Disclosure

- I do not have a vested interest in or affiliation with any corporate organization offering financial support or grant monies for this continuing education activity, or any affiliation with an organization whose philosophy could potentially bias my presentation.

- The views expressed in this presentation are my own and do not necessarily reflect those of the Veterans Health Administration.

Objectives

**Objectives for Pharmacists:**
- Outline the mechanism of action, dosing, common adverse drug events, storage parameters, contraindications, and potential indications for the cardiovascular medications discussed based upon current FDA indications and pertinent primary literature.
- Recognize pertinent pipeline medications.

**Objectives for Technicians:**
- Recognize the therapeutic classes and potential indications for the cardiovascular medications discussed.
- List the approved dosage forms, strengths, and storage parameters for the cardiovascular medications discussed.

Overview

- Savaysa™ (edoxaban)
- Corlanor® (ivabradine)
- Kengreal™ (cangrelor)
- Entresto™ (sacubitril/valsartan)
- Pipeline medications

Approval Timeline

- Edoxaban
- Ivabradine
- Cangrelor

- February
- March
- April
- May
- June
- July
Edoxaban (Savaysa™)

- MOA: Factor Xa inhibitor
- Indication:
  - Reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation
  - Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) following 5-10 days of initial therapy with a parenteral anticoagulant

Edoxaban: Mechanism of Action

Edoxaban: Dosing

<table>
<thead>
<tr>
<th>Indication</th>
<th>CrCl 15 – 50 mL/min, weight ≤ 60 kg, certain P-gp inhibitors</th>
<th>CrCl 50 – 95 mL/min</th>
<th>CrCl &lt; 15</th>
</tr>
</thead>
<tbody>
<tr>
<td>DVT or PE</td>
<td>30 mg once daily</td>
<td>60 mg once daily</td>
<td>Not recommended</td>
</tr>
</tbody>
</table>

Edoxaban: ENGAGE AF–TIMI 48

- Phase 3, randomized, double-blind, double-dummy, multinational, non-inferiority trial
- Edoxaban 60 mg daily (or 30 mg)
- Edoxaban 30 mg daily (or 15 mg)
- Warfarin titrated to INR of 2.0 - 3.0

- Primary endpoint
  - Composite of stroke and systemic embolic events

Edoxaban: ENGAGE AF–TIMI 48 Results

<table>
<thead>
<tr>
<th>Warfarin (N=7036)</th>
<th>High-Dose (N=7035)</th>
<th>High-Dose vs. Warfarin</th>
<th>Low-Dose (N=7034)</th>
<th>Low-Dose vs. Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st Outcome</td>
<td>1.50%/year</td>
<td>1.18% /year</td>
<td>0.79 (0.63–0.99; p&lt;0.001)</td>
<td>1.61%/year</td>
</tr>
<tr>
<td></td>
<td>(0.87–1.3; p=0.005)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Major Bleed

<table>
<thead>
<tr>
<th>Warfarin (N=7036)</th>
<th>High-Dose (N=7035)</th>
<th>High-Dose vs. Warfarin</th>
<th>Low-Dose (N=7034)</th>
<th>Low-Dose vs. Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3.43%/year</td>
<td>2.75%/year</td>
<td>0.80 (0.71–0.91; p&lt;0.001)</td>
<td>1.61%/year</td>
</tr>
<tr>
<td></td>
<td>(0.41–0.55; p&lt;0.001)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Edoxaban: Hokusai VTE

- Multinational, double-blind, non-inferiority study
  - Edoxaban 60 mg daily (or 30 mg)
  - Warfarin titrated to INR of 2.0 - 3.0
- Primary endpoint:
  - Recurrent symptomatic venous thromboembolism

Edoxaban: Hokusai VTE Results

<table>
<thead>
<tr>
<th></th>
<th>Edoxaban (n=4118)</th>
<th>Warfarin (n=4122)</th>
<th>HR (95% CI; p value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>First major or clinically relevant non-major bleeding</td>
<td>8.5%</td>
<td>10.3%</td>
<td>0.81 (0.71 - 0.94; P=0.004) (for superiority)</td>
</tr>
</tbody>
</table>

Edoxaban: Boxed Warnings and Contraindications

- Boxed Warnings
  1. Reduced efficacy with CrCl >95 mL/min
  2. Premature discontinuation
  3. Spinal/epidural hematoma
- Contraindications
  1. Active pathological bleeding

Ivabradine (Corlanor®)

- Indication: Reduce the risk of hospitalization for worsening heart failure in patients with stable, symptomatic chronic heart failure with:
  - Left ventricular ejection fraction ≤ 35%
  - Sinus rhythm with resting heart rate ≥ 70 beats per minute
- AND WHO ARE EITHER
  - On maximally tolerated doses of beta-blockers
  - Contraindication to beta-blocker use

Ivabradine: Mechanism of Action

- Mechanism:
  - Ica inhibits the slow (Ica) and fast intrinsic (If) currents in the sinoatrial node
  - Selectively inhibits the sinoatrial node currents with no effect on beta-adrenergic myocardial inotropic effects


http://www.multivu.com/players/English/7414051-amgen-corlanor-fda-approval/gallery/image/5e85ff6d-252d-4cf7b6b4-1295a03b9078.HR.jpg
**Ivabradine: Dosing**

- Initiate at 5 mg twice daily with meals
  - Consider 2.5 mg twice daily in select patients

<table>
<thead>
<tr>
<th>Heart Rate</th>
<th>Dose Adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 60 bpm</td>
<td>↑ dose by 2.5 mg BID to max of 7.5 mg BID</td>
</tr>
<tr>
<td>50-60 bpm</td>
<td>Maintain dose</td>
</tr>
<tr>
<td>&lt; 50 bpm or symptoms</td>
<td>↓ dose by 2.5 mg BID; if current dose is 2.5 mg twice daily, discontinue therapy*</td>
</tr>
</tbody>
</table>

*Two weeks*

**Ivabradine: SHIFT**

- International, multicenter, randomized, double-blind, placebo-controlled study for patients on standard of care therapies
  - Ivabradine 5mg BID X 14 d, then titrated to HR/tolerability
  - Placebo

- Primary endpoint
  - Composite of cardiovascular death and hospitalization for worsening heart failure

**Ivabradine: SHIFT Results**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Ivabradine (N = 3241)</th>
<th>Placebo (N = 3264)</th>
<th>HR (95% CI; p value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st Outcome</td>
<td>24.5%</td>
<td>28.7%</td>
<td>0.82 (0.75 - 0.90; &lt;0.0001)</td>
</tr>
</tbody>
</table>

18% reduction in CV death or hospital admission for worsening heart failure

**Ivabradine: Adverse reactions**

- Potential for fetal toxicity
- Phosphenes
- Bradycardia
- Atrial fibrillation
- Hypertension

**Ivabradine: Contraindications**

- Contraindications
  - Acute decompensated heart failure
  - BP < 90/50 mmHg
  - Sick sinus syndrome, Sinoatrial block, 3rd degree AV block
  - Resting heart rate < 60 bpm at baseline
  - Severe hepatic impairment
  - Pacemaker dependence
  - Concomitant use of strong cytochrome P450 3A4 (CYP3A4) inhibitors

**Ivabradine: Dosage forms**

- Tablets: 5 mg and 7.5 mg
- Packaged in bottles
Cangrelor (Kengreal™)

- **Indication:** Adjunct to percutaneous coronary intervention (PCI) to reduce risk of periprocedural MI, repeat coronary revascularization, and stent thrombosis in patients who are:
  1. Not been treated with a P2Y12 platelet inhibitor
  2. Not receiving a glycoprotein IIb/IIIa inhibitor

Cangrelor: Dosing

1. **Bolus:** 30 mcg/kg IV bolus
   - Prior to PCI
2. **Infusion:** 4 mcg/kg/min
   - Minimum of two hours or duration of PCI
3. **Oral:**
   - Clopidogrel: 600 mg immediately after discontinuation
   - Prasugrel: 60 mg immediately after discontinuation
   - Ticagrelor: 180 mg at any time during infusion or immediately after discontinuation

Cangrelor: CHAMPION-PHOENIX

- Randomized, multi-national, double-blind, double-dummy, superiority trial
- **Cangrelor:** 1) Bolus: 30 mcg/kg 2) Infusion: 4 mcg/kg/min for 2 hours or duration of procedure 3) Clopidogrel 600 mg
- **Clopidogrel:** 600 mg or 300 mg
- Primary endpoint: Composite of death from any cause, MI, revascularization, or stent thrombosis within 48 hours

Cangrelor: CHAMPION-PHOENIX Results

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Cangrelor (N=5472)</th>
<th>Clopidogrel (N=5470)</th>
<th>HR (95% CI; p value)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1°</strong></td>
<td>4.7%</td>
<td>5.9%</td>
<td>0.78 (0.66–0.93; 0.005)</td>
</tr>
<tr>
<td><strong>GUSTO Severe</strong></td>
<td>0.2%</td>
<td>0.1%</td>
<td>1.50 (0.53–4.22; 0.44)</td>
</tr>
</tbody>
</table>

Cangrelor: Contraindications

- Contraindications
  1. Significant active bleeding
  2. Hypersensitivity to cangrelor
Cangrelor: Dosage form and stability

- Injection: Cangrelor 50 mg per 10 mL vial
- Each vial must be reconstituted and then diluted in a NS or D5W 250 mL bag
  - Concentration of 200 mcg/mL
- Stability: 12-24 hours (depending on solution) at room temperature

Sacubitril/valsartan (Entresto™)

- Indication: Reduce the risk of cardiovascular death and hospitalization for heart failure in patients with a reduced ejection fraction and NYHA Class II-IV HF
- MOA
  - Sacubitril → neprilysin inhibitor
  - Valsartan → angiotensin II receptor blocker
- PARADIGM-HF

Sacubitril/valsartan: Dosing

- Initial: 49/51 mg (sacubitril/valsartan) BID
  - Reduced initial dose: 24/26 mg BID
  - Not on ACEi or ARB or taking low dose
  - Severe renal impairment
  - Moderate hepatic impairment
- Titrate: Double dose after 2 - 4 weeks
  - Target 97/103 mg BID

Pipeline Medications

- Idarucizumab
- PCSK9 Inhibitors

Questions?

New Drugs Track: Developments in Cardiovascular Pharmacotherapy

Christina Coakley, PharmD, BCPS

OWNING CHANGE: Taking Charge of Your Profession