Impact of venous thromboembolism on clinical management and therapy after hip and knee arthroplasty

William D. Fisher, MD

From the Department of Orthopaedic Surgery, McGill University Health Centre, Montréal, Que.

Correspondence to:
Dr. W.D. Fisher
Division of Orthopaedic Surgery
McGill University Health Centre
1650 Cedar Ave.
Montréal QC H3G 1A4
wfisher@sympatico.ca

Postoperative deep vein thrombosis (DVT) occurs most often in the large veins of the legs in patients undergoing major joint arthroplasty and major surgical procedures. These patients remain at high risk for venous thromboembolic events. In patients undergoing total hip or total knee arthroplasty (THA or TKA, respectively), different patterns of altered venous hemodynamics and hypercoagulability have been found, thus the rate of distal DVT is higher than that of proximal DVT after TKA. In addition, symptomatic venous thromboembolism (VTE) occurs earlier after TKA than THA; however, most of those events occur after hospital discharge. Consequently, extended thromboprophylaxis after discharge should be considered and is particularly important after THA owing to the prolonged risk period for VTE. Evidence-based guideline recommendations for the prevention of VTE in these patients have not been fully implemented. This is partly owing to the limitations of traditional anticoagulants, such as the parenteral route of administration or frequent coagulation monitoring and dose adjustment, as well as concerns about bleeding risks. The introduction of new oral agents (e.g., dabigatran etexilate and rivaroxaban) may facilitate guideline adherence, particularly in the outpatient setting, owing to their oral administration without the need for routine coagulation monitoring. Furthermore, the direct Factor Xa inhibitor rivaroxaban has been shown to be more effective than enoxaparin in preventing VTE.

La thrombose veineuse profonde (TVP) postopératoire affecte le plus souvent les veines de gros calibre des jambes chez des patients qui subissent une arthroplastie ou une intervention chirurgicale majeure. Ces patients demeurent exposés à un risque élevé d'événements thromboemboliques veineux. Chez les patients soumis à une intervention pour prothèse totale de la hanche ou du genou (PTH ou PTG, respectivement), on a observé différents types d'altération de l'hémodynamie veineuse et d'hypercoagulabilité, qui expliqueraient le taux plus élevé de TVP distale que de TVP proximale après la PTG. En outre, la thromboembolie veineuse symptomatique se manifeste plus tôt après la PTG qu'après la PTH; toutefois, ces événements surviennent pour la plupart après le congé hospitalier. Il faut par conséquent, envisager une thromboprophylaxie prolongée après le congé, plus particulièrement dans les cas de PTH, parce que la période durant laquelle les patients risquent de présenter une thromboembolie veineuse est plus longue. Les recommandations formulées dans les lignes directrices factuelles pour la prévention de la thromboembolie veineuse chez ces patients n'ont pas été entièrement mises en œuvre. Cela est attribuable en partie à certains inconvénients des anticoagulants classiques, comme leur voie d'administration parentérale, ou le suivi étroit de l'hémostase et les ajustements posologiques, mais aussi au risque hémorragique. L'avènement de nouveaux agents oraux (p. ex., le dabigatran étexilate et le rivaroxaban) pourrait faciliter l'application des lignes directrices, notamment dans le contexte des soins ambulatoires, parce que ces médicaments s'administrent par voie orale et ne nécessitent pas de suivi régulier de l'hémostase. De plus, l'inhibiteur direct du facteur Xa rivaroxaban s'est révélé plus efficace que l'énoxaparine en prévention de la thromboembolie veineuse.

Deep vein thrombosis (DVT) occurs most often in the large veins of the legs, and it may lead to pulmonary embolism (PE). Venous thromboembolism (VTE), comprising DVT and PE, is one of the leading causes of mortality and morbidity. In the United States, PE causes about 300 000 deaths per year.[1] It is estimated that 12% of the annual deaths occurring in the European Union are associated with VTE.[2] Despite advances in surgical technique

and clinical management, patients undergoing major joint arthroplasty in the lower limbs remain at high risk for VTE. Without thromboprophylaxis, the incidence of venographically detected DVT is 42.0%–57.0%, and that of PE is 0.9%–28.0% after total hip arthroplasty (THA).[3] In patients undergoing total knee arthroplasty (TKA), the risk for VTE is up to 85.0%, and for PE is 1.5%–10.0%.[3]

A failure to prevent VTE may result in hospital readmission or a delayed hospital discharge. It could also lead to long-term morbidity from sequelae of VTE, such as pulmonary hypertension, recurrent thrombosis[4] or post-thrombotic syndrome (a condition that affects at least one-third of the patients who experience DVT[5] and may result in long-term disability). Although the incidence of fatal PE is now less common as a result of routine thromboprophylaxis, symptomatic VTE continues to be reported in patients within 3 months after surgery.[6,7] The data from the Global Orthopaedic Registry of THA and TKA showed that most cases of symptomatic VTE occurred after hospital discharge.[8]

Over the past 30 years, the natural history of VTE after total joint arthroplasty has become better defined.[9] This article provides an overview of the pathogenesis and the natural history of VTE after THA and TKA and compares the different characteristics and their impact on clinical practice. Trends in current thromboprophylaxis are discussed, and new oral anticoagulants (e.g., dabigatran etexilate and rivaroxaban) that may overcome the limitations of conventional agents are presented.

PATHOGENESIS OF VTE

The pathogenesis of VTE is associated with a triad of interdependent factors (Virchow's triad): injury to the vessel wall, hypercoagulability of blood and venous stasis.

During major orthopedic surgery (such as THA and TKA), substantial trauma to the soft tissues and bone is inevitable. Injury to the vascular wall causes raised levels of tissue factor, one of the potent activators of coagulation. Activation of coagulation results in the generation of excessive amounts of thrombin, which then leads to thrombus formation and platelet activation.[10] In addition, mechanical destruction of the bone marrow during these surgical procedures can also cause release of marrow cells and cell fragments into the circulation.[11] The type and extent of surgery may also have different impacts on hemodynamics and thrombosis.[12,13] After THA, the activation of coagulation was reported to continue for more than 5 weeks.[14]

Cessation or a decrease in blood flow may occur during manipulation of the limb during surgery. Distension of the vessel wall as a result of the pooled blood can also cause further endothelial damage and the subsequent activation of coagulation.[15] There is evidence that blood flow is reduced in both legs after joint arthroplasty, mostly on the same side of the body as the operation.[13]

However, different patterns of altered venous hemodynamics have been observed in patients undergoing THA or TKA. After TKA, venous blood flow is temporarily reduced for up to 6 days, whereas it is reduced for more than 6 weeks after THA.[12,13] Moreover, venous flow in the operated leg has been shown to be significantly lower in patients with DVT than in those without DVT.[12] Manipulation of the limb and the use of a tourniquet in patients undergoing TKA also contribute to venous stasis. In addition, postoperative immobilization and swelling of the leg after surgery are among the other reasons contributing to the reduced venous return and thus increase the risk of DVT. Most clinically relevant DVTs occur in the lower extremities.[16]

OVERVIEW OF THE NATURAL HISTORY OF VTE

The location and extent of the thrombus affects prognosis and may also correlate with disease recurrence. Thrombosis in the lower extremities is classified as either proximal to the origin of the popliteal vein below the knee or distal (in the calf) vein thrombosis. Thrombi that occur in association with surgery frequently start in the deep vein of the calf, mostly originating in the valve cusps.[9] Most of these distal DVTs are clinically silent, and more than half of them resolve spontaneously.[17] Symptoms are typically observed when the thrombus extends proximally into the veins of the thigh, from where it is more likely to embolize and result in PE. There is a notable difference in the incidence of distal (mostly asymptomatic) versus proximal (mostly symptomatic) DVTs after THA and TKA. A higher rate (58%) of distal, compared with proximal (14%), DVTs has been reported in patients undergoing TKA.[18] Another study reported that the incidence of distal and proximal DVTs was 47% and 11%, respectively, in patients undergoing TKA compared with 19% and 15%, respectively, in patients undergoing THA.[19]

Although DVTs often begin intraoperatively, as shown in venographic and leg-scanning studies, some appear to start much later, frequently after hospital discharge.[9] Among patients with postdischarge VTE, some may have asymptomatic DVT early after surgery (e.g., within 1 day after TKA), which then extends to involve the proximal veins. Factors that may allow a small, silent thrombus to enlarge or the development of a new thrombus include the prolonged impairment of venous function,[12] sustained hypercoagulability[14] and impairment of the endogenous anticoagulant or fibrinolytic systems.[20,21]

The profile of postoperative VTE also differs with the type of surgical procedure. Using data from the Global Orthopaedic Registry, Warwick and colleagues[8] reported that the mean time to symptomatic VTE was 21.5 days after THA and 9.7 days after TKA. Venous thromboembolism was diagnosed after hospital discharge in about three-quarters of patients who had THA and half of those

who had TKA.[8] These different temporal patterns of symptomatic VTE occurrence after THA and TKA may reflect the differences in their pathogenesis or natural history.[12,14]

CURRENT GUIDELINE RECOMMENDATIONS

The American College of Chest Physicians (ACCP) has published regular guidelines for the prevention of VTE since 1986. The eighth ACCP guidelines in 2008 recommend a minimum of 10 days' prophylaxis for both THA and TKA. In patients undergoing THA, it is recommended that thromboprophylaxis be extended beyond 10 days and up to 35 days after surgery. The ACCP guidelines now also suggest (at a lower level of evidence) extending thromboprophylaxis for up to 35 days after TKA. The recommended thromboprophylactic regimens include low-molecular-weight heparins (LMWHs), the synthetic indirect Factor Xa inhibitor fondaparinux or dose-adjusted vitamin K antagonists (VKAs). The use of acetylsalicylic acid alone is not recommended as the sole method of thromboprophylaxis.[3] Prophylactic regimens of the recommended drugs have been studied extensively in both patients undergoing THA and TKA, and their efficacy in reducing VTE has been demonstrated in a number of randomized controlled trials.[22]

The ACCP guidelines recommend the use of mechanical thromboprophylaxis with intermittent pneumatic compression devices in patients with a high risk of bleeding, with pharmacologic thromboprophylaxis substituted as soon as the risk of bleeding decreases.[3] Mechanical methods increase venous blood flow and/or reduce stasis with the lack of bleeding potential, which is clearly an advantage in these patients. However, these mechanical methods have not been studied in a large enough patient population to determine if there is a reduction in the risk of death or PE.[3]

The American Association of Orthopaedic Surgeons (AAOS) has recently published guidelines on the prevention of fatal PE for patients undergoing THA or TKA. The AAOS guidelines have rejected the use of venographically detected asymptomatic DVT as a valid outcome when assessing the efficacy of thromboprophylaxis in clinical studies, and instead consider fatal PE as the only clinically relevant outcome.[22,23] Both ACCP and AAOS guidelines, however, regard the prevention of fatal PE as the most important goal of thromboprophylaxis.[22,23]

Although widespread implementation of the ACCP guidelines has resulted in significant improvements in the number of high-risk patients receiving appropriate in-hospital prophylaxis, studies have shown there are still opportunities to further improve guideline adherence, particularly in the outpatient setting. Because the risk of VTE extends well beyond the duration of inpatient management, it is crucial that patients continue to receive adequate postdischarge thromboprophylaxis to prevent late-occurring VTE.

WHAT PROPHYLAXIS DO PATIENTS RECEIVE IN ROUTINE PRACTICE?

Almost all patients undergoing TKA or THA now receive some form of prophylaxis for VTE, but there is considerable variation in routine practice, and a large proportion of patients do not receive the prophylaxis recommended in the ACCP guidelines, especially in the outpatient setting. Using data from the Global Orthopaedic Registry, the adherence of clinicians from the United States and 12 other countries to the ACCP guidelines was evaluated. The results provided a picture of prophylaxis practice in patients undergoing TKA and THA in these countries.[24] In patients undergoing THA, overall compliance was 47% in the United States and 62% in other countries. In those undergoing TKA, overall compliance was 61% in the United States and 69% in other countries. Surprisingly, compliance with warfarin use was even worse. In the United States, compliance was 33% in patients undergoing THA and 48% in those undergoing TKA.[24] Although warfarin is administered orally, it has several drawbacks, including the requirement for frequent coagulation monitoring and dose adjustment.

ISSUES IN THE IMPLEMENTATION OF EXTENDED PROPHYLAXIS

Risk of bleeding complications with anticoagulant therapy

Many orthopedic surgeons fear the risk of bleeding associated with the introduction of anticoagulant prophylaxis for VTE prevention.[25,26] This may be partly owing to the time courses of these events. If bleeding occurs, it may occur earlier than VTE and seriously compromise the result of the surgery. By contrast, surgeons may not always witness VTE, especially fatal PE, as these events are likely to occur after hospital discharge.

It is important to note that bleeding events are not unexpected after any surgery, affecting about 2%–3% of patients even when no anticoagulants are used.[27] The reported major bleeding rates (including surgical-site bleeding) with the LMWH enoxaparin in recent randomized trials for the prevention of VTE range from 1.3%–1.6%.[28–30] Furthermore, a meta-analysis of 9 trials of extended-duration (up to 42 days) VTE prophylaxis with heparins after THA or TKA showed that there was no significant increase in major bleeding despite the marked reduction in symptomatic VTE. Only a small 1.2% increase in minor bleeding was observed compared with patients receiving postdischarge placebo or untreated controls.[31] An increase in the rate of postoperative surgical-site bleeding has not been reported with extended thromboprophylaxis in these trials.

One of the important issues is the timing of thromboprophylaxis, preoperative or postoperative initiation, and

how soon after surgery anticoagulants should be started. In one randomized trial, the major bleeding rate was significantly higher with preoperative LMWH (started 2 hr preoperatively) but not with postoperative thromboprophylaxis compared with warfarin.[3] The influence of the timing of the first postoperative dose on bleeding risk has also been reported with fondaparinux. In a meta-analysis of 4 orthopedic studies, the frequency of major bleeding events was significantly higher in the fondaparinux group compared with the enoxaparin group (2.9% v. 1.7%). The rate of major bleeding was higher when the first dose of fondaparinux was given less than 6 hours after wound closure, but delaying the start to 6 hours after surgery reduced the risk of bleeding complications significantly without decreasing its effectiveness.[32] In addition, there was no difference in fatal bleeding, bleeding leading to reoperation or bleeding in a critical organ. As a result, the ACCP guidelines recommend starting 12 hours preoperatively, 12–24 hours postoperatively or 4–6 hours postoperatively at half the standard dose.

A favourable risk–benefit profile has also been demonstrated with extended warfarin prophylaxis in patients undergoing THA. Out-of-hospital extended warfarin therapy (for 4 more wk) was associated with a lower rate of VTE compared with patients who discontinued warfarin postdischarge; the absolute difference in the incidence of venous thromboembolic events was 4.6%. The rate of major bleeding in patients receiving extended warfarin was 0.5%, compared with none in the control group.[33]

Taken together, extended prophylaxis with anticoagulants (particularly in patients undergoing THA) has a favourable risk–benefit profile, without a significant increase in major bleeding events (including surgical-site bleeding), if the dosage, starting time and treatment duration are appropriate.

Other potential barriers

The asymptomatic nature of many thrombi may also contribute to the underutilization of appropriate thromboprophylaxis. Owing to patients' short hospital stay, surgeons may not be aware of the true incidence of VTE because the mean time for the development of symptomatic VTE after THA (21.5 d) and TKA (9.7 d)[8] is well beyond the length of stay in hospital after surgery (3–4 d in the United States).[24] Therefore, DVT may progress to a fatal PE some time after hospital discharge. The risk of fatal PE remains for several months after surgery; autopsy studies indicate that fatal PE is often only a postmortem diagnosis.[34]

The limitations of conventional anticoagulants may also contribute to the lack of utilization of extended prophylaxis regimens. These include the parenteral route of administration with the LMWHs and fondaparinux, which can be problematic for patients in the long term and for home use. Some discharged patients cannot or will not perform self-injection, resulting in the need for home visits by health care professionals for up to 20% of patients. The use of VKAs (e.g., warfarin, particularly in the United States) is associated with many drawbacks, particularly their variable anticoagulation response, numerous food–drug and drug–drug interactions and genetic variations that necessitate frequent coagulation monitoring and dose adjustment.

NEW ORAL AGENTS FOR THE PREVENTION OF VENOUS THROMBOEMBOLISM AFTER TOTAL HIP AND TOTAL KNEE ARTHROPLASTY

There has been a drive to develop new oral agents that directly target specific factors in the coagulation cascade in an attempt to overcome some of the drawbacks with the traditional agents. These include the direct thrombin inhibitors (e.g., dabigatran etexilate) and direct Factor Xa inhibitors (e.g., rivaroxaban). Each is orally administered and does not require routine coagulation monitoring. Other new agents (e.g., apixaban, edoxaban, YM150 and betrixaban) are at various stages of clinical development, and some have shown promise in phase-II and -III trials (Table 1).

Dabigatran etexilate

Dabigatran etexilate is a new oral direct thrombin inhibitor. Because the pharmacokinetic profile (e.g., plasma concentration) of dabigatran etexilate is not substantially altered by age, sex or body weight, a fixed dose of dabigatran etexilate can be used in most patients.[35–37] However, in patients with moderate renal impairment and in elderly patients (> 75 yr), a lower daily dose (i.e., 150 mg instead of 220 mg) is recommended. Dabigatran etexilate is contraindicated in patients with severe renal impairment (creatinine clearance < 0.50 mL/s).[37] Its efficacy and safety in thromboprophylaxis after TKA and THA have been evaluated in 4 large, double-blind, industry-sponsored, randomized phase-III trials.[28–30,38] In all these trials, dabigatran etexilate at doses of 150 mg or 220 mg once daily (220 mg once daily in the RE-NOVATE II trial[38]), starting with a half-dose 1–4 hours postoperatively, was compared with subcutaneous enoxaparin. The primary efficacy outcome was total VTE (a composite of venographically detected or symptomatic DVT and/or symptomatic PE and all-cause mortality). The primary safety outcome was the occurrence of bleeding events during treatment. Major bleeding events were defined as fatal, retroperitoneal, intracranial, intraocular or intraspinal bleeding; bleeding warranting treatment cessation or leading to reoperation; clinically overt bleeding (including surgical-site bleeding) associated with a 20 g/L or more fall in hemoglobin; or clinically overt bleeding leading to a transfusion of 2 of more units of packed red blood cells or whole blood.

In the RE-NOVATE trial[28] (patients undergoing THA with a duration of prophylaxis of 28–35 d) and the

RE-MODEL trial[29] (patients undergoing TKA with a duration of prophylaxis of 6–10 d), both doses of dabigatran etexilate (starting 1–4 hr after surgery) were as effective as 40 mg of enoxaparin once daily for the primary efficacy outcome. Similar rates of major VTE (a composite of proximal DVT and PE) and VTE-related death were observed between the dabigatran etexilate and enoxaparin groups. The RE-NOVATE II trial compared dabigatran etexilate (220 mg) with enoxaparin (40 mg) once daily (treatment duration 28–35 d) in patients undergoing THA.[38] The results showed that dabigatran etexilate was as effective as enoxaparin for the primary efficacy outcome and was more effective than enoxaparin for the prevention of major VTE, with a relative risk (RR) reduction of 46%.

The rate of major bleeding was not statistically significant between the 2 groups.[38] However, in the RE-MOBILIZE trial in patients undergoing TKA (duration of prophylaxis 12–15 d), both doses of dabigatran etexilate (starting 6–12 hr after surgery) were not as effective as enoxaparin (30 mg twice daily) for the primary efficacy outcome,[30] possibly owing to the higher dose of enoxaparin (30 mg twice daily), and the later starting time with dabigatran compared with the RE-MODEL trial. In all 3 trials, dabigatran etexilate had a similar safety profile to enoxaparin.

A meta-analysis of the RE-MODEL and RE-NOVATE trials combined (2-trial analysis), and also including the RE-MOBILIZE trial (3-trial analysis), did not find any significant differences between dabigatran and enoxaparin in any of the outcomes analyzed, either in the 2- or 3-trial analysis.[39] This meta-analysis of RE-MODEL and RE-NOVATE supports the conclusions of the individual trials that a 220 mg dose of dabigatran etexilate once daily is as effective as 40 mg of enoxaparin once daily and has a similar safety profile.

Rivaroxaban

Rivaroxaban is an oral direct Factor Xa inhibitor and has been found to have predictable pharmacokinetics and pharmacodynamics. Because age, sex, body weight and mild-to-moderate renal impairment have had no clinically relevant influence on the pharmacokinetic and pharmacodynamic profiles of rivaroxaban, it can be used at a fixed dose (e.g., 10 mg once daily) with no need for routine coagulation monitoring or dose adjustment.[40–44] Unlike warfarin, it has a low propensity for food–drug or drug–drug interactions.

The RECORD program comprised 4 industry-sponsored phase-III studies investigating the efficacy and safety of rivaroxaban (10 mg once daily beginning 6–8 hr after surgery) in patients undergoing THA and TKA.[45–48] The primary efficacy outcome was total VTE (composite of DVT, nonfatal PE and all-cause mortality). The secondary efficacy outcome was the incidence of major VTE (composite of proximal DVT, nonfatal PE or death from PE). The primary safety outcome was the incidence of major bleeding events, defined as bleeding that was fatal, bleeding into a critical organ, bleeding requiring reoperation, clinically overt extrasurgical-site (which is different from the definition used for dabigatran etexilate studies) bleeding associated with a fall in hemoglobin of at least 20 g/L, or requiring a transfusion of 2 or more units of blood. Clinically relevant nonmajor bleeding, the composite of surgical-site bleeding and excessive wound hematoma (hemorrhagic wound complications), and other nonmajor bleeding events were among the other safety outcomes measured.

Consistent with previous studies showing the benefit of extended thromboprophylaxis in patients undergoing THA,[31] the RECORD2 trial demonstrated that extended

Table 1. Summary of clinical studies of new oral anticoagulant agents in the prevention of venous thromboembolism after major orthopedic surgery					
Study	Phase	Surgery	Dosing	Comparator(s)	Status
Dabigatran etexilate*					
RE-NOVATE	III	THA	150 and 220 mg od	Enoxaparin	Completed
RE-MODEL	III	TKA	150 and 220 mg od	Enoxaparin	Completed
RE-MOBILIZE	III	TKA	150 and 220 mg od	Enoxaparin‡	Completed
RE-NOVATE II	III	THA	220 mg od	Enoxaparin	Completed
Rivaroxaban†					
RECORD1	III	THA	10 mg od	Enoxaparin	Completed
RECORD2	III	THA	10 mg od	Enoxaparin	Completed
RECORD3	III	TKA	10 mg od	Enoxaparin	Completed
RECORD4	III	TKA	10 mg od	Enoxaparin‡	Completed
Apixaban					
ADVANCE-1 (NCT00371683)	III	TKA	2.5 mg bid	Enoxaparin‡	Completed
ADVANCE-2 (NCT00452530)	III	TKA	2.5 mg bid	Enoxaparin	Completed
ADVANCE-3 (NCT00423319)	III	THA	2.5 mg bid	Enoxaparin	Completed
YM150					
ONYX	II	THA	3–60 mg od	Enoxaparin	Completed
ONYX-2	II	THA	5–120 mg od	Enoxaparin	Completed
PEARL-1 (NCT00408239)	II	TKA	Escalating doses (bid or od)	Enoxaparin	Completed
PEARL-2 (NCT00595426)	II	TKA	bid or od	Warfarin	Completed
ONYX-3 (NCT00902928)	II/III	THA	bid or od	Enoxaparin	Ongoing
Edoxaban (DU-176b)					
NCT00107900	II	THA	Dose ranging	—	Completed
NCT00398216	II	THA	Dose ranging	Dalteparin	Completed
Betrixaban					
EXPERT	II	TKA	15 or 40 mg od	Enoxaparin‡	Completed

bid = twice daily; od = once daily; THA = total hip arthroplasty; TKA = total knee arthroplasty; VTE = venous thromboembolism.
*Dabigatran etexilate was approved in the European Union and Canada for the prevention of VTE after THA and TKA in 2008.
†Rivaroxaban was approved in the European Union, Canada and several other countries for the prevention of VTE after THA and TKA in 2008.
‡Enoxaparin 30 mg bid.
Source: www.clinicaltrials.gov.

prophylaxis with rivaroxaban (31–39 d after surgery) was significantly more effective than short-duration prophylaxis with enoxaparin (40 mg once daily for 10–14 d) followed by placebo. The RR reduction was 79% for total VTE, 88% for major VTE and 80% for symptomatic VTE.[46] The RECORD1 trial showed that the rivaroxaban regimen was significantly more effective than the enoxaparin regimen (40 mg once daily) in reducing total VTE and major VTE (RR reduction 70% and 88%, respectively) in patients undergoing THA with a treatment duration of 31–39 days.[45]

The efficacy and safety of rivaroxaban for the prevention of VTE have also been investigated in patients undergoing TKA. In the RECORD3 trial, the rivaroxaban regimen was significantly more effective than the enoxaparin regimen (40 mg once daily beginning preoperatively and continuing for 10–14 d after surgery). The RR reduction was 49% for total, 62% for major and 66% for symptomatic VTE (all significant reductions).[47] In the RECORD4 trial, however, the rivaroxaban regimen only showed significantly better efficacy than the enoxaparin regimen (30 mg twice daily starting postoperatively for a duration of 10–14 d) in reducing total VTE (RR reduction 31%).[48]

In all 4 RECORD studies, there was no significant difference in the incidence of major or clinically relevant nonmajor bleeding or hemorrhagic wound complications between the rivaroxaban and the enoxaparin regimens.

A prespecified pooled analysis of the 4 RECORD studies showed that rivaroxaban regimens significantly reduced the incidence of clinically important symptomatic VTE and death compared with enoxaparin regimens. The analysis also showed that there was no significant difference between the 2 groups in the rates of treatment-emergent major bleeding or surgical complications. However, the composite of major and clinically relevant nonmajor bleeding rates was significantly higher for the rivaroxaban regimens than for the enoxaparin regimens (3.19% v. 2.55%) for the total treatment duration pool (planned treatment period 31–39 d for THA and 10–14 d for TKA).[49] This difference appears to be driven primarily by clinically relevant nonmajor bleeding events. In addition, the inclusion of the placebo phase in the RECORD2 trial (during which patients in the rivaroxaban group continued to receive active medication, whereas those in the enoxaparin group received only placebo) must be taken into account. Importantly, the incidence of observed surgical adverse events (postprocedural infection, postoperative wound infection, incision-site hemorrhage, operative hemorrhage, wound dehiscence, hemarthrosis) was not different between the 2 groups.[50]

Discussion

Although the high risk of VTE in patients undergoing major orthopedic surgery is well recognized, understanding the pathogenesis and the natural history of VTE is essential for the optimal prevention and management of these events. Different patterns of altered venous hemodynamics and hypercoagulability after THA and TKA may contribute to the different characteristics of thrombus formation after surgery in these patients. Although most early DVTs start in the calf and are clinically silent, there is evidence that (in the absence of treatment) up to one-quarter of isolated distal DVTs extend to involve the proximal veins, where they are more likely to be symptomatic and increase the risk of PE.[9] A higher incidence of distal DVT has been found after TKA compared with THA.[3,18,19] Moreover, symptomatic VTE occurs about 11 days sooner after TKA than THA, with about one-half and two-thirds of the events being diagnosed after hospital discharge in patients who had TKA and THA, respectively. Thus, the differences in the pathogenesis and characteristics of VTE after THA and TKA should be reflected in their clinical management, such that a shorter duration (ACCP recommendation of 10 d) of thromboprophylaxis may be sufficient for patients undergoing TKA, whereas extended prophylaxis after THA is particularly important owing to the prolonged risk for VTE. With the increasingly shorter hospital stays after THA and TKA (currently 3–4 d in the United States),[24] it has become clear that thromboprophylaxis must be continued at home or in a rehabilitation centre after hospital discharge. Patients who received postdischarge extended prophylaxis (up to 42 d) had a significantly lower incidence of symptomatic VTE compared with patients who received postdischarge placebo or untreated controls, although the absolute risk reduction was greater after THA (1.4% v. 4.3%) than TKA (1.0% v. 1.4%), reflecting the difference in the pathogenesis of the thromboembolic events after these 2 surgical procedures.[31] The RECORD2 study with rivaroxaban provided further evidence for the benefit of extended versus short-term prophylaxis in patients undergoing THA and showed a significant reduction in the incidence of major, symptomatic and total VTE without any significant increase in major bleeding or surgical-site bleeding and excessive wound hematoma or other clinically relevant nonmajor bleeding.[46]

The limitations of conventional agents (e.g., parenteral administration, or periodic coagulation monitoring and dose adjustment) are among the potential barriers to the implementation of guideline recommendations for the prevention of VTE. With the advent of new oral anticoagulants (e.g., dabigatran etexilate, rivaroxaban), continuing out-of-hospital thromboprophylaxis for durations recommended in the guidelines should be easier owing to their oral route of administration without the need for routine coagulation monitoring. Moreover, rivaroxaban regimens have been shown to be more effective than enoxaparin regimens for the prevention of VTE after both THA and TKA, with no significant difference in the incidence of major bleeding or surgical adverse events. Thus, rivaroxaban

could potentially improve the quality and reliability of post-operative patient care and overall clinical outcomes.

References

1. Heit JA, Cohen AT, Anderson FA, et al. Estimated annual number of incident and recurrent, non-fatal and fatal venous thromboembolism (VTE) events in the US [abstract]. *Blood* 2005;106:267A.

2. Cohen AT, Agnelli G, Anderson FA, et al. Venous thromboembolism (VTE) in Europe. The number of VTE events and associated morbidity and mortality. *Thromb Haemost* 2007;98:756-64.

3. Geerts WH, Bergqvist D, Pineo GF, et al. Prevention of venous thromboembolism: American College of Chest Physicians evidence-based clinical practice guidelines (8th edition). *Chest* 2008;133(6 Suppl):381S-453S.

4. Zhu T, Martinez I, Emmerich J. Venous thromboembolism: risk factors for recurrence. *Arterioscler Thromb Vasc Biol* 2009;29:298-310.

5. Kahn SR. Frequency and determinants of the postthrombotic syndrome after venous thromboembolism. *Curr Opin Pulm Med* 2006;12: 299-303.

6. Geerts WH, Pineo GF, Heit JA, et al. Prevention of venous thromboembolism: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest* 2004;126:338S-400S.

7. White RH, Zhou H, Romano PS. Incidence of symptomatic venous thromboembolism after different elective or urgent surgical procedures. *Thromb Haemost* 2003;90:446-55.

8. Warwick D, Friedman RJ, Agnelli G, et al. Insufficient duration of venous thromboembolism prophylaxis after total hip or knee replacement when compared with the time course of thromboembolic events: findings from the Global Orthopaedic Registry. *J Bone Joint Surg Br* 2007;89:799-807.

9. Kearon C. Natural history of venous thromboembolism. *Circulation* 2003;107:I22-30.

10. Mann KG, Brummel K, Butenas S. What is all that thrombin for? *J Thromb Haemost* 2003;1:1504-14.

11. Dahl OE. Mechanisms of hypercoagulability. *Thromb Haemost* 1999; 82:902-6.

12. McNally MA, Mollan RA. Total hip replacement, lower limb blood flow and venous thrombogenesis. *J Bone Joint Surg Br* 1993;75:640-4.

13. McNally MA, Bahadur R, Cooke EA, et al. Venous haemodynamics in both legs after total knee replacement. *J Bone Joint Surg Br* 1997; 79:633-7.

14. Dahl OE, Aspelin T, Arnesen H, et al. Increased activation of coagulation and formation of late deep venous thrombosis following discontinuation of thromboprophylaxis after hip replacement surgery. *Thromb Res* 1995;80:299-306.

15. Kroegel C, Reissig A. Principle mechanisms underlying venous thromboembolism: epidemiology, risk factors, pathophysiology and pathogenesis. *Respiration* 2003;70:7-30.

16. Spencer FA, Emery C, Lessard D, et al. The Worcester Venous Thromboembolism study: a population-based study of the clinical epidemiology of venous thromboembolism. *J Gen Intern Med* 2006; 21:722-7.

17. Kim YH, Oh SH, Kim JS. Incidence and natural history of deep-vein thrombosis after total hip arthroplasty. A prospective and randomised clinical study. *J Bone Joint Surg Br* 2003;85:661-5.

18. Stulberg BN, Insall JN, Williams GW, et al. Deep-vein thrombosis following total knee replacement. An analysis of six hundred and thirty-eight arthroplasties. *J Bone Joint Surg Am* 1984;66:194-201.

19. Cordell-Smith JA, Williams SC, Harper WM, et al. Lower limb arthroplasty complicated by deep venous thrombosis. Prevalence and subjective outcome. *J Bone Joint Surg Br* 2004;86:99-101.

20. Lindahl TL, Lundahl TH, Nilsson L, et al. APC-resistance is a risk factor for postoperative thromboembolism in elective replacement of the hip or knee — a prospective study. *Thromb Haemost* 1999;81:18-21.

21. Meltzer ME, Doggen CJ, de Groot PG, et al. The impact of the fibrinolytic system on the risk of venous and arterial thrombosis. *Semin Thromb Hemost* 2009;35:468-77.

22. Eikelboom JW, Karthikeyan G, Fagel N, et al. American Association of Orthopedic Surgeons and American College of Chest Physicians guidelines for venous thromboembolism prevention in hip and knee arthroplasty differ: What are the implications for clinicians and patients? *Chest* 2009;135:513-20.

23. American Academy of Orthopaedic Surgeons (AAOS). *American Academy of Orthopaedic Surgeons clinical guideline on prevention of symptomatic pulmonary embolism in patients undergoing total hip or knee arthroplasty.* Rosemont (IL): AAOS; 2007. Available: www aaos org/Research /guidelines/PE_guideline pdf (accessed 2009 Jun. 13).

24. Friedman RJ, Gallus AS, Cushner FD, et al. Physician compliance with guidelines for deep-vein thrombosis prevention in total hip and knee arthroplasty. *Curr Med Res Opin* 2008;24:87-97.

25. Fisher WD, Turpie AG. Outpatient thromboprophylaxis after hip or knee surgery: discrepancies and concerns. *CMAJ* 2008;178:1571-2.

26. Kakkar AK, Davidson BL, Haas SK. Compliance with recommended prophylaxis for venous thromboembolism: improving the use and rate of uptake of clinical practice guidelines. *J Thromb Haemost* 2004; 2:221-7.

27. Levine MN, Gent M, Hirsh J, et al. Ardeparin (low-molecular-weight heparin) vs graduated compression stockings for the prevention of venous thromboembolism. A randomized trial in patients undergoing knee surgery. *Arch Intern Med* 1996;156:851-6.

28. Eriksson BI, Dahl OE, Rosencher N, et al. Dabigatran etexilate versus enoxaparin for prevention of venous thromboembolism after total hip replacement: a randomised, double-blind, non-inferiority trial. *Lancet* 2007;370:949-56.

29. Eriksson BI, Dahl OE, Rosencher N, et al. Oral dabigatran etexilate vs. subcutaneous enoxaparin for the prevention of venous thromboembolism after total knee replacement: the RE-MODEL randomized trial. *J Thromb Haemost* 2007;5:2178-85.

30. RE-MOBILIZE Writing Committee; Ginsberg JS, Davidson BL, Comp PC, et al. The oral thrombin inhibitor dabigatran etexilate vs the North American enoxaparin regimen for the prevention of venous thromboembolism after knee arthroplasty surgery. *J Arthroplasty* 2009;24:1-9.

31. Eikelboom JW, Quinlan DJ, Douketis JD. Extended-duration prophylaxis against venous thromboembolism after total hip or knee replacement: a meta-analysis of the randomised trials. *Lancet* 2001; 358:9-15.

32. Turpie AG, Bauer KA, Eriksson BI, et al. Fondaparinux vs enoxaparin for the prevention of venous thromboembolism in major orthopedic surgery: a meta-analysis of 4 randomized double-blind studies. *Arch Intern Med* 2002;162:1833-40.

33. Prandoni P, Bruchi O, Sabbion P, et al. Prolonged thromboprophylaxis with oral anticoagulants after total hip arthroplasty: a prospective controlled randomized study. *Arch Intern Med* 2002;162:1966-71.

34. Karwinski B, Svendsen E. Comparison of clinical and postmortem diagnosis of pulmonary embolism. *J Clin Pathol* 1989;42:135-9.

35. Stangier J, Rathgen K, Stahle H, et al. The pharmacokinetics, pharmacodynamics and tolerability of dabigatran etexilate, a new oral direct thrombin inhibitor, in healthy male subjects. *Br J Clin Pharmacol* 2007;64:292-303.

36. Stangier J, Stähle H, Rathgen K, et al. Pharmacokinetics and pharmacodynamics of the direct oral thrombin inhibitor dabigatran in healthy elderly subjects. *Clin Pharmacokinet* 2008;47:47-59.

37. *Pradaxa® summary of product characteristics*. Germany: Boehringer Ingelheim International GmbH; 2008. Available: http://vte.pradaxa .com/content/dam/internet/pm/vte/com_EN/documents/Pradaxa _SPC_EMEA.pdf (accessed 2011 June 17).

38. Eriksson BI, Dahl OE, Huo MH, et al. Oral dabigatran versus enoxaparin for thromboprohylaxis after primary total hip arthroplasty (RE-NOVATE II). *Throm Haemost* 2011;105:721-9.

39. Wolowacz SE, Roskell NS, Plumb JM, et al. Efficacy and safety of dabigatran etexilate for the prevention of venous thromboembolism following total hip or knee arthroplasty. A meta-analysis. *Thromb Haemost* 2009;101:77-85.

40. *Xarelto® summary of product characteristics*. Berlin (Germany): Bayer Schering Pharma 2009. Available: www.xarelto.com/html/downloads /Xarelto_Summary_of_Product_Characteristics_May2009.pdf (accessed 2010 Feb. 15).

41. Kubitza D, Becka M, Voith B, et al. Safety, pharmacodynamics, and pharmacokinetics of single doses of BAY 59-7939, an oral, direct factor Xa inhibitor. *Clin Pharmacol Ther* 2005;78:412-21.

42. Mueck W, Becka M, Kubitza D, et al. Population model of the pharmacokinetics and pharmacodynamics of rivaroxaban — an oral, direct Factor Xa inhibitor — in healthy subjects. *Int J Clin Pharmacol Ther* 2007;45:335-44.

43. Mueck W, Eriksson BI, Bauer KA, et al. Population pharmacokinetics and pharmacodynamics of rivaroxaban — an oral, direct factor Xa inhibitor — in patients undergoing major orthopaedic surgery. *Clin Pharmacokinet* 2008;47:203-16.

44. Mueck W, Borris LC, Dahl OE, et al. Population pharmacokinetics and pharmacodynamics of once- and twice-daily rivaroxaban for the prevention of venous thromboembolism in patients undergoing total hip replacement. *Thromb Haemost* 2008;100:453-61.

45. Eriksson BI, Borris LC, Friedman RJ, et al. Rivaroxaban versus enoxaparin for thromboprophylaxis after hip arthroplasty. *N Engl J Med* 2008;358:2765-75.

46. Kakkar AK, Brenner B, Dahl OE, et al. Extended duration rivaroxaban versus short-term enoxaparin for the prevention of venous thromboembolism after total hip arthroplasty: a double-blind, randomised controlled trial. *Lancet* 2008;372:31-9.

47. Lassen MR, Ageno W, Borris LC, et al. Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty. *N Engl J Med* 2008;358:2776-86.

48. Turpie AGG, Lassen MR, Davidson BL, et al. Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty (RECORD4): a randomised trial. *Lancet* 2009;373:1673-80.

49. Turpie AGG, Lassen MR, Kakkar AK, et al. A pooled analysis of four pivotal studies of rivaroxaban for the prevention of venous thromboembolism after orthopaedic surgery: effect on symptomatic venous thromboembolism and death, and bleeding [abstract]. *Haematologica* 2009;94(Suppl 2):212.

50. Turpie AGG, Lassen MR, Eriksson BI, et al. Rivaroxaban for the prevention of venous thromboembolism after hip or knee arthroplasty. *Thromb Haemost* 2011;105:444-53.