52% compared with warfarin (p <.0001), but increase gastrointestinal bleeding by about 24% (p = .04). Overall, the new agents demonstrate a favorable benefit-to-risk profile compared with warfarin, and their relative efficacy and safety are maintained across a wide spectrum of atrial fibrillation patients, including those over the age of 75 years and those with a prior history of stroke. Based on these findings, dabigatran, rivaroxaban, and apixaban are licensed as alternatives to warfarin for stroke prevention in nonvalvular atrial fibrillation, and edoxaban is under regulatory consideration for this indication. Nonvalvular atrial fibrillation is defined as that occurring in patients without mechanical heart valves or severe rheumatic valvular disease, particularly mitral stenosis and/or regurgitation.

Dabigatran, rivaroxaban, and apixaban have been compared with enoxaparin for thromboprophylaxis after elective hip or knee arthroplasty. Currently, only rivaroxaban and apixaban are licensed for this indication in the United States. Rivaroxaban and dabigatran are also licensed for treatment of DVT or PE. Apixaban and edoxaban have also been investigated for treatment of patients with venous thromboembolism, but have not yet been approved for this indication. Rivaroxaban is licensed in Europe for prevention of recurrent ischemic events in patients who have been stabilized after an acute coronary syndrome. In this setting, rivaroxaban is usually administered in conjunction with dual antiplatelet therapy with aspirin and clopidogrel.

DOSING For stroke prevention in patients with nonvalvular atrial fibrillation, rivaroxaban is given at a dose of 20 mg once daily with a dose reduction to 15 mg once daily in patients with a creatinine clearance of 15–49 mL/min; dabigatran is given at a dose of 150 mg twice daily with a dose reduction to 75 mg twice daily in those with a creatinine clearance of 15–30 mL/min; and apixaban is given at a dose of 5 mg twice daily with a dose reduction to 2.5 mg twice daily for patients with a creatinine >1.5 g/dL, for those 80 years of age or older, or for patients who weigh <60 kg.

For thromboprophylaxis after elective hip or knee replacement surgery, rivaroxaban is given at a dose of 10 mg once daily, whereas apixaban is given at a dose of 2.5 mg twice daily. For treatment of patients with DVT or PE, rivaroxaban is started at a dose of 15 mg twice daily for 3 weeks; the dose is then reduced to 20 mg once daily thereafter. After a minimum of a 5 day course of treatment with heparin or LMWH, dabigatran is given at a dose of 150 mg twice daily.

MONITORING Although designed to be administered without routine monitoring, there are situations where determination of the anticoagulant activity of the new oral anticoagulants can be helpful. These include assessment of adherence, detection of accumulation or overdose, identification of bleeding mechanisms, and determination of activity prior to surgery or intervention. For qualitative assessment of anticoagulant activity, the prothrombin time can be used for factor Xa inhibitors and the aPTT for dabigatran. Rivaroxaban and edoxaban prolong the prothrombin time more than apixaban. In fact, because apixaban has such a limited effect on the prothrombin time, anti-factor Xa assays are needed to assess its activity. The effect of the drugs on tests of coagulation varies depending on the time that the blood is drawn relative to the timing of the last dose of the drug and the reagents used to perform the tests. Chromogenic anti-factor Xa assays and a dilute thrombin clotting time with appropriate calibrators provide quantitative assays to measure the plasma levels of the factor Xa inhibitors and dabigatran, respectively.

SIDE EFFECTS Like all anticoagulants, bleeding is the most common side effect of the new oral anticoagulants. The new agents are associated with less intracranial bleeding than warfarin. The increased risk of intracranial bleeding with warfarin likely reflects the reduction in functional levels of factor VII, which precludes efficient thrombin generation at sites of microvascular bleeding in the brain. Because the new oral anticoagulants target downstream coagulation enzymes, they produce less impairment of hemostatic plug formation at sites of vascular injury.

A downside of the new oral anticoagulants is the increased risk of gastrointestinal bleeding. This likely occurs because unabsorbed active drug in the gut exacerbates bleeding from lesions. Although dabigatran etexilate is a prodrug, only 7% is absorbed. Although the remainder passes through the gut, at least two-thirds is metabolically activated to dabigatran by gut esterases.

Dyspepsia occurs in up to 10% of patients treated with dabigatran; this problem improves with time and can be minimized by administering the drug with food. Dyspepsia is rare with rivaroxaban, apixaban, and edoxaban.

PERIPROCEDURAL MANAGEMENT Like warfarin, the new oral anticoagulants must be stopped before procedures associated with a moderate or high risk of bleeding. The drugs should be held for 1–2 days, or longer if renal function is impaired. Assessment of residual anticoagulant activity before procedures associated with a high bleeding risk is prudent.

MANAGEMENT OF BLEEDING There are no specific antidotes for the new oral anticoagulants. With minor bleeding, holding one or two doses of drug is usually sufficient. The approach to serious bleeding is similar to that with warfarin except that vitamin K administration is of no benefit. Thus, the anticoagulant and antiplatelet drugs should be held, the patient should be resuscitated with fluids and blood products as necessary, and, if possible, the bleeding site should be identified and managed. Coagulation testing will determine the extent of anticoagulation. and renal function should be assessed so that the half-life of the drug can be calculated. Timing of the last dose of anticoagulant is important; administration of oral activated charcoal may help to prevent absorption of drug administered in the past 2–4 h. If bleeding continues or is life-threatening, procoagulants, such as prothrombin complex concentrate (either unactivated or activated) or factor VIIa, can be administered, although the evidence of their effectiveness is limited. Dialysis removes dabigatran from the circulation in patients with renal impairment; dialysis does not remove rivaroxaban, apixaban, or edoxaban because unlike dabigatran, these drugs are highly protein-bound.

PREGNANCY As small molecules, the new oral anticoagulants can all pass through the placenta. Consequently, these agents are contraindicated in pregnancy, and when used by women of childbearing potential, appropriate contraception is important.

ONGOING INVESTIGATIONS Although the lack of antidotes has created concern about the risk of bleeding events in patients taking the new oral anticoagulants, emerging postmarketing data suggest that the rates of bleeding in the real-world setting are similar to those reported in the trials. Nonetheless, specific antidotes are under development. These include a humanized mouse monoclonal antibody fragment against dabigatran and a recombinant variant of factor Xa that serves as a decoy for the oral factor Xa inhibitors. Neither agent is currently available for clinical use.

FIBRINOLYTIC DRUGS

ROLE OF FIBRINOLYTIC THERAPY

Fibrinolytic drugs can be used to degrade thrombi and are administered systemically or can be delivered via catheters directly into the substance of the thrombus. Systemic delivery is used for treatment of acute MI, acute ischemic stroke, and most cases of massive PE. The goal of therapy is to produce rapid thrombus dissolution, thereby restoring antegrade blood flow. In the coronary circulation, restoration of blood flow reduces morbidity and mortality rates by limiting myocardial damage, whereas in the cerebral circulation, rapid thrombus dissolution decreases the neuronal death and brain infarction that produce irreversible brain injury. For patients with massive PE, the goal of thrombolytic therapy is to restore pulmonary artery perfusion.

Peripheral arterial thrombi and thrombi in the proximal deep veins of the leg are most often treated using catheter-directed thrombolytic therapy. Catheters with multiple side holes can be used to enhance drug delivery. In some cases, intravascular devices that fragment and extract the thrombus are used to hasten treatment. These devices can be used alone or in conjunction with fibrinolytic drugs.