Novel Oral Anticoagulants for VTE Prevention in Orthopedic Surgery: Overview of Phase 3 Trials

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As a result of reading this article, physicians should be able to:

1. Recognize the limitations of currently recommended approaches to thromboprophylaxis in patients undergoing total hip and knee arthroplasty.
2. Compare the efficacy vs risk of various therapeutic options in specific patient populations.
3. Critically review available data for existing therapies and new anticoagulant agents in the prevention of venous thromboembolism in orthopedic surgery.
4. Identify the pharmacokinetic properties that may influence clinical practice.

ABSTRACT
Outpatient use of anticoagulants to prevent venous thromboembolism after total hip or knee arthroplasty may be hampered either by requirements for parenteral administration or high variability and frequent monitoring of anticoagulant activity. Trials of the new oral direct factor Xa inhibitors rivaroxaban and apixaban and the direct thrombin inhibitor dabigatran indicate that they can be administered in fixed doses without monitoring and that they generally have efficacy at least equivalent to enoxaparin, although with potential minor differences in the balance of efficacy vs risk for bleeding. This article reviews the results and pharmacokinetic properties that may influence their use in clinical practice.

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Total knee arthroplasty (TKA) and total hip arthroplasty (THA) are increasingly common orthopedic surgical procedures. Results from a nationwide inpatient survey performed in the United States indicated that during 2004, approximately 225,900 THAs and 431,485 TKAs were performed. This was a 37% increase in primary THAs and a 53% increase in primary TKAs compared with 2000. It is estimated that nearly 600,000 THAs and 1.4 million TKAs will be performed in 2015. Published data also show a projected doubling of THAs and a fourfold increase in TKAs by 2030.

Patients undergoing THA or TKA are at an increased risk for venous thromboembolism (VTE) (deep vein thrombosis [DVT] and pulmonary embolism [PE]). A review of the literature indicates that, without prophylaxis, the incidence of venographically confirmed DVT is 42% to 57% after THA and 41% to 85% after TKA. A review of results from clinical trials suggests that the frequency of VTE has declined over time with refinement of surgical procedures, improvement of prophylaxis, and better overall patient care. This has been demonstrated for warfarin prophylaxis in TKA (but not THA) via a meta-analysis of trial results. Data from the enoxaparin arms of trials in THA in the late 1980s and 1990s showed VTE rates typically in the region of 11% to 20% in various trials vs unfractionated heparin,7 and 13% from the pooled results of comparators with warfarin,7 whereas in the comparator arms of most clinical trials of fondaparinux, ximelagatran, dabigatran, rivaroxaban, and apixaban in the past 10 years, VTE has been detected in approximately 4% to 9% of the patients assigned to enoxaparin.7 In TKA, rates of VTE in the enoxaparin groups have been approximately 25% to 40% in most cases, although in recent comparisons with apixaban and rivaroxaban, lower rates have been observed, in the range of 9% to 24%.24-26

It is important to note that VTE subsequent to either TKA or THA has become a postsurgical complication that occurs outside the hospital in many or even most patients. Results from the Global Orthopaedic Registry indicated that the median lengths of stay for patients undergoing TKA and THA in the United States are 3 and 4 days, respectively. Results from this registry also showed that the mean times to VTE were 21.5 days for THA and 9.7 days for TKA. These results indicate that thromboembolic events following THA or TKA are an outpatient problem and that agents used for prophylaxis against VTE following THA or TKA must be used outside the hospital, where issues that influence patient compliance with prescribed treatment are likely to have increased importance.

**CURRENT APPROACHES TO PROPHYLAXIS AGAINST VTE**

Current guidelines for thromboprophylaxis in patients undergoing elective THA and TKA recommend low-molecular-weight heparin (LMWH) at a standard dose, started 12 hours preoperatively or 12 to 24 hours postoperatively, or 4 to 6 hours postoperatively at half the usual high-risk dose and then increasing to the standard dose the following day. Fondaparinux is also recommended, with a starting dose of 2.5 mg initiated 6 to 24 hours postoperatively. Adjusted-dose vitamin K antagonists started preoperatively or the evening of the surgical day to achieve international normalized ratio (INR) (target, 2.5; range, 2.0-3.0) is also recommended. Thus, while adherence to guidelines for warfarin administration is most often considered in patients receiving long-term or even lifelong treatment (eg, those with atrial fibrillation who are at risk for cerebrovascular accidents), it is also important in the setting of joint arthroplasty.

Low-molecular-weight heparin is used more extensively in Europe than in the United States for prophylaxis against VTE in patients who have undergone THA or TKA.7 This intervention also has important limitations, particularly when used in the outpatient setting. It must be administered parenterally, which requires patient training with associated cost. Low-molecular-weight heparin is also contraindicated in patients with severe renal insufficiency and in those with a history of heparin-induced thrombocytopenia.8 Fondaparinux, a synthetic pentasaccharide factor (F) Xa inhibitor, is also administered parenterally; it is not recommended for use in patients with body weight <50 kg or aged >75 years, and a dosing adjustment is required in patients with severe renal insufficiency.
NEW ORAL ANTICOAGULANTS FOR VTE PROPHYLAXIS

The results summarized in the preceding section suggest that there are 2 major unmet needs for anticoagulation in the orthopedic surgical setting: safety and ease of use.39 The primary safety concern is the risk for major or clinically relevant nonmajor bleeding, which remains the key concern of orthopedic surgeons. Physicians involved in the treatment of patients undergoing THA or TKA also desire a drug that can be administered orally with little or no requirement for anticoagulation monitoring.39

Recent research efforts directed at identification of small-molecule inhibitors of coagulation factors as novel therapies for thrombotic disorders have been particularly successful in developing orally available molecules to directly inhibit the key proteases, FIIa (thrombin) and FXa. Three novel oral anticoagulants, the direct FIIa inhibitor dabigatran and the direct FXa inhibitors rivaroxaban and apixaban, are currently in clinical use or late-stage clinical trials, and others are in phase 2/3 trials.40,41 Rivaroxaban and dabigatran are approved in Europe and Canada for prevention of VTE in patients undergoing THA or TKA, and dabigatran is now approved for stroke prevention in patients with atrial fibrillation in the United States.42-44

This review focuses on clinical results for new agents being developed for prophylaxis against VTE in patients undergoing THA or TKA and which have published full results from phase 3 studies in such patients. Pharmacokinetic and pharmacodynamic properties of new agents that may influence their clinical utility are also briefly considered. With the completion of the phase 3 clinical trial programs for the novel oral anticoagulants dabigatran, rivaroxaban, and apixaban in THA and TKA, and the recent approvals of rivaroxaban and dabigatran, it is timely to review results from pivotal studies of their efficacy and safety.

PHARMACOKINETIC CHARACTERISTICS

Rivaroxaban, apixaban, and dabigatran all have a rapid onset of action after oral administration and dose-proportional pharmacokinetics and pharmacodynamics after single and multiple dosing.45-47 Plasma elimination half-lives are 12 to 14 hours for rivaroxaban, 12 hours for apixaban, and 9 to 13 hours for dabigatran. Rivaroxaban, dabigatran and apixaban have been evaluated in phase 3 trials with a once-daily dose preoperatively, and with twice-daily dosing postoperatively.42,43,44

Other pharmacokinetic characteristics with the potential to influence convenience of use in clinical practice include the fact that a higher proportion of dabigatran (80%) compared with rivaroxaban (66%) or apixaban (25%) is excreted via the kidneys.44 Thus the lower of the 2 available dabigatran doses is recommended in patients with moderate renal impairment and in elderly patients undergoing THA or TKA.43,49,50 The effect of renal impairment on rivaroxaban clearance is moderate. Caution is required in patients who have moderate renal impairment and are concomitantly taking medications that may increase plasma rivaroxaban concentrations.42,51 Rivaroxaban is not recommended and dabigatran is contraindicated in patients with severe renal insufficiency.

There are also differences among new oral anticoagulants with respect to risk for clinically significant drug interactions. Rivaroxaban is not recommended in patients receiving concomitant treatment with strong cytochrome P450 3A4 (CYP3A4) and P-glycoprotein inhibitors and should be used with caution with strong CYP3A4 inducers.42 and the lower dabigatran dose is recommended for patients taking the strong P-glycoprotein inhibitors amiodarone or verapamil.43 Both ketoconazole and diltiazem increase exposure to apixaban by less than two-fold, indicating that apixaban is not a sensitive CYP3A4 substrate.52 Rifampin decreases exposure to apixaban by approximately 50%,53 which suggests that strong inducers of both CYP3A4 and P-glycoprotein should be co-administered with caution.

CLINICAL EFFICACY AND SAFETY FOR VTE PROPHYLAXIS

Overall, although the trials of dabigatran, rivaroxaban, and apixaban had many similarities, it is important to note differences, such as timing for initiation of the study drug and comparators, duration of therapy, and definition of study endpoints (Tables 1, 2).

Apixaban

Apixaban has been evaluated in 3 large-scale studies of patients undergoing orthopedic surgery: 2 in TKA and 1 in THA. In all 3 trials, the primary efficacy outcome was total VTE, defined as the composite of symptomatic DVT and asymptomatic DVT (detected by mandatory venography at the end of the treatment period), confirmed nonfatal PE, and all-cause mortality during the specified treatment period. Efficacy and bleeding results for these studies are summarized in Figure 1.

ADVANCE-1 included 3195 patients undergoing elective TKA who were randomized to 10 to 14 days of treatment with apixaban 2.5 mg twice daily started 12 to 24 hours postoperatively, or 30 mg enoxaparin twice daily started 12 to 24 hours postoperatively (North American regimen). The primary outcome measure occurred in 9% of patients in the apixaban group and 8.8% of patients in the enoxaparin group. Although numerically similar, the data did not meet prespecified noninferiority criteria for the relative risk for apixaban compared with enoxaparin (P=.06 for noninferiority). However, the incidence of VTE events in the enoxaparin group was much lower than expected. Rates of the composite of major VTE (any proximal DVT, nonfatal PE, or VTE-related death) and all-cause death were similar in the 2 groups (2.1% vs 1.6%). Major bleeding occurred in 0.7% of apixaban patients and 1.4% of enoxaparin pa-
The composite of major bleeding and clinically relevant nonmajor bleeding occurred in 2.9% of patients in the apixaban group and 4.3% in the enoxaparin group (P = .03). The safety and efficacy results from ADVANCE-1 prompted the conclusion that apixaban offered effective thromboprophylaxis with lower rates of clinically relevant bleeding compared with enoxaparin.24

ADVANCE-2 included 3057 patients undergoing elective TKA who were randomized to 10 to 14 days of treatment with apixaban 2.5 mg twice daily started 12 to 24 hours postoperatively, or enoxaparin 40 mg once daily started 12 hours preoperatively. The primary efficacy outcome was reported for 14.5% of patients randomized to apixaban and 19.7% of those who were randomized to enoxaparin (P < .001 for noninferiority and for superiority). The incidence of major VTE was also lower with apixaban vs enoxaparin (0.5% vs 1.1%; 1-sided P < .001 for noninferiority and 2-sided P = .01 for superiority). Major bleeding was reported for 0.8% of patients treated with apixaban vs 0.7% of those treated with enoxaparin (P = .54). Major or clinically relevant nonmajor bleeding occurred in 4.8% vs 5.0% of apixaban and enoxaparin patients, respectively (P = .72).16

Thus, results for apixaban support the conclusion that it is at least as effective as LMWH for the prevention of VTE in patients who have undergone THA or TKA and that it is associated with a similar risk for bleeding.

Rivaroxaban

The efficacy and safety of rivaroxaban have been assessed in 2 phase 3 trials of patients undergoing TKA and 2 trials of patients undergoing THA. As with apixaban, the primary efficacy endpoint was total VTE, being the composite of symptomatic and asymptomatic DVT (detected by mandatory venography at the end of the treatment period), nonfatal PE, and all-cause mortality during the specified treatment period. Figure 2 shows a summary of efficacy and bleeding results for patients enrolled in these phase 3 studies.

The RECORD 4 trial enrolled 3148 patients undergoing TKA who were randomized to 10 to 14 days of treatment with ri-
varoxaban 10 mg once daily initiated 6 to 8 hours postoperatively, or enoxaparin 30 mg twice daily initiated 12 to 24 hours postoperatively. The primary efficacy outcome occurred in 6.9% of patients in the rivaroxaban group and in 10.1% of those in the enoxaparin group \( (P=.0118) \). Major VTE occurred in 1.2% of patients with rivaroxaban vs 2.0% with enoxaparin. Overall, 0.7% of patients in the rivaroxaban group and 0.3% of those in the enoxaparin group had major bleeding. The rates of major or clinically relevant nonmajor bleeding were 3.0 vs 2.3%, respectively.26

The RECORD 3 trial enrolled 2531 patients undergoing TKA who were randomized to 10 to 14 days of treatment with rivaroxaban 10 mg once daily initiated 6 to 8 hours postoperatively, or enoxaparin 40 mg once daily beginning 12 hours preoperatively. In this study, the primary efficacy outcome occurred in 9.6% of rivaroxaban patients and in 18.9% of enoxaparin patients \( (P<.001) \). Major VTE occurred in 1.0% vs 2.6% of the rivaroxaban and enoxaparin groups, respectively \( (P=.01) \). Safety results from RECORD 3 indicated that major bleeding occurred in 0.6% of patients in the rivaroxaban group and 0.5% of patients in the enoxaparin group. Major or clinically relevant nonmajor bleeding occurred in 3.3% vs 2.7%, respectively, of patients treated with rivaroxaban or enoxaparin.23

The RECORD 1 trial included 4542 patients undergoing THA who were randomized to 31 to 39 days of treatment with rivaroxaban 10 mg once daily beginning 6 to 8 hours after wound closure, or enoxaparin 40 mg once daily initiated the night before surgery. Results from RECORD 1 indicated that rivaroxaban was more effective than enoxaparin, with the primary endpoint occurring in 1.1% and 3.7% of the rivaroxaban and enoxaparin groups, respectively \( (P<.001) \). Major VTE occurred in 0.2% of patients in the rivaroxaban group compared with 2% of patients in the enoxaparin group \( (P<.001) \). Major bleeding occurred in 0.3% and 0.1% of the rivaroxaban and

### Table 2

**Definitions for Major Bleeding Events**

<table>
<thead>
<tr>
<th><strong>Apixaban</strong></th>
<th><strong>Rivaroxaban</strong></th>
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</thead>
<tbody>
<tr>
<td><strong>ADVANCE-1</strong></td>
<td>Acute, clinically overt bleeding accompanied by 1 or more of the following:</td>
</tr>
<tr>
<td></td>
<td>Decrease in hemoglobin of ( \geq 2 \text{ g/dL} ) over 24 h</td>
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<td></td>
<td>Transfusion of ( \geq 2 ) units of packed red blood cells</td>
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<td></td>
<td>Overt bleeding occurring in at least 1 of the following critical sites:</td>
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<tr>
<td></td>
<td>Intracranial, intraspinal, intraocular (not conjunctiva), pericardial,</td>
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<td></td>
<td>an operated joint and requires reoperation or intervention,</td>
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<td></td>
<td>intramuscular with compartment syndrome, retroperitoneal</td>
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<tr>
<td></td>
<td>Fatal bleeding</td>
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<tr>
<td><strong>ADVANCE-2</strong></td>
<td>As for ADVANCE-1</td>
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<tr>
<td><strong>ADVANCE-3</strong></td>
<td>As for ADVANCE-1</td>
</tr>
<tr>
<td><strong>RECORD 4</strong></td>
<td>Fatal bleeding</td>
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<td></td>
<td>Occurring in a critical organ (eg, retroperitoneal, intracranial,</td>
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<td></td>
<td>intraocular, or intraspinal)</td>
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<td></td>
<td>Necessitated operation</td>
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<tr>
<td></td>
<td>Outside the surgical site and associated with:</td>
</tr>
<tr>
<td></td>
<td>A fall in hemoglobin of ( \geq 2 \text{ g/dL} )</td>
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<tr>
<td></td>
<td>Or required an infusion of ( \geq 2 ) units of blood</td>
</tr>
<tr>
<td><strong>RECORD 3</strong></td>
<td>Fatal bleeding</td>
</tr>
<tr>
<td></td>
<td>Involving a critical organ</td>
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<tr>
<td></td>
<td>Required reoperation</td>
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<tr>
<td></td>
<td>Clinically overt bleeding outside the surgical site associated with:</td>
</tr>
<tr>
<td></td>
<td>A decrease in hemoglobin of ( \geq 2 \text{ g/dL} )</td>
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<tr>
<td></td>
<td>Or requiring infusion of ( \geq 2 ) units of blood</td>
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<tr>
<td><strong>RECORD 1</strong></td>
<td>As for RECORD 3</td>
</tr>
<tr>
<td><strong>RECORD 2</strong></td>
<td>As for RECORD 3</td>
</tr>
<tr>
<td><strong>Dabigatran</strong></td>
<td><strong>RE-MOBILIZE</strong></td>
</tr>
<tr>
<td></td>
<td>Clinically overt bleeding in excess of expected, and associated with a</td>
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<td></td>
<td>fall in hemoglobin of 2 g/mL and/or leading to transfusion of ( \geq 2 ) units</td>
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<tr>
<td></td>
<td>of packed red blood cells or whole blood</td>
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<tr>
<td></td>
<td>Symptomatic retroperitoneal, intracranial, intraocular, or intraspinal</td>
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<tr>
<td></td>
<td>bleeding</td>
</tr>
<tr>
<td></td>
<td>Bleeding requiring treatment cessation and/or operation</td>
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<tr>
<td><strong>RE-MODEL</strong></td>
<td>Clinically overt bleeding associated with a fall in hemoglobin of ( \geq 20 \text{ g/L} )</td>
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<tr>
<td></td>
<td>Clinically overt bleeding leading to transfusion of ( \geq 2 ) units of packed</td>
</tr>
<tr>
<td></td>
<td>red blood cells or whole blood</td>
</tr>
<tr>
<td></td>
<td>Fatal, retroperitoneal, intracranial, intraocular, or intraspinal bleeding</td>
</tr>
<tr>
<td></td>
<td>Bleeding warranting treatment cessation or leading to reoperation</td>
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<tr>
<td><strong>RE-NOVATE</strong></td>
<td>As for REMODEL</td>
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<tr>
<td><strong>RE-NOVATE II</strong></td>
<td>As for REMODEL</td>
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enoxaparin groups, respectively. Major or clinically relevant nonmajor bleeding occurred in 3.2% vs 2.5%, respectively, of the patients in the 2 groups.14

The RECORD 2 trial enrolled 2509 patients undergoing THA who were randomized to rivaroxaban 10 mg once daily for 31 to 39 days initiated postoperatively (as above), or enoxaparin 40 mg once daily beginning the night prior to surgery and reinitiated 6 to 8 hours after wound closure for a duration of 10 to 14 days (ie, shorter than rivaroxaban). In this study, the primary endpoint occurred in 2% and 9.3% of patients in the rivaroxaban and enoxaparin groups, respectively ($P<.0001$); the respective frequencies of major VTE were 0.2% and 2% ($P<.001$). The incidence of any on-treatment bleeding was 6.6% in the rivaroxaban group vs 5.5% in the enoxaparin group. The incidence of major bleeding was <0.1% in each group, and those for major or clinically relevant nonmajor bleeding were 3.4% for rivaroxaban vs 2.8% for enoxaparin.15

A pooled analysis of the 3 trials (RECORD1-3) comparing rivaroxaban with enoxaparin 40 mg daily also found a significantly lower rate of symptomatic VTE and all-cause mortality with rivaroxaban than with enoxaparin and similar rates of major bleeding.54 Similar findings came from a pooled analysis of all 4 trials.55 However, different analyses have shown significantly higher rates of major and clinically relevant nonmajor bleeding with rivaroxaban compared with enoxaparin.56,57

Thus, results from the individual rivaroxaban trials indicated efficacy for VTE prevention superior to that for enoxaparin with similar bleeding risk.

Dabigatran

The safety and efficacy of dabigatran for the prevention of VTE in patients undergoing TKA or THA have been assessed in the RE-MODEL, RE-MOBILIZE, RE-NOVATE, and RE-NOVATE II trials. The primary efficacy outcome in each of these studies was a composite of total VTE (venographic or symptomatic) and all-cause mortality during treatment. Figure 3 shows a summary of efficacy and bleeding results in these studies of dabigatran.

In the RE-MOBILIZE study, 3016 patients undergoing TKA were randomized to 12 to 15 days of treatment with dabigatran 220 mg and 150 mg once daily (initiated with a half dose 6 to 12 hours postoperatively), or the North American regimen of enoxaparin 30 mg twice daily (initiated 12 to 24 hours postoperatively). Dabigatran 220 and 150 mg once daily showed VTE rates of 31.1% and 33.7% and were inferior to enoxaparin (25.3%; $P = .023$ and
Results for the composite of major VTE and VTE-related death did not differ significantly across treatment groups (3.0% and 3.4% for the high and low dabigatran doses, respectively, vs 2.2% for enoxaparin). Rates of major bleeding for the high and low dabigatran doses were each 0.6% vs 1.4% for enoxaparin. The respective frequencies of clinically relevant nonmajor bleeding were 2.5% and 2.2% vs 2.4%.22

The RE-MODEL trial included 2076 patients undergoing TKA who were randomized to 6 to 10 days of treatment with 1 of 2 doses of dabigatran (220 mg and 150 mg once daily, initiated with a half dose 1 to 4 hours postoperatively), or the European regimen of enoxaparin 40 mg subcutaneously once daily (initiated on the evening before surgery). In this trial, the primary efficacy outcome occurred in 36.4% of the dabigatran 220 mg group and 40.5% of the 150 mg group vs 37.7% of the enoxaparin group. Both dabigatran doses were noninferior to enoxaparin. Rates of major VTE or VTE-related death were 2.6% and 3.8% for 220 mg and 150 mg dabigatran vs 3.5% for enoxaparin. Major bleeding rates were 1.5% and 1.3% in the dabigatran 220 and 150 mg groups, respectively, vs 1.3% in the enoxaparin group. Clinically relevant nonmajor bleeding occurred in 5.9% of those in the dabigatran 220 mg group, 6.8% of those in the dabigatran 150 mg group, and 5.3% of those in the enoxaparin group.20

In the RE-NOVATE trial, 3493 patients undergoing THA were randomized to 28 to 35 days of treatment with dabigatran 220 mg or 150 mg once daily (initiated with a half dose 1 to 4 hours postoperatively), or enoxaparin 40 mg once daily (initiated the night before surgery). The primary efficacy outcome was the composite of total VTE (venographic or symptomatic) and death from all causes during treatment. The primary efficacy endpoint occurred in 6% of patients in the dabigatran 220 mg group, 8.6% of patients in the dabigatran 150 mg group, and 6.7% of patients in the enoxaparin group. Both dabigatran doses were noninferior to enoxaparin. The respective values for major VTE or VTE-related death were 3.1%, 4.3%, and 3.9%. There was no significant difference in major bleeding rates with either dose of dabigatran (2.0% for 220 mg and 1.3% for 150 mg) compared with enoxaparin (1.6%). Rates of clinically relevant nonmajor bleeding were 4.2%, 4.7%, and 3.5%, respectively.13

In the RE-NOVATE II trial, 2055 patients undergoing THA were randomized to 28 to 35 days of treatment with dabigatran 220 mg once daily (initiated with a half dose 1 to 4 hours postoperatively) or enoxaparin 40 mg once daily (initiated the night before surgery). The primary efficacy outcome was the composite of total VTE (venographic or symptomatic) and death from all causes during treatment. This endpoint occurred in 7.7% of patients in the dabigatran group and 8.8% of those in the enoxaparin group (P<.001 for noninferiority). The composite of major VTE or VTE-related death occurred less often in the dabigatran group (2.2%) than in the enoxaparin group (4.2%; P=.03). Major bleeding occurred in 1.4% of dabigatran patients vs 0.9% of enoxaparin patients.17

Pooled results of the first 3 dabigatran trials show similar rates of both major VTE/VTE-related mortality and bleeding to those in the enoxaparin comparator groups.58

Thus, results for dabigatran indicate efficacy comparable to that for enoxaparin when dosed according to the European regimen, but not the North American regimen, and similar risk for bleeding.

DISCUSSION

Deep vein thrombosis and PE are major causes of morbidity and mortality after THA and TKA.3 Although patients frequently receive prophylaxis for thromboembolism post-arthroplasty, there is substantial variability in treatment regimens, and physicians may use suboptimal strategies, including failing to continue prophylaxis after hospital discharge due to the
possibility of treatment-associated postoperative bleeding.41,59 This is an important issue because the majority of thromboembolic events occur >4 days postoperatively, after the time when most patients in the United States undergoing THA or TKA have been discharged from the hospital.27,28 New agents have the potential to make anticoagulant treatment easier as they are available for oral administration in fixed doses with no requirement for routine monitoring (largely due to their predictable anticoagulant response and relatively wide therapeutic window) and have short half-lives, a rapid onset of action, and low risk for food and drug interactions.

Even with the new oral agents, bleeding remains an important postoperative consideration in patients receiving prophylaxis. The rates of bleeding associated with apixaban, dabigatran, and rivaroxaban have been demonstrated to be similar to enoxaparin in multiple phase 3 clinical trials. In a prior study of LMWH and graduated compression stockings vs graduated compression stockings alone for 14 days or until discharge in patients who underwent knee surgery, the rate of major bleeding was 2.5% in patients receiving LMWH with compression stockings compared to 2.4% with compression stockings alone. As compression stockings are known not to cause bleeding, these results demonstrate that postoperative bleeding occurs even without the administration of anticoagulants.60 There are a number of patient factors that contribute to an increased risk of major bleeding in patients undergoing THA and TKA. These factors include increased age, renal dysfunction, history of bleeding, recent gastrointestinal bleed, recent hemorrhagic stroke, and the concomitant use of drugs that may cause bleeding, including aspirin and other antithrombotics.3,61

Comparison of newer agents reviewed in this paper is limited by a lack of head-to-head studies. While one might consider evaluation of absolute levels of VTE and bleeding vs historical controls, this approach would also fail to provide useful information. First, the frequency of VTE with a given anticoagulant may vary from one trial to another based on a number of features of study design, including patient risk factors for thromboembolic events, comorbid disease and concomitant medications, anticoagulant treatment regimen (dose and initiation/duration of therapy), and adjudication of both thromboembolic and bleeding events. In addition, the overall rate of postsurgical VTE appears to be declining in patients who have undergone THA or TKA, possibly due to refinement of surgical procedures and better overall care. Meta-analysis of comparator-corrected efficacy results for newer agents has been performed for dabigatran and rivaroxaban vs enoxaparin, but is limited by differences in timing of administration and dosing of the enoxaparin comparator in the studies described.57

Nevertheless, the 3 recent series of trials of apixaban, rivaroxaban, and dabigatran were largely internally consistent in their respective designs and adjudication. This offers some tentative insight into the relative efficacy/safety of prophylaxis regimens. The 2 most common regimens for enoxaparin are 30 mg twice daily starting 12 to 24 hours postoperatively (North American regimen)62 and 40 mg once daily starting 12 hours preoperatively (European regimen).63 In North America, because of the perceived risk of hemorrhage, treatment with enoxaparin is commonly commenced postoperatively, usually not until the morning following surgery.64 The European regimen is based on the premise that DVT is most likely to begin at the time of surgery and that preoperative initiation of prophylaxis is required to minimize the occurrence of these events.65

On theoretical grounds, there are risks and benefits associated with each approach. A postoperative initiation of enoxaparin may result in less bleeding, but there may be reduced protection against VTE, and vice versa for preoperative initiation of prophylaxis. However, the higher total daily dose of enoxaparin used in the North American (postoperative) regimen may compensate for this pattern. In the 3 series of trials reviewed in this article, the North American regimen appears to be more efficacious based on VTE rates assessed on venograms (Figures 1-3), making the new drugs appear better vs the European dose; however, clinically, the rates of symptomatic VTE and VTE-related death do not appear to be significantly different.13,20,22-26

**CONCLUSION**

The new oral anticoagulants appear to fulfill many of the unmet needs for prophylaxis against VTE in patients who are undergoing THA or TKA. Perhaps most importantly, these new drugs are effective, have acceptable safety profiles, and are convenient to use in the outpatient setting during the extended postsurgical period, when most thromboembolic events occur. As data continue to emerge for new anticoagulants, meta-analytic and other approaches may permit more meaningful comparisons and help guide selection from the increasing number of available agents.

**REFERENCES**


