Oral Anticoagulants: What’s New?

Sallie Young, Pharm.D., BCPS (AQ-Cardiology)
Clinical Pharmacy Specialist, Cardiology
Penn State Hershey Medical Center
syoung1@hmc.psu.edu
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Conflict of Interest Disclosure

Lexi-Comp
  – Content Consultant
Oral Anticoagulant Uses

• Multiple reasons for oral anticoagulant use
  – VTE prophylaxis
  – Atrial fibrillation/flutter
  – VTE - pulmonary embolism (PE) and/or deep vein thrombosis (DVT)
  – Mechanical heart valves or ventricular assist devices
  – Hypercoagulable states
Ideal Characteristics of a New Oral Anticoagulant

- Multiple indications
- Once daily dosing
- No drug interactions
- No dietary restrictions
- Antidote availability
- Inexpensive

- Predictable response
- Wide therapeutic window
- No monitoring required
- Does not cross placenta or into breast milk
Oral Anticoagulation Options

• Until recently warfarin was only oral anticoagulant available in US

• Required patient education on…
  • Medication and diet consistency
  • Frequency of INR monitoring
  • Use of multiple tablet sizes
  • Alternating doses on different days
  • And much more!

Image accessed 3/27/12 from http://www.nongnu.org/ratpoison/ratpoison.png
Poor Adherence to Therapy

- Of 125,195 Canadian patients >65 years old starting warfarin for AFib over 13 year period:
  - 8.9% did not fill a second warfarin prescription
  - 31.8% discontinued therapy within a year
  - 43.2% discontinued therapy within 2 years
  - 61.3% discontinued therapy within 3 years
- Median time to discontinuation 2.9 years

Gomes et al. *Arch Intern Med* Published online: 10/22/12. doi:10.1001/archinternmed.2012.4485
Current US Anticoagulation Options

- Warfarin (Coumadin®)
- Dabigatran (Pradaxa®) – Approved 2010
- Rivaroxaban (Xarelto®) – Approved 2011
- Apixaban (Eliquis®) – Approved 2012

Will edoxaban (Lixiana) be approved in 2014??
Clotting Cascade

**Factor Xa Inhibitors** – rivaroxaban, apixaban

**Vitamin K Antagonist** (factors 2, 7, 9, 10, protein C and S) - Warfarin

**Direct Thrombin Inhibitor** - dabigatran

Review of Newly Approved Oral Anticoagulants
Dabigatran Etexilate

- Dabigatran etexilate is a prodrug rapidly converted to the active form, dabigatran, in the body
- Reversible, direct thrombin inhibitor
  - Inhibits formation of thrombin (factor IIa) therefore preventing formation of fibrin clots
  - Inhibits free and clot bound thrombin as well as thrombin-induced platelet aggregation

Dabigatran Uses

• FDA approved indication
  – Reduction in the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation

• Potential future uses
  – Treatment of venous thromboembolism (VTE, including deep vein thrombosis and pulmonary embolism)
  – Prevention of VTE after orthopedic surgery, such as hip and knee replacement*

Dabigatran Pharmacokinetics

• Onset of activity within 2 hours
• Low bioavailability (3-7%)
• Half-life 12-17 hours (in healthy pts)
• No involvement of the CYP450 system however is a p-glycoprotein substrate
• Cleared renally primarily as glucuronide acid conjugate
• Prolongs aPTT in non-linear fashion

Pradaxa Prescribing Information. April 2013.
Dabigatran Elimination

• As renal function declines, the half-life of the drug increases

<table>
<thead>
<tr>
<th>Renal Function (CrCl)</th>
<th>Dabigatran Half Life</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal (~80 mL/min)</td>
<td>12-17 hours (14-17 hours in elderly)</td>
</tr>
<tr>
<td>Mild - Moderate impairment</td>
<td>15-18 hours</td>
</tr>
<tr>
<td>(30-50 mL/min)</td>
<td></td>
</tr>
<tr>
<td>Severe impairment</td>
<td>28 hours</td>
</tr>
<tr>
<td>(&lt;30 mL/min)</td>
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</tr>
</tbody>
</table>

**Dabigatran Atrial Fibrillation Dosing**

- **Usual dose:** 150 mg orally twice daily
- **Reduce** to 75 mg orally twice daily* when
  - CrCl 15-30 mL/min
  - *Consider if* CrCl 30-50 mL/min + p-glycoprotein inhibitors (dronedarone or oral ketoconazole)
- **Avoid** in patients with
  - CrCl <15 mL/min or those on dialysis
  - CrCl 15-30 mL/min + p-glycoprotein inhibitors

*Renal dosing based on pharmacokinetic analysis (not patient data) at time of FDA approval. Pradaxa Prescribing Information. April 2013.
Dabigatran

- Monitoring: Routine laboratory testing is not necessary
- Diet interactions
  - None - vitamin K intake has no effect
  - May be taken with or without food
- Capsules may not be opened as the drug bioavailability increases by 75%!
  - Should not be administered via feeding tube or with applesauce/pudding
Dabigatran Adverse Effects

- Similar incidence of bleeding to warfarin
  - Major bleeding was not significantly different when compared to warfarin in RE-LY trial
  - Increased gastrointestinal bleeding (dose dependant)

- Gastrointestinal upset
  - Incidence higher (35%) than with warfarin (24%)
  - Dyspepsia, abdominal pain, GERD, esophagitis, erosive gastritis, gastrointestinal ulcer

Dabigatran Drug Interactions

- Does not involve CYP450 enzymes in the liver
- P-glycoprotein inducers (ex. rifampin) - decrease dabigatran levels/efficacy; Product labeling says: “Generally Avoid”
- P-glycoprotein inhibitors (ketoconazole, dronedarone) increase dabigatran levels/toxicity
- Use with other antiplatelet medications, including NSAIDs - increases bleeding risk due to thrombin-induced platelet aggregation

Pradaxa Prescribing Information. April 2013.
Dabigatran Safety Considerations

- Should be swallowed whole - cannot be given via feeding tube
- Absorption after gastric bypass?
- Pregnancy category C
- Not appropriate for use in patients with mechanical heart valves – 2 cases of thrombosed valves in literature

Rivaroxaban (Xarelto)

- Factor Xa inhibitor
  - Highly selective
- Exerts activity by blocking the active site on factor Xa
  - Does not require cofactor (such as antithrombin)
  - Inhibits free and clot-associated factor Xa
Rivaroxaban Uses

FDA Approved Indications

• Prophylaxis of deep vein thrombosis (DVT), which may lead to pulmonary embolism (PE) in patients who are undergoing knee or hip replacement surgery

• Prevention of stroke or systemic embolism in non-valvular atrial fibrillation patients

• Treatment of DVT, PE, and Reduction in the Risk of Recurrence of DVT and of PE
Rivaroxaban Pharmacokinetics

• Onset of activity 2-4 hours
• Bioavailability >80% for 10 mg, 66% for 20 mg
  – Food increases bioavailability (↑ 39% mean AUC)
• Half-life 5-9 hours (elderly 9-12 hrs)
• Highly and reversibly bound to plasma proteins
• Undergoes CYP450 metabolism (3A4/5 and 2J2 substrate) but no circulating metabolites
  – P-glycoprotein and ABCG2 substrate
• Excreted via renal (66%) and non-renal (28%) mechanisms

ACCP CHEST Guidelines 9th Ed. CHEST 2012;141:e44S-e88S.
Rivaroxaban for VTE Prophylaxis

- Prophylaxis of DVT/PE in adult patients undergoing hip and knee replacement surgery
  - CrCl ≥30 ml/min: 10 mg PO once daily
  - CrCl <30 mL/min or dialysis: Avoid use
  - Initial dose should be taken at least 6 to 10 hours after surgery once hemostasis has been established
    - Caution with epidural/spinal anesthesia catheter placement/removal or if traumatic puncture
  - Duration: 35 days after THR, 12 days for TKR

Xarelto Prescribing Information. August 2013.
Rivaroxaban for Atrial Fibrillation

• Prevention of stroke or systemic embolism in non-valvular atrial fibrillation patients
  – CrCl >50 ml/min: 20 mg po once daily with the evening meal
  – CrCl 15-50 ml/min: 15 mg po once daily with the evening meal
  – CrCl<15 mL/min or dialysis: AVOID USE

Xarelto Prescribing Information. August 2013.
Rivaroxaban for VTE Treatment

- Treatment of DVT, PE, and Reduction in the Risk of Recurrence of DVT and of PE: **15 mg orally twice daily** with food for the **first 21 days** for the initial treatment of acute DVT or PE
- After the initial treatment period, **20 mg orally once daily** with food for the remaining treatment and the long-term reduction in the risk of recurrence of DVT and of PE
  - Labeling recommends to avoid use in pts with CrCl <30 mL/min!

Xarelto Prescribing Information. August 2013.
Rivaroxaban Drug Interactions

• CYP3A4/P-glycoprotein (P-gp) inducers
  – AVOID, significant ↓ in AUC & Cmax; lower efficacy
  – Examples: carbamazepine, phenytoin, rifampin, St. John's wort

• CYP3A4/P-gp inhibitors
  – AVOID, significant ↑ in AUC & Cmax; toxicity
  – Examples: ketoconazole, itraconazole, ritonavir, conivaptan

• Concomitant use of antiplatelet agents
  – ↑ bleeding time

Xarelto Prescribing Information. August 2013.
Rivaroxaban ADRs

• Similar bleeding to warfarin
  – Similar incidence of major and nonmajor clinically relevant bleeding to warfarin in ROCKET-AF trial
  – Intracranial hemorrhage 0.8% vs. 1.2% in warfarin group (p=0.02)
  – Critical and fatal bleeding significantly less in rivaroxaban patients

• Non-bleeding: wound secretion, extremity pain, muscle spasm, syncope, pruritis and blisters

Xarelto Prescribing Information. August 2013.
Rivaroxaban

• No interaction with PF-4 so appears safe in pts with history of HIT
• Pregnancy category C

Apixaban (Eliquis)

• Factor Xa inhibitor
  – Highly selective

• Exerts activity by blocking the active site on factor Xa
  – Does not require cofactor (such as antithrombin)
  – Inhibits free and clot-associated factor Xa
Apixaban Uses

- Received approval 12/28/12
- FDA Approved Indication
  - To reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation

Eliquis Prescribing Information. December 2012.
Apixaban Pharmacokinetics

- Onset of activity 1-3 hours
- Bioavailability ~50%; no affect with food
- Half-life ~12 hours
- Protein binding 87%, Vd ~21 liters
- CYP450 3A4 metabolism
- P-glycoprotein substrate
- Primarily hepatic (45-55%) metabolism; 27% renal

Apixaban for Atrial Fibrillation

- **Recommended dose**: 5 mg twice daily
  - *Reduce* dose to 2.5 mg twice daily in patients with any two of the following risk factors:
    - Age $\geq$ 80 years
    - Body weight $\leq$ 60 kg
    - Serum creatinine $\geq$ 1.5 mg/dL

- **Contraindicated in patients if**
  - CrCl $<$ 15 mL/min or dialysis, or
  - Severe hepatic dysfunction
Apixaban Drug Interactions

• If concomitant use of strong dual inhibitors of CYP 3A4 & p-glycoprotein
  • Examples: ketoconazole, itraconazole, ritonavir, clarithromycin
    – *Reduce* dose to 2.5 mg twice daily
    – *AVOID* if patient has 2 of the following risk factors:
      • Age ≥80 years
      • Body weight ≤60 kg
      • Serum creatinine ≥1.5 mg/dL

Eliquis Prescribing Information. December 2012.
Apixaban Drug Interactions

• CYP3A4/P-glycoprotein (P-gp) inducers
  – AVOID, significant ↓ in AUC & Cmax; lower efficacy
  – Examples: carbamazepine, phenytoin, rifampin, St. John's wort

• Concomitant use of antiplatelet agents
  – ↑ bleeding time
Apixaban

Adverse Effects

• Significantly less bleeding than warfarin
  – In ARISTOTLE trial where apixaban was compared to
    warfarin, major bleeding as well as clinically relevant
    nonmajor bleeding was identified in significantly less
    patients on apixaban

• Hypersensitivity reaction, syncope
  – Both reported in <0.1% patients

Pregnancy category B

Eliquis Prescribing Information. December 2012.
Medication Safety Issues with Factor Xa Inhibitors

• Dosing varies based on indication and level of renal impairment
  – Contraindicated with any type of dialysis
• Identification of dosing with drug interactions
• Timing of dose(s)
  – Rivaroxaban for AFib is with evening meal and if ordered as “daily”, default is 1700
• Not all factor Xa inhibitors can it be crushed and administered via feeding tube (drug dependant)
• Challenges related to epidural/spinal therapy management
Relevant Clinical Trials
### Approved Indications

<table>
<thead>
<tr>
<th>Indication</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke and systemic embolism prevention in nonvalvular AF</td>
<td>US, E, C</td>
<td>US, E, C</td>
<td>US, E, C</td>
</tr>
<tr>
<td>VTE prevention in THA</td>
<td>E, C</td>
<td>US, E, C</td>
<td>E, C</td>
</tr>
<tr>
<td>VTE prevention in TKA</td>
<td>E, C</td>
<td>US, E, C</td>
<td>E, C</td>
</tr>
<tr>
<td>DVT/PE treatment</td>
<td></td>
<td>US, E, C</td>
<td></td>
</tr>
<tr>
<td>Risk Reduction in the Recurrence of DVT/PE</td>
<td></td>
<td>US, E, C</td>
<td></td>
</tr>
<tr>
<td>Secondary prevention of ACS</td>
<td></td>
<td>E</td>
<td></td>
</tr>
</tbody>
</table>

AF = atrial fibrillation; VTE = venous thromboembolism; THA = total hip arthroplasty; TKA = total knee arthroplasty; DVT = deep vein thrombosis; PE = pulmonary embolism; ACS = acute coronary syndromes

US = FDA; E = European Medicines Agency; C = Canadian Health Products and Food Branch
Atrial Fibrillation

• Anticoagulation decreases the risk of stroke or systemic embolism in patients with nonvalvular AF
  – Risk of stroke may be predicted by CHADS$_2$ or CHADS$_2$-VASc score

• All 3 agents have same FDA indication
# Comparison of AF Trials

<table>
<thead>
<tr>
<th></th>
<th>RE-LY</th>
<th>ROCKET AF</th>
<th>ARISTOTLE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
<td>18,113</td>
<td>14,264</td>
<td>18,201</td>
</tr>
<tr>
<td><strong>VKA naive</strong></td>
<td>50%</td>
<td>37%</td>
<td>43%</td>
</tr>
<tr>
<td><strong>Design</strong></td>
<td>PROBE design</td>
<td>Randomized, double-blind, double-dummy study</td>
<td>Randomized, double-blind, double-dummy study</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td>Dabigatran</td>
<td>Rivaroxaban</td>
<td>Apixaban</td>
</tr>
<tr>
<td></td>
<td>2 different doses</td>
<td>1 dose (with dose adaptation for moderate renal impairment)</td>
<td>1 dose with reduction if ≥2 of following: age ≥80 yrs, weight ≤60 kg or SCr &gt;1.5 mg/dL</td>
</tr>
<tr>
<td><strong>Regimen</strong></td>
<td>Twice daily</td>
<td>Once daily</td>
<td>Twice daily</td>
</tr>
<tr>
<td><strong>Primary outcome</strong></td>
<td>Efficacy: Composite of all-cause stroke and non-CNS systemic embolism</td>
<td>Efficacy: Composite of all-cause stroke and non-CNS systemic embolism</td>
<td>Efficacy: Composite of all-cause stroke and non-CNS systemic embolism</td>
</tr>
<tr>
<td></td>
<td>Safety: Composite of major and clinically relevant non-major bleeding events</td>
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<td>Safety: Composite of major and clinically relevant non-major bleeding events</td>
</tr>
</tbody>
</table>
# Comparison of AF Trials

<table>
<thead>
<tr>
<th></th>
<th>RE-LY Dabigatran</th>
<th>ROCKET AF Rivaroxaban</th>
<th>ARISTOTLE Apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TTR (median)</strong></td>
<td>67%</td>
<td>58%</td>
<td>66%</td>
</tr>
<tr>
<td><strong>CHADS2 (mean)</strong></td>
<td>2.1</td>
<td>3.7</td>
<td>2.1</td>
</tr>
<tr>
<td><strong>Previous TIA/CVA</strong></td>
<td>20%</td>
<td>55%</td>
<td>19.5%</td>
</tr>
<tr>
<td><strong>Primary efficacy outcome HR</strong></td>
<td>0.66* (150 mg dose)</td>
<td>0.88</td>
<td>0.79*</td>
</tr>
<tr>
<td><strong>Hem CVA rate: HR</strong></td>
<td>0.24* (150 mg dose)</td>
<td>0.24*</td>
<td>0.51*</td>
</tr>
<tr>
<td><strong>Ischemic CVA: HR</strong></td>
<td>0.75* (150 mg dose)</td>
<td>0.99</td>
<td>0.92</td>
</tr>
<tr>
<td><strong>Major Bleeding rate</strong></td>
<td>3.1% (150 mg dose)</td>
<td>3.6%</td>
<td>2.13%*</td>
</tr>
</tbody>
</table>

HR=Hazard ratio  *=statistically significant as compared to warfarin
AHA/ASA Science Advisory: Oral Antithrombotic Agents for the Prevention of Stroke in Nonvalvular AF

• Prevention of first and recurrent stroke
  – Warfarin (Class I recommendation)
  – Dabigatran (class I recommendation)
  – Rivaroxaban (Class IIa recommendation)
  – Apixaban (Class I recommendation)

• “The selection of an antithrombotic agent should be individualized on the basis of risk factors, cost, tolerability, patient preference, potential for drug interactions, and other clinical characteristics, including time in INR therapeutic range if the patient has been taking warfarin.”

Apixaban: AF

• AVERROES
  – Compared apixaban 5 mg bid with aspirin 81-324 mg/day in patients deemed unsuitable for warfarin therapy
  – Primary efficacy EP (stroke or systemic embolism): Apixaban superior to aspirin alone (1.6% vs. 3.7%; p<0.001)
  – Primary safety EP (major bleed): no difference
    • No increase in ICH

Venous Thromboembolism (VTE)

- Includes pulmonary embolism (PE) and deep vein thrombosis (DVT)
  - Associated with morbidity and mortality
- May occur from a variety of different conditions
  - Orthopedic surgery (TKA or THA) common population in prophylaxis trials
VTE Prophylaxis - Dabigatran

- Dabigatran 220 mg or 150 mg once daily studied
- RE-MODEL & RE-NOVATE: non-inferior to enoxaparin 40 mg subQ once daily in THA pts
- RE-MOBILIZE: *inferior* to enoxaparin 30 mg bid after TKA
  - Outcome difference attributed to use of higher enoxaparin dose and delay in starting after surgery (12-24 hrs)
- Not FDA approved indication
  - European dose 220 mg daily (150 mg daily for CrCl, age or drug interactions)

VTE Prophylaxis – Rivaroxaban

<table>
<thead>
<tr>
<th>Study</th>
<th>Comparison Group to Rivaroxaban 10 mg daily x 14-35 days (started after surgery)</th>
<th>Efficacy DVT/nonfatal PE/death any cause</th>
<th>Safety Major bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>RECORD-1 (THA)</td>
<td>Enoxaparin 40 mg q24 x35d (started before surgery)</td>
<td>Rivaroxaban better than enoxaparin in VTE/death</td>
<td>No significant difference in major bleeding incidence</td>
</tr>
<tr>
<td>RECORD-2 (THA)</td>
<td>Enoxaparin 40 mg q24 x10-14d (started before surgery)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RECORD-3 (TKA)</td>
<td>Enoxaparin 40 mg q24 x10-14d (started before surgery)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RECORD-4 (TKA)</td>
<td>Enoxaparin 30 mg q12 x11-15d (after surgery)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

TKA=total knee arthroplasty; THA= total hip arthroplasty
VTE Prophylaxis - Rivaroxaban

• Medically Ill Patients: MAGELLAN: rivaroxaban 10 mg daily noninferior to enoxaparin 40 mg once daily at 10 days however higher incidence of bleeding
  – Extended treatment: rivaroxaban superior to placebo at 35 days

VTE Prophylaxis - Apixaban

- ADOPT: apixaban 2.5 bid noninferior to enoxaparin; apixaban had higher major bleed (longer duration)
- ADVANCE-3: apixaban superior to enoxaparin with similar major bleeds

2012 CHEST Guidelines

• “In patients undergoing THA or TKA, we recommend use of one of the following for a minimum of 10-14 days rather than no antithrombotic prophylaxis: LMWH, fondaparinux, apixaban, dabigatran, rivaroxaban, LDUH, adjusted-dose VKA, aspirin (all Grade 1B), or an IPCD (Grade 1C)”
  – Note: new anticoagulants were not included in hip fracture recommendations

LDUH: low dose unfractionated heparin  IPCD: intermittent pneumatic compression device
2012 CHEST Guidelines

• “In patients undergoing THA or TKA, irrespective of the concomitant use of an IPCD or length of treatment, we suggest the use of **LMWH in preference** to the other agents we have recommended as alternatives: fondaparinux, **apixaban**, **dabigatran**, **rivaroxaban**, LDUH (all Grade 2B), adjusted-dose VKA, or aspirin (all Grade 2C)”
  
  – Authors cited possibility of increased bleeding (rivaroxaban) and lack of long-term safety data (dabigatran, rivaroxaban)

VTE Treatment - Dabigatran

- RE-COVER: Dabigatran 150 mg bid was noninferior to LMWH + adjusted dose warfarin for treatment of VTE
  - Similar bleeding incidence between groups
  - Patients had CrCl ~50 mL/min
- Not FDA approved indication

VTE Treatment - Rivaroxaban

• FDA approved indication
• Trial dosing: 15 mg bid x 3 weeks followed by 20 mg once daily (**NOTE: almost all pts had CrCl >30 mL/min)
• EINSTEIN DVT & EINSTEIN-Extension
  – Noninferior to warfarin in acute DVT treatment without an increase in bleeding
  – Superior efficacy in continued tx study (6-12 mo) with placebo
• EINSTEIN-PE
  – Non-inferior to warfarin with lower incidence of major bleeding

VTE Treatment - Apixaban

• AMPLIFY: Apixaban 10 mg bid x 7 days then 5 mg bid compared with conventional therapy (enoxaparin/warfarin)

• Apixaban was noninferior to conventional therapy with less bleeding
  – Includes major bleeding as well as major/nonmajor clinically significant bleeding

• AMPLIFY-EXT: apixaban 2.5 or 5 mg bid vs. placebo; both apixaban doses better than placebo without increase in major bleeding

• Not FDA approved indication

2012 CHEST Guidelines

• **DVT**: “In patients with DVT of the leg and no cancer, we suggest **VKA therapy over LMWH** for long-term therapy (Grade 2C). For patients with DVT and no cancer who are not treated with VKA therapy, we suggest **LMWH over dabigatran or rivaroxaban** for long-term therapy (Grade 2C)”

• **PE** - Same as above

• Cancer patients: **LMWH preferred over VKA** with same recommendation on new oral anticoagulants

Where to Get Additional Information
Pharmacy Anticoagulation Resources Website

- Available from: http://infonet/pharmacy
Pharmacy Anticoagulation Resources Website

Anticoagulation Resources

1. Formulary options

2. Dosing/protocols/guidelines
   a. Unfractionated heparin
      i. Heparin protocol
      ii. HIT monitoring
      iii. Heparin Reversal Information
   b. Low Molecular Weight Heparins
      i. Dosing Guidelines
      ii. Enoxaparin syringe rounding
      iii. LMWH dosing in Morbidly obese patients
      iv. LMWH Reversal Information
      v. How to write an outpatient prescription for LMWH
   c. Direct thrombin inhibitors
      i. Argatroban protocol
      ii. Dabigatran Frequently Asked Questions
      iii. Dabigatran Reversal Information
   d. Selective Xa Inhibitors
      i. Fondaparinux overview
      ii. Rivaroxaban Frequently Asked Questions
      iii. Apixaban/Rivaroxaban Reversal Information
      iv. Apixaban Frequently Asked Questions
   a. Warfarin
      i. Warfarin protocol
      ii. Evidence based INR adjustment – coming soon
      iii. Anticoagulation Clinic Forms and Personnel
      iv. Warfarin handbook available from Printing Services (Phone #534-1758), Order #63685

3. Management of Heparin-induced thrombocytopenia

4. Guidelines for management of Neuraxial procedures In patients on Anticoagulants

5. FFP Guidelines for Non-Cardiac Surgery
Pharmacy Anticoagulation Resources Website

• Contains various anticoagulation related documents/guidelines
  – FAQ on oral anticoagulants – including dosing, drug interactions, conversion information
  – Reversal guidelines for anticoagulants
  – Neuraxial recommendations for anticoagulants
  – Warfarin handbook (electronic pdf)
  – Much, much more!
Things to think about....
Concomitant Antiplatelet Agents

- Use of aspirin and antiplatelet agents increases risk of bleeding
- Aspirin doses should be $\leq 100$ mg/day
- Use of warfarin preferred in patients on “triple therapy” – including aspirin, ADP antagonists and anticoagulant
Converting to and from new oral anticoagulants

• Consideration of the following
  – Drug clearance should be taken into consideration - Hepatic or renal failure?

• Administration times?
  – What time to stop current therapy?
  – INR may not be accurate

• Duplicate therapy – remember any dose would provide VTE prophylaxis (or more)
Prior to Surgical Procedure

• No antidote/reversal agent available
  – ***Renal function impacts duration of effect***
  – Allow appropriate time for drug clearance prior to surgical procedures or epidural/spinal injections

• Recommendations provided on the Anticoagulation Resources Website for
  – When to stop prior to procedures
  – When safe to initiate neuraxial procedures
In Case of Bleeding...

- No antidote or reversal agent at this time
- Symptomatic management for bleeding
  - Fluid replacement, hemodynamic support
  - Start measures to support good renal function (fluids, avoiding nephrotoxins, etc)
- Dialysis removes up to 60% of dabigatran
  - Rivaroxaban and apixaban - ↑ protein binding so no effect

ACCP CHEST Guidelines 9th Ed. CHEST 2012;141:e44S-e88S.
Life-Threatening Bleeding

- **LIMITED** data and no consensus statement available
- Recommendations on Anticoagulation Resources Website; orderset to be implemented soon
- Dabigatran, rivaroxaban, apixaban
  - FEIBA (activated prothrombin complex concentrates or aPCC)
    - CHEST guidelines for dabigatran recommend only if dilutional coagulopathy
    - Recombinant factor VIIa
- Hopefully more research/agents in the future
Patient Counseling Pointers
Patient Counseling

• Activity level recommendations are the same as with warfarin
  – Avoid dangerous activities (no sky diving, caution when icy, etc…)
• Should be taken at same time of day (every 12 hrs or with evening meal)
• If dose missed, take it as soon as possible but do not double up
Patient Counseling

- Avoid taking NSAIDS or aspirin unless instructed
- Patient should report any adverse effects to provider (bleeding, GI related)
- Remind any healthcare provider about use of an anticoagulant prior to procedures (dental, surgical) or spinal/epidural catheter placement/removal
Dabigatran

- 75 and 150 mg capsules
- Capsules only good for 4 months once bottle is opened
  - Blister packs available
- Instruct patients to swallow the capsules whole
  - Breaking, chewing, or emptying the contents of the capsule can result in increased exposure

Rivaroxaban

• 10, 15 and 20 mg non-scored tablets
  – 10 and 15 mg tablets are round
  – 20 mg tablets are triangular
• 15 and 20 mg tablets should be taken with food due to reduced bioavailability
• If miss BID dose, may take 2 tabs together
• Tablets may be crushed and administered via gastric feeding tube
  – May not be given via a NJ, J-tube or GJ tube

Xarelto Prescribing Information. December 2011.
Apixaban

- 2.5 and 5 mg tablets
  - 2.5 mg round
  - 5 mg oval-shaped
- May be given with or without food
- No information on feeding tube administration therefore not recommended at this time

Eliquis Prescribing Information. December 2012.
Future Treatment Options
**Future Treatment Options**

- Multiple oral factor Xa inhibitors in clinical trials

<table>
<thead>
<tr>
<th>Factor Xa Inhibitor</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idraparinux</td>
<td>No further investigation at this time; excessive bleeding risk (idraparinux)</td>
</tr>
<tr>
<td>Idrabiotaparinux (SQ)</td>
<td></td>
</tr>
<tr>
<td>Betrixaban</td>
<td>Dose ranging studies now</td>
</tr>
<tr>
<td><strong>Edoxaban</strong></td>
<td>ENGAGE AF-TIMI 48 of AF pts published STARS J-V better than Japanese low enoxaparin dose for VTE prophylaxis in THR</td>
</tr>
<tr>
<td>Otamixaban</td>
<td>??</td>
</tr>
</tbody>
</table>
Edoxaban

- Once daily factor Xa inhibitor
- Most likely to be considered for FDA approval in 2014
- Time to onset: 1-2 hours
- Half-life 9-12 hours
- CYP3A4 and p-glycoprotein substrate
- Elimination: ~35% renal, ~65% hepatic

Edoxaban

**Acute VTE**
- Hokusai VTE trial showed edoxaban 60 mg daily was noninferior to warfarin with less major or clinically relevant bleeding

**AF**
- ENGAGE AF-TIMI 18 showed edoxaban 30 mg or 60 mg once daily noninferior to warfarin with less major bleeding

**Both studies dose reduced for CrCl 30-50 mL/min or weight <60kg**

Patients in Whom to Consider Use of New Oral Anticoagulants

- Allergy/intolerance to warfarin
- Trouble maintaining therapeutic INRs
- Those without access to monitoring
- Patients without significant renal or hepatic impairment
- Patients not on interacting medications
- Able to be compliant with medications
Before Initiating New Oral Anticoagulant…

• More expensive than warfarin (higher copay)
• Compliant patient?
  – Twice daily dosing required for dabigatran
  – Missed doses increase risk of thromboembolism
• Bleeding risk?
  – No reversal agent is available if bleeding occurs or emergent procedure necessary
Special Populations

• Mechanical heart valve?
  – Case report of treatment failure in 2 patients switched from warfarin to dabigatran
  – No randomized trials in these pts
  – Avoid; BLACK BOX WARNING for dabigatran

• Gastric bypass?
  – Absorption could be altered
  – Impact of the acidic core of dabigatran unknown

To Wrap It All Up...

• The new oral anticoagulants are alternatives to warfarin for patients who need anticoagulation
• As more agents gain FDA approval, increased use expected
• Providers should consider dosing based on indication, adjustment for other disease states, drug interactions & need for patient education