Target Specific Oral Anticoagulants (TSOAs)

Learning Objectives
1. Discuss the pharmacology of TSOAs
2. Discuss the indications and contraindications for the TSOAs
3. Review the kinetic profiles of the various TSOAs

A Historical Perspective: Anticoagulant Therapies

Kinetic Profiles of Warfarin vs. Non-VKAs

Coagulation Cascade
Drug Interactions

Adapted from: Ansell J. Chest 2008;133:160S-98S.

Warfarin Drug Interactions

- Many pharmacokinetic and pharmacodynamic drug interactions
- Dietary vitamin K interactions
- Managed by frequent coagulation laboratory monitoring

Adapted from: Ansell J. Chest 2008;133:160S-98S.

Cumulative Effects

Non-VKA Drug Interactions: P-glycoprotein

Absorption varies depending on inhibition or induction of P-gp by other drugs


P-glycoprotein Drug Interactions

- P-glycoprotein (P-gp) is a drug efflux pump found in the gut, liver, kidney, blood-brain barrier, and cancer cells. It pumps drugs out of cells and into the gut, bile, and/or urine for excretion.
- Inducers and inhibitors of P-gp
  - Inducers: increase the activity of P-gp
  - Inhibitors: block the action of P-gp
- When P-gp inducers or inhibitors are taken with other medications that are transported by P-gp, they can alter the elimination of that medication
- Drugs may be transported by P-gp and also inhibit or induce it at the same time
- Inducers and inhibitors can be subdivided into strong, moderate or weak based on how much of an effect they have on P-gp

Non-VKA Drug Interactions: P-glycoprotein

Absorption varies depending on inhibition or induction of P-gp by other drugs


Drug-Drug Interactions with Dabigatran

<table>
<thead>
<tr>
<th>P-Glycoprotein Effect</th>
<th>Interactions</th>
<th>Specific Examples</th>
<th>Recommended Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inducer of dabigatran metabolism</td>
<td>Reduces exposure to dabigatran</td>
<td>Rifampin</td>
<td>Avoid concomitant use</td>
</tr>
<tr>
<td>Inhibitor of dabigatran metabolism</td>
<td>Increases exposure to dabigatran</td>
<td>Ketoconazole, Dronedarone</td>
<td>• Consider decreasing dose to 75 mg bid in patients with CrCl 30-50 ml/min \n• Avoid concomitant use of dabigatran and P-gp inhibitors in patients with CrCl 15-30 ml/min</td>
</tr>
</tbody>
</table>
Drug-Drug interactions with Rivaroxaban

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Effect</th>
<th>Examples</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dual CYP 3A4 and P-gp inhibitors</td>
<td>Increased rivaroxaban exposure and pharmacokinetics effects</td>
<td>Ketoconazole, Fluconazole, Itraconazole</td>
<td>Avoid concomitant use</td>
</tr>
<tr>
<td>Dual CYP 3A4 and P-gp inducers</td>
<td>Decreased rivaroxaban exposure and possibly decreased efficacy</td>
<td>Carbamazepine, Phenytoin, Rifampicin, St. John's Wort</td>
<td>Avoid concomitant use</td>
</tr>
</tbody>
</table>

Oral Anticoagulants: Administration Issues

<table>
<thead>
<tr>
<th>Warfarin</th>
<th>Dolobraban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bioavailability</td>
<td>100%</td>
<td>6%</td>
<td>80%</td>
</tr>
<tr>
<td>Formulation</td>
<td>May be crushed</td>
<td>Cannot crush/ chew</td>
<td>May be crushed, may be placed in G-tube, or not in G-tube</td>
</tr>
<tr>
<td>Food</td>
<td>With or without</td>
<td>15 and 30 mg with longest meal of day</td>
<td>With or without</td>
</tr>
<tr>
<td>GI adverse effects</td>
<td>Rare</td>
<td>Dyspepsia (~10%)</td>
<td>Rare</td>
</tr>
</tbody>
</table>

Oral Anticoagulants: Labeled Indications

**Non-VKA Oral Anticoagulants:**

<table>
<thead>
<tr>
<th>Indication</th>
<th>U.S.</th>
<th>Canada</th>
<th>Europe</th>
</tr>
</thead>
<tbody>
<tr>
<td>VTE prophylaxis after hip replacement and knee replacement</td>
<td>Rivaroxaban</td>
<td>Apixaban</td>
<td>Edoxaban</td>
</tr>
<tr>
<td>VTE treatment</td>
<td>Dabigatran</td>
<td>Rivaroxaban</td>
<td>Apixaban</td>
</tr>
<tr>
<td>Non-valvular atrial fibrillation</td>
<td>Dabigatran</td>
<td>Rivaroxaban</td>
<td>Apixaban</td>
</tr>
</tbody>
</table>

Kinetic Profiles of Warfarin vs. Non-VKAs

<table>
<thead>
<tr>
<th>Warfarin</th>
<th>Dolobraban</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak (Tmax)</td>
<td>72–96 h</td>
<td>1–3 h</td>
<td>1–3 h</td>
<td>1–2 h</td>
</tr>
<tr>
<td>Protein binding</td>
<td>99%</td>
<td>35%</td>
<td>92–95%</td>
<td>84%</td>
</tr>
<tr>
<td>Renal clearance</td>
<td>N/A</td>
<td>80%</td>
<td>33%</td>
<td>25%</td>
</tr>
<tr>
<td>Metabolism of CYP3A4 involved</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Pgp substrates</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>(15 normal renal function)</td>
<td>20–60 h</td>
<td>13.0 h</td>
<td>8.3 h</td>
<td>15.1 h</td>
</tr>
<tr>
<td>Antidote</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Dosing</td>
<td>Daily</td>
<td>BID Daily</td>
<td>BID Daily</td>
<td></td>
</tr>
</tbody>
</table>

Pharmacokinetic Comparison of TSOA’s

<table>
<thead>
<tr>
<th>TSOA</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak for activity</td>
<td>150 mg</td>
<td>Anti-HA</td>
<td>Anti-HA</td>
<td>Anti-HA</td>
</tr>
<tr>
<td>Protein binding</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Bioavailability</td>
<td>6%–80%</td>
<td>&gt; 50%</td>
<td>&gt; 50%</td>
<td>&gt; 50%</td>
</tr>
<tr>
<td>Time to peak Qt</td>
<td>0.5 hr (delayed by food)</td>
<td>3 hr (delayed by food)</td>
<td>3 hr (delayed by food)</td>
<td></td>
</tr>
<tr>
<td>Dosing interval</td>
<td>Once daily</td>
<td>Twice daily</td>
<td>Twice daily</td>
<td></td>
</tr>
<tr>
<td>Drug interactions</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

**CYP and P-gp inhibitors:**

CYP 3A4: Ketoconazole, Ritonavir, Itraconazole, Isoniazid, Rifampin, Phenytoin

P-gp mediators: Raltegravir, Dolutegravir, Maraviroc, Rilpivirine

**References:**

Idarucizumab (Praxbind®)  
Antidote for Dabigatran

### Pharmacology

**Pronunciation:** Idarucizumab: "eye-dar-ee-zoo-um"  
- Drug: prax· bind

**Class:** Humanized monoclonal antibody fragment

**Formulation:** 2.5g/50ml single-use vials

**Route:** IV

**Metabolism:** Protein catabolism, primarily renally

**Elimination:** Urine (12-33%), idarucizumab-dabigatran complex renally cleared

**Half-life:** 47 minutes (initially); 10.3 hours (terminal)

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**Dosage Modifications**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication</th>
<th>U.S. Labeled Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>VTE Treatment</td>
<td>CrCl &gt; 30ml/min: 150mg BD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CrCl &gt; 30ml/min: Avoid Use</td>
</tr>
<tr>
<td></td>
<td>Non-valvular atrial fibrillation</td>
<td>CrCl &gt; 30ml/min: 150mg BD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CrCl 15-30ml/min: 75mg BD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CrCl &lt; 15ml/min: Avoid Use</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>Hip replacement</td>
<td>10mg daily x 21 days</td>
</tr>
<tr>
<td></td>
<td>Knee replacement</td>
<td>10mg daily x 12 days</td>
</tr>
<tr>
<td></td>
<td>VTE Treatment</td>
<td>CrCl &gt; 50ml/min: Avoid Use</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CrCl 15-50ml/min: 30mg daily</td>
</tr>
<tr>
<td></td>
<td>Non-valvular atrial fibrillation</td>
<td>CrCl &gt; 50ml/min: 30mg daily</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CrCl &lt; 50ml/min: Avoid Use</td>
</tr>
</tbody>
</table>

**Dosing for Dabigatran (Pradaxa®)**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication</th>
<th>U.S. Labeled Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>VTE or PE Treatment</td>
<td>150 mg PO twice daily with CrCl &gt; 30ml/min after 5-10 days of parental anticoagulation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>150 mg PO twice daily with CrCl &gt; 30ml/min after previous treatment</td>
</tr>
<tr>
<td></td>
<td>Non-valvular atrial fibrillation (NVA)</td>
<td>150 mg PO twice daily with CrCl &gt; 30ml/min for patients with CrCl 15 to 30 ml/min</td>
</tr>
<tr>
<td></td>
<td>Prophylaxis of VTE and PE following hip replacement surgery</td>
<td>150mg PO first day, then 30mg once daily for patients with CrCl &gt; 30ml/min</td>
</tr>
</tbody>
</table>

**Direct Factor Xa Inhibitors**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Usual Dosing</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apixaban (Eliquis®)</td>
<td>5mg twice daily</td>
<td>Interacts with inhibitors &amp; inducers of CYP3A4</td>
</tr>
<tr>
<td>Edoxaban (Savaysa®)</td>
<td>60mg once daily</td>
<td>Should not be used in patients with a CrCl&lt;55 ml/min</td>
</tr>
<tr>
<td>Rivaroxaban (Xarelto®)</td>
<td>20mg once daily</td>
<td>Should be taken with the evening meal; interacts with inhibitors &amp; inducers of CYP3A4 and P-gp</td>
</tr>
</tbody>
</table>

**Direct Thrombin Inhibitor**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Usual Dosing</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran (Pradaxa®)</td>
<td>150mg twice daily</td>
<td>Must be dispensed and stored in the original container; tablets should not be broken, crushed or chewed; dispense is common; interacts with inhibitors &amp; inducers of P-gp; dialyzable; reversal agent</td>
</tr>
</tbody>
</table>

**Vitamin K Antagonist**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Usual Dosing</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin (Coumadin®)</td>
<td>2-10mg once daily</td>
<td>Interacts with many other drugs; has dietary restrictions; INR monitoring; reversal agent</td>
</tr>
</tbody>
</table>

**Patient considerations when initiating anticoagulation therapy**
Pros & Cons of TSOAs vs. Warfarin

**Pros**
- No INR monitoring required
- Bridging therapy likely not needed
- Short half life allows easier peri-operative management
- Convenient for rural patients or those with other barriers to clinic visits
- Fewer drug/drug/disease interactions
- Potentially better efficacy & safety for patients with poor INR control on warfarin
- Increased patient satisfaction
- Less complex patient/family education

**Cons**
- No clear advantage over well-controlled warfarin
- TSOAs with BID dosing may have negative impact on compliance
- Missed doses place a patient at higher risk for adverse events due to short half life
- No specific antidote or monitoring parameter for most of the newer agents (TSOAs)
- Higher incidence of GI side effects & discontinuation rate
- Lack of monitoring may foster non-compliance
- Renal monitoring & dose adjustment required
- Higher out-of-pocket costs & copays for newer agents

So what type of patients should we consider as good candidates for TSOA therapy?
- History of poor INR control on warfarin despite good compliance
- Considerable barriers to routine monitoring, such as physical or transportation issues
- Documented warfarin allergy
- Documented history of non-hemorrhagic adverse effects with warfarin
- Documented, confirmed warfarin failure such as an ischemic stroke while consistently therapeutic on warfarin

Prior to initiating a TSOA the patient should be evaluated for the following:
- Appropriate and approved indication for the specific TSOA agent
- Adequate insurance coverage or prescription assistance before starting TSOA agent
- Adequate renal function
- Compliance history
- Lack of medication interactions that would preclude the use of specific TSOA agents
- History of any clinical conditions that might preclude use of a TSOA agent (i.e. history of GI bleed, advanced age, low body weight, etc.)
- Ability to comply with prescribed follow-up plan

Transition of TSOAs

**Switching between Agents**

**Transitioning to Edoxaban**
- From warfarin to other VAs – Discontinue warfarin and start edoxaban when INR > 2.5
- From oral anticoagulants other than VAs – Discontinue current oral anticoagulant and initiate edoxaban at time of the next scheduled dose of the previous anticoagulant
- From LMWH – Discontinue LMWH and initiate edoxaban at the time of the next scheduled administration of LMWH
- From UFH – Discontinue heparin infusion and initiate edoxaban 4 hours later

**Transitioning from Edoxaban**
- To warfarin — Discontinue edoxaban and start the other oral anticoagulant at the time of the next dose of edoxaban
- To parenteral anticoagulants – Discontinue edoxaban and start the parenteral anticoagulant at the time of the next dose of edoxaban
- To warfarin (end option)
  - If starting edoxaban 40mg/day, reduce dose to 10mg/day and begin warfarin concurrently
  - If starting edoxaban 30mg/day, reduce from 15mg/day and begin warfarin concurrently
  - INR must be checked at least twice before reducing to the usual dose of edoxaban to maintain the influence on INR measurements
Switching to Rivaroxaban

• From warfarin to rivaroxaban – Discontinue warfarin and start rivaroxaban as soon as INR is below 3.0

• From anticoagulant other than warfarin to rivaroxaban – Start rivaroxaban 0 to 2 hours prior to next scheduled evening administration of the drug and omit administration of the other anticoagulant

• From unfractionated heparin continuous infusion to rivaroxaban – Stop infusion and start rivaroxaban at the same time

Switching from Rivaroxaban

• From rivaroxaban to warfarin – no clinical trial data are available; INR measurements made during coadministration with warfarin may not be useful for determining the appropriate dose of warfarin

• Consider the use of heparin or LMWH as a bridge – i.e., start heparin infusion/LMWH and warfarin when next dose of rivaroxaban is due. Discontinue the parenteral anticoagulant when the INR is therapeutic

Switching to Dabigatran from warfarin or parenteral anticoagulants

• Converting from warfarin: Discontinue warfarin and initiate dabigatran when INR < 2.0

• Converting from parenteral anticoagulant: Give dabigatran 0-2 hours before time for next dose of the parenteral drug that was to have been administered or initiate at time of discontinuing continuous IV heparin

Switching from Dabigatran to warfarin or parenteral anticoagulants

• CVCl > 50 ml/min: start warfarin 3 days before discontinuing dabigatran

• CVCl 30-50 ml/min: start warfarin 2 days before discontinuing dabigatran

• CVCl 15-30 ml/min: start warfarin 1 day before discontinuing dabigatran

• CVCl < 15 ml/min: no recommendation can be made

• Because dabigatran can increase INR, the INR will better reflect warfarin’s effect only after dabigatran has been stopped for at least 2 days

• Converting to parenteral anticoagulant: wait 12 hours (CVCl > 30 ml/min) or 48 hours (CVCl < 30 ml/min) after last dabigatran dose before initiating parenteral anticoagulant

Switching between Apixaban and anticoagulants other than warfarin

• Discontinue one being taken, and begin the other at the next scheduled dose

Switching between Apixaban and warfarin

• Switching from warfarin to apixaban: Discontinue warfarin and initiate apixaban when INR = 2.0

• Switching from apixaban to warfarin: Apixaban affects INR, so measurements during coadministration with warfarin may not determine appropriate warfarin dose (consider the use of heparin or LMWH as a bridge)
Cockcroft and Gault Creatine Clearance Estimation

- **Cockcroft and Gault Equation:**
  - CrCl = \((140 - \text{age}) \times \text{Weight}/(\text{SCr} \times 72)\) (x 0.85 for females)
  - For patients with less than or equal to IBW, use **actual body weight**
  - For patients in between IBW and 120% of IBW, use IBW
  - Male: IBW = 50 kg + (2.3 x inches over 5 feet)
  - Female: IBW = 45.5 kg + (2.3 inches over 5 feet)
  - For patients with equal to or greater than 120% of IBW, use **adjusted body weight**
    - Adjusted body weight = IBW + 0.4 x (Actual body weight - IBW)
  - For elderly patients (>65 years of age) with SCr < 1.0 mg/dl, please round up SCr to 1.0 mg/dl for the calculation


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**Patient Case**

- TM is a 74 YO female who is newly diagnosed with the condition of Atrial Fibrillation. TM lives in a very rural area of the country where lab testing is very difficult to get therefore warfarin is not an option. TM's physician would like to start this patient on endoxaban, one of the newer TSOAs but consults with you first before ordering this medication.

- **TM's height, weight and serum creatinine are as follows:**
  - Height: 5’1”
  - Weight: 140 lbs
  - SCr = 1.6

- What is TM's estimated CrCl based upon the above information utilizing the Cockcroft and Gault equation?
- Based upon this information is TM a candidate for endoxaban?
- If so what dose of endoxaban would you recommend?

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**Patient Case TM**

- First calculate this TM's ideal body weight (IBW):
  - IBW = 45.5 kg + (2.3 x inches over 5 feet)
  - IBW = 45.5 kg + (2.3 x 1)
  - IBW = 47.8 kg

- What is the % difference between the actual and IBWs?
  - 64 kg - 47.8 kg = 16.2 kg
  - (This is greater than 120% of the IBW)

- Second calculate TM's adjusted body weight (ABW):
  - ABW = IBW + 0.4 x (actual body weight - IBW)
  - ABW = 47.8 kg + 0.4 x (64 kg - 47.8 kg)
  - ABW = 54.28 kg

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**Patient Case TM**

- Third, now calculate the CrCl for TM:
  - CrCl = \((140 - \text{age}) \times \text{weight}/(\text{SCr} \times 72)\) (x 0.85 for females)
  - CrCl = \((140 - 74) \times 54.28/(1.6 \times 72)\) (x 0.85)
  - CrCl = 26.44 ml/min

- What is TM's estimated CrCl based upon the above information utilizing the Cockcroft and Gault equation?
  - Answer: 26.44 ml/min

- Based upon this information is TM a candidate for endoxaban?
  - Answer: Yes

- If so what dose of endoxaban would you recommend?
  - Answer: 30 mg PO once daily
References

- FDA: Information on Praxbind [http://www.fda.gov/NewsEvents/PressAnnouncements/ucm467300.htm]
- Pharmacist’s Letter Document #320506, May 2016
- Pradaxa (Package Insert Online). Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc.
- Elisquis (Package Insert Online). Princeton NJ: Bristol-Myers Squibb Company
- Savaysa (Package Insert Online). Tokyo Japan: Daiichi Sankyo, Inc.
- Xarelto (Package Insert Online). Titusville NJ: Janssen Pharmaceuticals, Inc.

References