Oct. 26, 2017

Direct Oral Anticoagulants: An Update

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Assistant Professor of Medicine
Cooper Heart Institute
Direct Oral Anticoagulants: DISCLAIMERS

- No Conflicts of Interest

- So what DO we call them?

DOACs

TSOACs ↔ NOACs
Oral Anticoagulants

- Dabigatran (Pradaxa)
- Rivaroxaban (Xarelto)
- Apixaban (Eliquis)
DOACs: OBJECTIVES

1. DOACs in Atrial Fibrillation (Afib)
2. Original Trials/Updated Trials/Emerging indications
3. Cooper University Hospital /DOAC Reversal Data
History: Anticoagulation Committee

- Multidisciplinary team including Cardiology, Pharmacy, Laboratory, Trauma, Surgery and Neurosurgery, Hospitalists, Emergency

- Originally formed in 2008 to address hospital issues of heparin, enoxaparin, and warfarin

- ...like no baseline PT/PTT/INR when initiating heparin and warfarin...
In 2009 we began to ‘hear about’ new oral medications coming out which could possibly replace warfarin for atrial fibrillation.

Focus of the committee completely changed with introduction of the first NOAC in Oct 2010.

Still address safety issues of initiation, dosing and reversal of anticoagulation, but now with focus on DOACs.
Timeline 2010-2017
<table>
<thead>
<tr>
<th>Nov 2011</th>
<th>Dabigatran (Pradaxa®)</th>
<th>Rivaroxaban (Xarelto®)</th>
<th>Apixaban (Eliquis®)</th>
<th>Edoxaban (Savaysa®)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonvalvular Atrial Fibrillation</td>
<td>✗</td>
<td>✗</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Venous Thromboembolism Treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thromboprophylaxis, Knee and Hip Replacement</td>
<td></td>
<td>✗</td>
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</tbody>
</table>
# DOACs: FDA Approvals

**July 2014**

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran (Pradaxa®)</th>
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## DOACs: FDA Approvals

### March 2015

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<td>✗</td>
<td>✗</td>
<td>✗</td>
<td>✗</td>
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<td></td>
<td>✗</td>
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### DOACs: FDA Approvals

**January 2016**

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<tbody>
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<td>×</td>
<td>×</td>
<td>×</td>
<td>×</td>
</tr>
<tr>
<td>Venous Thromboembolism Treatment</td>
<td>×</td>
<td>×</td>
<td>×</td>
<td>×</td>
</tr>
<tr>
<td>Thromboprophylaxis Knee and Hip Replacement</td>
<td>×</td>
<td>×</td>
<td>×</td>
<td>×</td>
</tr>
</tbody>
</table>
Coagulation cascade.

Intrinsic Pathway (Contact Activation)
- XII
- XI
- IX

Extrinsic Pathway (Tissue Factor)
- Tissue Factor
- Factor Xa Inhibitors (-AT)
  - Apixaban and Rivaroxaban
- Direct Thrombin Inhibitors
  - Dabigatran

VKAs

Fibrinogen ➔ Fibrin Clot

Craig T. January et al. Circulation. 2014;130:e199-e267
## DOAC Pharmacokinetics

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MOA</strong></td>
<td>Direct Thrombin Inhibitor</td>
<td>Factor Xa Inhibitor</td>
<td>Factor Xa Inhibitor</td>
<td>Factor Xa Inhibitor</td>
</tr>
<tr>
<td><strong>Half-life</strong></td>
<td>13 hours</td>
<td>5-9 hours</td>
<td>8-15 hours</td>
<td>10-15 hours</td>
</tr>
<tr>
<td><strong>Time to peak</strong></td>
<td>1 -2 hours</td>
<td>2 to 4 hours</td>
<td>3 to 4 hours</td>
<td>1 to 2 hours</td>
</tr>
<tr>
<td><strong>Protein binding</strong></td>
<td>35%</td>
<td>95% (to albumin)</td>
<td>87%</td>
<td>55%</td>
</tr>
<tr>
<td><strong>Metabolism</strong></td>
<td>Hepatic, hydrolyzed</td>
<td>Hepatic via CYP3A4/5 and CYP2J2</td>
<td>Hepatic via CYP3A4/5; substrate of P-glycoprotein (P-gp)</td>
<td>Minimal via hydrolysis</td>
</tr>
<tr>
<td><strong>Excretion</strong></td>
<td>Urine: 80%</td>
<td>Urine: 66%</td>
<td>Urine (~27% as parent drug); feces</td>
<td>Urine 50%</td>
</tr>
</tbody>
</table>
Cooper Anticoagulant Usage (2014-2016)

Number of Patients

- APIXABAN
- DABIGATRAN
- RIVAROXABAN
- WARFARIN

2014 2015 2016
Atrial Fibrillation
Atrial Fibrillation: Updated Guidelines

- AHA/ACC/HRS AF Guidelines Updated March 2016
- Focus on CHA2DS2-VASc score
- In most cases, aspirin alone is no longer recommended
- A bigger role for DOACs-equivalent with warfarin
- ....LOE-B for DOACs, LOE-A for warfarin
CHA2DS2-VASc: Risk of Stroke

- **CHA2DS2-VASC Score:**
  - **0** - no anticoagulation
  - **1** - Either no anticoagulation, ASA, or oral anticoagulation
  - **2 or greater** - oral anticoagulation

<table>
<thead>
<tr>
<th>CHA2DS2-Vasc score</th>
<th>Risk of stroke each year</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Very close to 0</td>
</tr>
<tr>
<td>1</td>
<td>1.3% (1 in 77)</td>
</tr>
<tr>
<td>2</td>
<td>2.2% (1 in 45)</td>
</tr>
<tr>
<td>3</td>
<td>3.2% (1 in 31)</td>
</tr>
<tr>
<td>4</td>
<td>4.0% (1 in 25)</td>
</tr>
<tr>
<td>5</td>
<td>6.7% (1 in 15)</td>
</tr>
<tr>
<td>6</td>
<td>9.8% (1 in 10)</td>
</tr>
<tr>
<td>7</td>
<td>9.6% (1 in 10)</td>
</tr>
<tr>
<td>8</td>
<td>6.7% (1 in 15)</td>
</tr>
<tr>
<td>9</td>
<td>15.2% (1 in 6)</td>
</tr>
</tbody>
</table>
Warfarin v Nothing AF : Reduces CVA by 67%

Initial Trials
Dabigatran/Rivaroxaban/Apixaban/Edoxaban
RE-Ly Dabigatran
## RE-Ly Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Dabigatran 110 mg</th>
<th>Dabigatran 150 mg</th>
<th>Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized</td>
<td>6015</td>
<td>6076</td>
<td>6022</td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>71.4</td>
<td>71.5</td>
<td>71.6</td>
</tr>
<tr>
<td>Male (%)</td>
<td>64.3</td>
<td>63.2</td>
<td>63.3</td>
</tr>
<tr>
<td>CHADS2 score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean</td>
<td>2.1</td>
<td>2.2</td>
<td>2.1</td>
</tr>
<tr>
<td>0-1 (%)</td>
<td>32.6</td>
<td>32.2</td>
<td>30.9</td>
</tr>
<tr>
<td>2 (%)</td>
<td>34.7</td>
<td>35.2</td>
<td>37.0</td>
</tr>
<tr>
<td>3+ (%)</td>
<td>32.7</td>
<td>32.6</td>
<td>32.1</td>
</tr>
<tr>
<td>Prior stroke/TIA (%)</td>
<td>19.9</td>
<td><strong>20.3</strong></td>
<td>19.8</td>
</tr>
<tr>
<td>Prior MI (%)</td>
<td>16.8</td>
<td>16.9</td>
<td>16.1</td>
</tr>
<tr>
<td>CHF (%)</td>
<td>32.2</td>
<td><strong>31.8</strong></td>
<td>31.9</td>
</tr>
<tr>
<td>Baseline ASA (%)</td>
<td>40.0</td>
<td>38.7</td>
<td>40.6</td>
</tr>
<tr>
<td>Warfarin Naïve (%)</td>
<td>49.9</td>
<td>49.8</td>
<td><strong>51.4</strong></td>
</tr>
</tbody>
</table>
RE-Ly  Stroke or Systemic Embolism

Dabigatran 110 vs. Warfarin

Dabigatran 150 vs. Warfarin

Non-inferior p-value  Superior p-value

<0.001  0.34

<0.001  <0.001

Dabigatran better  0.75  1.00  1.25  1.50  Warfarin better

HR (95% CI)
Rocket AF-Rivaroxaban
## Baseline Demographics

<table>
<thead>
<tr>
<th></th>
<th>Rivaroxaban (N=7081)</th>
<th>Warfarin (N=7090)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CHADS₂ Score (mean)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 (%)</td>
<td>3.48</td>
<td>3.46</td>
</tr>
<tr>
<td>3 (%)</td>
<td>13</td>
<td>13</td>
</tr>
<tr>
<td><strong>Average 3.6</strong></td>
<td><strong>43</strong></td>
<td><strong>44</strong></td>
</tr>
<tr>
<td>4 (%)</td>
<td>29</td>
<td>28</td>
</tr>
<tr>
<td>5 (%)</td>
<td>13</td>
<td>12</td>
</tr>
<tr>
<td>6 (%)</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td><strong>Prior VKA Use (%)</strong></td>
<td>62</td>
<td>63</td>
</tr>
<tr>
<td><strong>Congestive Heart Failure (%)</strong></td>
<td>63</td>
<td>62</td>
</tr>
<tr>
<td><strong>Hypertension (%)</strong></td>
<td>90</td>
<td>91</td>
</tr>
<tr>
<td><strong>Diabetes Mellitus (%)</strong></td>
<td>40</td>
<td>39</td>
</tr>
<tr>
<td><strong>Prior Stroke/TIA/Embolism (%)</strong></td>
<td>55</td>
<td>55</td>
</tr>
<tr>
<td><strong>Prior Myocardial Infarction (%)</strong></td>
<td>17</td>
<td>18</td>
</tr>
</tbody>
</table>

Based on Intention-to-Treat Population
## Rocket-AF Primary Outcome
**Stroke and Systemic Embolism**

<table>
<thead>
<tr>
<th></th>
<th>Rivaroxaban</th>
<th>Warfarin</th>
<th>Event Rate</th>
<th>Event Rate</th>
<th>HR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>On Treatment</strong></td>
<td></td>
<td></td>
<td>1.70</td>
<td>2.15</td>
<td>0.79</td>
<td>0.015</td>
</tr>
<tr>
<td>N= 14,143</td>
<td></td>
<td></td>
<td>(0.65,0.95)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>ITT</strong></td>
<td></td>
<td></td>
<td>2.12</td>
<td>2.42</td>
<td>0.88</td>
<td>0.117</td>
</tr>
<tr>
<td>N= 14,171</td>
<td></td>
<td></td>
<td>(0.74,1.03)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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*Event Rates are per 100 patient-years*

*Based on Safety on Treatment or Intention-to-Treat thru Site Notification populations*
Aristotle-Apixaban
ARISTOTLE: Baseline *Identical* to ReLy

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Apixaban (n=9120)</th>
<th>Warfarin (n=9081)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Qualifying risk factors, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age ≥75 yrs</td>
<td>31</td>
<td>31</td>
</tr>
<tr>
<td>Prior stroke, TIA, or SE</td>
<td>19</td>
<td>20</td>
</tr>
<tr>
<td>Heart failure or reduced LV EF</td>
<td>35</td>
<td>36</td>
</tr>
<tr>
<td>Diabetes</td>
<td>25</td>
<td>25</td>
</tr>
<tr>
<td>Hypertension</td>
<td>87</td>
<td>88</td>
</tr>
<tr>
<td>Renal function (Cl\textsubscript{Cr} ml/min), %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal (&gt;80)</td>
<td>41</td>
<td>41</td>
</tr>
<tr>
<td>Mild impairment (&gt;50 – 80)</td>
<td>42</td>
<td>42</td>
</tr>
<tr>
<td>Moderate impairment (&gt;30 – 50)</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>Severe impairment (≤ 30)</td>
<td>1.5</td>
<td>1.5</td>
</tr>
</tbody>
</table>
ARISTOTLE: Summary

- **Perceived** better safety data-separated out high risk patient.. >80 y/o, <60kg, creat>1.5 who got 2.5 BID dose

- Reduced stroke and systemic embolism by 21% (p=0.01)

- Reduced major bleeding by 31% (p<0.001)

- Reduced mortality by 11% (p=0.047)
Edoxaban
# Phase III Trials: Bleeding Profiles

Compared to WARFARIN:

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran (RE-LY)</th>
<th>Rivaroxaban (ROCKET-AF)</th>
<th>Apixaban (ARISTOTLE)</th>
<th>Edoxaban (ENGAGE AF-TIMI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major bleeding</td>
<td>↓</td>
<td>same</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Intracranial Bleeding</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>GI Bleeding</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Fatal Bleeding</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
</tbody>
</table>
Post Marketing: Afib Pivotal Registries

- Multiple post marketing registries

- REACH, J-TRACE, ORBIT-AF, ORBIT-AF II, Dresden

- In general-use of VKAs *suboptimal* in real life (TTR)

- DOACs w steady increase globally, regional differences

- **Overall DOACs at least as effective as VKAs with slightly lower bleeding events**
Which to Choose?

IT DEPENDS
# DOAC Monitoring? Not Really. *Think D-Dimer*

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<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PT/INR</strong></td>
<td>Sensitive</td>
<td>Sensitive</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Normal PT/INR excludes significant drug levels</td>
<td>Normal PT/INR excludes significant drug levels</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>aPTT</strong></td>
<td>Sensitive</td>
<td>Sensitive</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>normal aPTT excludes excess drug levels</td>
<td>normal aPTT excludes excess drug levels</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Thrombin Time</strong></td>
<td>Sensitive</td>
<td>Sensitive</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Normal TT excludes excess drug levels</td>
<td>Normal TT excludes excess drug levels</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Anti-Xa Activity</strong></td>
<td>Sensitive</td>
<td>Sensitive</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>excludes significant drug levels</td>
<td>excludes significant drug levels</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Best Test</strong></td>
<td>TT have best correlation throughout therapeutic range, but are not standardized across laboratories</td>
<td>Anti-Xa activity calibrated to the agent is the preferred assay, but is not widely available</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
DOAC: *Pre-Op and Post-Op Management*

- **Not Warfarin**... it is not 4-5 days prior to surgery!
- Consider if surgery is low, medium or high risk
- Consider creatinine clearance
Pre-op & Post-op Management

- **Low**
  - Days before/after procedure:
    - Day -6 to -3: Continue anticoagulation but consider missing one dose or performing procedure at trough drug concentration.
    - Day -2: Dabigatran with CrCl > 50 ml/min.
    - Day -1 to 0: Dabigatran with CrCl 31–50 ml/min.
    - Day 1 to 4: Rivaroxaban/apixaban with CrCl > 30 ml/min.

- **Moderate**
  - Days before/after procedure:
    - Day -6 to -3: Continue anticoagulation but consider missing one dose or performing procedure at trough drug concentration.
    - Day -2: Dabigatran with CrCl > 50 ml/min.
    - Day -1 to 0: Dabigatran with CrCl 31–50 ml/min.
    - Day 1 to 4: Rivaroxaban/apixaban with CrCl > 30 ml/min.

- **High**
  - Days before/after procedure:
    - Day -6 to -3: Continue anticoagulation but consider missing one dose or performing procedure at trough drug concentration.
    - Day -2: Dabigatran with CrCl > 50 ml/min.
    - Day -1 to 0: Dabigatran with CrCl 31–50 ml/min.
    - Day 1 to 4: Rivaroxaban/apixaban with CrCl > 30 ml/min.

Patient receiving anticoagulant: [Diagram symbol]
Patient may continue/restart anticoagulant if judged appropriate: [Diagram symbol]
Anticoagulation must be stopped: [Diagram symbol]
Factor Reversal
Urgent Reversal for Life Threatening Bleeding

STOP THE BLEED
SAVE A LIFE

1. APPLY PRESSURE WITH HANDS
2. APPLY DRESSING AND PRESS
3. APPLY Tourniquet
   WRAP  WIND  SECURE  TIME

CALL 911

Illustration by Ciné-Med.
PCCs—Prothrombin Complex Concentrates

- Human Plasma Derived
- Most contain II, VII, IX, X, with some VII
- Virally inactivated, *no need to crossmatch*
- Quicker and more complete reversal
- Preferred over FFP due to *volume and thaw time*
PCC-Prothrombin Complex Concentrates

- PCCs- average cost $7,000

- ‘4 factor’ PCC, w Factors II, VII, IX, X, otherwise known as FEIBA (factor eight inhibition bypassing activity)

- ‘4 factor’ PCC, w Factors II, VII, IX, X, otherwise known as Kcentra (only approved for warfarin reversal)

- ‘3 factor’ PCC, w Factors II, IX, X and a smaller amount of VII—otherwise known as Profilnine
Preferred Cooper PCC: Kcentra (4PCC)

- **Mechanism of Action**
  - Kcentra increases in the levels of the vitamin K-dependent coagulation factors, and protein C and protein S
  - II, IX, and X (intrinsic coagulation pathway)
  - VII (extrinsic coagulation pathway)

- **Onset of action:**
  - Rapid; significant INR decline *within 10 minutes*

- **Duration:**
  - ~6 to 8 hours
Coagulation cascade.

Craig T. January et al. Circulation. 2014;130:e199-e267
Cooper Anticoagulant Usage (2014-2016)

![Bar chart showing the usage of different reversal factors.](chart.png)

- **Warfarin (Coumadin)**: The largest category with a significant number of patients.
- **Rivaroxaban (Xarelto)**: A smaller category compared to Warfarin.
- **Apixaban (Eliquis)**: The smallest category with very few patients.
- **Dabigatran (Pradaxa)**: A very small category.

Source of Life Threatening Bleeding:
- **Other**
- **Pre-op**
- **GI**
- **ICH**

Patients

<table>
<thead>
<tr>
<th>Source</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin (Coumadin)</td>
<td></td>
</tr>
<tr>
<td>Rivaroxaban (Xarelto)</td>
<td></td>
</tr>
<tr>
<td>Apixaban (Eliquis)</td>
<td></td>
</tr>
<tr>
<td>Dabigatran (Pradaxa)</td>
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</tbody>
</table>
Life Threatening Reversals

**Total Cost per Agent 2014-2016**

August 2014
Pharmacy blood factors transition from blood bank to pharmacy
Anticoagulation Reversal Order-Set

Order Sets

- **Anticoagulation Reversal - ADULT**
  - **Add Order**

Adult Anticoagulation Reversal Guidelines

- **Warfarin (Coumadin) Reversal**
  - **Add Order**
  - Warfarin (COUMADIN) reversal guidelines
    - INR less than 5 without serious bleeding: 0 of 1 selected
    - INR 5-10 without serious bleeding: 0 of 1 selected
    - INR greater than 10 without serious bleeding: 0 of 1 selected
    - Serious bleeding regardless of INR or Emergency Surgery: 0 of 1 selected
    - Life-threatening bleeding in patients with INR of 2 or higher (fatal bleeding from any source, hemodynamic instability requiring transfusion): 0 of 3 selected
    - Surgery: Urgent (surgery within 24 - 48 hours): 0 of 1 selected

- **Apixaban (Eliquis), Rivaroxaban (Xarelto), Edoxaban (Savaysa) Reversal**

- **Dabigatran (Pradaxa) Reversal**

- **Enoxaparin (Lovenox) Reversal**

- **Heparin Reversal**

- **Fondaparinux (Arixtra) Reversal**

- **Argatroban Reversal**

- **Bivalirudin (Angiomax) Reversal**

- **Alteplase (Activase) Reversal**

- **Ad-hoc Orders**
  - **Add Order**
Dabigatran Reversal

- FDA Approval October 2015
- FDA approved when reversal of the anticoagulant effects of dabigatran is needed
  - For emergency surgery/urgent procedures
  - In life-threatening or uncontrolled bleeding
- Available at CUH
  - $3500/dose
Dabigatran Reversal: URGENT Surgery

Check coagulation status:
- TT, aPTT, PT/INR
- CBC, basic metabolic panel

APTT and TT normal: dabigatran levels low
APTT and TT prolonged: Dabigatran anticoagulant effect may still be present

Last dose of Dabigatran < 12 hours

Idarucizumab (PRAKBIND) IV 5g x 1

Uncontrolled life-threatening bleeding during surgery
- Fatal bleeding from any source, hemodynamic instability requiring RBC transfusion, retinal and cerebral bleeds

Consider 4-Factor PCC
- Koentra 50 units/kg x 1

Last dose of Dabigatran > 12 hours

Use of reversal agent not indicated if last dose given > 12 hours prior to surgery

Uncontrolled life-threatening bleeding during surgery
- Fatal bleeding from any source, hemodynamic instability requiring RBC transfusion, retinal and cerebral bleeds
Dabigatran Reversal: Life Threatening Bleeding

Check coagulation status:
- TT, aPTT, PT/INR
- CBC, BMP

It is not recommended to wait for results before initiating reversal
- APTT and TT normal: dabigatran levels low
- APTT and TT prolonged: dabigatran anticoagulant effect may still be present

MINOR- MODERATE BLEEDING
- Mechanical compression
- Supportive care with IVF and RBC as needed, in accordance with hospital transfusion policy

SEVERE AND LIFE THREATENING BLEEDING
- Idarucizumab (PRAXBIND) 5g x 1
- Hemodynamically unstable
- Intracranial hemorrhage: Neurosurgery consult STAT
- Hematology Oncology Consult STAT
- Continued bleeding
- Consider 4-Factor PCC: Kcentra 50 units/kg x 1

*Fatal bleeding from any source, hemodynamic instability requiring RBC transfusion, retinal and cerebral bleeds
Anti-Xa Reversal: **URGENT** Surgery

Check coagulation status:
- aPTT, PT/INR
- CBC, basic metabolic panel

PT and INR normal: Factor Xa anticoagulant levels low
PT and INR prolonged: Factor Xa anticoagulant effect may still be present

LAST DOSE < 12 HOURS
- KCENTRA 50 units/kg x 1
- Uncontrolled life-threatening bleeding during surgery
  - Fatal bleeding from any source, hemodynamic instability requiring RBC transfusion, retinal and cerebral bleeds
  - Consider Coagulation Factor VIII: Novoseven 90mcg/kg x 1

LAST DOSE > 12 HOURS
- Use of reversal agent is not indicated if last dose given > 12 hours prior to surgery
- Uncontrolled life-threatening bleeding during surgery
  - Fatal bleeding from any source, hemodynamic instability requiring RBC transfusion, retinal and cerebral bleeds
Anti-Xa Reversal: Life Threatening Bleeding

Check coagulation status:
- aPTT, PT, INR
- CBC, basic metabolic panel, type and screen

PT and INR normal: Factor Xa anticoagulant levels low
PT and INR prolonged: Factor Xa anticoagulant effect may still be present

MINOR: MODERATE BLEEDING
- Mechanical compression
- Supportive care with IV fluids and RBC as needed, in accordance with hospital transfusion policy

SEVERE AND LIFE THREATENING BLEEDING
- Hemorrhage from any source, hemodynamic instability requiring RBC transfusion, retinal and cerebral bleeds

- Intracranial hemorrhage: Neurosurgery consult STAT
- Hematology Oncology Consult

4-Act FPC: KCENTRA 50 units/kg x 1
- Massive Transfusion Protocol if needed

Continued bleeding

Coagulation Factor VIII:
Novoseven 90 mcg/kg x 1

Continued bleeding

Check coagulation status:
- PT/INR

PT and INR normal: Factor Xa anticoagulant levels low
PT and INR prolonged: Factor Xa anticoagulant effect may still be present

- Tranexamic Acid 1000mg over 10 minutes (loading dose), then 1000mg over 8 hours
Anti-Xa Reversal: *Investigational*

**Andexanet *Investigational***

- A modified Xa
  - mutated catalytic site $\rightarrow$ binds anti-Xa and neutralizes the effect, *Increased affinity for Xa inhibitors*, compared to human factor Xa
  - modified tail $\rightarrow$ doesn’t interact with other coagulation factors
- Lack of pro-coagulant effects (inactivated)
Emerging Indications
PIioneer AF-PCI

PCI (with stent placement); paroxysmal, persistent, or permanent nonvalvular AF

N = 2000
1:1:1

Rivaroxaban 2.5 mg BID + DAPT*
Rivaroxaban 15 mg QD + low-dose aspirin

Intended DAPT duration:
1, 6, or 12 months

VKA + DAPT
INR 2.0-3.0

VKA + low-dose aspirin

End of treatment at 12 months

≤ 72 hours after sheath removal, INR must be ≤ 2.5 at time of randomization

Primary Outcome Measures: Clinically significant bleeding (composite of TIMI major bleeding, minor bleeding, and bleeding) requiring medical attention
Secondary Outcome Measures: Composite of CV death, MI, and stroke

*DAPT = low-dose aspirin + clopidogrel, prasugrel, or ticagrelor

ClinicalTrials.gov website.[7]
Those undergoing PCI with stenting, w AFIB:

- Rixaroxaban 15 mg daily plus P2Y$_{12}$ inhibitor (clopidogrel, prasugrel or ticagrelor) for 12 months

- Rivaroxaban 2.5 mg BID plus DAPT (ASA 75-100, plus clopidogrel, prasugrel or ticagrelor) for 1, 6 or 12 months

- Warfarin (INR 2-3) plus DAPT for 1, 6 or 12 month
Time to all-cause death or first recurrent hospitalization.

Riva 15mg + P2Y_{12} vs. VKA + DAPT
HR: 0.79 (95% CI: 0.66 – 0.94), p = 0.008
ARR: 7.0%
NNT: 15

Riva 2.5mg + DAPT vs. VKA + DAPT
HR: 0.75 (95% CI: 0.62 – 0.90), p = 0.002
ARR: 10.0%
NNT: 10

Riva 15mg + P2Y_{12}

VKA + DAPT

Riva 2.5mg + DAPT

No. at Risk

<table>
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<tr>
<th>Treatment</th>
<th>0</th>
<th>30</th>
<th>60</th>
<th>90</th>
<th>180</th>
<th>270</th>
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<tbody>
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<td>Riva 15mg + P2Y_{12}</td>
<td>696</td>
<td>609</td>
<td>582</td>
<td>559</td>
<td>496</td>
<td>437</td>
<td>322</td>
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<tr>
<td>Riva 2.5mg + DAPT</td>
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<td>607</td>
<td>570</td>
<td>548</td>
<td>493</td>
<td>454</td>
<td>367</td>
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<tr>
<td>VKA + DAPT</td>
<td>697</td>
<td>592</td>
<td>540</td>
<td>490</td>
<td>422</td>
<td>369</td>
<td>272</td>
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</tbody>
</table>

Time to first recurrent hospitalization caused by cardiovascular or bleeding event.

My Problem with the Study (the fine print)

- Not powered for superiority or noninferiority
- 75% men
- 75% older than 65
- 95% white
- 65% had DES, 35% BMS
- Warfarin TTR was 65%
- Warfarin group had a higher percentage of smokers
- Around 90% of the DAPT was clopidogrel, with very low % of patients on prasugrel or ticagrelor
• DOACs have rapidly evolved

• Reversal protocols and antidotes are available with more on the horizon

• Cooper Anticoagulation Committee will continue to update policies based on new evidence.