Objectives

• Explain the pharmacology of dabigatran.

• Compare the advantages and disadvantages of dabigatran and warfarin.

• Determine the possible role of dabigatran in therapy.
Dabigatran

• Direct thrombin inhibitor

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

Clinical Pharmacology

• Competitive inhibitor of thrombin

• Free and clot bound thrombin

• Increases the following:
  – Activated partial thrombin time (aPTT)
  – Ecarin clotting time (ECT)
  – International normalized ratio (INR)
### Dabigatran versus Warfarin - Indications

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indications (FDA-approved)</th>
<th>Drug Class</th>
<th>Dosage Forms Available</th>
<th>CC Formulary Status</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dabigatran</strong> (Pradaxa®)</td>
<td>Risk reduction of stroke and systemic embolism in patients with non-valvular atrial fibrillation</td>
<td>Thrombin Inhibitor</td>
<td>Oral Capsule</td>
<td>Under review</td>
</tr>
<tr>
<td><strong>Warfarin</strong>  (Coumadin®)</td>
<td>Prophylaxis and/or treatment of thromboembolic complications associated with atrial fibrillation and/or cardiac valve replacement Prophylaxis and/or treatment of venous thromboembolism and pulmonary embolism Risk reduction of death, recurrent myocardial infarction (MI), stroke, and systemic embolization after MI</td>
<td>Vitamin K Antagonist</td>
<td>Oral Capsule Powder for reconstitution to intravenous (IV) solution</td>
<td>Oral Capsule (F) IV (FR) Restricted to patients with short bowel syndrome or who are taking nothing by mouth (NPO)</td>
</tr>
</tbody>
</table>

F- Formulary; FR- Formulary Restricted; NF- Non-formulary

---

**Contact system:**

FII, FVII, FVIII, FIX, FX, FXIIa, Plasmin, Protein C, Protein S, Thrombomodulin, Activated Protein C, Tissue Factor Pathway Inhibitor (TFPI), Prothrombin (F II), Thrombin (F Ila)

**Cellular injury:**

FVIIIa, FVIIa, FIX, FX, FVa, Fibronectin, Fibrinogen, Fibrin monomer, Fibrin multimer, Factor XIII, Factor XII

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**Diagram:**

- Contact system components: FII, FVII, FVIII, FIX, FX, FXIIa, Plasmin, Protein C, Protein S, Thrombomodulin, Activated Protein C, TFPI, Prothrombin (F II), Thrombin (F Ila)
- Cellular injury components: FVIIIa, FVIIa, FIX, FX, FVa, Fibronectin, Fibrinogen, Fibrin monomer, Fibrin multimer, Factor XIII, Factor XII
Pharmacokinetics- Absorption

- Dabigatran etexilate mesylate is a pro-drug

- Bioavailability ~3-7% (not affected by meals)
  - Absorption favors an acidic environment

- Do not open the capsule
  - Increases bioavailability to 75%

- Dabigatran etexilate mesylate is a P-glycoprotein substrate

Pharmacokinetics- Distribution and Metabolism

- Metabolism
  - Dabigatran etexilate mesylate (pro-drug) is absorbed → dabigatran (active) by esterase-catalyzed hydrolysis
  - Conjugation
  - No cytochrome P450 (CYP450) metabolism and no induction or inhibition of CYP450
Pharmacokinetics- Elimination

- 80% of absorbed dabigatran is eliminated through the kidneys

- Half life ($t_{\frac{1}{2}}$) ~12-17 hours

Pharmacokinetic Comparison

<table>
<thead>
<tr>
<th>Drug</th>
<th>Absorption</th>
<th>Distribution</th>
<th>Metabolism</th>
<th>Excretion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>Bioavailability: 3-7%</td>
<td>Protein binding: 35%</td>
<td>Converted to active form by esterases in the plasma</td>
<td>Renal- 7% unchanged drug</td>
</tr>
<tr>
<td>(Pradaxa®)</td>
<td>$C_{max}$: 1 hour</td>
<td>$Vd= 50-70 L$</td>
<td>Conjugation to active acyl glucuronides No CYP effects</td>
<td>Fecal $t_{\frac{1}{2}}= 12-17$ hours</td>
</tr>
<tr>
<td></td>
<td>P-glycoprotein efflux transporter substrate</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Warfarin (Coumadin®)

- Bioavailability: ~100%
- $C_{max}$: 4 hours
- Protein binding: 99%
- $Vd=0.14 L$
- CYP 450 2C9 (major)
- CYP3A4, CYP2C19, CYP2C8, CYP1A2 (minor)
- Renal- 92% inactive metabolites
- $t_{\frac{1}{2}}= 20-60$ hours

Cmax- maximum concentration; CYP- Cytochrome P450 isoenzymes
Clinical Efficacy- PETRO

• Phase II
• Randomized
• Blinded

• 502 patients
  – 300 mg dabigatran
  – 150 mg dabigatran
  – 50 mg dabigatran
  – open label warfarin

• Each group further split into aspirin (ASA) 81mg, 325 mg, no ASA

Clinical Efficacy- PETRO (continued)

• Primary Outcome
  – Incidence of bleeding

• Pharmacokinetic studies were also performed

J Cardiol. 2007;100(9):1419-1426
Clinical Efficacy - PETRO (continued)

• **Inclusion**
  – Atrial fibrillation + coronary artery disease +
  – Hypertension (HTN) with medical treatment
  – Diabetes
  – Symptomatic heart failure
  – Ejection fraction <40%
  – Age >75 years

• **Exclusion**
  – Prosthetic valves
  – Myocardial infarction within 30 days
  – Creatinine clearance (CrCl) <30 mL/min

**Clinical Efficacy - PETRO (continued)**

• Warfarin group within INR 2-3 57% of the time

• Major bleeding was only found in the Dabigatran 300 mg with ASA group
  – p< 0.02 when compared to dabigatran 300 mg without ASA

• Dabigatran 50 mg group had 2 systemic embolic events

• General correlation with dabigatran dose and aPTT, but not linear

• **Author’s Conclusion:** Dabigatran 150 mg twice daily shows anticoagulant effect and is well tolerated
Clinical Efficacy- RE-LY

- Phase III
- Randomized
- Non-inferiority
- Multi-center

- 18,113 patients
  - 150 mg dabigatran twice daily
  - 110 mg dabigatran twice daily
  - Warfarin to INR 2-3

Clinical Efficacy- RE-LY (continued)

- Inclusion
  - Atrial fibrillation PLUS
    - Previous Stroke, TIA, systemic embolism
    - EF <40%
    - Symptomatic heart failure
    - Age >75 years
    - Age >65 PLUS
      - Diabetes
      - Documented CAD
      - HTN

- Exclusion
  - Prosthetic valves
  - Conditions with increased risk of bleeding
  - Reversible cause of atrial fibrillation
  - Plan to perform surgery to cure atrial fibrillation
  - CrCl <30 mL/min
  - Liver abnormalities

Clinical Efficacy- RE-LY (continued)

• Primary Study Outcome
  – Stroke or systemic embolism

• Primary Safety Outcome
  – Major Hemorrhage

• Primary Net Clinical Benefit Outcome
  – Composite of stroke, systemic, embolism, myocardial infarction, death, and major hemorrhage

• Secondary Outcomes
  – Stroke
  – Systemic embolism
  – Death
  – Myocardial Infarction
  – Pulmonary embolism
  – Transient ischemia attack
  – Hospitalization

Mean age ~71 years

63% male

13% concomitantly using proton pump inhibitors

CHADS$_2$ ~2.1

Warfarin group was therapeutic 64% of the time
Primary Outcome of Stroke or Systemic Embolism

Adverse Events- RE-LY

<table>
<thead>
<tr>
<th></th>
<th>Warfarin n=6022 (%)</th>
<th>Dabigatran 110 mg n=6015 (%)</th>
<th>Dabigatran 150 mg n=6076 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major Bleeding</td>
<td>322 (3.36)</td>
<td>375 (2.71)</td>
<td>397 (3.11)</td>
</tr>
<tr>
<td>Life threatening</td>
<td>212 (1.8)</td>
<td>145 (1.22)</td>
<td>175 (1.45)</td>
</tr>
<tr>
<td>Non-Life threatening</td>
<td>208 (1.76)</td>
<td>198 (1.66)</td>
<td>226 (1.88)</td>
</tr>
<tr>
<td>GI</td>
<td>120 (1.02)</td>
<td>133 (1.12)</td>
<td>182 (1.51)</td>
</tr>
<tr>
<td>Intracranial Bleed</td>
<td>87 (0.74)</td>
<td>27 (0.23)</td>
<td>36 (0.30)</td>
</tr>
</tbody>
</table>
Clinical Efficacy- RE-LY (continued)

• Author’s conclusion
  – Dabigatran 110 mg and 150 mg were non-inferior to warfarin in the primary outcome
  – Dabigatran 150 mg was superior to warfarin in preventing stroke and systemic embolism
  – Myocardial infarction rates were higher in dabigatran treated patients

Safety

• Contraindications
  – Active bleeding
  – Previous anaphylactic reaction to dabigatran

• Warnings/Precautions
  – NSAIDS
  – Antiplatelet agents
  – Fibrinolytics
  – P-glycoprotein inducers
    – Rifampin
    – St. John’s Wort
## Dabigatran vs. Warfarin - Safety Comparison

<table>
<thead>
<tr>
<th>Contraindications</th>
<th>Dabigatran (Pradaxa®)</th>
<th>Warfarin (Coumadin®)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypersensitivity to formulation</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Active bleeding</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Pregnancy</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Hemorrhagic tendencies or blood dyscrasias</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Threatened abortion, eclampsia, preeclampsia</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Unsupervised patients with senility, alcoholism, psychosis, or lack of patient cooperation</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Inadequate laboratory monitoring</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Recent surgery</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Malignant hypertension</td>
<td></td>
<td>✓</td>
</tr>
</tbody>
</table>

## Warnings and Precautions

<table>
<thead>
<tr>
<th>Warnings and Precautions</th>
<th>Dabigatran (Pradaxa®)</th>
<th>Warfarin (Coumadin®)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Other medications known to cause bleeding</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>P-glycoprotein inducers</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Surgery</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Inconsistent vitamin K intake</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Heparin-induced Thrombocytopenia</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Purple Toe Syndrome</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Pregnancy Category</td>
<td>C</td>
<td>X</td>
</tr>
</tbody>
</table>

| Lactation Caution                                                                       | ✓                      | ✓                    |

| Black Box Warning                                                                       |                        | ✓                    |
### Adverse Reactions

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran (Pradaxa®) (%)</th>
<th>Warfarin (Coumadin®) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intracranial Hemorrhage</td>
<td>0.3</td>
<td>0.8</td>
</tr>
<tr>
<td>Life Threatening Bleed</td>
<td>1.5</td>
<td>1.9</td>
</tr>
<tr>
<td>Major Bleed</td>
<td>3.3</td>
<td>3.6</td>
</tr>
<tr>
<td>Any Gastrointestinal Bleed</td>
<td>6.1</td>
<td>4.0</td>
</tr>
<tr>
<td>Major Gastrointestinal Bleed</td>
<td>1.6</td>
<td>1.1</td>
</tr>
<tr>
<td>Any Bleed</td>
<td>16.6</td>
<td>18.4</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>11.3</td>
<td>5.8</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>6.5</td>
<td>5.7</td>
</tr>
<tr>
<td>Any Gastrointestinal Reaction</td>
<td>35</td>
<td>24</td>
</tr>
</tbody>
</table>

### Risk Evaluation and Mitigation Strategy (REMS)

- **Goal**
  - Properly educate patients on signs and symptoms of bleeding

- **Medication Guide**
  - Every outpatient new Rx and refill Rx Describes
    - Signs and symptoms of bleeding
    - Proper administration
    - Common side effects
Drug Interactions

- P-glycoprotein inducers
  - Rifampin significantly decreases exposure of dabigatran

- P-glycoprotein inhibitors
  - Ketoconazole
  - Amiodarone
  - Quinidine
  - Clarithromycin
  - Verapamil

- Maximum concentration (Cmax) and area-under-the-curve (AUC) are increased
- No dosage adjustment needed

Comparison - Drug Interactions

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran (Pradaxa®)</th>
<th>Warfarin (Coumadin®)</th>
</tr>
</thead>
<tbody>
<tr>
<td>P-glycoprotein inducers</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>P-glycoprotein inhibitors</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Clopidogrel (Plavix®)</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Vitamin K content in diet</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Alcohol Use</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Acetaminophen</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Antibiotics</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Amiodarone</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Steroids</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Anti-thyroid Agents</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>CYP2C9 inducers</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>CYP2C9 inhibitors</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Contraceptives</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Cranberry</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Sulfonamide Derivatives</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>HMG-CoA Reductase Inhibitors</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Edema</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Heart Failure</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Infection</td>
<td></td>
<td>✓</td>
</tr>
</tbody>
</table>
**Monitoring**

- **Baseline**
  - CrCl

- **Periodically**
  - CrCl

- **If bleeding or urgent surgery**
  - ECT: not commercially available in the United States
  - aPTT: not linearly correlated to degree of anticoagulation

---

**Comparison - Monitoring**

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran (Pradaxa®)</th>
<th>Warfarin (Coumadin®)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Renal Function</strong></td>
<td>✓ (At baseline and periodically)</td>
<td></td>
</tr>
<tr>
<td><strong>ECT</strong></td>
<td>If necessary to assess bleeding risk</td>
<td></td>
</tr>
<tr>
<td><strong>INR</strong></td>
<td>✓ (At least monthly)</td>
<td></td>
</tr>
</tbody>
</table>
Dosing and Administration

• Dosing
  – Normal Renal function
    – 150 mg orally twice daily
  – If CrCl 15-30mL/min
    – 75 mg orally twice daily
    – This dose has never been clinically tested and dose is indirectly based on pharmacokinetic study

• Swallow capsules whole
  – Opening capsules will increase the bioavailability up to 75%

• Take missed dose within 6 hours of next scheduled dose

• Don’t double the dose

Figure 1. Simulated mean steady state total dabigatran plasma concentration for patients with normal renal function and moderate renal impairment administered 150 mg twice daily (bid) and severe renally impaired patients administered 75 mg daily (q4d) and every other day (qod)
Conversions

**Warfarin to dabigatran**
- Discontinue warfarin and monitor the INR
- When INR falls below 2, initiate dabigatran

**Dabigatran to warfarin:**
- CrCl >50 mL/min, start warfarin 3 days before discontinuing dabigatran
- CrCl 31-50 mL/min, start warfarin 2 days before discontinuing dabigatran
- CrCl 15-30 mL/min, start warfarin 1 day before discontinuing
dabigatran
- *Monitor INR after dabigatran discontinuing for 2 days*

Conversions (continued)

**Converting to dabigatran from parental anticoagulants:**

- Dabigatran should be initiated between 0 and 2 hours before the next scheduled dose of a scheduled parenteral anticoagulant.

- If a continuous infusion of an anticoagulant is being used, the first dose of dabigatran should be administered at the time of discontinuation of the intravenous medication.
Conversions (continued)

• Surgery and Interventions:
  – If possible, dabigatran should be discontinued before surgery or other invasive procedures.
  – Discontinue dabigatran for 1 to 2 days when CrCl >50 mL/min and for 3-5 days when CrCl <50 mL/min.
  – A longer discontinuation period should be considered in those patients undergoing major surgery, spinal puncture, or when complete hemostasis is required.

Product Availability and Storage

• Capsules-75- and 150-mg in bottle of 60
  • Once a bottle is opened, it MUST be used within 30 days
## Comparison - Cost

<table>
<thead>
<tr>
<th>Drug</th>
<th>AWP</th>
<th>Institution Acquisition Cost</th>
<th>Cost of Course of Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran 75 mg</td>
<td>The price for 75 mg is not yet loaded in ABC, but is expected to be identical to the 150 mg dosage form</td>
<td></td>
<td>7 days: TBD 30 days: TBD</td>
</tr>
<tr>
<td>Dabigatran 150 mg</td>
<td>$4.05 per capsule $240 per month</td>
<td>$3.38</td>
<td>7 days: $47.32 30 days: $202.80</td>
</tr>
<tr>
<td>Warfarin 5 mg</td>
<td>$0.58-$0.97 per tablet $17.40-$29.10 per month</td>
<td>$0.04</td>
<td>7 days: $0.28 30 days: $1.20</td>
</tr>
</tbody>
</table>

## Conclusions

- Novel direct thrombin inhibitor to prevent stroke in patients with non-valvular atrial fibrillation

- Predictable pharmacokinetic profile and little need for monitoring

- Dabigatran 150 mg is as safe as warfarin

- Dabigatran 150 mg is superior to warfarin in preventing stroke and systemic embolism
**Concerns**

- Renal dosing
- Dosing in extremes of weight
- Potential for misuse
- No reversal agent