# CARDIOVASCULAR – FACTOR Xa INHIBITORS - ORAL

## Drug Class

- **Oral Factor Xa Inhibitors, or Direct Oral Anticoagulants (DOACs)**
- **Oral Agents:**
  - Apixaban
  - Edoxaban
  - Rivaroxaban
- **Parenteral Agent:**
  - Fondaparinux

**Fast Facts**

- ✓ *These anticoagulants can be reversed by andexanet alfa and aPCC.*
- ✓ *Unlike heparin or fondaparinux, oral factor Xa inhibitors do not require antithrombin to work.*

## Main Indications or Uses

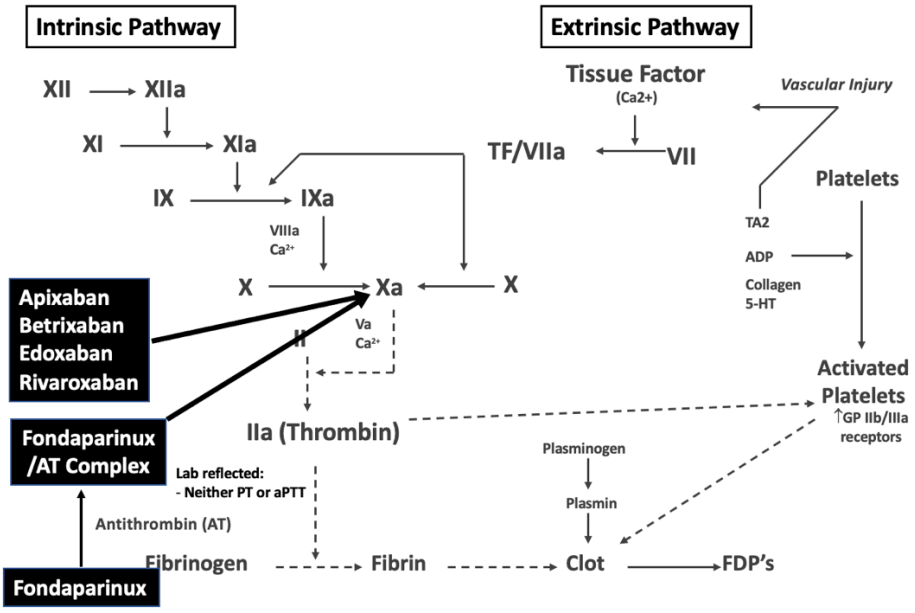
- **Acute/Chronic Care:**
  - Venous Thromboembolism [VTE, including deep vein thrombosis (DVT) or pulmonary embolism (PE)]
    - Treatment and prophylaxis
  - Nonvalvular Atrial Fibrillation (AF) for stroke prevention

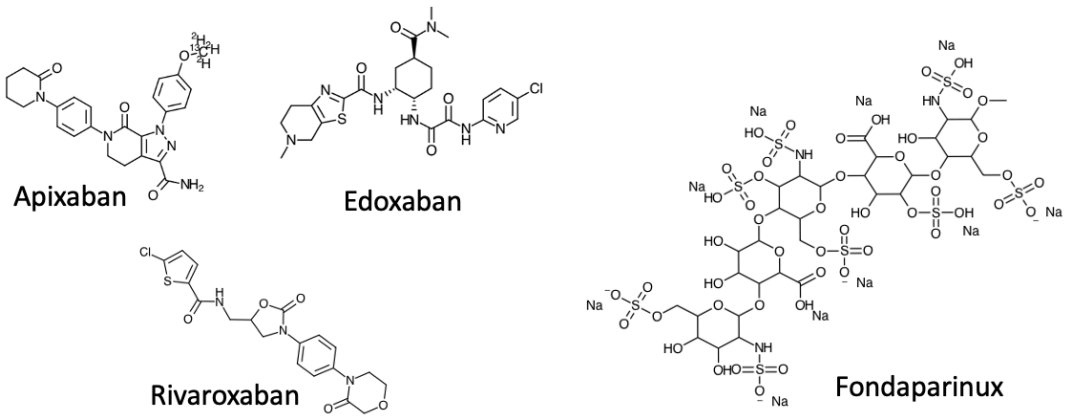
## Primary Net Benefit

- Oral Factor Xa inhibitors (oral FXa) have antithrombotic therapeutic benefits that are as good as warfarin (rivaroxaban) and superior to warfarin (apixaban), with less routine monitoring and fewer drug interactions (but unfortunately still some that are relevant).
  - They make up a good portion of the DOACs available.

## High-Yield Basic Pharmacology

- **Mechanism of Action**
  - Oral factor Xa (FXa) inhibitors prevent the conversion of prothrombin to thrombin by directly, selectively, and reversibly inhibiting free and clot-bound FXa.
    - FXa is part of the prothrombinase complex that catalyzes the conversion of prothrombin to thrombin.
    - Thrombin promotes platelet activation and fibrin clot formation; therefore, preventing the conversion of prothrombin to thrombin affects both.
  - Oral FXa inhibitors differ in their mechanism of action compared to the parenteral agent, fondaparinux.
    - Unlike oral FXa inhibitors, fondaparinux requires antithrombin in order to inhibit FXa. Without antithrombin, fondaparinux would not confer any therapeutic benefit.
      - This matters clinically since patients with the hypercoagulable disorder, antithrombin deficiency, are not good candidates for fondaparinux-based anticoagulation therapy.
      - This is due to the structural differences between the FXa inhibitors and their molecular weight.
        - The structural differences also allow for oral administration since fondaparinux's structure is a synthetic pentasaccharide molecule.




- **Pharmacokinetic and Pharmacodynamic Considerations**
  - **Basic Pharmacokinetics**
    - Peak plasma levels are achieved within 2 hours, comparable to the initiation of parenteral heparin.
      - This rapid and reliable onset of action permits patients to be discharged from emergency departments on apixaban or rivaroxaban for VTE treatment to follow up in an outpatient setting.
        - Edoxaban requires at least 5 days of initial parenteral anticoagulation to serve as "bridge therapy".
    - FXa half-lives are shorter than warfarin (average 40 hours); therefore, their therapeutic effects will decrease faster, which increases the risk of stroke or VTE with noncompliance.
      - Rivaroxaban: 5-9 hours
      - Apixaban and edoxaban: approximately 12 hours
    - Administer rivaroxaban 15-20 mg with food to increase bioavailability.
    - Elimination:

- With the exception of edoxaban, apixaban and rivaroxaban are eliminated in part by phase 1 metabolic pathways of the CYP450 enzyme system, especially CYP3A4.
- They are also eliminated by the efflux cell membrane transporter, P-gp.
  - Apixaban and rivaroxaban also utilize BCRP for elimination.
  - Edoxaban only utilizes P-gp for most of its elimination.

- **Renal Function Considerations**
  - Edoxaban
    - CrCl > 95 mL/min or < 15 mL/min: Avoid due to unreliable anticoagulation
  - Rivaroxaban for AF:
    - CrCl 15-50 mL/min: 15 mg daily
    - CrCl < 15 mL/min: Avoid
- **Hepatic Function Considerations**
  - Apixaban: Avoid with Child-Pugh Class C
  - Rivaroxaban or edoxaban: Avoid with Child-Pugh Class B or C

## High-Yield Clinical Knowledge

- **Place in Therapy**
  - **Mechanical Valves**
    - Avoid oral FXa inhibitors for patients with mechanical valves.
- **Dosing, Dosage Forms, and/or Administration**
  - **Apixaban Dose Adjustments**
    - Patients receiving apixaban for nonvalvular AF should receive a reduced dose of 2.5 mg twice daily if they have at least two of the following:
      - Age ≥ 80 years
      - Wt ≤ 60 kg
      - SCr ≥ 1.5 mg/dL.
    - Apixaban is not recommended in patients with CrCl < 25 mL/min or on hemodialysis.
      - Some data exists to suggest apixaban's use in this population is at least as effective and safe compared to warfarin.
        - An observational study supported the use of apixaban by demonstrating a reduced incidence of stroke but had a relatively high rate of major and intracerebral bleeding as well as drug discontinuation.
        - Circulation. 2018; 138:1519–1529.
  - **Edoxaban Dosing Considerations**
    - Unlike the other available oral FXa inhibitors and warfarin, edoxaban's use for VTE and AF is limited to specific populations.
      - VTE Treatment is permitted after 5 days of initial therapy with a parenteral anticoagulant.
  - **Rivaroxaban Additional Indications**
    - Acute Coronary Syndrome (after initial management)
      - 2.5 mg twice daily in combination with aspirin and clopidogrel
    - Stable Coronary Artery Disease or Peripheral Artery Disease
      - 2.5 mg twice daily in combination with aspirin
        - Do not use if dual antiplatelet therapy is planned.
    - The increased risk of bleeding must be considered in a patient-specific manner.
      - Do not use for these indications if therapeutic anticoagulation is required for another indication.
- **Contraindications**
  - Active pathological bleeding is the major contraindication to FXa inhibitor use.
- **Warnings or Boxed Warnings**
  - Premature discontinuation of anticoagulation will increase the risk of thrombotic events unless the patient is appropriately transitioned to an alternative therapy.

### Knowledge Integration

- ✓ *FXa inhibitors may have utility in special populations, but evidence limits their use.*
- ✓ *For example, low molecular weight heparins are preferred in oncology patients with VTE.*

  - Specific recommendations exist for each agent and depend on the anticoagulant being transitioned from and transitioned to.
- Epidural or spinal hematomas may occur in patients undergoing spinal procedures and can result in poor outcomes, including paralysis.
- Patients with triple-positive antiphospholipid syndrome should be anticoagulated with warfarin due to a higher risk of recurrent VTE with FXa inhibitors.
- Patients who have undergone bariatric surgery may have reduced absorption of FXa inhibitors.
- Edoxaban
  - Patients with nonvalvular AF must have a CrCl ≤ 95 mL/min.
    - Patients who had AF with CrCl > 95 mL/min demonstrated increased stroke risk with edoxaban compared to those treated with warfarin.
  - May cause an increased risk of bleeding in patients with gastrointestinal or genitourinary cancers
- Rivaroxaban
  - Older patients tend to exhibit higher rivaroxaban concentrations than younger patients, primarily due to reduced clearance.

- **Adverse Effects**
  - Bleeding is the major adverse effect of anticoagulants.
    - Epistaxis, hemoptysis, blood (bright or dark) in stools, red or tea-colored urine, increased bruising, heavy menstrual periods, bleeding gums, swollen joints after falls, dizziness, paleness, anemia, fatigue
  - Elevated liver enzymes
- **Reversal of Oral Factor Xa Inhibitors**
  - Prothrombin complex concentrate (PCC) can reverse the antithrombotic effects of FXa inhibitors in patients with acute major bleeding, those who require emergent surgical intervention, and/or those with supratherapeutic INRs.
    - Kcentra (PCC) dosing utilizes a low fixed-dose regimen, which reduces thrombosis risk.

  Andexanet alfa
    - It directly binds and sequesters oral FXa inhibitors, halting their antithrombotic actions.
    - It also inhibits Tissue Factor Pathway Inhibitor (TFPI), which increases tissue factor-initiated thrombin production.
- **Drug, Supplement, Food, and/or Disease Interactions**
  - **Drug Interactions**
    - The most significant drug interactions include those with CYP3A4 and P-glycoprotein involvement.
      - Apixaban: Avoid with strong CYP3A4 inducers
      - Edoxaban: Avoid with strong P-glycoprotein inducers and inhibitors
      - Rivaroxaban: Avoid with strong CYP3A4 and P-glycoprotein inducers and inhibitors
- **Monitoring**
  - Reduced clinical monitoring is considered an advantage of oral FXa inhibitors over warfarin.
    - However, when patient-specific factors contribute to increased FXa inhibitor concentrations (i.e., renal or hepatic impairment), clinically relevant bleeding can occur and be difficult to monitor.
  - Labs to monitor before initiation and periodically
    - Complete blood count
    - Serum creatinine
    - Liver function tests (albumin, total protein, bili, aPTT, and PT)
    - Liver enzyme tests (AST, ALT, AlkPhos)
- **Storage and/or Handling**
  - Use rivaroxaban suspension within 60 days of reconstitution.
- **Patient Education**
  - Patients should be educated on the signs/symptoms of bleeding.
  - Patients should be educated on how and when to seek care if they experience a fall or other injury.
- **Special Populations**
  - **Obesity**

- Patients who weigh more than 120 kg have not been adequately prospectively studied to develop strong recommendations regarding oral FXa inhibitor use in this population.
  - Subgroup analyses of ARISTOTLE, ROCKET-AF, and EINSTEIN have suggested apixaban and rivaroxaban maintain clinical efficacy and safety compared to warfarin in patients up to 150 kg.
    - Properly calibrated anti-Xa monitoring can help guide oral FXa inhibitor therapy in obese patients.
- **Geriatrics**
  - Apixaban may be the preferred option in geriatric patients due to a lower risk of major and gastrointestinal bleeding.
- **Pediatrics**

  Rivaroxaban may be used in infants (after oral feeding for 10 days) through 12 years for thromboprophylaxis after the Fontan procedure for congenital heart disease, for VTE, and to reduce the risk of recurrent VTE.

## High-Yield Core Evidence

- **AMPLIFY**
  - This randomized, double-blind study compared apixaban with the combination of subcutaneous enoxaparin followed by warfarin for acute venous thromboembolism.
  - There was no difference in the primary efficacy outcome (recurrent symptomatic VTE or death related to VTE) between the apixaban group and the conventional therapy group.
  - Fewer patients on apixaban experienced the composite safety endpoint (major bleeding and clinically relevant nonmajor bleeding) and major bleeding (treated as an independent outcome) compared to conventional therapy.
  - The authors concluded that a fixed-dose regimen of apixaban alone was non-inferior to conventional therapy for treating acute venous thromboembolism and was associated with significantly less bleeding.
  - NEJM. 2013 Aug 29;369(9):799-808.
- **ROCKET-AF**
  - ROCKET-AF was a landmark, multicenter, prospective, randomized, double-blind trial of patients with nonvalvular AF that compared the effect of rivaroxaban or warfarin in preventing the primary endpoint of stroke or systemic embolism.
  - At a mean follow-up of 2 years, rivaroxaban was non-inferior to warfarin for the composite endpoint of stroke or systemic embolism without increasing bleeding rates.
  - In the ITT analysis, rivaroxaban maintained a non-inferior effect but did not meet statistical significance for superiority.
  - There was no difference in the incidence of major and nonmajor clinically relevant bleeding between the rivaroxaban and warfarin groups.
  - The authors concluded that in patients with AF, rivaroxaban was non-inferior to warfarin for the prevention of stroke or systemic embolism.
  - NEJM. 2011 Sep 8;365(10):883-91.
- **ARISTOTLE**
  - This was a landmark multicenter, double-blind, randomized trial that compared apixaban to warfarin in patients with AF and at least one additional risk factor for stroke with a primary outcome of ischemic or hemorrhagic stroke or systemic embolism.
  - Patients receiving apixaban had a significantly lower incidence of ischemic or hemorrhagic stroke compared to the warfarin group and met both pre-defined criteria for noninferiority and superiority.
  - Significantly fewer patients who received apixaban experienced major bleeding and death from any cause compared with patients receiving warfarin.
  - The authors concluded that apixaban was superior to warfarin in patients with AF for preventing stroke or systemic embolism, caused less bleeding, and resulted in lower mortality.
  - NEJM. 2011 Sep 15;365(11):981-92.
- **ENGAGE AF-TIMI**
  - This was a randomized, double-blind, double-dummy trial comparing two once-daily regimens of edoxaban with warfarin in patients with moderate to high risk AF.

- Edoxaban 30 mg was shown to be noninferior to warfarin regarding the primary endpoint (stroke or systemic embolism), and edoxaban 60 mg was superior to warfarin.
- Major bleeding was more frequent with warfarin compared with both doses of edoxaban.
- The authors concluded that both once-daily regimens of edoxaban were noninferior to warfarin with respect to the prevention of stroke or systemic embolism and were associated with significantly lower rates of bleeding and death from cardiovascular causes.
- NEJM. 2013 Nov 28;369(22):2093-104.

## High-Yield Fast-Facts

- **$CHA_2DS_2$-VASc Risk Scoring System for AF**
  - The $CHA_2DS_2$-VASc risk scoring system has been recommended for stroke risk stratification in patients with AF to assist in determining anticoagulation needs.
- **TEG Coagulation Test**
  - Thromboelastography (TEG) is used to determine coagulopathy in the acute care setting. This test is primarily used when hemorrhage is observed or suspected, not for therapeutic monitoring.
- **Antithrombin**
  - Unlike fondaparinux, these agents are all oral and do not require the presence of antithrombin to work.

### HIGH-YIELD BOARD EXAM ESSENTIALS

- **CLASSIC AGENTS:** Apixaban, edoxaban, rivaroxaban
- **DRUG CLASS:** Oral FXa inhibitors
- **INDICATIONS:** Nonvalvular AF, VTE (treatment and prophylaxis)
- **MECHANISM:** Prevent the conversion of prothrombin to thrombin by direct, selective, and reversible inhibition of free and clot-bound FXa.
- **SIDE EFFECTS:** Bleeding
- **CLINICAL PEARLS:**
  - Oral FXa inhibitors have a shorter onset of action than warfarin, which allows earlier discharge depending on the drug and indication. Oral FXa inhibitor half-lives are also shorter, which can result in faster reductions in efficacy with noncompliance or interruptions than warfarin.
  - Edoxaban should not be used in patients that have either normal renal function (CrCl > 95 mL/min) or severely impaired renal function (CrCl < 15 mL/min).
  - Andexanet alfa can reverse these agents.

| COMPARISON OF ANTICOAGULANTS BY DRUG CLASS<br>High-Yield Med Reviews | | | | | |
|---|---|---|---|---|---|
| **Variable** | **Warfarin** | **Unfractionated Heparin** | **Low Molecular Weight Heparin** | **Direct Xa Inhibitor** | **Direct Thrombin Inhibitor** |
| **Medications** | Coumadin, Jantoven | Heparin sodium | Dalteparin<br>Enoxaparin | Fondaparinux<br>Apixaban<br>Edoxaban<br>Rivaroxaban | Argatroban<br>Bivalirudin<br>Desirudin<br>Dabigatran |
| **MW** | 308 | 3,000-30,000 | 2,000-10,000 | 1,728 / 435 | 500-7,000 |
| **Route Given** | PO; IV (rare) | SC, IV | SC, IV | F: SUBQ; A/E/R: PO | SC, IV; D: PO |
| **Mechanism of Action** | Inhibits activation of II, VII, IX, & X | Binds to AT and inhibits factors Xa:IIa at 1:1 ratio | Binds to AT and inhibits factors Xa:IIa at >1:1 ratio | F: Binds to AT to inhibit factor Xa only; others bind directly to Xa | Directly inhibits factor II only |
| **Needs Titration** | Yes ++ | Yes ++ | No | +/- | No |
| **Onset of Action** | Delayed, 5-7 days | Acute; immediate | Acute; 1-2 hours | Acute; 1-2 hours | Acute; Immediate |
| **Duration of Action** | Days | IV: 2-3 hours | SC: 12 hours | 24 hours | N/A; D: >12 hours |
| **Affected by Food** | Yes (Vit K containing) | No | No | No | N/A; D: Negligible |
| **Monitoring** | PT/INR | aPTT, anti-Xa, ACT | Anti-Xa levels | none | aPTT/ACT; D: None |
| **Renal Adjustments** | No | No | Yes | Yes | Yes |
| **CYP450 Enzymes** | 2C9 >> 3A4 | None | None | F: No, A/E/R: 3A4 | None |
| **Transporters** | None | None | None | P-gp, +/- BCRP | P-gp |
| **Precipitates Emboli** | Yes (early on) | +/- (during HIT) | +/- (during HIT) | No | No |
| **Cause HIT** | No | Yes; 0.5-5% | Yes; 0.1-1.3% | F: -/+, A/E/R: No | No |
| **Cross Placenta** | Yes | No | No | Maybe | No |
| **Antidote** | Vitamin K, aPCC | Protamine, FFP | Protamine, FFP | F: aPCC; Andexanet alfa | Idarucizumab, FFP |

**Table: Drug Class Summary**

| Oral Factor Xa Inhibitors - Drug Class Review<br>High-Yield Med Reviews | | | |
|---|---|---|---|
| **Mechanism of Action:** *Oral FXa Inhibitors (apixaban, edoxaban, rivaroxaban) provide direct, reversible, and selective FXa inhibition, preventing the conversion of prothrombin to thrombin.* | | | |
| **Class Effects:** *Increase clotting time, decrease the risk of thrombosis, have drug interactions via P-gp & CYP3A4, and require renal dose adjustments* | | | |
| **Generic Name** | **Brand Name** | **Main Indication(s) or Uses** | **Notes** |
| **Apixaban** | Eliquis | ▪ Atrial fibrillation<br>▪ Treatment of VTE<br>▪ Heparin-induced thrombocytopenia<br>▪ Left ventricular thrombus (treatment, prophylaxis) | ▪ **Dosing (Adult):**<br>– AF: 5 mg twice daily<br>– DVT/PE: 10 mg twice daily for 7 days, then 5 mg twice daily<br>▪ **Dosing (Peds):** N/A<br>▪ **CYP450 Interactions:** Substrate of CYP1A2, CYP2C19, CYP2C8/9, CYP3A4, and BCRP, P-gp<br>▪ **Renal or Hepatic Dose Adjustments:**<br>– AF: Reduce to 2.5 mg twice daily if:<br>– Age ≥ 80 years<br>– Wt ≤ 60 kg<br>– SCr ≥ 1.5 mg/dL<br>– Child-Pugh C - Not recommended<br>▪ **Dosage Forms:** Oral (tablet) |
| **Edoxaban** | Savaysa | ▪ Atrial fibrillation<br>▪ Treatment of VTE | ▪ **Dosing (Adult):**<br>– AF: 60 mg daily<br>– DVT/PE<br>– Wt > 60 kg: 60 mg daily<br>– Wt ≤ 60 kg: 30 mg daily<br>▪ **Dosing (Peds):** N/A<br>▪ **CYP450 Interactions:** Substrate P-gp<br>▪ **Renal or Hepatic Dose Adjustments:**<br>– CrCl > 95 mL/min OR < 15 mL/min: Not recommended<br>– CrCl 15 to 50 mL/min: 30 mg daily<br>– Child-Pugh B or C: Not recommended<br>▪ **Dosage Forms:** Oral (tablet) |
| **Rivaroxaban** | Xarelto | ▪ Atrial fibrillation<br>▪ Treatment of VTE<br>▪ Heparin-induced thrombocytopenia<br>▪ Coronary artery disease<br>▪ Left ventricular thrombus (treatment, prophylaxis)<br>▪ Peripheral artery disease<br>▪ Superficial vein thrombosis | ▪ **Dosing (Adult):**<br>– AF: 20 mg daily with food<br>– DVT/PE: 15 mg twice daily w/ food for 21 days followed by 20 mg daily w/ food<br>▪ **Dosing (Peds):** Administer after oral feeding for at least 10 days.<br>– Dose and frequency based on weight<br>▪ **CYP450 Interactions:** Substrate of CYP2J2, CYP3A4, and BCPR, P-gp<br>▪ **Renal or Hepatic Dose Adjustments:**<br>– AF: 15 mg daily with food if CrCl 15 to 50 mL/min<br>– CrCl is < 15 mL/min: Avoid<br>▪ **Dosage Forms:** Oral (tablet), suspension |