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Rivaroxaban and dabigatran etexilate: two new oral anticoagulants for extended postoperative prevention of venous thromboembolism after elective total hip arthroplasty

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Abstract Extended thromboprophylaxis is vital in patients undergoing total hip arthroplasty (THA) because of the prolonged risk of venous thromboembolism (VTE). Despite evidence that extended prophylaxis can reduce the incidence of symptomatic VTE in this high-risk patient population and the evidence-based guideline recommendations, a large proportion of patients still do not receive an adequate duration of thromboprophylaxis. This is partly due to the limitations of conventional anticoagulants, such as the subcutaneous route of administration or the requirement for routine coagulation monitoring and dose adjustment. New oral anticoagulants (such as the direct thrombin inhibitor dabigatran etexilate and the Factor Xa inhibitor rivaroxaban) could address the current unmet need. Phase III clinical studies in VTE prevention in patients undergoing THA and total knee arthroplasty (TKA) showed that dabigatran etexilate was non-inferior to the EU regimen of enoxaparin, but did not achieve non-inferiority to the US regimen of enoxaparin. In contrast, rivaroxaban demonstrated superiority to both enoxaparin regimens for the prevention of VTE after THA and TKA, without a significant increase in major bleeding rates. Their convenient, once-daily, fixed dosing, with no need for routine coagulation monitoring, could facilitate adherence to evidence-based guideline recommendations of extended thromboprophylaxis after THA.

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Introduction

In parallel with the growing elderly population, the rate of elective total hip arthroplasty (THA) is also increasing, particularly in developed countries. In 2005, the number of THAs per year in USA was approximately 250,000, and it is estimated that this will increase by 174% to 572,000 by 2030 [1]. In England and Wales, there were approximately 80,000 THAs in 2007, and the demand for THAs is predicted to increase.

It has been reported that venous thromboembolism (VTE) is the most frequent cause of emergency re-admission after THA surgery [2]. Without thromboprophylaxis, the incidence of venographic deep vein thrombosis (DVT) is 40–60% [3, 4]. Studies have shown that asymptomatic proximal DVT is associated with increased mortality [5], indicating that asymptomatic events are also clinically relevant. In USA, pulmonary embolism (PE) causes almost 300,000 deaths per annum [6]. It is estimated that 12% of the annual deaths occurring in France, Germany, Italy, Spain, Sweden, and UK are due to VTE, varying from 10% in UK to 14% in Italy [7].

A large number of randomized clinical trials have demonstrated that adequate use of thromboprophylaxis after THA can significantly reduce the burden of VTE on patients and the healthcare system [8]. With increasingly shorter hospital stays, it is no longer appropriate to consider prophylaxis for in-hospital use alone. Indeed, extended prophylaxis with anticoagulants in patients with THA after hospital discharge has been shown to significantly reduce

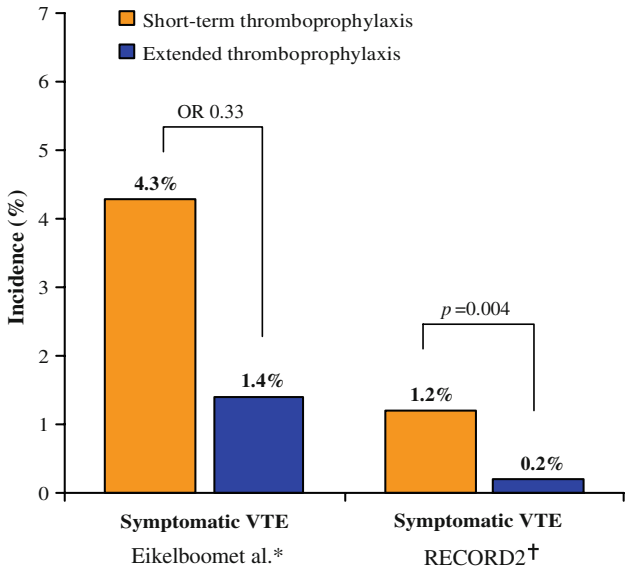

Fig. 1 Incidence of symptomatic venous thromboembolism (VTE) in trials comparing extended-duration with short-term thromboprophylaxis. Symptomatic VTE in trials comparing out-of-hospital, extended-duration, low molecular weight heparin (LMWH) or unfractionated heparin (UFH) with placebo or untreated control after THA [9] (*asterisk*). Symptomatic VTE after extended-duration rivaroxaban versus short-term enoxaparin after THA [10] (*dagger*)

the incidence of symptomatic VTE when compared with placebo or untreated controls (Fig. 1) [9, 10]. However, there is low adherence to evidence-based guidelines, and a large proportion of patients do not receive the guideline-recommended duration of thromboprophylaxis [11–14]. This is due to a perceived increased risk of postoperative bleeding when using prophylactic anticoagulant therapy, which has long been a concern among the orthopedic surgical community (Table 1).

The asymptomatic nature of DVT may also contribute to the underutilization of appropriate thromboprophylaxis after THA. Due to short hospital stays, surgeons may not be aware of the true incidence of VTE in their patients. The time course of developing symptomatic venous thromboembolic events after THA has been reported to occur at a mean of 21.5 days [12]; therefore, DVT may progress to a fatal PE some time after hospital discharge [15].

The current anticoagulants also pose logistical problems for postoperative care. The parenteral route of administration with low molecular weight heparins (LMWHs) and fondaparinux—the current standard of care in Europe, as well as the requirement for regular coagulation monitoring and the increased bleeding risk with oral vitamin K antagonists (such as warfarin; more frequently used in USA in this indication), may contribute to the lack of application of extended prophylaxis regimens [16].

After a brief review of the traditional anticoagulants, this article will present the clinical evidence to support the use of the newly approved oral anticoagulants for extended prophylaxis in patients undergoing THA, and indicate how these new agents may facilitate adherence to evidence-based guideline recommendations for thromboprophylaxis in patients undergoing THA.

Table 1 Summary of clinical studies of new oral anticoagulant agents in the prevention of venous thromboembolism after major orthopedic surgery

Study	Phase	Patient population	Dosing	Comparator(s)	Status
Dabigatran etexilate					
BISTRO II	II	THA/TKA	50–225 mg bid 300 mg od	Enoxaparin	Completed [47]
RE-NOVATE	III	THA	150 and 220 mg od	Enoxaparin	Completed [29]
RE-MODEL	III	TKA	150 and 220 mg od	Enoxaparin	Completed [30]
RE-MOBILIZE	III	TKA	150 and 220 mg od	Enoxaparin[a]	Completed [31]
Rivaroxaban					
ODIXa-HIP	II	THA	5–60 mg bid/od	Enoxaparin	Completed [48]
ODIXa-HIP2	II	THA	5–60 mg bid	Enoxaparin	Completed [49]
ODIXa-KNEE	II	TKA	5–60 mg bid	Enoxaparin[a]	Completed [50]
ODIXa-HIP-od	II	THA	5–40 mg od	Enoxaparin	Completed [39]
RECORD1	III	THA	10 mg od	Enoxaparin	Completed [40]
RECORD2	III	THA	10 mg od	Enoxaparin	Completed [10]
RECORD3	III	TKA	10 mg od	Enoxaparin	Completed [41]
RECORD4	III	TKA	10 mg od	Enoxaparin[a]	Completed [42]

THA total hip arthroplasty, *TKA* total knee arthroplasty, *VTE* venous thromboembolism

[a] Enoxaparin 30 mg bid; bid, twice daily; od, once daily

Traditional anticoagulants

Unfractionated heparins (UFHs) and LMWHs are indirect anticoagulants that target multiple enzymes in the coagulation cascade and enhance the activity of the plasma cofactor antithrombin, which, in turn, inhibits thrombin and FXa. A meta-analysis of nine studies showed that extended prophylaxis with LMWH or UFH after hospital discharge (total treatment duration 27–42 days) further decreased the incidence of symptomatic VTE in patients undergoing THA, compared with those who received placebo or untreated controls post-discharge [1.4 vs. 4.3%; odds ratio (OR) 0.33; 95% confidence interval (CI) 0.19–0.56], without increasing major bleeding (0.1 vs. 0.3%; OR 0.62; 95% CI 0.22–1.75) [9].

Although LMWHs reduce the incidence of symptomatic and asymptomatic venous thromboembolic events while maintaining acceptable bleeding rates, their parenteral route of administration can be problematic for patients in the long term and for home use. Two Canadian studies have reported that 19 or 39% of patients require daily nurse assistance with subcutaneous injections of LMWH in the outpatient setting [17, 18]. Furthermore, results from a randomized study in Sweden assessing the cost-effectiveness of 10 and 30 days of once-daily (od) enoxaparin for the prevention of VTE after THA have shown that cost-effectiveness is lost when <50% of the patients can self-administer the subcutaneous injections [19].

Fondaparinux, an indirect specific FXa inhibitor, is a synthetic analog of the pentasaccharide sequence responsible for the binding of UFH and LMWH to antithrombin [20]. A meta-analysis of four phase III trials revealed a 55.2% relative risk reduction (RRR) for the prevention of VTE with fondaparinux when compared with the LMWH enoxaparin [21–25]. However, as with the LMWHs, fondaparinux requires parenteral administration.

Until the recent approvals of dabigatran and rivaroxaban for VTE prophylaxis after elective THA and total knee arthroplasty (TKA), VKAs, such as warfarin, were the only oral anticoagulant available. VKAs inhibit the hepatic synthesis of biologically active forms of the vitamin K-dependent clotting factors II, VII, IX, and X and the anticoagulant proteins C and S [26]. Although VKAs have been shown to reduce the incidence of VTEs in patients undergoing major orthopedic surgery [4, 27], they are not widely used for thromboprophylaxis after major orthopedic surgery in Europe due to concerns about their slow onset of action, variable patient responses that necessitate routine coagulation monitoring and dose adjustment, and multiple food and drug interactions [27].

Therefore, there is an unmet need for a convenient, effective antithrombotic agent that does not increase the risk of bleeding and can be administered orally, without the need for routine coagulation monitoring for both hospital and home use.

Newly approved oral anticoagulants for VTE prevention after THA

Dabigatran etexilate

Dabigatran etexilate (Boehringer Ingelheim) is a new oral, od, direct thrombin inhibitor. It has a rapid onset of action and estimated half-lives of 8–10 h and 14–17 h with single- and multiple-dose administration, respectively. Due to its predictable pharmacokinetics (PK) and pharmacodynamics (PD), it can be given at a fixed dose without the need for routine coagulation monitoring [28]. Based on the results from phase II dose-finding studies in patients undergoing THA and TKA, doses of 150 and 220 mg were selected for phase III studies.

The phase III RE-NOVATE trial investigated dabigatran etexilate versus enoxaparin for the prevention of VTE after THA in 3,494 patients [29]. Patients were randomized to receive oral dabigatran etexilate 150 or 220 mg od, starting with a half-dose 1–4 h after surgery, or subcutaneous enoxaparin 40 mg od, starting the evening before surgery, for 28–35 days. The primary efficacy outcome of this study was the composite of total VTE and all-cause mortality during treatment. The primary safety outcome was the occurrence of bleeding events during treatment. Major bleeding events were defined as follows: clinically overt bleeding associated with a $\geq$2 g/dL fall in hemoglobin; clinically overt bleeding leading to a transfusion of $\geq$2 units of packed cells or whole blood; fatal, retroperitoneal, intracranial, intraocular, or intraspinal bleeding; or bleeding warranting treatment cessation or leading to re-operation. Both doses of dabigatran etexilate (150 and 220 mg) were non-inferior to enoxaparin 40 mg od (8.6 and 6.0%, respectively, vs. 6.7%; $P < 0.0001$ for non-inferiority vs. enoxaparin) for the primary efficacy outcome. The incidence of major VTE (proximal DVT and PE) was also similar between both doses of dabigatran and enoxaparin (4.3 and 3.1%, respectively, vs. 3.9%). Symptomatic DVT occurred in 0.8% (150 mg) and 0.5% (220 mg) of patients receiving dabigatran, and in 0.1% of those receiving enoxaparin. The frequency of symptomatic PE was 0.1, 0.4, and 0.3% for dabigatran 150, 220, and enoxaparin, respectively. Major bleeding occurred in 1.3% (150 mg) and 2.0% (220 mg) of patients receiving dabigatran etexilate and in 1.8% of those receiving enoxaparin. The incidence of clinically relevant non-major bleeding was 4.7 and 4.2% for patients receiving dabigatran 150 and 220 mg, respectively, compared with 3.5% for those who received enoxaparin.

Two phase III studies for VTE prevention after TKR, RE-MODEL and RE-MOBILIZE, have also been published.

The RE-MODEL study showed that dabigatran was non-inferior to enoxaparin 40 mg od for both safety and efficacy [30]; in the RE-MOBILIZE study, however, the non-inferiority criteria compared with the North American regimen enoxaparin [30 mg twice daily (bid)] was not met [31].

Dabigatran etexilate—starting with half of the full dose [110 mg od or 75 mg in patients with moderate renal impairment, within 1–4 h of surgery, followed by the full dose of 220 mg (or 150 mg) od thereafter for 28–35 days after THA, and 10 days after TKA]—was approved in the European Union and Canada in 2008. Clinical studies in other non-orthopedic indications are currently ongoing.

Rivaroxaban

Rivaroxaban (Bayer Schering Pharma AG, Wuppertal, Germany; Johnson & Johnson Pharmaceutical Research & Development, L.L.C., Raritan, NJ, USA) is an oral, direct FXa inhibitor [32]. It also inhibits prothrombinase activity, as well as free and clot-associated FXa activity [32, 33].

It has a half-life of 7–11 h [33–35]. Rivaroxaban is well tolerated, with a rapid onset of action, reaching peak plasma concentrations within 2–4 h. It has predictable PK and PD, thus can be given at a fixed dose with no need for routine coagulation monitoring [33]. Additionally, it has no known food–drug or drug–drug interactions [36–38]. Based on the results from phase II studies, a dose of 10 mg od was regarded as an optimal dose in terms of efficacy and safety, and was chosen for the phase III RECORD studies [39].

The RECORD (regulation of coagulation in orthopedic surgery to prevent deep vein thrombosis and PE) program consisted of four phase III studies, two of which were performed in patients after THA (RECORD1, RECORD2). The primary efficacy outcome of these studies was the composite of DVT, PE, and all-cause mortality. The main secondary efficacy outcome was major VTE, defined as the composite of proximal DVT, non-fatal PE, or death from VTE. Other efficacy outcomes included the incidence of any DVT, symptomatic VTE during treatment and follow-up, and death during the follow-up period. The primary safety outcome was major bleeding that is defined as follows: fatal bleeding; bleeding into a critical organ (e.g. retroperitoneal, intracranial, intraocular, or intraspinal); bleeding requiring re-operation; and clinically overt extra-surgical-site bleeding associated with a fall in hemoglobin $\geq$2 g/dL or requiring an infusion of $\geq$2 units of blood or packed cells. Clinically relevant non-major bleeding, hemorrhagic wound complications, and other non-major bleeding events were among the other safety outcomes.

In RECORD2, extended prophylaxis with rivaroxaban was compared with short-term enoxaparin followed by placebo for the prevention of VTE after THA in 2,509 patients [10]. Patients received subcutaneous enoxaparin 40 mg od, beginning the evening before surgery, continuing for 10–14 days (short-term prophylaxis) and followed by placebo until day 35 $\pm$ 4, or oral rivaroxaban 10 mg od, beginning 6–8 h after surgery and continuing for 35 $\pm$ 4 days (extended prophylaxis). The primary efficacy outcome occurred in 2.0% of patients receiving extended prophylaxis with rivaroxaban compared with 9.3% of patients given short-term prophylaxis with enoxaparin (RRR 79%; $P < 0.0001$). The incidence of major VTE was also significantly lower among patients who received the extended rivaroxaban regimen (0.6%) compared with those who received the short-term enoxaparin regimen (5.1%; RRR 88%; $P < 0.0001$). Symptomatic VTE occurred in 0.2% of patients who received rivaroxaban and 1.2% of patients who received enoxaparin (RRR 80%; $P = 0.004$). The rate of major bleeding was similar in both groups (<0.1% of patients), despite the longer use of rivaroxaban. There was no significant difference in the rates of clinically relevant non-major bleeding (3.3 vs. 2.7%) and hemorrhagic wound complications (1.6 vs. 1.7%) between rivaroxaban and enoxaparin groups. RECORD2 is the largest single study to date to demonstrate that patients receiving extended thromboprophylaxis experience fewer venous thromboembolic events (including symptomatic VTE) compared with short-term thromboprophylaxis, without a significant increase in bleeding events.

The RECORD1 trial compared extended prophylaxis with rivaroxaban with extended enoxaparin for the prevention of VTE after THA [40]. Patients received either oral rivaroxaban 10 mg od, started 6–8 h after surgery for 35 $\pm$ 4 days, or subcutaneous enoxaparin 40 mg od, started the evening before surgery. The primary efficacy outcome occurred in 1.1% of patients treated with rivaroxaban, compared with 3.7% of patients who received enoxaparin (RRR 70%; $P < 0.001$). There was also a marked reduction in the occurrence of major VTE for rivaroxaban when compared with enoxaparin (0.2 vs. 2.0%, respectively; RRR 88%; $P < 0.001$). The observed incidence of symptomatic VTEs was similar between rivaroxaban and enoxaparin (0.3 and 0.5%, respectively; $P = 0.22$). Major bleeding occurred in 0.3% of patients in the rivaroxaban group versus 0.1% of patients in the enoxaparin group; clinically relevant non-major bleeding occurred in 2.9 versus 2.4% of patients receiving rivaroxaban and enoxaparin, respectively. The incidence of hemorrhagic wound complications was 1.5% in rivaroxaban-treated and 1.7% in enoxaparin-treated patients.

In two phase III studies after TKA (RECORD3, RECORD4), rivaroxaban 10 mg od was shown to be superior to both European and North American regimens of enoxaparin (40 mg od and 30 mg bid) without any significant increase in major bleeding rates [41, 42].

Rivaroxaban (10 mg od) started 6–10 h after surgery was approved in 2008 in the European Union and several other countries for VTE prevention after TKA (treatment duration of 2 weeks) and THA (treatment duration of 5 weeks).

Discussion and conclusions

The new oral agent dabigatran etexilate, an oral direct thrombin inhibitor, was shown to be as effective as the European enoxaparin regimen (40 mg od, started in the evening before surgery) for extended thromboprophylaxis after THA, whereas the oral direct Factor Xa inhibitor rivaroxaban demonstrated superiority for the prevention of VTE when compared with the European enoxaparin regimen. There was no significant difference in major bleeding for both rivaroxaban and dabigatran etexilate when compared with enoxaparin. Furthermore, the RECORD2 study provided further evidence for the benefit of extended versus short-term thromboprophylaxis after THA. Extended thromboprophylaxis with rivaroxaban was significantly more effective than short-term prophylaxis with enoxaparin in the prevention of total, major, and symptomatic VTE in patients undergoing THA, without compromising patient safety.

When compared with the preferred enoxaparin regimen in North America (30 mg bid, started 12–24 h postoperatively) in TKA patients, however, the two drugs performed differently. Rivaroxaban was shown to be superior [42], and dabigatran was shown to be inferior, to enoxaparin for the primary efficacy endpoint [31]. It should be noted that the design of the two studies with dabigatran etexilate (RE-MOBILIZE and RE-MODEL) in patients undergoing TKA was different. First, in the RE-MOBILIZE trial, the initial dose of dabigatran etexilate was given later at 6–12 h after surgery instead of 1–4 h. Secondly, the dose of enoxaparin was higher: a 30 mg bid regimen was used instead of the 40 mg od regimen. Thirdly, therapy duration was 12–15 days instead of 6–10 days. Therefore, the different results from these two trials with dabigatran etexilate in TKR patients (RE-MODEL and RE-MOBILIZE) may reflect the higher daily dose of enoxaparin used as a comparator and/or the delayed start of dabigatran etexilate in the RE-MOBILIZE trial. Whether the observed different efficacies of rivaroxaban and dabigatran etexilate can be attributed to their different mechanisms of action (i.e. direct Factor Xa inhibition vs. direct thrombin inhibition) is still to be demonstrated.

To date, direct comparisons between pre- and postoperative administration of the same antithrombotic drug in clinical trials have not been reported, but there are indications of an increased risk of bleeding with preoperative dosing and an increased risk of thrombosis with postoperative dosing [43]. However, with an appropriate dose and timing of the first administration in relation to the operation, these risks can be minimized. Both rivaroxaban and dabigatran etexilate are administered postoperatively, based on a number of dose-finding studies that have helped to identify the dose with the optimal balance between efficacy and safety. A postoperative start of prophylaxis has clear advantages. First, there is no risk of an enhanced blood loss during surgery; secondly, the use of neuraxial anesthesia (spinal/epidural anesthesia) is made easier because the patient is not under the influence of an anticoagulant at the time of lumbar puncture. When spinal/epidural puncture is employed, patients treated with antithrombotic agents are at risk of developing an epidural or spinal hematoma [44]. The risk of these events may be increased by the use of postoperative indwelling epidural catheters. Dabigatran etexilate is not recommended in patients undergoing anesthesia with postoperative indwelling epidural catheters, whereas, with rivaroxaban, an epidural catheter is not to be removed earlier than 18 h after the last administration [35, 45].

In contrast to rivaroxaban and dabigatran etexilate, the LMWH enoxaparin is given preoperatively in the EU, which could be a disadvantage in patients requiring spinal/epidural anesthesia because of an assumed increased risk of spinal hematoma formation. Interestingly, a recent small study in patients undergoing THA showed that intraoperative UFH in combination with mechanical devices significantly reduced D-dimer levels on the first day post-surgery, without an increase in bleeding complications [46]. However, whether this intraoperative use of heparin has any impact on the overall risk of VTE in patients undergoing THA is not known.

In conclusion, because rivaroxaban and dabigatran etexilate can be given orally at a fixed dose without the need for routine coagulation monitoring, they could offer greater convenience for patients and healthcare professionals compared with traditional anticoagulants (such as LMWH and warfarin), particularly in the outpatient setting. The introduction of these new agents into clinical practice could improve adherence to current guidelines for extended thromboprophylaxis to prevent VTE after THA, and provide new, realistic opportunities for orthopedic surgeons to improve postoperative patient care, and, in the case of rivaroxaban, also the added benefit of improved efficacy.

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