Eur J Orthop Surg Traumatol (2009) 19:529–533
DOI 10.1007/s00590-009-0475-1

GENERAL REVIEW

Rivaroxaban for venous thromboembolism prevention after total knee arthroplasty: RECORD3 findings

Walter Ageno

Received: 24 March 2009 / Accepted: 13 April 2009 / Published online: 28 April 2009

Abstract Patients undergoing major orthopaedic surgery are at considerable risk for venous thromboembolism in the days and weeks after surgery. Consequently, thromboprophylaxis after major orthopaedic surgery, including total hip arthroplasty (THA) and total knee arthroplasty (TKA), is regarded as a standard element of the post-surgical care of such patients. A range of agents are available for use as thromboprophylaxis, including low molecular weight heparins, fondaparinux or warfarin. Rivaroxaban—a novel, oral direct Factor Xa inhibitor—was recently assessed as a potential alternative to current prophylactic strategies in phase III clinical trials carried out in the setting of major orthopaedic surgery. Rivaroxaban was compared to enoxaparin both in patients undergoing THA and in patients undergoing TKA. Based on the positive results of these studies, rivaroxaban has recently received marketing approval in the European Union and Canada. Here, we review the clinical database to support the use of this agent after TKA.

Keywords Anticoagulants · Arthroplasty · Knee · Rivaroxaban · Thromboembolism

Introduction

Patients undergoing major orthopaedic surgery face an increased risk for venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), in the days and weeks after their operation [1]. In recent years, the routine use of anticoagulants has played a significant role in reducing the morbidity and mortality associated with VTE after major orthopaedic surgery, including total knee arthroplasty (TKA) [2]. Venographic DVT and proximal DVT occur within 7–14 days in 40–60 and 10–30% of patients who receive no thromboprophylaxis after major orthopaedic surgery. With routine thromboprophylaxis, fatal PE is now uncommon, although symptomatic VTE occurs in 1.3–10% of patients within 3 months of surgery [2].

Currently, the most commonly used anticoagulants are the subcutaneously administered low molecular weight heparins (LMWHs such as enoxaparin) and the synthetic pentasaccharide fondaparinux (a selective indirect Factor Xa inhibitor). Their use is strongly recommended in international guidelines [2]. Also recommended in the guidelines is the use of vitamin K antagonists, such as warfarin. However, their use is hampered by the need for frequent coagulation monitoring and the unpredictable pharmacological profile of this agent, with numerous adverse food and drug interactions and the potential risk for major bleeding events. Acetylsalicylic acid alone is not recommended by the American College of Chest Physicians (ACCP) for prophylaxis in this patient group [2].

The ACCP guidelines for VTE prevention after TKA have recently been updated and now suggest anticoagulation for up to 35 days after surgery (grade 2B) [2], which is an extension to the minimum of 10-day prophylaxis suggested in previous guidelines (grade 1A) [1]. Consequently, there is a clinical need for new oral anticoagulants that effectively reduce the risk of VTE after major orthopaedic surgery, without an increased risk of bleeding events, and which ideally would provide a practical route of administration once patients are discharged from hospital [3]. In

W. Ageno (✉)
Department of Clinical Medicine, Ospedale di Circolo, University of Insubria, Viale Borri 57, 21100 Varese, Italy
e-mail: walter.ageno@uninsubria.it

addition, anticoagulants that reduce the time spent in hospital after surgery and can be taken easily by patients at home would be advantageous.

New oral anticoagulants—dabigatran and rivaroxaban—target specific elements of the coagulation cascade to maintain or improve the benefit–risk profile [4–7]. Dabigatran is a direct thrombin inhibitor; inhibition of thrombin activity prevents the penultimate step in clot formation—the conversion of fibrinogen to fibrin, a basic component of a clot. Rivaroxaban is a direct Factor Xa inhibitor and targets an earlier step of the coagulation cascade prior to the conversion of prothrombin to thrombin. Both dabigatran and rivaroxaban have recently been approved for VTE prevention after TKA and total hip arthroplasty (THA) in the European Union and Canada.

In this paper, we will review the clinical trial data now supporting the clinical use of rivaroxaban for VTE prevention after TKA and the potential role of this agent in routine post-surgical management of TKA patients.

Pharmacological characteristics of rivaroxaban

The pharmacological profile of rivaroxaban has been extensively investigated in a series of preclinical studies. These studies have shown that rivaroxaban has a rapid onset of action [8], and high oral bioavailability [5, 9]. The maximal plasma concentration (C_{max}) of this agent is reached in 2–4 h after oral administration, with no evidence of substantial accumulation [9, 10]. Importantly, for an oral agent that may be used in the outpatient setting, food restrictions are not necessary with rivaroxaban [11] and studies have confirmed a lack of clinically relevant interactions with medications that might be concomitantly prescribed in patients after TKA [12–15].

Predictable pharmacokinetics (PK) is an important characteristic for new oral anticoagulants. Rivaroxaban demonstrated predictable PK and pharmacodynamics (PD) in patients undergoing TKA or THA [16, 17] and patients do not require monitoring. In addition, age, renal function and body weight had only small effects on the PK/PD profile of rivaroxaban, suggesting fixed doses of rivaroxaban can be given to patients [18–20].

Venous thromboembolism prevention after major orthopaedic surgery

Rivaroxaban underwent an extensive phase II development programme. An open-label study in patients undergoing THA provided proof of principle for rivaroxaban [21]. This dose-escalation study confirmed efficacy in VTE prevention of rivaroxaban at doses of 2.5–30 mg given twice daily (bid) or 30 mg once daily (od) relative to the LMWH comparator enoxaparin 40 mg od. Two further phase IIb studies of rivaroxaban given bid confirmed these observations for the prevention of VTE after THA [22] and TKA [23]. Finally, similar major bleeding rates and efficacy in VTE prevention at least comparable with enoxaparin were demonstrated in a further phase IIb study of rivaroxaban given od for the prevention of VTE after THA [24].

Phase II programme in TKA

The phase II analyses aimed to determine an appropriate dosing regimen for phase III evaluation after TKA. Rivaroxaban was assessed relative to enoxaparin in 621 patients undergoing TKA [23]. Patients received total daily doses of 5, 10, 20, 40 or 60 mg oral rivaroxaban (bid), starting 6–8 h after wound closure and continuing every 12 ± 2 h for 5–9 days after surgery. As this study was conducted in the USA, enoxaparin 30 mg bid was initiated the morning after surgery (12–24 h after surgery) and continued every 12 ± 2 h in accordance with the usual North American practice. Rivaroxaban at a total daily dose of 5–20 mg achieved similar efficacy to enoxaparin in patients undergoing TKA. The primary endpoint of the composite of DVT, non-fatal PE and all-cause mortality occurred between 23.3% (10 mg bid) and 40.4% (5 mg bid) in the rivaroxaban arm and 44.3% in the enoxaparin arm. Major bleeding events also occurred at a similar frequency between the two treatment arms. There was a flat dose–response relationship between rivaroxaban and the primary efficacy endpoint ($p = 0.29$) across the dose range studied, confirming the wide therapeutic window for this agent. Doses up to 20 mg total rivaroxaban per day provided comparable safety in terms of an incidence of major bleeding events similar to that of enoxaparin.

The od dosing study in patients undergoing THA [24] demonstrated the efficacy and safety of rivaroxaban doses of 5–40 mg od relative to enoxaparin. As the study was conducted in Europe, the enoxaparin regimen was 40 mg od, starting the evening before surgery. When efficacy and safety were considered, these data supported the selection of a daily dose of 10 mg as the optimal dose for investigation in phase III. Support for this dosing regimen for use in the phase III TKR analyses was provided by a pooled analysis of data from two phase II studies [22, 23], which demonstrated no significant difference between dose–response relationships with rivaroxaban after THA and TKA [25]. Based on these supporting analyses, the same dose—10 mg od—was selected for the TKA phase III study. Therefore, the phase II programme showed that the 10 mg dose provided effective anticoagulation that rivaroxaban has a wide therapeutic window and that once-daily dosing was suitable for TKA and THA.

Phase III programme

Based on the results of the phase II od dosing study, rivaroxaban 10 mg od was further evaluated for the prevention of VTE in four phase III studies (RECORD1–4) in >12,500 patients undergoing THA or TKA. RECORD1 [26] and RECORD2 [27] evaluated extended thromboprophylaxis (5 weeks) after THA in 4,591 and 2,509 patients, respectively. RECORD3 investigated thromboprophylaxis (10–14 days) in 2,531 patients undergoing TKA [28] and RECORD4 studied rivaroxaban (10–14 days) in 3,149 patients also undergoing TKA [29]. RECORD3 compared rivaroxaban with enoxaparin administered according to the European enoxaparin regimen, i.e. 40 mg once daily, and RECORD4 compared rivaroxaban with enoxaparin administered according to the North American regimen, i.e. 30 mg twice daily. We will now review the results of RECORD3, the first study on rivaroxaban in patients undergoing TKA, and briefly give the results of RECORD4.

RECORD3 study design

RECORD3 was a double-blind study in which patients were randomized to receive oral rivaroxaban (10 mg od) or subcutaneous enoxaparin (40 mg od) for 10–14 days. Patients then underwent mandatory, bilateral venography. The primary efficacy endpoint was the composite of total VTE (any DVT, non-fatal PE and all-cause mortality within 13–17 days of surgery). Secondary efficacy outcomes included major VTE (i.e. proximal DVT, non-fatal PE or death related to VTE) and symptomatic VTE. The main safety endpoint was major bleeding starting after the first blinded dose and ≤2 days after the last dose of study medication. Major bleeding was defined as bleeding that was fatal, involved a critical organ or required reoperation, or clinically overt bleeding outside the surgical site that was associated with a decrease in the haemoglobin level of ≥2 g/dl or requiring an infusion of ≥2 units of blood. Also assessed were any bleeding or major bleeding occurring between intake of the first dose of study medication and 2 days after the last dose, non-major bleeding including haemorrhagic wound complications (excessive wound haematoma or bleeding at the surgical site), other adverse events and death.

RECORD3 baseline characteristics

Patients in both arms had similar baseline characteristics. The mean age of patients was 67.6 years and their mean body weight was 80.7 kg. The majority of patients in both treatment arms were female (rivaroxaban 70.2%, enoxaparin 66.3%) and/or Caucasian (rivaroxaban 82%, enoxaparin 80.5%), with only a small proportion of patients presenting with a history of VTE (rivaroxaban 3.9%, enoxaparin 3.4%). The majority of patients in both treatment arms presented for primary TKA (rivaroxaban 96.4%, enoxaparin 95.7%), with <3% of patients in either arm presenting for revision of implants. The distribution of anaesthesia type was similar between the treatment arms, with regional anaesthesia only being the preferred method (rivaroxaban 64.4%, enoxaparin 62.5%). Finally, the duration of surgery was around 1.5 h in both treatment arms.

RECORD3 results

Prophylaxis with rivaroxaban was significantly more effective than prophylaxis with enoxaparin in all primary and secondary efficacy outcomes (9.6 vs. 18.9% for the primary efficacy endpoint; $p < 0.001$) (Fig. 1). The incidence of major bleeding was similar in both the rivaroxaban and enoxaparin groups (Fig. 2). In all, 0.6% (7/1,220) of patients who received rivaroxaban experienced a major bleeding event compared with 0.5% (6/1,239) of those who received enoxaparin ($p = 0.77$). The incidence of any bleeding event and non-major bleeding was also similar between the two study arms (Fig. 2). Post-operative wound infection occurred less frequently in the rivaroxaban group (7 patients, 0.6%) than in the enoxaparin group (11 patients, 0.9%).

Based on the RECORD1–4 pooled analysis, once-daily rivaroxaban regimens show a significantly lower incidence of symptomatic VTE and all-cause mortality at all time points compared with enoxaparin regimens, with low and/or similar rates of treatment-emergent bleeding events based on the definition of major bleeding used in the RECORD programme and when haemorrhagic wound complications and surgical site bleeding events were added to major bleeding (which closely equates to the more commonly used phase II definition) [30].

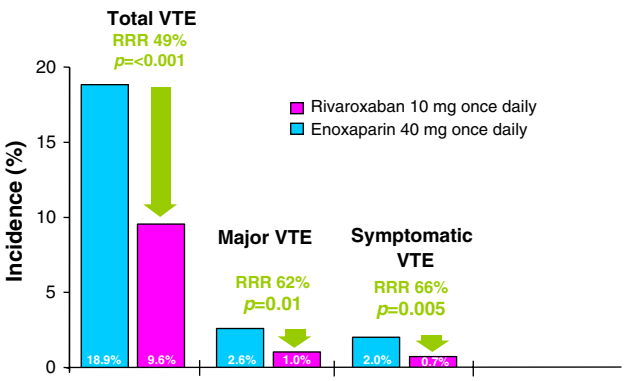

Fig. 1 Efficacy outcomes in patients undergoing total knee arthroplasty and receiving either rivaroxaban or enoxaparin as thromboprophylaxis [28]. *VTE* venous thromboembolism

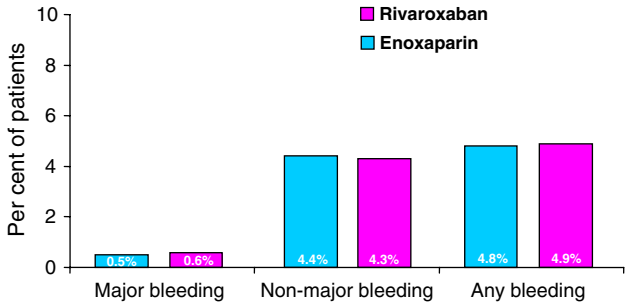

Fig. 2 Safety outcomes in patients undergoing total knee arthroplasty and receiving either rivaroxaban or enoxaparin as thromboprophylaxis [28]

A wider evaluation of tolerability in this study revealed that the incidence of adverse events was similar for rivaroxaban and enoxaparin. The incidence of drug-related (as assessed by the investigators) adverse events was comparable between the rivaroxaban and enoxaparin arms (12.0 and 13.0%, respectively). Importantly, there was no evidence of compromised liver safety due to rivaroxaban, increased cardiovascular events or reactivation of coagulation after treatment cessation.

RECORD4 results

Rivaroxaban showed significantly better efficacy than the North American enoxaparin regimen for short-term prophylaxis after TKA (6.9 vs. 10.1%, respectively, for the primary efficacy endpoint; $p = 0.012$). The rates of major bleeding were 0.7 versus 0.3% ($p = 0.110$), respectively.

Further areas of investigation for rivaroxaban

Ongoing studies are investigating a variety of clinical settings. Phase III studies have recently been completed demonstrating the efficacy and safety of VTE prevention with rivaroxaban among patients undergoing THA. Extended-duration rivaroxaban has been shown to be more effective than standard enoxaparin (RECORD1) and short-duration enoxaparin followed by placebo (RECORD2) with similar rates of major bleeding for VTE prevention after THA [26, 27]. Rivaroxaban is also being studied for the treatment of VTE; the EINSTEIN DVT (NCT00440193) and EINSTEIN PE (NCT00439777) are ongoing evaluations in patients with DVT or PE, respectively, randomly assigned to rivaroxaban or enoxaparin plus a vitamin K. A further phase III study, MAGELLAN (NCT00571649), is ongoing to evaluate the efficacy of rivaroxaban in VTE prevention in medically ill patients. The ROCKET AF phase III study, in which rivaroxaban is being compared with warfarin for the prevention of stroke in ~14,000 patients with atrial fibrillation, is underway [31].

Discussion

RECORD3 was the first phase III study to demonstrate the efficacy and safety of an oral, direct Factor Xa inhibitor in the prevention of VTE after TKA. In this head-to-head comparison, rivaroxaban proved superior to enoxaparin in reducing the incidence of total VTE, major VTE and symptomatic VTE. The incidence of major bleeding was similar with rivaroxaban compared with enoxaparin in this setting.

Rivaroxaban is an important new treatment option in patients undergoing elective TKA for use both in hospital and in the outpatient setting, given the lack of requirement for monitoring, the oral route of administration and the favourable drug interaction profile.

Acknowledgments The author would like to thank Li Wan for editorial assistance in the preparation of the manuscript, with funding from Bayer HealthCare AG. Also, the steering committee members and investigators of the RECORD3 study and phase II clinical trials. The sponsor, Bayer HealthCare AG, had access to the manuscript prior to submission and provided consent for the submission of the manuscript.

Conflict of interest statement The author was involved in the steering committee of one of the trials discussed in this review and received honoraria as a speaker from Bayer Healthcare AG.

References

1. Geerts WH, Pineo GF, Heit JA et al (2004) Prevention of venous thromboembolism: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest 126:338S–400S
2. Geerts WH, Bergqvist D, Pineo GF et al (2008) Prevention of venous thromboembolism: American College of Chest Physicians evidence-based clinical practice guidelines (8th edition). Chest 133:381–453
3. Ansell J, Bergqvist D (2004) Current options in the prevention of thromboembolic disease. Drugs 64:1–5
4. Weitz JI, Bates SM (2005) New anticoagulants. J Thromb Haemost 3:1843–1853
5. Perzborn E, Strassburger J, Wilmen A et al (2005) In vitro and in vivo studies of the novel antithrombotic agent BAY 59-7939—an oral, direct Factor Xa inhibitor. J Thromb Haemost 3:514–521
6. Biemond BJ, Perzborn E, Friederich PW, Levi M, Buetehorn U, Büller HR (2007) Prevention and treatment of experimental thrombosis in rabbits with rivaroxaban (BAY 59-7939)—an oral, direct Factor Xa inhibitor. Thromb Haemost 97:471–477
7. Turpie AG (2007) Oral, direct Factor Xa inhibitors in development for the prevention and treatment of thromboembolic diseases. Arterioscler Thromb Vasc Biol 27:1238–1247
8. Tersteegen A, Burkhardt N (2007) Rivaroxaban—an oral, direct Factor Xa inhibitor—binds rapidly to Factor Xa. J Thromb Haemost 5(Suppl 2):(Abstract P-W-651)
9. Kubitza D, Becka M, Wensing G et al (2005) Safety, pharmacodynamics, and pharmacokinetics of BAY 59-7939—an oral, direct Factor Xa inhibitor—after multiple dosing in healthy male subjects. Eur J Clin Pharmacol 61:873–880
10. Kubitza D, Becka M, Voith B, Zuehlsdorf M, Wensing G (2005) Safety, pharmacodynamics, and pharmacokinetics of single doses of BAY 59-7939, an oral, direct factor Xa inhibitor. Clin Pharmacol Ther 78:412–421

11. Kubitza D, Becka M, Zuehlsdorf M, Mueck W (2006) Effect of food, an antacid, and the H2 antagonist ranitidine on the absorption of BAY 59-7939 (rivaroxaban), an oral, direct Factor Xa inhibitor, in healthy subjects. J Clin Pharmacol 46:549–558
12. Kubitza D, Becka M, Mueck W, Zuehlsdorf M (2006) Safety, tolerability, pharmacodynamics, and pharmacokinetics of rivaroxaban—an oral, direct Factor Xa inhibitor—are not affected by aspirin. J Clin Pharmacol 46:981–990
13. Kubitza D, Becka M, Mueck W, Zuehlsdorf M (2007) Rivaroxaban (BAY 59-7939)—an oral, direct Factor Xa inhibitor—has no clinically relevant interaction with naproxen. Br J Clin Pharmacol 63:469–474
14. Kubitza D, Becka M, Zuehlsdorf M, Mueck W (2006) No interaction between the novel, oral, direct Factor Xa inhibitor BAY 59-7939 and digoxin. J Clin Pharmacol 46:702 (Abstract 11)
15. Kubitza D, Becka M, Mueck W, Zuehlsdorf M (2007) Co-administration of rivaroxaban—a novel, oral, direct Factor Xa inhibitor—and clopidogrel in healthy subjects. Eur Heart J 28(Suppl 1):189 (Abstract P1272)
16. Mueck W, Eriksson BI, Bauer KA et al (2008) Population pharmacokinetics and pharmacodynamics of rivaroxaban—an oral, direct Factor Xa inhibitor—in patients undergoing major orthopaedic surgery. Clin Pharmacokinet 47:203–216
17. Mueck W, Borris LC, Dahl OE et al (2008) Population pharmacokinetics and pharmacodynamics of once and twice-daily rivaroxaban for the prevention of venous thromboembolism in patients undergoing total hip replacement. Thromb Haemost 100:453–461
18. Halabi A, Maatouk H, Klause N et al (2006) Effect of renal impairment on the pharmacology of rivaroxaban (BAY 59-7939)—an oral, direct Factor Xa inhibitor. Blood 108:(Abstract 913)
19. Kubitza D, Becka M, Zuehlsdorf M, Mueck W (2007) Body weight has limited influence on the safety, tolerability, pharmacokinetics, or pharmacodynamics of rivaroxaban (BAY 59-7939) in healthy subjects. J Clin Pharmacol 47:218–226
20. Kubitza D, Becka M, Roth A, Mueck W (2008) Dose-escalation study of the pharmacokinetics and pharmacodynamics of rivaroxaban in healthy elderly subjects. Curr Med Res Opin 24:2757–2765
21. Eriksson BI, Borris LC, Dahl OE et al (2007) Dose-escalation study of rivaroxaban (BAY 59-7939)—an oral, direct Factor Xa inhibitor—for the prevention of venous thromboembolism in patients undergoing total hip replacement. Thromb Res 120:685–693
22. Eriksson BI, Borris LC, Dahl OE et al (2006) Oral, direct Factor Xa inhibition with BAY 59-7939 for the prevention of venous thromboembolism after total hip replacement. J Thromb Haemost 4:121–128
23. Turpie AG, Fisher WD, Bauer KA et al (2005) BAY 59-7939: an oral, direct factor Xa inhibitor for the prevention of venous thromboembolism in patients after total knee replacement. A phase II dose-ranging study. J Thromb Haemost 3:2479–2486
24. Eriksson BI, Borris LC, Dahl OE et al (2006) A once-daily, oral, direct Factor Xa inhibitor, rivaroxaban (BAY 59-7939), for thromboprophylaxis after total hip replacement. Circulation 114:2374–2381
25. Fisher WD, Eriksson BI, Bauer KA et al (2007) Rivaroxaban for thromboprophylaxis after orthopaedic surgery: pooled analysis of two studies. Thromb Haemost 97:931–937
26. Eriksson BI, Borris LC, Friedman RJ et al (2008) Rivaroxaban versus enoxaparin for thromboprophylaxis after hip arthroplasty. N Engl J Med 358:2765–2775
27. Kakkar AK, Brenner B, Dahl OE et al (2008) Extended duration rivaroxaban versus short-term enoxaparin for the prevention of venous thromboembolism after total hip arthroplasty: a double-blind, randomised controlled trial. Lancet 372:31–39
28. Lassen MR, Ageno W, Borris LC et al (2008) Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty. N Engl J Med 358:2776–2786
29. Turpie AGG, Bauer KA, Berkowitz SD et al (2008) Once-daily oral rivaroxaban compared with subcutaneous enoxaparin every 12 hours for thromboprophylaxis after total knee replacement: RECORD4. Blood 112:35 (ASH Annual Meeting Abstracts)
30. Turpie AGG, Lassen MR, Kakkar AK et al (2008) A pooled analysis of four pivotal studies of rivaroxaban for the prevention of venous thromboembolism after orthopaedic surgery: effect on symptomatic venous thromboembolism, death, and bleeding. Blood 112:36 (ASH Annual Meeting Abstracts)
31. UK Clinical Research Network (2008) Study portfolio. Available via UK Clinical Research Network. http://public.ukcrn.org.uk/search/StudyDetail.aspx?StudyID=3924. Accessed 5 December 2008