Rivaroxaban (Xarelto®)

Pharmacologic Category: Factor Xa Inhibitor

Pharmacodynamic/kinetics:

- $T_{1/2}$ ~ 5 to 9 hrs (given normal renal function)
- Time to peak, plasma: 2 to 4 hrs

Dosing Guidelines: Page provider if dose is not appropriate

1. **Nonvalvular Atrial Fibrillation**

Creatinine Clearance	Recommended Dose
> 50 ml/min	20 mg QDAY (with evening meal)
15-50 ml/min	15 mg QDAY (with evening meal)
< 15 ml/min or HD patient	AVOID USE

2. **Postoperative Prophylaxis (Knee or Hip)**
   - Dose = 10 mg QDAY (AVOID USE if CrCl < 15 ml/min)
   - Initiate therapy after hemostasis has been established (~10 hrs postoperatively)
   - Use for 12 days for knee replacement
   - Use for 35 days for hip replacement

3. **VTE Treatment**

Creatinine Clearance	Recommended Dose
>/= 15 ml/min*	15 mg BID for 21 days, then 20 mg QDAY (with food)
< 15 ml/min*	AVOID USE

4. **Prophylaxis for VTE Recurrence**

Creatinine Clearance	Recommended Dose
>/= 15 ml/min*	10 mg QDAY after 6 months of treatment dose
< 15 ml/min*	AVOID USE

5. **CAD/PAD**
   - 2.5 mg BID, plus aspirin 75-100 mg QDAY

6. **Prophylaxis of VTE in acutely ill medical patients**

Creatinine Clearance	Recommended Dose
>/= 15 ml/min*	10 mg QDAY for a total of 31-39 days
< 15 ml/min*	AVOID USE

*New manufacturer recommendations for CrCl cutoffs. Use clinical judgement for new starts.

Conversion Guidance:

- **Rivaroxaban to Warfarin**
  - Discontinue rivaroxaban and initiate both warfarin and a parenteral anticoagulant at the time the next rivaroxaban dose would have been administered (12 to 24 hrs)
  - Or, overlap rivaroxaban and warfarin for >/= 2 days until INR is therapeutic
- **Warfarin to Rivaroxaban**
  - Discontinue warfarin and start rivaroxaban when INR < 3.0
- **Enoxaparin to Rivaroxaban**
  - Initiate rivaroxaban 0-2 hrs before time of next scheduled dose of *enoxaparin* would have been administered
- **Fondaparinux to Rivaroxaban**
  - Initiate rivaroxaban 0-2 hrs before time of next scheduled dose of *fondaparinux* would have been administered
- **Dabigatran to Rivaroxaban**
  - Initiate rivaroxaban 0-2 hrs before time of next scheduled dose of *dabigatran* would have been administered
- **Heparin to Rivaroxaban**
  - Stop heparin infusion and initiate rivaroxaban simultaneously
- **Rivaroxaban to Heparin drip/LMWH/Fondaparinux**
  - Initiate heparin drip/LMWH/fondaparinux when next dose of rivaroxaban would have been administered (12 or 24 hrs)

Recommendation for Discontinuation Prior to Surgery:

- Discontinue at least 24 hours prior to surgery
- CONSIDER RENAL FUNCTION:
  - CrCl > 90 ml/min ☮stop 1 day prior to procedure
  - CrCl 30-90 ml/min ☮stop 2-3 days prior to procedure
  - CrCl < 30 ml/min ☮stop 4 days prior to procedure

Reversal:

- Andexanet alfa (Andexxa): non-formulary
- Not dialyzable
- Prothrombin Complex Concentrate (Kcentra), APCC (FEIBA), or recombinant factor VIIa (NovoSeven RT) can be used

****** <u>IMPORTANT NOTE</u>: Rivaroxaban can contribute to INR elevation, therefore, initial INR measurements after initiating warfarin may be unreliable******

Apixaban (Eliquis®)

Pharmacologic Category: Factor Xa Inhibitor

Pharmacodynamics/Kinetics:

- $T_{1/2}$ of ~12 hours
- Time to peak, plasma: 1 to 3 hours

Dosing Guidelines: Call provider if dose is inappropriate

1. **Nonvalvular Atrial Fibrillation**
   Normal Dose: 5 mg BID (May be taken without regard to food.)
   Dose adjustment: 2.5 mg BID for patients with any TWO following characteristics
   - Age ≥ 80 years
   - Body weight ≤ 60 kg
   - Serum creatinine ≥ 1.5 mg/dl

2. **Postoperative Thromboprophylaxis (Knee or Hip)**
   - Dose = 2.5 mg twice daily
   - Initiate therapy after hemostasis has been established (~12-24 hours postoperatively)
   - Use for 12 days for knee replacement
   - Use for 35 days for hip replacement

3. **DVT/PE Treatment**
   - Treatment Dose: 10 mg BID for 7 days followed by 5 mg BID
   - Dose adjustment: None necessary; however, patients with a SCr >2.5 mg/dL or CrCl <25 mL/minute were excluded from the clinical trials

4. **Reduction in the risk of recurrence of DVT/PE**
   - 2.5 mg BID after at least 6 months of treatment for DVT/PE
   - Dose adjustment: None necessary; however, patients with a SCr >2.5 mg/dL or CrCl <25 mL/minute were excluded from the clinical trials

Conversion Guidance:

- **Apixaban to Warfarin**
  - Discontinue apixaban and initiate both warfarin and a parenteral anticoagulant at the time the next apixaban dose would have been administered (12 hours)
  - Or, overlap apixaban and warfarin for >/= 2 days until INR is therapeutic
- **Warfarin to Apixaban**
  - Discontinue warfarin and start apixaban when INR < 2.0
- **Lovenox to Apixaban**
  - Discontinue lovenox and initiate apixaban when next scheduled dose of lovenox would have been administered
- **Fondaparinux to Apixaban**
  - Discontinue fondaparinux and initiate apixaban when next scheduled dose of fondaparinux would have been administered
- **Dabigatran to Apixaban**
  - Discontinue dabigatran and initiate apixaban when next scheduled dose of dabigatran would have been administered

- **Heparin to Apixaban**
  - Stop heparin infusion and initiate apixaban simultaneously
- **Apixaban to Heparin drip/LMWH/Fondaparinux**
  - Initiate heparin drip/LMWH/fondaparinux when next dose of apixaban would have been administered (12 hours)

Recommendation for Discontinuation Prior to Surgery:

- Discontinue 48 hours prior to surgery when bleeding risk of procedure is moderate-to-high
- Discontinue 24 hours prior to surgery when bleeding risk of procedure is low
- CONSIDER RENAL FUNCTION:
  - CrCl < 60 ml/min → Consider holding 2-3 days prior to procedure
  - CrCl < 50 ml/min → Consider holding 3 or more days prior to procedure

Reversal Agents:

- Andexanet alfa (Andexxa): non-formulary
- Not dialyzable
- Prothrombin Complex Concentrate (Kcentra), APCC (FEIBA), or recombinant factor VIIa (NovoSeven RT) can be used

******IMPORTANT NOTE: Apixaban can contribute to INR elevation, therefore, initial INR measurements after initiating warfarin may be unreliable.******

Dabigatran (Pradaxa®)

Pharmacologic Category: Thrombin Inhibitor

Pharmacodynamics/Kinetics:

- $T_{1/2}$ of ~12 to 17 hrs (normal renal function)
- Time to peak, plasma: 1 hr (delayed 2 hrs by food with no effect on bioavailability)
- Do not open capsule (increases bioavailability by 75%)

Dosing Guidelines: Call provider if dose is inappropriate

***** Use with extreme caution or consider other treatment options in patients >/= 75 years of age**

1. **Nonvalvular Atrial Fibrillation**

Creatinine Clearance	Recommended Dose
> 30 ml/min	150 mg BID
15-30 ml/min **OR** 30-50 ml/min with use of P-gp inhibitor (dronedarone, ketoconazole)	75 mg BID
< 15 ml/min or HD patient **OR** < 30 ml/min with use of P-gp inhibitor	Avoid Use

2. **DVT/PE Treatment**

Creatinine Clearance	Recommended Dose
> 30 ml/min	Parenteral anticoagulant x 5-10 days, then 150 mg BID
</= 30 ml/min or HD patient **OR** < 50 ml/min + P-gp inhibitors	Avoid Use

3. **VTE Prophylaxis following Hip Replacement Surgery**

Creatinine Clearance	Recommended Dose
> 30 ml/min	110 mg for first day, then 220 mg once daily for 28-35 days
</= 30 ml/min or HD patient **OR** < 50 ml/min + P-gp inhibitors	Avoid Use

Conversion Guidance:

- **Dabigatran to Warfarin**
  - CrCl > 50 ml/min → Start 3 days before stopping dabigatran
  - CrCl 31-50 ml/min → Start 2 days before stopping dabigatran
  - CrCl 15-30 ml/min → Start 1 day before stopping dabigatran
- **Warfarin to Dabigatran**
  - Discontinue warfarin and start dabigatran when INR < 2.0
- **Parenteral Anticoagulant to Dabigatran**
  - Initiate dabigatran 0-2 hours before time of next scheduled dose (Lovenox) or at the time of d/c for the continuously administered parenteral drug (Heparin)
- **Dabigatran to Parenteral Anticoagulant**
  - Wait 12 hours (CrCl ≥ 30 ml/min) or 24 hours (CrCl < 30 ml/min) after the last dose of dabigatran.
- **Dabigatran to Rivaroxaban**
  - Initiate Rivaroxaban 0-2 hours before time of next scheduled dose of Dabigatran would have been administered

Recommendations for Discontinuation Prior to Surgery:

- CrCl ≥ 50 ml/min → Stop 1-2 days prior to procedure
- CrCl < 50 ml/min → Stop 3-5 days prior to procedure
- Recommend 2 days (≥ 50 ml/min) or 5 days (< 50 ml/min) for patients undergoing MAJOR surgery

Reversal:

- Praxbind (idarucizumab) 5 gm IV (given as two separate 2.5 gm doses no more than 15 minutes apart)
- Hemodialysis
- FFP and PRBCs can be used.

******<u>IMPORTANT NOTE</u>: Pradaxa can contribute to INR elevation. Warfarin's effect on INR will be better reflected after dabigatran has been stopped for ≥ 2 days.******

Edoxaban (Savaysa®) - Non-formulary

Pharmacologic Category: Factor Xa Inhibitor

Pharmacodynamic/kinetics:

- T1/2 ~ 10 to 14 hrs (given normal renal function)
- Time to peak, plasma: 1 to 2 hrs

Dosing Guidelines: Call provider if dose is not appropriate

1. Nonvalvular Atrial Fibrillation

Creatinine Clearance	Recommended Dose
> 95 ml/min	AVOID USE – increased risk of ischemic stroke compared to warfarin
51-95 ml/min	60 mg QDAY
15-50 ml/min	30 mg QDAY
< 15 ml/min or HD patient	AVOID USE

2. DVT/PE Treatment

Creatinine Clearance	Recommended Dose
> 50 ml/min (Some experts do not recommend using if CrCl > 95 ml/min)	Parenteral anticoagulant x 5-10 days, then 60 mg QDAY if > 60 kg 30 mg QDAY if ≤ 60 kg
> 50 ml/min + PGP inhibitor (verapamil, quinidine, short-term use azithromycin, clarithromycin, erythromycin, itraconazole, ketoconazole)	30 mg QDAY
15-50 ml/min	30 mg QDAY
< 15 ml/min	AVOID USE

Conversion Guidance:

- **Edoxaban to Warfarin – 3 methods**
  - Edoxaban bridging (60mg dose): if on 60 mg dose, reduce the dose to 30 mg and begin warfarin concomitantly. Measure INR prior to daily edoxaban dose (at least weekly), and once INR ≥ 2, discontinue edoxaban.
  - Edoxaban bridging (30mg dose): If on 30 mg dose, reduce the dose to 15 mg and begin warfarin concomitantly. Measure INR prior to daily edoxaban dose (at least weekly), and once INR ≥ 2, discontinue edoxaban.
  - Parenteral anticoagulation bridging: discontinue edoxaban. Initiate heparin drip/LMWH/fondaparinux when next dose of edoxaban would have been administered and begin warfarin concomitantly. Once INR ≥ 2, discontinue parenteral anticoagulant.
- **Warfarin to Edoxaban**
  - Discontinue warfarin and start edoxaban when INR ≤ 2.5
- **Enoxaparin to Edoxaban**
  - Initiate edoxaban when the next scheduled dose of enoxaparin would have been administered

- **Fondaparinux to Edoxaban**
  - Initiate edoxaban when the next scheduled dose of fondaparinux would have been administered
- **Non-vitamin-K-dependent Oral Anticoagulant (NOAC) to Edoxaban**
  - Initiate edoxaban when the next scheduled dose of NOAC would have been administered
- **Heparin to Edoxaban**
  - Stop heparin infusion and initiate edoxaban 4 hrs later
- **Edoxaban to Heparin drip/LMWH/Fondaparinux**
  - Initiate heparin drip/LMWH/fondaparinux when next dose of edoxaban would have been administered
- **Edoxaban to Non-vitamin-K-dependent Oral Anticoagulant (NOAC)**
  - Initiate NOAC when next dose of edoxaban would have been administered

Recommendation for Discontinuation Prior to Surgery:

- Discontinue 24 hours prior to surgery for procedures with low risk of bleeding
- Discontinue 48 hours prior to surgery for procedures with high risk of bleeding
- CONSIDER RENAL FUNCTION
  - CrCl > 50 ml/min ☮ consider holding 1-2 days
  - CrCl </= 50 ml/min ☮consider holding 3 or more days

Reversal Agents:

- No specific antidote
- Not dialyzable
- Prothrombin Complex Concentrate (Kcentra), APCC (FEIBA), or recombinant factor VIIa (NovoSeven RT) can be used

****** <u>IMPORTANT NOTE</u>: Edoxaban can contribute to INR elevation, therefore, initial INR measurements after initiating warfarin may be unreliable******