Clinical Experience With Novel Oral Anticoagulants for Thromboprophylaxis After Elective Hip and Knee Arthroplasty

Cory Messerschmidt, Richard J. Friedman

Abstract—Anticoagulant medications help to reduce the risk of thromboembolic events after total hip arthroplasty and total knee arthroplasty. Traditionally, this has been accomplished with medications, such as low–molecular-weight heparin and warfarin. However, these traditional anticoagulants possess a variety of shortcomings that leave much room for improvement. A new class of oral anticoagulants is now available, and present a more convenient option for safe and efficacious thromboprophylaxis in post arthroplasty patients, particularly in the outpatient setting. This review focuses on the direct thrombin inhibitor, dabigatran, and the selective factor Xa inhibitors, rivaroxaban and apixaban, and the clinical data to date about their use in total hip arthroplasty and total knee arthroplasty patients. (Arterioscler Thromb Vasc Biol. 2015;35:771-778. DOI: 10.1161/ATVBAHA.114.303400.)

Key Words: anticoagulant agents ■ pulmonary embolism ■ venous thrombosis

Total hip arthroplasty (THA) and total knee arthroplasty (TKA) are among the most common orthopaedic procedures performed today. In 2010, the number of THA and TKA procedures performed in the United States was 332,000 and 719,000, respectively. These numbers are expected to grow to 572,000 and 3.48 million THA and TKA procedures by 2030.

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Although THA and TKA improve mobility and quality of life, these patients are among those at highest risk for venous thromboembolism (VTE), which includes both deep vein thrombosis (DVT) and pulmonary embolism (PE). Without thromboprophylaxis, the incidence of proximal DVT is 18% to 36% after THA and 5% to 22% after TKA, and incidence of PE is 0.9 to 2.8% after THA and 1.5% to 10% after TKA. The 35-day baseline untreated risk for symptomatic VTE is estimated at 4.3% overall, and the incidence of fatal PE has been found to be as high as 2% after total joint arthroplasty. With increasing numbers of THA and TKA procedures, the number of VTE events is expected to rise.

Aside from fatal PE, other significant long-term complications can arise from VTE events, including post-thrombotic syndrome, chronic pulmonary hypertension, and risk of recurrent VTE events. Post-thrombotic syndrome, which involves pain, swelling, and skin changes in the affected extremity, occurs in 23% to 60% of patients within 2 to 3 years of a episode of DVT, and can be severe in 10% of cases. Approximately 3.8% of patients who sustain a PE are diagnosed with chronic thromboembolic pulmonary hypertension within 2 years. Interestingly, index VTE provoked by surgery carries a much lower relative risk of recurrent VTE in the first year after stopping anticoagulant therapy (about one third) than if attributed to other nonsurgical factors, although risk of recurrence is still present (=1.0%). Furthermore, 10% of patients who experience a VTE event after THA or TKA are readmitted to the hospital within 3 months after the VTE event, resulting in an increasing economic burden.

The risk of VTE events after THA and TKA can be decreased significantly with the use of pharmacological thromboprophylaxis. Low–molecular-weight heparins (LMWHs), vitamin K antagonists (VKAs) such as warfarin, and fondaparinux have reduced the cumulative incidence of symptomatic VTE between 1.7% and 2.3% within 3 months of THA and TKA, respectively.

Important consideration must be given to the timing of most VTE events. The median length of hospital stay for THA or TKA outside the United States is 10 days, whereas in the United States it is 3 days for THA and 4 days for TKA, and getting shorter. Results from the Global Orthopaedic Registry showed that the mean times to a symptomatic VTE event were 21.5 days for THA and 9.7 days for TKA, occurring after the median time to discharge in 75% of THA and 57% of the TKA patients. Thus, with the current trend toward shorter hospital stays, the majority of VTE events occur in the...
Overview of Traditional Anticoagulants

Traditionally, LMWH and VKAs have been the most widely used thromboprophylactic agents after THA and TKA. LMWHs are indirect anticoagulants that target multiple enzymes in both the intrinsic and the extrinsic pathways of the coagulation cascade, binding to antithrombin and enhancing its inhibitory activity against thrombin and factor Xa (FXa).13 Fondaparinux has been shown to be more efficacious than enoxaparin in reducing the incidence of venographic VTE and also has an associated increased risk of bleeding depending on the initial timing of administration after THA and TKA.14

Fondaparinux, another parental anticoagulant, is a synthetic pentasaccharide that mimics the antithrombin-binding sequence of heparin, and functions as an indirect inhibitor of FXa, but not thrombin.13 Fondaparinux has been shown to be more efficacious than enoxaparin in reducing the incidence of venographic VTE and also has an associated increased risk of bleeding depending on the initial timing of administration after surgery.15-16

VKAs have a long track record of use for thromboprophylaxis of THA and TKA patients. Warfarin acts by inhibiting synthesis of vitamin K–dependent clotting factors II, VII, IX, and X, acting on multiple sites in the coagulation cascade.17 Studies have shown that VKAs reduce the incidence of VTE in patients undergoing major orthopedic surgery compared with placebo,18 but are not as effective as parenteral anticoagulants in reducing venographic DVT incidence.12

Limitations of Traditional Anticoagulants

Traditional anticoagulants carry several limitations in patients undergoing THA or TKA. LMWH and fondaparinux are inconvenient in the outpatient setting because of subcutaneous administration. Many patients do not like self-injecting, and administration often requires additional help in the form of patient training and home-care visits, which incur significant cost. In addition, there is risk of heparin-induced thrombocytopenia with LMWHs. Fondaparinux carries additional limitations, as it is not recommended for patients <50 kg or aged >75 years, and those with moderate or severe renal impairment.19

VKAs have a slow onset and offset of action, as well as a narrow therapeutic window, with a target internationalized normalized ratio of 2 to 3. Its complex pharmacodynamics require frequent coagulation monitoring and dose adjustment to achieve therapeutic levels, often using additional resources and causing potential confusion for patients. In addition, there is a propensity for interaction with other drugs and various foods based on their vitamin K content, and its metabolism is vulnerable to numerous genetic polymorphisms. Surgeon compliance with American College of Chest Physicians guidelines reflect the difficulties associated with warfarin administration, with compliance achieved in 82% of patients for start time and duration of prophylaxis, but only 33% of patients when dose intensity was included.10 Other studies have shown that patients taking warfarin for postoperative prophylaxis are often outside the recommended internationalized normalized ratio range (48% below and 10% above the range after hospital discharge), which can increase the risk for either VTE or bleeding.20,21

New Oral Anticoagulants

New anticoagulants should be focused on improving the areas where traditional anticoagulants fall short, whereas providing similar or better efficacy and safety profiles. They should have fixed daily dosing as a result of predictable pharmacokinetics, with no requirement for coagulation monitoring, convenient oral administration, and fewer drug–drug and drug–food interactions.

Currently, there are 3 new oral anticoagulants that have completed phase III clinical trials in patients undergoing THA and TKA. Two of these agents, rivaroxaban and apixaban, are approved for use worldwide for DVT prophylaxis in patients undergoing TKA or THA. Dabigatran does not currently have an indication for VTE prophylaxis in the United States but does in other parts of the world. Use of these medications is not limited to joint replacement surgery; all the 3 are also approved in the United States for treatment of DVT and PE, prophylaxis for DVT and PE recurrence, and stroke prevention in nonvalvular atrial fibrillation.22-24

Dabigatran

Dabigatran etexilate is a potent oral direct thrombin inhibitor. It is a prodrug that is rapidly converted to dabigatran, where it binds to the active site of both free and clot-bound thrombin, inhibiting the conversion of fibrinogen to fibrin.25 Dabigatran...
has low bioavailability (≈6%).26 reaches peak concentration within 2 hours of administration,27 and has a mean-terminal elimination half-life that ranges from 12 to 14 hours in healthy volunteers,27,28 and 14 to 17 hours in patients undergoing orthopaedic surgery.29 Dabigatran etexilate is completely metabolized to dabigatran by microsomal carboxylesterases in the liver, with no cytochrome P450 enzyme metabolism.27 Renal excretion of unchanged dabigatran is the predominant elimination pathway (≈80%).30

**Rivaroxaban**

Rivaroxaban is an oxazolidinone derivative, which functions as a potent oral, direct FXa inhibitor. It binds rapidly and competitively to the active site of both circulating FXa and FXa bound within prothrombinase complex.26 Rivaroxaban is highly basic and has a high bioavailability (≈80%)11 reaching peak concentrations 2 to 4 hours after administration;26 it has a mean-terminal elimination half-life ranging from 5 to 9 hours in healthy subjects, and 10 to 13 hours in elderly subjects.31,32 It is metabolized by the cytochrome P450 (CYP) enzymes (CYP3A4 and CYP2J2), as well as other CYP-independent mechanisms in the liver, and is therefore, contraindicated in severe liver disease.51 Rivaroxaban has a dual mechanism of excretion, with 66% renally excreted (=one half of which is intact drug), and the remainder excreted fecally as unchanged drug.34

**Apixaban**

Apixaban is another potent, oral direct FXa inhibitor. Similar to rivaroxaban, it binds rapidly and competitively to the active site of FXa, diminishing the conversion of prothrombin to thrombin.26 Apixaban has high oral availability (≈52%)35 and is metabolized primarily through cytochrome P450 enzymes (CYP3A4 and CYP3A5), as well as other CYP enzymes to a lesser extent; it is therefore, contraindicated in severe liver disease.36 It reaches peak concentrations within 3 to 4 hours after administration, and has a mean-terminal elimination half-life of 8 to 15 hours in young, healthy subjects.35 Excretion is by multiple routes, with 55% fecal, and only 25% renal.37

**Clinical Trials**

A series of phase III randomized double-blinded clinical trials have looked at both the efficacy and safety of dabigatran, rivaroxaban, and apixaban for thromboprophylaxis in primary outcome measures of composite DVT, nonfatal PE, and all-cause mortality.42 A pooled analysis of the data from these 4 clinical trials confirmed these findings, showing that both the doses of dabigatran were as effective as enoxaparin in reducing the risk of major VTE and VTE-related mortality, with a similar bleeding profile.43

**Rivaroxaban**

The 4 RECORD trials looked at the efficacy and safety of rivaroxaban in thromboprophylaxis after TKA and THA compared with enoxaparin.44-47 RECORD 1 (n=4541) and 2 (n=2509) looked at rivaroxaban in THA patients, whereas RECORD 3 (n=2531) and 4 (n=3148) in TKA patients. Rivaroxaban 10 mg once daily started 6 to 8 hours after wound closure was compared with enoxaparin 40 mg once daily started 12 hours before surgery and restarted 6 to 8 hours after wound closure (RECORD 1, 2, and 3) or enoxaparin 30 mg twice daily started 12 to 24 hours after wound closure (RECORD 4). Duration of treatment was 28 to 35 days for RECORD 1, and 10 to 14 days for RECORD 3 and 4. RECORD 2 incorporated a placebo arm to evaluate extended prophylaxis, with patients receiving either rivaroxaban for 31 to 39 days (with concomitant 10–14 days of subcutaneous placebo) or enoxaparin for 10 to 14 days (with continuation of oral placebo for 21–25 days).

In all the 4 RECORD trials, rivaroxaban demonstrated superior efficacy compared with enoxaparin for the primary outcome measures of composite DVT, nonfatal PE, and all-cause mortality. In addition, RECORD 2 showed that extended
thromboprophylaxis with rivaroxaban was significantly more effective than short-term enoxaparin followed by placebo in prevention of total, major, and symptomatic VTE after THA. There were no significant differences in the incidence of major bleeding, and there were no significant differences in the rates of adverse events, such as cardiovascular events or liver enzyme abnormalities.

A pooled analysis of the 4 RECORD studies (n=12383) showed that rivaroxaban significantly reduced the composite of symptomatic VTE and all-cause mortality when compared with enoxaparin (0.6% versus 1.3%; hazard ratio, 0.42; 95% confidence interval, 0.29–0.63), with similar safety profiles, although there was a trend toward a higher risk of major bleeding and significantly higher risk of clinically relevant bleeding. The RECORD trials are, therefore, the first to ever show a statistically significant decrease in the rate of symptomatic DVT, not just venographic DVT rates. Other meta-analyses have suggested that rivaroxaban was associated with a significant increased risk of bleeding when compared with enoxaparin, despite better efficacy of thromboprophylaxis. However, this may have been influenced by the timing of the initial postoperative dose.

The XAMOS study (n=17701), the only completed phase IV noninterventional study of the new oral anticoagulants to date, assessed the safety and efficacy of rivaroxaban in routine clinical practice in patients undergoing major orthopaedic surgery compared with standard-of-care prophylaxis. Results confirmed the favorable risk-benefit profile seen in the 4 RECORD studies, with a significantly lower incidence of symptomatic VTE between rivaroxaban and standard-of-care prophylaxis (0.65% versus 1.02%; odds ratio, 0.63; 95% confidence interval, 0.45–0.89), with no statistical difference in treatment emergent major bleeding (0.40% versus 0.34%; odds ratio, 1.19; 95% confidence interval, 0.73–1.95).

Apixaban

The 3 ADVANCE trials evaluated the efficacy and safety of apixaban in TKA and THA patients compared with enoxaparin. ADVANCE 1 compared a 10- to 14-day course of apixaban 2.5 mg twice daily with enoxaparin 30 mg twice daily in TKA patients (n=3195), both started 12 to 24 hours after surgery. Results showed a similar efficacy with the composite of total VTE plus all-cause mortality, although prespecified noninferiority statistical criteria were not met because of lower than expected event rates. However, the composite incidence of major and clinically relevant nonmajor bleeding was significantly less with apixaban compared with enoxaparin.

Subsequent ADVANCE 2 and ADVANCE 3 studies compared apixaban 2.5 mg twice daily started 12 to 24 hours after surgery with enoxaparin 40 mg once daily started 12 hours before surgery (±3 hours) and continued after surgery according to the investigator’s standard of care. ADVANCE 2 used a 10- to 14-day course in patients undergoing TKA (n=3057), whereas ADVANCE 3 looked at patients undergoing THA (n=3866) for 35 days. Both the studies showed a significant reduction in total VTE and all-cause mortality in the apixaban groups compared with enoxaparin, with no difference in major and clinically relevant nonmajor bleeding.

Clinical Considerations

Periprocedural Management

Doses of the new oral anticoagulants should be held in advance of surgery or invasive procedures, although they have a quicker clearance time than warfarin. The usual empirical approach involves discontinuation of the anticoagulant before surgery, with the timing of discontinuation dependent on the specific half-life of the drug, the patient’s renal function (CrCl, with prolonged drug half-life as CrCl decreases), and surgical risk of bleeding.

There is no universal consensus about timing of discontinuation, but general recommendation is for discontinuation at least 24 hours before low-risk surgery (≥2–3 half-lives), and 2 to 4 days before high-risk surgery (≥5 half-lives) in patients with appropriate renal function (longer with renal impairment). Similarly, timing of resumption of medications takes into account the same considerations of half-life, renal function, and bleeding risk, with general recommendation for resumption of medications 24 hours after low-risk surgery, and 48 to 72 hours after high-risk surgery (again, longer with renal impairment).

Reversal

There are no specific antidotes available for the new oral anticoagulants, although need for reversal is infrequent if renal function is adequate according to the 2012 Thrombosis and Hemostasis Summit of North America, for most cases of clinically relevant bleeding, supportive care and discontinuation of the anticoagulant is recommended and often sufficient, given their relatively short half-lives.

If oral drug intake is within a couple hours of presentation, oral-activated charcoal offers a low side effect treatment option. Because protein binding is low with dabigatran, it can be dialyzed, and should be considered in patients with impaired renal function. Use of procoagulant reversal agents, such as unactivated and activated prothrombin complex concentrate or recombinant factor VIIa are being investigated for use in severe or life-threatening bleeding, but no consensus has been reached on their use in this setting.

Drug–Drug and Drug–Food Interactions

The new oral anticoagulants have significantly fewer drug–drug interactions compared with warfarin, but there are still potential interactions to be aware of, specifically with inhibitors and inducers of CYP3A4 and P-glycoprotein (P-gp). Dabigatran is a substrate for P-gp, and thus should avoid concurrent use with P-gp inducers (eg, rifampin) and inhibitors (eg, amiodarone, ketoconazole, verapamil, and quinidine).

Both rivaroxaban and apixaban should be avoided in patients taking other strong CYP3A4 and P-gp dual inhibitors, such as azole antifungals (eg, ketoconazole and itraconazole) and protease inhibitors (eg, lopinavir/ritonavir, ritonavir, and indinavir/ritonavir), which may increase risk of bleeding. Conversely, both should be avoided with other strong dual inducers of CYP3A4 and P-gp (eg, carbamazepine, phenytoin, rifampin, and St. John wort), which could result in subtherapeutic concentrations.

In contrast to warfarin, there are no drug–food interactions with the new oral anticoagulants, and therefore, no need...
to alter or monitor diet. In addition, there is no significant increase in major bleeding in comparison with enoxaparin when taken concomitantly with single antiplatelet agents, such as NSAIDs, aspirin or clopidogrel, which may not total joint arthroplasty patients take regularly.46,61

Hepatic/Renal Impairment

Dabigatran, rivaroxaban, and apixaban are all partially cleared renally, thus renal function should be assessed by calculating the CrCl by the Cockcroft–Gault method before initiation of treatment. Dabigatran should not be used in patients with severe renal impairment (CrCl <30 mL/min), and a lower 150 mg dose should be used in those with moderate renal impairment (CrCl=30–50 mL/min). With rivaroxaban, there is no need for dose adjustment with moderate renal impairment (CrCl=30–49 mL/min). Rivaroxaban has not been studied in orthopaedic patients undergoing total joint arthroplasty with CrCl <30 mL/min, but has been approved in stroke and atrial fibrillation in patients with a CrCl=15 to 29 mL/min. Apixaban should be used with caution in those with severe renal impairment (CrCl=15–29 mL/min), and contraindicated when CrCl <15 mL/min.24 Liver disease can alter drug metabolism, as well as coagulation factor synthesis, and anticoagulants must be used with caution in these patients. Dabigatran is not recommended for use in patients with liver enzymes >2× the upper limit of normal.23 Rivaroxaban is not recommended for use in patients with Child–Pugh class B or C hepatic impairment.22 It is recommended that apixaban should be used with caution in patients with mild or moderate hepatic impairment, and avoided with more severe hepatic impairment.24

Clinical Experience To Date

As use of the new oral anticoagulants in THA and TKA patients grows, data are emerging about outcomes in routine clinical practice. Rivaroxaban is the most analyzed in recent cohort studies. A large retrospective cohort from the German ORTHO-TEP registry looked at 5061 consecutive patients receiving either rivaroxaban or LMWH, and showed lower rate of symptomatic VTE (rivaroxaban 2.1% versus LMWH 4.1%; P=0.005) and statistically significant lower rates of major bleeding (rivaroxaban 2.9% versus LMWH 7.0%; P=0.001) with fewer surgical complications (rivaroxaban 1.1% versus LMWH 3.7%; P<0.001). Another large Canadian retrospective cohort (n=24 321) looking at use of rivaroxaban or LMWH on hospital discharge after TKA or THA, found a lower 30-day risk of rehospitalization for VTE (rivaroxaban 0.47% versus LMWH 0.81%; P=0.001), with no difference in hospitalizations for major bleeding (rivaroxaban 0.18% versus LMWH 0.20%; P=0.700).61

Other recent studies have raised concerns about bleeding and wound drainage with the use of rivaroxaban, and may be related to the timing of the first dose. A British retrospective cohort showed a significant increase in return to the operating room with wound complications (rivaroxaban 3.94% versus LMWH 1.8%; P=0.046), whereas another British study found significantly fewer wound complications in the LMWH group versus rivaroxaban (rivaroxaban 3.85% versus LMWH 2.81%; P=0.005), although there were significantly more symptomatic DVTs in the LMWH group (rivaroxaban 0.36% versus LMWH 0.91%; P=0.004). Again, these differences may be related to the timing of the initial postoperative dose. Although published studies gave the initial dose 6 to 8 hours after surgery, most clinicians are uncomfortable with this early dosing, and routinely give the initial postoperative dose 18 to 24 hours postoperatively, usually the morning after surgery.

Clinical data on dabigatran and apixaban is limited to date. A Scandinavian study looking at dabigatran versus enoxaparin found a significant longer duration of wound discharge after drain removal (dabigatran 2.2±2.7 days versus enoxaparin 1.2±1.9 days; P<0.05), as well as significant increase in serous discharge on third and seventh postoperative days for dabigatran versus enoxaparin (P<0.05).66

Current Guidelines

Current evidence-based clinical practice guidelines about thromboprophylaxis in patients undergoing THA and TKA have evolved with increasing consensus. The ninth edition of the American College of Chest Physicians guidelines published in 2012 recommends thromboprophylaxis with anticoagulants for a minimum of 10 to 14 days in patients undergoing THA or TKA (grade 1B), and thromboprophylaxis should be extended in the outpatient period for ≤35 days from the day of surgery (grade 2B). With regard to start time, recommendation is starting either 12 hours or more preoperatively or 12 hours or more postoperatively for patients undergoing THA or TKA, rather than within 4 hours or less preoperatively or 4 hours or less postoperatively (grade 1B).

Acceptable options for anticoagulation now include low-dose unfractionated heparin, LMWH, fondaparinux, VKAs, aspirin, as well as the new oral anticoagulants apixaban, dabigatran, and rivaroxaban, although the use of LMWH is preferred based on its longer clinical track record compared with the new oral agents (grade 2B).3 In 2011, the American Academy of Orthopaedic Surgeons published an updated series of clinical practice guidelines. Their recommendation was for the use of pharmacological agents or compressive devices for VTE prevention in patients undergoing THA or TKA, but could not recommend for or against a specific prophylactic regimen (grade of recommendation: moderate).63 One universally accepted recommendation is that patients do not require routine duplex screening on hospital discharge, as treatment for asymptomatic clots may incur additional and unnecessary risks, as well as no hospital reimbursement for a never event in THA and TKA patients. Also, a negative scan at discharge provides no information about the patients’ condition at any time in the future and, therefore, cannot help to determine who does and does not require prophylaxis and for how long.

Perhaps, most important are the recent changes made to the 2014 Surgical Care Improvement Project measures, which states that patients undergoing THA or TKA receive appropriate prophylaxis within 24 hours before surgery to 24 hours after surgery, with a broadened list of acceptable agents, including the new oral anticoagulants.68 This brings the American College of Chest Physicians and American
Academy of Orthopaedic Surgeons guidelines and the Surgical Care Improvement Project measures into better agreement on VTE prophylaxis. Because hospitals must ensure that they meet Surgical Care Improvement Project measures for VTE prophylaxis to avoid Medicare penalties, the use of new oral anticoagulants is now an acceptable alternative.

Conclusions
The new oral anticoagulants present a promising frontier for thromboprophylaxis after THA and TKA. They improve on many of the shortcomings of traditional anticoagulants. Clinical trial data show that they are safe and efficacious, and convenient to use in the outpatient setting, where most VTE events occur and compliance is an issue. More clinical experience is needed, but as many of the current guidelines now reflect, they are gaining popularity and present another option for VTE prophylaxis after THA and TKA surgery.

Disclosures
None.

References


**Significance**

Thromboembolic events are a significant cause of morbidity and mortality in total hip and knee arthroplasty patients. Fortunately, prophylactic anticoagulation helps to minimize these risks, and the new oral anticoagulants present a convenient option for prophylaxis. Given their recent rise in popularity and use, this review article uniquely summarizes not only the results of the phase III clinical trials but also new data on their use in clinical practice, as well as clinical practice considerations. As clinical data and experience increases, practitioners can better determine which anticoagulants are safe and efficacious for thromboprophylaxis in total hip and knee arthroplasty patients.
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