Rivaroxaban for the prevention and treatment of venous thromboembolism

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ABSTRACT

Venous thromboembolism (VTE) is a common and often life-threatening cardiovascular disorder. Patients undergoing total hip replacement or total knee replacement surgery are at increased risk of VTE. In this setting, clinical practice guidelines recommend the use of low molecular weight heparins, vitamin K antagonists or fondaparinux for the prevention of VTE. However, the use of these anticoagulants is beset by practical difficulties that reduce compliance to therapy and adherence to recommended guidelines. New oral anticoagulants (OACs) that are administered in fixed doses without the need for monitoring are now being introduced to clinical practice. Rivaroxaban, dabigatran and apixaban are either approved or in advanced stages of clinical development for the prevention and/or treatment of VTE. This article provides an overview of the phase III clinical development programmes for these novel OACs, with special focus on rivaroxaban. With encouraging data already emerging, the promise of a simplified single-drug approach for VTE treatment is on the horizon.

Venous thromboembolism (VTE) is a collective term that encompasses deep vein thrombosis (DVT) and pulmonary embolism (PE). VTE, the third most common cardiovascular disease worldwide [1] with >1.5 million and an estimated 600 000 venous thromboembolic events per year in the EU and US, respectively [2,3], imposes a substantial economic burden on healthcare systems [4]. In addition to the risk of VTE recurrence, sequelae, such as post-thrombotic syndrome or chronic thromboembolic pulmonary hypertension, markedly increase the risk of disability and adversely affect patients' quality of life. The risk of VTE rises considerably with age from an annual rate of <5 per 100 000 children to >400 per 100 000 adults >80 years old, and the recurrence rate ranges from 5 to 10% per year [5].

VTE PREVENTION AFTER TOTAL HIP OR KNEE REPLACEMENT

Patients undergoing orthopaedic surgery are at a high risk of thromboembolic events [6]. The 8th American College of Chest Physicians (ACCP) consensus guidelines

recommend prophylactic anticoagulation with either low molecular weight heparin (LMWH), fondaparinux or a vitamin K antagonist (VKA) for a minimum of 10 days and up to 35 days after surgery for patients undergoing elective total hip replacement (THR), while the same duration of extended prophylaxis is suggested for high-risk total knee replacement (TKR) [7]. TKR and THR orthopaedic surgeries are suitable indications in which to test novel anticoagulants [6]. Rivaroxaban is an oral, direct factor Xa inhibitor in advanced development for the prevention and treatment of thromboembolic disorders. The RECORD programme of four phase III trials together compared rivaroxaban 10 mg once daily (od) with enoxaparin 40 mg od (RECORD1–3) or enoxaparin 30 mg twice daily (bid) (RECORD4) for the prevention of VTE after elective THR or TKR in more than 12 500 patients. The primary efficacy outcome for all four studies was a composite of any DVT, non-fatal PE and all-cause mortality (total VTE) with a secondary efficacy outcome of major VTE (a composite of proximal DVT, non-fatal PE and VTE-related death). The principal safety outcome was major bleeding observed after the

first dose and up to 2 days after the last dose. Major bleeding was defined as bleeding that was fatal, into a critical organ, required re-operation or clinically overt extra-surgical-site bleeding. Major bleeding did not include surgical-site bleeding events unless they required re-operation or were fatal.

EFFICACY AND SAFETY OUTCOMES: RECORD 1–4

For RECORD1, rivaroxaban (10 mg od for 5 weeks) was more effective for thromboprophylaxis than subcutaneous enoxaparin (40 mg od for 5 weeks) in reducing the incidence of total VTE (relative risk reduction [RRR] = 70%) and major VTE (RRR = 88%) after elective THR [8]. In the RECORD2 study, which evaluated patients undergoing elective THR, extended-duration thromboprophylaxis with rivaroxaban (10 mg od for 5 weeks) showed a lower incidence in the risk of total VTE (RRR = 79%) and major VTE (RRR = 88%) compared with short-term thromboprophylaxis with subcutaneous enoxaparin (40 mg od for 2 weeks followed by oral placebo) [9]. RECORD3 showed that rivaroxaban (10 mg od for up to 2 weeks) lowered the incidence of total and major VTE (RRR = 49 and 62%, respectively) compared with subcutaneous enoxaparin (40 mg od for up to 2 weeks) in patients after elective TKR [10]. The RECORD4 study demonstrated that rivaroxaban (10 mg od) reduced the incidence of total VTE (RRR = 31%) compared with subcutaneous enoxaparin (30 mg bid) for up to 2 weeks after elective TKR [11].

The rates of major bleeding in all four studies were comparable between the treatment groups. With the exception of RECORD2, the other three trials all compared similar durations of prophylaxis. RECORD2 confirmed that a longer duration of post-operative thromboprophylaxis after THR is more efficacious than short-term treatment, which was consistent with current guideline recommendations of extended thromboprophylaxis after THR.

A pooled analysis of the RECORD1–3 trials investigated whether rivaroxaban 10 mg od was more effective than the European regimen of enoxaparin 40 mg od (begun on the evening before surgery) in reducing the incidence of the composite of symptomatic VTE and all-cause mortality determined at 2 weeks (the enoxaparin-controlled period common to all three trials) and at the end of the treatment period (up to day 42 in RECORD1 and 2 and up to day 17 in RECORD3), respectively [12]. The principal safety outcome was the incidence of major

bleeding starting after the first dose, up to 2 weeks and up to the end of the planned medication. Other safety outcomes included haemorrhagic wound complications (composite of excessive wound haematoma and investigator-reported surgical-site bleeding) observed up to 2 days after the last intake of study medication. Results from the pooled analysis are summarized in *Table I*.

Patients assigned to the rivaroxaban treatment group had a 56% RRR in symptomatic VTE and all-cause mortality at the 2-week time point and a 62% RRR for the total treatment duration. At each time point, major bleeding rates and incidence of haemorrhagic wound complications were similar between the two treatment groups. The pooled analysis demonstrated the superiority of rivaroxaban 10 mg od compared with enoxaparin 40 mg od in reducing the composite of symptomatic VTE and all-cause mortality without an increased risk of major bleeding. Based on the RECORD programme, rivaroxaban has been approved in more than 100 countries worldwide, including Canada and the EU, for VTE prevention after elective THR or TKR surgery in adults.

Dabigatran etexilate (hereafter referred to as dabigatran), an oral, direct thrombin inhibitor, was evaluated in the RE-NOVATE [13] and RE-MODEL [14] non-inferiority, phase III trials involving patients from Europe, South Africa and Australia undergoing THR and TKR surgery, respectively. In both studies, patients were randomized to receive either dabigatran 150 mg or 220 mg od (with a half dose of 75 mg or 110 mg, respectively, started 1–4 h post-operatively) or subcutaneous enoxaparin 40 mg od given on the evening before surgery. For the primary efficacy outcome of a composite of the total incidence of VTE and all-cause mortality, data from both RE-NOVATE (8.6, 6.0 and 6.7% for dabigatran 150 mg od, dabigatran 220 mg od and enoxaparin 40 mg od, respectively) and RE-MODEL (40.5, 36.4 and 37.7% for dabigatran 150 mg od, dabigatran 220 mg od and enoxaparin 40 mg od, respectively) reported that both dabigatran doses were non-inferior to enoxaparin 40 mg od [13,14]. In both studies, no significant difference in the rates of major bleeding was observed between the groups (RE-NOVATE, 1.3, 2.0 and 1.6%, respectively; RE-MODEL, 1.3, 1.5 and 1.3%, respectively) [13,14].

In contrast, data from the RE-MOBILIZE study failed to demonstrate non-inferiority of dabigatran compared with the North American enoxaparin regimen of 30 mg bid in the primary efficacy outcome of total VTE and all-cause mortality [15].

Following the submission of efficacy and safety data from the phase III RE-NOVATE and RE-MODEL studies, dabigatran was approved in Europe, Canada and a number of other countries worldwide for thromboprophylaxis after THR or TKR.

The ADVANCE-2 [16] and ADVANCE-3 [17] trials demonstrated that apixaban, another oral factor Xa inhibitor, was more effective than the European dosing regimen of enoxaparin for the prevention of VTE in patients undergoing elective TKR and THR, respectively. However, compared with the North American enoxaparin regimen, apixaban failed to demonstrate non-inferiority for the primary efficacy outcome of a composite of asymptomatic and symptomatic DVT, non-fatal PE and all-cause mortality after elective TKR surgery [18].

Apixaban has recently received a positive response from the European Medicines Agency's Committee for Medicinal Products for Human Use for the prevention of VTE in patients undergoing elective TKR and THR.

Of the three novel oral anticoagulants (OACs), only rivaroxaban has demonstrated superiority vs. the North American enoxaparin regimen of 30 mg bid for the prevention of VTE after TKR.

VTE TREATMENT AND PREVENTION OF RECURRENT EVENTS

For the treatment of VTE and prevention of recurrent events, the ACCP guidelines recommend initial treatment with either LMWHs, unfractionated heparins or fondaparinux, with maintenance therapy or secondary prevention with a VKA for at least 3 months [19]. In patients with cancer-associated thrombosis, LMWH is recommended for secondary prevention [19].

EINSTEIN is a global clinical development programme consisting of a series of pivotal phase III studies evaluating the efficacy and safety of rivaroxaban in the treatment and/or prevention of recurrent, symptomatic VTE in patients with acute symptomatic DVT or PE. The dosing regimen used in the EINSTEIN programme was determined based on previous phase II studies [20,21]. While a dose of rivaroxaban 20 mg od was found to be as effective as higher doses at preventing recurrence after DVT [21], a second dose-ranging trial reported that twice-daily regimens resulted in a higher rate of thrombus regression during the initial 3 weeks of treatment, compared with the standard of care [20]. Consequently, twice-daily dosing was considered beneficial for the treatment of established thrombosis during the acute

Table I RECORD1–3: pooled analysis of outcomes.

	Rivaroxaban (%)	Enoxaparin (%)	RRR (%)	P
At 2 weeks (primary efficacy outcome)				
Symptomatic VTE and all-cause mortality	0.4	0.8	56	0.005
Major bleeding	0.2	0.2	–	0.662
Haemorrhagic wound complications	1.6	1.7	–	–
At end of treatment period (secondary efficacy outcome)				
Symptomatic VTE and all-cause mortality	0.5	1.3	62	<0.001
Major bleeding	0.3	0.2	–	0.305
Haemorrhagic wound complications	1.7	1.8	–	–

ns, non-significant; RRR, relative risk reduction; VTE, venous thromboembolism.

phase. Bleeding rates with rivaroxaban were also observed to be similar to those with LMWH/VKA across both phase II trials. Taken together, it was concluded that a maintenance dose of rivaroxaban 20 mg od following an initial 3-week course of rivaroxaban at a greater dose intensity of 15 mg bid should be used in the phase III clinical trials.

The EINSTEIN Extension study compared the efficacy and safety of rivaroxaban 20 mg od with placebo in the secondary prevention of recurrent symptomatic VTE after an initial 6 or 12 months' prophylaxis with VKA or rivaroxaban. The primary efficacy outcome was symptomatic recurrent VTE (a composite of recurrent DVT, non-fatal PE and fatal PE). The study reported a significant 82% RRR in symptomatic recurrent venous thromboembolic events after 6 to 12 months of extended treatment with rivaroxaban compared with placebo (1.3 vs. 7.1%; $P < 0.001$) (*Figure 1*). Major bleeding occurred in four patients treated with rivaroxaban and in no patients treated with placebo [22]. None of these bleeding events was fatal nor occurred in a critical site.

The recently published EINSTEIN DVT study demonstrated that rivaroxaban was non-inferior in the treatment for DVT compared with initial enoxaparin treatment followed by a VKA (standard of care). The primary efficacy outcome of recurrent symptomatic VTE occurred in 2.1% of subjects in the rivaroxaban group and 3.0% of patients receiving standard therapy (hazard ratio [HR] 0.68; 95% confidence interval, 0.44–1.04; $P < 0.001$ for non-inferiority). There was no difference between the treatment arms for the principal safety outcome of a composite of major and non-major
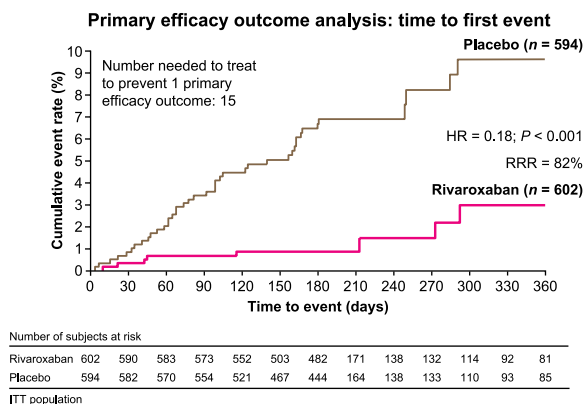
Figure 1 EINSTEIN extension: primary efficacy outcome (symptomatic recurrent venous thromboembolism, i.e. composite of recurrent deep vein thrombosis, non-fatal or fatal pulmonary embolism or unexplained death where pulmonary embolism cannot be excluded), time to first event (intention to treat [ITT] population). HR, hazard ratio; RRR, relative risk reduction.

Figure 2 EINSTEIN DVT: primary efficacy outcome (symptomatic recurrent venous thromboembolism, i.e. composite of recurrent deep vein thrombosis, fatal or non-fatal pulmonary embolism), time to first event (a) and principal safety outcome (composite of major and non-major clinically relevant bleeding), time to first event (b).

clinically relevant bleeding events (8.1% in both treatment groups, $P = 0.77$). Net clinical benefit, a pre-specified secondary outcome defined as the composite of the primary efficacy outcome plus major bleeding, demonstrated an improvement for rivaroxaban compared with standard therapy (2.9 vs. 4.2%, respectively; HR 0.67; 95% confidence interval, 0.47–0.95; $P = 0.03$) [22]. Kaplan–Meier curves for the time to first event for both the primary efficacy outcome of symptomatic recurrent VTE and the principal safety outcome are shown in *Figure 2a,b* [22]. Rivaroxaban is currently undergoing evaluation in patients with acute symptomatic PE with or without symptomatic DVT (EINSTEIN PE [23]) and for the prevention of VTE in hospitalized medically ill patients (MAGELLAN [24]).

Dabigatran was investigated for the treatment of acute symptomatic VTE in the RE-COVER study [25]. Patients with VTE were randomized to receive either dabigatran 150 mg bid or warfarin once daily for 6 months. All patients received an initial treatment of either unfractionated heparin or a LMWH.

For the primary endpoint of recurrent symptomatic VTE and VTE-related deaths, dabigatran was found to be non-inferior to warfarin (2.4 and 2.1%, respectively; HR 1.10; $P < 0.001$ for non-inferiority). Although major bleeding was not significantly different between the two treatment arms (1.6% of patients on dabigatran vs. 1.9% of patients on warfarin), when combined with clinically relevant non-major bleeding, a significant difference emerged (5.6 vs. 8.8% for dabigatran and warfarin, respectively; HR 0.63; $P = 0.002$).
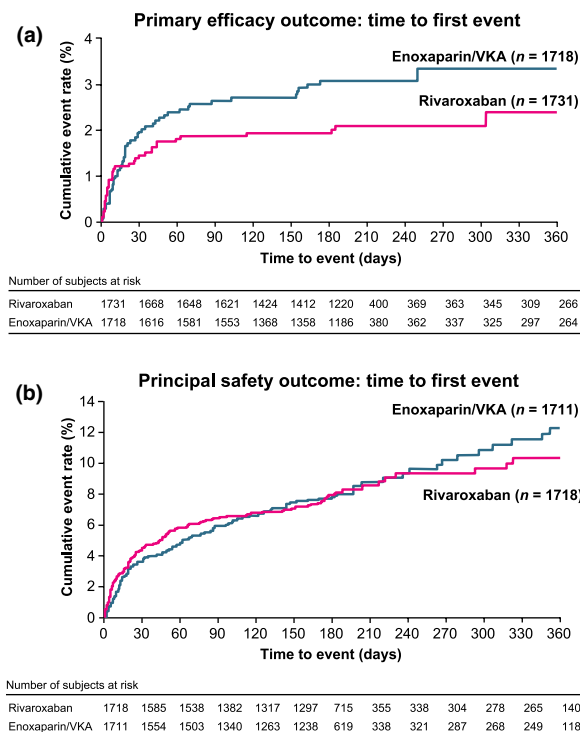
RE-MEDY [26] and RE-SONATE [27] are ongoing extension studies to RE-COVER designed to explore the safety and efficacy of dabigatran for the long-term treatment of VTE.

The phase III VTE treatment programme currently underway for apixaban consists of the 6-month AMPLIFY [28] and 12-month AMPLIFY-EXT [29] trials. AMPLIFY will investigate apixaban compared with enoxaparin plus warfarin in patients with acute DVT or PE, whereas AMPLIFY-EXT is a placebo-controlled study.

POTENTIAL ADVANTAGES OF NEW ANTICOAGULANT AGENTS

Low molecular weight heparins and VKAs are the current standard of care for VTE management and, while effective, are limited by a number of factors. LMWHs are inconvenient for long-term outpatient use because of their parenteral route of administration. VKAs, most notably warfarin, have a narrow therapeutic

range requiring frequent international normalized ratio (INR) monitoring and dose adjustments. In addition, the intensity of anticoagulation can be difficult to control because of drug and dietary interactions [1]. On average, patients maintain a target INR level only about 50–70% of the time [30], while compliance is affected by the need for restrictions on diet and alcohol intake, anxiety regarding bleeding and potential drug interactions and the burden of regular clinic visits [31]. Moreover, non-adherence to guidelines may lead to suboptimal clinical outcomes [32].

The difficulties associated with current standard of care have driven the development of a new generation of OAC agents. Rivaroxaban, dabigatran and apixaban all have a rapid onset of action [33], while fixed dosing and the demonstration of predictable pharmacology promise an end to routine coagulation monitoring, thereby offering distinct advantages over warfarin. With encouraging results emerging from phase III studies, the new generation OACs promise a greatly simplified single-drug approach to the management of anticoagulation with the prospect of improving compliance and guideline adherence.

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