Direct Oral Anticoagulants: Factor IIa and Xa Inhibitors

Jessica LeClair, PharmD, MBA
PGY-1 Pharmacy Resident
Anuja Rizal, PharmD, CACP
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Learning objectives
• Discuss the pharmacology of the Direct Oral Anticoagulants (DOACs) - Factor IIa and Xa Inhibitors
• Discuss the indications and contraindications for DOACs - Factor IIa and Xa Inhibitors
• Review the kinetic profiles of the DOACs - Factor IIa and Xa Inhibitors

Patient Case Introduction
• JJ is an 86 year old Caucasian male weighing 65kg with non-valvular atrial fibrillation managed on warfarin since his diagnosis in 2004.
• JJ no longer drives and is having difficulty adhering to frequent appointments to monitor his INR. His TTR is ~45%
• JJ saw a commercial on television for Eliquis® and is inquiring additional information

Coagulation cascade

Oral anticoagulant therapies through the years

Faculty disclosure
• Anuja Rizal and I have no actual or potential conflicts of interest associated with this presentation.
Pharmacokinetics of DOACs

<table>
<thead>
<tr>
<th>Inhibitor of</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
<th>Betrixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inh (T_max, hours)</td>
<td>2</td>
<td>2.4</td>
<td>1.3</td>
<td>1.2</td>
<td>3.4</td>
</tr>
<tr>
<td>Bioavailability (%)</td>
<td>7</td>
<td>66</td>
<td>50</td>
<td>62</td>
<td>34</td>
</tr>
<tr>
<td>Renal / Fecal excretion (%)</td>
<td>&gt;80 / 82-88</td>
<td>66 / 26</td>
<td>25 / 46-56</td>
<td>35 / 62</td>
<td>17.8 / 85</td>
</tr>
<tr>
<td>Metabolism</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Minimal (&lt;4%)</td>
<td>Minimal (&lt;1%)</td>
</tr>
<tr>
<td>Pgp substrate</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Half-life (hours)</td>
<td>12-17</td>
<td>5-9</td>
<td>12</td>
<td>10-14</td>
<td>19-27</td>
</tr>
</tbody>
</table>


Dabigatran (Pradaxa®)

FDA Approved Indications
- Reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation
- Treating deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients who have been treated with a parenteral anticoagulant for 5-10 days

Boxed warning: Upon discontinuation, the risk of thrombotic events, especially stroke, is increased. If dabigatran must be discontinued for a reason other than pathological bleeding, consider the use of another anticoagulant during the time of interruption.

Pradaxa® (dabigatran) [package insert]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc. 2015.

Direct oral anticoagulants (DOACs)

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Brand Name</th>
<th>FDA Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Nonvalvular atrial fibrillation</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>Pradaxa®</td>
<td>+</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>Xarelto®</td>
<td>+</td>
</tr>
<tr>
<td>Apixaban</td>
<td>Eliquis®</td>
<td>+</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>Savaysa®</td>
<td>+</td>
</tr>
<tr>
<td>Betrixaban</td>
<td>Bevyxxa®</td>
<td>+</td>
</tr>
</tbody>
</table>

Pradaxa® (dabigatran) [package insert]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc. 2015.

Dabigatran (Pradaxa®)

Renal function
- Dialing: Non-valvular AFib. & DVT/PE Treatment
  - GFR > 30 mL/min: 150 mg PO BID
  - GFR 15-30 mL/min: 75 mg PO BID
  - GFR < 15 mL/min: Not recommended

Dosing: AFib: Indefinite
- Provoked DVT: 3 months
- Unprovoked DVT: ≥ 3 months

Pradaxa® (dabigatran) [package insert]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc. 2015.

Dabigatran (Pradaxa®)

Contraindications
- Serious hypersensitivity to dabigatran or any component of the formulation
- Active pathological bleeding
- Patients with mechanical prosthetic heart valve(s)

Clinical Pearls and Patient Counseling
- Administer with full glass of water to avoid dyspepsia
- Do NOT break, crush, chew, or open capsules, as this increases bioavailability by up to 75%
- Leave capsules in original container and use within 4 months of opening

Pradaxa® (dabigatran) [package insert]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc. 2015.
DDIs with Dabigatran (Pradaxa®)

**P-gp inhibitors:** can lead to increased exposure of dabigatran and risk of bleeding
- NAFD + CrCl 30-50mL/min: consider dabigatran 75mg PO BID
- NAFD + CrCl <30mL/min: avoid
- VTE + CrCl <50mL/min: avoid

**P-gp inducers:** avoid use due to reduced exposure to dabigatran and reduced efficacy

**Anticoagulant, antiplatelets, NSAIDs, SSRIs, SNRIs:** may increase bleeding risk
- Applicable to all DOACs

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**Clinical trials supporting Dabigatran (Pradaxa®)**

| Evidence for NVM vs. warfarin | RE-CY
|-------------------------------|------------------
| Superior; ischemic and hemorrhagic stroke, vascular mortality | Non-inferior
| Higher risk of GB and major bleeding in patients >75 year old | Not approved for TTR
| RE-MODEL, RE-MOBILIZE, RE-NOVATE (I/II) | Non-inferior

| Evidence for VTE prophylaxis for THR and TKR vs. enoxaparin | RE-NOVATE I and II
|-------------------------------------------------------------|------------------
| Non-inferior | Non-inferior
| RE-COVER | Non-inferior: current VTE and mortality
| RE-MODEL, RE-MOBILIZE, RE-NOVATE (I/II) | Similar major bleeding, lower clinically relevant non-major bleeding

| Evidence for VTE management vs. LMWH/VKA | RE-COVER
|------------------------------------------|------------------
| Non-inferior: re-current VTE and mortality | Non-inferior: non-warfarin, similar major bleeding
| RE-SONARATE | Non-inferior: placebo, higher major bleeding
| RE-MEDY | Non-inferior: warfarin, similar major bleeding

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**Rivaroxaban (Xarelto®)**

**FDA Approved indications**
- Reducing stroke risk in non-valvular atrial fibrillation
- Prophylaxis for postoperative DVT
- Deep vein thrombosis (DVT), pulmonary embolism (PE) treatment

**Boxed warning:** Spinal or epidural hematomas may occur with neuraxial anesthesia (epidural or spinal anesthesia) or spinal puncture in patients who are anticoagulated, may result in long-term or permanent paralysis.

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**Rivaroxaban (Xarelto®)**

**Renal Function**
- **Non-valvular AFB:** 20 mg PO daily with the evening meal, 10 mg PO daily without regards to meals, 15 mg PO BID for 3 weeks followed by 20 mg PO daily
- **DVT/PE Treatment:**
  - **CrCl 15-50 mL/min:** 15 mg PO daily without the evening meal, Do NOT use in CrCl <30 mL/min, Do NOT use in CrCl <30 mL/min
  - **CrCl <15 mL/min:** Avoid use

**Duration of Treatment**
- **Indefinite:** Knee replacement and Hip replacement. Minimum of 10-14 days and extended duration of up to 35 days
- **Provoked DVT:** 3 months
- **Unprovoked DVT:** ≥ 3 months

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Xarelto® (package insert) Titusville, NJ: Janssen Pharmaceuticals, Inc. 2015

Rivaroxaban (Xarelto®) (package insert) NJ: Janssen Pharmaceuticals, Inc. 2016

Pradaxa® (Pradaxa®) (package insert) Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc. 2015

Amidoxime Guide. Thrombophilia and Anticoagulation Clinic, Minneapolis Heart Institute* 2016.

Xarelto® (rivaroxaban) (package insert) Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc. 2015

Rivaroxaban (Xarelto®) (package insert) NJ: Janssen Pharmaceuticals, Inc. 2015
Rivaroxaban (Xarelto®)

**Contraindications**
- Severe hypersensitivity to rivaroxaban or any component of the formulation
- Active pathological bleeding

**Clinical Pearls/Patient Counseling**
- The 15 and 20 mg tablets should be administered with food, the 10 mg tablets may be administered with or without food
- Tablets may be crushed and mixed with applesauce or suspended with 50 mL of water to be delivered through NGT, after administration oral or enteral feeding should immediately follow the dose

CYP3A4 drug interaction

- Cytochrome-P450: class of enzymes responsible for biotransformation of drugs; located mainly in the liver, though extrahepatic metabolism also occurs in the kidneys, skin, gastrointestinal tract, and lungs.
- When CYP3A4 inhibitors or inducers are taken with other drugs metabolized by CYP3A4, the drug’s usually metabolism is altered
- Inhibitors and inducers are categorized as strong, moderate, or weak depending on their effect on CYP3A4

<table>
<thead>
<tr>
<th>Strong Inhibitors</th>
<th>Strong Inducers</th>
</tr>
</thead>
<tbody>
<tr>
<td>clarithromycin, erythromycin</td>
<td>Rifampin</td>
</tr>
<tr>
<td>Fluconazole, itraconazole, ketoconazole</td>
<td>Carbamazepine</td>
</tr>
<tr>
<td>Ritonavir</td>
<td>Phenytoin</td>
</tr>
<tr>
<td>St. John’s Wort</td>
<td></td>
</tr>
</tbody>
</table>

**Clinical trials supporting Rivaroxaban (Xarelto®)**

<table>
<thead>
<tr>
<th>Indication</th>
<th>Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evidence for NOAF vs. warfarin</td>
<td>ROCKET-AF</td>
</tr>
<tr>
<td>Evidence for VTE prophylaxis for THR and TKR vs. enoxaparin</td>
<td>RECORD 1, 2, 3, and 4</td>
</tr>
<tr>
<td>Evidence for VTE management vs. LMWH/VKA</td>
<td>EINSTEIN</td>
</tr>
<tr>
<td>Evidence for VTE risk reduction after initial treatment</td>
<td>EINSTEIN-EXT</td>
</tr>
</tbody>
</table>

**Apixaban (Eliquis®)**

**FDA Approved Indications**
- Decrease the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation
- Prophylaxis of deep vein thrombosis (DVT), which may lead to pulmonary embolism (PE), in patients who have undergone hip or knee replacement surgery
- Treatment of DVT and PE, and decrease the risk of recurrent DVT and PE following initial therapy

**Boxed Warning:** When used to prevent stroke in patients with non-valvular atrial fibrillation, an increased risk of stroke may occur upon apixaban discontinuation if patient is not adequately anticoagulated with an alternative anticoagulant.

**DDIs with Rivaroxaban (Xarelto®)**

- Combined P-gp and strong CYP3A4 inhibitors: avoid use due to increased exposure of rivaroxaban (from 30-160%) and risk of bleeding
- Combined P-gp and strong CYP3A4 inducers: avoid use due to reduced exposure to rivaroxaban (up to 50%) and reduced efficacy
- Combined P-gp and moderate CYP3A4 inhibitors Crl 15-80 mL/min: avoid use unless benefit determined to outweigh risk
- Anticoagulant, antiplatelets, NSAIDs, SSRIs, SNRIs: may increase bleeding risk
- Applicable to all DOACs

**Apixaban (Eliquis®)**

<table>
<thead>
<tr>
<th>Renal Function</th>
<th>Non-valvular Atrial Fibrillation</th>
<th>DVT Prophylaxis</th>
<th>Treatment of DVT and PE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal renal function (standard dosing)</td>
<td>5mg PO BID</td>
<td>Hip: 2.5mg PO BID 12-24 hours post-op for 35 days</td>
<td>10mg PO BID for 7 days, followed by 5mg PO BID</td>
</tr>
<tr>
<td>CrCl 30-50mL/min</td>
<td>No dosage adjustment provided</td>
<td>No dosage adjustment necessary except patients with a SrCr &gt;2.5mg/dL or CrCl &lt;25mL/min were excluded from trials</td>
<td></td>
</tr>
<tr>
<td>CrCl &lt;15mL/min</td>
<td>Not recommended</td>
<td>See above</td>
<td></td>
</tr>
</tbody>
</table>
Apixaban (Eliquis®)

**Contraindications**
- Severe hypersensitivity reaction to apixaban (anaphylaxis) or any component of the formulation
- Active pathological bleeding

**Clinical Pearls and Patient Counseling**
- Tablets may be crushed and suspended in 60mL D5W and immediately delivered through an NGT

**DDIs with Apixaban (Eliquis®)**
- Combined P-gp and strong CYP3A4 inhibitors: can lead to increased exposure of apixaban and risk of bleeding
  - Doses >2.5mg BID: reduce dose by 50%
  - 2.5mg BID: avoid use
- Combined P-gp and strong CYP3A4 inducers: avoid use due to reduced exposure to apixaban and reduced efficacy
  - Applicable to all DOACs

**Clinical trials supporting Apixaban (Eliquis®)**

<table>
<thead>
<tr>
<th>Indication</th>
<th>Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evidence for NVAF vs. warfarin</td>
<td>ARISTOTLE</td>
</tr>
<tr>
<td>- Superior: hemorrhagic stroke, vascular mortality, major bleeding</td>
<td></td>
</tr>
<tr>
<td>- Lower risk ICH and fatal bleeding</td>
<td></td>
</tr>
<tr>
<td>Evidence for VTE prophylaxis for THR vs. enoxaparin</td>
<td>ADVANCE 2 and 3</td>
</tr>
<tr>
<td>- Superior with no difference in bleeding</td>
<td></td>
</tr>
<tr>
<td>Evidence for VTE management vs. LMWH/VKA</td>
<td>AMPLIFY</td>
</tr>
<tr>
<td>- Non-inferior: re-current VTE and mortality</td>
<td></td>
</tr>
<tr>
<td>- Lower risk of major bleeding</td>
<td></td>
</tr>
<tr>
<td>Evidence for VTE risk reduction after initial treatment</td>
<td>AMPLIFY-EXT</td>
</tr>
<tr>
<td>- Superior vs. placebo, similar major bleeding</td>
<td></td>
</tr>
</tbody>
</table>

DDIs Guide. Thrombophilia and Anticoagulation Clinic, Minneapolis Heart Institute® 2016.

**Apixaban (Eliquis®)**

<table>
<thead>
<tr>
<th>Non-valvular AFib</th>
<th>DVT Prophylaxis</th>
<th>Treatment of DVT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of Treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indefinite</td>
<td>Hid: 35 days</td>
<td>Proroked DVT:</td>
</tr>
<tr>
<td></td>
<td>Knee: 12 days</td>
<td>3 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Unprovoked DVT:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;3 months</td>
</tr>
</tbody>
</table>

**Patient Case**

- JJ is an appropriate candidate to be started on apixaban, due to his TTR being less than 65%.
  - What dose of apixaban would you recommend?
    - Apixaban 2.5mg PO BID with or without food due to age >80 and SCr >1.5
  - How long would the duration of therapy be?
    - Indefinite for a fib

**Patient Case**

You review JJ’s medication list:
- Warfarin 5mg PO daily MWF, 10 mg all other days
- Clarithromycin 250 mg every 12 hours for 7 to 14 days
- Rosuvastatin 10mg PO daily
- Acetaminophen 500mg PO PRN headaches

Which medication is a combined P-gp and strong CYP3A4 inhibitor?
- Clarithromycin
Edoxaban (Savaysa®)

FDA Approved Indications
- Decrease the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation
- Treatment of DVT and PE, following 5-10 days of initial therapy with a parenteral anticoagulant

Edoxaban (Savaysa®)

Boxed Warning:
- Reduced efficacy in non-valvular atrial fibrillation patients with CrCl >95 mL/minute (increases the risk of ischemic stroke)
- When used to prevent stroke in patients with non-valvular atrial fibrillation, an increased risk of stroke may occur upon edoxaban discontinuation if patient is not adequately anticoagulated with an alternative anticoagulant
- Spinal or epidural hematomas may occur with neuraxial anesthesia (epidural or spinal anesthesia) or spinal puncture in patients who are anticoagulated; may result in long-term or permanent paralysis.

Edoxaban (Savaysa®)

CONTRAINDICATIONS
- Severe hypersensitivity reaction to edoxaban (anaphylaxis) or any component of the formulation
- Active pathological bleeding

DDIs with Edoxaban (Savaysa®)

P-gp inhibitors: can lead to increased exposure of edoxaban and risk of bleeding
- NVAF: no dose reduction recommended
- VTE: 30mg PO once daily

P-gp inducers: avoid use due to reduced exposure to dabigatran and reduced efficacy

Anticoagulant, antiplatelets, NSAIDs, SSRIs, SNRIs: may increase bleeding risk
- Applicable to all DOACs

Clinical trials supporting Edoxaban (Savaysa®)

<table>
<thead>
<tr>
<th>Indication</th>
<th>Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evidence for NVAF vs. warfarin</td>
<td>ENGAGE AF-TIMI 48</td>
</tr>
<tr>
<td>Evidence for VTE prophylaxis for THR vs. enoxaparin</td>
<td>Not approved for these indications</td>
</tr>
<tr>
<td>Evidence for VTE management vs. LMWH/VKA</td>
<td>Hokusai 2</td>
</tr>
<tr>
<td>Evidence for VTE risk reduction after initial treatment</td>
<td>Not approved for this indication</td>
</tr>
</tbody>
</table>

Daiichi Sankyo, Thrombophilia and Anticoagulation Clinic, Minneapolis Heart Institute® 2016.
Betrixaban (Bevyxxa®)

FDA Approved Indications
- VTE prophylaxis

Boxed warning: Spinal or epidural hematomas may occur with neuraxial anesthesia (epidural or spinal anesthesia) or spinal puncture in patients who are anticoagulated; may result in long-term or permanent paralysis.

Renal function

<table>
<thead>
<tr>
<th>Function</th>
<th>Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatinine clearance &gt; 30 mL/min</td>
<td>160 mg as a single dose on day 1, followed by 80 mg once daily</td>
</tr>
<tr>
<td>Creatinine clearance 30–60 mL/min or concomitant P-gp inhibitor</td>
<td>80 mg single dose, followed by 40 mg once daily</td>
</tr>
<tr>
<td>Creatinine clearance &lt; 15 mL/min</td>
<td>Not recommended</td>
</tr>
</tbody>
</table>

Duration: 35 to 42 days

Contraindications
- Serious hypersensitivity to betrixaban or any component of the formulation
- Active pathological bleeding

Clinical Pearls and Patient Counseling
- Administer with food at the same time each day

DDIs with Betrixaban (Bevyxxa®)

- P-gp inhibitors: can lead to increased exposure of betrixaban and risk of bleeding
  - Reduce dose: initial single dose 80 mg followed by 40 mg once daily
- Anticoagulant, antiplatelets, NSAIDs, SSRIs, SNRIs: may increase bleeding risk
  - Applicable to all DOACs

Clinical trial supporting Betrixaban (Bevyxxa®)

<table>
<thead>
<tr>
<th>Indication</th>
<th>Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evidence for prevention of VTE vs enoxaparin in acutely ill hospitalized patients</td>
<td>APEX</td>
</tr>
<tr>
<td>Non-superior in cohort 1 (patients who had elevated D-Dimer level)</td>
<td></td>
</tr>
<tr>
<td>Protocol specified that all subsequent analyses were considered to be exploratory, but suggested benefit with betrixaban</td>
<td></td>
</tr>
<tr>
<td>Lower major and fatal bleeding, higher clinically relevant non-major bleeding</td>
<td></td>
</tr>
</tbody>
</table>

2018 CHEST Guideline Updates for Atrial Fibrillation
DOACs recommended over VKA

Patients eligible for oral anticoagulation, recommend DOACs over VKA
- Recommend VKA TTR >70%, action required if TTR <65% to improve TTR or switch to DOAC
- Indications where VKA or LMWH preferred: mechanical heart valves, DDIs (HAART, rifampin, phenytoin), pregnancy or breastfeeding, and cancer

PPI consideration

- AF patients on aspirin + DOAC, recommend adding a PPI to minimize risk of GI bleeding

Pregnant and lactating women

Pregnant women:
- Switch DOAC with VKA between week 6-12 and replace by LMWH
- Replace DOACs in the 36th week of gestation
- Avoid DOACs for women attempting conception; for those on DOACS suggest switching to VKA rather than LMWH when attempting conception

Lactating women:
- Recommend using warfarin or UFH for women who wish to breast feed

AF patients with acute stroke

- AF patients who have an acute stroke with no contraindications should be started on a DOAC for secondary prevention within 2 weeks of the stroke

Chronic kidney disease

- Mild CKD (stage II, CrCl 60-89 mL/min): oral anticoagulation dosed the same as patients without CKD
- Moderate CKD (stage III, CrCl 30-59 mL/min): oral anticoagulation if CHA2DS2-VASc score ≥2 with renally dosed DOAC or VKA
- Severe non-dialysis CKD (stage IV, CrCl 15-30 mL/min): use VKA or selected DOACs (rivaroxaban 15mg daily, apixaban 2.5mg BID, edoxaban 30mg daily, dabigatran 75mg BID)
- ESRD (CrCl <15 mL/min or dialysis dependent): individualized decision making, suggest VKA over DOAC; apixaban 5mg BID is approved in HD
Antithrombotic prophylaxis bridging

• Patients on antithrombotic prophylaxis with DOAC, suggest preoperative management without bridging

Weak recommendation, low quality evidence

Patients refusing DOACs

• Recommend reinforcing educational messages at each visit with the patient and reconsider treatment decisions

Ungraded consensus-based statement

Transitioning between anticoagulants

Transitioning from a DAOC

<table>
<thead>
<tr>
<th>To</th>
<th>Warfarin</th>
<th>Heparin</th>
<th>LMWH</th>
<th>Another DOAC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>Start warfarin 1,2, or 3 days before stopping dabigatran based on CrCl. CrCl ≥50: 3 days CrCl 30-50: 2 days CrCl 15-30: 1 day</td>
<td>Start 12 hours (CrCl ≥30) or 24 hours (CrCl &lt;30) after the last dose of dabigatran</td>
<td>Stop dabigatran and start new DOAC when the next dose would have been given</td>
<td>Stop dabigatran and start new DOAC when the next dose would have been given</td>
</tr>
<tr>
<td>Betrixaban</td>
<td>Limited data</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Transitioning to a DAOC

<table>
<thead>
<tr>
<th>To</th>
<th>Warfarin</th>
<th>Heparin</th>
<th>LMWH</th>
<th>Another DOAC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>Stop warfarin and monitor INR, start dabigatran when INR &lt;2</td>
<td>Stop warfarin and monitor INR, start rivaroxaban when INR &lt;3</td>
<td>Stop warfarin and monitor INR, start apixaban when INR &lt;2</td>
<td>Stop warfarin and monitor INR, start edoxaban when INR &lt;2.5</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>Stop heparin and start DOAC at the same time</td>
<td>Stop heparin and start edoxaban 4 hours later</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LMWH</td>
<td>Stop LMWH and start DOAC when the next dose of LMWH would have been given</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Warfarin</td>
<td>Start 12 hours (CrCl ≥30) or 24 hours (CrCl &lt;30) after the last dose of dabigatran</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heparin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LMWH</td>
<td>Stop LMWH and start DOAC when the next dose of LMWH would have been given</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Limited data
### Interruption of DOACs for scheduled procedures

<table>
<thead>
<tr>
<th>Drug</th>
<th>Renal Function (mL/min)</th>
<th>Low bleeding risk procedure</th>
<th>High bleeding risk procedure</th>
<th>Resumption of DOAC after low risk procedure</th>
<th>Resumption of DOAC after high risk procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>CrCl &gt;50</td>
<td>2 days before</td>
<td>3 days before</td>
<td>Resume the day after procedure</td>
<td>Resume 2-3 days after procedure</td>
</tr>
<tr>
<td></td>
<td>CrCl 30-50</td>
<td>3 days before</td>
<td>3 days before</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>CrCl 15-30</td>
<td>4 days before</td>
<td>4 days before</td>
<td></td>
<td></td>
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<tr>
<td>Rivaroxaban</td>
<td>CrCl &gt;50</td>
<td>2 days before</td>
<td>3 days before</td>
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<td></td>
<td>CrCl 30-50</td>
<td>4-5 days before</td>
<td>3 days before</td>
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<tr>
<td></td>
<td>CrCl 15-30</td>
<td>4 days before</td>
<td>4 days before</td>
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<tr>
<td>Edoxaban</td>
<td>CrCl &gt;50</td>
<td>2 days before</td>
<td>3 days before</td>
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<tr>
<td></td>
<td>CrCl ≥40</td>
<td>3 days before</td>
<td>4-5 days before</td>
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<tr>
<td></td>
<td>CrCl 15-30</td>
<td>4 days before</td>
<td>4 days before</td>
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<tr>
<td>Betrixaban</td>
<td>CrCl &gt;50</td>
<td>2 days before</td>
<td>3 days before</td>
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### DOACs vs. warfarin

**Pros**
- Improved clinical outcomes
- NO INR monitoring required; therefore, less frequent office visits
- No need for bridging
- Fewer drug and diet interactions

**Cons**
- Twice daily dosing with select DOACs
- Missed doses place patient at higher risk of thrombosis due to short half-life
- Higher incidence of GI side effects leading to discontinuation
- Renal monitoring and dose adjustments required
- Higher costs


### Monitoring of all DOACs

- Routine monitoring of coagulation tests is not required
- Adherence monitoring of coagulation tests is required
- Bleeding risk assessment
- Creatinine Clearance
- Drug interaction assessment and counseling

Cuker A. J Am Coll Cardiol. 2014 Sep 16;64(11):1128-39

### Monitoring of all DOACs

- Renal and hepatic function should be evaluated before initiation of DOAC and at least annually
  - Renal dosing adjustments
  - DOACs are not recommended in severe hepatic dysfunction

January CT J Am Coll Cardiol. 2019 Jan 21; pii: S0735-1097(19)3019-8

### Adherence concerns

- Poor Adherence = Poor Outcomes
  - 28% of patients are non-adherent to dabigatran
  - 13% increase in all-cause mortality and stroke for each 10% decrease in adherence

- Increased adherence has been demonstrated with pharmacist-led monitoring
  - Recommend 1 visit every 3 months for DOAC adherence monitoring, which is likely much less often than warfarin visits for INR monitoring


### Laboratory considerations: direct thrombin inhibitor (Dabigatran)

- Dabigatran level: reference range 45-95 ng/mL
  - Trough level drawn ≤30 minutes prior to the next scheduled dose
- Thrombin time (TT)
  - Normal TT rules out clinically significant levels of dabigatran
- aPTT
  - Use if above unavailable, less sensitive than TT
- PT/INR
  - Less sensitive than TT or aPTT

Cuker A. J Am Coll Cardiol. 2014 Sep 16;64(11):1128-39
Laboratory considerations: factor Xa inhibitors (apixaban, edoxaban, rivaroxaban)

- Heparin level = anti-Xa
  - This assay used to calculate heparin levels shows linear correlation with increasing levels of factor Xa inhibitors
  - Anti-Xa level <0.1 U/mL rules out clinically significant levels of factor Xa inhibitors
- PT/INR: due to variability in results, not recommended
  - Apixaban and rivaroxaban:
    - PT shows some correlation with direct factor Xa inhibitor levels, correlation with INR is weaker
    - Normal PT rules out clinically significant levels of factor Xa inhibitors
  - Edoxaban:
    - No good correlation with PT

Cuker A. J Am Coll Cardiol. 2014 Sep 16;64(11):1128-39

Lab considerations: DOAC serum levels

- Commercial assays are available, but reference ranges are variable and not correlated to safety, efficacy, or clinical outcomes
- Indications for serum levels include:
  - Patients undergoing emergent surgery
  - Dialysis or CKD patients at risk of accumulation leading to toxic drug levels
  - Detection of DDIs to guide dose adjustments
  - Evaluation of absorption in obese patients
  - Evaluation of adherence


Reversal of DOACs

- Idarucizumab (Praxbind®): Antidote for dabigatran
- Andexanet Alfa (Andexxa®): Antidote for Direct Xa inhibitors

Please see "Available Strategies to Reverse Anticoagulant Medications" CE presentation for additional information

Conclusion

- The DAOCs consist of the direct thrombin inhibitor dabigatran and the factor Xa inhibitors are rivaroxaban, apixaban, edoxaban, and betrixaban
- The pharmacokinetics, pharmacology, indications, dosing, and other considerations are DOAC specific and vary between the drug class
- There are dose adjustments recommended, dependent on patient’s renal function and concomitant use of P-gp or CYP3A4 inhibitors or inducers

THANK YOU

Please feel free to email me with any questions: jeleclair@uchc.edu