Practical Aspects Of Using Direct Oral Anticoagulants

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Disclosures

- I have no conflicts of interest
Objectives

- Identify appropriate use and dosing for different direct oral anticoagulants
- Describe use of direct oral anticoagulants in specific patient populations
- Describe peri-procedural management and reversal of direct oral anticoagulants
History of Oral Anticoagulants

1948 – Warfarin commercially available as rat poison

1954 – Warfarin approved by FDA for medical use in humans

1978 – Mechanism of warfarin discovered

2004 – Ximelagatran reject by the FDA for hepatotoxicity

2009 – Dabigatran FDA Approved
Coagulation Cascade

Contact activation (intrinsic) pathway
Damaged surface

Tissue factor (extrinsic) pathway
Tissue factor

Warfarin
Dabigatran
Rivaroxaban
Apixaban
Edoxaban

http://upload.wikimedia.org/wikipedia/commons/9/9f/Coagulation_simple.svg
Warfarin

- Vitamin K Antagonist – inhibiting Factors II, VII, IX and X
- Mainstay of therapy for over 60 years
- Dose varies but usually adjusted to target INR goal 2-3
- Disadvantages:
  - monitoring
  - drug-drug interactions
  - drug-food interactions
  - long onset and offset of action
  - inter-individual variation
What’s in a name?

- New (or Novel) Oral Anticoagulants
- Non Vitamin K Oral Anticoagulants (NOACs)
- Target Specific Oral Anticoagulants (TSOACs)
- Direct Oral Anticoagulants (DOACs)
Pharmacokinetics/Pharmacodynamics

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bioavailability</td>
<td>3-7%</td>
<td>80-100%</td>
<td>50%</td>
<td>62%</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Hepatic (glucuronidation)</td>
<td>Hepatic (CYP3A4/5)</td>
<td>Hepatic (CYP3A4/5)</td>
<td>Hepatic (CYP3A4)</td>
</tr>
<tr>
<td>Renal Excretion</td>
<td>80%</td>
<td>36%</td>
<td>27%</td>
<td>50%</td>
</tr>
<tr>
<td>Half Life</td>
<td>12-17 hours</td>
<td>5-9 hours</td>
<td>12 hours</td>
<td>10-14 hours</td>
</tr>
<tr>
<td>Drug Interactions</td>
<td>P-gp inhibitors</td>
<td>Strong 3A4 inhibitors</td>
<td>P-gp inhibitors &amp; strong 3A4 inhibitors</td>
<td>Strong 3A4 inhibitors</td>
</tr>
</tbody>
</table>

P-glycoprotein Inhibitors: ketoconazole, cyclosporine, quinidine, verapamil, P-glycoprotein; CYP3A4
Strong 3A4 Inhibitors: amiodarone, ketoconazole, fluoxetine, erythromycin

DOACs have been studied for:

- Prevention of thromboembolic complications in atrial fibrillation
- Acute treatment of venous thromboembolism
- Venous thromboembolism prophylaxis after orthopedic surgery
- Venous thromboembolism prophylaxis in medically ill patients
- Treatment of acute coronary syndromes
Direct Oral Anticoagulants for Non-valvular Atrial Fibrillation
Dabigatran (Pradaxa®)

- October 19, 2010 - FDA approved for the prevention of stroke in patients with non-valvular atrial fibrillation

*The NEW ENGLAND JOURNAL of MEDICINE*

Dabigatran versus Warfarin in Patients with Atrial Fibrillation

Stuart J. Connolly, M.D., Michael D. Ezekowitz, M.B., Ch.B., D.Phil., Salim Yusuf, F.R.C.P.C., D.Phil., John Eikelboom, M.D., Jonas Oldgren, M.D., Ph.D., Amit Parekh, M.D., Janice Pogue, M.Sc., Paul A. Reilly, Ph.D., Ellison Themeles, B.A., Jeanne Varrone, M.D., Susan Wang, Ph.D., Marco Alings, M.D., Ph.D., Denis Xavier, M.D., Jun Zhu, M.D., Rafael Diaz, M.D., Basil S. Lewis, M.D., Harald Darius, M.D., Hans-Christoph Diener, M.D., Ph.D., Campbell D. Joyner, M.D., Lars Wallentin, M.D., Ph.D., and the RE-LY Steering Committee and Investigators*
RE-LY Trial

- Interventions:
  - Dabigatran 110 mg twice daily
  - Dabigatran 150 mg twice daily
  - Open label warfarin adjusted to INR goal 2-3

- Concomitant use of aspirin (< 100 mg/day) and other antiplatelet agents were permitted

RE-LY Trial

- Primary Outcomes:
  - Efficacy: Stroke or Systemic Embolism
  - Safety: Major Hemorrhage

- Major Hemorrhage: reduction in Hgb < 20 g/L, transfusion ≥ 2 units of blood, or symptomatic bleeding in a critical area
# Table 2. Efficacy Outcomes, According to Treatment Group.

<table>
<thead>
<tr>
<th>Event</th>
<th>Dabigatran, 110 mg (N=6015)</th>
<th>Dabigatran, 150 mg (N=6076)</th>
<th>Warfarin (N=6022)</th>
<th>Dabigatran, 110 mg vs. Warfarin</th>
<th>Dabigatran, 150 mg vs. Warfarin</th>
<th>Dabigatran, 150 mg vs. 110 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no. of patients</td>
<td>%/yr</td>
<td>no. of patients</td>
<td>%/yr</td>
<td>no. of patients</td>
<td>%/yr</td>
</tr>
<tr>
<td>Stroke or systemic embolism *</td>
<td>182</td>
<td>1.53</td>
<td>134</td>
<td>1.11</td>
<td>199</td>
<td>1.69</td>
</tr>
<tr>
<td>Stroke</td>
<td>171</td>
<td>1.44</td>
<td>122</td>
<td>1.01</td>
<td>185</td>
<td>1.57</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>14</td>
<td>0.12</td>
<td>12</td>
<td>0.10</td>
<td>45</td>
<td>0.38</td>
</tr>
<tr>
<td>Ischemic or unspecified</td>
<td>159</td>
<td>1.34</td>
<td>111</td>
<td>0.92</td>
<td>142</td>
<td>1.20</td>
</tr>
<tr>
<td>Nondisabling stroke</td>
<td>60</td>
<td>0.50</td>
<td>44</td>
<td>0.37</td>
<td>69</td>
<td>0.58</td>
</tr>
<tr>
<td>Disabling or fatal stroke</td>
<td>112</td>
<td>0.94</td>
<td>80</td>
<td>0.66</td>
<td>118</td>
<td>1.00</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>86</td>
<td>0.72</td>
<td>89</td>
<td>0.74</td>
<td>63</td>
<td>0.53</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>14</td>
<td>0.12</td>
<td>18</td>
<td>0.15</td>
<td>11</td>
<td>0.09</td>
</tr>
<tr>
<td>Hospitalization</td>
<td>2311</td>
<td>19.4</td>
<td>2430</td>
<td>20.2</td>
<td>2458</td>
<td>20.8</td>
</tr>
<tr>
<td>Death from vascular causes</td>
<td>289</td>
<td>2.43</td>
<td>274</td>
<td>2.28</td>
<td>317</td>
<td>2.69</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>446</td>
<td>3.75</td>
<td>438</td>
<td>3.64</td>
<td>487</td>
<td>4.13</td>
</tr>
</tbody>
</table>

*Stroke or systemic embolism includes hemorrhagic stroke, ischemic or unspecified stroke, nondisabling stroke, and disabling or fatal stroke.
## 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>
<th>Dabigatran, 110 mg, vs. Warfarin</th>
<th>Dabigatran, 150 mg, vs. Warfarin</th>
<th>Dabigatran, 150 mg vs. 110 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no. of patients</td>
<td>%/yr</td>
<td>no. of patients</td>
<td>%/yr</td>
<td>Relative Risk (95% CI)</td>
<td>P Value</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>322</td>
<td>2.71</td>
<td>375</td>
<td>3.11</td>
<td>0.80 (0.69–0.93)</td>
<td>0.003</td>
</tr>
<tr>
<td>Life threatening Life</td>
<td>145</td>
<td>1.22</td>
<td>175</td>
<td>1.45</td>
<td>0.68 (0.55–0.83)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Non-life threatening</td>
<td>198</td>
<td>1.66</td>
<td>226</td>
<td>1.88</td>
<td>0.94 (0.78–1.15)</td>
<td>0.56</td>
</tr>
<tr>
<td>Gastrointestinal†</td>
<td>133</td>
<td>1.12</td>
<td>182</td>
<td>1.51</td>
<td>1.10 (0.86–1.41)</td>
<td>0.43</td>
</tr>
<tr>
<td>Minor bleeding</td>
<td>1566</td>
<td>13.16</td>
<td>1787</td>
<td>14.84</td>
<td>0.79 (0.74–0.84)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Major or minor bleeding</td>
<td>1740</td>
<td>14.62</td>
<td>1977</td>
<td>16.42</td>
<td>0.78 (0.74–0.83)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Intracranial bleeding</td>
<td>27</td>
<td>0.23</td>
<td>36</td>
<td>0.30</td>
<td>0.31 (0.20–0.47)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Extracranial bleeding</td>
<td>299</td>
<td>2.51</td>
<td>342</td>
<td>2.84</td>
<td>0.94 (0.80–1.10)</td>
<td>0.45</td>
</tr>
<tr>
<td>Net clinical benefit outcome</td>
<td>844</td>
<td>7.09</td>
<td>832</td>
<td>6.91</td>
<td>0.92 (0.84–1.02)</td>
<td>0.10</td>
</tr>
</tbody>
</table>
RE-LY Trial

• Discussion
  • Side Effects: Dyspepsia (150 mg – 11.3%, warfarin 5.8%)
  • Higher rate of discontinuation with dabigatran
  • Higher incidence of AMI with dabigatran

• Authors’ conclusion
  • Dabigatran 150 mg BID was associated with lower rates of stroke and systemic embolism but similar rates of major hemorrhage as compared to warfarin

Rivaroxaban (Xarelto®)

- November 4, 2011 – FDA approved for prevention of stroke in patients with non-valvular atrial fibrillation

Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation

Manesh R. Patel, M.D., Kenneth W. Mahaffey, M.D., Jyotsna Garg, M.S., Guohua Pan, Ph.D., Daniel E. Singer, M.D., Werner Hacke, M.D., Ph.D., Günter Breithardt, M.D., Jonathan L. Halperin, M.D., Graeme J. Hankey, M.D., Jonathan P. Piccini, M.D., Richard C. Becker, M.D., Christopher C. Nessel, M.D., John F. Paolini, M.D., Ph.D., Scott D. Berkowitz, M.D., Keith A.A. Fox, M.B., Ch.B., Robert M. Califf, M.D., and the ROCKET AF Steering Committee, for the ROCKET AF Investigators*
ROCKET – AF Trial

- Intervention
  - Rivaroxaban 20 mg daily
    - 15 mg daily if CrCl 30-49 ml/min
  - Dose-adjusted warfarin to INR goal 2-3

- Concomitant use of aspirin < 100 mg daily was permitted as well as monotherapy with thienopyridines

ROCKET – AF Trial

• Primary Outcomes:
  • Efficacy: Composite of stroke and systemic embolism
  • Safety: Composite of major and non-major clinical bleeding

• Major bleeding: clinically overt bleeding associated with a fatal outcome, critical site/organ, fall in Hgb ≥ 2 g/dL, transfusion of ≥ 2 units of blood or permanent disability

• Non-major clinically relevant bleeding: clinically overt bleeding that does not meet criteria for major bleeding but requires medical intervention or attention

ROCKET – AF Trial

Table 2. Primary End Point of Stroke or Systemic Embolism.*

<table>
<thead>
<tr>
<th>Study Population</th>
<th>Rivaroxaban</th>
<th></th>
<th>Warfarin</th>
<th></th>
<th>Hazard Ratio (95% CI)†</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Patients</td>
<td>No. of Events</td>
<td>Event Rate</td>
<td>No. of Patients</td>
<td>No. of Events</td>
<td>Event Rate</td>
</tr>
<tr>
<td>Per-protocol, as-treated</td>
<td>6958</td>
<td>188</td>
<td>1.7</td>
<td>7004</td>
<td>241</td>
<td>2.2</td>
</tr>
<tr>
<td>population‡</td>
<td>no./100 patient-yr</td>
<td></td>
<td></td>
<td>no./100 patient-yr</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Safety, as-treated population</td>
<td>7061</td>
<td>189</td>
<td>1.7</td>
<td>7082</td>
<td>243</td>
<td>2.2</td>
</tr>
<tr>
<td>Intention-to-treat population</td>
<td>7081</td>
<td>269</td>
<td>2.1</td>
<td>7090</td>
<td>306</td>
<td>2.4</td>
</tr>
<tr>
<td>During treatment</td>
<td>188</td>
<td>1.7</td>
<td>240</td>
<td>2.2</td>
<td>0.79 (0.66–0.96)</td>
<td>0.02</td>
</tr>
<tr>
<td>After discontinuation</td>
<td>81</td>
<td>4.7</td>
<td>66</td>
<td>4.3</td>
<td>1.10 (0.79–1.52)</td>
<td>0.58</td>
</tr>
</tbody>
</table>

ROCKET – AF Trial

<table>
<thead>
<tr>
<th>Variable</th>
<th>Rivaroxaban (N=7111)</th>
<th>Warfarin (N=7125)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Event Rate no./100 patient-yr</td>
<td>Events</td>
<td>Event Rate no./100 patient-yr</td>
</tr>
<tr>
<td>Principal safety end point: major and nonmajor clinically relevant bleeding§</td>
<td>1475 (20.7)</td>
<td>14.9</td>
<td>1449 (20.3)</td>
<td>14.5</td>
</tr>
<tr>
<td>Major bleeding</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>395 (5.6)</td>
<td>3.6</td>
<td>386 (5.4)</td>
<td>3.4</td>
</tr>
<tr>
<td>Decrease in hemoglobin ≥2 g/dl</td>
<td>305 (4.3)</td>
<td>2.8</td>
<td>254 (3.6)</td>
<td>2.3</td>
</tr>
<tr>
<td>Transfusion</td>
<td>183 (2.6)</td>
<td>1.6</td>
<td>149 (2.1)</td>
<td>1.3</td>
</tr>
<tr>
<td>Critical bleeding¶</td>
<td>91 (1.3)</td>
<td>0.8</td>
<td>133 (1.9)</td>
<td>1.2</td>
</tr>
<tr>
<td>Fatal bleeding</td>
<td>27 (0.4)</td>
<td>0.2</td>
<td>55 (0.8)</td>
<td>0.5</td>
</tr>
<tr>
<td>Intracranial hemorrhage</td>
<td>55 (0.8)</td>
<td>0.5</td>
<td>84 (1.2)</td>
<td>0.7</td>
</tr>
<tr>
<td>Nonmajor clinically relevant bleeding</td>
<td>1185 (16.7)</td>
<td>11.8</td>
<td>1151 (16.2)</td>
<td>11.4</td>
</tr>
</tbody>
</table>
ROCKET – AF Trial

- Discussion
  - Higher rate of discontinuation than other trials (~14%)
  - Trend towards higher event rates after discontinuation of rivaroxaban
  - ~35% of patients were also taking aspirin

- Authors’ Conclusions
  - Rivaroxaban is non-inferior to warfarin in the prevention of stroke or systemic embolism in patients with atrial fibrillation
Apixaban (Eliquis®)

ARISTOTLE Trial

- **Intervention**
  - Apixaban 5 mg BID
    - 2.5 mg BID if ≥ 2 of the following: age ≥ 80, weight < 60 kg, and SCr ≥ 1.5
  - Dose adjusted warfarin to INR goal 2-3

- Concomitant use of aspirin < 165 mg was permitted as well as monotherapy with thienopyrodines

ARISTOTLE Trial

- Primary Outcomes:
  - Efficacy: stroke or systemic embolism
  - Safety: Major bleeding

### Table 2. Efficacy Outcomes.*

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Apixaban Group (N = 9120)</th>
<th>Warfarin Group (N = 9081)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with Event no.</td>
<td>Patients with Event no.</td>
<td>Event Rate %/yr</td>
<td>Event Rate %/yr</td>
<td>Hazard Ratio (95% CI)</td>
</tr>
<tr>
<td><strong>Primary outcome: stroke or systemic embolism</strong></td>
<td>212</td>
<td>1.27</td>
<td>265</td>
<td>1.60</td>
</tr>
<tr>
<td><strong>Stroke</strong></td>
<td>199</td>
<td>1.19</td>
<td>250</td>
<td>1.51</td>
</tr>
<tr>
<td><strong>Ischemic or uncertain type of stroke</strong></td>
<td>162</td>
<td>0.97</td>
<td>175</td>
<td>1.05</td>
</tr>
<tr>
<td><strong>Hemorrhagic stroke</strong></td>
<td>40</td>
<td>0.24</td>
<td>78</td>
<td>0.47</td>
</tr>
<tr>
<td><strong>Systemic embolism</strong></td>
<td>15</td>
<td>0.09</td>
<td>17</td>
<td>0.10</td>
</tr>
<tr>
<td><strong>Key secondary efficacy outcome: death from any cause</strong></td>
<td>603</td>
<td>3.52</td>
<td>669</td>
<td>3.94</td>
</tr>
<tr>
<td><strong>Other secondary outcomes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Stroke, systemic embolism, or death from any cause</strong></td>
<td>752</td>
<td>4.49</td>
<td>837</td>
<td>5.04</td>
</tr>
<tr>
<td><strong>Myocardial infarction</strong></td>
<td>90</td>
<td>0.53</td>
<td>102</td>
<td>0.61</td>
</tr>
<tr>
<td><strong>Stroke, systemic embolism, myocardial infarction, or death from any cause</strong></td>
<td>810</td>
<td>4.85</td>
<td>906</td>
<td>5.49</td>
</tr>
<tr>
<td><strong>Pulmonary embolism or deep-vene thrombosis</strong></td>
<td>7</td>
<td>0.04</td>
<td>9</td>
<td>0.05</td>
</tr>
</tbody>
</table>
ARISTOTLE Trial

### 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</td>
<td>Event Rate</td>
<td>Patients with Event</td>
<td>Event Rate</td>
</tr>
<tr>
<td></td>
<td>no.</td>
<td>%/yr</td>
<td>no.</td>
<td>%/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>
ARISTOTLE Trial

- Discussion
  - Rate of discontinuation was lower for apixaban than warfarin
  - 4.7% of patient in apixaban group received reduce dose
  - ~31% of patients also took aspirin

- Authors’ Conclusion
  - Apixaban reduced the rate of stroke or systemic embolism, caused less bleeding and resulted in lower mortality as compared to warfarin in patients with non-valvular atrial fibrillation

Edoxaban (Savaysa™)

• January 8, 2015 – FDA approved for the prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation

**ORIGINAL ARTICLE**

**Edoxaban versus Warfarin in Patients with Atrial Fibrillation**

Robert P. Giugliano, M.D., Christian T. Ruff, M.D., M.P.H., Eugene Braunwald, M.D., Sabina A. Murphy, M.P.H., Stephen D. Wiviott, M.D., Jonathan L. Halperin, M.D., Albert L. Waldo, M.D., Michael D. Ezekowitz, M.D., D.Phil., Jeffrey L. Weitz, M.D., Jindřich Špinar, M.D., Witold Ruzyillo, M.D., Mikhail Ruda, M.D., Yukihiro Koretsune, M.D., Joshua Betcher, Ph.D., Minggao Shi, Ph.D., Laura T. Grip, A.B., Shirali P. Patel, B.S., Indravadan Patel, M.D., James J. Hanyok, Pharm.D., Michele Mercuri, M.D., and Elliott M. Antman, M.D., for the ENGAGE AF-TIMI 48 Investigators*
ENGAGE AF – TIMI 48 Trial

- **Intervention**
  - Edoxaban 30 mg daily
  - Edoxaban 60 mg daily
  - Dose adjusted warfarin to INR goal 2-3

- Edoxaban dose was cut in half in either group if a patient had CrCl 30-50 ml/min, weight ≤ 60 kg, or concomitant use of verapamil, dronedarone, or quinidine

NEJM 2013; 369:2093-104.
ENGAGE AF – TIMI 48 Trial

- Primary Outcomes:
  - Efficacy: time to first stroke or systemic embolic event
  - Safety: major bleeding during treatment

NEJM 2013; 369:2093-104.
## Table 2. Efficacy End Points.

<table>
<thead>
<tr>
<th>End Point</th>
<th>Warfarin (N=7036)</th>
<th>High-Dose Edoxaban (N=7035)</th>
<th>High-Dose Edoxaban vs. Warfarin</th>
<th>Low-Dose Edoxaban (N=7034)</th>
<th>Low-Dose Edoxaban vs. Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no. of patients</td>
<td>% of patients/yrs</td>
<td>Hazard Ratio (95% CI)</td>
<td>no. of patients</td>
<td>% of patients/yrs</td>
</tr>
<tr>
<td>Primary end point</td>
<td>with event</td>
<td></td>
<td>P Value</td>
<td>with event</td>
<td></td>
</tr>
<tr>
<td>Modified intention-to-treat population in the treatment period↑</td>
<td>232</td>
<td>1.50</td>
<td>0.79 (0.63-0.99)‡</td>
<td>253</td>
<td>1.61</td>
</tr>
<tr>
<td>Intention-to-treat population in the overall study period↓</td>
<td>337</td>
<td>1.80</td>
<td>0.87 (0.73-1.04)‡</td>
<td>383</td>
<td>2.04</td>
</tr>
<tr>
<td>Event during the 30-day transition¶</td>
<td>7</td>
<td>—</td>
<td>—</td>
<td>7</td>
<td>—</td>
</tr>
<tr>
<td>Stroke</td>
<td>317</td>
<td>1.69</td>
<td>0.88 (0.75-1.03)</td>
<td>360</td>
<td>1.91</td>
</tr>
<tr>
<td>Hemorrhagic</td>
<td>90</td>
<td>0.47</td>
<td>0.54 (0.38-0.77)</td>
<td>&lt;0.001</td>
<td>30</td>
</tr>
<tr>
<td>Ischemic</td>
<td>235</td>
<td>1.25</td>
<td>1.00 (0.83-1.19)</td>
<td>333</td>
<td>1.77</td>
</tr>
<tr>
<td>Nondisabling and nonfatal</td>
<td>190</td>
<td>1.01</td>
<td>0.80 (0.65-0.99)</td>
<td>214</td>
<td>1.13</td>
</tr>
<tr>
<td>Disabling or fatal</td>
<td>135</td>
<td>0.71</td>
<td>0.97 (0.76-1.23)</td>
<td>152</td>
<td>0.80</td>
</tr>
<tr>
<td>Fatal</td>
<td>86</td>
<td>0.45</td>
<td>0.92 (0.68-1.25)</td>
<td>73</td>
<td>0.38</td>
</tr>
<tr>
<td>Systemic embolic event</td>
<td>23</td>
<td>0.12</td>
<td>0.65 (0.34-1.24)</td>
<td>29</td>
<td>0.15</td>
</tr>
</tbody>
</table>

NEJM 2013; 369:2093-104.
### 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 with event</td>
<td>% of patients/yr</td>
<td>no. of patients with event</td>
<td>% of patients/yr</td>
<td>Hazard Ratio (95% CI)</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>Fatal</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>Bleeding into a critical organ or area</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>Overt bleeding with blood loss of ≥2 g/dl</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>Any intracranial bleeding</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>Fatal intracranial bleeding</td>
<td>42</td>
<td>0.27</td>
<td>24</td>
<td>0.15</td>
<td>0.58 (0.35–0.95)</td>
</tr>
<tr>
<td>Gastrointestinal bleeding</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>Upper gastrointestinal tract</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>Lower gastrointestinal tract</td>
<td>81</td>
<td>0.52</td>
<td>96</td>
<td>0.62</td>
<td>1.20 (0.89–1.61)</td>
</tr>
</tbody>
</table>
ENGAGE AF – TIMI 48 Trial

• Discussion
  • No difference in rate of MI
  • ~25% of patients received reduced dose
  • ~29% of patient also took aspirin; 2.3% thienopyridine

• Authors’ Conclusion
  • Both doses of edoxaban were non-inferior to warfarin in preventing stroke and systemic embolism in patients with atrial fibrillation and were associated with lower rates of bleeding and death from cardiovascular causes

NEJM 2013; 369:2093-104.
### DOACs for AFib

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Usual dose for AFib</strong></td>
<td>150 mg BID</td>
<td>20 mg daily</td>
<td>5 mg BID</td>
<td>60 mg daily</td>
</tr>
<tr>
<td><strong>Alternative dosing</strong></td>
<td>Yes (not studied) - 75 mg BID for CrCl 15 - 30 ml/min</td>
<td>Yes - 15 mg daily for CrCl &lt; 50 ml/min</td>
<td>Yes - 2.5 mg BID if 2 or more of the following: age ≥ 80 yr, wt ≤ 60 kg or SCr ≥ 1.5</td>
<td>Yes (not for CrCl &gt; 95 ml/min) - 30 mg daily for CrCl 15-50 ml/min</td>
</tr>
<tr>
<td><strong>Avg CHADS$_2$</strong></td>
<td>2.2</td>
<td>3.48</td>
<td>2.1</td>
<td>2.8</td>
</tr>
<tr>
<td><strong>TTR</strong></td>
<td>64%</td>
<td>55%</td>
<td>62.2%</td>
<td>64.9%</td>
</tr>
<tr>
<td><strong>Major Bleeding</strong></td>
<td>Similar</td>
<td>Similar</td>
<td>Reduced</td>
<td>Reduced</td>
</tr>
<tr>
<td><strong>GI Bleed</strong></td>
<td>Increased</td>
<td>Increased</td>
<td>Similar</td>
<td>Similar</td>
</tr>
</tbody>
</table>

**CHADS$_2$** is a risk score for stroke in patients with atrial fibrillation, where C is Congestive heart failure, H is Hypertension, A is Age ≥ 75 years, D is Diabetes, S is Stroke/TIA, and 2 is the score range. A CHADS$_2$ score of 2 or more is an indication for anticoagulation. **TTR** (Time in Therapeutic Range) is a measure of the percentage of time a patient's INR is within the target range recommended for their risk of stroke. **GI Bleed** refers to gastrointestinal bleeding, which is a common side effect of anticoagulants.
Direct Oral Anticoagulants for Venous Thromboembolism
Dabigatran (Pradaxa®)

- April 7, 2014 - FDA approved for treatment of venous thromboembolism

**The NEW ENGLAND JOURNAL of MEDICINE**

**Dabigatran versus Warfarin in the Treatment of Acute Venous Thromboembolism**

Sam Schulman, M.D., Clive Kearon, M.D., Ajay K. Kakkar, M.D., Patrick Mismetti, M.D., Sebastian Schellong, M.D., Henry Eriksson, M.D., David Baanstra, M.Sc., Janet Schnee, M.D., and Samuel Z. Goldhaber, M.D., for the RE-COVER Study Group*
RE-COVER Trial

- **Treatment**
  - Dabigatran 150 mg BID (n = 1273)
  - Warfarin (n = 1266)

- **Primary Endpoint: Recurrent VTE or VTE related death**
  - Dabigatran (2.4%) vs Warfarin (2.1%), HR 1.10 (p <0.001)

- **Safety Endpoint: Major bleeding**
  - Dabigatran (1.6%) vs Warfarin (1.9%), HR 0.82

RE-COVER Trial

- Discussion
  - Dabigatran had higher rates of GI bleeding
  - 3% dyspepsia with dabigatran
  - Initial parenteral anticoagulant therapy ~9 days

- Authors’ Conclusion
  - Dabigatran was just as effective and safe as warfarin in the treatment of acute venous thromboembolism
Rivaroxaban (Xarelto®)

- November 2, 2012 – FDA approved for the treatment of venous thromboembolism
EINSTEIN Trial

- **Treatment:**
  - Rivaroxaban 15 mg BID x21 days, followed by 20 mg qDay (n = 1718)
  - Enoxaparin-VKA (n = 1705)

- **Primary Endpoint: Recurrent VTE:**
  - Rivaroxaban (2.1%) vs Warfarin (3.0%), p < 0.001

- **Safety Endpoint: Major bleeding or clinically relevant non-major bleeding**
  - Rivaroxaban (8.1%) vs Warfarin (8.1%), p = 0.77

NEJM 2010;363:2499510.
EINSTEIN Trial

- Discussion
  - Open label
  - Parenteral anticoagulant < 48 hours

- Author’s Conclusion
  - Rivaroxaban was noninferior to enoxaparin-warfarin for the treatment of venous thromboembolism

NEJM 2010;363:2499510.
Apixaban (Eliquis®)

- August 21, 2014 - FDA approved for the treatment of acute venous thromboembolism

The NEW ENGLAND JOURNAL of MEDICINE

Oral Apixaban for the Treatment of Acute Venous Thromboembolism

Giancarlo Agnelli, M.D., Harry R. Buller, M.D., Ph.D., Alexander Cohen, M.D., Madelyn Curto, D.V.M., Alexander S. Gallus, M.D., Margot Johnson, M.D., Urszula Masiukiewicz, M.D., Raphael Pak, Ph.D., John Thompson, Ph.D., Gary E. Raskob, Ph.D., and Jeffrey I. Weitz, M.D., for the AMPLIFY Investigators*
AMPLIFY Trial

- Treatment
  - Apixaban 10 mg BID x 7 days, followed by 5 mg BID (n = 2691)
  - Enoxaparin-warfarin (n = 2704)

- Primary Endpoint: Recurrent VTE
  - Apixaban (2.3%) vs warfarin (2.7%), p < 0.001

- Safety Endpoint: Major bleeding
  - Apixaban (0.6%) vs warfarin (1.8%), p < 0.001

AMPLIFY Trial

- Discussion
  - Parenteral anticoagulation for < 48 hours

- Authors Conclusions
  - Apixaban in noninferior to conventional therapy for treatment of acute venous thromboembolism
Edoxaban (Savaysa™)

- January 8, 2015 – FDA approved for treatment of acute venous thromboembolism

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Edoxaban versus Warfarin for the Treatment of Symptomatic Venous Thromboembolism

The Hokusai-VTE Investigators*
Hokusai – VTE Trial

- Treatment
  - Edoxaban 60 mg qDay (n = 4118)
    - 30 mg qDay for CrCl 30-50 ml/min or weight < 60 kg
  - Enoxaparin-warfarin (n = 4122)

- Primary Endpoint: Recurrent VTE
  - Edoxaban (3.2%) vs Warfarin (3.5%), HR 0.89 (p < 0.001)

- Safety Endpoint: Major or clinically relevant non-major bleeding
  - Edoxaban (8.5%) vs Warfarin (10.3%), HR 0.81 (p = 0.004)

Hokusai – VTE Trial

• Discussion
  • Enrolled higher risk patients including PE with right ventricular dysfunction
  • Initial parenteral anticoagulant therapy

• Authors’ Conclusions
  • Edoxaban was noninferior to warfarin therapy for the treatment of VTE and caused less bleeding

# DOACs for VTE

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Usual dose for VTE</strong></td>
<td>150 mg BID</td>
<td>15 mg BID x21 days, then 20 mg daily</td>
<td>10 mg BID x 7 days, then 5 mg BID</td>
<td>60 mg daily</td>
</tr>
<tr>
<td><strong>Initial Parenteral Anticoagulant Necessary</strong></td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Cancer Patients</strong></td>
<td>~5%</td>
<td>6.8%</td>
<td>2.5%</td>
<td>9.2%</td>
</tr>
<tr>
<td><strong>TTR</strong></td>
<td>60%</td>
<td>58%</td>
<td>Not reported</td>
<td>63.5%</td>
</tr>
<tr>
<td><strong>Recurrent VTE</strong></td>
<td>Similar</td>
<td>Reduced</td>
<td>Similar</td>
<td>Similar</td>
</tr>
<tr>
<td><strong>Bleeding</strong></td>
<td>Similar</td>
<td>Similar</td>
<td>Reduced</td>
<td>Reduced</td>
</tr>
</tbody>
</table>
Other Indications

- VTE Prophylaxis After Orthopedic Surgery

<table>
<thead>
<tr>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hip replacement: 220 mg daily for up to 35 days</td>
<td>Hip replacement: 10 mg daily for up to 35 days Knee replacement: 10 mg daily for 12 days</td>
<td>Hip replacement: 2.5 mg BID for 35 days Knee replacement: 2.5 mg BID for 12 days</td>
</tr>
</tbody>
</table>

- NOT FDA approved for ACS or VTE prophylaxis in medically ill patients
  - Bleeding outweighed benefit
Practical Considerations

- Specific Populations
- Peri-procedural management
- Monitoring and Reversibility
Special Populations to Consider

- Renal Impairment
- Obesity
- Elderly
- Gastrointestinal Disease
- Dual Antiplatelet Therapy
- Pregancy
- Non-Compliance
DOACs & Renal Impairment

- All DOACs are renally excreted to some degree
- Patients with est. CrCl $\leq$ 30 ml/min (or CrCl $\leq$ 25 ml/min or SCr $> 2.5$ mg/dl in ARISTOTLE) were excluded from clinical trials
**DOAC PK/PD & Renal Dysfunction**

**Dabigatran**
- $C_{\text{max}}$ ↑ by 1.7-2.1x
- AUC ↑ by 3.2-6.3x with CrCl 15-49 ml/min

**Rivaroxaban**
- $C_{\text{max}}$ ↑ by 12%
- AUC ↑ by 52% with CrCl 30-49 ml/min

**Apixaban**
- No ↑ in $C_{\text{max}}$
- AUC ↑ 44% with CrCl 15-29 ml/min

**Edoxaban**
- Total exposure ↑
- CrCl <30 ml/min: 72%
- Peritoneal dialysis: 93%

DOACs & Renal Impairment

• **VTE Trials**
  - Excluded patients with CrCl ≤ 30 ml/min
  - No dose reduction in renal impairment
  - 6-9% of patients had moderate renal impairment (CrCl 30-50 ml/min)

• **Afib Trials**
  - RELY, ROCKET-AF, and ENGAGE-AF excluded patients with a CrCl ≤ 30 ml/min
  - ARISTOTLE excluded patients with CrCl ≤ 25 ml/min or SCr > 2.5 mg/dl
  - 17-19% of patients had moderate renal impairment (CrCl 30-50 ml/min)
Renal Dysfunction & Afib

**RE-LY**
Similar efficacy regardless of renal function

**ROCKET-AF**
Patients with 20% reduction in CrCl had ↓ CVA & ↑ GI bleeding

**ARISTOTLE**
Apixaban superior regardless of renal function

**ENGAGE-AF**
Similar efficacy & 24%↓ bleeding

Worse outcomes with CrCl > 95 ml/min

DOACs & Renal Impairment

- Rivaroxaban and apixaban have dosing recommendations per the manufacturer and FDA for use in ESRD
  - Based on PK/PD trials in HD patients
  - Used surrogate markets as endpoints (anti-Xa levels, PTT, INR)
  - No safety or efficacy outcomes
DOACs & Obesity

- Weight is a factor in many PK/PD properties
- Dabigatran & Rivaroxaban
  - Extremes of weight (<50 kg or >120 kg) do not affect pharmacology
- Apixaban
  - Weight < 50 kg have 20-30% increased exposure
  - Weight > 120 kg have 23-30% less exposure
- Edoxaban
  - No PK/PD data available for extremes of weight
DOACs & Elderly

• Elderly patients have decreased drug clearance
• Elderly people are at greater bleeding risk
• Afib trials
  • Average age 70-78 years
• VTE trials
  • Average age 55-58 years
DOACs & Gastrointestinal Disease

- DOACs vary largely in terms of their absorption/bioavailability (3-100%)
- Increased rates of GI bleeds with dabigatran and rivaroxaban
- Dabigatran has a side effect of dypepsia
  - Capsule is formulated with tartaric acid to increase absorption
  - Use of PPIs or H2 Blockers do not alter absorption
- Patients with severe hepatic impairment were excluded from clinical trials

DOACs & Dual Antiplatelet Therapy

- Rivaroxaban and apixaban were both studied in combination with dual antiplatelet therapy for Acute Coronary Syndromes
  - ATLAS trial
    - Rivaroxaban 2.5 mg BID and 5 mg BID showed a decrease in mortality from MI and stroke, however this was outweighed by increase in major bleeding (2.1 vs 0.6 %, p <0.0001) and intracranial hemorrhage (0.6 vs 0.2 %, p = 0.04)
  - APPRAISE-2 trial
    - Apixaban 5 mg BID vs. placebo
    - Terminated early due to increase in major bleeding (1.3 vs 0.5 %, p = 0.001) and intracranial hemorrhage (0.3 vs 0.1 %, p =0.03)

DOACs & Pregnancy

- No Data = DO NOT USE
DOACs & Noncompliant Patients

- On/Off direct anticoagulant effect
- Somewhat short half life ($t_{1/2} = 5-17$ hrs)
- Rebound thrombotic events with abrupt discontinuation
# Summary of Special Populations

<table>
<thead>
<tr>
<th>Population</th>
<th>Preferred Anticoagulant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal Impairment</td>
<td>Rivaroxaban, Apixaban, Heparin</td>
</tr>
<tr>
<td>Obesity</td>
<td>Dabigatran, Rivaroxaban, Enoxaparin</td>
</tr>
<tr>
<td>Elderly</td>
<td>Warfarin, Apixaban</td>
</tr>
<tr>
<td>History of GI Bleed</td>
<td>Apixaban, Edoxaban</td>
</tr>
<tr>
<td>Hepatic Impairment</td>
<td>Warfarin</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>Enoxaparin, Heparin</td>
</tr>
<tr>
<td>Non-compliant Patients</td>
<td>Warfarin, Rivaroxaban, Edoxaban</td>
</tr>
</tbody>
</table>
Real World Data

• Effectiveness and Safety of Dabigatran, Rivaroxaban, and Apixaban versus Warfarin in Nonvalvular Atrial Fibrillation
  • Methods: using large US insurance database, they identified patients with nonvalvular afib who were prescribed a DOAC; each cohort was propensity score matched
  • Conclusions
    • Apixaban was associated with lower risk of both stroke and major bleeding
    • Dabigatran was associated with similar risk of stroke but lower risk of major bleeding
    • Rivaroxaban was associated with similar risk of both stroke and major bleeding

JAHA 2016;5:e003725
Switching to DOACs

- From Warfarin:
  - Dabigatran: start when INR < 2.0
  - Apixaban: start when INR < 3.0
  - Rivaroxaban: start when INR < 2.0
  - Edoxaban: start when INR ≤ 2.5
Switching to DOACs

- From UFH:
  - Start apixaban/rivaroxaban/dabigatran when UFH infusion stopped
  - Start edoxaban 4 hours after UFH infusion stopped
- From LMWH:
  - Start DOAC at the time of next schedule dose of LWWH
Switching from DOACs

- To Warfarin:
  - Stop apixaban/rivaroxaban, switch to UFH/LMWH and bridge to warfarin
  - Overlap dabigatran:
    - If CrCl > 50 ml/min: overlap for 3 days
    - If CrCl 30-50 ml/min: overlap for 2 days
    - If CrCl < 30 ml/min: overlap for 1 day
  - Reduce edoxaban dose by 50% and discontinue when INR ≥ 2
Switching from DOACs

- To UFH:
  - Start heparin bolus/infusion at the end of the dosing interval of the previous DOAC (i.e. 12 hrs for twice daily, 24 hrs for once daily)
  - May need to wait longer depending on DOAC and renal impairment

- To LMWH:
  - Start LMWH at the end of the dosing interval of DOAC
## Peri-Procedural Management

<table>
<thead>
<tr>
<th>Drug</th>
<th>Low Bleeding Risk Procedure</th>
<th>High Bleeding Risk Procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dabigatran</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CrCl ≥ 50:</td>
<td>hold for 1-2 days</td>
<td>CrCl ≥ 50: hold for 3-4 days</td>
</tr>
<tr>
<td>CrCl 30-50:</td>
<td>hold for 2-3 days</td>
<td>CrCl 30-50: hold for 4-5 days</td>
</tr>
<tr>
<td>CrCl &lt;30:</td>
<td>hold for 3-4 days</td>
<td>CrCl &lt;30: hold for 5-6 days</td>
</tr>
<tr>
<td><strong>Apixaban</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CrCl ≥ 50:</td>
<td>hold for 1 day</td>
<td>CrCl ≥ 50: hold for 2 days</td>
</tr>
<tr>
<td>CrCl 15-49:</td>
<td>hold for 2 days</td>
<td>CrCl 15-49: hold for 3-4 days</td>
</tr>
<tr>
<td><strong>Rivaroxaban</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CrCl ≥ 30:</td>
<td>hold for 1 day</td>
<td>CrCl ≥ 30: hold for 2 days</td>
</tr>
<tr>
<td>CrCl &lt; 30:</td>
<td>hold for 2 days</td>
<td>CrCl &lt; 30: hold for 3 days</td>
</tr>
<tr>
<td><strong>Edoxaban</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CrCl ≥ 30:</td>
<td>hold for 1 day</td>
<td>CrCl ≥ 30: hold for 2 days</td>
</tr>
<tr>
<td>CrCl &lt; 30:</td>
<td>hold for 2 days</td>
<td>CrCl &lt; 30: hold for 3-4 days</td>
</tr>
</tbody>
</table>

## Monitoring of DOACs

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>aPTT</td>
<td>↑↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>PT/INR</td>
<td>↑↑</td>
<td>↑↑↑</td>
<td>↑</td>
<td>↑↑↑</td>
</tr>
<tr>
<td>ECT</td>
<td>↑↑↑↑↑</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Anti-Xa</td>
<td>N/A</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>TT</td>
<td>↑↑</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

ECT = Ecarin Clotting Time  
TT = Thrombin Time  
**PT/INR effect will depend on reagent used in lab; a normal value does not equate to normal coagulation**
Reversal of DOACs

- Minor Bleeding
  - Hold DOAC and supportive care

- Major Bleeding
  - Idarucizumab (Praxbind)
    - 5 gm IV bolus (administered as two 2.5 gm doses 15 minutes apart)
    - Contains 4 gm of sorbitol – not for patients with hereditary fructose intolerance
    - Monitoring PTT at baseline, 2 and 12 hours after dose
  - Recombinant Factor VIIa (Novoseven)
  - Prothrombin Complex Concentrate (PCC)
Other Special Considerations

- Dabigatran
  - Capsules must be swallowed whole. Do not open contents and dilute.
  - Should be stored in original container

- Apixaban, Rivaroxaban, and Edoxaban
  - Tablets are not scored, therefore do not cut in half
  - May be crushed and mixed with water to administer
  - Rivaroxaban should be taken with food
Future of DOACs

- Use and popularity continue to increase
- Betrixaban currently being reviewed by the FDA for prevention of venous thromboembolism in medically ill patients
- Andexanet-Alpha currently being studied for reversal of Factor Xa Inhibitors (including enoxaparin and fondaparinux)
  - Recombinant modified human factor X decoy protein
Practical Aspects Of Using Direct Oral Anticoagulants

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