Rivaroxaban
A novel, oral, direct factor Xa inhibitor in clinical development for the prevention and treatment of thromboembolic disorders

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Summary
Rivaroxaban (Xarelto®) is a novel, oral, direct Factor Xa (FXa) inhibitor in late-stage development for the prevention and treatment of thromboembolic disorders. Rivaroxaban inhibits clot-associated and free FXa activity, and prothrombinase activity, and reduces thrombin generation. In animal models, rivaroxaban prevented venous and arterial thrombosis, and was effective at treating venous thrombosis. Rivaroxaban has high oral bioavailability, a rapid onset of action and predictable pharmacokinetics. In phase II studies, rivaroxaban was effective and well tolerated for the prevention of venous thromboembolism (VTE) after major orthopaedic surgery, and for the treatment of deep vein thrombosis. In a phase III study, rivaroxaban demonstrated significantly superior efficacy to enoxaparin for thromboprophylaxis after total knee arthroplasty, with similar low bleeding. Rivaroxaban is also being assessed for the treatment and secondary prevention of VTE, prevention of stroke in patients with atrial fibrillation and secondary prevention in patients with acute coronary syndrome. Rivaroxaban is a promising alternative to current pharmacological agents for thromboembolic disorders.

Anticoagulant therapy is required for the prevention and treatment of venous and arterial thromboembolic conditions. Without thromboprophylaxis, hospital-acquired deep vein thrombosis (DVT) occurs in 10–40% of medical or general surgical patients, rising to a much higher incidence (40–60%) in patients undergoing major orthopaedic surgery (1). Of these thrombi, 25–33% involve the proximal deep veins. These thrombi are more likely to embolize, resulting in pulmonary embolism (PE), which accounts for approximately 10% of all in-hospital deaths (1). In terms of the arterial system, patients with atrial fibrillation (AF) are at a five-fold increased risk of stroke compared with the general population because stasis in the atria can cause the development of clots that travel to the brain (2). Thrombosis is also an underlying cause of acute coronary syndrome (unstable angina or myocardial infarction) (3), and, because these patients remain at high risk of recurrent events, secondary preventative therapy is required.

Guidelines recommend the use of low molecular weight heparins (LMWHs), vitamin K antagonists (VKAs) or fondaparinux (an indirect factor Xa [FXa] inhibitor) for thromboprophylaxis in patients undergoing major orthopaedic surgery, although VKAs are rarely used for this indication in Europe (1). The recommended duration of prophylaxis is at least 10 days after total knee arthroplasty (TKA), total hip arthroplasty (THA) or hip fracture surgery (HFS). Furthermore, extended prophylaxis for up to 28–35 days after surgery is recommended for patients undergoing THA or HFS (1). Although LMWHs and fondaparinux are effective anticoagulants, they are administered parenterally, which limits their use, particularly in the outpatient setting. For the secondary prevention of stroke in patients with AF, VKAs such as warfarin are the indicated treatments for most patients, due to their oral route of administration (1, 4). However, warfarin is widely underused in clinical practice, particularly in high-risk elderly patients, despite evidence that it significantly reduces the risk of stroke (5–7). There are several barriers to warfarin use, including unpredictable pharmacokinetics (PK) and pharmacodynamics (PD), which lead to a narrow therapeutic window and the requirement for frequent monitoring, as well as a high propensity for drug and food interactions (8, 9).

Clearly, there is a need for further advancement in the standards of care in anticoagulant therapy, addressing both physician concerns and patient needs. Ideally, a new anticoagulant would be orally adminis-
Rivaroxaban – a novel, once-daily, oral, direct factor Xa inhibitor

Predclinical studies

Rivaroxaban is an oxazolidinone derivative that binds with high potency and selectivity directly to FXa, without requiring cofactors. In vitro enzyme assays have shown that inhibition of human FXa by rivaroxaban is concentration dependent, with a $K_I$ of 0.4 nM (14, 15). At concentrations up to 20 μM, rivaroxaban is >10 000-fold more selective for FXa than for related serine proteases (14).

Anticoagulant activity has been demonstrated with rivaroxaban in human plasma, where it doubled prothrombin time (PT) and activated partial thromboplastin time (aPTT) at 0.23 μM and 0.69 μM, respectively. Rivaroxaban effectively inhibited prothrombinase activity on platelet surfaces ($IC_{50}$ 2.1 nM), indicating the high affinity of rivaroxaban for FXa within the prothrombinase complex (14). This is further supported by data showing that rivaroxaban (10–80 nM) provided concentration-dependent inhibition of thrombin generation after activation of the extrinsic tissue factor pathway in plasma, with complete inhibition achieved at 80 nM (16). Of note, maximal inhibition of thrombin generation of only 60% has been observed with the indirect FXa inhibitor fondaparinux (17), suggesting that rivaroxaban can more effectively access the active site of FXa within the prothrombinase complex. In separate analyses, rivaroxaban did not impair agonist-induced platelet aggregation in human platelet-rich plasma (18, 19), which suggests that rivaroxaban has no direct effects on platelet aggregation.

The antithrombotic effects of rivaroxaban have been confirmed in vivo in several animal models. In a rat venous thrombosis model (modified Wessler), intravenous rivaroxaban – administered prophylactically – dose-dependently reduced thrombus formation, inhibited FXa activity and prolonged PT (14). At the dose of 0.3 mg/kg body weight, almost complete inhibition of thrombus formation was achieved, with 65% inhibition of FXa activity and approximately three-fold prolongation of PT (14). Similar results were observed with prophylactic administration of rivaroxaban in an arterial thrombosis model (arteriovenous-shunt) in rats and rabbits (Fig. 2) (14), suggesting that rivaroxaban could be suitable for use in both arterial and venous thromboembolic disorders. Crucially, bleeding times were not prolonged at an antithrombotic-effective dose of rivaroxaban in these models (14). As well as prophylactic use, results from a study using an experimental rabbit jugular vein thrombosis model found that oral rivaroxaban significantly reduced thrombus growth, demonstrating the potential of rivaroxaban to treat thrombosis (20).

**Fig. 1** Potential enzymatic targets within the coagulation cascade (ovals: potential targets for an anticoagulant; rectangles: most effective anticoagulation by inhibition)
The preclinical profile of rivaroxaban indicates that it is a direct FXa inhibitor that combines anticoagulant activity with a low bleeding tendency, which suggests that it may have a wide therapeutic window.

**Clinical pharmacology overview**

Rivaroxaban has high oral bioavailability, a rapid onset of action, predictable, dose-proportional PK at steady state and a half-life consistent with od dosing in target populations (13, 21–23). Approximately half of the rivaroxaban dose is metabolized by the liver (no major active metabolites); the other half is excreted as unchanged drug. The metabolites and unchanged drug are eliminated primarily by renal excretion (66%); however, hepatic clearance via the faecal/biliary route plays an important role as a secondary route of elimination (28%) (24). In all phase I studies conducted to date, rivaroxaban was found to be well tolerated.

**Single-dose pharmacokinetics and pharmacodynamics:** In a dose-escalation study in healthy male subjects (13), peak rivaroxaban plasma concentrations were reached within two hours of administration of single oral doses of rivaroxaban 1.25–80 mg, with a median time to peak plasma concentration (t\text{max}) of 112 minutes for 5 mg, and 120 minutes for 80 mg. Maximum inhibition of FXa activity was achieved within 1–4 hours of rivaroxaban dosing. For doses of rivaroxaban greater than 5 mg, low levels of inhibition of FXa activity were still observed 24 hours after dosing, providing an initial indication that od dosing of rivaroxaban may be possible. Prolongation of PT followed a similar profile to that of FXa inhibition, and both were closely correlated with rivaroxaban plasma concentrations. Rivaroxaban had no direct effect on thrombin and no effect on antithrombin activity. As observed in preclinical studies (18, 19), rivaroxaban was found to have no direct effects on agonist-induced platelet aggregation, in healthy men (25).

**Multiple-dose pharmacokinetics and pharmacodynamics:** The PK and PD of rivaroxaban were further investigated in a multiple-dose study in healthy male subjects (21). Dosing regimens were 5 mg given once, twice (bid) or three times daily, and 10 mg, 20 mg or 30 mg bid, for seven days. Peak plasma concentrations of rivaroxaban were reached 3–4 hours after administration for all dosing regimens. Rivaroxaban demonstrated dose-proportional PK (normalized area under the curve [AUC] and maximum plasma concentration \([C_{\text{max}}]\)) at steady state for all doses (5 mg, 10 mg, 20 mg and 30 mg bid). No significant accumulation of rivaroxaban occurred with multiple dosing, as evidenced by the accumulation ratio \(R_{\text{AUC}}\) (AUC at steady state, relative to AUC after a single dose), which was close to 100% for all dose regimens (range 85–113%). The terminal half-life of rivaroxaban on day 7 was up to nine hours. As in the single-dose study, onset of inhibition of FXa activity occurred rapidly, with maximal inhibition achieved within 2–3 hours of rivaroxaban dosing at all dose levels. Inhibition of FXa activity was dose-dependent across all dosing regimens, and maximal inhibition was similar for initial dosing and at steady state (Fig. 3a). Following the first dose of rivaroxaban, maximum inhibition of FXa activity was 22%, 33%, 56% and 68% after doses of 5 mg, 10 mg, 20 mg, and 30 mg, respectively. Inhibition was maintained for at least 12 hours after all doses. PT and aPTT were dose-dependently prolonged to a similar extent as FXa inhibition, with peak prolongations occurring at 1–4 hours (Fig. 3b); PT correlated strongly with rivaroxaban plasma concentrations (correlation coefficient of 0.958).

The PK and PD of rivaroxaban have also been assessed in patients undergoing major orthopaedic surgery (23). As for the studies in healthy subjects, rivaroxaban was found to have predictable PK/PD in patients undergoing THA, which were similar for od or bid dosing, supporting the selection of od dosing for further investigation.

**Impact of age, gender, body weight and hepatic impairment:** A further study investigated the effect of age (>75 years) and
gender on the PK and PD of rivaroxaban in healthy subjects (22). Elderly subjects had an increased AUC compared with younger subjects, primarily due to decreased renal function (associated with age). The $C_{\text{max}}$ of rivaroxaban was unaffected by age. The half-life of rivaroxaban was up to 12 hours in elderly subjects. Gender had no significant effect on any of the PK or PD parameters of rivaroxaban. A separate study found only a small influence of extremes of body weight ($\leq 50$ or $>120$ kg) on rivaroxaban PK, requiring no dose adjustments (26). The PK and PD of rivaroxaban were not found to be altered to a clinically relevant extent in subjects with mild hepatic impairment, compared with healthy subjects (27).

**Interaction studies**

A desirable characteristic for any new anticoagulant, in addition to oral administration and no requirement for monitoring, is a low propensity for food and drug interactions, which improves convenience for patients who may require concomitant medications. Rivaroxaban did not demonstrate a clinically significant interaction with naproxen (25) or acetylsalicylic acid (28). This is relevant because a large proportion of the target population for rivaroxaban will be elderly patients, who may be receiving concomitant treatment with these agents. The combination of rivaroxaban and enoxaparin resulted in a moderate additive effect with respect to anti-FXa activity (29). Other PD parameters, such as aPTT and PT, and bleeding time, were unaffected compared with rivaroxaban alone (29). Likewise, the PK properties of rivaroxaban were not altered by enoxaparin. The PK parameters of rivaroxaban were not significantly affected by co-administration with ranitidine or antacid (30). Additionally, there was no clinically relevant interaction between rivaroxaban and digoxin (31). Food was found to improve the predictability of rivaroxaban PK (30). However, food restrictions are not necessary for patients taking rivaroxaban.

Taken together, these studies suggest that rivaroxaban has predictable PK and pharmacology in healthy subjects, which makes it unlikely to require monitoring. This should allow convenient fixed dosing, with no restrictions for age, gender, weight or co-administration with commonly used medications.

**Clinical studies overview**

Rivaroxaban has been investigated in an extensive phase II programme, including four studies in venous thromboembolism (VTE) prevention after major orthopaedic surgery and two studies in the treatment and secondary prevention of VTE. Results have also been reported from the first phase III study of rivaroxaban in VTE prevention after major orthopaedic surgery.

**Prevention of venous thromboembolism after major orthopaedic surgery:** The four large studies of rivaroxaban for the prevention of VTE after major orthopaedic surgery included nearly 3000 patients (32–35). For consistency, and to enable results to be easily compared across the different studies, each study used the same assessment parameters and endpoints, and the same blinded central adjudication committee. The primary efficacy endpoint was the composite of any DVT (proximal and distal); non-fatal, objec-

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**Figure 3** Dose-dependent inhibition of factor Xa activity (A) and prothrombin time (B) by rivaroxaban in healthy men; reproduced with kind permission by Springer Science + Business Media from Kubitz et al. (21).
tively confirmed PE; and all-cause mortality. Major VTE (proximal DVT, PE and VTE-related death) was assessed as a secondary efficacy endpoint. The primary safety endpoint was major bleeding. Enoxaparin, administered according to prescribing information in Europe or North America, was included as the active comparator in all four studies; however, because these were phase I studies, they were not powered to detect differences between rivaroxaban and enoxaparin.

The first of the studies was an open-label, proof-of-principle study in 625 patients undergoing THA, where patients received rivaroxaban (2.5–30 mg bid; or 30 mg od) or enoxaparin 40 mg od (32). Rivaroxaban was initiated 6–8 hours postsurgery and enoxaparin was first administered the evening prior to surgery; both agents were continued for 5–9 days after surgery. All doses of rivaroxaban were similarly effective with respect to the primary efficacy endpoint, with an incidence of 22.2%, 23.8%, 20.0%, 10.2%, 17.4% and 15.1% for rivaroxaban 2.5 mg, 5 mg, 10 mg, 20 mg, 30 mg bid and 30 mg od, respectively, which was similar to enoxaparin (16.8%). A flat dose/response relationship was observed between rivaroxaban and the primary efficacy endpoint (p = 0.0504). The incidence of major VTE was generally similar for rivaroxaban and enoxaparin, and was found to dose-dependently decrease with increasing rivaroxaban dose (p = 0.0108). As expected for an anticoagulant, the incidence of the primary safety endpoint – major bleeding – dose-dependently increased with rivaroxaban (p = 0.0008). The efficacy demonstrated across the 12-fold dose range investigated in this study provided preliminary evidence of the wide therapeutic window of rivaroxaban, as well as confirming the viability of od dosing (32).

Following the encouraging results of the proof-of-principle study, two further studies of identical design were conducted, one in patients undergoing TKA (n = 709) (33) and the other in patients undergoing THA (n = 726) (34). Both assessed the efficacy of bid dosing of rivaroxaban 2.5 mg, 5 mg, 10 mg, 20 mg or 30 mg relative to enoxaparin. Rivaroxaban was effective for the prevention of VTE across the wide range of doses tested, with efficacy similar to enoxaparin (Tab. 1). As would be expected based on previous studies (1), the incidence of VTE was higher in the TKA study compared with the THA study. A flat dose/response relationship was observed for rivaroxaban in terms of the primary efficacy endpoint in both studies. The incidence of major VTE with rivaroxaban was generally similar to that observed with enoxaparin in both studies (Tab. 1). Rivaroxaban also demonstrated a consistent safety profile across the two studies. At total daily doses of

<table>
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<th>study</th>
<th>result</th>
<th>rivaroxaban (total daily dose)</th>
<th>Enoxaparin*</th>
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<tr>
<td>TKA rivaroxaban bid (33)</td>
<td>primary efficacy endpoint, n/N (%)</td>
<td>20/63 (31.7) 14/60 (23.3) 15/59 (25.4)</td>
<td>31/70 (44.3)</td>
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<tr>
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<td>major VTE, n/N (%)</td>
<td>2/63 (3.2) 4/60 (6.7) 0/59 (0.0)</td>
<td>3/70 (4.3)</td>
</tr>
<tr>
<td>THA rivaroxaban bid (34)</td>
<td>primary efficacy endpoint, n/N (%)</td>
<td>16/104 (15.4) 12/101 (11.9) 18/99 (18.2)</td>
<td>18/106 (17.0)</td>
</tr>
<tr>
<td></td>
<td>major VTE, n/N (%)</td>
<td>3/104 (2.9) 1/101 (1.0) 3/99 (3.0)</td>
<td>5/106 (4.7)</td>
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5–20 mg, the incidence of major bleeding with rivaroxaban was similar to that of enoxaparin (0.8–2.3% with rivaroxaban and 1.5–1.9% for enoxaparin). The incidence of major bleeding increased at higher doses of rivaroxaban and there was a significant dose/response relationship between rivaroxaban and major bleeding in both the knee and hip studies (p = 0.0007 and p = 0.045, respectively). However, there were no significant differences between rivaroxaban and enoxaparin for major bleeding. Results from these two studies confirmed the wide therapeutic window of rivaroxaban and suggested that the optimal daily dose range for VTE prevention is 5–20 mg.

To explore the efficacy and safety of od rivaroxaban dosing and identify the optimal dose for phase III studies, a fourth phase II study was conducted in patients undergoing THA (n = 873) (35). The efficacy of rivaroxaban across an eight-fold dose range (5–40 mg od) was similar to that of enoxaparin for the primary efficacy endpoint, with an incidence of 14.9%, 10.6%, 8.5%, 13.5% and 6.4% in patients receiving 5 mg, 10 mg, 20 mg, 30 mg and 40 mg rivaroxaban, respectively, and 25.2% in patients receiving enoxaparin (Fig. 4). These results were similar to those obtained in the bid dosing studies (33, 34), indicating that there is no difference in the risk of VTE with od administration of rivaroxaban compared with bid administration. With respect to the secondary endpoint, major VTE, a significant dose/response relationship was seen for rivaroxaban (p = 0.0072), in line with findings in the proof-of-principle study. For the primary safety endpoint, the two lower doses of rivaroxaban (5 mg and 10 mg) showed a similarly low rate of major bleeding to enoxaparin (2.3% and 0.7%, respectively, compared with 1.9%). There was a significant trend in the dose/response relationship between rivaroxaban and major bleeding (p = 0.039). However, there were no significant differences between any dose of rivaroxaban and enoxaparin with respect to major bleeding, although the study was not powered to detect differences between the two agents.

Comprehensive liver monitoring was utilized in the three double-blind phase II studies, and no signal for compromised liver safety due to rivaroxaban was observed. There were no dose-dependent increases in alanine aminotransferase (ALT) levels, and any ALT increases associated with rivaroxaban were transient.

These studies demonstrated the consistent profile of rivaroxaban for the prevention of VTE in patients undergoing major orthopaedic surgery. Similar efficacy and safety findings were observed in each study, all of which confirmed the wide therapeutic window of rivaroxaban. Considering both efficacy and safety across all the studies, rivaroxaban 10 mg od was considered to provide the optimal risk/benefit balance for VTE prevention after major orthopaedic surgery (Fig. 4). As well as the efficacy and safety results with this dose in the od study, 10 mg od falls within the dose range identified as effective and well tolerated in the two bid studies. Therefore, rivaroxaban 10 mg od was chosen for investigation in phase III studies in VTE prevention after major orthopaedic surgery.

The promising phase II results were recently confirmed when data from the first phase III study, RECORD3, were presented at the International Society on Thrombosis and Haemostasis congress. Rivaroxaban 10 mg od demonstrated superior efficacy (relative risk reduction of 49% for the primary efficacy endpoint; p < 0.001) to enoxaparin 40 mg od, with similar safety (36).

Treatment and secondary prevention of venous thromboembolism: Two phase IIb studies have been conducted to assess the efficacy and safety of rivaroxaban for the treatment and secondary prevention of VTE (37, 38). Patients with acute, symptomatic, objectively confirmed, proximal DVT, without symptomatic PE, received three months’ treatment with rivaroxaban 10 mg, 20 mg or 30 mg bid or 40 mg od in one study (ODIXa-DVT study) or rivaroxaban 20 mg, 30 mg or 40 mg od in a second study (EINSTEIN-DVT study); in both studies, rivaroxaban was compared with standard therapy.

In the ODIXa-DVT study (37), the primary efficacy endpoint (improvement in thrombotic burden at day 21 [assessed by quantitative compression ultrasonography; 24-point improvement in thrombus score] without recurrent symptomatic VTE or VTE-related death) was achieved in 53.0%, 59.2%, 56.9%, and 43.8% of patients receiving rivaroxaban 10 mg, 20 mg, 30 mg bid, or 40 mg od, respectively, compared with 45.9% of patients treated with enoxaparin/VKA. There was no significant trend in the dose/response relationship between rivaroxaban bid and the primary efficacy endpoint (p = 0.67). Symptomatic, recurrent VTE at three months occurred in 1.0%, 1.0%, 0.9%, 1.8% and 0.9% of patients receiving rivaroxaban 10 mg, 20 mg, 30 mg bid, 40 mg od and standard therapy, respectively. In the EINSTEIN-DVT study (38), symptomatic, recurrent VTE or deterioration of ultrasound, or perfusion lung scan at three months occurred in 6.0%, 5.4% and 6.6% of patients receiving rivaroxaban 20 mg, 30 mg and 40 mg od, respectively, and in 9.9% of patients receiving standard therapy. The incidence of major bleeding with rivaroxaban at three months was low in both studies: 1.7–3.3% in the ODIXa-DVT study, compared with no events for standard therapy, and 0.7–1.5% in the EINSTEIN-DVT study compared with 1.5% for standard therapy.

There was no signal for compromised liver safety in the ODIXa-DVT or EINSTEIN-DVT studies; observed increases in liver enzyme levels were not dose-dependent with rivaroxaban and were generally transient (37, 38).

These studies showed that rivaroxaban, given od or bid for three months, was as effective and well tolerated as standard therapy for the treatment of acute, symptomatic DVT. Thrombus regression at three weeks was greater with rivaroxaban bid than od, suggesting bid dosing may provide an advantage shortly after DVT formation (39). Comparison of bleeding rates at three months with rivaroxaban od and bid suggested that od dosing may confer a slight advantage. Therefore, phase III studies of rivaroxaban for the treatment of VTE will investigate an intensified initial bid regimen followed by convenient, long-term rivaroxaban 20 mg od.
Ongoing development

Phase III development of rivaroxaban is well progressed. The REgulation of Coagulation in major Orthopaedic surgery reducing the Risk of DVT and PE (RECORD) programme comprises four studies involving approximately 12,000 patients. The studies are investigating rivaroxaban 10 mg od compared with enoxaparin for the prevention of VTE after THA (RECORD 1 and 2) or TKA (RECORD 3 and 4). In addition, the THA studies will investigate extended prophylaxis (5 weeks) with rivaroxaban. Results from the first of these studies, RECORD 3, have now been reported (36). The efficacy and safety of rivaroxaban in the treatment and long-term secondary prevention of DVT or PE is being assessed in the three EINSTEIN studies, involving approximately 7,500 patients. In these studies, rivaroxaban is being administered at 15 mg bid for the first three weeks after VTE, after which a convenient 20 mg od dose is being utilized. The results of the phase II studies in VTE treatment and secondary prevention were also dose-finding for the use of rivaroxaban for stroke prevention in AF. A large, randomized, double-blind study comparing rivaroxaban 20 mg od with warfarin for the prevention of stroke in approximately 14,000 patients with AF is ongoing (Rivaroxaban Once daily oral direct FXa inhibition Compared with Vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation; ROCKET AF). A phase IIb study, Anti-Xa Therapy to Lower cardiovascular events in Addition to aspirin with/without thienopyridine therapy in Subjects with Acute Coronary Syndrome (ATLAS ACS TIMI 46), is underway in patients with acute coronary syndrome.

Conclusions

Rivaroxaban is an oral, direct FXa inhibitor, and has demonstrated selective, direct inhibition of FXa activity. As well as oral administration, several key characteristics support the convenience of rivaroxaban, including od dosing, predictable PK, allowing fixed dosing without restrictions for age, gender or weight, and a low propensity for drug-drug interactions. Therefore, rivaroxaban should not require routine coagulation monitoring. An extensive phase II clinical development programme has shown that rivaroxaban has potential for the prevention of VTE and treatment of DVT. In the first of four phase III studies in VTE prevention after major orthopaedic surgery (RECORD 3), rivaroxaban demonstrated a significantly superior reduction in the composite endpoint of DVT, PE and all-cause mortality compared with enoxaparin, with similar, low bleeding rates for the two agents. On the basis of the available information on rivaroxaban presented here, it would appear to offer much potential as an alternative to available agents for the prevention and treatment of thromboembolic disorders.

References

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Das Institut für Immunologie und Transfusionsmedizin sucht zum nächstmöglichen Zeitpunkt

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Die Bereitschaft zur wissenschaftlichen Arbeit wird erwartet, die Möglichkeit zur weiteren wissenschaftlichen Qualifikation ist gegeben. Bewerbungen sollten bis zum 30. Oktober 2007 an

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