

Oral anticoagulants: Pharmacologic management update

Stay-up-to-date to avoid complications and achieve the best treatment for patients.

By Nancy Haugen, PhD, RN

MILLIONS of people in the United States take anticoagulants to prevent deep venous thrombosis (DVT), pulmonary embolism (PE), and stroke associated with atrial fibrillation. The mainstays of anticoagulant therapy are heparin and warfarin. Both have disadvantages and limitations. For years warfarin was the only oral anticoagulant, but new medications are just as effective and have fewer disadvantages and limitations.

When you understand how anticoagulants work, you can ensure that patients achieve optimal outcomes and avoid complications.

3 steps of hemostasis

To promote hemostasis, the body engages three processes: vasoconstriction, platelet plug development, and clot formation.

After a vessel injury, *vasoconstriction* decreases the vessel diameter, reducing blood flow to the injured area. Platelets in the blood aggregate there and stick together to form a *platelet plug*. Platelets activate fibrin required to help form and maintain the plug. For a clot to form, two intersecting pathways must be initiated. (See *Follow the pathway*.)

Anticoagulants alter hemostasis by inhibiting a component of the coagulation process. Different anticoagulants focus on different components in the process, but the outcome is either clot prevention or clot extension. Anticoagulants don't dissolve a clot that's already formed.

The oral anticoagulants current-

ly available in the United States include warfarin, direct thrombin inhibitors, and direct factor Xa inhibitors. (See *Oral anticoagulants: Pros and cons*.)

Warfarin

Warfarin affects the four vitamin K-dependent clotting factors: II (prothrombin), VII, IX, and X. In the intestines, warfarin blocks vitamin K epoxide reductase, the enzyme required to convert vitamin K to its active form.

Pharmacokinetics: Warfarin is readily absorbed in the GI tract and metabolized by the liver using the cytochrome P-450 pathway through the CYP1A2, CYP2C9, and CYP3A4 systems. It's excreted by the kidneys. When warfarin is in the blood circulation, 99% binds to the plas-

ma protein albumin, which may delay its initial response by 8 to 12 hours. When discontinuing the medication, anticoagulant effects are observed for 2 to 5 days as the plasma-bound drug becomes free drug.

Therapeutic uses: Warfarin is primarily used to prevent DVT and PE, especially in patients with prosthetic heart valves and atrial fibrillation. It's also used to reduce the risk of recurrent transient ischemic attacks and myocardial infarctions.

Dosage: Warfarin is available in various strengths, from 1-mg to 10-mg tablets. The required dosage is determined using prothrombin time/international normalized ratio (PT/INR) (a standardized method measuring the blood's clotting ability). The normal INR is 1. The goal PT/INR for anticoagulant therapy is 2 to 3.5 times baseline, depending on the condition being treated. Dosages are individualized, so establishing the goal INR can take several weeks because of warfarin's long half-life. As needed, dosage adjustments are made during therapy based on PT/INR. PT/INR is measured daily during the first 5 days of treatment, two times a week for the next 1 to 2 weeks, and then every 2 to 4 weeks thereafter.

Drug monitoring can be done at an inpatient or outpatient lab or by the patient at home using handheld devices. Findings are monitored by a provider to evaluate whether the dosage should be maintained or changed. Handheld devices provide reliable PT/INR results to improve anticoagulant control, but they're



LEARNING OBJECTIVES

1. Compare indications, dosages, pharmacokinetics, adverse effects, and contraindications of warfarin, direct thrombin inhibitors, and direct factor Xa inhibitors.
2. Discuss nursing considerations related to oral anticoagulants.

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Follow the pathway

expensive and aren't always covered by insurance.

Adverse effects: Warfarin's main adverse effect is bleeding. When bleeding requires treatment (as opposed to simply discontinuing the medication), vitamin K₁ (phytonadione) is used to reverse the drug's impact on the development of vitamin K₁-dependent clotting factors. Vitamin K₁ is administered orally (preferred) or intravenously. When given by I.V., it should be diluted and administered slowly; a rapid infusion rate can cause severe anaphylactic reactions including flushing, hypotension, and cardiovascular collapse. The goal of vitamin K₁ use is controlling excessive bleeding, not blocking all anticoagulation activity. Therefore, dosages should be small, no matter the administration route. Warfarin reversal with vitamin K₁ can take several days.

In the past, patients were taught to avoid foods with vitamin K (for example, green leafy vegetables, Brussels sprouts, kale, spinach, collard greens, liver). Patients should be taught to maintain consistency in their consumption of foods with vitamin K, not avoid them. Inconsistency is what affects warfarin's effectiveness.

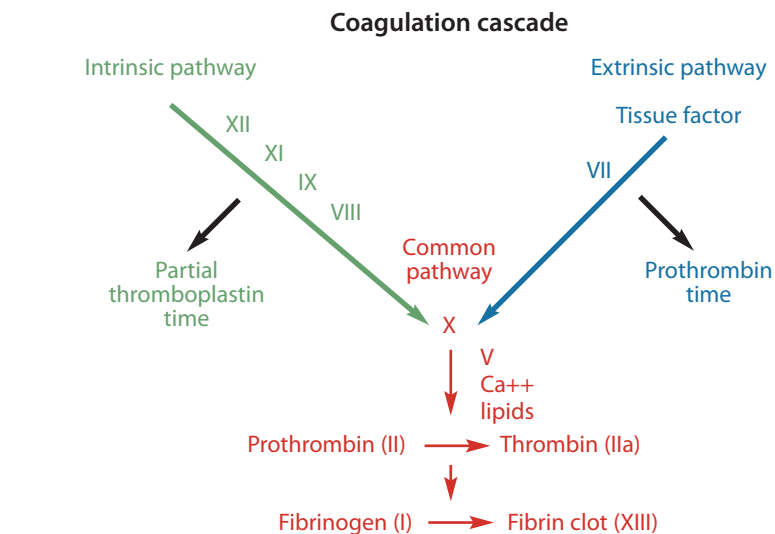
Contraindications: Contraindications for warfarin include open wounds; active bleeding; severe thrombocytopenia; active ulcer disease; eye, brain, or spinal cord surgery; pregnancy; lactation; uncontrolled hypertension; severe vitamin K deficiency; liver disease; and alcoholism. Warfarin should be used with extreme caution in patients with hemophilia, increased capillary permeability, dissecting aneurysm, and women anticipating an abortion.

Drug-to-drug interactions: Warfarin should not be used with any drugs that will increase bleeding. Because warfarin is metabolized by cytochrome P-450 pathways, it interacts extensively with other medications. The cytochrome P-450 pathway involves a group of en-

zymes responsible for drug metabolism. When multiple drugs are metabolized through this pathway, metabolism and biotransformation of each of the drugs is altered and can result in changes in toxicity, pharmacologic impact, and drug-to-drug interactions.

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Warfarin also has significant interactions with other drugs that bind to plasma proteins. These interactions will either increase bleeding and anticoagulant effects or decrease anticoagulant effects. Before administering warfarin, verify that the patient's currently prescribed medications are safe to take with warfarin, and instruct the patient to contact his or her healthcare provider before taking any new medication or herbal supplement.

Direct thrombin inhibitors

Direct thrombin inhibitors include

dabigatran etexilate, bivalirudin, desirudin, and argatroban. Only dabigatran is available for oral administration. Direct thrombin inhibitors block the action of thrombin circulating in the blood and already bound in a clot, preventing the conversion of fibrinogen to fibrin, the activation of factor XIII, the conversion of soluble fibrin to insoluble fibrin, and thrombin-mediated platelet activation and aggregation.

Pharmacokinetics: Dabigatran etexilate is rapidly absorbed in the GI tract and converted to its active form, dabigatran, by the gut and P-glycoprotein. Food, particularly a high-fat meal, delays dabigatran absorption, but doesn't reduce the amount of drug absorbed. Peak drug concentrations occur in about 2 hours, and protein binding is minimal. Dabigatran is eliminated unchanged by the kidneys. The drug's

normal half-life is 12 to 17 hours and increases to 18 hours or more with renal impairment.

Therapeutic uses: Direct thrombin inhibitors prevent and treat DVT, stroke, and systemic embolisms in patients with nonvalvular atrial fibrillation (NVAF). They're also prescribed following knee- or hip-replacement surgery and to treat DVT and PE in patients after treatment with a parenteral anticoagulant for 5 to 10 days.

Dosages: Direct thrombin inhibitor dosages are treatment specific. Instruct patients to swallow dabigatran capsules intact. If the capsule is opened, chewed, or crushed, the rate of absorption can be increased by 75%. Food doesn't impact medication absorption. (See *Dabigatran dosages and indications*.)

Adverse effects: Bleeding, erosive gastritis, hemorrhagic gastritis, and GI reflux, hemorrhage, and ulcers are the main adverse effects of dabigatran. Some GI symptoms may be reduced by taking a proton-pump inhibitor or histamine receptor blocker. If GI effects aren't reduced, a different anticoagulant should be tried. Idarucizumab is a dabigatran-specific antidote for life-threatening bleeding or emergency surgery.

Contraindications: Dabigatran shouldn't be given to patients who have active bleeding or a prosthetic heart valve, and patients who are undergoing surgery of the spinal cord, brain, or eye. Dabigatran shouldn't be used during pregnancy.

Drug-to-drug interactions: Increased or decreased effects of direct thrombin inhibitors are due to CYP pathway inhibition or induction. Concurrent administration of dabigatran with anticoagulants, antiplatelet agents, or nonsteroidal anti-inflammatory agents increases the risk of bleeding. Other drugs that can increase bleeding risk when given with dabigatran include cyclosporine, dronedarone, itraconazole, ketoconazole,



Oral anticoagulants: Pros and cons

Knowing the advantages and disadvantages of oral anticoagulants will help ensure safe patient treatment.

Drug category	Advantages	Disadvantages
Warfarin	<ul style="list-style-type: none"> • Long-term outcome data • Prothrombin time/international normalized ratio monitoring • Has antidote: Vitamin K₁ 	<ul style="list-style-type: none"> • Frequent monitoring • Slow onset with a prolonged duration • Potential bleeding risk • Many drug-to-drug interactions
Direct thrombin inhibitors (dabigatran etexilate)	<ul style="list-style-type: none"> • Rapid onset • Standardized dosing regardless of age or weight • Predictable drug response • Few food and drug interactions • Lower risk of bleeding and hemorrhagic stroke • No required laboratory monitoring • Has antidote: Idarucizumab 	<ul style="list-style-type: none"> • Minimal long-term outcome data • No laboratory monitoring (no monitoring is convenient for the patient, but it means that clinicians don't have lab data to assess patient response) • GI disturbances
Direct factor Xa inhibitors (rivaroxaban, apixaban, edoxaban)	<ul style="list-style-type: none"> • Fixed, treatment-specific dosing • Rapid onset • Lower risk of bleeding • No required laboratory monitoring 	<ul style="list-style-type: none"> • Minimal long-term outcome data • On-time dosage important • No laboratory monitoring • No antidote for bleeding

tacrolimus, amiodarone, quinidine, erythromycin, verapamil, azole antifungals, and HIV protease inhibitors. Drugs and supplements that can decrease the effectiveness of dabigatran include carbamazepine, dexamethasone, fosphenytoin, phenytoin, rifampin, carbamazepine, dexamethasone, tipranavir, and St. John's wort.

Direct factor Xa inhibitors

Direct factor Xa inhibitors (rivaroxaban, apixaban, edoxaban, and be-

trixaban) decrease thrombin production and prevent clot formation. Information about rivaroxaban, the first orally administered direct Xa inhibitor, is presented below. The other oral direct factor Xa inhibitors have similar actions and pharmacokinetics.

Pharmacokinetics: After oral administration, the bioavailability of rivaroxaban is high, even though it binds to protein. A peak plasma level occurs 2 to 4 hours after administration, and the drug has a

Dabigatran dosages and indications

Oral dosages of dabigatran etexilate are based on specific indications. Adjustments are required based on the patient's renal creatinine clearance.

Indication	Dosage
Nonvalvular atrial fibrillation	75 to 150 mg twice daily
PE or DVT treatment or recurrence risk reduction	150 mg twice daily
PE or DVT risk reduction after hip-replacement surgery	110 mg 1 to 4 hours after surgery and after achieving hemostasis, then 220 mg once daily Therapy duration: 28 to 35 days

PE: pulmonary embolism; DVT: deep vein thrombosis

half-life of 24 hours. Rivaroxaban is partially metabolized by the CYP3A4 isoenzyme in the cytochrome P-450 pathway and is a substrate for P-glycoprotein (a transporter involved in removing rivaroxaban from the body). Rivaroxaban elimination occurs via the urine and feces.

Therapeutic uses: Direct factor Xa inhibitors are used to prevent PE and DVT after total hip- or knee-replacement surgery, prevent stroke and intravascular events in patients with NVAf, and treat DVT and PE.

Dosage: Direct factor Xa inhibitor dosage is treatment specific. These medications should be taken at approximately the same time daily, with or without food. (See *Direct factor Xa inhibitor dosages and indications*.)

Adverse effects: Adverse effects of direct factor Xa inhibitors include bleeding, hematoma, dizziness, rash, GI distress, anemia, muscle spasms, and arm or leg pain. In addition, when rivaroxaban is discontinued before treatment completion, a thrombotic event or stroke may occur. To prevent this outcome, a different anticoagulant should be used to replace rivaroxaban when it's discontinued.

Contraindications: All direct factor Xa inhibitors are contraindicated in patients with active bleeding. These medications should be discontinued at least 18 hours or two half-lives before spinal or epidural

Oral anticoagulant dosages are prescribed based on the focus of treatment, so medication errors can have deleterious effects.

procedures. Patients with moderate or severe liver impairment (Child-Pugh B or C) or with any liver disease associated with coagulopathy should not take direct factor Xa inhibitors. Safe use of these medications in pregnancy hasn't been established.

Drug-to-drug interactions: Drugs that inhibit or induce the CYP3A4 enzyme and P-glycoprotein (amiodarone, quinidine, diltiazem, verapamil, ranolazine, and macrolide antibiotics) can increase or decrease direct factor Xa inhibitor levels. Drugs and supplements that decrease the effects of direct inhibitors (carbamazepine, phenytoin, rifampin, and St. John's wort) can potentially cause a thrombotic event. All medications that increase bleeding—including anticoagulants, antiplatelet agents, and nonsteroidal anti-inflammatory agents—are contraindicated.

Nursing considerations and discharge planning

Oral anticoagulant dosages are prescribed based on the focus of treatment, so medication errors (too much or too little medication) can have deleterious effects. Teach patients the signs and symptoms of bleeding (including increased bruising, petechia, hematomas, increased heart rate, decreased blood pressure, red or black stools, cloudy or discolored urine, headache, and pelvic or lumbar pain).

Discharge planning and patient education should include oral and written instructions about how patients can decrease the risk of bleeding.

- Take medication as prescribed.
- Follow provider instructions when a dosage is missed.
- Monitor for bleeding.
- Attend follow-up monitoring appointments if required.
- Make lifestyle changes to reduce bleeding risk:
 - shave with an electric razor
 - use a soft-bristle toothbrush and waxed floss
 - wear cut-resistant gloves when using knives, and keep knives sharpened to reduce slippage
 - avoid activities and behaviors (playing contact sports, increased alcohol consumption) with the potential for falling or self-injury
 - remove or rearrange items (furniture, area rugs) in the home that may pose an injury or fall risk
 - wear a helmet when bike riding
 - wear a medical alert bracelet
 - contact a healthcare provider before taking any newly prescribed or over-the-counter medication, vitamin, or herbal supplement.

Stay current

Warfarin has been the mainstay of oral anticoagulant therapy for more

Direct factor Xa inhibitor dosages and indications

Direct factor Xa inhibitors require precise dosages based on indication. Patients with hepatic or renal impairment require dosage adjustments to prevent increased serum drug levels.

Medication	Indications	Dosages (Oral)
Rivaroxaban	Heparin-induced thrombocytopenia treatment	15 mg twice daily until platelet recovery, then decrease to 20 mg daily until day 30
	Deep vein thrombosis (DVT) prevention after knee or hip replacement	10 mg daily starting 6 to 10 hours after surgery Knee replacement: 12 days Hip replacement: 35 days
	Stroke and embolism prevention in patients with nonvalvular atrial fibrillation (NVAf)	20 mg daily
	DVT and pulmonary embolism (PE) treatment	15 mg twice daily for the first 21 days, then decrease to 20 mg daily
Apixaban	Stroke and embolism prevention in patients with NVAf	5 mg twice daily
	DVT and PE treatment and prophylaxis to prevent DVT and PE recurrence	10 mg twice daily for 7 days, then 5 mg twice daily After 6 months of therapy, 2.5 mg twice daily
	DVT and PE prevention after knee or hip replacement	2.5 mg daily for 12-24 hours after surgery Knee replacement: 2.5 mg twice daily for 12 days Hip replacement: 2.5 mg twice daily for 35 days
Betrixaban	Venous thromboembolism (VTE) prevention in adults hospitalized for acute medical illness who are at risk for thromboembolic complications because of moderate or severe restricted mobility	Initial single dose: 160 mg, then 80 mg daily Therapy duration: 35-42 days
Edoxaban	Stroke and embolism prevention in patients with NVAf	60 mg daily
	DVT and PE treatment after 5 to 10 days of initial therapy with a parenteral anticoagulant	Body weight < 60 kg: 30 mg daily Body weight > 60 kg: 60 mg daily

than 50 years, but newer medications are replacing it as standard therapy. These newer oral anticoagulants work by directly inhibiting thrombin or factor Xa.

As the population ages, the use of oral anticoagulants to prevent DVT, PE, and stroke will increase.

Stay up-to-date about these medications' indications and adverse effects to ensure the best treatment for your patients. ★

Nancy Haugen is associate dean, prelicensure and undergraduate programs, at the Samuel Merritt University School of Nursing in Oakland, California.

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Please mark the correct answer online.**1. The contact activation pathway of the coagulation cascade**

- includes factor VII.
- is measured with prothrombin time.
- is activated by clotting factor XII.
- is activated by external trauma.

2. The tissue factor pathway of the coagulation cascade

- includes factor VII.
- is measured by clotting time.
- is activated by internal trauma.
- includes factors IX and VIII.

3. An advantage of dabigatran etexilate is

- slower onset of action.
- standard dosing regardless of age or weight.
- that it can be reversed with vitamin K.
- the plethora of long-term outcome data.

4. Which drug can be reversed with idarucizumab?

- Apixaban
- Warfarin
- Edoxaban
- Dabigatran etexilate

5. Your patient with nonvalvular atrial fibrillation is prescribed dabigatran etexilate. What dose would you expect to see ordered?

- 75 to 110 mg twice daily
- 150 mg twice daily
- 220 mg once daily
- 110 to 150 mg three times daily

6. A direct factor Xa inhibitor indicated for the treatment of heparin-induced thrombocytopenia is

- apixaban.
- rivaroxaban.
- betrixaban.
- edoxaban.

7. Which statement about the pharmacokinetics of warfarin is correct?

- It's metabolized by the liver using the cytochrome P-450 pathway.
- It's metabolized by the liver using the cytochrome CYP1A5 pathway.
- After discontinuation, anticoagulant effects are observed for 5 to 7 days.
- After discontinuation, anticoagulant effects are observed for 7 to 10 days.

8. In a patient who has been prescribed warfarin, the prothrombin time/international normalized ratio (PT/INR) will be measured

- every 8 weeks after the goal INR has been established.
- two times a week during the first week of treatment.
- every 4 to 6 weeks after the goal INR has been established.
- daily during the first 5 days of treatment.

9. Which information about foods with vitamin K should you provide to a patient taking warfarin?

- Maintain consistency in consumption of foods with vitamin K.
- Avoid consuming foods with vitamin K.
- Base consumption of food with vitamin K on INR results.
- Consume extra amounts of food with vitamin K.

10. A drug that decreases the effectiveness of dabigatran etexilate is

- amiodarone.
- a nonsteroidal anti-inflammatory agent.
- dexamethasone.
- an HIV protease inhibitor.

11. The peak plasma level for rivaroxaban is

- 2 to 4 hours after administration.
- 4 to 6 hours after administration.
- 6 to 8 hours after administration.
- 8 to 10 hours after administration.

12. Direct factor Xa inhibitors should be discontinued at least how many hours before a spinal or epidural procedure?

- 4 hours
- 8 hours
- 18 hours
- 48 hours

13. Your patient who had a pulmonary embolus is being switched from heparin to edoxaban 7 days after initiation of heparin. He weighs 70 kg, so you expect the dose to be

- 30 mg daily.
- 60 mg daily.
- 80 mg daily.
- 100 mg daily.

14. All of the following lifestyle instructions for a patient taking an oral anticoagulant are correct, except

- Use a hard-bristle toothbrush.
- Wear cut-resistant gloves when using knives.
- Wear a helmet when bike riding.
- Avoid contact sports.