

Novel Anticoagulants

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Currently, the only oral anticoagulants licensed for long-term use are the vitamin K antagonists (VKAs), such as warfarin. Although effective, the VKAs are difficult to administer because the dose varies from person to person reflecting common genetic polymorphisms that affect drug metabolism, differences in dietary vitamin K intake and numerous drug-drug interactions. Consequently, frequent monitoring and dose adjustments are necessary to ensure that the level of anticoagulation is maintained within the therapeutic range. Such monitoring is inconvenient for patients and physicians and costly for the health care system. More importantly, even with monitoring, the international normalized ratio (INR) is frequently above or below the therapeutic range, which places patients at risk for bleeding or thrombosis, respectively. Because of the limitations of VKAs, they are often underused, particularly in patients with atrial fibrillation (AF) who require such treatment to reduce the risk of stroke. Therefore, there is a large unmet need for oral anticoagulants that are at least as effective and safe as VKAs, but are easier to administer.

The new oral anticoagulants were developed to overcome the limitations of VKAs. Targeting either thrombin or factor Xa, the new drugs have a rapid onset of action after oral administration and produce a predictable level of anticoagulation with fixed dosing because food has no effect on their activity and there are few drug-drug interactions. Because the anticoagulant response is so predictable with the new oral anticoagulants, routine coagulation monitoring is unnecessary. Therefore, the new oral anticoagulants are more convenient to administer than VKAs.

Dabigatran etexilate, which targets thrombin, and rivaroxaban, apixaban and edoxaban, which target factor Xa, are the drugs in the most advanced stages of clinical development. Dabigatran etexilate and rivaroxaban are already licensed in Europe and Canada, but not in the United States, for short-term prophylaxis after elective hip or knee replacement surgery. Based on the promising results of studies comparing these new oral agents with subcutaneous enoxaparin for short-term thromboprophylaxis, the drugs are now being compared with warfarin for long-term indications.

Dabigatran etexilate was compared with warfarin for stroke prevention in patients with AF and for treatment of established venous thromboembolism (VTE) in the phase III RE-LY and RE-COVER trials, respectively. In the RE-LY trial, the lower dose dabigatran regimen (110 mg twice daily) was non-inferior to warfarin for prevention of stroke and systemic embolism, but was associated with significantly less major bleeding, whereas the higher dose dabigatran regimen (150 mg twice daily) was superior to warfarin for prevention of stroke and systemic embolism, and was associated with a similar rate of major bleeding. The rate of intracranial bleeding was significantly lower with both doses of dabigatran than it was with warfarin. In the RE-COVER trial where dabigatran was compared with warfarin for treatment of acute VTE, dabigatran (150 mg twice daily) was non-inferior to warfarin for prevention of recurrent VTE or VTE-related mortality and rates of major bleeding were similar. Based on these results, dabigatran etexilate appears to be a viable alternative to warfarin.

Ongoing studies are comparing rivaroxaban, apixaban or edoxaban with warfarin for stroke prevention in patients with AF or for VTE treatment. Rivaroxaban and apixaban also are being investigated for VTE prevention in medically ill patients, or as adjuncts to antiplatelet therapy for prevention of recurrent ischemic events in patients with acute coronary syndromes.

Based on the promising results thus far, we are likely to soon have a number of alternatives to VKAs. Although more convenient to administer than VKAs, the new oral anticoagulants have some potential drawbacks. We do not yet know whether the absence of coagulation monitoring will adversely affect patient care because compliance will be more difficult to assess. Even if periodic monitoring is performed, appropriate assays will need to be developed because each agent has different effects on routine tests of coagulation. In addition, there are no specific antidotes for the new agents, which may be problematic when urgent reversal is needed. Finally, the new oral anticoagulants will cost more than warfarin and payers are unlikely to absorb the increased cost unless the new drugs prove to be more cost effective. Despite these potential drawbacks, however, the new oral anticoagulants represent a major advance and are likely to change our approach to long-term anticoagulation therapy.