Inpatient Management Of Novel Oral Anticoagulants

COL (ret) Anthony S. Ramage DO
Critical Care Medicine
Eisenhower Army Medical Center
Conflict of Interest Disclosure

• Speakers Bureau
  – Boehringer Ingelheim
  • Manufacturer of dabigitran (Pradaxa)
Disclaimer

This presentation was prepared by Anthony S. Ramage DO in his personal capacity. The opinions expressed in this article are the author's own and do not reflect the view of Eisenhower Army Medical Center, The United State Army or the United States government.
Outline

• Overview of the Therapeutic Class
  – AFIB
  – Assessment of Bleeding Risk (SPAF perspective)
  – VTE
• Peri-Procedural Management
• Bleeding Management
  – Life threatening
84 year Korean female presents with new onset atrial fibrillation. She has no prior hx of CVA or TIA. She has a remote history of MI with a preserved EF and no anginal symptoms. She is a very active competitive ballroom dancer. She is a previous smoker but quit following her MI 25 years ago. She has HTN on single drug therapy but is not well controlled on a low dose beta blocker. You add an ACE-inhibitor to her BP regimen and increase the beta blocker to achieve rate control. She has no hx of CHF. Based on her CHA2 DS2-VASc score of 5 you decide to anticoagulate her. Her renal function is normal for age with an estimated GFR of 75ml/min.
Q1. Which oral anti-coagulant would you prescribe for this patient?

1. Warfarin target INR 2-3
2. Dabigitran 150 mg po BID
3. Rivaroxaban 20 mg po daily
4. Apixaban 5 mg po BID
5. Edoxaban 60mg po daily
Q2. Which of the following therapeutic regimens will increase this patient’s risk for intracranial bleeding the most?

1. Warfarin target INR 2-3
2. Dabigitran 150 mg po BID
3. Rivaroxaban 20 mg po daily
4. Apixaban 5 mg po BID
5. Edoxaban 60 mg daily
Nomenclature
What’s In a Name

• NOAC
  – Novel oral anticoagulant
  – Non Vitamin k
  – Non-monitored

• TSOAC
  – Target Specific Oral Anticoagulant
    • Better but warfarin is target specific (4 targets)

• DOAC
  – Direct oral anticoagulant
    • Most descriptive
    • Recommended by ISTH
Apixaban
Rivaroxaban
Edoxaban

Xa Inhibitor

Common Coagulation Cascade

Prothrombin II

Fibrinogen

Thrombin

Fibrin

Thrombus

Dabigatran

VIIa/TF

IXa

X
## DOAC vs. Warfarin General Comparison

<table>
<thead>
<tr>
<th>Features</th>
<th>Warfarin</th>
<th>New Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset</td>
<td>Slow</td>
<td>Rapid</td>
</tr>
<tr>
<td>Dosing</td>
<td>Variable</td>
<td>Fixed</td>
</tr>
<tr>
<td>Food effect</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Drug interactions</td>
<td>Many</td>
<td>Few</td>
</tr>
<tr>
<td>Monitoring</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Half-life</td>
<td>Long</td>
<td>Short</td>
</tr>
<tr>
<td>Antidote</td>
<td>Yes</td>
<td></td>
</tr>
</tbody>
</table>
# DOAC Current Indications

<table>
<thead>
<tr>
<th>Indications</th>
<th>SPAF</th>
<th>VTE Acute/Long term</th>
<th>DVT prophylaxis THA/TKA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigitran</td>
<td>Yes</td>
<td>Yes/Yes</td>
<td>No (Yes; CAN,EU)</td>
</tr>
<tr>
<td>Rivaroxiban</td>
<td>Yes</td>
<td>Yes/Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Apixiban</td>
<td>Yes</td>
<td>Yes/Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>Yes</td>
<td>Yes/Yes</td>
<td>No (Yes JPN)</td>
</tr>
</tbody>
</table>
Atrial Fibrillation Controlled Trials

Novel Anticoagulants

- **FIIa Inhibitor**
  - **Dabigatran**
    - Open Label
    - Two Doses
    - Twice Daily
    - RE-LY 2009

- **Fxa Inhibitor**
  - **Rivaroxaban**
    - Double Blind
    - Single Dose
    - Once Daily
    - ROCKET-AF 2011
  - **Apixaban**
    - Double Blind
    - Single Dose
    - Twice Daily
    - ARISTOTLE 2011
  - **Edoxaban**
    - Double Blind
    - Two Doses
    - Once Daily
    - ENGAGE 2013

**Novel Anticoagulants**

**FIIa Inhibitor**

**Dabigatran**

- Open Label
- Two Doses
- Twice Daily
- RE-LY 2009

**Fxa Inhibitor**

- **Rivaroxaban**
  - Double Blind
  - Single Dose
  - Once Daily
  - ROCKET-AF 2011

- **Apixaban**
  - Double Blind
  - Single Dose
  - Twice Daily
  - ARISTOTLE 2011

- **Edoxaban**
  - Double Blind
  - Two Doses
  - Once Daily
  - ENGAGE 2013
## Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>RE-LY (Dabigatran)</th>
<th>ROCKET-AF (Rivaroxaban)</th>
<th>ARISTOTLE (Apixaban)</th>
<th>ENGAGE AF (Edoxaban)</th>
</tr>
</thead>
<tbody>
<tr>
<td># Randomized</td>
<td>18,113</td>
<td>14,264</td>
<td>18,201</td>
<td>21,105</td>
</tr>
<tr>
<td>Age, years</td>
<td>72 (63-81)</td>
<td>73 (65-78)</td>
<td>70 (63-76)</td>
<td>72 (64-78)</td>
</tr>
<tr>
<td>Female, %</td>
<td>37</td>
<td>40</td>
<td>35</td>
<td>38</td>
</tr>
<tr>
<td>Paroxysmal AF</td>
<td>32</td>
<td>18</td>
<td>15</td>
<td>25</td>
</tr>
<tr>
<td>VKA naive</td>
<td>50</td>
<td>38</td>
<td>43</td>
<td>41</td>
</tr>
<tr>
<td>Aspirin Use</td>
<td>40</td>
<td>36</td>
<td>31</td>
<td>29</td>
</tr>
</tbody>
</table>

Distribution by CHADS Scores

**RELY**
- CHADS 0-1: 32%
- CHADS 2: 35%
- CHADS 3-6: 33%

**ARISTOTLE**
- CHADS-1: 34%
- CHADS 2: 36%
- CHADS 3-6: 30%

**ROCKET**
- CHADS 2: 87%
- CHADS 3-6: 13%

**ENGAGE**
- CHADS 2: 53%
- CHADS 3-6: 47%

# Atrial Fibrillation Trials
## Dosing Comparison

<table>
<thead>
<tr>
<th>Drug</th>
<th>RE-LY</th>
<th>ROCKET-AF</th>
<th>ARISTOTLE</th>
<th>ENGAGE AF-TIMI 48</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dabigatran</td>
<td>Rivaroxaban</td>
<td>Apixaban</td>
<td>Edoxaban</td>
</tr>
<tr>
<td>N</td>
<td>18,113</td>
<td>14,266</td>
<td>18,201</td>
<td>21,105</td>
</tr>
<tr>
<td>Dose (mg)</td>
<td>150, 110</td>
<td>20</td>
<td>5</td>
<td>60, 30</td>
</tr>
<tr>
<td>Frequency</td>
<td>bid</td>
<td>qd</td>
<td>bid</td>
<td>qd</td>
</tr>
<tr>
<td>Initial Dose adj*</td>
<td>No</td>
<td>20 → 15 mg</td>
<td>5 → 2.5 mg</td>
<td>60 → 30 mg**</td>
</tr>
<tr>
<td>Dose adj (%)</td>
<td>0</td>
<td>21</td>
<td>4.7</td>
<td>&gt; 25</td>
</tr>
<tr>
<td>Dose adj after randomization</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Design</td>
<td>PROBE</td>
<td>double blind</td>
<td>double blind</td>
<td>double blind</td>
</tr>
</tbody>
</table>

* Dose adjusted in patients with ↓ drug clearance.
** Dose adjustments throughout study period

PROBE = prospective, randomized, open-label, blinded end point evaluation

Ruff CR et al. Am Heart J 2010; 160:635-41
You previously made the decision to place your 84 year old ballroom dancer on dabigitran (bias alert) 150 mg po BID. At her three month f/u visit you note that her renal function has deteriorated. Her eGFR is now 50 mL/min down from previous 75 mL/min. You address her blood pressure control and discuss other risk factors for AKI. You begin a work up and see her back in 2 weeks. Her renal function has deteriorated again and her eGFR is down to 40mL/min.
Q3. What should you do now about her chronic anticoagulation?

1. Switch to warfarin target INR 2-3
2. Decrease dabigitran to 75 mg po BID
3. Switch to Rivaroxaban 15 mg po daily
4. Switch to Apixaban 2.5 mg po BID
5. Switch to Edoxaban 30 mg po daily
Dosing Considerations
Renal Impairment

• DOAC’s should be avoided in unstable renal function.
• All DOAC’s require renal adjustments. Most important with dabigitran (80% renal)
• eGFR may be misleading in patients>70
• Lower limits of renal fxn depend on the indication. You need better renal fxn for VTE indications
• Edoxaban cannot be used if CrCL>95
## Dosing Schedules

### Atrial Fibrillation

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dosing Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dabigatran</strong></td>
<td>CrCl $&gt; 30$ cc/min: 150 mg, BID</td>
</tr>
<tr>
<td>75mg, 150mg</td>
<td>CrCl 15 to 30 cc/min: 75 mg, BID</td>
</tr>
<tr>
<td></td>
<td>Avoid $&lt; 15$ cc/min</td>
</tr>
<tr>
<td><strong>Apixaban</strong></td>
<td>CrCl $&gt; 15$ cc/min: 5 mg, BID</td>
</tr>
<tr>
<td>2.5mg, 5mg</td>
<td>Any 2 ($&gt; 80$ yrs, $&lt; 60$ kg, SCr $&gt; 1.5$mg/dL: 2.5 mg, BID)</td>
</tr>
<tr>
<td></td>
<td>Avoid $&lt; 15$ cc/min</td>
</tr>
<tr>
<td><strong>Rivaroxaban</strong></td>
<td>CrCl $&gt; 50$ cc/min: 20 mg, Qday</td>
</tr>
<tr>
<td>10mg, 15mg, 20mg</td>
<td>CrCl 15-50 cc/min: 15 mg, Qday</td>
</tr>
<tr>
<td></td>
<td>Avoid CrCl $&lt; 15$ cc/min</td>
</tr>
<tr>
<td><strong>Edoxaban</strong></td>
<td>CrCl$&gt; 95$ ml/min: not recommended</td>
</tr>
<tr>
<td>15mg, 30mg, 60mg</td>
<td>CrCl$&gt; 50$&lt;95 :60 mg</td>
</tr>
<tr>
<td></td>
<td>CrCl$&gt; 15$ml/min$&lt; 50$ ml/min : 30 mg</td>
</tr>
<tr>
<td></td>
<td>Cr/Cl$&lt; 15$ ml/min: not recommended</td>
</tr>
</tbody>
</table>
## Trial Metrics

<table>
<thead>
<tr>
<th></th>
<th>RE-LY (Dabigatran)</th>
<th>ROCKET-AF (Rivaroxaban)</th>
<th>ARISTOTLE (Apixaban)</th>
<th>ENGAGE AF (Edoxaban)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Follow-Up, years</td>
<td>2.0</td>
<td>1.9</td>
<td>1.8</td>
<td>2.8</td>
</tr>
<tr>
<td>Median TTR</td>
<td>66</td>
<td>58</td>
<td>66</td>
<td>68</td>
</tr>
<tr>
<td>Lost to Follow-Up, N</td>
<td>20</td>
<td>32</td>
<td>90</td>
<td>1</td>
</tr>
</tbody>
</table>

*TTR, time in therapeutic range

Meta Analysis: Stroke or SEE

- **RE-LY [150 mg]**: Risk Ratio (95% CI) 0.88 (0.75 - 1.03)
- **ROCKET AF**: Risk Ratio (95% CI) 0.80 (0.67 - 0.95)
- **ARISTOTLE**: Risk Ratio (95% CI) 0.88 (0.75 - 1.02)
- **ENGAGE AF-TIMI 48 [60 mg]**: Risk Ratio (95% CI) 0.66 (0.53 - 0.82)
- **Combined (Random Effects Model)**: Risk Ratio (95% CI) 0.81 (0.73 - 0.91), p=<0.0001

Meta Analysis: Stroke or SEE

- **RE-LY [150 mg]**
- **ROCKET AF**
- **ARISTOTLE**
- **ENGAGE AF-TIMI 48 [60 mg]**
- **Combined (Random Effects Model):**
  - N=58,541
  - Heterogeneity p=0.13

Composite Endpoint Breakdown

Risk Ratio (95% CI)

Ischemic Stroke
- Risk Ratio: 0.92 (0.83 - 1.02)

Hemorrhagic Stroke
- Risk Ratio: 0.49 (0.38 - 0.64)

All-Cause Mortality
- Risk Ratio: 0.90 (0.85 - 0.95)

Favors NOAC
Favors Warfarin

Low Dose Regimens
Efficacy & Safety Outcomes

Dabigatran 110 mg & Edoxaban 30 mg

Risk Ratio (95% CI)

- Stroke or SEE: 1.03 (0.84 - 1.27)
- Ischemic Stroke: 1.28 (1.02 - 1.60)
- Hemorrhagic Stroke: 0.33 (0.23 - 0.46)
- MI: 1.25 (1.04 - 1.50)
- All-Cause Mortality: 0.89 (0.83 - 0.96)
- Major Bleeding: 0.65 (0.43 - 1.00)
- ICH: 0.31 (0.24 - 0.41)
- GI Bleeding: 0.89 (0.57 - 1.37)

Assessment of the Bleeding Risk
Atrial Fibrillation
Weighing the Benefit vs. Risk

Thromboembolic Risk
- CHADS2
- CHA2DS2Vasc

Bleeding Risk
- HASBLED Score
- ICH Risk
## Atrial Fibrillation

Weighing the Benefit vs. Risk

**CHADS$_2$VASc**

Developed to better define low risk patients

<table>
<thead>
<tr>
<th>Item</th>
<th>POINTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHF</td>
<td>1</td>
</tr>
<tr>
<td>HTN</td>
<td>1</td>
</tr>
<tr>
<td>Age $\geq$ 75</td>
<td>2</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1</td>
</tr>
<tr>
<td>Stroke/TIA/SEE</td>
<td>2</td>
</tr>
<tr>
<td>Vascular (MI, PAD)</td>
<td>1</td>
</tr>
<tr>
<td>Age 65-74</td>
<td>1</td>
</tr>
<tr>
<td>Sex$_{category}$ Female</td>
<td>1</td>
</tr>
<tr>
<td><strong>Max Score</strong></td>
<td><strong>9</strong></td>
</tr>
</tbody>
</table>
Weighing the Benefit vs. Risk
Average Thromboembolic Risk Without Anticoagulation
Danish Hospital Registry N= 182,678
(2% of population)

Increased fidelity compared to CHADS2 score

Anticoagulate ≥ 2 with rare exception
# Published Bleeding Risk Scores

## Patients on Oral Vitamin K Antagonist Anticoagulant Therapy

<table>
<thead>
<tr>
<th>Score</th>
<th>Low</th>
<th>Moderate</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kuijer et al. <em>Arch Intern Med</em> 1999;159:457.</td>
<td>0</td>
<td>1-3</td>
<td>&gt; 3</td>
</tr>
<tr>
<td>Gage et al. <em>Am Heart J</em> 2006;151:713.</td>
<td>&lt; 1</td>
<td>1.07 - 2.19</td>
<td>&gt; 2.19</td>
</tr>
</tbody>
</table>

- Low score:
  - Kuijer et al.: score 0
  - Beyth et al.: score 0
  - Gage et al.: score ≤ 1

- Moderate score:
  - Kuijer et al.: 1-3
  - Beyth et al.: 1-2
  - Gage et al.: 1.07 - 2.19

- High score:
  - Kuijer et al.: > 3
  - Beyth et al.: ≥ 3
  - Gage et al.: > 2.19

### Risk Factors

- **Kuijer et al.**
  - Score: 1.6 x age + 1.3 x sex + 2.2 x cancer; 1 point for ≥ 60 years of age, female or malignancy; 0 if none

- **Beyth et al.**
  - Score: ≥ 65 years of age; prior stroke; recent MI; Hct < 30%; +1 point for each

- **Gage et al.**
  - Score: HEMORR2HAGES score: liver/renal disease, EtOH abuse, malignancy, > 75 years old, low platelet count or function, rebleeding risk, uncontrolled Htn, anemia, genetic factors (CYP2C9) risk of fall or stroke; 1 point for each factor; 2 points for previous bleeding

- **Shireman et al.**
  - Score: (0.49 x age > 70) + (0.32 x female) + (0.58 x remote bleed) + (0.62 x recent bleed) + (0.71 x EtOH/drug abuse) + (0.27 x diabetes) + (0.86 x anemia) + (0.32 x antiplatelet drug use); 1 point for each; 0 if none

# HAS-BLED Score

Risk Score for Predicting Major Bleeding in Anticoagulated Patients with Atrial Fibrillation

<table>
<thead>
<tr>
<th>Factor</th>
<th>Weight (points)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension (&gt; 160 mm Hg systolic)</td>
<td>1</td>
</tr>
<tr>
<td>Abnormal renal or hepatic function</td>
<td>1-2</td>
</tr>
<tr>
<td>Stroke</td>
<td>1</td>
</tr>
<tr>
<td>Bleeding history or anemia</td>
<td>1</td>
</tr>
<tr>
<td>Labile INR (TTR &lt; 60%)</td>
<td>1</td>
</tr>
<tr>
<td>Elderly (age &gt; 75 years)</td>
<td>1</td>
</tr>
<tr>
<td>Drugs (antiplatelet, NSAID) or alcohol</td>
<td>1-2</td>
</tr>
</tbody>
</table>

- **High risk** (> 4%/year) ≥ 4
- **Moderate risk** (2-4%/year) 2-3
- **Low risk** (< 2%/year) 0-1

Major Bleeding

ISTH criteria

- Fatal Bleeding
- ICH
- Bleeding into any critical area or organ (spinal, ocular, articular, muscular with compartment syndrome)
- Active bleeding and a 2g/dL drop in Hgb or transfusion of 2 units pRBC’s.
Limitations of Major Bleeding and HASBLED

• Wide spectrum of bleeding
• Insufficient counterbalance to the “weight” of ischemic stroke
• Outside of ICH major bleeding rarely results in significant morbidity and almost never death
• Predicts bleeding events on warfarin only
All DOACS: Major Bleeding

- RE-LY [150 mg]: Risk Ratio (95% CI) 0.94 (0.82 - 1.07)
- ROCKET AF: Risk Ratio (95% CI) 1.03 (0.90 - 1.18)
- ARISTOTLE: Risk Ratio (95% CI) 0.71 (0.61 - 0.81)
- ENGAGE AF-TIMI 48 [60 mg]: Risk Ratio (95% CI) 0.80 (0.71 - 0.90)
- Combined: Risk Ratio (95% CI) 0.86 (0.73 - 1.00) (p=0.06)

All DOACS: Major Bleeding

Heterogeneity p=0.001

Weighing the Benefit vs. Risk
Thromboembolic Risk Without Anticoagulation Stratified by HASBLED score

Circulation. 2012 May;125(19):2298-307
Distribution of Major Bleeding
HASBLED Predicts GI Bleeding Risk

GI Bleeds

ICH < 1% of major bleeds

Epistaxis
GU bleeding
Articular
Muscular

Seminars in Hematology, 2014-04-01, Volume 51, Issue 2, Pages 102-111
Q4. Which of the following factors DOES NOT increase the risk of intracranial bleeding in patients who are anti-coagulated?

A. Advanced age (>70)
B. High Blood Pressure (>160/90)
C. History of falls
D. Labile INR (for those on coumadin)
E. Concomitant anti-platelet therapy

38% 8% 8% 23% 23%
The Myth of Falls Risk

• A Hx of Falls has never been a validated risk factor for bleeding risk in anti-coagulated patients.
• Among the leading reasons physicians don’t anticoagulate
• Patient would have to fall 300 times/year for the risk to outweigh the benefit

Intracranial Hemorrhage Risk Reduction

• Choice of Anticoagulant
  – DOACS significantly lower risk
  – First year of anticoagulation on warfarin is greatest risk

• Blood pressure control

• Advanced Age

• Concomitant antiplatelet therapy

• Falls Mitigation (makes us feel better)

• Future Directions
  – ID Cerebral amyloid angiopathy (CAA)
VTE Trials
A 60 year old male 12 days s/p TKA presents with sudden onset of chest pain, dyspnea and light headedness. His initial vitals reveal a HR of 120, BP of 94/60 and SaO2 of 84% on room air. His Sao2 corrects to 95% on 6L NC. You suspect a pulmonary embolus and want to initiate anticoagulation immediately.
Q5. Which agent will you prescribe initially?

1. Rivaroxiban 15 mg po BID
2. Apixaban 10 mg po BID
3. Enoxaparin 1mg/kg SQ BID
4. Dabigitran 150 mg po BID
5. Unfractionated heparin 80u/kg IV bolus followed by 18 U/kg/hr continuous infusion
## DOAC VTE Trials

<table>
<thead>
<tr>
<th></th>
<th>RECOVER I-II</th>
<th>Einstein DVT/PE</th>
<th>Amplify</th>
<th>Hokusai</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug</td>
<td>Dabigatran</td>
<td>Rivaroxaban</td>
<td>Apixaban</td>
<td>Edoxaban</td>
</tr>
<tr>
<td># Randomized</td>
<td>2359</td>
<td>3449/4832</td>
<td>5395</td>
<td>8240</td>
</tr>
<tr>
<td>Mean Age</td>
<td>55</td>
<td>56/58</td>
<td>57</td>
<td>56</td>
</tr>
<tr>
<td>Dose (mg)</td>
<td>150 BID*</td>
<td>15 mg BID</td>
<td>10 BID</td>
<td>60, 30*</td>
</tr>
<tr>
<td>Frequency of PE (%)</td>
<td>31</td>
<td>1/100</td>
<td>34</td>
<td>40</td>
</tr>
<tr>
<td>Dose Adjustment</td>
<td>No</td>
<td>15-20 QD</td>
<td>5 BID</td>
<td>60 → 30</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>Day 21</td>
<td>Day 7</td>
<td>30 → 15</td>
</tr>
<tr>
<td>Frequency of PE (%)</td>
<td>0</td>
<td>21</td>
<td>7</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>15-20 QD</td>
<td>5 BID</td>
<td>60 → 30</td>
</tr>
<tr>
<td>Length of therapy (mos)</td>
<td>6</td>
<td>3,6,12^</td>
<td>6</td>
<td>3,6,12^</td>
</tr>
<tr>
<td>Design</td>
<td>double blind</td>
<td>double blind</td>
<td>double blind</td>
<td>double blind</td>
</tr>
</tbody>
</table>

* Initial 5-10 days parenteral anticoagulant (enoxaparin)

^ Physician dependent

Van der Hulle et.al. J. Throm Haemostasis 12:320-328
Primary Efficacy Endpoint
Recurrent VTE

<table>
<thead>
<tr>
<th>Study</th>
<th>Risk Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RECOVER I-II</td>
<td>1.1 (0.66 - 1.84)</td>
</tr>
<tr>
<td>EINSTEIN DVT</td>
<td>0.70 (0.46 - 1.07)</td>
</tr>
<tr>
<td>EINSTEIN PE</td>
<td>1.13 (0.76-1.69)</td>
</tr>
<tr>
<td>AMPLIFY</td>
<td>0.84 (0.60 – 1.18)</td>
</tr>
<tr>
<td>HOKUSAI</td>
<td>0.83 (0.60 – 1.19)</td>
</tr>
<tr>
<td>Combined</td>
<td>0.97 (0.83 – 1.14)</td>
</tr>
</tbody>
</table>

Major Safety Outcomes VTE Pooled Risk

- **Major Bleeding**
- **Major GI Bleed**
- **Intracranial Bleed**
- **Fatal Bleeding**

**N=24,275**

<table>
<thead>
<tr>
<th>Safety Outcome</th>
<th>Risk Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major Bleeding</td>
<td>0.6 (0.41 - 0.86)</td>
</tr>
<tr>
<td>CRNMB</td>
<td>0.66 (0.58 - 0.99)</td>
</tr>
<tr>
<td>Fatal Bleeding</td>
<td>0.39 (0.16 – 0.94)</td>
</tr>
<tr>
<td>Major GI Bleed</td>
<td>0.36 (0.15 – 0.87)</td>
</tr>
</tbody>
</table>

After switching your 84 year old ballroom dancer to warfarin therapy you astutely recognize the possibility of renovascular disease unmasked by addition of the ACE-inhibitor. You stop the ACE-I and refer her for renovascular ultrasound. Your patient is too busy competing to bother with visits to the coumadin clinic and requests that she be put back on a DOAC. Her CrCl has stabilized at 45ml/min after stopping the ACE-i.
Q6. Would you comply with her request and if so, which anticoagulant would you choose?

1. Continue warfarin or nothing
2. Switch to dabigitran 110 mg po BID
3. Switch to rivaroxaban 20 mg po daily
4. Switch to apixaban 5 mg po BID
5. Switch to edoxaban 30 mg po daily
A week after switching your patient to edoxaban 30 mg once daily the renal ultrasound reveals bilateral RAS and you refer the patient to vascular surgery. The vascular surgeon wants to perform an angiogram with possible endovascular intervention. The surgeon calls you for advice on how to manage her edoxaban peri-operatively.
Q7. What is your guidance?

A. Hold edoxaban for 24 hours pre-op and resume 24 hours post-op
B. Hold edoxaban 48 hours pre-op and resume 24 hrs post-op
C. Hold edoxaban 72 hrs pre-op and bridge with LMWH until DOS then resume 24 hrs post-op
D. Continue edoxaban through the perioperative period
Peri-Procedural Management
Peri-Procedural Interruption
General Considerations

• Thromboembolic Risk
  – Drives the decision to bridge or not

• Procedural Risk
  – Drives the decision to resume therapy
  – Bleeding Risk of Patient
    • Adds to the procedural risk eg. (antiplatelet therapy, NSAID’s)

• Bridging
  – Far less need for bridging with DOAC’s
## Thromboembolic Risk Assessment

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>SPAF/ATE</th>
<th>VTE</th>
</tr>
</thead>
<tbody>
<tr>
<td>High &gt;10%/year risk of ATE or &gt;10%/mo risk of VTE</td>
<td>CHADS2 score 5 or 6</td>
<td>Recent VTE (&lt;3 months)</td>
</tr>
<tr>
<td>Rheumatic Valvular Disease</td>
<td>Recent Stroke or TIA (&lt;3 months)</td>
<td>Severe thrombophilia (Protein C/S and AT deficiency, APL Ab)</td>
</tr>
<tr>
<td>Intermediate (4-10%/year of ATE or 4-10% risk of VTE)</td>
<td>CHADS2 score 3 or 4</td>
<td>VTE past 3-12 months</td>
</tr>
<tr>
<td>Low ,4% risk of ATE or &lt;2% risk of VTE</td>
<td>CHADS2 score 0-2 (no prior stroke or TIA)</td>
<td>VTE &gt;12 mos ago</td>
</tr>
</tbody>
</table>
# Procedural Risk Assessment

<table>
<thead>
<tr>
<th>HIGH Risk</th>
<th>LOW Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>2-4% risk of Major Bleed</strong></td>
<td><strong>0-2% risk of Major Bleed</strong></td>
</tr>
<tr>
<td>CABG/Valve replacement/Sternotomy</td>
<td>Cholecystectomy</td>
</tr>
<tr>
<td>AAA repair or any major vascular case</td>
<td>Endoscopy without polypectomy or FNA</td>
</tr>
<tr>
<td>Any Oncologic Surgery</td>
<td>PM, Defibrillator placement, EPstudy</td>
</tr>
<tr>
<td>Laminectomy or major spine case</td>
<td>Simple dental extraction</td>
</tr>
<tr>
<td>TURP, kidney biopsy</td>
<td>Carpel tunnel repair</td>
</tr>
<tr>
<td>Polypectomy, variceal treatment, biliary sphincterotomy, pneumatic dilatation</td>
<td>TKR, THR, joint arthroscopy</td>
</tr>
<tr>
<td>PEG placement</td>
<td>Skin cancer excision</td>
</tr>
<tr>
<td>Multiple tooth extractions</td>
<td>Abdominal hernia, hemmoroidal, axillary node dissection, hydrocele repair</td>
</tr>
<tr>
<td>Any major surgery duration &gt; 45 minutes</td>
<td>cataracts</td>
</tr>
<tr>
<td></td>
<td>Bronchoscopy, non coronary angiography, cutaneous biopsies</td>
</tr>
</tbody>
</table>
## Preoperative Interruption

<table>
<thead>
<tr>
<th>Drug (dose)</th>
<th>Renal Function Cr/Cl</th>
<th>Low Bleeding Risk Surgery</th>
<th>High Bleeding Risk Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dabigitran 150 BID</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T ½ 14-17h</td>
<td>&gt;50ml/min</td>
<td>Skip 2 doses</td>
<td>Skip 4 doses</td>
</tr>
<tr>
<td>T ½ 16-18h</td>
<td>30-50ml/min</td>
<td>Skip 4 doses</td>
<td>Skip 6-8 doses</td>
</tr>
<tr>
<td><strong>Rivaroxiban 20 QD</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T ½ 8-9h</td>
<td>&gt;50ml/min</td>
<td>Skip one dose</td>
<td>Skip 2 doses</td>
</tr>
<tr>
<td>T ½ 9h</td>
<td>30-50 ml/min</td>
<td>Skip one dose</td>
<td>Skip 2 doses</td>
</tr>
<tr>
<td>T ½ 9-10h</td>
<td>15-30 ml/min</td>
<td>Skip two doses</td>
<td>Skip 3 doses</td>
</tr>
<tr>
<td><strong>Apixiban 5mg BID</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T ½ 7-8 h</td>
<td>&gt;50ml/min</td>
<td>Skip 2 doses</td>
<td>Skip 4 doses</td>
</tr>
<tr>
<td>T ½ 17-18h</td>
<td>30-50ml/min</td>
<td>Skip 4 doses</td>
<td>Skip 6 doses</td>
</tr>
<tr>
<td><strong>Edoxaban</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;50&lt;95 ml/min</td>
<td>Skip 2 doses</td>
<td>Skip 4 doses</td>
</tr>
<tr>
<td></td>
<td>&lt;50 ml/min</td>
<td>Skip 4 doses</td>
<td>Skip 6 doses</td>
</tr>
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</table>
Bridging with DOAC’s

• Bridging is generally not recommended
• Very high risk patients (ie. Recent VTE or CHADSVASC >6) may be considered for preoperative bridging) on a case by case basis
• May consider bridging pre and post op in patients anticipated to have prolonged ileus or complete bowel rest or gastric resection.
Resumption of Therapy

• Low Risk Bleeding Surgery
  – Resume therapy 24 hours after end of case

• High Bleeding Risk Surgery
  – Resume 48-72 hrs after end of case
  • Consider 72 hours in any case involving neuraxial anesthesia, sternotomy, CNS
Bleeding Management if the Era of DOAC’s
Initial Assessment

Severity and Location
Actively bleeding right now
Which agent are they taking
Timing of last dose
Overdose accidental or intentional
Renal (uremic) or hepatic (FHF) disease
Additional anti-platelet therapy (ASA clopidogrel)
Supportive Measures

• STOP the anti-coagulant
• Apply direct pressure when applicable
• Resuscitate the patient with pRBC’s and FFP and PLT’s 1:1:1 if hemodynamically unstable
• Limit crystalloid resuscitation. The patient is not bleeding NS nor LR
• Don’t delay surgery consultation while fixing coagulopathy
• Find the Source if not obvious. Treat like a trauma
Consider Emergent Reversal

- Hemorrhagic Shock
- Intracranial Bleed
- Intraspinal
- Pericardial
- Drug Overdose
- Emergency Surgery
Reversal Options

- Clotting Factors (developed primarily for treatment of Hemophilia A and B)
  - PCC
    - 3 factor Profilnine; Bebulin
    - 4 factor Kcentra
  - aPCC
    - FEIBA
  - rFVII

- Currently one FDA approved antidote

- Antifibrinolytics

- Anti-platelet reversal?
Prothrombin Complex Concentrates Available in the US

<table>
<thead>
<tr>
<th>Unactivated Prothrombin Complex Concentrates</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 factor Kcentra</td>
</tr>
<tr>
<td>3 factor Bebulin Profilnine</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Activated Prothrombin Complex Concentrate</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 factor FEIBA</td>
</tr>
</tbody>
</table>
rFVIIa

- Indicated for Hemophilia A and B with inhibitors and Glanzman thrombasthenia
- 97% of use is “off label” as a general hemostatic agent
- Widespread use by US military with equivocal results
- International registry created to capture efficacy and safety

J Trauma. 2010 Aug;69(2):353-9
rFVIIa

- Limited ex vivo and in vitro data was promising at reversing bleeding times
- Animal bleeding models failed to achieve hemostasis with dabigitran or rivaroxiban
- Limited case reports of success
- Increased incidence of ATE in off label use of rFVIIa

Antifibrinolytics

**Tranexamic acid**
- Indication: menorrhagia
- Failed to correct manual bleeding time in rat model
- 10-15 mg/kg IV
- Low thrombosis risk

**€ Aminocaproic acid**
- Broad Indication: Bleeding in the setting of increased fibrinolytic activity??? CABG
- Failed to correct manual bleeding time in rat model
- Low thrombosis risk
Desmopressin

• Routinely used for platelet dysfunction in uremia and Type I von Willebrand disease
• Routinely used for peri-operative ASA reversal
• No clinical data in DOAC’s
• Plausible as an adjunct in patients with concomitant ASA therapy
Intracranial Bleeds in the Era of DOAC

• Reversal is the priority
• Usually stable hemodynamically
• CNS imaging in an anticoagulated patient must be rapid and streamlined per local stroke response protocol
• Prepare for reversal while awaiting imaging
• Consult Neurosurgery as soon as images are available that confirm ICB. If imaging is delayed consider reversal
Dabigitran Reversal

Idarucizumab

• Monoclonal ab fragment
• 300x the binding affinity of thrombin
• Neutralizes dabigitran to undetectable levels within minutes
• Mild side effects (infusion site erythema)
• No effect on other thrombin substrates, did not activate platelets

Idaricizumab REVERSE AD

- 90 patients with life threatening bleeding or need for urgent surgery (50/50)
- Median age 76.5 with afib
- 2.5gms x 2 doses 15 minutes apart (split dose to allow measurement of clotting parameters)
- 1/3 ICB
- Endpoint dTT, ECT and pTT and dabigitran levels

Bauer, NEJM. 2015;373(6):569.
REVERSE-AD

- Complete pharmacologic reversal in 88-98% of patients after first 2.5 gm dose
- Could not ethically justify a control group
- >90% hemostasis at time of surgery
- 5 thrombotic events
- 18 deaths

Bauer, NEJM. 2015;373(6):569.
Xa Reversal

- andexanet alfa is a class specific reversal agent expected to be effective for rivaroxaban, apixiban edoxaban and enoxaparin. Clinical trials currently underway
- Initial phase II data shows reversal of anti-Xa activity of apixiban in healthy non-bleeding volunteers

Universal Reversal

• PER977 is a molecule in development designed to reverse DTI’s, Xa’s and heparins.
• Very effective against edoxaban reversing Xa inhibition in 10 minutes among 80 healthy volunteers

Extracorporeal Therapies

- Hemodialysis effective against dabigitran ONLY
- 50-75% removal of dabigitran in 5 bleeding patients after 4 hrs of IHD. Minor redistribution post dialysis
- Insufficient data for CRRT but limited data suggests not sufficient for acute bleeding
- Charcoal hemoperfusion theoretically beneficial for Xa inhibitors.

Fresh Frozen Plasma

• Little to no benefit in reversing effect of any DOAC

• Must be given as part of massive transfusion protocol in severe life threatening bleeding at ratio of 1:1 with PRBC’s.

• May use in combination with 3 factor PCC when reversing Xa’s.
Summary

• DOAC indications will continue to expand
• DOAC’s will continue to demonstrate superior safety
• Patients will continue to have bleeding complications associated with anticoagulation
• Reversal agents will continue to be developed making DOAC’s even safer
Questions?
Evaluation

- Please take < 90 seconds to evaluate this session.
- Time permitting, speaker will take questions following evaluation.
- Responses are not displayed and are important in maintaining high quality education.
The overall performance of the speaker:

1. Poor
2. Fair
3. Average
4. Good
5. Excellent

100%
How well were the learning objectives met?

1. Poor
2. Fair
3. Average
4. Good
5. Excellent
Did speaker present a balanced view of therapeutic options?

1. Yes
2. No
3. N/A

100% Yes
0% No
0% N/A
How useful will this session be in your practice?

1. Poor
2. Fair
3. Average
4. Good
5. Excellent

91% Excellent
As a result of this program, do you intend to change your patient care?

1. Yes
2. No

91% Yes
9% No
Thank you!