Introduction

Anticoagulant medications have served as the principle therapy to prevent thrombosis for a variety of cardiovascular diseases over many years. Heparin was the initial anticoagulant developed and used in clinical care; however, it is available only in a parenteral form that limits the duration of therapy.[1,2] With the discovery of oral vitamin K antagonists (VKAs), the indications broadened and the duration of anticoagulation therapy increased. Oral anticoagulants are now commonly prescribed medications around the world and are being utilized in the treatment of a wide variety of diseases for which prevention or resolution of thrombosis is needed.[3]

VKA medications (eg, warfarin, acenocoumarol, phenprocoumon) are currently the most commonly prescribed oral anticoagulants.[4] These agents work through the inhibition of clotting factors that are dependent upon vitamin K. The vitamin K-dependent factors include factors involved in the formation of thrombus (factors II, VII, IX, and X) and those that inhibit the formation of thrombus (protein C and protein S). During the initiation of a VKA, the effects of the drug are predominately on protein C and protein S. As a result, patients are transiently at an increased risk of thrombosis immediately after initiation of a VKA. This increased risk of thrombosis persists until the drug fully inhibits factors II, VII, IX, and X. After a few days of therapy, the effect of the drug on the coagulation factors predominates and the anticoagulant properties of the drug are manifest.[5] This class of medications has a long history of utilization and is currently indicated to prevent thromboembolism in a diverse group of patients including those with atrial fibrillation (AF), deep venous thrombosis, and mechanical heart valves.[3]

While VKAs are utilized throughout the world due to their broad indications and affordability, there are numerous challenges associated with their use. Genetic polymorphisms, concomitant medications, ongoing tobacco abuse and diet can affect the dose of warfarin required to achieve the desired level of anticoagulation.[6] As a result, the dosing of warfarin is highly variable and requires individualized testing and monitoring. This is especially problematic given that the therapeutic window required when using this drug is relatively narrow. Inadequate dosing can leave patients exposed to thrombotic complications, while excess dosing can expose patients to hemorrhagic complications such as intracranial hemorrhage and gastrointestinal bleeding. As a result of its narrow therapeutic window, observational studies of patients treated with warfarin have found they spend as much as 25% to 40% of their time outside the therapeutic window.[7] Similar results have been shown in patients participating in clinical trials in which only 50% to 70% of the time is spent in the therapeutic range. [8] Patients who spend large amounts of time outside the therapeutic range are at increased risk for both thrombotic and hemorrhagic complications (the former from inadequate anticoagulation and the latter from excess anticoagulation). Therefore, it is critical to maximize the amount of time in which patients are at the desired level of anticoagulation.

Importance of Pharmacokinetics and Pharmacodynamics

Knowledge of the pharmacokinetic and pharmacodynamic properties of an agent is necessary to understand how to use the medication in clinical practice. The pharmacokinetics of a drug describe how it reaches the site of action and how long it remains in the body. Drug absorption, distribution, metabolism, and excretion are the critical processes that determine the pharmacokinetics of a drug. Once at the site of action the pharmacodynamics of a drug, defined as the effects of the drug on the body, become important and determine the physiological action of the drug. Thus, the pharmacokinetics and pharmacodynamics of an agent determine the dose frequency and the level of dosing required to maintain safe and effective levels of anticoagulation.

The limitations of warfarin therapy led to the development of novel oral anticoagulants (NOACs). With improved pharmacodynamics and pharmacokinetics, these drugs are designed to have a predictable anticoagulant effect, resulting in safer drug administration. An ideal anticoagulant should be taken orally, have a rapid onset of action, and a rapid offset. In addition, its effects should be easily reversible given the potentially devastating effects that traumatic injuries or bleeding can have in patients on anticoagulation therapy. The ideal anticoagulant should also be efficacious and have reliable pharmacodynamics, with minimal off-treatment effects. Finally, the dosing of the ideal agent should result in reliable efficacy across a wide variety of comorbidities and patient states with minimal drug-drug interactions.
Pharmacodynamics of Novel Oral Anticoagulant Drugs

The pharmacodynamics of the different NOACs are relatively similar, in contrast to their pharmacokinetics, which are best understood in the context of each individual agent. The coagulation cascade is a complex system of multiple interrelated processes that are finely regulated to achieve a level of homeostasis that does not promote excess coagulation (and thus unintended thrombosis), while at the same time allowing for a level of thrombosis that is able to promote hemostasis and prevent spontaneous bleeding. Current NOACs target either factor Xa or thrombin, also known as factor IIa (Figure 1). Factor Xa serves as the link between the intrinsic and extrinsic coagulation systems. Activated factor Xa catalyzes the conversion of prothrombin to thrombin. Whereby factor Xa inhibitors (eg, rivaroxaban, apixaban, edoxaban) prevent the formation of thrombin, direct thrombin inhibitors (eg, dabigatran) directly target the coagulation cascade through the inhibition of thrombin. Inactive thrombin is unable to convert fibrinogen to fibrin, thus decreasing the formation of thrombus.

Figure 1. Overview of the coagulation cascade and the targets of action for different novel oral anticoagulant agents.[9]
The pharmacokinetics of a drug can be modified considerably by concomitant medications. This can result in either inadequate or excessive drug concentrations. Transporter proteins, which are located on cell membranes throughout the body, are key to determining both the intracellular and systemic levels of the drug. P-glycoprotein (P-gp), also known as multidrug resistance-1 or ABCB1, is one such transporter that has been shown to affect the levels of many cardiovascular drugs. P-gp is found in many locations throughout the body but transporters in the enteric, renal, and hepatic systems are most relevant to the pharmacokinetics of the NOACs. P-gp in the gastrointestinal tract limits drug absorption by transporting drugs out of cells. P-gp transporters in the liver and renal tubules mediate the elimination of drugs. Therefore, in the renal or hepatic systems, inhibitors of P-gp (amiodarone, verapamil, quinidine, ketoconazole, and clarithromycin) can increase drug levels, while P-gp inducers (rifampin, St. John's Wort, and carbamazepine) can decrease the levels of the drug and their effectiveness (Table 1).

Table 1. Effect of Novel Oral Anticoagulants on Plasma Levels From Drug-Drug Interactions and Clinical Factors, and Dosing Recommendations

<table>
<thead>
<tr>
<th>Drug Interaction</th>
<th>Via</th>
<th>Dabigatran</th>
<th>Apixaban</th>
<th>Edoxaban\textsuperscript{a}</th>
<th>Rivaroxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin</td>
<td>P-gp competition and CYP3A4 inhibition</td>
<td>+18%</td>
<td>No data yet\textsuperscript{§}</td>
<td>No effect</td>
<td>No effect</td>
</tr>
<tr>
<td>Digoxin</td>
<td>P-gp competition</td>
<td>No effect</td>
<td>No data yet\textsuperscript{§}</td>
<td>No effect</td>
<td>No effect</td>
</tr>
<tr>
<td>Verapamil</td>
<td>P-gp competition (and weak CYP3A4 inhibition)</td>
<td>+12%-180% (reduce dose and take simultaneously)\textsuperscript{†}</td>
<td>No data yet\textsuperscript{§}</td>
<td>+53% (SR) (reduce dose by 50%)\textsuperscript{‡}</td>
<td>Minor effect (use with caution if CrCl 15-50 mL/min) \textsuperscript{§}</td>
</tr>
<tr>
<td>Diltiazem</td>
<td>P-gp competition and weak CYP3A4 inhibition</td>
<td>No effect</td>
<td>+40%\textsuperscript{SmPC}\textsuperscript{‡}</td>
<td>No data yet\textsuperscript{§}</td>
<td>Minor effect (use with caution if CrCl 15-50 mL/min) \textsuperscript{§}</td>
</tr>
<tr>
<td>Quinidine</td>
<td>P-gp competition</td>
<td>+50%\textsuperscript{‡}</td>
<td>No data yet\textsuperscript{§}</td>
<td>+80% (reduce dose by 50%)\textsuperscript{‡}</td>
<td>+50%\textsuperscript{‡}</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>P-gp competition</td>
<td>+12%-60%\textsuperscript{‡}</td>
<td>No data yet\textsuperscript{§}</td>
<td>No effect</td>
<td>Minor effect (use with caution if CrCl 15-50 mL/min) \textsuperscript{§}</td>
</tr>
<tr>
<td>Dronedarone</td>
<td>P-gp and CYP3A4 inhibitor</td>
<td>+70%-100% (US: 2 x 75 mg)\textsuperscript{*}</td>
<td>No data yet\textsuperscript{§}</td>
<td>+85% (reduce dose by 50%)\textsuperscript{‡}</td>
<td>No data yet§</td>
</tr>
<tr>
<td>Ketoconazole; itraconazole; voriconazole; posaconazole</td>
<td>P-gp and BCRP competition; CYP3A4 inhibition</td>
<td>+140%-150% (US: 2 x 75 mg)\textsuperscript{*}</td>
<td>+100%\textsuperscript{SmPC}\textsuperscript{*}</td>
<td>No data yet</td>
<td>Up to +160%\textsuperscript{*}</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>Moderate CYP3A4 inhibition</td>
<td>No data yet\textsuperscript{§}</td>
<td>No data yet\textsuperscript{§}</td>
<td>No data yet\textsuperscript{§}</td>
<td>+42% (if systemically administered) \textsuperscript{‡}</td>
</tr>
<tr>
<td>Cyclosporin; tacrolimus</td>
<td>P-gp competition</td>
<td>No data yet\textsuperscript{§}</td>
<td>No data yet\textsuperscript{§}</td>
<td>No data yet\textsuperscript{§}</td>
<td>+50%\textsuperscript{‡}</td>
</tr>
<tr>
<td>Drug/Agent</td>
<td>Mechanism of Interaction</td>
<td>Percent Change</td>
<td>Data Availability</td>
<td>Data Availability</td>
<td>Data Availability</td>
</tr>
<tr>
<td>------------</td>
<td>--------------------------</td>
<td>----------------</td>
<td>-------------------</td>
<td>-------------------</td>
<td>-------------------</td>
</tr>
<tr>
<td>Clarithromycin; erythromycin</td>
<td>P-gp competition and CYP3A4 inhibition</td>
<td>+15%-20%‡</td>
<td>No data §</td>
<td>No data yet ‡§</td>
<td>+30%-54%‡</td>
</tr>
<tr>
<td>HIV protease inhibitors (eg, ritonavir)</td>
<td>P-gp and BCRP competition or inhibitor; CYP3A4 inhibition</td>
<td>No data yet §</td>
<td>Strong increase SmPC §</td>
<td>No data yet §</td>
<td>Up to +153%*</td>
</tr>
<tr>
<td>Rifampicin; St John's wort; carbamazepine; phenytoin; phenobarbital</td>
<td>P-gp/BCRP and CYP3A4/CYP2J2 inducers</td>
<td>-66%*</td>
<td>-54% SmPC*</td>
<td>-35%‡</td>
<td>up to -50%‡</td>
</tr>
<tr>
<td>Antacids (H2B; PPI; Al-Mg-hydroxide)</td>
<td>GI absorption</td>
<td>-12%-30%</td>
<td>No data yet §</td>
<td>No effect</td>
<td>No effect</td>
</tr>
</tbody>
</table>

### Other Factors

<table>
<thead>
<tr>
<th>Factor</th>
<th>Effect</th>
<th>Data Availability</th>
<th>Data Availability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥ 80 years</td>
<td>Increased plasma level</td>
<td>† ‡</td>
<td>No data yet ‡§</td>
</tr>
<tr>
<td>Age ≥ 75 years</td>
<td>Increased plasma level</td>
<td>†</td>
<td>No data yet ‡§</td>
</tr>
<tr>
<td>Weight ≤ 60 kg</td>
<td>Increased plasma level</td>
<td>†</td>
<td>† ‡</td>
</tr>
<tr>
<td>Renal function</td>
<td>Increased plasma level</td>
<td>†</td>
<td>†</td>
</tr>
<tr>
<td>Other increased bleeding risk</td>
<td>Pharmacodynamic interactions (antiplatelet drugs; NSAIDs; systemic steroid therapy; other anticoagulants); history of or active GI bleeding; recent surgery on critical organ (brain; eye); thrombocytopenia (eg, chemotherapy); HAS-BLED ≥ 3‡</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

BCRP = breast cancer resistance protein; NSAIDs = non-steroidal anti-inflammatory drugs; H2B = H2-blockers; PPI = proton pump inhibitors; P-gp = P-glycoprotein; GI = gastrointestinal; SmPC = Summary of product characteristics.

*Contraindicated/not recommended.
†Reduce dose (from 150 mg twice daily to 110 mg twice daily for dabigatran; from 20 mg to 15 mg once daily for rivaroxaban; from 5 mg twice daily to 2.5 mg twice daily for apixaban).
‡Consider dose reduction if another similarly marked factor is present.
§No data available; recommendation based on pharmacokinetic considerations.
a. No EMA approval yet. Needs update after final approval (SmPC).
b. Prespecified dose reduction has been tested in phase 3 clinical trial (to be published).

The hepatic system plays a major role in the activation and clearance of many medications. The metabolism of medications occurs through liver enzymes such as the cytochrome P450 system. This system contains a number of enzymes, known as cytochromes (CYPs), which metabolize a variety of different compounds. Drugs can affect CYPs by either inhibiting or inducing them. Inhibitors of CYP enzymes (eg, dronedarone, azole antifungal agents, rifampin) decrease the clearance of drugs metabolized in the liver. For anticoagulant therapies, decreased clearance would increase the degree of anticoagulation, leaving patients at risk for hemorrhagic complications. In contrast, medications that induce CYP enzymes can increase clearance of drugs metabolized in the liver, thereby decreasing the degree of anticoagulation and subjecting patients to an increased risk of thrombotic complications.

http://www.medscape.org/viewarticle/808338_print
Pharmacokinetics and Clinical Outcomes

The pharmacokinetic properties of oral anticoagulant medications are critical when considering their use in practice. Dosing is directly related to the pharmacokinetic properties of a drug since agents with a fast onset of action, an increased half life ($t_{1/2}$), a large volume of distribution, or a prolonged clearance can be dosed less frequently than medications with a slow onset, a short $t_{1/2}$, a small volume of distribution, or a rapid clearance. Regimens that require more-frequent dosing increase the likelihood that doses may be missed. Patients are more compliant when medications require less-frequent dosing. However, missed doses create a larger problem because patients are inadequately anticoagulated for a longer period of time. More-frequent dosing regimens increase the likelihood that doses may be missed, but a single missed dose results in a shorter total period of inadequate anticoagulation. As a result, the impact of the pharmacokinetics of a drug determine the frequency of dosing, patient compliance, and time without appropriate anticoagulation.[11]

Bleeding is another major concern with all anticoagulant medications. Poor understanding of the pharmacokinetics or of drug interactions can result in excess anticoagulation. This can increase the bleeding risk in patients since there is a relationship between the degree of anticoagulation and hemorrhagic events.[12] The risk factors associated with bleeding complications, such as female gender, increased age, low body weight, and renal dysfunction, are related to a small volume of distribution and/or decreased drug clearance that results in increased levels of drug.

Monitoring of Anticoagulation

Patients treated with warfarin require frequent monitoring to ensure that the level of anticoagulation stays within the desired therapeutic range. The NOACs were developed for use in clinical practice without the need for routine monitoring. The lack of monitoring is an appealing benefit of NOACs as this should decrease the number of patient visits, reduce healthcare utilization, and favorably impact the cost effectiveness of these agents.[13] However, patients treated with NOACs do require some routine monitoring. For example, many of the NOACs are cleared through the kidneys. Since worsening renal function can increase the anticoagulant effect of the NOACs, the European Society of Cardiology recommends that patients treated with these agents have routine monitoring of creatinine clearance (CrCl). Patients with CrCl ≥60 mL/min are recommended to undergo yearly monitoring, while patients with worse renal function should be monitored more closely (CrCl 30 to 59 mL/min every 6 months; CrCl 15 to 29 mL/min every 3 months).[10]

Clinical scenarios may also arise in which monitoring or measuring drug effect may be necessary. This includes patients on NOACs who develop bleeding, are exposed to excess dosing (due to overdosing, worsening liver/renal function or drug-drug interactions) or patients who require emergency surgery for which the degree of anticoagulation must be assessed preoperatively. International normalized ratio (INR) testing can be used to measure the anticoagulation effects of warfarin, but it is not useful in measuring the anticoagulant effect of the NOACs.[14] There are several other tests that can be used to make general assessments about the level of the anticoagulation. For instance, the anticoagulation effect of therapeutic doses of dabigatran can be measured using the activated partial thromboplastin time (aPTT). However, the relationship between the degree of anticoagulation and aPTT is not reliable at subtherapeutic doses. Factor Xa inhibitors at higher doses can also affect the prothrombin time (PT). Work is currently ongoing to improve the correlation of aPTT with factor Xa drug concentration; however, no test is yet ready to measure the anticoagulation effect of factor Xa inhibitors. Antifactor Xa chromogenic assays are commercially available for measuring the effects of factor Xa inhibitors but are not available for routine use in many laboratories. [18] Although chromogenic assays can be used to estimate the effects of a drug or make estimations of drug effect; to date, there are no published studies linking the results of antifactor Xa chromogenic assays with clinical outcomes.

Transitioning to Other Anticoagulants

In clinical practice, providers may need to change the anticoagulant being used. The transition from one anticoagulant to another can be challenging because it potentially could lead to either excess anticoagulation or a lack of anticoagulation. Thus, the healthcare provider must take into account the pharmacokinetics of both the agent that is being started and the agent that is being stopped in order to achieve a successful transition. Patients treated with a VKA who are transitioning to an NOAC should wait until after the INR is within a safe range before starting the NOAC ($≤2.0$ for dabigatran and apixaban, $≤3.0$ for rivaroxaban). The time period it takes for the INR to achieve the desired range is highly variable and depends on a variety of patient factors including the VKA being used by the patient, INR at the time of the last dose, current dose of VKA, and drug-drug interactions. When the decision has been made to transition from a VKA, frequent INR testing should be performed (approximately every 48 hours) until the INR achieves the target level. At that time, the NOAC can be started. Since the onset of anticoagulation is rapid, the patient spends little to no time with a subtherapeutic level of anticoagulation.
The need can also arise in which patients must switch from an NOAC to a VKA. This transition is more challenging and the methods are less well defined. For the current NOACs in clinical practice, a reasonable strategy is to continue the NOAC while starting a VKA. Once the INR approximates or exceeds 2.0, the NOAC should be stopped while the patient continues on only the VKA. Whether or not the dose of the NOAC should be adjusted during this period of overlap and whatever impact the simultaneous use of NOAC and VKA may have on the INR are issues that require further investigation. The ENGAGE AF-TIMI 48 trial is prospectively studying such an algorithm to ensure a smooth overlap of anticoagulation at the end of the trial from edoxaban to VKA.

There are multiple challenges in switching from an NOAC to a VKA since some of the NOACs affect the INR (eg, apixaban, edoxaban). The time for individuals to reach therapeutic levels on a VKA is also highly variable and in some patients it can take up to 2 weeks or longer. As a result, it is recommended that INR testing begin immediately prior to the initiating NOAC. It is also recommended to remeasure the INR 24 hours after the INR reaches 2.0 and the patient is on only VKA therapy, to assure continued adequate anticoagulation. Given the highly unpredictable nature of VKA dosing, the INR should be monitored once a week during the first month until stable values have been attained.

For hospitalized patients who are on heparin and need to transition to an NOAC, the pharmacokinetics of both heparin and the NOACs allow for a relatively simple transition. For patients being treated with intravenous unfractionated heparin, the infusion can be discontinued at the time the initial dose of NOAC is given. The half life of unfractionated heparin corresponds well with the onset of anticoagulation of the NOACs. For patients treated with low-molecular-weight heparins, the first dose of the NOAC can be given at the time the next low-molecular-weight heparin is due to be administered.

Reversal of Anticoagulation

The effect of warfarin can be reversed with oral, subcutaneous, or intravenous vitamin K, which can help overcome the vitamin K antagonism induced by warfarin. However, vitamin K does not immediately reverse the anticoagulant effect of warfarin.[16] If a more-rapid reversal of anticoagulation is needed, fresh frozen plasma or human prothrombin complex concentrate can be used to quickly, but only temporarily, reverse the effects of the VKA. There is tremendous interest in developing specific reversal agents for the NOACs in cases of life-threatening bleeding. Currently, none are available for use in clinical practice.[17] In cases of overdose, activated charcoal can be considered to limit the systemic absorption of the drug. Although a variety of agents (eg, recombinant factor VIIa, prothrombin complex concentrate, activated prothrombin complex concentrate) have the potential to be of clinical utility, none have yet been tested in patients with bleeding.[18]

Patients treated with NOACs may need surgery while being treated with these agents. If the surgery is elective, the patient should stop anticoagulation therapy 48 hours prior to the surgery (or longer in patients with chronic kidney disease). If the surgery is an emergency, efforts should be made to delay it until at least 12 hours after the last dose.

Which of the following increases a patient's risk of bleeding from novel oral anticoagulants?

- Use of antacids
- Low body weight
- Use of a medication that induces P-glucoprotein (P-gp)
- A diet low in vitamin K-containing foods

Patients who have bleeding events have been shown to:

- Have similar long-term outcomes when compared to patients who do not have bleeding
- Rarely have modifiable risk factors for bleeding
- Reduce medication dose or change concomitant medications to lower the risk of bleeding
- Not benefit from further anticoagulation

Save and Proceed
Novel Oral Anticoagulants Currently Approved for Use

Despite its widespread utilization, broad indications, and relatively inexpensive cost, the variety of challenges that arise due to treatment with warfarin have led to the development of NOACs that work through the inhibition of activated factor Xa, or thrombin. Currently, 3 NOACs are approved for use in clinical practice; additional agents are undergoing clinical testing and may be available in the future.

Apixaban

Apixaban is a factor Xa inhibitor currently approved for stroke prevention in atrial fibrillation (AF), based on several large-scale outcomes trials.[19] In the AVERROES trial, 5599 patients with AF who were not considered candidates for warfarin were randomly assigned in a double-blind fashion to either aspirin (81 to 324 mg) or apixaban (2.5 to 5 mg). Apixaban significantly reduced the incidence of stroke or systemic embolization compared to placebo (HR 0.45, 95% CI 0.32-0.62; \( P < 0.001 \)).[20] Similarly, the ARISTOTLE trial randomly assigned 18,201 patients with AF and at least one risk factor for stroke to either apixaban (5 mg twice daily) or warfarin (goal: INR 2-3) in a double-blind fashion. The primary end point of stroke or systemic embolization was reduced in patients treated with apixaban (HR 0.79, 95% CI, 0.66–0.95; \( P = .01 \)).[21] Apixaban has also been studied in patients either at risk for, or diagnosed with, venous thrombosis (Table 2).

Table 2. Clinical Studies of Apixaban

<table>
<thead>
<tr>
<th>Trial</th>
<th>Setting</th>
<th>Design</th>
<th>Dosage of Apixaban</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>AVERROES²⁰</td>
<td>Atrial fibrillation in patients unable to take warfarin</td>
<td>Apixaban vs aspirin</td>
<td>5 mg twice daily 2.5 mg twice daily for patients with 2 more risk factors for bleeding*</td>
<td>Apixaban reduces incidence of stroke or systemic embolism</td>
</tr>
<tr>
<td>ARISTOTLE²¹</td>
<td>Atrial fibrillation patients with at least 1 risk factor for stroke</td>
<td>Apixaban vs warfarin</td>
<td>5 mg twice daily 2.5 mg twice daily for patients with 2 more risk factors for bleeding*</td>
<td>Apixaban reduces incidence of stroke or systemic embolism</td>
</tr>
<tr>
<td>AMPLIFY-EXT²²</td>
<td>DVT previously treated with 6-12 months of anticoagulation</td>
<td>Apixaban vs placebo</td>
<td>5 mg twice daily or 2.5 mg twice daily</td>
<td>Extended therapy with apixaban reduces symptomatic recurrent VTE or death from VTE</td>
</tr>
<tr>
<td>ADOPT²³</td>
<td>DVT prophylaxis for medical patients</td>
<td>Apixaban (30 d) vs enoxaparin (6-14 days)</td>
<td>Apixaban 2.5 mg twice daily</td>
<td>Apixaban did not reduce death due to VTE, pulmonary embolism, symptomatic DVT or asymptomatic proximal DVT</td>
</tr>
<tr>
<td>ADVANCE²⁴</td>
<td>DVT after knee replacement</td>
<td>Apixaban vs enoxaparin</td>
<td>Apixaban 2.5 mg twice daily</td>
<td>Did not meet noninferiority margin</td>
</tr>
<tr>
<td>ADVANCE-2²⁵</td>
<td>DVT prophylaxis after knee replacement</td>
<td>Apixaban vs enoxaparin</td>
<td>Apixaban 2.5 mg twice daily</td>
<td>Reduction in DVT, nonfatal pulmonary embolism, death from any cause</td>
</tr>
<tr>
<td>ADVANCE-3²⁶</td>
<td>DVT prophylaxis after hip replacement</td>
<td>Apixaban vs enoxaparin</td>
<td>Apixaban 2.5 mg twice daily</td>
<td>Reduction in DVT, nonfatal pulmonary embolism, death from any cause</td>
</tr>
</tbody>
</table>
Risk factors for bleeding include age ≥80, body weight ≤60 kg, serum creatinine ≥1.5 mg/dL.

Pharmacokinetics and pharmacodynamics. Apixaban is absorbed from the gut and does not require hepatic conversion into an active agent (Table 3). It is highly bioavailable (estimated to be approximately 50%) and has a rapid onset, with peak-drug concentration occurring approximately 3 to 4 hours after administration. The t_{1/2} of the drug is ~13 hours, which is the primary rationale for the twice-daily dosing regimen. As a result, some evidence of anticoagulation will be present for at least 24 hours. The majority of the drug is cleared through elimination of unchanged molecule; however, some drug is cleared by metabolism through the CYP3A4 system.

Table 3. Comparative Pharmacokinetic Features of Anticoagulants

<table>
<thead>
<tr>
<th>Drug</th>
<th>Class</th>
<th>Bioavailability</th>
<th>Peak Plasma Level</th>
<th>Metabolism</th>
<th>Excretion</th>
<th>Volume of Distribution</th>
<th>t_{1/2}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran(^{27})</td>
<td>Direct thrombin inhibitor</td>
<td>7% (active agent is a prodrug)</td>
<td>1-2 h</td>
<td>Hepatic (via P-gp)</td>
<td>Urine (80%)</td>
<td>50-70 L</td>
<td>12-18 h</td>
</tr>
<tr>
<td>Rivaroxaban(^{28})</td>
<td>Reversible factor Xa inhibitor</td>
<td>66% (w/o food) &gt;80% (with food)</td>
<td>2-4 h</td>
<td>Hepatic</td>
<td>Urine (66%)</td>
<td>Fecal (28%)</td>
<td>~ 50 L</td>
</tr>
<tr>
<td>Apixaban(^{19})</td>
<td>Reversible factor Xa inhibitor</td>
<td>50%</td>
<td>3-4 h</td>
<td>Hepatic</td>
<td>Urine (27%)</td>
<td>Fecal (25%)</td>
<td>Biliary/Intestinal (remainder)</td>
</tr>
<tr>
<td>Edoxaban(^{29})</td>
<td>Reversible factor Xa inhibitor</td>
<td>62%</td>
<td>1-2 h</td>
<td>Hepatic</td>
<td>Urine (29%)</td>
<td>Fecal (65%)</td>
<td></td>
</tr>
</tbody>
</table>

There is also a component of renal clearance (~27%) that makes monitoring CrCl important. While the CYP3A4 system plays only a small role in the elimination of the drug, caution must be used when administered with strong inducers of both CYP3A4 and P-gp (Table 4). The concomitant use of drugs that are strong inhibitors of CYP3A4 (eg, diltiazem, quinidine, azole antifungal agents) is contraindicated. Monitoring the degree of anticoagulation in patients treated with apixaban is challenging because the PT, INR and aPTT are all affected by the drug. Chromogenic factor Xa can be used to monitor anticoagulation with apixaban.

Table 4. Medications With Important Interactions With Novel Oral Anticoagulant Medications

P-gp Inhibitors
- Amiodarone
- Clarithromycin
- Ketoconazole
Dosing. The current recommended dosage of apixaban for the prevention of stroke in patients with AF is 5 mg twice daily (Table 5). In patients with at least 2 out of 3 risk factors for bleeding (ie, age ≥80 years, body weight ≤60 kg, or serum creatinine ≥1.5 mg/dL), the recommended dosage is 2.5 mg twice daily. The 2.5-mg dose should also be considered in patients who are taking strong dual inhibitors of the CYP3A4 and P-gp systems (eg, ketoconazole, itraconazole, ritonavir, clarithromycin). Apixaban is contraindicated in patients with CrCl <15 mL/min.

Table 5. Important Dosing Considerations for Novel Oral Anticoagulant Medications Currently Approved by the US Food and Drug Administration for Use in Clinical Practice

<table>
<thead>
<tr>
<th>Drug</th>
<th>t½</th>
<th>Excretion</th>
<th>Approved Indications</th>
<th>Dosing</th>
<th>Important Drug Dosing Modifications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apixaban</td>
<td>13 h</td>
<td>Liver</td>
<td>Atrial fibrillation</td>
<td>5 mg twice daily</td>
<td>• Increase dose to 2.5 mg if 2 or more of the following: - age ≥80 years - body weight ≤60 kg - serum creatinine ≥1.5 mg/dL • Contraindicated if CrCl &lt;15 mL/min • Decrease dose to 2.5 mg with ketoconazole • Avoid use with rifampin</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>5-9 h</td>
<td>Renal</td>
<td>Atrial fibrillation</td>
<td>20 mg daily</td>
<td>• Use 15 mg if CrCl 15-50 mL/min • Avoid with combined P-gp and strong CYP3A4 inhibitors and inducers (ketoconazole, fluconazole, ritonavir, clarithromycin, erythromycin)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>or 15 mg daily</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>VTE treatment</td>
<td>20 mg daily</td>
<td>• 15 mg orally twice daily for 21 d then 20 mg daily • Avoid with combined P-gp and strong CYP3A4 inhibitors and inducers (ketoconazole, fluconazole, ritonavir, clarithromycin, erythromycin)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>VTE prevention</td>
<td>10 mg daily</td>
<td>• Avoid with combined P-gp and strong CYP3A4 inhibitors and inducers (ketoconazole, fluconazole, ritonavir, clarithromycin, erythromycin)</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>12-17 h</td>
<td>Renal</td>
<td>Atrial fibrillation</td>
<td>150 mg twice daily</td>
<td>• 110-mg twice daily dosage is approved by EMA but not FDA • 75-mg twice daily dosage is approved by FDA but has not been tested in clinical trials - Use if CrCl is 15-30 mL/min - Can consider if CrCl 30-50 mL/min and the patient is on strong P-gp inhibitor • Contraindicated if CrCl &lt;15 mL/min or the patient is on hemodialysis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>or 110 mg twice daily or 75 mg twice daily</td>
<td></td>
</tr>
</tbody>
</table>
EMA = European Medicines Agency; FDA = Food and Drug Administration; Pgp = P glycoprotein; VTE = venous thromboembolism.

Management considerations. Patients treated with apixaban may need to undergo surgery while anticoagulated. For elective surgery that is associated with a moderate-to-high risk of bleeding, it is reasonable to withhold apixaban for 48 hours prior to surgery. For minimally invasive or percutaneous procedures that are not associated with significant bleeding risk, apixaban can be withheld 24 hours prior to surgery. Emergency surgery should be delayed, if possible, until at least 12 hours after the last dose. If the emergency surgery cannot be delayed, there are currently no agents that have been shown to reduce bleeding through a reversal of anticoagulation.

Dabigatran

Dabigatran is a direct thrombin inhibitor that is currently approved for use in the prevention of stroke or systemic embolism in patients with AF. The basis of its approval was the RE-LY trial, a large, open label, outcomes trial in patients with AF. In this trial 18,113 patients with AF were randomly assigned to either dabigatran 150 mg twice daily, dabigatran 110 mg twice daily, or warfarin. Dabigatran 150 mg twice daily significantly reduced the incidence of stroke or systemic embolization compared with warfarin (HR 0.66, 95% CI 0.53-0.82; P <.001). Dabigatran 110 mg BID was noninferior to warfarin in reducing the incidence of stroke or systemic embolization compared with warfarin (HR 0.91, 95% CI 0.74-1.11; P <.001 for noninferiority). Dabigatran has also been studied in patients either at risk for, or diagnosed with, venous thrombosis (Table 6).

Table 6. Clinical Trials of Dabigatran

<table>
<thead>
<tr>
<th>Trial</th>
<th>Setting</th>
<th>Design</th>
<th>Dosage of Dabigatran</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>RE-LY</td>
<td>Atrial fibrillation</td>
<td>Dabigatran vs open-label warfarin</td>
<td>150 mg twice daily or 110 mg twice daily</td>
<td>Dabigatran 150 mg twice daily reduces incidence of stroke or systemic embolism; 110 mg twice daily is noninferior</td>
</tr>
<tr>
<td>RE-NOVATE</td>
<td>VTE-primary prevention after total hip replacement</td>
<td>Dabigatran vs enoxaparin 40 mg daily</td>
<td>220 mg or 110 mg daily</td>
<td>Dabigatran noninferior to enoxaparin</td>
</tr>
<tr>
<td>RE-NOVATE 2</td>
<td>VTE-primary prevention after total hip replacement</td>
<td>Dabigatran vs enoxaparin 40 mg daily</td>
<td>220 mg daily</td>
<td>Dabigatran noninferior to enoxaparin</td>
</tr>
<tr>
<td>RE-MOBILIZE</td>
<td>VTE-primary prevention following knee surgery</td>
<td>Dabigatran vs enoxaparin 30 mg twice daily</td>
<td>220 mg or 150 mg daily</td>
<td>Dabigatran worse than enoxaparin: did not reduce death, pulmonary embolism, DVT</td>
</tr>
<tr>
<td>RE-MODEL</td>
<td>VTE-primary prevention following knee surgery</td>
<td>Dabigatran vs enoxaparin 40 mg daily</td>
<td>220 mg or 150 mg daily</td>
<td>Dabigatran noninferior to enoxaparin</td>
</tr>
<tr>
<td>RE-SONATE</td>
<td>VTE-secondary prevention</td>
<td>Dabigatran vs placebo</td>
<td>150 mg twice daily</td>
<td>Reduction in recurrent or fatal thromboembolism</td>
</tr>
<tr>
<td>RE-MEDY</td>
<td>VTE-secondary prevention</td>
<td>Dabigatran vs enoxaparin</td>
<td>150 mg twice daily</td>
<td>Noninferior to enoxaparin for the reduction of recurrent or fatal thromboembolism</td>
</tr>
<tr>
<td>RE-COVER</td>
<td>VTE-acute therapy</td>
<td>Dabigatran vs warfarin</td>
<td>150 mg twice daily</td>
<td>Noninferior to warfarin; recurrent VTE or fatal pulmonary embolism</td>
</tr>
</tbody>
</table>

**Pharmacokinetics and pharmacodynamics.** Dabigatran is absorbed from the gut and hydrolyzed in the liver, which converts it into an active agent. In contrast to apixaban, it has low bioavailability that is estimated to be <10%. The t1/2 of the dabigatran is 12 to 17 hours. Since ~80% of the drug is cleared renally, the t1/2 may be prolonged in patients with renal dysfunction. As a result, this agent is not the first-line therapy in patients with renal dysfunction and monitoring CrCl is important. The P-gp system can also affect drug concentration. Use of dabigatran with P-gp inducers (eg, rifampin) may result in decreased anticoagulant effect. In contrast, P-gp inhibition may result in increased anticoagulant effect and may increase the risk of bleeding.

**Dosing.** Dabigatran is currently indicated only for patients with AF. In the RE-LY trial, doses of 150 mg twice daily and 110 mg twice daily were studied. The European Medicines Agency approved both doses of dabigatran. However, the FDA did not approve the 110 mg dose. The FDA approved a dosage of 75 mg twice daily for patients with severe renal dysfunction, despite this dose never having been tested in clinical trials. The 75 mg twice-daily dosage should be used in all patients with a CrCl of 15 to 30 mL/min. In addition, this dose should be used in patients with a glomerular filtration rate (GFR) of 30 to 50 mL/min who are being treated with either dronedarone or ketoconazole. Dabigatran is contraindicated with in patients with CrCl ≤15 mL/min.

**Management considerations.** There is no need to routinely monitor the level of anticoagulation in patients treated with dabigatran, although the aPTT can be used to determine the presence of an anticoagulant effect. However, because the relationship of aPTT and drug concentration is not linear, this test does not allow measurement of the degree of anticoagulation. Tests such as the Hemoclot -- dilute thrombin time (dTT) -- have been developed to measure the effect of dabigatran. If the dTT is normal, there is no anticoagulant effect. If the dTT is >200 ng/mL, 12 hours after dosing, the risk of bleeding has been shown to be increased.

Patients treated with dabigatran may need to undergo surgery while anticoagulated. In the absence of renal dysfunction, dabigatran can be withheld 1 to 2 days, like with the other NOACs. In patients with moderate renal dysfunction (GFR <50 mL/min) undergoing elective surgery associated with a moderate to high risk of bleeding, dabigatran should be withheld 3 to 5 days prior to surgery. This recommendation is longer than for the other NOACs due to the renal clearance of dabigatran, which has the potential to prolong the t1/2 of the drug. Emergency surgery should be delayed, if possible, until at least 12 hours after the last dose. If emergency surgery cannot be delayed, the patient is at increased risk of bleeding since there are no currently approved agents to reverse the anticoagulation effect. If there is life-threatening bleeding, dialysis or recombinant factor VII can be considered, although this has not been rigorously studied and data to determine its effectiveness are limited. Prothrombin complex concentrate can also be considered for life-threatening bleeding. The European Society of Cardiology recommends 25 U/kg. Dabigatran can then be restarted 6 to 8 hours following procedures with low bleeding risk. For procedures with higher bleeding risk (eg, neurosurgery), dabigatran should be restarted at least 48 to 72 hours after the procedure and the risk of bleeding has decreased.

The FDA has released specific information for transitioning from dabigatran to warfarin. It is recommended that warfarin be started 3 days before discontinuing dabigatran if the CrCl is >50 mL/min, 2 days before discontinuing dabigatran if the CrCl is between 31 to 50 mL/min, and 1 day before in patients with CrCl between 15 and 30 mL/min.

**Rivaroxaban**

Rivaroxaban is a factor Xa inhibitor currently approved for use in the prevention of stroke or systemic embolism in patients with AF, treatment of deep vein thrombosis/pulmonary embolism (DVT/PE), and for prophylaxis in DVT/PE. The basis for its approval in AF was the ROCKETAF trial, a large, double-blind, randomized outcomes trial in patients with atrial fibrillation. In this trial, 14,264 patients with AF were randomly assigned to either rivaroxaban 20 mg daily or warfarin. Rivaroxaban 20 mg daily was noninferior to warfarin in reducing the incidence of stroke or systemic embolization (HR 0.88; 95% CI, 0.74 to 1.03; P <.001 for noninferiority; P = .12 for superiority). Rivaroxaban has also been studied in patients at risk for, or diagnosed with, venous thrombosis, and is approved for this use in clinical practice (Table 7).
### Table 7. Clinical Trials of Rivaroxaban

<table>
<thead>
<tr>
<th>Trial</th>
<th>Setting</th>
<th>Design</th>
<th>Dosage of Rivaroxaban</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>ROCKET AF[43]</td>
<td>Atrial fibrillation</td>
<td>Rivaroxaban vs warfarin</td>
<td>20 mg daily</td>
<td>Rivaroxaban noninferior to warfarin in effect on stroke or systemic embolism</td>
</tr>
<tr>
<td>RECORD[44]</td>
<td>VTE-primary prevention after hip arthroplasty</td>
<td>Rivaroxaban vs enoxaparin 40 mg SQ daily</td>
<td>10 mg daily</td>
<td>Rivaroxaban reduced DVT, nonfatal pulmonary embolism, or death</td>
</tr>
<tr>
<td>RECORD-2[45]</td>
<td>VTE-primary prevention after hip arthroplasty</td>
<td>Extended duration rivaroxaban vs. enoxaparin 40 mg SQ daily</td>
<td>10 mg daily</td>
<td>Rivaroxaban for prolonged period after surgery reduced DVT, nonfatal pulmonary embolism, or death compared with short-term enoxaparin</td>
</tr>
<tr>
<td>RECORD-3[46]</td>
<td>VTE-primary prevention after knee arthroplasty</td>
<td>Rivaroxaban vs enoxaparin 40 mg SQ daily</td>
<td>10 mg daily</td>
<td>Rivaroxaban reduced DVT, nonfatal pulmonary embolism, or death</td>
</tr>
<tr>
<td>RECORD-4[47]</td>
<td>VTE-primary prevention after knee arthroplasty</td>
<td>Rivaroxaban vs enoxaparin 30 mg SQ every 12 hours</td>
<td>10 mg daily</td>
<td>Rivaroxaban reduced DVT, nonfatal pulmonary embolism, or death</td>
</tr>
<tr>
<td>EINSTEIN-PE[48]</td>
<td>VTE-acute symptomatic pulmonary embolism</td>
<td>Rivaroxaban vs enoxaparin/VKA</td>
<td>15 mg twice daily for 3 weeks, followed by 20 mg daily</td>
<td>Rivaroxaban was noninferior to standard therapy in reducing symptomatic VTE</td>
</tr>
<tr>
<td>EINSTEIN-DVT[48]</td>
<td>VTE-acute symptomatic DVT</td>
<td>Rivaroxaban vs enoxaparin/VKA</td>
<td>15 mg twice daily for 3 weeks, followed by 20 mg daily (3,6, or 12 months)</td>
<td>Rivaroxaban was noninferior to standard therapy in reducing recurrent VTE</td>
</tr>
<tr>
<td>EINSTEIN-EXT[48]</td>
<td>VTE-acute symptomatic DVT</td>
<td>Rivaroxaban vs enoxaparin/VKA</td>
<td>15 mg twice daily for 3 weeks, followed by 20 mg daily (additional 6 or 12 months after ENSTEIN-DVT)</td>
<td>Rivaroxaban had superior efficacy in reducing recurrent VTE</td>
</tr>
</tbody>
</table>

DVT = deep vein thrombosis; RECORD = Regulation of Coagulation in Orthopedic Surgery to Prevent Deep Venous Thrombosis and Pulmonary Embolism; ROCKETF = Rivaroxaban – Once-Daily, Oral, Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation; SQ = subcutaneous; VTE = venous thromboembolism.

**Pharmacokinetics and pharmacodynamics.** Rivaroxaban is absorbed from the gut and does not undergo metabolism in the liver to convert the drug into an active agent. In contrast to other drugs, absorption is affected by the administration of the drug with food. Food intake increases the absorption of the drug and current dosing guidelines recommend that the drug be taken with food. Rivaroxaban has a rapid onset with peak drug concentration occurring 2 to 4 hours after administration. It has minimal drug-drug interactions, and drug concentrations do not appear to be significantly affected by either the CYP450 or the P-gp systems. However, caution should be taken with the use of medications that inhibit both the CYP450 and the P-gp systems (eg, ketoconazole, fluconazole, ritonavir, clarithromycin, erythromycin) as the concomitant use of rivaroxaban with these medications...
may increase the anticoagulation effect of rivaroxaban. Similarly, drugs that induce both the CYP450 and the P-gp systems (eg, rifampicin) may decrease the levels of rivaroxaban, resulting in decreased anticoagulation.

**Dosing.** The t1/2 of rivaroxaban is 5 to 9 hours. However, the relatively large volume of distribution associated with this agent may allow for a longer period of anticoagulation than would be predicted based on the estimated terminal t1/2 alone. In addition, the once-daily dosing results in lower minimum drug concentration (compared to twice-daily dosing), which may be more important than the peak-plasma concentration in determining the risk of bleeding (which is higher with once-daily dosing). Renal function is important in determining the dose. The majority of the drug is cleared through the renal system; therefore renal dysfunction can increase drug concentration. Currently, rivaroxaban has multiple indications and dosing varies depending on the indication. In patients with nonvalvular AF, the approved dose of rivaroxaban is 20 mg, as described in the ROCKET AF trial. Since food intake enhances the absorption of rivaroxaban, the FDA recommends that the drug be taken with the evening meal. In patients with impaired renal function (CrCl between 15 and 50 mL/min), a lower dosage of rivaroxaban (15 mg daily) is recommended. Rivaroxaban is contraindicated in patients with stage V chronic kidney disease (CrCl <15 mL/min). In patients treated for VTE/PE or VTE prophylaxis (with the exception of post-surgical VTE prophylaxis), rivaroxaban 15 mg twice daily for 21 days, followed by rivaroxaban 20 mg daily, is recommended. For patients undergoing hip or knee surgery, dosing for VTE prophylaxis is 10 mg daily.

**Management considerations.** Patients who need to undergo invasive procedures while being treated with rivaroxaban should stop taking the drug 24 hours prior to the procedure. Emergency surgery should be delayed, if possible, until at least 12 hours after the last dose. If emergency surgery cannot be delayed, the patient is at increased risk of bleeding since there are no currently approved agents to reverse the anticoagulation effect. If there is life threatening bleeding, recombinant factor VII has been shown to reverse laboratory measures of anticoagulation, but there are no data on its clinical effectiveness.[50]

Rivaroxaban prolongs the PT/INR and the aPTT, and therefore these tests are not good measures of the level of anticoagulation. Instead, antifactor Xa levels can be used to measure the anticoagulant effect, without having to routinely monitor level of anticoagulation. Rivaroxaban can be restarted 6 to 8 hours following procedures with low bleeding risk. For procedures with higher bleeding risk (eg, neurosurgery), rivaroxaban should be restarted at least 48 to 72 hours after the procedure and the risk of bleeding has decreased.

### Novel Oral Anticoagulants Being Tested in Ongoing Clinical Trials

**Edoxaban**

Edoxaban is a factor Xa inhibitor approved in Japan for VTE prevention but not yet approved in the United States or the European Union. Definitive, large phase 3 outcomes trials with edoxaban are ongoing to prevent venous thromboembolism and treat patients with AF. The ENGAGE AF-TIMI 48 trial has enrolled 21,105 patients with AF at high risk of an embolic event to 1 of 2 doses of edoxaban (60 mg daily or 30 mg daily) or warfarin.[51] The primary end point of this trial is stroke or systemic embolism. In addition, edoxaban is being studied in patients at risk for, or diagnosed with, venous thrombosis (Table 8).

<table>
<thead>
<tr>
<th>Trial</th>
<th>Setting</th>
<th>Design</th>
<th>Dosage of Edoxaban</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>STARS E3</td>
<td>VTE-primary prevention after knee arthroplasty</td>
<td>Edoxaban vs enoxaparin 20 mg twice daily</td>
<td>60 or 30 mg daily</td>
<td>Trial has been presented at scientific meeting but has not yet been published</td>
</tr>
<tr>
<td>STARS J-5</td>
<td>VTE-primary prevention after hip arthroplasty</td>
<td>Edoxaban vs. Enoxaparin 20 mg twice daily</td>
<td>60 or 30 mg daily</td>
<td>Trial has been presented at scientific meeting but has not yet been published</td>
</tr>
<tr>
<td>ENGAGE AF-TIMI 48[51]</td>
<td>Atrial fibrillation</td>
<td>Edoxaban vs warfarin</td>
<td>30 or 60 mg daily</td>
<td>Trial ongoing</td>
</tr>
<tr>
<td>HOKUSAI-VTE</td>
<td>VTE-acute symptomatic DVT</td>
<td>Edoxaban vs enoxaparin/VKA</td>
<td></td>
<td>Primary end point is recurrent symptomatic</td>
</tr>
</tbody>
</table>
15 mg twice daily for 3 weeks, followed by 20 mg daily
VTE; trial has not yet been reported

DVT = deep vein thrombosis; ENGAGE AF-TIMI = Effective Anticoagulation With factor Xa next Generation in Atrial Fibrillation-Thrombolysis in Myocardial Infarction; STARS = Studying Thrombosis After Replacement Surgery; VKA = vitamin K antagonist

**Pharmacokinetics and pharmacodynamics.** Edoxaban is absorbed from the gut and does not undergo metabolism in the liver to convert the drug into an active agent. It has a rapid onset and peak-drug concentration occurs 1 to 2 hours after administration.[28] The t½ of edoxaban increases from 6 to 11 hours after one dose, to approximately 10 hours after multiple doses. The volume of distribution (120 L) is larger than apixaban or rivaroxaban. Edoxaban is a substrate for the P-gp system and drug levels can be affected by concomitant medication use affecting this system (eg, ketoconazole, clarithromycin). The concomitant use of digoxin does not increase the concentration of edoxaban in healthy volunteers.[52] In addition, full-dose aspirin has been shown to increase edoxaban concentrations and should be avoided.[53]

**Dosing.** Once-daily and twice-daily regimens, ranging from 15 to 120 mg, were evaluated in phase 2 studies. In a phase 2 trial of 1146 patients with AF, 60 mg twice daily caused excess bleeding compared to warfarin, and was prematurely discontinued. A dosage of 60 mg once daily caused less bleeding than 30 mg twice daily (ie, the same total daily dose), which led to the once-daily 60-mg dose carried forward into phase 3 testing.[54] In patients at high risk of bleeding (CrCl between 30 and 50 mL/min, weight ≤60 kg, or receiving a strong P-gp inhibitor (eg, verapamil, quinidine), the dose was reduced to half. Approximately 50% of the drug is cleared through the renal system and renal function is important in determining the dose. Because renal dysfunction can increase drug concentration, edoxaban was not studied in patients with CrCl <30 mL/min. Hokusai-VTE, the recently completed phase 3 study of edoxaban in patients with acute, asymptomatic venous thromboembolism, utilized a dose of 60 mg edoxaban daily.[55]

**Betrixaban**

Betrixaban is a factor Xa inhibitor that is currently being developed as an NOAC. The EXPLORE-Xa phase II study randomized 508 patients with AF to 1 of 3 doses of betrixaban (ie, 40 mg, 60 mg, 80 mg), or open-label warfarin.[56] The trial primary end point of bleeding was reduced in the 40 mg betrixaban daily arm compared with the warfarin arm. In the 60 mg and 80 mg groups, the bleeding rates were similar to those in the warfarin group.

There is comparatively little data published on betrixaban, but it is reported that betrixaban is eliminated almost entirely through the liver. The minimal renal clearance and long t½ of betrixaban raises the possibility that the once-daily dose may be safe in patients with renal dysfunction. Currently, betrixaban is being tested in the APEX study, which is a phase 3 trial enrolling patients at risk for venous thromboembolism and randomly assigning them to either betrixaban 80 mg daily or enoxaparin.

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Which of the NOACs is currently indicated for the treatment of atrial fibrillation and the treatment and prevention of venous thromboembolism?
- Apixaban
- Dabigatran
- Rivaroxaban
- Edoxaban

Which of the following NOACs is available as a prodrug that needs to be converted to its active form in the gut and liver?
- Dabigatran
- Apixaban
- Rivaroxaban
- Edoxaban
Conclusion

Warfarin has been a reliable oral anticoagulant since its development 6 decades ago. However, the difficulty in maintaining a consistent and safe degree of anticoagulation with this drug has led to the development of a variety of novel agents. These novel agents have reliable dosing and do not need frequent monitoring of anticoagulation levels. They also offer the potential to replace warfarin, and improve long-term outcomes and quality of life in patients with VTE or AF. These benefits depend upon an understanding of the pharmacokinetics of each available agent to aid in the selection of the most appropriate choice, and also an understanding of necessary dose modification based on the presence of renal/hepatic disease and the use of concomitant medications. Therefore, an understanding of these characteristics is key to ensuring the delivery of safe and appropriate levels of anticoagulation while using NOACs.

Since the pharmacokinetics of each oral anticoagulant is different, the selection of the most appropriate one is based on individual patient factors. Continuing warfarin would seem a reasonable choice in patients with minimal concomitant medications and well-controlled levels of anticoagulation (eg, INR levels between 2.0 and 3.0 for at least 75% of the time) who have been on a stable dose of warfarin for several years. In contrast, patients with INR levels that are difficult to control or who have lifestyles that prohibit the frequent monitoring required with warfarin may be best served with an NOAC.

In patients treated with an NOAC, patient characteristics, renal function and concomitant medications should guide the choice of an anticoagulant. All current NOACs have some element of renal clearance and require dose modifications based on CrCl. For example, patients with progressive renal insufficiency would not be good candidates for dabigatran given its predominant renal clearance, whereas those patients with stable, class IV chronic kidney disease (CrCl 15-30 mL/min) could begin a dosage of 75 mg twice daily. Prior to beginning therapy with any NOAC, all concomitant medications and potential drug-drug interactions that may affect drug concentration should be reviewed. For example, apixaban is not recommended in patients taking a strong CYP3A4 inhibitor, whereas rivaroxaban is generally safer unless the concomitant medication is also a strong P-gp inhibitor. Patients who are not compliant with twice-daily dosing might be better candidates for rivaroxaban (dosed once daily in AF) or a VKA. The application of these overall principles will maximize the benefits associated with oral anticoagulants and ensure their safe use.

Abbreviations

ADVANCE = Apixaban Versus Enoxaparin for Thromboprophylaxis After Knee or Hip Replacement
ADOPT = Apixaban Dosing to Optimize Protection from Thrombosis
AF = atrial fibrillation
AMPLIFY-EXT = Apixaban After the Initial Management of Pulmonary Embolism and Deep Vein Thrombosis with First-line Therapy- Extended Treatment
aPTT = activated partial thromboplastin time
APEX = Acute Medically Ill VTE Prevention With Extended Duration Betrixaban Study
ARISTOTLE = Apixaban for the Prevention of Stroke in Subjects With Atrial Fibrillation
AVERROES = A Phase III Study of Apixaban in Patients With Atrial Fibrillation
CrCl = creatinine clearance
CYP = cytochrome
dTT = dilute thrombin time
DVT = deep vein thrombosis
EMA = European Medicines Agency
ENGAGE AF-TIMI = Effective Anticoagulation With factor Xa next Generation in Atrial Fibrillation- Thrombolysis in Myocardial Infarction
GFR = glomerular filtration rate
INR = International Normalization Ratio
NOAC = novel oral anticoagulant
PE = pulmonary embolism
P-gp = P glycoprotein
PT = prothrombin time
References


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