Updated Guidelines on Outpatient Anticoagulation

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The American College of Chest Physicians provides recommendations for the use of anticoagulant medications for several indications that are important in the primary care setting. Warfarin, a vitamin K antagonist, is recommended for the treatment of venous thromboembolism and for the prevention of stroke in persons with atrial fibrillation, atrial flutter, or valvular heart disease. When warfarin therapy is initiated for venous thromboembolism, it should be given the first day, along with a heparin product or fondaparinux. The heparin product or fondaparinux should be continued for at least five days and until the patient's international normalized ratio is at least 2.0 for two consecutive days. The international normalized ratio goal and duration of treatment with warfarin vary depending on indication and risk. Warfarin therapy should be stopped five days before major surgery and restarted 12 to 24 hours postoperatively. Bridging with low-molecular-weight heparin or other agents is based on balancing the risk of thromboembolism with the risk of bleeding. Increasingly, self-testing is an option for selected patients on warfarin therapy. The ninth edition of the American College of Chest Physicians guidelines, published in 2012, includes a discussion of anticoagulants that have gained approval from the U.S. Food and Drug Administration since publication of the eighth edition in 2008. Dabigatran and apixaban are indicated for the prevention of systemic embolism and stroke in persons with nonvalvular atrial fibrillation. Rivaroxaban is indicated for the prevention of deep venous thrombosis in patients undergoing knee or hip replacement surgery, for treatment of deep venous thrombosis and pulmonary embolism, for reducing the risk of recurrent deep venous thrombosis and pulmonary embolism after initial treatment, and for prevention of systemic embolism in patients with nonvalvular atrial fibrillation. (*Am Fam Physician*. 2013;87(8):556-566. Copyright © 2013 American Academy of Family Physicians.)

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Warfarin (Coumadin), unfractionated heparin, and low-molecular-weight heparin (LMWH) are commonly used for the prevention and treatment of disorders such as systemic embolism associated with atrial fibrillation, stroke, and venous thromboembolism (VTE). LMWH allows for the initiation of anticoagulation therapy on an outpatient basis.

After decades during which warfarin was the only oral anticoagulation option, newer anticoagulants have the potential to change the management of coagulation disorders. This article focuses on the indications for and the goals and duration of anticoagulation therapy; describes methods to initiate therapy; and provides guidance on monitoring. Most of the recommendations are based on the American College of Chest Physicians (ACCP) evidence-based clinical practice guidelines *(Table 1)*.[1]

Warfarin, Heparin, and Heparin Analogues

WARFARIN

The anticoagulant effect of warfarin results from the inhibition of the cyclic interconversion of vitamin K in the liver. The reduced form of vitamin K is necessary for the carboxylation of the terminal regions of the vitamin K proteins, factors II, VII, IX, and X.[1] Without carboxylation, these vitamin K–dependent clotting factors do not become activated. Warfarin, similar in structure to vitamin K, interferes with the cyclic restoration of reduced levels of vitamin K. Therefore, warfarin indirectly reduces the

Table 1. Key Changes in the Ninth Edition of the American College of Chest Physicians Guidelines on Outpatient Management of Anticoagulation Therapy

Medication	*Recommendation*	*Implication for practice*
Dabigatran (Pradaxa)	Recommended over warfarin (Coumadin) in patients with nonvalvular atrial fibrillation who do not have severe renal impairment (grade 2B)	Simplification of anticoagulation management: no need for frequent dosage adjustments, INR monitoring Caution: no antidote for reversal
LMWH	Outpatients with solid tumors, additional risk factors for deep venous thrombosis, and low bleeding risk should receive prophylactic doses of LMWH (grade 2B)	—
Vitamin K	Revised recommendations for treatment of patients with supratherapeutic INRs who do not have significant bleeding For patients with an INR between 4.5 and 10, routine use of vitamin K is not recommended (grade 2B) For patients with an INR greater than 10 without significant bleeding, oral vitamin K is recommended (grade 2C)	Advocating more judicious and conservative use of vitamin K
Warfarin	Warfarin therapy at 10 mg daily for two days may be initiated in healthy outpatients with acute thromboembolism (grade 2C)	Helps to achieve therapeutic INR sooner and decreases the number of LMWH doses needed Patients at high risk of bleeding may be better suited for traditional dosing Caution: check INR after two or three doses
	If the patient was previously stable on warfarin and presents with an isolated INR of 0.5 or less above or below therapeutic range, the current dosage should be continued and the patient retested in one to two weeks (grade 2C)	Patients taking the same dose for at least three consecutive months are considered stable Physicians have the option of waiting until two consecutive INRs are outside the desired therapeutic range before changing the dose in previously stable patients who have not experienced a change in health, diet, or medication status; this method has not been associated with increased risk of bleeding or thromboembolism in observational studies Minimizes burdens of unnecessary testing and dose adjustment
	In previously stable patients with a single INR below the therapeutic range, routine heparin bridging is not recommended (grade 2C)	Applies to patients with two previous stable INRs INRs should be checked in one to two weeks to verify return to desired range Bridging may need to be considered in high-risk patients or in patients with continued subtherapeutic INRs Minimizing unnecessary heparin bridging will save money and decrease patient burden
	INR should be monitored up to every 12 weeks in patients who are stable, which is defined as having at least three months of consistent results with no need to adjust warfarin dosing (grade 2B)	Substantially lengthening the monitoring interval in stable patients (from every four weeks to up to every 12 weeks) will save money and enhance patient quality of life Candidates for extended monitoring should demonstrate the ability to be compliant with medication and to recognize the signs and symptoms of over- and underanticoagulation Caution: physicians should be alert for health or medication changes that may warrant more frequent monitoring

NOTE: *Grade 1 recommendations are strong recommendations that can be applied to most patients; grade 2 recommendations are weaker recommendations. Grade A recommendations are supported by high-quality evidence, grade B recommendations are based on randomized clinical trials with methodological flaws or inconsistent results, and grade C recommendations are based on weaker evidence.*

INR = international normalized ratio; LMWH = low-molecular-weight heparin.

Information from reference 1.

synthesis of these clotting factors. The anticoagulant effects of warfarin are delayed for several days after dosing changes, including therapy initiation. This is because of the variable half-lives of previously formed circulating clotting factors. Carboxylation inhibition can also result in a paradoxical increased risk of clotting when warfarin is initiated because of decreased levels of the vitamin K–dependent anticoagulant proteins C and S.[1]

Indications. Indications for initiating warfarin are listed in *Table 2*.[1] In persons with nonvalvular atrial fibrillation, clinicians often base the decision to start warfarin or LMWH on clinical risk estimates, such as the

Table 2. Indications for and Goals and Duration of Warfarin Therapy

Indication (ACCP recommendation grade)	*Target INR (range)*	*Duration of therapy (ACCP recommendation grade)*
DVT of the leg or PE*		
First episode (1B)	2.5 (2.0 to 3.0)	First episode of proximal DVT or PE due to surgery 3 months recommended over short-term use (1B), longer use (1B), or extended therapy (1B) First episode of proximal DVT or PE due to a reversible risk factor 3 months preferred over short-term use (1B), longer use (1B), or extended therapy (1B or 2B, depending on bleeding risk†) First episode of distal DVT due to surgery or a reversible risk factor 3 months preferred over short-term use (2C), longer use (1B), or extended therapy (1B) First episode of idiopathic proximal DVT or PE Low or moderate bleeding risk†: extended use recommended over 3 months (2B); high bleeding risk†: 3 months recommended over extended use (1B for DVT; 1B for PE) First episode of idiopathic distal DVT 3 months recommended over extended use (1B or 2B, depending on bleeding risk†)
Cancer (1B)	2.5 (2.0 to 3.0)	Active cancer and PE Low-molecular-weight heparin preferred over warfarin (Coumadin) Extended use recommended (1B or 2B, depending on bleeding risk†)
Antiphospholipid antibody (2B)	2.5 (2.0 to 3.0)	Antiphospholipid antibody and history of arterial or venous thrombosis Extended use with target INR of 2.5 recommended over higher range of 3.0 to 4.5 (2B)
Second episode (1B)	2.5 (2.0 to 3.0)	Two episodes of unprovoked DVT or PE Low (1B) or moderate bleeding risk†: extended therapy (2B) High bleeding risk†: 3 months (2B)
Atrial fibrillation or flutter		
Intermediate‡ to high§ risk of stroke‖ (1B)	2.5 (2.0 to 3.0)	Indefinite
Elective cardioversion (1B)	2.5 (2.0 to 3.0)	3 weeks before if scheduled and for 4 weeks after conversion (1B/2C)
Mitral stenosis (1B)	2.5 (2.0 to 3.0)	Indefinite
After stent placement and high risk of stroke (2C)	2.5 (2.0 to 3.0)	Bare-metal stent (1 month) and drug-eluting stent (3 to 6 months) as triple therapy with clopidogrel (Plavix) and aspirin (2C) After initial triple therapy, continue warfarin and a single antiplatelet agent until 12 months after stent placement (2C) After 12 months: warfarin alone (2C)
Coronary heart disease		
High-risk patients with myocardial infarction without a stent¶ (1B)	2.5 (2.0 to 3.0) with low-dose aspirin, 75 to 100 mg daily	3 months
High-risk patients with myocardial infarction and after stent placement¶ (2C)	2.5 (2.0 to 3.0)	Bare-metal stent: triple therapy with warfarin, low-dose aspirin, and clopidogrel in month 1; combination of warfarin with single antiplatelet agent in months 2 and 3 Drug-eluting stent: triple therapy with warfarin, low-dose aspirin, and clopidogrel for 3 to 6 months
Valvular heart disease		
Rheumatic mitral valve disease (1A if with atrial fibrillation or a history of systemic embolism; 1A if history of atrial thrombus; 2C if normal sinus rhythm and atrial diameter > 55 mm)	2.5 (2.0 to 3.0)	Long-term

continued

Table 2. Indications for and Goals and Duration of Warfarin Therapy *(continued)*

Indication (ACCP recommendation grade)	*Target INR (range)*	*Duration of therapy (ACCP recommendation grade)*
Valvular heart disease *(continued)*		
Mechanical prosthetic heart valves (aortic position [2C over low-range INR and 1B over high-range INR]; mitral position [2C over low-range INR])	Bileaflet or tilting-disk valves: 2.5 (2.0 to 3.0) in the aortic position, and 3.0 (2.5 to 3.5) in the mitral position	Long-term Recommended to use aspirin, 50 to 100 mg daily, with mechanical aortic or mitral valve and low bleeding risk
Bioprosthetic valves in the mitral position (2C)	2.5 (2.0 to 3.0)	3 months after insertion
Prevention of venous thromboembolism for orthopedic surgery		
Elective total hip or knee replacement and hip fracture surgery (1B)	2.5 (2.0 to 3.0)	10 to 14 days minimum (1B) 35 days for major orthopedic surgery (2B) Warfarin is second-line agent to low-molecular-weight heparin for total hip or total knee arthroplasty (2C)

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ACCP = American College of Chest Physicians; $CHADS_2$ = congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior ischemic stroke or transient ischemic attack (doubled); DVT = deep venous thrombosis; INR = international normalized ratio; PE = pulmonary embolism.

**—Recommendation to start warfarin on first day of treatment with a parenteral anticoagulant (unfractionated or low-molecular-weight heparin, or fondaparinux [Arixtra]); 1B.*

†—Risk factors that increase a patient's bleeding risk include advanced age, active gastric or duodenal ulcer, recent gastrointestinal bleeding, history of stroke, myocardial infarction, diabetes, and several laboratory abnormalities (e.g., elevated creatinine level, low platelet count, low hematocrit level).

‡—Defined as $CHADS_2$ score of 1.

§—Defined as $CHADS_2$ score of 2 or greater.

‖—Of note, in patients with a $CHADS_2$ score of 0, aspirin (75 to 325 mg daily) is recommended as an option; 2B.

¶—Patients with large anterior wall myocardial infarction who have left ventricular thrombus or who are at high risk of left ventricular thrombus (ejection fraction < 40 percent or anteroapical wall motion abnormality); 1B.

Information from reference 1.

$CHADS_2$ score, which assigns one point each for congestive heart failure, hypertension, age 75 years and older, and diabetes mellitus, and two points for prior ischemic stroke or transient ischemic attack.[1] For persons with a $CHADS_2$ score of 2 or higher, the ACCP guidelines recommend oral anticoagulation, and for persons with a score of 1, the guidelines recommend individualization of therapy and suggest oral anticoagulation rather than a combination of aspirin and clopidogrel (Plavix).[1]

Dosing. Patients on warfarin therapy should be treated using a systematic process to optimize effectiveness and minimize adverse effects. Health care professionals skilled in the initiation and assessment of therapy and adjustments in dosing can dramatically influence outcomes.[2,3]

When warfarin is initiated, the international normalized ratio (INR) may begin to respond after two to three days because of the depletion of factor VII. During this initial period, the patient can enter a hypercoagulable state caused by warfarin's effects on proteins C and S.[1] Heparin or LMWH should be administered with warfarin initiation and continued until the INR has been in the targeted therapeutic range for a minimum of 24 hours. Initial dosing of warfarin can vary depending on individual patient factors (e.g., age, bleeding risk, medication compliance history) and anticipated drug interactions.

In most patients, warfarin should be initiated as a maintenance dosage of 5 mg daily. Older patients and persons with liver disease, poor nutritional status, or heart failure may require lower initiation dosages.[1] For persons who are healthy enough to be treated as outpatients, the ACCP guidelines provide an alternative warfarin initiation dosage of 10 mg daily for the first two days of therapy, rather than the anticipated maintenance dosage.[1]

After baseline INR is determined, the next INR can be obtained after the patient has received two or three doses. Then, the frequency of INR monitoring decreases to twice weekly until the INR is within the therapeutic range, then weekly, every other week, and finally monthly.[1] The ACCP guidelines allow clinicians to consider INR monitoring up to every 12 weeks in patients who are stable (defined as having at least three months of consistent results with no need to adjust warfarin dosing). If a patient's INR becomes subtherapeutic or supratherapeutic, the frequency of monitoring should

Table 3. Management of Supratherapeutic INRs in Patients Without Significant Bleeding

INR	*Management*	*Vitamin K dosing*
Greater than goal INR, but < 4.5	Option 1: Decrease or hold dosage, increase frequency of monitoring, and resume at lower dosage once INR is within the therapeutic range	Not applicable
	Option 2: May continue current dosage if INR is minimally elevated (0.5 or less above therapeutic range in a previously stable patient; grade 2C)	
4.5 to 10	Hold next one or two doses, increase frequency of monitoring, and resume at lower dosage once INR is within the therapeutic range	Not applicable
	No vitamin K (grade 2B)	
> 10	Hold warfarin (Coumadin) and administer vitamin K (grade 2C), increase frequency of monitoring, repeat vitamin K as necessary, and resume warfarin at an appropriate dosage when INR is within the therapeutic range	2.5 to 5 mg orally as one dose

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INR = international normalized ratio.

Information from reference 1.

be increased until it stabilizes again. The ACCP provides recommendations for managing supratherapeutic INRs *(Table 3)*.[1]

Patients taking warfarin in the evening can adjust their dosing based on that day's INR results. If the INR is not within the desired therapeutic range after excluding explanatory factors, a 5 to 20 percent increase or decrease in the total weekly dosage is required.[4-6] Patients should be provided with the simplest regimen to achieve the new total weekly dosage.

Drug, Food, and Disease State Interactions. Warfarin is subject to many drug-drug, drug-food, and drug–disease state interactions. *eTable A* lists selected drug-drug interactions that are considered highly likely to potentiate or inhibit the effects of warfarin.

Some medications, such as amiodarone and rifampin, can impact a patient's INR long after the medication is discontinued.[1,7,8] A patient taking a medication with higher interaction potential, such as metronidazole (Flagyl), should be monitored more frequently.[9] Depending on the patient and the medication, a prophylactic reduction in warfarin dosage may also be advised.

Foods with high vitamin K concentrations, such as leafy green vegetables, have the potential to partially reverse the anticoagulation effects of warfarin.[8] A consistent diet is more important than limiting dietary vitamin K.[1]

Medical conditions such as diarrhea, heart failure, fever, hyperthyroidism, and liver disease can potentiate warfarin's effects. Conversely, conditions such as hypothyroidism can decrease the expected effects of warfarin.[1] Genetic factors can predispose patients to reduced warfarin requirements, as well as warfarin resistance. Although there is a small subset of patients who may have unexpected responses to warfarin, it is not currently recommended that patients undergo genetic testing.[1]

UNFRACTIONATED HEPARIN

Unfractionated heparin is a mixture of glycosaminoglycans that works by binding to antithrombin to inactivate thrombin (factor IIa) and factor Xa.[1] It also prevents the growth and potential propagation of clots. Considerations for parenteral medications are provided in *eTable B*.

Beyond increased bleeding risk, unfractionated heparin is associated with other adverse effects, such as heparin-induced thrombocytopenia. Heparin-induced thrombocytopenia should be suspected if a patient's platelet count decreases by at least 50 percent, or is less than 150×10^3 per μL after initiation of heparin. This generally occurs five to 14 days after initiation, and can occur after heparin is discontinued.

LOW-MOLECULAR-WEIGHT HEPARIN

Two LMWHs, dalteparin (Fragmin) and enoxaparin (Lovenox), are commonly used in clinical practice. LMWH is derived from unfractionated heparin and has an increased affinity for factor Xa relative to thrombin.[1] LMWH, which is given subcutaneously, has predictable absorption and degree of anticoagulation. Monitoring with measurement of anti–factor Xa levels is not routinely recommended, but is potentially useful in certain situations in which predictability of the degree of anticoagulation may be altered, such as changes in pharmacokinetics and pharmacodynamics (e.g., obesity, pregnancy) and accumulation (e.g., older age, kidney disease). In the outpatient setting, the usefulness of laboratory testing is limited to the assessment of bleeding events and therapeutic failures. It may also be of value to assess levels infrequently during the course of long-term therapy (i.e., when LMWH is used for more than just bridging therapy). Although LMWH has a similar bleeding risk and lower heparin-induced thrombocytopenia risk

compared with unfractionated heparin, a patient with a history of heparin-induced thrombocytopenia should not take LMWH.[1]

FONDAPARINUX

Fondaparinux (Arixtra) is a synthetic analogue of heparin. Unlike LMWH, fondaparinux is specific only to factor Xa and has no effect on thrombin formation. Like LMWH, fondaparinux is given subcutaneously and has predictable absorption and degree of anticoagulation. The ACCP guidelines recommend fondaparinux for general surgical prophylaxis in patients who have contraindications to LMWH.[1]

There are few data on the monitoring of fondaparinux. Anti–factor Xa levels can be used as long as fondaparinux (and not LMWH) is the reference standard in the assay.[1] Although the bleeding risk is similar to unfractionated heparin and LMWH, there is little heparin-induced thrombocytopenia risk with fondaparinux.

Bridging Unfractionated Heparin, LMWH, or Fondaparinux to Warfarin

In the treatment of VTE and pulmonary embolism, the parenteral anticoagulant should be overlapped with warfarin for a minimum of five days. In most cases, warfarin can be initiated on day 1, after the first dose of the parenteral agent has been given. Warfarin should not be initiated alone, and the parenteral anticoagulant should not be discontinued until the INR is in the therapeutic range for two consecutive days.

Depending on the patient's risk of thromboembolism and bleeding, bridging should occur when a patient's oral anticoagulation therapy needs to be interrupted *(eTable C)*. Interruption is common in patients undergoing surgery. For most persons who are not having a minor procedure, warfarin will be stopped approximately five days before surgery and restarted 12 to 24 hours postoperatively. LMWH should be restarted approximately 24 hours after the procedure, and it may be prudent to wait 48 to 72 hours before resuming the medication for patients at high risk of bleeding or who are undergoing major surgery.[1] Fondaparinux is not recommended for this indication.

For all warfarin indications, perioperative bridging is not indicated in patients at low risk of thromboembolism.[1] For patients with a high risk of thromboembolism, bridging with a therapeutic dose of unfractionated heparin or LMWH is indicated.[1] The ACCP guidelines are less clear about how patients with a moderate risk of thromboembolism should be treated.[1] Clinicians need to balance the individual's risk of thromboembolism, based on the medical history and surgical procedure, and risk of bleeding when determining what is optimal in persons in this moderate-risk category.

Newer Anticoagulants

The effectiveness of warfarin is well-established; however, it is a suboptimal anticoagulant because it requires frequent monitoring and dosage adjustments, and because of its potential for multiple drug-drug, drug-food, and drug–disease state interactions. It has a lengthy half-life and a delayed anticoagulant effect, and it often requires bridging therapy.

Since the approval of warfarin in 1954, no other oral option existed for patients who needed long-term anticoagulation therapy. This changed in 2010 with the U.S. Food and Drug Administration (FDA) approval of the oral direct thrombin inhibitor dabigatran (Pradaxa), in 2011 with the FDA approval of the oral direct factor Xa inhibitor rivaroxaban (Xarelto), and again in 2012 with the FDA approval of the oral factor Xa inhibitor apixaban (Eliquis). Characteristics of these anticoagulants are provided in *Tables 4 and 5*.[10-19]

DABIGATRAN

Dabigatran is available as a fixed-dose medication for the prevention of systemic embolism and stroke in patients with nonvalvular atrial fibrillation.[13] The ACCP guidelines recommend dabigatran, 150 mg twice daily, over warfarin for this indication when dosed appropriately for the patient's renal function.[1] Dabigatran does not require monitoring, dosage adjustments, or overlap with injectable anticoagulants such as heparin. Without applicable laboratory monitoring, there is no mechanism to establish if a patient's INR is subtherapeutic or supratherapeutic. If the patient's INR is supratherapeutic, there is no antidote for reversal. This can be problematic when determining the appropriate management in a patient who needs emergent surgery. The short half-life is potentially challenging when assessing the impact of noncompliance or missing the second daily dose. Limited data are available for patients with hepatic impairment and for patients who are obese. Thus, it is not acceptable to automatically consider all patients taking warfarin to be good candidates for dabigatran.

Adverse effects of dabigatran, 150 mg twice daily, compared with warfarin include dyspepsia (11.3 versus 5.8 percent; $P < .001$) and major gastrointestinal bleeding (1.51 versus 1.02 percent; $P < .001$). Dabigatran's safety profile needs further evaluation.[13]

Elevated transaminase levels in the Randomized Evaluation of Long-term Anticoagulation Therapy trial were

Table 4. Characteristics of Newer Oral Anticoagulants

Characteristic	*Apixaban (Eliquis)*	*Dabigatran (Pradaxa)*
Mechanism of action	Direct factor Xa inhibitor	Direct thrombin inhibitor
FDA boxed warning/ contraindications	FDA boxed warning: increased risk of stroke in patients with nonvalvular atrial fibrillation who discontinue apixaban without adequate continuous anticoagulation Contraindications: active pathological bleeding; history of serious hypersensitivity reaction to apixaban Use not recommended in patients with prosthetic heart valves or severe hepatic impairment; pregnant or breastfeeding patients	Contraindications: active pathological bleeding; history of serious hypersensitivity reaction to dabigatran; mechanical prosthetic heart valve Use not recommended in patients with bioprosthetic heart valves; pregnant or breastfeeding patients
Indications	Reduce risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation	Reduce risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation
Usual dosage	5 mg twice daily 2.5 mg twice daily if patient has at least 2 of the following: age 80 years or older, body weight of 132 lb (60 kg) or less, or serum creatinine level of 1.5 mg per dL or higher No data for patients on dialysis or with CrCl < 15 mL/min/1.73 m^2 or patients with moderate hepatic impairment Not recommended for patients with severe hepatic impairment 2.5 mg twice daily if patient is on a strong dual inhibitor of CYP3A4 and P-glycoprotein (e.g., ketoconazole, itraconazole [Sporanox], ritonavir [Norvir], clarithromycin [Biaxin]); avoid use of these drugs if patient is already taking 2.5 mg twice daily	150 mg twice daily CrCl 30 to 50 mL/min/1.73 m^2 and concurrent use of dronedarone (Multaq) or systemic ketoconazole: decrease dosage to 75 mg twice daily CrCl 15 to 30 mL/min/1.73 m^2: decrease dosage to 75 mg twice daily CrCl < 30 mL/min/1.73 m^2 and concurrent use of a P-glycoprotein inhibitor: avoid use CrCl < 15 mL/min/1.73 m^2: avoid use No data for patients on dialysis
Half-life	12 hours (with repeat dosing)	12 to 17 hours
Monitoring	None recommended	None recommended
Antidote	None available	None available
Drug interactions	See "usual dosage" for dose modification information Avoid use of strong dual inhibitor of CYP3A4 and P-glycoprotein in patients taking apixaban, 2.5 mg twice daily Avoid use of strong dual inducer of CYP3A4 and P-glycoprotein (e.g., carbamazepine [Tegretol], phenytoin [Dilantin], rifampin, St. John's wort) Increased bleeding risk with certain medications (e.g., clopidogrel [Plavix], nonsteroidal anti-inflammatory drugs)	See "usual dosage" for dose modification information Avoid concurrent use with P-glycoprotein inducers (e.g., rifampin) Evaluate P-glycoprotein inhibitors individually* Increased bleeding risk with certain medications (e.g., clopidogrel, nonsteroidal anti-inflammatory drugs)
Adverse effects	Bleeding	Bleeding, dyspepsia
Impact of renal impairment	See "usual dosage" for dose modification information	See "usual dosage" for dose modification information
Impact of hepatic impairment	See "usual dosage" for dose modification information Dosing recommendations for patients with moderate hepatic impairment are not available	No specific recommendations are made regarding hepatic impairment Limited information in this population
Comments	No objective way to monitor nonadherence Refer to package labeling for information on conversion from or to warfarin (Coumadin) or parenteral anticoagulants, and on intervention for surgery	Do not chew, break, open capsules; capsules must be dispensed in original container and not repackaged because of sensitivity to moisture No objective way to measure nonadherence Need more information about use in patients under and over ideal body weight Refer to package labeling for information on conversion from or to warfarin or parenteral anticoagulants, and on intervention for surgery

CrCl = creatinine clearance; CYP3A4 = cytochrome P450 3A4; DVT = deep venous thrombosis; FDA = U.S. Food and Drug Administration.

**—Amiodarone, clarithromycin, quinidine, and verapamil have been evaluated with dabigatran and do not require a dabigatran dosage adjustment, but should be used concurrently with caution. Other P-glycoprotein inhibitors should be evaluated on an individual basis.*

Rivaroxaban (Xarelto)
Direct factor Xa inhibitor
FDA boxed warning: increased risk of thrombotic events in patients with nonvalvular atrial fibrillation who discontinue rivaroxaban without adequate continuous anticoagulation; risk of epidural/spinal hematoma in patients receiving neuraxial anesthesia or in patients undergoing spinal puncture while taking rivaroxaban
Contraindications: active pathological bleeding; history of severe hypersensitivity reaction to rivaroxaban
Use not recommended in pregnant or breastfeeding patients
Prevent DVT in patients undergoing knee or hip replacement surgery
Reduce risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation
Treat DVT and pulmonary embolism
Reduce risk of recurrent DVT and pulmonary embolism after initial treatment
DVT prophylaxis: 10 mg once daily
DVT prophylaxis and CrCl < 30 mL/min/1.73 m^2: avoid use
Prevent stroke in patients with nonvalvular atrial fibrillation: 20 mg once daily
Prevent stroke in patients with nonvalvular atrial fibrillation and CrCl 15 to 50 mL/min/1.73 m^2: 15 mg once daily
Prevent stroke in patients with nonvalvular atrial fibrillation and CrCl < 15 mL/min/1.73 m^2: avoid use
Treat DVT and pulmonary embolism or reduce risk of future DVT and pulmonary embolism after initial treatment: 15 mg twice daily with food for 21 days, then 20 mg once daily for the remainder of the treatment interval (six months total) or for long-term risk reduction; avoid in patients with CrCl < 30 mL/min/1.73 m^2
5 to 9 hours
None recommended
None available
See "usual dosage" for dose modification information
Avoid with combined P-glycoprotein inhibitor and CYP3A4 inhibitor (e.g., ketoconazole, itraconazole, ritonavir, conivaptan [Vaprisol])
Avoid with combined P-glycoprotein inducer and CYP3A4 inducer (e.g., carbamazepine, phenytoin, rifampin, St. John's wort)
Increased bleeding risk with certain medications (e.g., clopidogrel, nonsteroidal anti-inflammatory drugs)
Bleeding
See "usual dosage" for dose modification information
Note differences in recommendation for dosage adjustments in renal impairment based on indication
Avoid if moderate (Child-Pugh class B) or severe (Child-Pugh class C) hepatic impairment or with any hepatic disease associated with coagulopathy
Rivaroxaban should be stopped 24 hours before major surgery
DVT prophylaxis
The first dose should be initiated 6 to 10 hours after surgery
Recommended duration of therapy is 12 days for total knee replacement and 35 days for total hip replacement
Prevent stroke in patients with atrial fibrillation
When transitioning from warfarin to rivaroxaban, give first dose of rivaroxaban when the international normalized ratio is less than 3

Information from references 10 through 19.

comparable to those seen with warfarin, and routine liver function test monitoring is not recommended.[11,13] Because of the effects of renal function on dabigatran, baseline and periodic renal function monitoring are recommended.

RIVAROXABAN

Rivaroxaban is indicated for prevention of deep venous thrombosis in patients undergoing knee or hip replacement surgery, for treatment of deep venous thrombosis and pulmonary embolism, for reducing the risk of recurrent deep venous thrombosis and pulmonary embolism after initial treatment, and for prevention of systemic embolism in patients with nonvalvular atrial fibrillation. It is expected to prolong the activated partial thromboplastin time and increase anti–factor Xa levels; however, the usefulness of monitoring has not been established. In four trials evaluating the role of rivaroxaban in the prevention of VTE in patients undergoing orthopedic surgery, rivaroxaban significantly reduced the primary outcome (total VTE and all-cause mortality) compared with enoxaparin, without significantly increasing bleeding risk.[14-19] In the ROCKET AF trial, rivaroxaban was shown to be noninferior to warfarin for the prevention of stroke or systemic embolism in patients with nonvalvular atrial fibrillation.[19] An important consideration in this trial is that in the warfarin arm, the time in therapeutic range was 55 percent, which is less than what is typically reported by anticoagulation clinics.

Rivaroxaban has been studied for the treatment of acute coronary syndromes. Similar to dabigatran, baseline and periodic renal function monitoring are recommended.

APIXABAN

Similar to dabigatran, apixaban is also indicated for the prevention of systemic embolism and stroke in patients with nonvalvular atrial fibrillation. In the ARISTOTLE and AVERROES trials, apixaban reduced the primary outcome of ischemic stroke, hemorrhagic stroke, and systemic embolism compared with warfarin and aspirin,

Table 5. Comparison of Newer Oral Anticoagulants with Enoxaparin and Warfarin

Component	*Apixaban (Eliquis) vs. warfarin (Coumadin)*	*Dabigatran (Pradaxa) vs. warfarin (Coumadin)*
Advantages	Fixed dose Fewer drug and food interactions No laboratory monitoring necessary Lower bleeding risk compared with warfarin	Fixed dose Fewer drug and food interactions No laboratory monitoring necessary
Disadvantages	Lack of long-term safety/effectiveness data No antidote No test for effectiveness or toxicity Renal dosing Twice-daily administration U.S. Food and Drug Administration boxed warning for increased risk of thrombotic events when apixaban discontinued in patients with nonvalvular atrial fibrillation Underweight patients and those with renal impairment may be at increased bleeding risk	Lack of long-term safety/effectiveness data (e.g., dyspepsia, hepatotoxicity, myocardial infarction) No antidote No test for effectiveness or toxicity Packaging does not allow redistribution to pill boxes Renal dosing Twice-daily administration Underweight patients and those with renal impairment may be at increased bleeding risk
Clinical application	By alleviating the need for frequent dose titrations and laboratory monitoring, especially with therapy initiation and new drug additions or deletions, apixaban possesses key clinical advantages compared with warfarin Warfarin's predictable adverse effect profile, once-daily administration, reversibility with vitamin K, and ability to be monitored for sub- and supratherapeutic dosing provide reassurance for the clinician	By alleviating the need for frequent dose titrations and laboratory monitoring, especially with therapy initiation and new drug additions or deletions, dabigatran possesses key clinical advantages compared with warfarin Warfarin's predictable adverse effect profile, once-daily administration, reversibility with vitamin K, and ability to be monitored for sub- and supratherapeutic dosing provide reassurance for the clinician

Information from references 10 through 19.

SORT: KEY RECOMMENDATIONS FOR PRACTICE

Clinical recommendation	*Evidence rating*	*References*
Patients taking warfarin (Coumadin) should be treated using systematic processes of care to optimize effectiveness and minimize adverse effects. Health care professionals skilled in the initiation and assessment of therapy and dosing adjustments can dramatically influence outcomes.	B	2, 3
In patients with atrial fibrillation and at least one other risk factor for stroke, newer agents (rivaroxaban [Xarelto] and dabigatran [Pradaxa]) that do not require frequent laboratory monitoring are as effective as warfarin for prevention of stroke or systemic embolism and have comparable risks of major bleeding.	A	11-19
Compared with usual clinic-based care, patient self-testing for international normalized ratios, with or without self-dosing of warfarin, is associated with significantly fewer deaths and thromboembolic complications without any increase in bleeding complications for a selected group of motivated patients who have completed appropriate training.	A	22-25

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, go to http://www.aafp.org/afpsort.xml.

respectively. There were also lower mortality rates in the apixaban group in both trials and a lower major bleeding rate in the apixaban group compared with warfarin in the ARISTOTLE trial.[20,21]

Five oral direct factor Xa inhibitors (i.e., betrixaban, TAK-442, darexaban, otamixaban, and edoxaban) are being assessed.[18] AZD0837, which is comparable to dabigatran, and tecarfarin, which is similar to warfarin, are also under investigation.[18]

Patient Self-Testing

Point-of-care monitors are typically used in primary care and anticoagulation clinics and have several advantages, including rapid INR acquisition and interpretation. These monitors make it possible for patients to check their INRs at home, which is referred to as patient self-testing. Reassuring data exist for the effective use of patient self-testing in selected patients who demonstrate monitor competency. Decreased mortality, enhanced

Rivaroxaban (Xarelto) vs. warfarin (Coumadin)	*Rivaroxaban (Xarelto) vs. enoxaparin (Lovenox)*
Fixed dose	Oral route of administration
Fewer drug and food interactions	At least as effective and possibly superior at reducing total venous thromboembolism without increasing major bleeding risk
No laboratory monitoring necessary	
Lack of long-term safety/effectiveness data	Lack of long-term safety/effectiveness data (e.g., hepatotoxicity)
No antidote	No antidote
No test for effectiveness or toxicity	No test for effectiveness or toxicity
Renal dosing	Cannot use in patients with moderate or severe hepatic impairment
Noncompliance with medication potentially more harmful	More drug interactions
U.S. Food and Drug Administration boxed warning for increased risk of thrombotic events when rivaroxaban discontinued in patients with nonvalvular atrial fibrillation	
Underweight patients and those with renal impairment may be at increased bleeding risk	
By alleviating the need for frequent dose titrations and laboratory monitoring, especially with therapy initiation and new drug additions or deletions, rivaroxaban possesses key clinical advantages compared with warfarin	Oral administration makes it easier to allow for longer duration of deep venous thrombosis prophylaxis in patients undergoing orthopedic surgery
Warfarin's predictable adverse effect profile, once-daily administration, relatively longer half-life, reversibility with vitamin K, and ability to be monitored for sub- and supratherapeutic dosing provide reassurance for the clinician	

INR control, decreased thromboembolic events, and an improvement in patient satisfaction and quality of life have been demonstrated with patient self-testing, all without an increase in bleeding complications.[22-24] In 2008, the Centers for Medicare and Medicaid Services expanded its patient self-testing coverage,[25] which is outlined in *eTable D.* The cost of patient self-testing, which is similar to the cost of newer oral anticoagulants, can be significant without reimbursement; however, self-testing is not appropriate for all patients on warfarin therapy[22-24] *(eTable D)*.

Data Sources: A PubMed search was completed in Clinical Queries using the key terms outpatient, anticoagulation, warfarin, dabigatran, rivaroxaban, heparin, low-molecular-weight heparin, dalteparin, enoxaparin, patient self-monitor, and INR. The search included meta-analyses, randomized controlled trials, clinical trials, clinical guidelines, and reviews. Also searched were the National Guideline Clearinghouse database, Essential Evidence Plus, UpToDate, the Cochrane database, and the Agency for Healthcare Research and Quality Clinical Guidelines and Evidence Reports. Search date: August 10, 2012.

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eTable A. Selected Warfarin Drug-Drug Interactions

Potentiate the effects of warfarin (Coumadin)*

- Antimicrobials
  - Ciprofloxacin (Cipro)
  - Clarithromycin (Biaxin)
  - Erythromycin
  - Isoniazid
  - Metronidazole (Flagyl)
  - Triazole antifungals
  - Trimethoprim/sulfamethoxazole (Bactrim, Septra)
- Cardiovascular
  - Amiodarone
  - Diltiazem
  - Fibric acid derivatives
  - Propafenone (Rythmol)
  - Statins

Potentiate the effects of warfarin* *(continued)*

- Complementary and alternative medicine products
  - Cranberry juice
  - Danshen
  - Fish oil
  - Ginkgo biloba
  - Red yeast rice
- Miscellaneous
  - Acetaminophen (dosages ≥ 1.3 g daily)
  - Alcohol (acute ingestion)
  - Cimetidine (Tagamet)
  - Corticosteroids†
  - Levothyroxine
  - Omeprazole (Prilosec)
  - Paroxetine (Paxil)
  - Phenytoin (Dilantin)†

Decrease the effects of warfarin

- Antimicrobials
  - Griseofulvin
  - Rifampin
- Central nervous system drugs
  - Barbiturates
  - Carbamazepine (Tegretol)
  - Chlordiazepoxide (Librium)
  - Trazodone
- Complementary and alternative medicine products
  - American ginseng
  - Coenzyme Q10
  - St. John's wort
- Miscellaneous
  - Cholestyramine (Questran)
  - Corticosteroids†
  - Mercaptopurine
  - Phenytoin†

**—Multiple medications increase bleeding risk because of antiplatelet activity (e.g., aspirin, salicylates, nonsteroidal anti-inflammatory drugs, heparin).*
†—Corticosteroids and phenytoin have variable effects on international normalized ratio.

Information from:

Antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. *2012;141(suppl 2).*

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eTable B. Unfractionated Heparin, LMWH, and Fondaparinux for Outpatient Treatment of Venous Thromboembolism in Adults

Dosage	*Dosage adjustment in patients with renal impairment*	*Half-life*	*Reversibility*	*Monitoring*
Unfractionated heparin*†				
333 units per kg SC first dose, followed by 250 units per kg SC twice daily	No adjustment	0.5 to 2 hours	Protamine	Activated partial thromboplastin time or anti–factor Xa levels Unfractionated heparin can be monitored using the activated partial thromboplastin time with an institution-specific goal range or with anti–factor Xa levels, typically using a goal of 0.3 to 0.7 IU per mL
LMWH*				
Enoxaparin (Lovenox) 1 mg per kg SC every 12 hours or 1.5 mg per kg SC every 24 hours†	1 mg per kg SC every 24 hours if CrCl < 30 mL/min/1.73 m^2	3 to 6 hours	NA	Anti–factor Xa levels in selected patients A peak level (4 hours after the dose is given) can be measured, with a goal of 0.6 to 1 unit per mL for twice-daily enoxaparin and 1.05 units per mL for dalteparin
Dalteparin (Fragmin)† 200 units per kg SC once daily	Use with caution and monitor anti–factor Xa levels in patients with CrCl < 30 mL/min/1.73 m^2	3 to 5 hours	NA	
Tinzaparin (Innohep) 175 anti–factor Xa IU per kg SC once daily for ≥ 6 days	Contraindicated in persons 90 years and older with CrCl ≤ 60 mL/min/1.73 m^2 Use with caution and monitor anti–factor Xa levels in patients with CrCl < 30 mL/min/1.73 m^2	3 to 4 hours	NA	
Fondaparinux (Arixtra)				
Weight < 111 lb (50 kg): 5 mg SC daily Weight 111 to 220 lb (50 to 100 kg): 7.5 mg SC daily Weight > 220 lb (100 kg): 10 mg SC daily	Use with caution in patients with CrCl 30 to 50 mL/min/1.73 m^2 Contraindicated in patients with CrCl ≤ 30 mL/min/1.73 m^2	18 hours	NA	Anti–factor Xa levels (only if fondaparinux is the reference standard for the assay)

CrCl = creatinine clearance; LMWH = low-molecular-weight heparin; NA = not available; SC = subcutaneously.

**—Begin warfarin and unfractionated heparin or LMWH on day 1.*

†—Unfractionated heparin and dalteparin are not approved by the U.S. Food and Drug Administration for treatment of acute deep venous thrombosis. Enoxaparin, 1.5 mg per kg daily, is not approved for outpatient management of acute deep venous thrombosis or for management of acute deep venous thrombosis in pregnant patients.

Information from:

Antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. *2012;141(suppl 2).*

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Comparisons
Unfractionated heparin vs. LMWH Considered equally effective and safe Unfractionated heparin may be better for patients with high bleeding risk because of short half-life and reversibility Unfractionated heparin may be favorable in patients with CrCl < 30 mL/min/1.73 m^2 LMWH has lower incidence of heparin-induced thrombocytopenia
Unfractionated heparin vs. LMWH Considered equally effective and safe Unfractionated heparin may be better for patients with high bleeding risk because of short half-life and reversibility Unfractionated heparin may be favorable in patients with CrCl < 30 mL/min/1.73 m^2 LMWH has lower incidence of heparin-induced thrombocytopenia
LMWH vs. fondaparinux Comparable effectiveness and safety Longer half-life for fondaparinux is advantageous (daily dosing) and potentially troublesome (adverse effects and lack of reversibility)

eTable C. Perioperative Management of Warfarin

Warfarin (Coumadin) indication		
Mechanical heart valve	*Chronic atrial fibrillation*	*VTE*
At least 1 of the following: Aortic valve prosthesis (caged-ball or tilting-disk) Mitral valve prosthesis (any) Stroke or TIA within past 6 months May also include: Patients with a history of stroke or TIA more than 3 months before surgery and a $CHADS_2$ score < 5 Patients undergoing surgeries with high risk of thromboembolism	At least 1 of the following: $CHADS_2$ score of 5 or 6 Rheumatic mitral valve disease Stroke or TIA within past 3 months May also include: Patients with a history of stroke or TIA more than 3 months before surgery and a $CHADS_2$ score < 5 Patients undergoing surgeries with high risk of thromboembolism	At least 1 of the following: Severe thrombophilia* VTE within past 3 months May also include: Previous thromboembolism during temporary vitamin K antagonist interruption Patients undergoing surgeries with high risk of thromboembolism
Aortic valve prosthesis (bileaflet) and at least 1 of the following: age older than 75 years; atrial fibrillation; congestive heart failure; diabetes mellitus; hypertension; prior stroke or TIA	$CHADS_2$ score of 3 or 4	At least 1 of the following: Active cancer§ Nonsevere thrombophilic condition‖ Recurrent VTE VTE within past 3 to 12 months
Aortic valve prosthesis (bileaflet) without atrial fibrillation and no other stroke risk factors	No prior stroke or TIA and $CHADS_2$ score ≤ 2	Single VTE occurred > 12 months ago and no other risk factors

$CHADS_2$ = congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior ischemic stroke or TIA (doubled); LMWH = low-molecular-weight heparin; TIA = transient ischemic attack; VTE = venous thromboembolism.

**—Such as protein C or S deficiency, antiphospholipid antibodies, or antithrombin deficiency.*

†—*Stop subcutaneous LMWH 24 hours before surgery.*

‡—*Surgeries with a higher risk of bleeding include urologic surgeries, large colon polyp resection, and surgeries that involve vascular organs or have extensive tissue injury potential. Bleeding risk in hospitalized patients has been linked to multiple factors including active gastric or duodenal ulcer, bleeding within 3 months before admission, and thrombocytopenia.*

§—*Defined as cancer treated within 6 months or palliative.*

‖—*Such as heterozygous factor V Leiden mutation.*

Risk level for VTE	*Bleeding risk category*	*Recommendation*
High (> 10% annual risk)	Very low (minor procedures)	Dental: continue warfarin with an oral prohemostatic agent or stop warfarin 2 to 3 days before procedure
		Dermatologic: continue warfarin and optimize local hemostasis
		Cataract: continue warfarin
	Low	Stop warfarin 5 days before surgery and restart 12 to 24 hours postoperatively
		VTE prophylaxis *and*
		Therapeutic dose of LMWH before the procedure† and beginning approximately 24 hours after the procedure
	High‡	Stop warfarin 5 days before surgery and restart 12 to 24 hours postoperatively
		VTE prophylaxis *and*
		Therapeutic dose of LMWH before the procedure† and beginning 48 to 72 hours after the procedure
Moderate (5 to 10% annual risk)	Very low (minor procedures)	Dental: continue warfarin with an oral prohemostatic agent or stop warfarin 2 to 3 days before procedure
		Dermatologic: continue warfarin and optimize local hemostasis
		Cataract: continue warfarin
	Low (base bridging on patient- and surgery-related factors‡)	Stop warfarin 5 days before surgery and restart 12 to 24 hours postoperatively
		Therapeutic dose of LMWH before the procedure† and beginning approximately 24 hours after the procedure
	High (base bridging on patient- and surgery-related factors‡)	Stop warfarin 5 days before surgery and restart 12 to 24 hours postoperatively
		VTE prophylaxis *and*
		Therapeutic dose of LMWH before the procedure† and beginning 48 to 72 hours after the procedure
Low (< 5% annual risk)	Very low (minor procedures)	Dental: continue warfarin with an oral prohemostatic agent or stop warfarin 2 to 3 days before procedure
		Dermatologic: continue warfarin and optimize local hemostasis
		Cataract: continue warfarin
	Low	Stop warfarin 5 days before surgery and restart 12 to 24 hours postoperatively
		Do not bridge
	High‡	Stop warfarin 5 days before surgery and restart 12 to 24 hours postoperatively
		Do not bridge

Information from:

Antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. *2012;141(suppl 2).*

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eTable D. Considerations for Patient Self-Testing of International Normalized Ratio

Centers for Medicare and Medicaid Services coverage includes patients:
In whom self-testing is prescribed by a physician
Taking warfarin (Coumadin) for long-term anticoagulation for venous thromboembolism, mechanical heart valves, or atrial fibrillation
Taking warfarin for at least three months before initiation of self-testing
Who do not require testing frequency greater than once weekly
Who participate in, and successfully complete, an anticoagulation education program*
Patients who may not be good self-testing candidates include those:
Who do not demonstrate monitor or instruction competency†
Who will be treated with warfarin for fewer than six months
With atypical international normalized ratio target ranges
With intellectual impairment
With known drug or alcohol abuse
With language barriers that cannot be overcome with the assistance of a family member

**—This program should explain the use of the monitor, the testing procedure, and performance of quality controls, and should assess continued appropriate monitor use.*

†—Competency is influenced by the patient's vision, manual dexterity, and ability to follow the monitor procedure correctly and consistently.

Information from:

Gardiner C, Williams K, Mackie IJ, Machin SJ, Cohen H. Patient self-testing is a reliable and acceptable alternative to laboratory INR monitoring. Br J Haematol. *2005;128(2):242-247.*

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