New Oral Antithrombotic Agents for the Prevention of Deep Venous Thrombosis and Pulmonary Embolism in Orthopedic Surgery

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abstract

As the population ages and medical care, along with a functional life style, continues to improve the health of this group, the number of joint replacement surgeries will continue to rise each year in the United States. This growing volume carries with it the risk of venous thromboembolism associated with joint replacement surgery. The American College of Chest Physicians and the American Academy of Orthopedic Surgery have provided guidelines for preventing this complication with the use of warfarin, low molecular weight heparins, pentasaccharides, and aspirin. These agents have had variable efficacy and safety preventing postoperative and out-of-hospital venous thromboembolism. New classes of oral agents, which inhibit Factor II or Factor X, have been shown to be an effective and safe class of anticoagulants that do not require monitoring or have food and drug interactions. This paper will review the current data on the new oral anticoagulants in joint replacement surgery.

Patients undergoing total hip and knee replacement surgery are a high-risk group for the development of postoperative deep venous thrombosis (DVT) and pulmonary embolism. Prophylaxis for the prevention of these complications has become the standard of care during the past 30 years.

The incidence of total venous thromboembolism (VTE) in joint replacement surgery without thromboprophylaxis ranges from 42% to 57% for total hip arthroplasty (THA) and 41% to 85% for total knee arthroplasty (TKA). Such a high incidence of VTE has resulted in the development of various thromboprophylaxis interventions in this patient population. This article reviews the currently recommended VTE prophylaxis and the new agents for the prevention of VTE in THA and TKA patients.

CURRENT VENOUS THROMBOEMBOLISM PROPHYLAXIS

Low molecular weight heparins and a pentasaccharide, which includes enoxaparin, dalteparin, and fondaparinux, have been shown to be highly effective and safe in joint replacement surgery. These drugs are administered subcutaneously once daily beginning 12 to 24 hours postoperatively and then continued once daily for up to 35 days postoperatively, do not require monitoring, and have no drug-drug or food interactions. The drawbacks associated with this group of anticoagulants include subcutaneous administration, which could impact extended prophylaxis use; drug accumulation in patients with changing renal status; lack of an antidote for fondaparinux; and partial reversibility with protamine for enoxaparin and dalteparin.

The vitamin K antagonist warfarin is a frequently used thromboprophylactic agent in the United States following THA and TKA. Warfarin has been shown to reduce the incidence of overall DVT, proximal DVT, and pulmonary embolism in these patient populations. The primary
Advantages of warfarin are the oral route of administration, delayed onset of action that allows surgical hemostasis, and the ability to be continued after hospital discharge. The shortcomings of warfarin are its slow onset of action, variable patient response, lower efficacy compared to low-molecular-weight heparins, the need for frequent international normalized ratio monitoring, and the complexity of both in-hospital and postdischarge supervision (Table 1).

**NEW ORAL ANTICOAGULANTS**

**Oral Direct Thrombin Inhibitors**

Dabigatran etexilate, a prodrug of dabigatran, which reversibly inhibits the active site of thrombin, has an oral bioavailability of 7% (Table 2). After oral administration, dabigatran etexilate is rapidly and completely converted to dabigatran by esterases. Plasma levels of dabigatran peak 2 hours after drug administration. Dabigatran has a half-life of 12 to 14 hours, which permits once- or twice-daily administration, and 80% of the drug is excreted unchanged by the kidneys.

Based on the results of phase II studies showing that dabigatran etexilate is effective for VTE prevention, 2 doses were studied in phase III for thromboprophylaxis after THA or TKA: 150 or 220 mg once daily, starting with a half-dose of 75 or 110 mg on the first day. The European-approved dose of enoxaparin, 40 mg once daily with the first dose given the evening before surgery, was used as the comparator in the dabigatran etexilate versus enoxaparin in prevention of VTE after TKA (RE-MODEL) and dabigatran etexilate compared with enoxaparin in prevention of VTE after THA (RE-NOVATE) trials. The dose of enoxaparin approved in North America, 30 mg twice daily starting 12 to 24 hours after surgery, was the comparator in the dabigatran etexilate versus enoxaparin in prevention of VTE after TKA (RE-MOBILIZE) trial.

In all 3 trials, the primary efficacyendpoint was total VTE, a composite of venographically detected or symptomatic DVT, nonfatal pulmonary embolism, and all-cause mortality. Tables 3 and 4 outline the design of these 3 trials as well as the primary outcomes.

In the RE-MODEL trial involving 2101 patients who underwent TKA, 6 to 10 days of either dose of dabigatran etexilate had efficacy similar to that of enoxaparin (36.4% for 220 mg of dabigatran, 40.5% for 150 mg of dabigatran, and 37.7% for enoxaparin). The incidence of major bleeding did not differ significantly among the 3 groups (1.3%, 1.5%, and 1.3%, respectively).

In the RE-NOVATE trial involving 3494 patients who underwent TKA, treatment with either dose of dabigatran etexilate for 28 to 35 days had efficacy similar to that of enoxaparin (6% for 220 mg of dabigatran, 8.6% for 150 mg of dabigatran, and 6.6% for enoxaparin). The incidence of major bleeding did not differ significantly among the 3 groups (2%, 1.3%, and 1.6%, respectively).

In the RE-MOBILIZE study of 2615 patients who underwent TKA, treatment with either dose of dabigatran etexilate for 28 to 35 days had efficacy similar to that of enoxaparin (6% for 220 mg of dabigatran, 8.6% for 150 mg of dabigatran, and 6.6% for enoxaparin). The incidence of major bleeding did not differ significantly among the 3 groups (2%, 1.3%, and 1.6%, respectively).
Dabigatran etexilate has been approved in Europe and Canada for VTE prevention after elective hip or knee arthroplasty. The 220-mg dose of dabigatran etexilate is recommended for the majority of patients, whereas the 150-mg dose is reserved for patients also taking amiodarone and for those at higher risk for bleeding, such as patients >75 years or with a creatinine clearance <50 mL/minute.

**Oral Factor Xa Inhibitors**

The oral factor Xa inhibitors are small molecules that bind reversibly to the active site of factor Xa. Although numerous agents in this class are under development, those in the most advanced stages are rivaroxaban and apixaban.

**Rivaroxaban.** An active compound with an oral bioavailability of 60% to 80%, rivaroxaban has a rapid onset of action and a half-life of 5 to 9 hours (Table 2). Rivaroxaban has a dual mode of elimination; one third is cleared as unchanged drug via the kidneys, one third is metabolized by the liver via CYP3A4-dependent and CYP3A4-independent pathways with the metabolites then excreted in the feces, and one third is metabolized in the liver with the inactive metabolites then eliminated via the kidneys. Rivaroxaban is a substrate for the transport protein glycoprotein (p-GP), and concomitant administration of potent inhibitors for both p-GP and CYP3A4, such as ketoconazole or ritonavir, is contraindicated because they increase plasma drug levels.²

The phase II Oral Direct Factor Xa Inhibitor (ODIXa) VTE prevention studies established the dose for the phase III RECORD trial program, which evaluated the efficacy and safety of rivaroxaban compared with enoxaparin in >12,000 patients who underwent THA or TKA.²⁻⁹ Tables 5 and 6 outline the design of these trials as well as the primary outcomes. The dose of rivaroxaban in all 4 RECORD trials was 10 mg once daily started 6 to 8 hours after wound closure. The European-approved dose of enoxaparin, 40 mg once daily (with the first dose given the evening before surgery), was used as the comparator in the RECORD 1, RECORD 2, and RECORD 3 trials, whereas the North American-approved dose of enoxaparin (30 mg twice daily starting 12 to 24 hours after surgery) was the comparator in the RECORD 4 trial.¹⁰⁻¹³ The primary efficacy endpoint in all of the trials was total
VTE, a composite of symptomatic or asymptomatic DVT, nonfatal pulmonary embolism, and all-cause mortality.

In the RECORD 1 trial, which included 4541 patients who underwent THA, a 31- to 39-day course of rivaroxaban significantly reduced the incidence of total VTE compared with an equal duration of treatment with enoxaparin (1.1% and 3.7%, respectively; \( P < 0.001 \)).

In the RECORD 2 trial involving 2509 patients who underwent THA, a 31- to 39-day course of rivaroxaban significantly reduced the incidence of total VTE compared with a 10- to 14-day course of enoxaparin followed by 21 to 25 days of placebo (2% and 9.3%, respectively; \( P < 0.001 \)).

In the RECORD 3 trial included 2531 patients who underwent TKA. A 10- to 14-day course of treatment with rivaroxaban significantly reduced the incidence of total VTE compared with an equal duration of treatment with enoxaparin (9.6% and 18.9%, respectively; \( P = 0.012 \)).

In the RECORD 4 trial involving 3148 patients who underwent TKA arthroplasty, a 10- to 14-day course of treatment with rivaroxaban significantly reduced the incidence of total VTE compared with an equal duration of enoxaparin at the higher 30-mg twice-daily dose (6.9% and 10.1%, respectively; \( P < 0.012 \)).

In both the RECORD 2 and RECORD 3 trials, rivaroxaban significant-
ly reduced the incidence of symptomatic VTE compared with enoxaparin.\textsuperscript{11,12} Rivaroxaban did not increase bleeding in any of the trials, but a pooled analysis of the 4 RECORD trials revealed a small but significant increase in major plus clinically relevant nonmajor bleeding with rivaroxaban. On the basis of these results, rivaroxaban has been approved in Europe and Canada for the prevention of VTE in patients undergoing elective hip or knee arthroplasty.

**Apixaban.** Apixaban is absorbed rapidly, and maximal plasma concentrations are achieved 3 hours after oral administration.\textsuperscript{2} The drug is cleared with a terminal half-life of 8 to 15 hours (Table 2). Apixaban is eliminated via multiple pathways, including hepatic metabolism via CYP3A4 and renal and intestinal excretion. Concomitant treatment with potent inhibitors of CYP3A4 is contraindicated in apixaban-treated patients.\textsuperscript{2}

On the basis of the results of a phase II study in patients who underwent TKA, the phase III apixaban for the prevention of thrombosis-related events (ADVANCE) program is comparing a 2.5-mg twice-daily dose of apixaban (started in the morning of the day after surgery) with enoxaparin in patients undergoing TKA or THA. Tables 7 and 8 outline the design of these trials as well as the primary outcomes.

In ADVANCE-1, which involved 3195 patients undergoing TKA, a 12-day course of apixaban had efficacy similar to an equal duration of treatment with enoxaparin (30 mg twice daily) with total VTE rates of 9% and 8.8%, respectively.\textsuperscript{14} Major bleeding rates were 0.7% with apixaban and 1.4% with enoxaparin (P=.053). Despite similar efficacy, apixaban did not meet the prespecified noninferiority goal because the event rates were lower than expected.

The ADVANCE-2 trial, which included 3057 patients undergoing TKA, compared the same apixaban regimen with an equal duration of treatment with enoxaparin at a dose of 40 mg once daily.\textsuperscript{15} In this trial, apixaban significantly reduced total VTE compared with enoxaparin (15% and 24%, respectively; \(P<.001\)) and was associated with a trend for less bleeding (4% and 5.0%, respectively; \(P=.09\)).

**CONCLUSION**

These new oral agents will change the approach to preventing DVT and pulmonary embolism in joint replacement surgery patients. The implementation of these antithrombotic agents will require a team approach among orthopedic surgery, anesthesia, and medical consultants in the care of joint replacement surgery.

**REFERENCES**


Feature Article


