SIDE EFFECTS Like all anticoagulants, the major side effect of warfarin is bleeding. A rare complication is skin necrosis. Warfarin crosses the placenta and can cause fetal abnormalities. Consequently, warfarin should not be used during pregnancy.

Bleeding At least half of the bleeding complications with warfarin occur when the INR exceeds the therapeutic range. Bleeding complications may be mild, such as epistaxis or hematuria, or more severe, such as retroperitoneal or gastrointestinal bleeding. Life-threatening intracranial bleeding can also occur.

To minimize the risk of bleeding, the INR should be maintained in the therapeutic range. In asymptomatic patients whose INR is between 3.5 and 10, warfarin should be withheld until the INR returns to the therapeutic range. If the INR is over 10, oral vitamin K should be administered, at a dose of 2.5–5 mg, although there is no evidence that doing so reduces the bleeding risk. Higher doses of oral vitamin K (5–10 mg) produce more rapid reversal of the INR but may render patients temporarily resistant to warfarin when the drug is restarted. Patients with serious bleeding need more aggressive treatment. These patients should be given 5–10 mg of vitamin K by slow IV infusion. Additional vitamin K should be given until the INR is in the normal range. Treatment with vitamin K should be supplemented with fresh-frozen plasma as a source of the vitamin K–dependent clotting proteins. Four factor prothrombin complex concentrates, which contain all four vitamin K–dependent clotting proteins, are the treatment of choice for (1) life-threatening bleeds, (2) rapid restoration of the INR into the normal range in patients requiring urgent surgery or intervention, and (3) patients who cannot tolerate the volume load of fresh-frozen plasma.

Warfarin-treated patients who experience bleeding when their INR is in the therapeutic range require investigation into the cause of the bleeding. Those with gastrointestinal or genitourinary bleeding often have an underlying lesion.

Skin necrosis A rare complication of warfarin, skin necrosis usually is seen 2–5 days after initiation of therapy. Well-demarcated erythematous lesions form on the thighs, buttocks, breasts, or toes. Typically, the center of the lesion becomes progressively necrotic. Examination of skin biopsies taken from the border of these lesions reveals thrombi in the microvasculature.

Warfarin-induced skin necrosis is seen in patients with congenital or acquired deficiencies of protein C or protein S. Initiation of warfarin therapy in these patients produces a precipitous fall in plasma levels of proteins C or S, thereby eliminating this important anticoagulant pathway before warfarin exerts an antithrombotic effect through lowering of the functional levels of factor X and prothrombin. The resultant procoagulant state triggers thrombosis. Why the thrombosis is localized to the microvasculature of fatty tissues is unclear.

Treatment involves discontinuation of warfarin and reversal with vitamin K, if needed. An alternative anticoagulant, such as heparin or LMWH, should be given in patients with thrombosis. Protein C concentrate can be given to protein C–deficient patients to accelerate healing of the skin lesions; fresh-frozen plasma may be of value if protein C concentrate is unavailable and for those with protein S deficiency. Occasionally, skin grafting is necessary when there is extensive skin loss.

Because of the potential for skin necrosis, patients with known protein C or protein S deficiency require overlapping treatment with a parenteral anticoagulant when initiating warfarin therapy. Warfarin should be started in low doses in these patients, and the parenteral anticoagulant should be continued until the INR is therapeutic for at least 2–3 consecutive days.

Pregnancy Warfarin crosses the placenta and can cause fetal abnormalities or bleeding. The fetal abnormalities include a characteristic embryopathy, which consists of nasal hypoplasia and stippled epiphyses. The risk of embryopathy is highest if warfarin is given in the first trimester of pregnancy. Central nervous system abnormalities can also occur with exposure to warfarin at any time during pregnancy. Finally, maternal administration of warfarin produces an anticoagulant effect in the fetus that can cause bleeding. This is of particular concern at delivery when trauma to the head during passage through the birth canal can lead to intracranial bleeding. Because of these potential problems, warfarin is contraindicated in pregnancy, particularly in the first and third trimesters. Instead, heparin, LMWH, or fondaparinux can be given during pregnancy for prevention or treatment of thrombosis.

Warfarin does not pass into the breast milk. Consequently, warfarin can safely be given to nursing mothers.

Special problems Patients with a lupus anticoagulant and those who need urgent or elective surgery present special challenges. Although observational studies suggested that patients with thrombosis complicating the antiphospholipid antibody syndrome required higher intensity warfarin regimens to prevent recurrent thromboembolic events, two randomized trials showed that targeting an INR of 2.0–3.0 is as effective as higher intensity treatment and produces less bleeding. Monitoring warfarin therapy can be problematic in patients with antiphospholipid antibody syndrome if the lupus anticoagulant prolongs the baseline INR; factor X levels can be used instead of the INR in such patients.

There is no need to stop warfarin before procedures associated with a low risk of bleeding; these include dental cleaning, simple dental extraction, cataract surgery, or skin biopsy. For procedures associated with a moderate or high risk of bleeding, warfarin should be stopped 5 days before the procedure to allow the INR to return to normal levels. Patients at high risk for thrombosis, such as those with mechanical heart valves, can be bridged with once- or twice-daily SC injections of LMWH when the INR falls to <2.0. The last dose of LMWH should be given 12–24 h before the procedure, depending on whether LMWH is administered twice or once daily. After the procedure, treatment with warfarin can be restarted.

New Oral Anticoagulants

New oral anticoagulants are now available as alternatives to warfarin. These include dabigatran, which targets thrombin, and rivaroxaban, apixaban, and edoxaban, which target factor Xa. All of these drugs have a rapid onset and offset of action and have half-lives that permit once- or twice-daily administration. Designed to produce a predictable level of anticoagulation, the new oral agents are more convenient to administer than warfarin because they are given in fixed doses without routine coagulation monitoring.

MECHANISM OF ACTION The new oral anticoagulants are small molecules that bind reversibly to the active site of their target enzyme. Table 143-9 summarizes the distinct pharmacologic properties of these agents.

INDICATIONS The new oral anticoagulants have been compared with warfarin for stroke prevention in patients with nonvalvular atrial fibrillation in four randomized trials that enrolled 71,683 patients. A meta-analysis of these data demonstrates that compared with warfarin, the new agents significantly reduce stroke or systemic embolism by 19% (p = .001), primarily driven by a 51% reduction in hemorrhagic stroke (p <.0001), and are associated with a 10% reduction in mortality (p <.0001). New oral anticoagulants reduce intracranial hemorrhage by

TABLE 143-9 COMPARISON OF THE PHARMACOLOGIC PROPERTIES OF THE NEW ORAL ANTICOAGULANTS

Characteristic	Rivaroxaban	Apixaban	Edoxaban	Dabigatran
Target	Factor Xa	Factor Xa	Factor Xa	Thrombin
Prodrug	No	No	No	Yes
Bioavailability	80%	60%	50%	6%
Dosing	qd (bid)	bid	qd	bid (qd)
Half-life	7–11 h	12 h	9–11 h	12–17 h
Renal	33% (66%)	25%	35%	80%
Monitoring	No	No	No	No
Interactions	3A4/P-gp	3A4/P-gp	P-gp	P-gp

Abbreviations: bid, twice a day; P-gp, P-glycoprotein; qd., once a day.