Objectives

• Discuss the advantages and disadvantages of the new oral anticoagulants (NOAC) compared to warfarin
• Review the pharmacology and indications of each agent
• Compare the efficacy and safety of agents in clinical trials
• List agents in the pipeline for reversal of the new oral anticoagulants
Have you prescribed any of the following new oral anticoagulants?
(Please raise hand as the name is called out)

A. Dabigatran (Pradaxa)
B. Rivaroxaban (Xarelto)
C. Apixaban (Eliquis)
D. Edoxaban (Savaysa)

What have you prescribed them for?
(Please raise hand as indication is called out)

A. Stroke prevention in A-Fib
B. Cardioversion for A-fib
C. Stroke prevention with prosthetic heart valves
D. VTE Prophylaxis for hip or knee replacement
E. DVT/PE Treatment or Recurrence
F. Bridging before or after procedures to warfarin
Warfarin: The Original Oral Anticoagulant

• Vitamin K antagonist
• Approved by the FDA for treatment of thromboembolic complications in 1955
• Used by millions of people for decades
• Was the only oral anticoagulant for over 50 years
• However...
Characteristics of the Ideal Anticoagulant

<table>
<thead>
<tr>
<th>Ideal Anticoagulant</th>
<th>Warfarin</th>
<th>NOAC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral Administration</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Fixed Dosing</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Predictable PK/PD</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Rapid Onset/Offset of Action</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>No/Few Drug or Food Interactions</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>No Routine Monitoring</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Low Risk of Hemorrhage</td>
<td>+/-</td>
<td>+/-</td>
</tr>
<tr>
<td>Use in Severe Liver Disease</td>
<td>-</td>
<td>?</td>
</tr>
<tr>
<td>Use in Severe Renal Disease</td>
<td>+</td>
<td>?</td>
</tr>
<tr>
<td>Available Antidote</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Inexpensive</td>
<td>+</td>
<td>-</td>
</tr>
</tbody>
</table>

PK/PD: Pharmacokinetics/Pharmacodynamics


Old and **New** Anticoagulants

- **Unfractionated heparin (UFH)**
- **Low-molecular weight heparin (LMWH)**
  - Enoxaparin (Lovenox)
  - Dalteparin (Fragmin)
- **Indirect anti-Xa Inhibitors**
  - Fondaparinux (Arixtra)
- **Direct anti-Xa Inhibitors**
  - Rivaroxaban (Xarelto)
  - Apixiban (Eliquis)
  - Edoxaban (Savaysa)
  - Betrixaban
    - Phase III clinical trials
- **Direct Thrombin Inhibitors**
  - Bivalrudin (Angiomax)
  - Lepirudin (Refludan)
  - Argatroban
  - Ximelagatran (Exanta)
    - Did not gain FDA approval
  - **Dabigatran (Pradaxa)**
- **Vitamin K Antagonists**
  - Warfarin (Coumadin)
  - Tecafarin
    - Phase III clinical trials

*Italicized* = parenteral route
**Indirect Anti-Xa Inhibitors**
- LMWH, UFH, fondaparinux

**Direct Anti-Xa Inhibitors**
- Rivaroxaban, apixiban, edoxaban

**Vitamin K Antagonists**
- Warfarin
- Tecafarin

**FDA Approval Timeline**

- Dabigatran Approved for A-Fib: 10/19/2010
- Rivaroxaban Approved for VTE Prophylaxis: 3/14/2014
- Apixaban Approved for VTE Prophylaxis: 3/14/2014
- Dabigatran Approved for DVT/PE Treatment: 4/7/2014
- Rivaroxaban Approved for DVT/PE Treatment: 11/2/2012
- Apixaban Approved for A-Fib and DVT/PE Treatment: 8/21/2014
- Apixaban Approved for DVT/PE Treatment: 8/21/2014
- Edoxaban Approved for A-Fib and DVT/PE Treatment: 8/21/2015

### FDA Approved Oral Anticoagulants

<table>
<thead>
<tr>
<th>Generic (Brand)</th>
<th>Class</th>
<th>Cost/month (AWP)*</th>
<th>Dosing Freq.</th>
<th>FDA Approved Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin (Coumadin)</td>
<td>Vitamin K Antagonist</td>
<td>~$80** with monitoring</td>
<td>Daily</td>
<td>A-fib, including valvular VTE Prevention, DVT/PE Treatment/Recurrence, 2nd MI Prevention</td>
</tr>
<tr>
<td>Dabigatran (Pradaxa)</td>
<td>Direct Thrombin Inhibitor</td>
<td>$377.64</td>
<td>BID</td>
<td>Non-valvular A-fib DVT/PE Treatment/Recurrence</td>
</tr>
<tr>
<td>Rivaroxaban (Xarelto)</td>
<td>Factor Xa Inhibitor</td>
<td>$377.64 (starter pack: $1641.99)</td>
<td>Daily</td>
<td>Non-valvular A-fib VTE Prevention (THR/TKR), DVT/PE Treatment/Recurrence</td>
</tr>
<tr>
<td>Apixiban (Eliquis)</td>
<td>Factor Xa Inhibitor</td>
<td>$377.99</td>
<td>BID</td>
<td>Non-valvular A-fib VTE Prevention (THR/TKR), DVT/PE Treatment/Recurrence</td>
</tr>
<tr>
<td>Edoxaban (Savaysa)</td>
<td>Factor Xa Inhibitor</td>
<td>$332.64</td>
<td>Daily</td>
<td>Non-valvular A-fib DVT/PE Treatment</td>
</tr>
</tbody>
</table>

** Pharmacist’s/Prescriber’s Letter
AWP: Average Wholesale Price; AF: Atrial Fibrillation; VTE: Venous Thromboembolism; THR: Total Hip Replacement; TKR: Total Knee Replacement; DVT: Deep Vein Thrombosis; PE: Pulmonary Embolism

### Pharmacokinetics and Pharmacodynamics

<table>
<thead>
<tr>
<th>Property</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>MOA</td>
<td>Direct IIa Inhibitor</td>
<td>Direct Xa Inhibitor</td>
<td>Direct Xa Inhibitor</td>
<td>Direct Xa Inhibitor</td>
</tr>
<tr>
<td>Bioavailability</td>
<td>3-7%</td>
<td>80%</td>
<td>50%</td>
<td>62%</td>
</tr>
<tr>
<td>Tmax</td>
<td>1-6 hours</td>
<td>2-4 hours</td>
<td>2-4 hours</td>
<td>1-2 hours</td>
</tr>
<tr>
<td>T½</td>
<td>12-17 hours 15-34h (↓ renal)</td>
<td>5-12 hours 11-19h (elderly)</td>
<td>7-15 hours</td>
<td>10-14 hours</td>
</tr>
<tr>
<td>Hepatic metabol</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Minimal</td>
</tr>
<tr>
<td>Drug Interactions</td>
<td>P-gp</td>
<td>CYP3A4</td>
<td>CYP3A4, P-gp</td>
<td>P-gp</td>
</tr>
<tr>
<td>Protein Binding</td>
<td>35%</td>
<td>92%</td>
<td>87%</td>
<td>55%</td>
</tr>
<tr>
<td>Dialyzable</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Measurement</td>
<td>ECT, TT</td>
<td>Anti-Xa, PT, aPTT</td>
<td>Anti-Xa, PT, aPTT</td>
<td>Anti-Xa, PT, aPTT</td>
</tr>
<tr>
<td>Renal Elimination</td>
<td>80%</td>
<td>35%</td>
<td>27%</td>
<td>50%</td>
</tr>
<tr>
<td>Renal Dosing</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes?</td>
<td>Yes</td>
</tr>
<tr>
<td>Antidote</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

Monitoring

• No routine lab monitoring for level of anticoagulation
  – Factor Xa inhibitors: anti-Xa, PT, or aPTT but no clear goals
  – Direct Thrombin inhibitors: ECT (ecarin clotting time) or TT (thrombin time) but no clear goals

• Safety Monitoring
  – Baseline: CBC, Scr, LFTs, PT, aPTT
  – q12months: CBC, Scr, LFTs
  – q6months: Scr if CrCl 30-60mL/min, elderly, fragile
  – q3months: Scr if CrCl 15-30mL/min

• S/sx VTE or bleeding
• Concurrent medications
• Adherence

Drug Interactions

• More drugs interact than outlined in the product labeling
• EHRA guidelines provide useful information on increases in AUC based on available data
  – Product specific whether to reduce dose or not recommended

<table>
<thead>
<tr>
<th>Strong P-gp Inhibitors</th>
<th>Strong CYP3A4 Inhibitors</th>
<th>Strong P-gp and CYP3A4 Inducers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ketoconazole</td>
<td>Ketoconazole</td>
<td>Rifampin</td>
</tr>
<tr>
<td>Dronaderone</td>
<td>Dronaderone</td>
<td>St. John’s Wort</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>Amiodarone</td>
<td>Carbamazepine</td>
</tr>
<tr>
<td>Verapamil</td>
<td>Clarithromycin</td>
<td>Phenytoin</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>Erythromycin</td>
<td>Phenobarbital</td>
</tr>
<tr>
<td>Erythromycin</td>
<td></td>
<td>Ritonavir</td>
</tr>
</tbody>
</table>

Transitioning from Warfarin to NOAC

**Label Recommendations**

- Start when INR < 3  
  - Rivaroxaban
- Start when INR ≤ 2.5  
  - Edoxaban
- Start when INR < 2  
  - Dabigatran  
  - Apixaban

**Practical Recommendations**

- A-Fib or Acute VTE  
  - Assess thrombotic vs. bleeding risk  
    - E.g. CHA₂DS₂-VASC and HAS-BLED
- INR > 2.5  
  - Consider actual INR and warfarin t½  
  - Check INR when suspect ≤ 2.5
- INR 2 – 2.5  
  - Start now or next day
- INR < 2  
  - Start now

---

Which oral anticoagulants are FDA approved for stroke prevention in non-valvular A-Fib? (choose all that apply)

A. Warfarin (Coumadin)  
B. Dabigatran (Pradaxa)  
C. Rivaroxaban (Xarelto)  
D. Apixaban (Eliquis)  
E. Edoxaban (Savaysa)
# Major Clinical Trials

<table>
<thead>
<tr>
<th></th>
<th>Stroke Prophylaxis/AF</th>
<th>VTE Prevention</th>
<th>DVT/PE Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran (Pradaxa)</td>
<td>RE-LY</td>
<td>RE-NOVATE RE-MOBILIZE</td>
<td>RE-COVER I RE-COVER II</td>
</tr>
<tr>
<td></td>
<td></td>
<td>RE-MODEL</td>
<td>RE-MEDY</td>
</tr>
<tr>
<td>Rivaroxaban (Xarelto)</td>
<td>ROCKET-AF</td>
<td>RECORD 1-4</td>
<td>EINSTEIN DVT EINSTEIN PE</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>EINSTEIN EXT</td>
</tr>
<tr>
<td>Apixaban (Eliquis)</td>
<td>ARISTOTLE AVERROES</td>
<td>ADVANCE 1-3</td>
<td>AMPLIFY AMPLIFY EXT</td>
</tr>
<tr>
<td>Edoxaban (Savaysa)</td>
<td>ENGAGE AF – TIMI 48</td>
<td>STARS E-3 STARS J-5</td>
<td>HOKUSAI-VTE</td>
</tr>
<tr>
<td></td>
<td></td>
<td>STARS J-4</td>
<td></td>
</tr>
</tbody>
</table>

Adapted from Dobesh PP, Smythe MA. Handout. APhA Annual Meeting. San Diego (CA), March 2015.

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# Non-valvular A-Fib: Efficacy Evaluation from Clinical Trials

- **Prevention of stroke or systemic embolism:**
  - All agents at least non-inferior to warfarin
    - All FDA approved
  - Dabigatran and apixaban demonstrated superiority to warfarin
  - Rivaroxaban and edoxaban only demonstrated superiority to warfarin in per-protocol analysis

- **Hemorrhagic stroke**
  - All agents significantly better than warfarin

- **Ischemic stroke**
  - Only dabigatran significantly better than warfarin
Non-valvular A-Fib: Safety Evaluation from Clinical Trials

- Major bleeding
  - Apixaban and edoxaban significantly less than warfarin
  - No difference with dabigatran and rivaroxaban
- All cause mortality
  - Only apixaban significantly lower than warfarin ($p=0.01$)
  - All agents provide approximately 10% reduction in all cause mortality

Variability in A-Fib Clinical Trials

<table>
<thead>
<tr>
<th></th>
<th>RE-LY (Dabigatran)</th>
<th>ROCKET-AF (Rivaroxaban)</th>
<th>ARISTOTLE (Apixaban)</th>
<th>ENGAGE (Edoxaban)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>18,113</td>
<td>14,266</td>
<td>18,206</td>
<td>21,105</td>
</tr>
<tr>
<td>Dosing Frequency</td>
<td>BID</td>
<td>Daily</td>
<td>BID</td>
<td>Daily</td>
</tr>
<tr>
<td>Blinding</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>%VKA Naïve</td>
<td>50%</td>
<td>38%</td>
<td>43%</td>
<td>41%</td>
</tr>
<tr>
<td>Age (years)</td>
<td>71</td>
<td>73</td>
<td>70</td>
<td>72</td>
</tr>
<tr>
<td>Mean CHADS$_2$</td>
<td>2.2</td>
<td>3.5</td>
<td>2.1</td>
<td>2.8</td>
</tr>
<tr>
<td>CHADS$_2$ $\geq$ 3 (%)</td>
<td>32%</td>
<td>87%</td>
<td>30%</td>
<td>77%</td>
</tr>
<tr>
<td>% ASA ($&lt;165$mg)</td>
<td>40%</td>
<td>36%</td>
<td>30%</td>
<td>29%</td>
</tr>
<tr>
<td>Exclude DAPT</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

TTR: Time in therapeutic range; DAPT: dual antiplatelet therapy
Dosing in A-Fib

<table>
<thead>
<tr>
<th>Creatinine Clearance</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 95 mL/min</td>
<td>150mg BID</td>
<td>20mg daily</td>
<td>5mg BID</td>
<td>Avoid Use</td>
</tr>
<tr>
<td>51-95 mL/min</td>
<td></td>
<td>15mg daily</td>
<td>2.5mg BID if ≥ 2 of the following: Age ≥ 80, Weight ≤ 60kg, Scr ≥ 1.5mg/dL</td>
<td>60mg daily</td>
</tr>
<tr>
<td>31-50 mL/min</td>
<td></td>
<td>15mg daily</td>
<td></td>
<td>30mg daily** (may also use lower dose if weight ≤ 60kg or on P-gp inhibitor)</td>
</tr>
<tr>
<td>15-30 mL/min</td>
<td>75mg BID*</td>
<td></td>
<td></td>
<td>HD: 5mg BID* No HD: Avoid Use</td>
</tr>
<tr>
<td>&lt; 15 mL/min</td>
<td>Avoid Use</td>
<td>Avoid Use</td>
<td>HD: 5mg BID* No HD: Avoid Use</td>
<td>Avoid Use</td>
</tr>
</tbody>
</table>

*Dose based off pharmacokinetic modeling only (not studied in clinical trials)

** Dosing for CrCl 15-30ml/min based off pharmacokinetic modeling only (not studied in clinical trials)

---

Dosing in A-Fib

- **Dabigatran**
  - 150 mg twice daily for most patients
  - CrCl 15 to 30 mL/min – 75 mg twice daily

- **Rivaroxaban**
  - 20 mg once daily with food for most patients
  - CrCl 15 to 50 mL/min – 15 mg once daily with food

- **Apixaban**
  - 5 mg twice daily for most patients
  - Patients with 2 or more of the following: age ≥ 80 years, weight ≤ 60 kg, SCR ≥ 1.5 mg/dL – 2.5 mg twice daily

- **Edoxaban**
  - 60 mg once daily if CrCl > 50 to ≤ 95 mL/min
  - CrCl > 95 mL/min – avoid use
  - 30 mg once daily if patient has CrCl 15 to 50 mL/min, weight ≤ 60 kg or use of certain p-glycoprotein inhibitors

---

*Tiffany R. Shin, PharmD, BCACP

**New Oral Anticoagulants**

Family Medicine Spring Symposium

April 10, 2015
AHA/ACC/HRS 2014 Stroke Prevention in AF
Select Guideline Recommendations

• CHA₂DS₂-VASc score ≥ 2 OAC Therapy:
  – Warfarin (INR 2-3) [Class I; Level A]
  – Direct thrombin inhibitor (dabigatran) [Class I; Level B]
  – Factor Xa inhibitor (rivaroxaban, apixaban) [Class I; Level B]

• Dabigatran should not be used in patient with AF and a mechanical heart valve (Harm) [Class III; Level B]

• Patients unable to maintain a therapeutic INR on warfarin should receive dabigatran, rivaroxaban, or apixaban [Class I; Level C]

• Renal function should be evaluated prior to and annually with dabigatran, rivaroxaban, or apixaban [Class I, Level B]

• CHA₂DS₂-VASc score ≥ 2 and moderate-severe CKD, it is reasonable to consider reduced doses of dabigatran, rivaroxaban, or apixaban, but safety and efficacy have not been established [Class IIb, Level C]

• Dabigatran and rivaroxaban are not recommended in patients with AF and end-stage CKD or on hemodialysis due to lack of clinical trial evidence (no benefit) [Class III; Level C]


Which oral anticoagulants are FDA approved for VTE prevention after hip or knee replacement surgery?
(choose all that apply)

A. Warfarin (Coumadin)
B. Dabigatran (Pradaxa)
C. Rivaroxaban (Xarelto)
D. Apixaban (Eliquis)
E. Edoxaban (Savaysa)
Major Clinical Trials

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</tr>
<tr>
<td></td>
<td></td>
<td>RE-MOBILIZE</td>
<td>RE-COVER II</td>
</tr>
<tr>
<td></td>
<td></td>
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<td>RE-MEDY</td>
</tr>
<tr>
<td>Rivaroxaban (Xarelto)</td>
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<td>RECORD 1-4</td>
<td>EINSTEIN DVT</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>EINSTEIN PE</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
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<td></td>
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</tr>
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<td></td>
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<td></td>
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</tbody>
</table>

Adapted from Dobesh PP, Smythe MA. Handout. APhA Annual Meeting. San Diego (CA), March 2015.

VTE Prevention in THR or TKR Evaluation from Clinical Trials

- **Dabigatran (150mg or 220mg daily)**
  - THR: non-inferior to enoxaparin 40mg daily
  - TKR: non-inferior to enoxaparin 40mg daily, but inferior to enoxaparin 30mg q12h
  - Similar rates of major bleeding
  - NOT FDA APPROVED

- **Rivaroxaban (10mg daily)**
  - THR: Superior to enoxaparin 40mg daily
  - TKR: Superior to enoxaparin 40mg daily and 30mg q12h
  - Similar rate of major bleeding

- **Apixaban (2.5mg BID)**
  - THR: Superior to enoxaparin 40mg daily
  - TKR: Superior to enoxaparin 40mg daily and non-inferior to enoxaparin 30mg q12h
  - Significantly less major bleeding
Dosing VTE Prevention

- Dabigatran
  - Study doses 150mg or 220mg daily
  - Not FDA Approved
- Rivaroxaban
  - Beginning at least 6-10 hours after surgery
  - THR: 10mg once daily for 35 days
  - TKR: 10mg one daily for 12 days
- Apixaban
  - Beginning at least 12-24 hours after surgery
  - THR: 2.5mg BID for 35 days
  - TKR: 2.5mg BID for 12 days
- Edoxaban
  - Not FDA Approved

Which oral anticoagulants are FDA approved for DVT/PE treatment?
(choose all that apply)

A. Warfarin (Coumadin)
B. Dabigatran (Pradaxa)
C. Rivaroxaban (Xarelto)
D. Apixaban (Eliquis)
E. Edoxaban (Savaysa)
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<td></td>
<td></td>
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</tr>
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<td></td>
<td></td>
<td>EINSTEIN PE</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>EINSTEIN EXT</td>
</tr>
<tr>
<td>Apixaban (Eliquis)</td>
<td>ARISTOTLE AVERROES</td>
<td>ADVANCE 1-3</td>
<td>AMPLIFY</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>AMPLIFY EXT</td>
</tr>
<tr>
<td>Edoxaban (Savaysa)</td>
<td>ENGAGE AF – TIMI 48</td>
<td>STARS E-3</td>
<td>HOKUSAI-VTE</td>
</tr>
<tr>
<td></td>
<td></td>
<td>STARS J-5</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>STARS J-4</td>
<td></td>
</tr>
</tbody>
</table>

Adapted from Dobesh PP, Smythe MA. Handout. APhA Annual Meeting, San Diego (CA), March 2015.

DVT/PE Treatment: Efficacy Evaluation from Clinical Trials

- First recurrent VTE or death compared to conventional therapy for:
  - Tx of acute DVT/PE: all non-inferior
  - Prevention of recurrent DVT/PE:
    - Apixaban and rivaroxaban superior
    - Dabigatarn non-inferior
    - Edoxaban study >12 months not complete
DVT/PE Treatment: Safety Evaluation from Clinical Trials

• Major bleeding compared to conventional therapy
  – Rivaroxaban for PE, apixaban, and edoxaban significantly less
  – Dabigatran and rivaroxaban for DVT had similar rates

• First episode of major or clinically relevant non-major bleeding compared to conventional therapy
  – Dabigatran, apixaban (acute), and edoxaban significantly less
  – Rivaroxaban and apixaban (extension) had similar rates

Dosing DVT/PE Treatment or Prevention of Recurrence

• Dabigatran
  – 150mg BID after 5-10 days of parenteral anticoagulation

• Rivaroxaban
  – 15mg BID x 21 days, then 20mg daily

• Apixaban
  – 10mg BID x 7 days, then 5mg BID
    • Dose may be further decreased to 2.5mg BID after 6 months

• Edoxaban
  – 60mg daily after 5-10 days parenteral anticoagulation
  – 30mg daily after 5-10 days parenteral anticoagulation, if CrCl 15-30mL/min, weight ≤ 60kg, or on certain P-gp inhibitors (e.g. ketoconazole, dronedarone, clarithromycin)
Regular Adult Dosing for Oral Anticoagulation

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke prophylaxis in A-Fib (non-valvular)</td>
<td>150mg BID</td>
<td>20mg daily w/ food</td>
<td>5mg BID</td>
<td>60mg daily (CrCl &lt;95mL/min)</td>
</tr>
<tr>
<td>VTE Prophylaxis after Total Knee Replacement</td>
<td>Not FDA Approved</td>
<td>10mg daily for 12 days</td>
<td>2.5mg BID for 12 days</td>
<td>Not FDA Approved</td>
</tr>
<tr>
<td>VTE Prophylaxis after Total Hip Replacement</td>
<td>Not FDA Approved</td>
<td>10mg daily for 35 days</td>
<td>2.5mg BID for 35 days</td>
<td>Not FDA Approved</td>
</tr>
<tr>
<td>DVT/PE Treatment</td>
<td>150mg BID (following 5-10 days of parenteral anticoagulation)</td>
<td>15mg BID for 3 wks, then 20mg daily w/ food</td>
<td>10mg BID for 7 days, then 5mg BID</td>
<td>60mg daily (following 5-10 days of parenteral anticoagulation)</td>
</tr>
<tr>
<td>DVT/PE Prevention of Recurrence</td>
<td>150mg BID</td>
<td>20mg daily w/ food</td>
<td>2.5mg BID</td>
<td>60mg daily (Not specifically approved)</td>
</tr>
</tbody>
</table>


Evidence (or Lack of) for Off-Label Use

- **Mechanical Heart Valves**
  - RE-ALIGN Study: Dabigatran vs. Warfarin
    - Increased risk of thromboembolism and bleeding in dabigatran group
    - Recommend against use
  - Evidence lacking for all other agents

- **Cardioversion**
  - Sub-analysis of major clinical trials for dabigatran, rivaroxaban, and apixaban showed similar outcomes to warfarin
    - Included anticoagulation for at least 3 wks prior and 4 wks after and/or TEE prior to cardioversion
    - Lacks power, not primary outcome
  - No studies regarding edoxaban

Evidence (or Lack of) for Off-Label Use

• Cancer
  – Dabigatran or warfarin in patients with VTE and cancer study
    • Pooled analysis of 2 studies
    • No difference in bleeding or VTE occurrence but did not compare to LMWH; LMWH better at preventing VTE than warfarin in cancer
  – Evidence lacking (<6% of clinical trial patients)

• Bridging agent (in place of LMWH or UF) with warfarin
  – All agents can increase INR an unknown amount
  – Evidence lacking

Management of Severe Bleeding

• Stop anticoagulant
• Compress bleed, if possible
• Fluid replacement, transfusion
• Consider:
  – Hemodialysis (dabigatran only)
  – Activated charcoal
  – Fresh frozen plasma (FFP)
  – Prothrombin complex concentrate (PCC) or aPCC (FEIBA)
  – Recombinant Factor VIIa (NovoSeven)

No proven reversal agent or antidote available yet
Via Christi Anticoagulation Reversal
Order Set

RIVAROXABAN REVERSAL
- Discontinue rivaroxaban
- Treatment should only be given if the patient is actively bleeding (select one and then reevaluate)
  - Fresh frozen plasma 3 units x1
  - Prothrombin complex concentrate 50 units/kg IV x1
    (see PCC orders VC-2179 and MAG for more information)
    OR
  - Recombinant Factor VIIa 20 mcg/kg x1 and fresh frozen plasma 3 units x1

DABIGATRAN REVERSAL
- Discontinue dabigatran
- Acute hemodialysis is preferred treatment of overdose (2-3 hours will remove approximately 60% dabigatran)
- Treatment should only be given if the patient is actively bleeding (select one and then reevaluate)
  - Fresh frozen plasma 3 units x1
  - Prothrombin complex concentrate 50 units/kg IV x1
    (see PCC orders VC-2179 and MAG for more information)
    OR
  - Recombinant Factor VIIa 20 mcg/kg x1 and fresh frozen plasma 3 units x1

Reversal Agents in the Pipeline

- Aripazine (PER977, ciraparantag)
  - Synthetic small molecule (D-arginine compound), binds factor Xa and factor IIa
  - May reverse: Heparin, LMWH, and all NOAC
  - Healthy volunteer study

- Andexanet (PRT064445), r-Antidote
  - Recombinant, modified factor Xa molecule which binds to factor Xa inhibitors
  - May reverse: Factor Xa inhibitors
  - Healthy volunteer study

- Idarucizumab (BI 655075), aDabi-Fab
  - Humanized antibody fragment directed against dabigatran
  - May reverse: Dabigatran
  - Phase III study is ongoing

Agent Specific
Clinical Pearls/Counseling Points

<table>
<thead>
<tr>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Potential ↑ risk MI</td>
<td>• Increased risk of VTE if stopped abruptly</td>
<td>• May have least bleeding risk of NOACs (but no head to head)</td>
<td>• Newest agent, no clear benefit over other NOACs</td>
</tr>
<tr>
<td>• Dialyzable</td>
<td>• Take doses &gt;10mg with food</td>
<td>• Hemodialysis dosing available</td>
<td>• Avoid use if normal-above normal renal function (CrCl &gt;95mL/min)</td>
</tr>
<tr>
<td>• Bridge with parenteral therapy for DVT/PE tx</td>
<td>• Food ↑ bioavailability</td>
<td>• BID dosing available</td>
<td>• Bridge with parenteral therapy for DVT/PE tx</td>
</tr>
<tr>
<td>• BID dosing, with or without food</td>
<td>• May crush tablets immediately before use and mix with apple sauce</td>
<td>• BID dosing with or without food</td>
<td>• Daily dosing with or without food</td>
</tr>
<tr>
<td>• More GI side effects than other agents</td>
<td>• No GI</td>
<td>• No pill boxes!</td>
<td>• No head-to-head studies; choose agent based on patient-specific factors</td>
</tr>
<tr>
<td>• Swallow whole</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Must be kept in original container</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

No head-to-head studies; choose agent based on patient-specific factors

FDA Approved Oral Anticoagulants

<table>
<thead>
<tr>
<th>Generic (Brand)</th>
<th>Class</th>
<th>Cost/month (AWP)*</th>
<th>Dosing Freq.</th>
<th>FDA Approved Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin (Coumadin)</td>
<td>Vitamin K Antagonist</td>
<td>~$80** with monitoring</td>
<td>Daily</td>
<td>A-fib, including valvular VTE Prevention DVT/PE Treatment/Recurrence 2nd MI Prevention</td>
</tr>
<tr>
<td>Dabigatran (Pradaxa)</td>
<td>Direct Thrombin Inhibitor</td>
<td>$377.64</td>
<td>BID</td>
<td>Non-valvular A-fib DVT/PE Treatment/Recurrence</td>
</tr>
<tr>
<td>Rivaroxaban (Xarelto)</td>
<td>Factor Xa Inhibitor</td>
<td>$377.64 (starter pack: $1641.99)</td>
<td>Daily</td>
<td>Non-valvular A-fib VTE Prevention (THR/TKR) DVT/PE Treatment/Recurrence</td>
</tr>
<tr>
<td>Apixiban (Eliquis)</td>
<td>Factor Xa Inhibitor</td>
<td>$377.99</td>
<td>BID</td>
<td>Non-valvular A-fib VTE Prevention (THR/TKR) DVT/PE Treatment/Recurrence</td>
</tr>
<tr>
<td>Edoxaban (Savaysa)</td>
<td>Factor Xa Inhibitor</td>
<td>$332.64</td>
<td>Daily</td>
<td>Non-valvular A-fib DVT/PE Treatment</td>
</tr>
</tbody>
</table>

**Pharmacist’s/Prescriber’s Letter
AWP: Average Wholesale Price; AF: Atrial Fibrillation; VTE: Venous Thromboembolism; THR: Total Hip Replacement; TKR: Total Knee Replacement; DVT: Deep Vein Thrombosis; PE: Pulmonary Embolism
Good candidates for New Oral Anticoagulants

• Reason for anticoagulation is FDA approved
  – Recommend against prescribing off-label
    • If using off-label\textarrow{\textbullet} DOCUMENT!!
• Poor control with warfarin in the past not due to adherence problems
• Taking many drugs that interact with warfarin (especially intermittent administration)
• Patient can afford new agents
  – Insurance with reasonable co-pay

Poor candidates for New Oral Anticoagulants

• Reason for anticoagulation besides FDA approved indications
• Relatively stable on warfarin with no problems
• Taking strong P-gp or CYP3A4 inhibitors/inducers
  – May manage by decreasing dose, but some medications contraindicated
• Unable to afford new agents
• Non-adherent patients
• High bleeding risk??
  – Apixaban may be best
  – Avoid in dual antiplatelet therapy
• High fall risk??
New Oral Anticoagulants

Tiffany R. Shin, PharmD, BCACP
Clinical Assistant Professor
University of Kansas School of Pharmacy

ADDITIONAL SLIDES
Transitioning from NOAC to Warfarin

- Dabigatran
  - CrCl > 50mL/min: initiate warfarin 3 days before D/C dabigatran
  - CrCl 30-50mL/min: initiate warfarin 2 days before D/C dabigatran
  - CrCl 15-30mL/min: initiate warfarin 1 day before D/C dabigatran
  - CrCl <15mL/min: no recommendation available

- Rivaroxaban and Apixaban
  - Discontinue NOAC, start parenteral anticoagulation plus warfarin, D/C parenteral anticoagulant when warfarin INR therapeutic
  - OR may initiate warfarin 3-5 days before D/C rivaroxaban or apixaban

- Edoxaban
  - Decrease dose 50%, start warfarin and continue edoxaban until INR >2
  - OR may D/C edoxaban and use parenteral anticoagulant to transition

Holding NOAC Prior to Procedures

- Dabigatran
  - CrCl >50mL/min: hold 1-2 days prior
  - CrCl <50mL/min: hold 3-5 days prior

- Rivaroxaban and Edoxaban
  - Hold 24 hours prior to procedure

- Apixaban
  - High risk bleed: hold 48 hours prior
  - Low risk bleed: hold 24 hours prior

- Restart NOAC as soon as patient is stabilized, may use parenteral anticoagulants if unable to take orally