Slide 1

DRUG INTERACTIONS WITH NEW ORAL ANTICOAGULANTS

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Lake Placid, New York

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Disclosures

None

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Objectives

- Provide an overview of the pharmacology and pharmacokinetics of rivaroxaban, apixaban, and dabigatran
- Identify the bleeding profile of the new oral anticoagulants (NOACs)
- Compare and contrast the drug-drug interactions (DDIs) of warfarin, rivaroxaban, apixaban, and dabigatran
- Describe the implications of pharmacogenomics on NOACs
**Slide 4**

**Anticoagulant Medications Available on the US Market**

- **1943** • Heparin approved by FDA
- **1954** • Warfarin approved by FDA
- **1993** • Enoxaparin approved by FDA
- **2000** • Argatroban approved by FDA
- **2001** • Fondaparinux approved by FDA
- **2010** • Dabigatran approved by FDA
- **2012** • Rivaroxaban approved by FDA
- **2013** • Apixaban approved by FDA

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**Advantages and Disadvantages of NOACs**

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fast onset/offset of action</td>
<td>Short half-life</td>
</tr>
<tr>
<td>No routine monitoring</td>
<td>No routine monitoring</td>
</tr>
<tr>
<td>Standardized dosing</td>
<td>No coagulation assay specific to anticoagulation effect</td>
</tr>
<tr>
<td>Fewer drug interactions</td>
<td>Lack of antidote</td>
</tr>
<tr>
<td>Cost</td>
<td></td>
</tr>
</tbody>
</table>

**Slide 6**

**Oral Anticoagulant Pharmacology**

- **Vitamin K Antagonists**: Warfarin
- **Oral Factor Xa Inhibitors**: Rivaroxaban, Apixaban
- **Direct Thrombin Inhibitor**: Dabigatran

[Anesthesia UK](http://www.frca.co.uk/article.aspx?articleid=100096)
NOAC Agents

<table>
<thead>
<tr>
<th>NOAC</th>
<th>Onset of Action</th>
<th>Atrial Fibrillation</th>
<th>CrCl &gt; 50 mL/min</th>
<th>CrCl 30-50 mL/min</th>
<th>CrCl 15-30 mL/min</th>
<th>DVT/PE</th>
<th>Reduction in DVT/PE Recurrence</th>
<th>DVT Prophylaxis After Hip or Knee Replacement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pradaxa®</td>
<td>Fast</td>
<td>150 mg PO BID (150 mg PO once daily)</td>
<td>150 mg PO BID (150 mg PO once daily)</td>
<td>75 mg PO BID (not studied)</td>
<td>20 mg PO once daily</td>
<td>150 mg PO BID (150 mg PO once daily)</td>
<td>150 mg PO BID (20 mg PO once daily)</td>
<td>2.5 mg PO BID</td>
</tr>
<tr>
<td>Xarelto®</td>
<td>Fast</td>
<td>20 mg PO once daily</td>
<td>15 mg PO once daily</td>
<td>15 mg PO once daily</td>
<td>2.5 mg PO BID</td>
<td>15 mg PO once daily</td>
<td>15 mg PO BID</td>
<td>2.5 mg PO BID</td>
</tr>
<tr>
<td>Eliquis®</td>
<td>Fast</td>
<td>5 mg PO BID IF &gt;2 of the following: ≥80 years, Body weight ≤60 kg, SCr ≥1 mg/dL</td>
<td>20 mg PO once daily</td>
<td>10 mg PO BID X7 days, then 5 mg PO BID</td>
<td>N/A</td>
<td>10 mg PO once daily</td>
<td>2.5 mg PO BID</td>
<td>N/A</td>
</tr>
</tbody>
</table>

NOAC Pharmacokinetics

- **Dabigatran**: Bioavailability: 50% (without food), >80% (with food)
- **Rivaroxaban**: Bioavailability: 50%
- **Apixaban**: Bioavailability: 3-7%

Risk of Any Anticoagulant

- BLEEDING!
- BLEEDING!
- BLEEDING!
### Slide 10: Rivaroxaban Bleeding Profile Review

<table>
<thead>
<tr>
<th>Event</th>
<th>RECORD 1</th>
<th>RECORD 2</th>
<th>RECORD 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major Bleeding</td>
<td>395 (5.6)</td>
<td>386 (5.4)</td>
<td>40 (1.0)*</td>
</tr>
<tr>
<td>Fatal Bleeding</td>
<td>27 (0.4)*</td>
<td>55 (0.8)*</td>
<td>3 (&lt;0.1)</td>
</tr>
<tr>
<td>Gastrointestinal Bleeding</td>
<td>221 (3.1)*</td>
<td>140 (2.0)*</td>
<td>1 (&lt;0.1)</td>
</tr>
<tr>
<td>Intracranial Bleeding</td>
<td>55 (0.77)*</td>
<td>84 (1.18)*</td>
<td>3 (&lt;0.1)</td>
</tr>
</tbody>
</table>

* = statistically significant

### Slide 11: Apixaban Bleeding Profile Review

<table>
<thead>
<tr>
<th>Event</th>
<th>ARISTOTLE</th>
<th>AVERROES</th>
<th>ADVANCE 1-3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major Bleeding</td>
<td>327 (2.13)*</td>
<td>462 (3.09)*</td>
<td>44 (1.4)</td>
</tr>
<tr>
<td>Fatal Bleeding</td>
<td>10 (0.06)</td>
<td>37 (0.24)</td>
<td>4 (&lt;0.1)</td>
</tr>
<tr>
<td>Gastrointestinal Bleeding</td>
<td>105 (0.76)</td>
<td>119 (0.86)</td>
<td>12 (0.4)</td>
</tr>
<tr>
<td>Intracranial Bleeding</td>
<td>52 (0.33)*</td>
<td>122 (0.80)*</td>
<td>11 (0.4)</td>
</tr>
</tbody>
</table>

* = statistically significant

### Slide 12: Dabigatran Bleeding Profile Review

<table>
<thead>
<tr>
<th>Event</th>
<th>RELY</th>
<th>RE-MEDY</th>
<th>VTE Secondary Prevention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major Bleeding Event (MBE)</td>
<td>375 (3.1)</td>
<td>397 (3.4)</td>
<td>37 (1.4)</td>
</tr>
<tr>
<td>Fatal Bleeding</td>
<td>--</td>
<td>--</td>
<td>1 (0.04)</td>
</tr>
<tr>
<td>Intracranial Bleeding</td>
<td>36 (0.3)*</td>
<td>87 (0.74)*</td>
<td>2 (0.1)</td>
</tr>
<tr>
<td>Gastrointestinal Bleeding</td>
<td>182 (1.51)*</td>
<td>120 (1.02)*</td>
<td>15 (0.6)</td>
</tr>
</tbody>
</table>

* = statistically significant
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**Drug Metabolism and Interactions**

Cytochrome P450
P-glycoprotein

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**Cytochrome P450 Enzymes**

- Heme-containing enzymes bound to membranes within a cell
  - Essential for metabolism of chemicals and many medications
- Six subtypes metabolize 90% of drugs
  - 1A2, 2C9, 2C19, 2D6, 3A4, 3A5
  - 2 most significant: 3A4, 2D6
- Clinically significant drug interactions
  - Induction of enzymes → Decreased level of substrate drug
  - Inhibition of enzymes → Increased level of substrate drug
- Genetic polymorphisms may occur
  - Alter metabolism of chemicals and medications

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**CYP3A4 Agents**

<table>
<thead>
<tr>
<th>Substrates</th>
<th>Inhibitors</th>
<th>Inducers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alprazolam</td>
<td>Clarithromycin</td>
<td>Carbamazepine</td>
</tr>
<tr>
<td>Amlodipine</td>
<td>Diltiazem</td>
<td>Phenobarbital</td>
</tr>
<tr>
<td>Apixaban</td>
<td>Erythromycin</td>
<td>Phenytoin</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>Grapefruit</td>
<td>Rifampin, rifabutin</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>Itraconazole</td>
<td>St. John's Wort</td>
</tr>
<tr>
<td>Diazepam</td>
<td>Ketoconazole</td>
<td>St. John's Wort</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>Nelfinavir</td>
<td>St. John's Wort</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>Ritonavir</td>
<td>St. John's Wort</td>
</tr>
<tr>
<td>Sildenafil</td>
<td>Telithromycin</td>
<td>St. John's Wort</td>
</tr>
<tr>
<td>Zolpidem</td>
<td>Verapamil</td>
<td>St. John's Wort</td>
</tr>
<tr>
<td>Zolpidem</td>
<td>Verapamil</td>
<td>St. John's Wort</td>
</tr>
</tbody>
</table>

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**P-Glycoprotein (P-gp)**

- Plasma membrane efflux transporter located in the intestinal lumen and kidneys
- Involved with metabolism in enterocytes and hepatocytes
- Involved with elimination in kidneys
- Pumps drug back into intestinal lumen, reducing the bioavailability of orally administered drugs
- DDIs
  - P-gp inhibitors
    - Increased drug bioavailability
  - P-gp inducers
    - Decreased drug bioavailability
  - P-gp competitors
    - Increased drug bioavailability

**Reference**: CMAJ 2004;170:1531-2

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**P-gp Inducers and Inhibitors**

<table>
<thead>
<tr>
<th>Inducers</th>
<th>Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine</td>
<td>Amiodarone</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>Nelfinavir</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>Clarithromycin</td>
</tr>
<tr>
<td>Nebivolol</td>
<td>Cilostazol</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Dipyridamole</td>
</tr>
<tr>
<td>Phaeopterin</td>
<td>Quindinequinine</td>
</tr>
<tr>
<td>Rifampin</td>
<td>Diltiazem</td>
</tr>
<tr>
<td>St. John’s Wort</td>
<td>Diclofenac</td>
</tr>
<tr>
<td>Tetrabenazine</td>
<td>Dexamethasone</td>
</tr>
<tr>
<td>Trazodone</td>
<td>Lovastatin</td>
</tr>
<tr>
<td>Tadalafil</td>
<td>Verapamil</td>
</tr>
<tr>
<td>Tenofovir</td>
<td>Ketorolac</td>
</tr>
<tr>
<td>Ketoconazole</td>
<td>Tamoxifen</td>
</tr>
</tbody>
</table>

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**Dual CYP3A4 and P-gp Metabolism**

**Reference**: Ann Pharmacother 2013;47:1478-87
### Slide 22

**Dual 3A4/P-gp Agents**

<table>
<thead>
<tr>
<th>Substrates</th>
<th>Inhibitors</th>
<th>Inducers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apixaban</td>
<td>Amiodarone</td>
<td>Carbamazepine</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>Cimetidine</td>
<td>Phenytoin</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>Clarithromycin</td>
<td>Rifampicin</td>
</tr>
<tr>
<td>Doxercet</td>
<td>Erythromycin</td>
<td>St John's Wort</td>
</tr>
<tr>
<td>Pimozide</td>
<td>Fluconazole</td>
<td>Tacrolimus</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>Ketoconazole</td>
<td>Itraconazole</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>Ritonavir</td>
<td>Saquinavir</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>Verapamil</td>
<td>Voriconazole</td>
</tr>
</tbody>
</table>

### Slide 23

**Rivaroxaban Metabolism**

- Bioavailability: 66% (without food) >80% (with food)

### Slide 24

**Rivaroxaban Pharmacokinetic Interactions**

- Strong CYP3A4/P-gp inhibitors
  - Bioavailability increased by ~2.5 times
  - May increase risk of hemorrhage
  - Management
    - Avoid combination with strong inhibitors
    - Consider therapy modification with moderate inhibitors

- Strong CYP3A4/P-gp inducers
  - Bioavailability decreased by about 50%
  - May decrease efficacy
  - Management
    - Avoid combination with strong inducers
    - Monitor therapy with moderate inducers

Xarelto® [package insert]. Titusville, NJ: Janssen Pharmaceuticals, Inc; Revised August 2014

Thromb Haemost 2010;103:572-85
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Rivaroxaban Pharmacokinetic Interactions

<table>
<thead>
<tr>
<th>Drug</th>
<th>Effect on Rivaroxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Remdesivir</td>
<td>IV infusion (M concentrations)</td>
</tr>
<tr>
<td>Osimertinib</td>
<td>Type II inhibitor (M concentrations)</td>
</tr>
<tr>
<td>Vemurafenib</td>
<td>Type II inhibitor (M concentrations)</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>Type II inhibitor (M concentrations)</td>
</tr>
<tr>
<td>Palbociclib</td>
<td>Type I inhibitor (M concentrations)</td>
</tr>
<tr>
<td>Alemtuzumab</td>
<td>10% decrease (M concentrations)</td>
</tr>
<tr>
<td>Venetoclax</td>
<td>17% decrease (M concentrations)</td>
</tr>
</tbody>
</table>

**Slide 26**

Rivaroxaban Pharmacokinetic Interactions

- **Drugs Affecting Gastric pH**
  - Absorption and bioavailability of rivaroxaban not affected by gastric pH
  - No significant changes in AUC and C_{max} when given together with ranitidine or an aluminum-magnesium hydroxide antacid
  - No significant changes when given with omeprazole
Slide 28
Pharmacodynamic Interactions: Rivaroxaban and Antiplatelets/NSAIDs

- Aspirin
  - ROCKET-AF warfarin versus rivaroxaban
  - Concomitant aspirin in 36.3%
  - Independent risk factor for major bleeding
- Clopidogrel
  - Concomitant administration in healthy subjects
  - Increase in bleeding time by 30-45%
- NSAIDs
  - No clinically relevant effect of naproxen on bleeding time and clotting parameters in pharmacokinetic study
  - Possible may increase bleeding risk
  - Package insert: Avoid concomitant antiplatelet and NSAID use unless the risk outweighs the benefit

Slide 29
Pharmacodynamic Interactions: Antiplatelet Therapy

- ATLAS ACS 2-TIMI 51 Trial
  - Recent acute coronary syndrome
    - > 98% on aspirin, > 90% on thienopyridine
  - Rivaroxaban ↓ death from cardiovascular causes
    - Bleeding rate 2.1% vs 0.6%

Slide 30
Rivaroxaban and Prolonged Coagulation Markers in Elderly Woman on Multiple Medications

- Case report of 88-year old female on rivaroxaban 15 mg daily for atrial fibrillation
  - Concomitant medications: mirtazapine, nebivolol, digitoxin, lisinopril, gliclazide, amlodipine, valproate

<table>
<thead>
<tr>
<th>Day of Admission</th>
<th>INR</th>
<th>aPTT, sec</th>
<th>Anti-Factor Xa, U/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1</td>
<td>NA</td>
<td>108</td>
<td>NA</td>
</tr>
<tr>
<td>Day 12</td>
<td>2.26</td>
<td>35.0</td>
<td>38.3</td>
</tr>
</tbody>
</table>

Heart Disease weekly
Slide 31

**Rivaroxaban and Prolonged Coagulation Markers in Elderly Woman on Multiple Medications**

- Overestimation of renal function
  - Authors used MDRD to calculate renal function
  - CrCl of ~27 mL/min according to Cockroft-Gault method
  - Exclusion criteria for ROCKET-AF

- Potential drug interactions
  - Weak CYP3A4 inhibitors: Mirtazapine, amlodipine, valproate

- Elderly
  - Median age 73 in ROCKET-AF
  - Little data about metabolism in elderly patients

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**Rivaroxaban and Gastrointestinal Bleed in HIV Patient on HAART Therapy**

- Case
  - Right malleolus fracture requiring surgery
  - Rivaroxaban 10 mg daily for six weeks for VTE prophylaxis

- DDI ADE
  - 52 y/o male on rivaroxaban 10 mg PO daily
  - Rivaroxaban-ritonavir
  - GI bleed

- Right malleolus fracture requiring surgery
  - Rivaroxaban 10 mg daily for six weeks for VTE prophylaxis

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**Fatal Pulmonary Emboli in Patient on Rivaroxaban and Rifampicin**

- Case
  - 67 year old female on rivaroxaban 20 mg once daily

- DDI ADE
  - Rivaroxaban-rifampicin
  - Fatal PE

- Patient presents short of breath, diaphoretic, tachycardic
- PE not highly suspected
- Rivaroxaban therapy
- Prolonged PT of 21.6 sec
- 12 hours later patient deteriorated and died
- Autopsy: extensive central pulmonary emboli
Patient with Hemopericardium on Rivaroxaban and Saw Palmetto

<table>
<thead>
<tr>
<th>Case</th>
<th>Rivaroxaban</th>
<th>Hemopericardium</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 year old male</td>
<td>Rivaroxaban</td>
<td>Hemopericardium</td>
</tr>
</tbody>
</table>

- Spontaneous hemopericardium occurs in 2.5 – 11% of patients receiving anticoagulation
- First reported published case occurring with rivaroxaban
- Mechanism likely due to inhibition of metabolism by saw palmetto

Apixaban Metabolism

- Bioavailability 50%

Apixaban Drug-Drug Interactions

- Strong CYP3A4/P-gp Inhibitors
  - May increase risk of hemorrhage
  - Management
    - In patients taking >2.5 mg dose, reduce dose by 50%
    - In patients already taking the 2.5 mg dose, avoid combination
- Strong CYP3A4/P-gp Inducers
  - May decrease efficacy
  - Management
    - Avoid combination
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Apixaban Pharmacokinetic Interactions

<table>
<thead>
<tr>
<th>Vs</th>
<th>Apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monoclonal antibodies</td>
<td>No effect</td>
</tr>
<tr>
<td>Statins</td>
<td>No effect</td>
</tr>
<tr>
<td>Heparin</td>
<td>No effect</td>
</tr>
<tr>
<td>Sulfonamides</td>
<td>No effect</td>
</tr>
<tr>
<td>Non-steroidal anti-inflammatory drugs</td>
<td>No effect</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>No effect</td>
</tr>
<tr>
<td>Anti-platelets</td>
<td>No effect</td>
</tr>
<tr>
<td>Antacids</td>
<td>No effect</td>
</tr>
</tbody>
</table>

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Apixaban Pharmacokinetic Interactions

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Pharmacokinetic Interactions: Drugs Affecting Gastric pH

- Absorption and bioavailability of apixaban not affected by gastric pH
  - No significant changes in AUC and C_max when given together with famotidine
Pharmacodynamic Interactions: Apixaban and Antiplatelets

- Concurrent antiplatelets according to clinician
  - 97% on ASA
  - 81% on ASA + P2Y12
- Trial terminated early
- Increased incidence of bleeds reported with little efficacy
- Package insert: Avoid antiplatelets when possible

Pharmacodynamic Interactions: Apixaban and NSAIDs

- NSAIDs
  - Naproxen has been reported to produce 50% increase in apixaban AUC and 60% increase in Cmax
  - No clinically relevant increase in bleeding time seen

A patient comes to refill her rivaroxaban prescription and is also purchasing a bottle of St John’s Wort. You become concerned about the St John’s Wort because:

- A. St. John’s Wort is a strong CYP3A4 inhibitor and may cause bleeding
- B. St. John’s Wort is a strong CYP2J2 inducer and rivaroxaban therapy may fail
- C. St. John’s Wort is a strong CYP3A4 inducer and rivaroxaban therapy may fail
- D. You are not concerned about this combination
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Dabigatran Metabolism

![Dabigatran Metabolism Diagram](image)

**Slide 44**

Dabigatran Pharmacokinetic Interactions

- P-gp inducers
  - ↓ dabigatran concentration
- P-gp inhibitors
  - ↑ dabigatran concentration
- P-gp competitors
  - ↑ dabigatran concentration
- Acid suppression therapy
  - ↓ dabigatran absorption and bioavailability

**Slide 45**

Dabigatran and P-gp Inducers

- Avoid concomitant use of dabigatran and strong P-gp inducers
  - Package Insert: Avoid rifampin
    - 88% decrease in AUC and 87% decrease in Cmax if given after 7 days of rifampin
    - No interaction 7 days after rifampin discontinuation
  - Additional P-gp inducers that may interact:
    - Carbamazepine
    - Dexamethasone
    - Nefazodone
    - Paclitaxel
    - Phenytoin
    - Phrazepin
    - St John’s Wort
    - Tegretol
    - Venlafaxine
    - Vinblastine
    - Vincaleukoblastine

Pradaxa® [package insert]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc; Revised September 2014


Am J Health-Syst Pharm. 2011;68:1506-1519
Dabigatran and P-gp Inhibitors

<table>
<thead>
<tr>
<th>CrCl (mL/min)</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;50</td>
<td>May coadminister P-gp inhibitors + No dose adjustment required</td>
</tr>
<tr>
<td>30-50</td>
<td>Dronedarone and ketoconazole ↓ dabigatran dose to 75 mg BID + Verapamil, amiodarone, quinidine, clarithromycin, and ticagrelor: - No dose adjustment required - Interaction with verapamil may be avoided by administering both drugs at same time</td>
</tr>
<tr>
<td>&lt;30</td>
<td>Avoid dabigatran use with P-gp inhibitors</td>
</tr>
</tbody>
</table>

Dabigatran and P-gp Competitors

- P-gp substrates:
  - Clopidogrel, digoxin
- Phase I studies:
  - 30-40% ↑ dabigatran exposure with clopidogrel load
  - No change in dabigatran concentration at steady state

Dabigatran and Drugs Affecting Gastric pH

- Low pH required for dabigatran absorption
- Capsules contain dabigatran-coated pellets with tartaric acid core
  - Phase I Trials
    - PPIs: 30% ↓ in bioavailability
    - H2RAs: no effect on bioavailability
  - Phase III RE-LY Trial
    - PPIs: 12.5% ↓ in bioavailability
    - H2RAs: no effect on bioavailability
  - Interaction not clinically significant
Dabigatran Pharmacodynamic Interactions

- Increased bleeding risk if used with other drugs that have bleeding risk
  - Examples: antiplatelet agents, NSAIDs, anticoagulants
  - RE-LY Trial:
    - Increased bleeding risk when used with aspirin or clopidogrel
    - Similar bleeding rate with warfarin + aspirin vs. dabigatran + aspirin

Bleeding Rate by Antiplatelet Use

- Dabigatran 150 mg + Antiplatelet
- Warfarin + Antiplatelet
- Warfarin

Event Rate (% per year)

- HR = 1.87 (95% CI: 1.54, 2.27)
- HR = 2.14 (95% CI: 1.75, 2.61)

Circulation 2013;127:634

Dabigatran and Dronedarone Interaction-Induced Bleeding: Study Overview

- Background:
  - Dronedarone increases dabigatran concentration via P-gp inhibition
  - Clinical significance of interaction not established
- Objective:
  - Compare bleeding rate of dabigatran alone vs. dabigatran + dronedarone
- Methods:
  - Design: Retrospective, data mining analysis
  - Database: FDA Adverse Event Reporting System (FAERS)
  - 217,362 cases evaluated for presence of bleeding based on use of:
    - Dabigatran alone
    - Dronedarone alone
    - Dabigatran + dronedarone
    - Neither dabigatran or dronedarone

Rate of Bleeding Events

- Dabigatran + Dronedarone
- Dabigatran
- Dronedarone
- No Dabigatran or Dronedarone

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Dabigatran and Dronedarone Interaction-Induced Bleeding: Study Conclusions

- Conclusion:
  - Similar likelihood of reporting bleeding events to FAERS among patients using dabigatran alone vs. dabigatran + dronedarone

- Limitations:
  - Data from FAERS limited by reporting
  - Renal function not reported → dosing cannot be evaluated

- Applicability to Practice:
  - Trial limited by reporting → follow package insert recommendations

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Dabigatran and Amiodarone Interaction-Induced Coagulopathy

- Case: 82 year old female presents with nausea, vomiting, dizziness, and weakness
- Medications: dabigatran (150 mg BID), amiodarone, carvedilol, simvastatin, furosemide

- Basic Metabolic Panel:
  - SCr 1.78 mg/dL increased from 1 mg/dL 1 week prior
  - BUN 40 mg/dL increased from 20 mg/dL 1 week prior

- Coagulation Panel:
  - INR: 7.25 (1)
  - PTT: 135 seconds (25-35 seconds)
  - Fibrinogen: 80 mg/dL (200-400 mg/dL)
  - Thrombin Time: 120 seconds (>20 seconds)

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Dabigatran and Amiodarone Interaction-Induced Coagulopathy Continued

- Possible cause of excess anticoagulation:
  - Acute kidney injury (SCr increase to >1.5 times baseline)
  - Concomitant amiodarone use
  - Result: ↓ clearance and ↑ exposure to dabigatran

- Evidence of excess dabigatran exposure:
  - Abnormal INR, PTT, fibrinogen level, and thrombin time
  - Thrombin time and scatrin clotting time are most sensitive clotting assays for dabigatran activity in blood
A 58 year old male patient (CrCl 42 mL/min) will be started on anticoagulation for atrial fibrillation. He is also on phenytoin for seizures and enalapril for hypertension. His physician asks you to recommend a dose for dabigatran.

You would respond the following:

A. Start the patient on dabigatran 150 mg by mouth twice daily
B. Start the patient on dabigatran 75 mg by mouth twice daily since the CrCl < 50 mL/min
C. Rivaroxaban or apixaban would be a better choice since phenytoin is a P-gp inducer and may cause dabigatran therapy to fail
D. All NOACs should be avoided with phenytoin due to risk for anticoagulant therapy failure since phenytoin induces both CYP3A4 and P-gp

A physician would like to prescribe pantoprazole to a patient on rivaroxaban. She calls you to confirm that it is okay to use a proton pump inhibitor (PPI) or H2 receptor antagonist (H2RA) with NOACs. You tell her:

A. It is safe to use H2RAs with NOACs but PPIs should not be used
B. Both PPIs and H2RAs should be avoided with NOACs
C. PPIs and H2RAs must be avoided with dabigatran only
D. PPIs and H2RAs have not been shown to significantly decrease NOAC absorption and may be used with NOACs
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**Drug Interactions: Warfarin vs. NOACs**

<table>
<thead>
<tr>
<th>CYP450 Substrate</th>
<th>Warfarin</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary: CYP2C9</td>
<td>None</td>
<td>Primary: CYP3A4/5</td>
<td>None</td>
<td>Primary: CYP3A4/5</td>
</tr>
<tr>
<td>Secondary: CYP2C8, 2C19, 2C18</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cytochrome P450 Inactivator</th>
<th>Warfarin</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>High</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

**Risk of Interactions**
- Many (food with high vitamin K content inhibit anticoagulant effect)
- None (food delays time to peak concentration but may administer without regard to meal)
- Minimal (grapefruit juice may increase concentration via CYP3A4 inhibition)

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**Drug Interactions: Warfarin vs. NOACs**

<table>
<thead>
<tr>
<th>PROS</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Not a P-gp substrate</td>
<td>• Many food interactions</td>
</tr>
<tr>
<td>• INR monitoring may make use safe and effective despite interactions and can be used to monitor adherence</td>
<td>• Monitoring difficult in presence of DDIs</td>
</tr>
<tr>
<td>• Can be given with aspirin in some patients</td>
<td>• Renal elimination may complicate dosing</td>
</tr>
<tr>
<td>• Ability to reverse warfarin effect</td>
<td>• Not recommended with aspirin for some patients</td>
</tr>
<tr>
<td>• Genomic dosing allows for tailored therapy</td>
<td>• Inability to reverse agents in case of bleeding</td>
</tr>
</tbody>
</table>

---

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**Effect of Pharmacogenomics on NOAC Therapy**

- Increased risk of bleeding
- Increased risk of thrombosis
- Variation in response to NOACs
- Personalized therapy

---
Introduction to Pharmacogenomics

People may respond differently to drugs due to genetic variability.

Pharmacogenomics
- Study of effect of multiple genes on drug

Pharmacogenetics
- Study of effect of a single gene on drug response

Goal: Provide PERSONALIZED medicine to produce optimal patient response.

Role of Pharmacogenomics in Warfarin Therapy
- Pharmacogenomics have known important role
  - CYP2C9: primary enzyme that metabolizes warfarin
  - Vitamin K epoxide reductase complex subunit 1 (VKORC1): site of warfarin action
  - Polymorphisms present to different extent among ethnic groups
- Pharmacogenetic dosing algorithms available
- Pharmacogenetic testing available
- Pharmacogenetic testing and dosing not routinely recommended
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Role of Pharmacogenetics in Warfarin Therapy

<table>
<thead>
<tr>
<th>VKORC1</th>
<th>CYP2C9</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GG</strong></td>
<td>*1/*1</td>
</tr>
<tr>
<td></td>
<td>*1/*2</td>
</tr>
<tr>
<td></td>
<td>*1/*3</td>
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<td></td>
<td>*2/*2</td>
</tr>
<tr>
<td></td>
<td>*2/*3</td>
</tr>
<tr>
<td></td>
<td>*3/*3</td>
</tr>
</tbody>
</table>

**VKORC1**
- Wild type
- Small ↓ in VKORC1 expression

**CYP2C9**
- Wild type
- 30% ↓ in enzyme activity
- 80% ↓ in enzyme activity

*Clinic Pharmac Ther 2014;96:17-19.

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Role of Pharmacogenomics in NOAC Therapy

- Limited data regarding role of pharmacogenomics
- Potential for pharmacogenetic variability exists
- May impact safe and effective use


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Pharmacogenetics of NOACs

- NOACs are P-gp substrates
  - ABCB1 gene encodes for P-gp
  - Single nucleotide polymorphisms (SNPs) in ABCB1 promoter and exon regions may affect concentrations of P-gp substrates
  - ABCB1 genotype may influence NOAC concentration

*Pharmacotherapy. 2011; 31:1-26.*
Pharmacogenetics of Rivaroxaban
- Metabolized via CYP3A4/5 and CYP2J2
  - Variations in CYP450 enzymes may affect PK
  - Factor Xa inhibitor
  - Variations at site of action may affect PD

Genetic Testing for NOACs
- Genetic Testing Availability
  - Primarily used for research purposes
  - Available commercially to guide medication selection
  - First available test: Amplichip CYP450 test thru Roche Diagnostics
    - Now offered by multiple companies (e.g. Iverson Genetics, Advanced Genomics)
  - Insurances often approve when appropriate
  - Cost ~$500
- Role of Genetic Testing for NOACs
  - May help ensure appropriate therapy
  - No recommendations available for use of genotyping data
  - Lack of data regarding benefit
  - Currently not recommended for warfarin or NOACs

Conclusions
- NOACs commonly used for anticoagulation in atrial fibrillation, DVT, and PE
- NOACs have less drug-drug and drug-food interactions than warfarin
  - Some significant NOAC interactions may affect safe and effective use
- Pharmacokinetic interactions of NOACs:
  - Rivaroxaban and apixaban should be avoided with strong CYP3A4/P-gp inhibitors or inducers such as phenytoin
  - Dabigatran should be avoided with strong P-gp inducers such as rifampin
  - Dabigatran's dose should be adjusted if used with strong P-gp inhibitors such as ketoconazole in patients with renal impairment
Pharmacodynamic Interactions:
- NOACs have ↑ risk of bleeding if taken with other drugs that increase bleeding risk
- Due to lack of available lab monitoring, vigilance in management of DDIs essential
- Pharmacogenetics may affect NOAC concentration and effect
- Pharmacogenetics may play a greater role in NOAC management in future