A Replacement for Warfarin
The Search Continues

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Vitamin K antagonists (VKAs) such as warfarin are the only oral anticoagulants currently available for clinical use. Warfarin has numerous limitations, including slow onset and offset of action, a narrow therapeutic window, and a metabolism that is affected by diet, drugs, and genetic polymorphisms. Because of its unpredictable dose response, warfarin requires careful coagulation monitoring to ensure that a therapeutic anticoagulant effect is achieved. Variable dose requirements, concern about the risk of bleeding, and the need for frequent coagulation monitoring have prompted the development of new oral anticoagulants to replace warfarin. With a predictable anticoagulant response and little potential for food or drug interactions, these new agents have been designed to be administered in fixed doses without coagulation monitoring. Consequently, these drugs have the potential to simplify long-term anticoagulant therapy.

The features of the new oral anticoagulants in the most advanced stages of clinical development are listed in the Table and are compared with those of warfarin. Unlike warfarin, which reduces the functional levels of factors II (prothrombin), VII, IX, and X, these novel agents are directed against the active site of factor Xa or thrombin, the enzymes responsible for thrombin generation and fibrin formation, respectively (see the Figure). Rivaroxaban and apixaban target factor Xa, whereas dabigatran etexilate inhibits thrombin.

Rivaroxaban is a small molecule directed against the active site of factor Xa. After oral administration, it is absorbed in the stomach and small intestine with a bioavailability of 60% to 80%. Peak plasma levels are achieved in 3 hours, and the drug circulates with a half-life of 9 hours. Rivaroxaban is cleared via 2 pathways: ~65% is excreted unchanged in the urine, and the remainder is eliminated through the biliary/fecal route. Because of the predominance of the renal pathway of excretion, the half-life of rivaroxaban is prolonged in the elderly and in patients with renal impairment. Apixaban has properties similar to those of rivaroxaban except that the clearance of apixaban is mainly via the biliary/fecal route. Therefore, apixaban is less likely to accumulate in patients with renal insufficiency than is rivaroxaban.

As direct inhibitors of factor Xa, rivaroxaban and apixaban inactivate free factor Xa and factor Xa incorporated within the prothrombinase complex equally well. In contrast, indirect factor Xa inhibitors such as fondaparinux have reduced capacity to inhibit factor Xa when it is incorporated within the prothrombinase complex. Whether inhibition of platelet-bound factor Xa endows direct factor Xa inhibitors with an advantage over indirect inhibitors remains to be established.

The clinical development of rivaroxaban is more advanced than that of apixaban. Favorable early results with rivaroxaban for the prevention of venous thromboembolism (VTE) in patients undergoing major orthopedic surgery prompted its recent evaluation in phase II clinical trials for the treatment of patients with acute symptomatic VTE. In the present issue of Circulation, Angelli and colleagues report the results of the Oral Direct Factor Xa Inhibitor BAY 59-7939 in Patients With Acute Symptomatic Deep-Vein Thrombosis (ODIXa-DVT) study, a phase II randomized trial of rivaroxaban for the treatment of DVT. In that trial, 613 patients with symptomatic proximal DVT who did not have pulmonary embolism were randomized to receive fixed-dose oral rivaroxaban (at doses of 10, 20, or 30 mg twice daily or 40 mg once daily) or subcutaneous enoxaparin (at a dose of 1 mg/kg twice daily), followed by a VKA. Allocation to rivaroxaban or enoxaparin/VKA treatment was open label, but patients and investigators were blinded to the dose of rivaroxaban, and all outcomes were adjudicated centrally without knowledge of treatment allocation. The primary efficacy outcome was improvement in thrombotic burden (assessed by repeating the compression ultrasound and comparing the test results with those done at baseline) without recurrent symptomatic VTE or VTE-related death. The primary efficacy outcome occurred in 44% to 59% of patients receiving rivaroxaban and in 46% of those randomized to enoxaparin/VKA. There was no indication of a dose–efficacy relationship with rivaroxaban, but the incidence of bleeding (major plus minor) was higher with increasing doses of rivaroxaban, ranging from 5.0% to 11.6%, compared with a rate of 6.3% in patients treated with enoxaparin/VKA. Symptomatic VTE or death occurred in 2.1% of patients treated with rivaroxaban and in 0.9% of those given enoxaparin/VKA.

The ODIXa-DVT study is one of a pair of phase II trials evaluating the efficacy and safety of rivaroxaban for the treatment of DVT. Its companion study, the as-yet unpublished EINSTEIN-DVT trial, was of similar design but compared once-daily rivaroxaban (in doses of 20, 30, or 40 mg) with a heparin (either unfractionated heparin or low-molecular-weight heparin), followed by a VKA, in 543 patients with symptomatic DVT without associated symptomatic pulmonary embolism.
The primary efficacy outcome was deterioration in thrombotic burden (assessed by repeating the compression ultrasound and perfusion lung scan at 12 weeks and comparing the results with those obtained at baseline) or symptomatic recurrent VTE. This outcome occurred in 5.4% to 6.6% of patients randomized to rivaroxaban and in 9.9% of those given heparin/VKA. Again, there was no evidence of a dose–efficacy relationship with rivaroxaban, but in contrast to the results of the ODIXa-DVT trial, there was no dose response for bleeding. Clinically relevant bleeding occurred in 2.9% to 7.5% of patients randomized to rivaroxaban and in 8.8% of those treated with heparin/VKA.

The lack of a dose–efficacy response for rivaroxaban in the ODIXa-DVT trial, which evaluated total daily rivaroxaban doses ranging from 20 to 60 mg, and in the EINSTEIN-DVT trial, which examined daily doses ranging from 20 to 40 mg, suggests that there is a plateau for efficacy in this dose range. The significant dose relationship for bleeding with twice-daily administration, but not with once-daily dosing, raises the possibility that dose frequency might influence bleeding risk independently of dose intensity. This could occur if the sustained drug levels achieved with twice-daily dosing confer a greater bleeding risk than the high peak levels obtained with once-daily drug administration. However, comparison across these trials is potentially confounded by differences in the comparators, cointerventions, and outcome definitions. In the ODIXa-DVT trial, the major bleeding rates with 40 mg rivaroxaban once daily or 20 mg twice daily were both 1.7%, whereas the minor bleeding rates were 9.9% and 7.7% with once-daily and twice-daily dosing, respectively. These findings suggest that if dose frequency does influence the bleeding risk, its effect is likely to be minor.

The results of the ODIXa-DVT and EINSTEIN-DVT trials provide proof of principle for the efficacy and safety of rivaroxaban for the treatment of DVT. On the basis of these trials, the 20-mg once-daily dose of rivaroxaban has been chosen for evaluation in phase III randomized trials of rivaroxaban for the treatment of VTE and for the prevention of stroke in atrial fibrillation. However, has the optimal dose been identified in these phase II trials? The lack of a dose–efficacy response with daily rivaroxaban doses ranging from 20 to 60 mg suggests that lower doses also may be effective. For example, it is possible that the 10-mg once-daily dose that is currently being evaluated in phase III studies for the prevention of VTE in major orthopedic surgery would maintain efficacy while reducing the risk of bleeding. Support for the concept that lower anticoagulant doses may reduce bleeding without compromising antithrombotic efficacy is provided by the results of the Organization to Assess Strategies for Ischemic Syndromes 5 (OASIS-5) trial. In this study, the dose of fondaparinux used for VTE prophylaxis was as effective as conventional treatment doses of enoxaparin at preventing recurrent ischemia in patients with non–ST-elevation acute coronary syndromes. However, this low-dose fondaparinux regimen was associated with a 50% reduction in the risk of major and minor bleeding.
These observations raise the possibility that more work should be done to determine the optimal dose of rivaroxaban to carry forward into the phase III program.

The composite primary efficacy outcomes in the ODIXa-DVT and EINSTEIN-DVT trials were driven primarily by changes in thrombotic burden as assessed by repeated compression ultrasonography and perfusion lung scanning. Previous studies have shown that venographic assessment of thrombus burden using the Marder score is a valid surrogate for recurrent DVT. Compression ultrasonography has largely replaced venography because compression ultrasonography is noninvasive and obviates the need for injection of contrast dye. In the ODIXa-DVT trial, changes in compression ultrasound findings were quantified with an adapted Marder score. Although this is a logical approach, such an ultrasound scoring system has never been directly compared with its venographic counterpart. Nonetheless, assessment of thrombus burden with repeated compression ultrasound examinations has been used successfully in phase II dose-finding studies with other anticoagulants. Unexpected hepatotoxicity during recent randomized evaluation of ximelagatran, the first oral direct thrombin inhibitor, has prompted intense scrutiny of the potential hepatic side effects of new oral anticoagulants, including rivaroxaban. During the first 3 weeks of treatment in the ODIXa-DVT trial, the incidence of alanine aminotransferase elevations >3 times the upper limit of normal was significantly lower in patients treated with rivaroxaban than it was in those given enoxaparin/VKA. This is not surprising because enoxaparin is known to transiently increase the levels of transaminases. After 3 weeks, the incidences of alanine aminotransferase elevations were low with both treatments. No patients in the enoxaparin/VKA group stopped treatment because of elevated liver enzymes, whereas 3 patients stopped treatment early in the rivaroxaban group, 2 of whom died soon thereafter of unrelated hepatic causes (metastatic malignancy and acute hepatitis B, respectively). There has been no suggestion of adverse hepatic effects with rivaroxaban in phase II trials for VTE prevention, but more long-term data are needed.

While the studies with rivaroxaban are well underway, apixaban and dabigatran etexilate are being evaluated in parallel development programs. Building on data from phase II trials for the prevention and treatment of VTE after major orthopedic surgery, for VTE prevention in medical patients, and for stroke prevention in atrial fibrillation. In contrast to rivaroxaban, a twice-daily regimen is being evaluated for these indications.

Of the new oral anticoagulants, dabigatran etexilate is the drug in the most advanced stages of development. An oral direct thrombin inhibitor, dabigatran etexilate is a double prodrug that undergoes esterase-mediated conversion to dabigatran, a small molecule that targets the active site of thrombin. A phase III trial comparing 2 different doses of once-daily oral dabigatran etexilate with subcutaneous dalteparin for VTE prophylaxis after knee replacement surgery revealed similar efficacy and safety. Other phase III orthopedic trials have been completed, and phase III studies evaluating dabigatran etexilate for VTE treatment and for stroke prevention in atrial fibrillation are ongoing.

Which is the better target, factor Xa or thrombin? Head-to-head trials of oral direct factor Xa and thrombin inhibitors are needed to address this question. Nonetheless, with the results of these clinical trials beginning to unfold, we are coming closer to finding a safer and more convenient replacement for warfarin.

Disclosures
Dr Weitz is a consultant for Bayer and served as a member of the independent central adjudication committee for ODIXa-DVT. Dr Eikelboom has received consulting fees and/or research funding from companies that are developing new anticoagulants (Bristol-Myers Squibb, Boehringer Ingelheim, Johnson & Johnson, Pfizer, and Sanofi-Aventis).

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