Brief Review of TSOACs

SHIN-YU LEE, PHARMD, BCACP
CHRISTINA S. WANG, PHARMD
10 minute overview of the target specific oral anticoagulants
5 minute Q & A
Highlight differences among the 4 agents
  - Key counseling points
  - Handout given today is a summary of today’s presentation
Any questions regarding referral to 1M ACC (anticoagulation clinic) or administrative questions please email:
  - Shin-Yu Lee, PharmD, BCACP
  - shin-yu.lee@sfdph.org
Target Specific Oral Anticoagulants

- Dabigatran (Pradaxa)
- Rivaroxaban (Xarelto)
- Apixaban (Eliquis)
- Edoxaban (Savaysa)
<table>
<thead>
<tr>
<th></th>
<th>SFHP M-CAL</th>
<th>Healthy SF</th>
<th>Anthem BC M-CAL</th>
<th>M-CAL</th>
<th>MCR</th>
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</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>PA required</td>
<td>Non-formulary</td>
<td>Non-formulary</td>
<td>Non-formulary</td>
<td>😞</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>😊</td>
<td>😊</td>
<td>😊</td>
<td>😊</td>
<td>😊</td>
</tr>
<tr>
<td>Apixaban</td>
<td>😊</td>
<td>Non-formulary</td>
<td>😊</td>
<td>Non-formulary</td>
<td>😊</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>Non-formulary</td>
<td>Non-formulary</td>
<td>Non-formulary</td>
<td>Non-formulary</td>
<td>Most plans do not cover</td>
</tr>
</tbody>
</table>

Most plans do not cover Edoxaban.
# Indications

<table>
<thead>
<tr>
<th></th>
<th>Mechanical Valves</th>
<th>Valvular Afib</th>
<th>APLS (+)</th>
<th>Clotting Disorder</th>
<th>1°/2° PCV PAH</th>
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</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apixaban</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Edoxaban</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

Not well studied... thus not indicated
Meta-analysis: Efficacy of TSOACs – Stroke and Systemic Embolism

TSOACs decrease stroke and systemic embolism risk by 19%

## Indications

<table>
<thead>
<tr>
<th></th>
<th>Non-valvular Afib</th>
<th>DVT/PE Tx</th>
<th>Recurrent DVT/PE Tx</th>
<th>VTE px s/p hip/knee replacement</th>
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</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Hip only</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Hip + Knee</td>
</tr>
<tr>
<td>Apixaban</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>
## Bleed Risk Comparison with Warfarin: Major Bleeding

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>TSOACs</th>
<th>VKAs</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
</tr>
<tr>
<td>1.1.1 Major bleeding</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EINSTEIN-DVT, 2010</td>
<td>14</td>
<td>1718</td>
<td>20</td>
<td>1711</td>
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<td>RE-MEDY, 2013</td>
<td>13</td>
<td>1430</td>
<td>25</td>
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<td>RE-COVER II, 2014</td>
<td>15</td>
<td>1279</td>
<td>22</td>
<td>1289</td>
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<tr>
<td>RE-COVER, 2009</td>
<td>20</td>
<td>1274</td>
<td>24</td>
<td>1265</td>
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<tr>
<td>AMPLIFY, 2013</td>
<td>15</td>
<td>2676</td>
<td>49</td>
<td>2689</td>
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<td>J-ROCKET AF, 2012</td>
<td>26</td>
<td>639</td>
<td>30</td>
<td>639</td>
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<tr>
<td>EINSTEIN-PE, 2012</td>
<td>26</td>
<td>2412</td>
<td>52</td>
<td>2405</td>
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<tr>
<td>HOKUSAI-VTE, 2013</td>
<td>56</td>
<td>4118</td>
<td>66</td>
<td>4122</td>
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<td>ARISTOTLE, 2011</td>
<td>327</td>
<td>9088</td>
<td>462</td>
<td>9052</td>
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<td>ROCKET AF, 2011</td>
<td>395</td>
<td>7111</td>
<td>386</td>
<td>7125</td>
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<td>RE-LY, 2009</td>
<td>741</td>
<td>12091</td>
<td>421</td>
<td>6022</td>
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<tr>
<td>ENGAGE-AF-TIMI-48, 2013</td>
<td>672</td>
<td>14014</td>
<td>524</td>
<td>7012</td>
</tr>
</tbody>
</table>

**Subtotal (95% CI)**

<table>
<thead>
<tr>
<th>Events</th>
<th>Total</th>
<th>M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>2320</td>
<td>2081</td>
<td>0.72 [0.62, 0.85]</td>
</tr>
</tbody>
</table>

Total events: 2320
Heterogeneity: Tau² = 0.04; Chi² = 48.96, df = 11 (P < 0.00001); I² = 78%
Test for overall effect: Z = 3.98 (P < 0.0001)

Favours [TSOACs] Favour [VKAs]
Dabigatran (Pradaxa)

- Dosing
  - Twice daily
- Special storage requirements (in original packaging)
  - Moisture protection
  - Special bottle cap or unit dosing packaging
  - Capsules cannot be opened or crushed
- Formulated with tartaric acid
  - Consider use with PPI
- *Safer* in liver disease/hepatic dysfunction
- Reversal agent available
Rivaroxaban (Xarelto)

- **Dosing**
  - Once daily
  - Always with a full meal
  - Doses ≥15mg/day

- **Avoid in:**
  - Child/Pugh class B/C
  - Concomitant administration with strong CYP3A4 and P-glycoprotein inducers and inhibitors
Apixaban (Eliquis)

- **Dosing**
  - Twice daily
- **Least renally cleared**
- **Avoid in:**
  - Concomitant use with strong CYP3A4 or P-glycoprotein inducers and inhibitors
  - Child-Pugh Class C
Edoxaban (Savaysa)

- **Dosing**
  - Once daily
- **Contraindicated if:**
  - CrCl > 95mL/min
- **Avoid in:**
  - Child-Pugh Class B/C
- **Newest TSOAC**
  - Not available on most insurance formularies
- **Minimal CYP3A4 interactions?**
Choosing a TSOAC

- TSOACs are often chosen/preferred for the following reasons:
  - Guideline recommendation
    - CHEST 2016 recommends using TSOACs over VKA for treatment of DVT/PEs requiring short treatment duration (3-6 months)
  - No dietary restrictions
    - Warfarin requires consistent intake of foods high in vitamin K
  - Active EtOH or recent h/o of EtOH use
  - Unable to attend INR monitoring appointments
  - Difficulty with venipunctures for INRs
Choosing a TSOAC

- **Weight**
  - International Society of Thrombosis and Hemostasis 2016:
    - Recommends caution with use in patients >120kg or BMI >40kg/m²

- **Adherence and Persistence**
  - Frequency of administration - QDAY vs. BID
  - Administration and storage

- **Food Insecurity**
  - Rivaroxaban requires co-administration with a meal
References


References

Bleed Risk Comparison with Warfarin

<table>
<thead>
<tr>
<th>Drug</th>
<th>ICH</th>
<th>GI bleed</th>
<th>Other major bleed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>Less</td>
<td>More</td>
<td>More</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>Less</td>
<td>More</td>
<td>Similar</td>
</tr>
<tr>
<td>Apixaban</td>
<td>Less</td>
<td>Similar</td>
<td>Less</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>Less</td>
<td>More</td>
<td>Less (newest drug)</td>
</tr>
</tbody>
</table>

Other Major bleeds defined:
• Clinically overt
• Bleed at a critical site or contributory factor to death
• Hgb decrease >2g/dL
• Transfusion >2 units PRBCs
Safety Profiles – ISMP Q4-2014

- Dabigatran
  - Highest reports of serious ADRs
  - Largest # of patient deaths
  - Most reported severe hemorrhages
- Apixaban
  - Fewest ADR reports
  - Fewest patient deaths
- Rivaroxaban
  - Most dispensed on outpatient side
  - ? More thromboembolic events?