheduled for pacemaker implantation in OR a week from today. This patient is maintained on Dabigatran 150mg twice daily for AF. PMH is significant for CKD, and her CrCl is 40 ml/min. How many days ago Dabigatran should be discontinued in this patient before surgery?

A. 24 hours
B. 48 hours
C. 72 hours
D. 96 hours
Question

• When should Dabigatran be resumed in this patient?

A. 24 hours
B. 48 hours
C. 72 hours
D. 96 hours
Objectives

- Describe pharmacodynamics and pharmacokinetics of Novel Oral Anticoagulants.
- Describe evidence-based literature for bleeding risk associated with Novel Oral Anticoagulants.
- Recommend preoperative management timelines for various Novel Oral Anticoagulants.
- Describe management of perioperative bleeding due to Novel Oral Anticoagulants.
NOACs/DOACs

- Rivaroxaban (Xarelto®)
- Dabigatran (Pradaxa®)
- Apixaban (Eliquis®)
- Edoxaban (Savaysa®)
Warfarin

• Still First-line Agent
• Limitations:
  – Slow Onset
  – Slow Offset
  – Narrow Therapeutic Index
  – Food/Drug Interactions
NOACs vs Warfarin

• Advantages
  – No INR monitoring required
  – No bridging required
  – Good safety profile
  – Easier to manage around surgical procedures
  – Fewer drug/food interactions

NOACs vs Warfarin

• Disadvantages:
  - Cost
  - Compliance
  - Dosage modification in renal impairment
  - No specific antidotes for Rivaroxaban, Apixaban and Edoxaban (yet)
  - Higher incidence of GI bleeds

Pharmacodynamics of NOACs

Pharmacodynamics of NOACs

- Factor Xa
- Prothrombin (Factor II)
- Thrombin (Factor Ia)
- Fibrinogen (Factor I)
- Fibrin (Factor Ia)
- Clot

NOACs:
- Rivaroxaban
- Enoxaparin
- Edoxaban
- Dabigatran
## Pharmacological Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Rivaroxaban (Xarelto)</th>
<th>Apixaban (Eliquis)</th>
<th>Edoxaban (Savaysa)</th>
<th>Dabigatran (Pradaxa)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Target</strong></td>
<td>Factor Xa</td>
<td>Factor Xa</td>
<td>Factor Xa</td>
<td>Factor IIa</td>
</tr>
<tr>
<td><strong>Prodrug</strong></td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Preparations</strong></td>
<td>10, 15, 20mg</td>
<td>2.5, 5mg</td>
<td>15, 30, 60mg</td>
<td>75, 110, 150mg</td>
</tr>
<tr>
<td><strong>Dose Schedule</strong></td>
<td>OD</td>
<td>BID</td>
<td>OD</td>
<td>BID</td>
</tr>
<tr>
<td><strong>Interactions</strong></td>
<td>CYP3A4 and P-gp inhibitors</td>
<td>CYP3A4 and P-gp inhibitors</td>
<td>CYP3A4 and P-gp inhibitors</td>
<td>P-gp inhibitors</td>
</tr>
</tbody>
</table>

**Lexicomp Online®, Lexi-Drugs®, Hudson, Ohio: Lexi-Comp, Inc.; March 22, 2017**
Pharmacokinetics

• Rivaroxaban:
  – Absorption - Rapid
  – Metabolism - Hepatic via CYP3A4/5 and CYP2J2
  – Excretion - Urine 66% primarily via active tubular secretion [~36% as unchanged drug; 30% as inactive metabolites]
  – Time to Peak Plasma - 2 to 4 hours
  – Half-life - Terminal: 5 to 9 hours; Elderly: 11 to 13 hours
Pharmacokinetics

- **Rivaroxaban**

<table>
<thead>
<tr>
<th></th>
<th>CrCl &gt; 50</th>
<th>CrCl 30-50</th>
<th>CrCl 15-30</th>
<th>CrCl &lt; 15</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Atrial Fibrillation</strong></td>
<td>20mg QD</td>
<td>15mg QD</td>
<td>Avoid</td>
<td></td>
</tr>
<tr>
<td><strong>Post-op thromboprophylaxis</strong></td>
<td>10mg QD</td>
<td>10mg QD, use with caution</td>
<td>Avoid use</td>
<td>Avoid</td>
</tr>
<tr>
<td>Knee – 12-14 days</td>
<td>Hip – 35 days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Treatment of DVT/PE</strong></td>
<td>15mg BIDx21 days, then 20mg QD</td>
<td>Use with caution</td>
<td>Avoid use</td>
<td>Avoid</td>
</tr>
<tr>
<td><strong>Secondary Prophylaxis</strong></td>
<td>20mg QD</td>
<td>Use with caution</td>
<td>Avoid use</td>
<td>Avoid</td>
</tr>
</tbody>
</table>
Pharmacokinetics

- Apixaban:
  - Metabolism - Hepatic, predominantly via CYP3A4/5
  - Excretion – Urine (~27% as parent drug)
  - Time to peak: 3 to 4 hours
  - Half-life elimination: ~12 hours
Pharmacokinetics

• Apixaban:
  – Dose: 5mg twice daily
  – Dose reduction to 2.5mg twice daily if 2+ of the following:
    • Age \( \geq 80 \) years
    • Body weight \( \leq 60 \)kg
    • Scr \( \geq 1.5 \)mg/dl
  – AVOID in CrCl <15 ml/min

Pharmacokinetics

- Edoxaban
  - Metabolism - Minimal via hydrolysis, conjugation and oxidation by CYP3A4; predominant metabolite (M-4) is active (<10% of parent compound)
  - Excretion - Urine (primarily unchanged)
  - Time to peak - 1 to 2 hours
  - Half-life elimination - 10 to 14 hours

Savaysa (edoxaban) [prescribing information]. Parsippany, NJ: Daiichi Sankyo; September 2016.
Pharmacokinetics

- **Edoxaban:**
  - CrCl 51-95 ml/min – No dosage adjustment necessary
  - CrCl 15-50 ml/min – 30mg once daily
  - CrCl < 15 ml/min – Use is not recommended

Use not recommended in Nonvalvular AF if CrCl > 95 ml/min
Pharmacokinetics

• Dabigatran
  - Absorption: Rapid; initially slow postoperatively
  - Metabolism: Hepatic; dabigatran etexilate is rapidly and completely hydrolyzed to dabigatran (active form) by plasma and hepatic esterases; dabigatran undergoes hepatic glucuronidation to active acylglucuronide isomers (similar activity to parent compound; accounts for <10% of total dabigatran in plasma)
  - Half-life elimination: 12-17 hours; Elderly: 14-17 hours; Mild-to-moderate renal impairment: 15-18 hours; Severe renal impairment: 28 hours
  - Time to peak, plasma: Dabigatran: 1 hour; delayed 2 hours by food (no effect on bioavailability)
  - Excretion: Urine (80%)
Pharmacokinetics

- Dabigatran:
  - Prodrug
  - Use not recommended if CrCl < 30ml/min
  - Antidote - Idaracizumab

Pradaxa (dabigatran) [prescribing information]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals Inc; November 2015.
FDA Boxed Warning

• Epidural or spinal hematomas may occur in patients treated with apixaban who are receiving neuraxial anesthesia or undergoing spinal puncture. Consider these risks when scheduling patients for spinal procedures. Factors that can increase the risk of developing epidural or spinal hematomas in these patients include use of indwelling epidural catheters; concomitant use of other drugs that affect hemostasis, such as non-steroidal anti-inflammatory drugs (NSAIDs), platelet inhibitors, other anticoagulants; a history of traumatic or repeated epidural or spinal punctures; a history of spinal deformity or spinal surgery; optimal timing between the administration and neuraxial procedures is not known.

• Consider the benefits and risks before neuraxial intervention in patients anticoagulated or to be anticoagulated.

# NOACs and Neuraxial Anesthesia

<table>
<thead>
<tr>
<th>Drug</th>
<th>Interval For Catheter Placement OR Neuraxial Procedure After Last Dose</th>
<th>Interval For Catheter Removal After Most Recent Dose</th>
<th>RECOMMENDED Interval To Restart Med After Neuraxial Procedure OR Removal of Epidural Catheter</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rivaroxaban</td>
<td>CrCl&gt;50 – 2 Days CrCl&lt;50 – 3 Days</td>
<td>48 Hours</td>
<td>24 Hours</td>
</tr>
<tr>
<td>Apixaban</td>
<td>CrCl&gt;50 – 3 Days CrCl&lt;50 – 4 Days</td>
<td>48 Hours</td>
<td>24 Hours</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>CrCl&gt;50 – 3 Days CrCl&lt;50 – 5 Days</td>
<td>48 Hours</td>
<td>24 Hours</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>CrCl&gt;50 – 4 Days CrCl&lt;50 – 7 Days</td>
<td>48 Hours</td>
<td>24 Hours</td>
</tr>
</tbody>
</table>
Clinical Trials

• Landmark Studies
  • RE-LY Trial – Dabigatran
  • ROCKET AF Trial – Rivaroxaban
  • ARISTOTLE Trial – Apixaban
  • ENGAGE AF Trial - Edoxaban
### Rates of Bleeding Events: ROCKET AF

| Variable                                                           | Rivaroxaban (N=7111) | Warfarin (N=7125) | Hazard Ratio (95% CI) | P Value  
|--------------------------------------------------------------------|-----------------------|-------------------|-----------------------|---------
| Principal safety end point: major and nonmajor clinically relevant bleeding‡ | 1475 (20.7) 14.9    | 1449 (20.3) 14.5  | 1.03 (0.96–1.11)      | 0.44    
| Major bleeding                                                     |                       |                   |                       |         
| Any                                                                | 395 (5.6) 3.6         | 386 (5.4) 3.4     | 1.04 (0.90–1.20)      | 0.58    
| Decrease in hemoglobin ≥2 g/dl                                     | 305 (4.3) 2.8         | 254 (3.6) 2.3     | 1.22 (1.03–1.44)      | 0.02    
| Transfusion                                                        | 183 (2.6) 1.6         | 149 (2.1) 1.3     | 1.25 (1.01–1.55)      | 0.04    
| Critical bleeding‡                                                 | 91 (1.3) 0.8          | 133 (1.9) 1.2     | 0.69 (0.53–0.91)      | 0.007   
| Fatal bleeding                                                     | 27 (0.4) 0.2          | 55 (0.8) 0.5      | 0.50 (0.31–0.79)      | 0.003   
| Intracranial hemorrhage                                           | 55 (0.8) 0.5          | 84 (1.2) 0.7      | 0.67 (0.47–0.93)      | 0.02    
| Nonmajor clinically relevant bleeding                             | 1185 (16.7) 11.8     | 1151 (16.2) 11.4  | 1.04 (0.96–1.13)      | 0.35    

*All analyses of rates of bleeding are based on the first event in the safety population during treatment.

† Hazard ratios are for the rivaroxaban group as compared with the warfarin group and were calculated with the use of Cox proportional-hazards models with the study group as a covariate.

‡ Two-sided P values are for superiority in the rivaroxaban group as compared with the warfarin group.

§ Minimal bleeding events were not included in the principal safety end point.

¶ Bleeding events were considered to be critical if they occurred in intracranial, intraspinal, intraocular, pericardial, intraarticular, intramuscular (with compartment syndrome), or retroperitoneal sites.

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## Major Bleeding by Site – ROCKET AF

<table>
<thead>
<tr>
<th></th>
<th>Rivaroxaban (N=7111)</th>
<th>Warfarin (N=7125)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major bleeding, no. (%)</td>
<td>395 (5.55)</td>
<td>386 (5.42)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>224 (3.15)</td>
<td>154 (2.16)</td>
</tr>
<tr>
<td>Intracranial</td>
<td>55 (0.77)</td>
<td>84 (1.18)</td>
</tr>
<tr>
<td>Macroscopic hematuria</td>
<td>26 (0.37)</td>
<td>21 (0.29)</td>
</tr>
<tr>
<td>Bleeding associated with non-cardiac surgery</td>
<td>19 (0.27)</td>
<td>26 (0.36)</td>
</tr>
<tr>
<td>Intraocular/Retinal</td>
<td>17 (0.24)</td>
<td>24 (0.34)</td>
</tr>
<tr>
<td>Intraarticular</td>
<td>16 (0.23)</td>
<td>21 (0.29)</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>13 (0.18)</td>
<td>14 (0.20)</td>
</tr>
</tbody>
</table>

### Table 3. Safety Outcomes, According to Treatment Group.

<table>
<thead>
<tr>
<th>Event</th>
<th>Dabigatran, 110 mg</th>
<th>Dabigatran, 150 mg</th>
<th>Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no. of patients</td>
<td>%/yr</td>
<td>no. of patients</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>322</td>
<td>2.71</td>
<td>375</td>
</tr>
<tr>
<td>Life threatening</td>
<td>145</td>
<td>1.22</td>
<td>175</td>
</tr>
<tr>
<td>Non–life threatening</td>
<td>198</td>
<td>1.66</td>
<td>226</td>
</tr>
<tr>
<td>Gastrointestinal†</td>
<td>133</td>
<td>1.12</td>
<td>182</td>
</tr>
<tr>
<td>Minor bleeding</td>
<td>1566</td>
<td>13.16</td>
<td>1787</td>
</tr>
<tr>
<td>Major or minor bleeding</td>
<td>1740</td>
<td>14.62</td>
<td>1977</td>
</tr>
<tr>
<td>Intracranial bleeding</td>
<td>27</td>
<td>0.23</td>
<td>36</td>
</tr>
<tr>
<td>Extracranial bleeding</td>
<td>299</td>
<td>2.51</td>
<td>342</td>
</tr>
<tr>
<td>Net clinical benefit outcome‡</td>
<td>844</td>
<td>7.09</td>
<td>832</td>
</tr>
</tbody>
</table>

* Data are shown for all patients who had at least one event. All analyses were based on the time to the first event. Hemorrhagic stroke was a subcategory of stroke in the efficacy analysis and in the safety analysis is also counted as major, life-threatening bleeding and as part of intracranial bleeding.
† Gastrointestinal bleeding could be life threatening or non–life threatening.
‡ The net clinical benefit outcome was the composite of stroke, systemic embolism, pulmonary embolism, myocardial infarction, death, or major bleeding.
### Table 3. Bleeding Outcomes and Net Clinical Outcomes.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Apixaban Group (N = 9088)</th>
<th>Warfarin Group (N = 9052)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients with Event no.</td>
<td>Event Rate %/yr</td>
<td>Patients with Event no.</td>
<td>Event Rate %/yr</td>
</tr>
<tr>
<td>Primary safety outcome: ISTH major bleeding†</td>
<td>327</td>
<td>2.13</td>
<td>462</td>
<td>3.09</td>
</tr>
<tr>
<td>Intracranial</td>
<td>52</td>
<td>0.33</td>
<td>122</td>
<td>0.80</td>
</tr>
<tr>
<td>Other location</td>
<td>275</td>
<td>1.79</td>
<td>340</td>
<td>2.27</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>105</td>
<td>0.76</td>
<td>119</td>
<td>0.86</td>
</tr>
<tr>
<td>Major or clinically relevant nonmajor bleeding</td>
<td>613</td>
<td>4.07</td>
<td>877</td>
<td>6.01</td>
</tr>
<tr>
<td>GUSTO severe bleeding</td>
<td>80</td>
<td>0.52</td>
<td>172</td>
<td>1.13</td>
</tr>
<tr>
<td>GUSTO moderate or severe bleeding</td>
<td>199</td>
<td>1.29</td>
<td>328</td>
<td>2.18</td>
</tr>
<tr>
<td>TIMI major bleeding</td>
<td>148</td>
<td>0.96</td>
<td>256</td>
<td>1.69</td>
</tr>
<tr>
<td>TIMI major or minor bleeding</td>
<td>239</td>
<td>1.55</td>
<td>370</td>
<td>2.46</td>
</tr>
<tr>
<td>Any bleeding</td>
<td>2356</td>
<td>18.1</td>
<td>3060</td>
<td>25.8</td>
</tr>
<tr>
<td>Net clinical outcomes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke, systemic embolism, or major bleeding</td>
<td>521</td>
<td>3.17</td>
<td>666</td>
<td>4.11</td>
</tr>
<tr>
<td>Stroke, systemic embolism, major bleeding, or death from any cause</td>
<td>1009</td>
<td>6.13</td>
<td>1168</td>
<td>7.20</td>
</tr>
</tbody>
</table>

* The bleeding outcomes were assessed in patients who received at least one dose of a study drug and events that occurred from the time the patients received the first dose of the study drug through 2 days after they received the last dose. The net clinical outcome includes all efficacy outcomes through the cutoff date for the efficacy analysis and bleeding outcomes that occurred from the time the patients received the first dose of the study drug through 2 days after they received the last dose. GUSTO denotes Global Use of Strategies to Open Occluded Coronary Arteries, and TIMI Thrombolysis in Myocardial Infarction.

† The comparison of the primary safety outcome of bleeding according to the International Society on Thrombosis and Haemostasis (ISTH) criteria is in the hierarchical sequence preserving a type I error.
## Table 3. Safety and Net Clinical End Points.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Warfarin (N=7012)</th>
<th>High-Dose Edoxaban (N=7012)</th>
<th>High-Dose Edoxaban vs. Warfarin</th>
<th>Low-Dose Edoxaban (N=7002)</th>
<th>Low-Dose Edoxaban vs. Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no. of patients</td>
<td>% of patients/yr</td>
<td>no. of patients/yr</td>
<td>no. of patients/yr</td>
<td>no. of patients/yr</td>
</tr>
<tr>
<td></td>
<td>with event</td>
<td></td>
<td>with event</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major bleeding</td>
<td>524</td>
<td>3.43</td>
<td>418</td>
<td>2.75</td>
<td>0.80 (0.71–0.91)</td>
</tr>
<tr>
<td></td>
<td>59</td>
<td>0.38</td>
<td>32</td>
<td>0.21</td>
<td>0.55 (0.36–0.84)</td>
</tr>
<tr>
<td></td>
<td>211</td>
<td>1.36</td>
<td>108</td>
<td>0.70</td>
<td>0.51 (0.41–0.65)</td>
</tr>
<tr>
<td></td>
<td>327</td>
<td>2.13</td>
<td>317</td>
<td>2.08</td>
<td>0.98 (0.84–1.14)</td>
</tr>
<tr>
<td></td>
<td>132</td>
<td>0.85</td>
<td>61</td>
<td>0.39</td>
<td>0.47 (0.34–0.63)</td>
</tr>
<tr>
<td></td>
<td>190</td>
<td>1.23</td>
<td>232</td>
<td>1.51</td>
<td>1.23 (1.02–1.50)</td>
</tr>
<tr>
<td></td>
<td>111</td>
<td>0.71</td>
<td>140</td>
<td>0.91</td>
<td>1.27 (0.99–1.63)</td>
</tr>
<tr>
<td></td>
<td>81</td>
<td>0.52</td>
<td>96</td>
<td>0.62</td>
<td>1.20 (0.89–1.61)</td>
</tr>
<tr>
<td></td>
<td>211</td>
<td>1.37</td>
<td>131</td>
<td>0.85</td>
<td>0.62 (0.50–0.78)</td>
</tr>
<tr>
<td>Bleeding during transition to open-label oral</td>
<td>6</td>
<td></td>
<td>4</td>
<td></td>
<td>5</td>
</tr>
<tr>
<td>anticoagulation therapy</td>
<td>15–30</td>
<td></td>
<td>3</td>
<td></td>
<td>13</td>
</tr>
<tr>
<td>Life-threatening bleeding</td>
<td>122</td>
<td>0.78</td>
<td>62</td>
<td>0.40</td>
<td>0.51 (0.38–0.70)</td>
</tr>
<tr>
<td>Clinically relevant nonmajor bleeding</td>
<td>1396</td>
<td>10.15</td>
<td>1214</td>
<td>8.67</td>
<td>0.86 (0.79–0.93)</td>
</tr>
<tr>
<td>Minor bleeding</td>
<td>714</td>
<td>4.89</td>
<td>604</td>
<td>4.12</td>
<td>0.84 (0.76–0.94)</td>
</tr>
<tr>
<td>Major or clinically relevant nonmajor bleeding</td>
<td>1761</td>
<td>13.02</td>
<td>1528</td>
<td>11.10</td>
<td>0.86 (0.80–0.92)</td>
</tr>
<tr>
<td>Any overt bleeding</td>
<td>2114</td>
<td>16.40</td>
<td>1865</td>
<td>14.15</td>
<td>0.87 (0.82–0.92)</td>
</tr>
<tr>
<td>Net clinical outcome††</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary</td>
<td>1462</td>
<td>8.11</td>
<td>1323</td>
<td>7.26</td>
<td>0.89 (0.83–0.96)</td>
</tr>
<tr>
<td>Secondary</td>
<td>987</td>
<td>5.23</td>
<td>883</td>
<td>4.64</td>
<td>0.88 (0.81–0.97)</td>
</tr>
<tr>
<td>Tertiary</td>
<td>1123</td>
<td>6.02</td>
<td>999</td>
<td>5.30</td>
<td>0.88 (0.81–0.96)</td>
</tr>
</tbody>
</table>

* Data are from the safety cohort during the treatment period (which began when the first dose of study drug was administered), with interval censoring of events during study-drug interruptions that lasted more than 3 days, except for net clinical outcomes, which are presented for the overall treatment period (which began at the time of randomization).
† The primary net clinical outcome was a composite of stroke, systemic embolic event, major bleeding, or death from any cause. The secondary net clinical outcome was a composite of disabling stroke, life-threatening bleeding, or death from any cause. The tertiary net clinical outcome was an exploratory composite of stroke, systemic embolic event, life-threatening bleeding, or death from any cause.
## NOACs compared to Warfarin

<table>
<thead>
<tr>
<th></th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
<th>Dabigatran</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke and systemic embolism</td>
<td>↓/=</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>=</td>
<td>↓</td>
<td>↓</td>
<td>=</td>
</tr>
<tr>
<td>Major GI bleeding</td>
<td>↑</td>
<td>=</td>
<td>↓/↑</td>
<td>↑</td>
</tr>
<tr>
<td>Intracranial hemorrhage</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>=</td>
<td>=</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
</tbody>
</table>

Perioperative Management

• Goals
  – Minimize preoperative subtherapeutic anticoagulation
  – Normal hemostasis during surgery
  – Balance bleeding and thrombembolic risks post-operatively
Perioperative Management

• Influencing Factors
  – Pharmacokinetics
  – Renal function
  – Elective vs urgent surgery
  – Bleeding risk of the procedure
  – Patient factors

Perioperative Management – Bleeding Risk

- Procedures not requiring discontinuation of anticoagulation:
  - dental
  - cataract surgery
  - superficial surgeries (skin biopsy)
- Procedures with low bleeding risk:
  - prostate/bladder biopsies
  - pacemaker implantation

Douketis JD, et al. Chest 2012; 141:e326S.
Perioperative Management – Bleeding Risk

- Procedures with high bleeding risk:
  - Major surgery
  - Spinal/epidural anesthesia
  - Lumbar puncture
  - TURP
  - Kidney biopsy

Douketis JD, et al. Chest 2012; 141:e326S.
# Bleeding Risk - Endoscopy

## Low Risk
- Diagnostic (EGD, Colonoscopy, flexible sigmoidoscopy) including biopsy
- ERCP without sphincterotomy
- EUS without FNA
- Capsule endoscopy
- Enteral stent dilation
- Enteroscopy

## High Risk
- Polypectomy
- Biliary or pancreatic sphincterotomy
- Pneumatic or bougie dilation
- PEG placement
- EUS with FNA
- Endoscopic hemostasis
- Cystogastrostomy
- Tumor ablation

High Risk Bleeding Conditions

- Atrial Fibrillation with h/o embolic events or valve disease
- Prosthetic Valve
- Coronary artery disease and stents
- Deep Venous Thrombosis/Pulmonary Embolus
- Stroke/Transient Ischemic Attack
- Hypercoagulable states

Douketis JD, et al. Chest 2012; 141:e326S.
## Perioperative Recommendations

<table>
<thead>
<tr>
<th>NOAC</th>
<th>CrCl (ml/min)</th>
<th>Half life (hours)</th>
<th>Low Bleeding Risk</th>
<th>High Bleeding Risk</th>
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</thead>
<tbody>
<tr>
<td>Rivaroxaban</td>
<td>&gt;50</td>
<td>8</td>
<td>≥ 24 hrs (1 dose)</td>
<td>≥ 48 hrs (2 doses)</td>
</tr>
<tr>
<td></td>
<td>30-50</td>
<td>11</td>
<td>≥ 24 hrs (1 dose)</td>
<td>≥ 48 hrs (2 doses)</td>
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<tr>
<td>Apixaban</td>
<td>&gt;50</td>
<td>8</td>
<td>≥ 24 hrs (2 doses)</td>
<td>≥ 48 hrs (4 doses)</td>
</tr>
<tr>
<td></td>
<td>25-50</td>
<td>11</td>
<td>≥ 24 hrs (2 doses)</td>
<td>≥ 48 hrs (4 doses)</td>
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<tr>
<td>Edoxaban</td>
<td>50-95</td>
<td>11</td>
<td>≥24 hrs (1 dose)</td>
<td>≥ 48 hrs (2 doses)</td>
</tr>
<tr>
<td></td>
<td>&lt;50</td>
<td>14</td>
<td>≥24 hrs (1 dose)</td>
<td>≥ 48 hrs (2 doses)</td>
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<tr>
<td>Dabigatran</td>
<td>&gt;50</td>
<td>14</td>
<td>≥ 24 hrs (2 doses)</td>
<td>≥ 48 hrs (4 doses)</td>
</tr>
<tr>
<td></td>
<td>30-50</td>
<td>18</td>
<td>≥ 48 hrs (4 doses)</td>
<td>≥ 96 hrs (8 doses)</td>
</tr>
</tbody>
</table>

Perioperative Recommendations

• Resumption of NOACs postoperatively
  – No bridging required for most patients
    • Rapid onset and offset
  – High bleeding risk
    • Resume 48-72 hours after surgery
  – Low bleeding risk
    • Resume 24 hours after surgery

Reversal of NOACs

- Dabigatran – Idarucizumab (Praxbind)
- Rivaroxaban
- Apixaban (No FDA approved Antidote)
- Edoxaban
- Andexanet Alfa (AnnexXa) – FDA rejected approval application by Portola Pharmaceuticals in August 2016.
- PER977, FXa
Idarucizumab

- Neutralizes the anticoagulant effect of Dabigatran within minutes.
- Humanized monoclonal antibody fragment (Fab) that binds specifically to dabigatran and its acylglucuronide metabolites.
- Has ~350 times higher affinity for Dabigatran than that of thrombin.
- Available in US as 2.5g/50ml Vial - $2100
Idarucizumab

- Dose: 5 g – Administered as 2 separate 2.5 g doses not more than 15 minutes apart – $4200
- May consider additional 5 g dose if
  - aPTT re-elevates
  - Clinically significant bleeding
  - Another urgent surgery required
- IV infusion should take no longer than 5 to 10 minutes
- Begin administration within 1 hour of removing the solution from the vial
Idarucizumab – RE-VERSE AD trial

- Idarucizumab rapidly and completely reversed the anticoagulant activity of dabigatran in 88 to 98% of patients
- No safety concerns
- Only 1 out of 90 patients had a thrombotic event within 72 hours of administration of Idarucizumab

Reversal of NOACs

- Prothrombin Complex Concentrate
  - Three-factor PCC
  - Four-factor PCC
- Recombinant Factor VIIa
- Fresh Frozen Plasma
- Adjunctive Therapies
  - DDAVP
  - TXA
PCC

• Three-factor PCC
  – Profilnine, Bebulin
  – Significant concentrations of Factor II, IX and X

• Four-factor PCC
  – Kcentra
  – Significant concentration of Factor II, VII, IX and X
PCC

• Four-factor PCC
  – Approved April 2013
  – Standard therapy for Warfarin related major bleeding
  – No high-quality evidence of efficacy and safety of PCC in major bleeding due to NOACs
  – Animal and in-vitro human data shows complete reversal of Rivaroxaban
  – No effect on increased aPTT due to Dabigatran
Reversal of NOACs

• Recombinant Factor VIIa
  – Variable effect on Rivaroxaban and Apixaban coagulation parameters in vitro
  – Twice the risk of thrombotic complications
  – Not used for NOAC bleeding

• FFP
  – Not shown to normalize coagulation parameters
  – Risks – Infection, TRALI, allergic reactions, volume overload
Reversal of NOACs – Adjunctive Therapies

- Desmopressin (DDAVP)
  - Used for pts with platelet dysfunction
  - No Clinical data
  - No increased risk of thrombosis

- Tranexamic Acid (TXA)
  - Antifibrinolytic
  - Used as adjunct to prevent major bleeding in various perioperative settings
  - No increased risk of thrombosis
Reversal of NOACs

- Andexanet Alfa
- Reversal agent for Rivaroxaban, Apixaban and Edoxaban in development
- Anti-factor Xa activity was reduced by 92-94% in patients treated with Apixaban and Rivaroxaban after Andexanet bolus in large scale study
- No serious adverse or thrombotic events were reported
- FDA requested more data about the Phase 3 trial and manufacturing process

Reversal Of NOACs

- **PER 977**
  - Direct thrombin inhibitors
  - Factor Xa inhibitors
  - Heparin

- **FXa**
  - All anticoagulants
Question

- What is the correct interval for neuraxial procedure after last dose of Rivaroxaban in a patient with PMH of AF and normal renal function?

A. 96 hours
B. 72 hours
C. 48 hours ✅
D. 24 hours
Question

• Which of the following medications does not increase the risk of GI bleeding in patients when compared to warfarin?

A. Dabigatran
B. Rivaroxaban
C. ✅ Apixaban
D. Edoxaban
A patient is scheduled for pacemaker implantation in OR a week from today. This patient is maintained on Dabigatran 150mg twice daily for AF. PMH is significant for CKD, and her CrCl is 40 ml/min. How many days ago Dabigatran should be discontinued in this patient before surgery?

A. 96 hours
B. 72 hours
C. 24 hours
D. 48 hours
Question

• When should Dabigatran be resumed in this patient?

A. 96 hours
B. 72 hours
C. 24 hours
D. 48 hours
Questions
References

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- Pradaxa (dabigatran) [prescribing information]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals Inc; November 2015.
- Praxbind (idarucizumab) [prescribing information]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc; September 2015.
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