Objectives

1. Identify new molecular entities approved in the last year that may be useful in the clinical care of older adults
2. Identify characteristics, such as dosing, pharmacokinetics, side effects, and monitoring that may require special attention in older adults
3. Recognize patients who may be candidates for these medications, taking into consideration other patient characteristics
Methods

• The FDA website (www.fda.gov) was reviewed for new molecular entity approvals from January 2014 through December 2014

• Drugs were included according to the following criteria:
  1) they had potential to be prescribed in the elderly population
  2) they were expected to have a significant influence on the care of elderly patients

<table>
<thead>
<tr>
<th>Drug: Brand (generic)</th>
<th>Approval</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Savaysa (edoxaban)</td>
<td>January 2015</td>
<td>A-fib, DVT/PE</td>
</tr>
<tr>
<td>TRULICITY (dulaglutide)</td>
<td>September</td>
<td>GLP-1 agonist for type 2 DM</td>
</tr>
<tr>
<td>BELSOMRA (suvorexant)</td>
<td>August</td>
<td>Orexin antagonist for insomnia (sleep onset/maint)</td>
</tr>
<tr>
<td>JARDIANCE (empagliflozin)</td>
<td>August</td>
<td>SGLT-2 inhibitor type 2 DM</td>
</tr>
<tr>
<td>STRIVERDI Respimat (olodaterol)</td>
<td>July</td>
<td>Once daily LABA for COPD</td>
</tr>
<tr>
<td>KERYDIN (tavaborole)</td>
<td>July</td>
<td>Topical tx of onychomycosis</td>
</tr>
<tr>
<td>JUBLIA (efinaconazole)</td>
<td>June</td>
<td>Topical tx of onychomycosis</td>
</tr>
<tr>
<td>ZONTIVITY (vorapaxar)</td>
<td>May</td>
<td>↓ risk of MI, stroke in high-risk</td>
</tr>
<tr>
<td>TANZEUM (albiglutide)</td>
<td>April</td>
<td>GLP-1 agonist type 2 DM</td>
</tr>
<tr>
<td>Farxiga (dapagliflozin)</td>
<td>January</td>
<td>SGLT-2 inhibitor type 2 DM</td>
</tr>
</tbody>
</table>

Diabetes Update

• GLP-1 agonists
  – Delayed *gastric emptying* and decreased *glucagon secretion*; increased *satiety* and glucose-dependent *insulin secretion*

• SGLT-2 inhibitors
  – Inhibition of the sodium-glucose transporter 2 promotes the renal excretion of glucose resulting in osmotic diuresis

### GLP-1 Agonists

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosing Instructions</th>
</tr>
</thead>
</table>
| Dulaglutide (Trulicity) | Single-use pens dosed as 0.75-1.5mg once weekly  
                          | Structural modification to prevent DPP-4 breakdown  
                          | Half-life = 5 days                                                                 |
| Liraglutide (Victoza)  | One pen which expires after 30 days  
                          | Daily administration: 0.6mg → 1.2mg → 1.8mg                                          |
| Exenatide (Byetta)     | Byetta: 5 or 10mcg (must titrate dose)  
                          | Bydureon: 2mg weekly *(complicated administration)*                                 |
| Albiglutide (Tanzeum)  | 30mg weekly and titrated to 50mg weekly  
                          | Fusion of DPP-4-resistant GLP-1 to human albumin  
                          | Half-life = 5-7 days  
                          | *(complicated reconstitution)*                                                       |

• All will lower A1c by 1-2%, have a low-risk of hypoglycemia, cause 3-5 kg of weight loss, and have a high cost
Tanzeum™ (albiglutide) package insert

SGLT-2 inhibitors

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Renal adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canagliflozin (Invokana)</td>
<td>100mg, 300mg</td>
<td>GFR 45-60, max 100mg QD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>GFR &lt; 45, do not use $375/mo</td>
</tr>
<tr>
<td>Dapagliflozin (Farxiga)</td>
<td>5mg, 10mg</td>
<td>GFR &lt; 60, do not use $375/mo</td>
</tr>
<tr>
<td>Empagliflozin (Jardiance)</td>
<td>10mg, 25mg</td>
<td>GFR &lt; 45, do not use $361/mo</td>
</tr>
</tbody>
</table>

- All will lower A1c by 0.5 to 0.7%, have a low-risk of hypoglycemia, cause 3-5 kg of weight loss, but high cost
- Side effects include **UTI, genital mycotic infections** and **orthostatic hypotension**
**Where do these drugs fit?**

### Monotherapy

**Metformin**

### 2-Drug Combo

- **SU**
- **TZD**
- **DPP-4 Inhibitor**
- **GLP-1 Agonist**
- **Insulin**
- *(SGLT-2 Inhibitor?)*

### 3-Drug Combo

- Any combo except:
  - DPP-4 + GLP-1
  - Insulin + SU
- OR: basal-bolus insulin

---

**Vorapaxar**

*(Zontivity™)*
Vorapaxar (Zontivity™)

- FDA-approved (May 8, 2014) for the reduction of thrombotic cardiovascular events in patients with a history of myocardial infarction (MI) or with peripheral arterial disease (PAD).

- Manufacturer
  - Merck & Co., Inc.

- Mechanism of action
  - Reversible antagonist of the protease-activated receptor-1 (PAR-1) on platelets, but effectively irreversible (long T₁/₂). Inhibits thrombin-induced and thrombin receptor agonist peptide (TRAP) induced platelet aggregation.

Vorapaxar (Zontivity™)

- Approved dosing
  - 2.08 mg tablets
  - Starting dose: 2.08 mg orally once daily, with or without food
  - Addition to aspirin and/or clopidogrel according to their indications or standard of care
  - Renal adjustment:
    - No dose adjustment is required
  - Hepatic impairment:
    - No dose adjustment in mild or moderate impairment
    - Not recommended in patients with severe impairment
Warnings and Precautions

• **Black Box Warning**
  – Antiplatelet agents increase the risk of bleeding, including ICH and fatal bleeding. Do not use in patients with active pathological bleeding or a history of stroke, TIA or ICH.

• **Warnings**
  – Increases the risk of bleeding in proportion to a patient’s underlying risk
  – Risk factors include: older age, low body weight, reduced renal or hepatic function, history of bleeding disorders and use of certain concomitant medications (anticoagulants, fibrinolytic therapy, chronic nonsteroidal anti-inflammatory drugs (NSAIDS), SSRIs, SNRIs)
  – Avoid use with warfarin

Vorapaxar (Zontivity™)

• **Side effects (> 2%)**
  – Anemia, depression, rashes, eruptions and exanthemas

• **Drug interactions**
  – Strong CYP3A Inhibitors
  – Strong CYP3A Inducers
  – Warfarin
  – Prasugrel

• **Cost:** AWP = $267/mo (RedBook Online®)

• **Special populations**
  – **Geriatrics:** relative risk of bleeding was similar across age groups. No overall differences in safety or effectiveness were observed between these patients and younger patients
  – **Hepatic impairment:** based on the inherent risk of bleeding in patients with severe hepatic impairment, vorapaxar is not recommended in such patients
Vorapaxar (Zontivity™)

• Use in Geriatric patients
  – In TRA 2P, in post-MI or PAD patients without a history of stroke or TIA, 33% of patients were >65 years of age and 9% were >75 years of age
  – Older patients are generally at a higher risk of bleeding; consider patient age before initiating
  – Metabolized by CYP3A4 and CYP2J2, and due to decreased liver function in the elderly, the half life of the drug will be increased

Evidence

• TRA 2P – TIMI 50 trial
  – Vorapaxar to reduce atherothrombotic events in patients with established atherosclerosis receiving standard therapy
  – ~ 27,000 patients with MI or ischemic stroke from 2 weeks to 12 months ago, or PAD randomized to vorapaxar 2.5mg daily or placebo for 30 months

  – Primary efficacy endpoint: composite of CV death, MI, or stroke
  – Primary safety endpoint: moderate or severe bleeding

Evidence -- Results

• Baseline characteristics
  – Median age = 61 years
  – 67% MI, 18% stroke, 14% PAD
  – Use of antiplatelets according to indication
    • MI: ASA (98%), *thienopyridine (78%)
    • Stroke: ASA (81%), *thienopyridine (24%), dipyridamole (19%)
    • PAD: ASA (88%), *thienopyridine (37%)

*Primarily clopidogrel; only 0.7% used prasugrel during the study


<table>
<thead>
<tr>
<th>Outcome</th>
<th>Vorapaxar</th>
<th>Placebo</th>
<th>Hazard ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Event</td>
<td>Events</td>
<td>Event</td>
</tr>
<tr>
<td></td>
<td>(n)</td>
<td>rate (%)</td>
<td>(n)</td>
<td>rate (%)</td>
</tr>
<tr>
<td>1º Outcome</td>
<td>1028</td>
<td>9.3</td>
<td>1176</td>
<td>10.5</td>
</tr>
<tr>
<td>MI</td>
<td>564</td>
<td>5.2</td>
<td>673</td>
<td>6.1</td>
</tr>
<tr>
<td>1º Safety -- bleeding</td>
<td>428</td>
<td>4.2</td>
<td>267</td>
<td>2.5</td>
</tr>
<tr>
<td>Intracranial bleeding*</td>
<td>102</td>
<td>1.0</td>
<td>53</td>
<td>0.5</td>
</tr>
<tr>
<td>Net Clinical Benefit</td>
<td>1315</td>
<td>11.7</td>
<td>1358</td>
<td>12.1</td>
</tr>
</tbody>
</table>

*Those with a history of stroke were stopped after 2 years due to increased risk of intracranial hemorrhage

Evidence -- Results

- Myocardial infarction pre-specified subgroup
  - ~ 18,000 with MI randomized

  - 1º endpoint: CV death, MI, or stroke
    • 8.1% vs. 9.7% (HR 0.8, 95% CI 0.72-0.89, p<0.0001)

- Mod-severe bleeding
  • 3.4% vs. 2.1% (HR 1.61, 95% CI 1.31-1.97, p<0.0001)

\[\text{Lancet 2012; 380: 1317–24.}\]

Vorapaxar (Zontivity™)

Conclusions

1. Vorapaxar reduced the risk of CV death, MI, or stroke among patients with stable atherosclerosis

2. The benefit of this therapy was most apparent in patients with a history of MI

3. Vorapaxar also increased the risk of moderate or severe bleeding, including ICH
   a. ICH occurred most frequently in patients with a history of stroke

\[\text{Zontivity™ Package Insert}\]
Where does Zontivity™ fit?

– Very likely higher risk of bleeding in the old-old population
– Should not use with other antiplatelet agents (besides clopidogrel), or warfarin
– Be aware of drug-drug interactions through the CYP3A4 system
– Potential role for patients with continued CVD despite standard of care antiplatelets

Belsomra™
(Suvorexant)
Belsomra™ (Suvorexant)

- FDA-approved (August 13, 2014) to treat difficulty in falling and staying asleep (insomnia).

- Manufacturer
  - Merck & Co., Inc.

- Mechanism of action
  - Orexin receptor antagonist
    - The orexin neuropeptide signaling system is a central promoter of wakefulness. Blocking neuropeptides orexin A and orexin B to receptors OX1r and OX2R is thought to suppress wake drive.

Belsomra™ Package Insert

Belsomra™ (Suvorexant)

- Schedule IV drug
  - Has been shown to produce similar effects as zolpidem on “drug liking” and other subjective measures in recreational polydrug users.

- Cost: AWP = Unknown

- Half-life = 12 hours

Belsomra™ Package Insert
Belsomra™ (Suvorexant)

**Approved dosing**
- Starting dose is 10 mg
  - Taken within 30 minutes of going to bed, with at least 7 hours of sleep remaining
- May increase to 20 mg
- No dose adjustment required for renal impairment
- Not recommended for patients with severe hepatic impairment

**Drug interactions**
- Moderate inhibitors of CYP3A
  - Ciprofloxacin, dilt/verapamil, GF juice, fluconazole
  - Recommended dose is 5 mg, which can be increased to 10 mg once daily
- Strong CYP3A inhibitors
  - Ketoconazole, itraconazole, posaconazole, clarithromycin
  - Do not use
- Efficacy may be reduced with strong CYP3A4 inducers (e.g. CBZ, PHB, PHT)
- Monitor digoxin with concomitant suvorexant
Belsomra™ (Suvorexant)

- **Contraindications**: Narcolepsy

- **Warnings/Precautions/Adverse effects**
  - CNS depressant effects and daytime impairment
  - Abnormal thinking and behavioral changes
  - Worsening of depression/suicidal ideation
  - Sleep paralysis, hypnagogic/hypnopompic hallucinations, cataplexy-like symptoms

Suvorexant (Belsomra™)

- **Use in Geriatric patients**
  - Next-day memory and balance in the elderly
    - Conflicting trial result data: 3 trials showed no significant effects but a 4th trial in healthy *non-elderly* subjects, showed a significant decrease in word recall and increase on body sway
  - Middle of the night safety in elderly subjects
    - 30 mg dosing resulted in impairment of balance but memory was not shown to be impaired
Efficacy of Belsomra™

1. In two studies, the efficacy was superior to placebo for sleep latency and sleep maintenance as assessed by PSG and subjective patient report

2. PSG → Faster sleep onset of ~ 10 minutes
   - 70 minutes at baseline to 35 minutes with suvorexant and 45 minutes with PBO at 3 months

3. Pt report → Faster sleep onset of ~ 10 minutes
   - 70-80 minutes at baseline to 40-50 minutes with suvorexant and 50-60 minutes with PBO at 10 months

Where does Belsomra™ fit?

• At this point, there is not a lot to differentiate this agent from other agents besides it’s different mechanism

• Scheduled which may limit use
Edoxaban (Savaysa™)

• FDA-approved (January 8, 2015) for non-valvular atrial fibrillation and treatment of DVT/PE
• Manufacturer
  – Daiichi Sankyo
• Mechanism of action
  – Factor Xa inhibitor
• Approved dosing: 60mg, 30mg, 15mg
  – Treatment of NVAF:
    • Assess CrCL before initiating therapy
    • 60 mg once daily in patients with CrCL >50 to ≤ 95 mL/min
    • 30 mg once daily in patients with CrCl 15-50 mL/min**
  – Treatment of DVT and PE:
    • 60 mg once daily
    • 30 mg once daily for patients with CrCl 15-50 mL/min** or body weight ≤60 kg or who use certain P-gp inhibitors (verapamil and quinidine, azithromycin, clarithromycin, erythromycin, itraconazole, ketoconazole)
  – ** Clinical trials did not include patients with a CrCl <30mL/min
Warnings and Precautions

• Warnings
  – Reduced efficacy in Afib patients with CrCl > 95 mL/min
    • Increased risk of ischemic stroke when taking 60 mg daily compared to warfarin (HR 2.16)
  – Premature discontinuation increases risk of ischemic events
  – Spinal/epidural hematoma may develop if patients have neuraxial anesthesia or spinal puncture
    • Can lead to long-term or permanent paralysis

• Side effects (> 2%)
  – Bleeding—only ADE different than PBO
  – Rash (3.6%)
  – Abnormal LFTs (7.8%)
  – Anemia (1.7%)

• Drug interactions
  – Rifampin
  – PGP inhibitors
  – Other antiplatelets

• Cost: unknown but likely comparable to other agents (≈$325/mo)

• Special populations
  – Geriatrics: nothing mentioned in PI
  – Hepatic impairment: not recommended in moderate or severe hepatic impairment
  – Renal impairment: dose reduction

Edoxaban (Savaysa™)
Edoxaban (Savaysa™): Evidence for NVAF

- Active controlled RCT: ENGAGE AF-TIMI 48
  - 21,105 pts for median 2.8 yrs
    - Mean CHADS\textsubscript{2} score = 2.8
    - Median age = 72 yrs
      - Age $\geq$ 75 yrs = 40%; age $\geq$ 80 = 17%
    - Excluded: CrCl $<$ 30 mL/min
- Edoxaban 60 mg once daily vs warfarin
  - 30 mg once daily if:
    - CrCl 30-50 mL/min (19% of study population)
    - Body weight $\leq$ 60kg
    - Concomitant use of verapamil, quinidine, dronedarone

Edoxaban (Savaysa™): Evidence for VTE

- Active controlled RCT: Hokusai-VTE study
- 8240 pts treated for 3-12mo
  - Median age = 56 yrs
    - Age ≥75 yrs: 13%
  - Hx cancer: 9%
  - Previous VTE: 19%
  - Excluded: CrCl <30 mL/min
- Edoxaban 60 mg once daily vs warfarin
  - 30 mg once daily if:
    - CrCl 30-50 mL/min (7% of study population)
    - Body weight ≤ 60kg
    - Concomitant use of potent PGP inhibitors

### Endpoint Warfarin Edoxaban HR P Value

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Warfarin</th>
<th>Edoxaban</th>
<th>HR</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>First recurrent VTE/VTE-death</td>
<td>3.5%</td>
<td>3.2%</td>
<td>0.89 (0.70-1.13)</td>
<td>&lt;0.001 for noninferiority</td>
</tr>
<tr>
<td>First major or clinically relevant non-major bleed</td>
<td>10.3%</td>
<td>8.5%</td>
<td>0.81 (0.71-0.94)</td>
<td>0.004 for superiority</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>1.6%</td>
<td>1.4%</td>
<td>0.84 (0.59-1.21)</td>
<td>NS for superiority</td>
</tr>
<tr>
<td>Clin relevant non-major bleeding</td>
<td>8.9%</td>
<td>7.2%</td>
<td>0.80 (0.68-0.93)</td>
<td>0.004 for superiority</td>
</tr>
<tr>
<td>Any bleeding</td>
<td>25.6%</td>
<td>21.7%</td>
<td>0.82 (0.75-0.90)</td>
<td>&lt;0.001 for superiority</td>
</tr>
</tbody>
</table>
# NOAC Data in Older Adults

<table>
<thead>
<tr>
<th>MOA</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct thrombin (IIa) inhibitor</td>
<td>Direct Xa Inhibitor</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

## NVAF Efficacy Compared to Warfarin
- ↓ ischemic stroke<sup>1,4</sup>
- ↓ death<sup>1</sup>
- No difference<sup>4</sup>
- ↓ stroke<sup>3</sup>/No difference<sup>4</sup>
- ↓ death<sup>3</sup>

## NVAF Bleeding Compared to Warfarin
- ↑ GI<sup>1,2</sup>
- ↑ major<sup>1</sup>
- ↓ ICH<sup>1,2</sup>
- No difference<sup>4</sup>
- ↓ major<sup>3,4</sup>
- ↓ total<sup>3</sup>
- ↓ ICH<sup>3</sup>

## VTE tx Efficacy Compared to Warfarin
- Unknown
- ↓ VTE/death<sup>4</sup>
- ↓ VTE/death<sup>4</sup>
- Unknown

## VTE tx Bleeding Compared to Warfarin
- Unknown
- No difference<sup>4</sup>
- No difference<sup>4</sup>
- Unknown

---


---

# NOAC Renal/Hepatic Comparison

<table>
<thead>
<tr>
<th>Renal Elimination</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>80%</td>
<td>36%</td>
<td>27%</td>
<td>50%</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CYP metabolism</th>
<th>None</th>
<th>CYP3A4/5</th>
<th>CYP2J2</th>
<th>CYP3A4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Minimal</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PGP Substrate</th>
<th>Yes</th>
<th>Yes</th>
<th>Yes</th>
<th>Yes</th>
</tr>
</thead>
</table>

## Drug Interactions

### Avoid in NVAF:
- PGP inducers (e.g. rifampin)
- PGP inhibitor + CrCl <30 mL/min

### In NVAF reduce dose:
- CrCl 30-50 mL/min + PGP inhibitors (dronedarone, ketoconazole)

### Avoid in VTE:
- CrCl <50 mL/min + PGP inhibitor

---

Avoid: PGP + strong CYP3A4 inducers (e.g. rifampin, CBZ)
Avoid: PGP + strong CYP3A4 inhibitors (e.g. ketoconazole, itraconazole)
Assess Risk: other PGP/CYP3A4 inhibitors (e.g. diltiazem)
Avoid: Strong PGP + CYP3A4 inhibitors (e.g. ketoconazole, clarithromycin)
Avoid: rifampin in VTE reduce dose: PGP inhibitors (verapamil and quinidine, azithromycin, clarithromycin, erythromycin, itraconazole, ketoconazole)
### NOAC Dosing Comparison

<table>
<thead>
<tr>
<th>Pradaxa (dabigatran)</th>
<th>Eliquis (apixaban)</th>
<th>Xarelto (rivaroxaban)</th>
<th>Savaysa (edoxaban)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AFib</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ClCr&gt;30: 150 mg twice daily</td>
<td>2.5 mg twice daily in patients with at least 2 of the following: age ≥80 years, body weight ≤60 kg, or Scr ≥1.5 mg/dl</td>
<td>ClCr&gt;50: 20 mg once daily with evening meal</td>
<td>ClCr &gt;95 mL/min DO NOT USE</td>
</tr>
<tr>
<td>ClCr 15-30: 75 mg twice daily</td>
<td>2.5 mg twice daily</td>
<td>ClCr 15-50: 15 mg once daily with evening meal</td>
<td>ClCr &gt;50 mL/min to &lt;95 mL/min: 60 mg once daily</td>
</tr>
<tr>
<td>ClCr&lt;15 or on dialysis: Avoid</td>
<td>ClCr 5 mg twice daily</td>
<td>ClCr&lt;15: Avoid</td>
<td>ClCr 15-50 mL/min to 30 mg once daily</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Acute VTE Tx</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>ClCr&gt;30: 150 mg twice daily starting after discontinuation of 5-10 days of parenteral anticoagulation</td>
<td>10 mg twice daily x 5 days, then 5 mg twice daily x 6 months, then 2.5 mg twice daily thereafter</td>
<td>ClCr&lt;30: Avoid</td>
<td>60 mg once daily starting after discontinuation of 5-10 days of parenteral anticoagulation</td>
</tr>
<tr>
<td>ClCr&lt;30 or on dialysis: Avoid</td>
<td>No dose adjustment required for renal impairment</td>
<td>ClCr&lt;30: Avoid</td>
<td>ClCr&gt;50 mL/min or body weight ≤60 kg or taking certain PGP inhibitors: 30 mg once daily after parenteral anticoagulation</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Long Term VTE Tx &amp; PPX</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>ClCr&gt;30: 150 mg twice daily</td>
<td>2.5 mg twice daily</td>
<td>No dose adjustment required for renal impairment</td>
<td>ClCr&gt;30: 20 mg once daily with food</td>
</tr>
<tr>
<td>ClCr&lt;30 or on dialysis: Avoid</td>
<td>ClCr&lt;30: Avoid</td>
<td></td>
<td>ClCr&lt;30: Avoid</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>VTE PPX Post THR/TKR Surgery</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Not FDA-approved for this indication</td>
<td>Hip replacement: 2.5 mg twice daily starting 12-24 hours post-op x 35 days</td>
<td>Knee replacement: 2.5 mg twice daily starting 12-24 hours post-op x 12 days</td>
<td>Not FDA-approved for this indication</td>
</tr>
<tr>
<td></td>
<td>Knee replacement, ClCr&gt;30, starting 6-10 hours post-op: 10 mg once daily x 12 days</td>
<td>ClCr 30-50: use caution/observe closely for bleeding</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ClCr&lt;30: Avoid</td>
<td>ClCr&lt;30: Avoid</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Switching from Warfarin</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Discontinue warfarin and start when INR&lt;2.0</td>
<td>Discontinue warfarin and start when INR&lt;3.0</td>
<td>Discontinue warfarin and start when INR&lt;2.5</td>
<td></td>
</tr>
</tbody>
</table>

### Where does Savaysa™ fit?

- **4th agent in NOAC group**
- **Somewhat complicated dosing regimen**
  - Like all others, must calculate CrCl
  - Requires LMWH bridge in acute VTE
  - PI includes lower dosing for CrCl 15-30mL/min, but these patients were excluded from clinical trials
  - Dosing does not quite match RCTs for NVAF
- **No DIs with CYP3A4 (diltiazem)**
- **No Phase IV data yet available**
**Medication updates**

- **Nexium (esomeprazole)**
  - Available over-the-counter and generically

- **Spiriva Respimat inhalation spray**
  - Handheld device delivering a slow-moving, soft mist that allows gentle and pleasant inhalation

- **Saxenda (liraglutide)**
  - New approval for chronic weight management at higher dose of 3mg daily

**Conclusions**

- Zontivity
- Belsomra
- Savaysa