Direct Oral Anticoagulants

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Objectives

• Identify the FDA approved indications for use, appropriate dosing, and monitoring parameters for each direct oral anticoagulant.
• Distinguish the key differences among the direct oral anticoagulants.
• Discuss perioperative management with direct oral anticoagulants.
• Acknowledge the impact of drug interactions when considering anticoagulation therapy.
• Review the currently available medication and medications still in clinical trials for the reversal of direct oral anticoagulants.
• List the newest recommendations related to direct oral anticoagulants from the 10th edition CHEST guidelines.

Direct Acting Oral Anticoagulants

• Dabigatran
• Rivaroxaban
• Apixaban
• Edoxaban
• Betrixaban – approved June 23, 2017
Drug Class

• Factor Xa inhibitor
  ▫ Rivaroxaban
  ▫ Apixaban
  ▫ Edoxaban
  ▫ Betrixaban

• Direct thrombin inhibitor
  ▫ Dabigatran

Indications for VTE Treatment & PPX

• VTE prophylaxis in the acute setting
  ▫ Betrixaban
• VTE prophylaxis post-op hip/knee replacement
  ▫ Apixaban
  ▫ Rivaroxaban
• VTE treatment/secondary prophylaxis
  ▫ Apixaban
  ▫ Rivaroxaban
  ▫ Edoxaban
  ▫ Dabigatran
Indications for Atrial Fibrillation

- **Only for non-valvular atrial fibrillation**
  - Apixaban
  - Rivaroxaban
  - Edoxaban
  - Dabigatran

Before we talk renal adjustments...

- **Weight, Scr, and Age**
  - Apixaban

- **Remember to calculate CrCl using ACTUAL body weight**
  - Dabigatran
  - Edoxaban
  - Rivaroxaban
  - Betrixaban

**Apixaban and Dabigatran**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Indication</th>
<th>Dose</th>
<th>Renal adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apixaban</td>
<td>Non-Valvular Afib</td>
<td>5 mg PO BID</td>
<td>Any 2 of the following: Age ≥ 80 yo, wgt ≤ 60 kg, Scr ≥ 1.5 mg/dl = 2.5 mg PO BID*</td>
</tr>
<tr>
<td></td>
<td>DVT/PE</td>
<td>10 mg PO BID x 7 days Then 5 mg PO BID x 6 months after 4 months of full treatment dosage</td>
<td>No adjustment*</td>
</tr>
<tr>
<td></td>
<td>Post op hip replacement</td>
<td>1.5 mg PO BID x 3 days</td>
<td>No adjustment; patients with CrCl ≤ 30 ml/min were excluded from trial</td>
</tr>
</tbody>
</table>

**Drug interactions:**
- Decrease dosage 50% for dosage > 2.5 mg PO BID AND receiving concomitant clarithromycin, oral ketoconazole, itraconazole, or ritonavir = decrease dose 50%.
- Avoid use with above medications if pt is taking 2.5 mg BID or has 2 of following (age, SCR, wt)

| Dabigatran | Non-Valvular Afib | 150 mg PO BID | CrCl 15–30 ml/min = 75 mg PO BID < 15 ml/min or ESRD = CI *
<table>
<thead>
<tr>
<th></th>
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<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DVT/PE</td>
<td>150 mg PO BID after 5–10 days of parenteral anticoagulant</td>
<td>No adjustment; patients with CrCl &lt; 30 ml/min were excluded from trial</td>
</tr>
<tr>
<td></td>
<td>Post op knee replacement</td>
<td>2.5 mg BID x 12 days</td>
<td>No adjustment; patients with CrCl &lt; 30 ml/min were excluded from trial</td>
</tr>
</tbody>
</table>

**Drug interactions:**
- CrCl 30–50 ml/min and receiving oral ketoconazole or dronedarone = 75 mg BID.
- CrCl 15–30 ml/min and receiving concomitant P glycoprotein inhibitors (amiodarone, clarithromycin, droxidopa, etc) = AVOID.
- Any P glycoprotein inducer (Rifampin, etc) = AVOID.

* Indicates with Scr > 2.5 mg/dl or CrCl < 15 ml/min were excluded from trial.
### Edoxaban, Rivaroxaban, and Betrixaban

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<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>Edoxaban</td>
<td>Non-Valvular Afib</td>
<td>60 mg daily</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>DVT/PE</td>
<td>60 mg PO daily after 5-10 days of parenteral anticoagulation</td>
<td>CrCl &gt; 95 ml/min = AVOID, CrCl 15-50 ml/min = 30 mg daily, CrCl &lt; 15 ml/min = AVOID</td>
</tr>
</tbody>
</table>

**Drug interactions:** Concomitant verapamil, quinidine, antituberculosis, clarithromycin, erythromycin, telithromycin, or rifampin; use of ketoconazole, rifampin, azole antifungals, or strong P-gp inhibitors; use of strong inhibitors of CYP3A4. Use with caution with strong inhibitors of CYP2C9/2C19, strong CYP3A4 inhibitors.

<table>
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</tr>
</thead>
<tbody>
<tr>
<td>Rivaroxaban</td>
<td>Non-Valvular Afib</td>
<td>20 mg PO daily</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>DVT/PE</td>
<td>15 mg PO BID x 21 days, then 20 mg PO daily with food</td>
<td>CrCl &lt; 30 ml/min = AVOID</td>
</tr>
<tr>
<td></td>
<td>Post op hip replacement</td>
<td>30 mg PO daily x 35 days</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Post op knee replacement</td>
<td>10 mg daily x 12-14 days</td>
<td>CrCl &lt; 30 ml/min = AVOID</td>
</tr>
</tbody>
</table>

**Drug interactions:** Concomitant vorapaxar, urokinase, St John’s Wort, itralizumab, abacavir, clarithromycin, amiodarone, elidelalisib, conivaptan, cimetidine, vorapaxar, idelalisib, ketoconazole, ritonavir/lopinavir, fluconazole, itraconazole, indinavir, carbamazepine, phenytoin, rifampin. Use with caution with strong inhibitors of CYP3A4, CYP2C9/2C19, CYP2C19, and CYP2C8.

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<th>Dose</th>
<th>Renal adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Betrixaban</td>
<td>VTE prophylaxis for hospitalized patients at risk for VTE</td>
<td>Initial: 160 mg orally as a single dose, followed by 80 mg once daily at the same time each day with food for 35 to 42 days</td>
<td>CrCl 15-30 mL/min = 80 mg X 1 dose, followed by 40 mg once daily for 35 to 42 days</td>
</tr>
</tbody>
</table>

**Drug interactions:** Concomitant use of P-gp inhibitors; additional dose of 80 mg orally as a single dose, followed by 40 mg once daily for 35 to 42 days.

### What about hepatic impairment?

- **Apixaban**
  - Mild impairment – Child-Pugh Class A: No adjustments
  - Moderate impairment – Child-Pugh Class B: Use with caution
  - Severe impairment – Child-Pugh Class C: Use is not recommended

- **Dabigatran**
  - No dosage adjustments per manufacturer. In patients with moderate impairment, no changes in exposure or pharmacodynamics were observed in a study.

- **Edoxaban**
  - Mild impairment – Child-Pugh Class A: No adjustments
  - Moderate to severe impairment – Child-Pugh Class B and C: Use is not recommended

- **Rivaroxaban**
  - Mild impairment – Child-Pugh Class A: No adjustments
  - Moderate impairment – Child-Pugh Class B or C: Avoid use

- **Betrixaban**
  - Use is not recommended

### Choosing the right medication

- Indication
- Patient’s lifestyle
- Compliance
- Dosing complexity
- Renal/Hepatic function
- Age
- Bleeding Risk
- Cost
Apixaban - Specific points

- Duration of therapy – orthopedic uses (knee - 12 days, hip - 35 days)
- VTE – dose change at 1 week
  - 10 mg BID X 7 days, then 5 mg BID
- May crush tablets and place in 60 ml of D5W for immediate delivery down NG tube
  - Can also mix with apple juice, applesauce, D5W, or water and give orally
  - Stable for up to 4 hours

Dabigatran - Specific points

- Initiation after 5-10 days of parenteral therapy (VTE)
- Storage
  - Do not store in pill organizer
  - Must use within 4 months of opening bottle
- Take with full glass of water
- With or without food
- Do not break, crush, chew, or open capsule
- Side effects
  - Stomach upset, indigestion

Edoxaban - Specific points

- Initiation of therapy
  - VTE requires 5-10 days of parenteral therapy
- Side effects can include rash
- Take with or without food
- Should not be used in patients who have a CrCl greater than 95 mL/min due to an increased risk of ischemic stroke
Rivaroxaban - Specific points

- Duration of therapy – orthopedic uses (knee - 12-14 days, hip - 35 days)
- VTE – dose change at 3 weeks
- Take with food (for doses 15 mg or greater)
- Crush or chew?
  - May be crushed and mixed in applesauce immediately prior to usage
  - NG tube – may be crushed and mixed in 50 ml of water. Administration should be followed by enteral feeding
- Missed dosage of 15 mg BID
  - Must get 30 mg in a day – two 15 mg doses can be given at once

Betrixaban

- Approved on June 23, 2017
- Only for use in the acute setting
- Take at same time each day with food

APEX trial

- Treatment groups
  - Enoxaparin 40 mg daily vs. betrixaban 160 mg X 1, then 80 mg daily for 35-42 days
  - Primary efficacy endpoint:
    - Composite of:
      - asymptomatic proximal DVT between day 32-47
      - Symptomatic proximal or distal DVT
      - Symptomatic non-fatal PE
      - Death from VTE
  - Three cohorts:
    - Patients with elevated D-dimer
    - Patients with elevated D-dimer or age > 75
    - Entire trial population
Results from APEX trial

- Primary end point, cohort 1
  - Did not show clinical significance ($P = 0.054$)
  - Therefore the rest of the analyses were considered "exploratory"
- Safety endpoints (betrixaban vs enoxaparin)
  - Major bleeding
    - 0.7% vs 0.6% ($P = 0.55$)
  - Major or clinically relevant non-major bleeding
    - 3.1% vs 1.6% ($P < 0.001$)


Transitioning from warfarin to DOACs

- Discontinue warfarin, then ...
  - Dabigatran & Apixaban
    - Initiate when INR is below 2
  - Rivaroxaban:
    - Initiate when INR is below 3
  - Edoxaban:
    - Initiate when INR is below 2.5
  - Betrixaban:
    - No information available

Transitioning from Dabigatran to warfarin

Adjust the start time of warfarin based on the patient’s CrCl:

<table>
<thead>
<tr>
<th>Recommended start of warfarin before discontinuing dabigatran</th>
<th>CrCl in mL/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 days</td>
<td>≤50</td>
</tr>
<tr>
<td>2 days</td>
<td>50-100</td>
</tr>
<tr>
<td>1 day</td>
<td>100-300</td>
</tr>
<tr>
<td>No recommendations can be made</td>
<td>&gt;300</td>
</tr>
</tbody>
</table>

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

Transitioning from Factor Xa inhibitors to warfarin

- Discontinue factor Xa inhibitor and initiate a parenteral anticoagulant and warfarin at the time when the next factor Xa dose would have been administered
- Continue parenteral anticoagulant until INR is therapeutic
- Includes Rivaroxaban, Apixaban, and Edoxaban

Perioperative Management of DOACs

<table>
<thead>
<tr>
<th>DOAC</th>
<th>Time of Last Dose Before Minor Procedure</th>
<th>Time of Last Dose Before Major Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>1 day</td>
<td>2 days</td>
</tr>
<tr>
<td>Rivaroxaban, apixaban, or edoxaban</td>
<td>1 day</td>
<td>2 days</td>
</tr>
<tr>
<td>Low CrCl</td>
<td>30–50 mL/min</td>
<td>1–2 days</td>
</tr>
<tr>
<td>High CrCl</td>
<td>&gt;50 mL/min</td>
<td>≥36 days</td>
</tr>
</tbody>
</table>

a. Therapy should generally be resumed 24 hours after a minor procedure and 48 hours after major surgery. If scheduled steps (1)–(5) for the rivaroxaban weight-based LMWH are used to bridge therapy it is performed with prophylactic LMWH (10 000 IU) and it is essential to wait 12 hours after the procedure. Baseline hematology includes 4pm immediately before and 12 pm on the following day at least.

- Low CrCl: ≤30 mL/min
  - 1 day after procedure
  - Resume DOACs 48–72 h after procedure
  - Resume DOACs when hemostasis is controlled (48–72 h after procedure)

- High CrCl: >50 mL/min
  - 1 day after procedure
  - Resume DOACs 48–72 h after procedure
  - Resume DOACs when hemostasis is controlled (48–72 h after procedure)

- Low CrCl: ≤30 mL/min
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  - Resume DOACs 48–72 h after procedure
  - Resume DOACs when hemostasis is controlled (48–72 h after procedure)
Drug Interactions

- Rivaroxaban, Apixaban, and Edoxaban
  - Metabolized by CYP3A4
  - Substrate for P-glycoprotein

- Dabigatran
  - Substrate for P-glycoprotein

Management of DOAC-related bleeding

- Idarucizumab
  - Approved in 2015 under accelerated approval
  - Neutralizes the anticoagulant effect of dabigatran by binding to dabigatran and its acylglucuronide metabolites
  - Indicated for life threatening bleeding or need for emergent surgery
  - 5 g (administered via 2 vials) IV
  - Dabigatran can be reinitiated 24 hours after administration
  - Not compatible with other medications
  - RE-VERSE AD trial
    - The anticoagulant effect of dabigatran was fully reversed in 88-98% of patients at 4 hours following administration of idarucizumab
    - Thrombotic events occurred in 5 patients (n = 90)

- Andexanet alpha
  - Bind factor Xa inhibitors
  - ANNEXA - A and ANNEXA - R trials
    - Phase 3: Studied the reversal effects on apixaban and rivaroxaban in healthy volunteers
    - Anti-factor Xa activity was reduced by 94% and 92% respectively with andexanet vs. 21% and 18% with placebo
    - No major thrombotic adverse events reported
  - ANNEXA-4
    - Ongoing Trial
    - Phase 3
      - Evaluating efficacy in patients with an acute major bleed
      - Estimated primary completion date – November 2022
    - A study of the PK/PD, safety, and tolerability in healthy subjects
      - Ongoing trial
      - Estimated primary completion date – September 2017

https://clinicaltrials.gov
Management of DOAC-related bleeding

- **Ciraparantag**
  - Binds to edoxaban, rivaroxaban, apixaban, dabigatran, and LMWH/UFH
  - **Phase I trial**
    - 80 healthy participants
    - In patients receiving a single intravenous dose of PER977 (100 to 300 mg) 3 hours after the administration of edoxaban, the whole-blood clotting time decreased to within 10% above the baseline value in 10 minutes or less, whereas in patients receiving placebo, the time to reach that level was much longer (approximately 12 to 15 hours)

- **Ongoing Study**
  - Phase 2 Placebo-Controlled, Single-Site, Single-Blind Study of Rivaroxaban Reversal by Ciraparantag as Measured by whole blood clotting time
  - Estimated study completion date: December 2017

[https://clinicaltrials.gov](https://clinicaltrials.gov)

CHEST guidelines 10th edition

- **Summary:**
  - Risk reduction for recurrent VTE with all of the DOACs appears to be similar to the risk reduction with VKA
  - Risk reduction for recurrent VTE among the different DOACs appears to be similar
  - Risk of bleeding with the DOACs, and particularly intracranial bleeding, is less than with VKA therapy based on patients with atrial fibrillation
    - GI bleeding may be higher with dabigatran, rivaroxaban, and edoxaban than with VKA therapy, although this has not been seen in patients with VTE
  - Risk of bleeding may be lower with apixaban than with the other DOACs
  - Risk that a major bleed will be fatal appears to be no higher for DOACs than for VKA therapy
  - Suggest that a DOAC is used in preference to VKA for the initial and long-term treatment of VTE in patients without cancer

Questions
References