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Review Article

RIVAROXABAN: AN ORAL DIRECT INHIBITOR OF FACTOR X-A

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ABSTARCT
Venous thrombo embolism (VTE), which includes deep vein thrombosis and pulmonary embolism, is a major cause of morbidity and mortality in patients undergoing major orthopaedic surgery, and routine thrombo prophylaxis has been the standard of care over the last 20 years. Currently available options for the prevention of venous thrombo embolism in major orthopedic surgery include low-molecular-weight heparins, vitamin K antagonists and, more recently, the synthetic pentasaccharide fondaparinux. Although effective, these drugs have several limitations, and new oral antithrombotics offering predictable, effective and safe anticoagulation are strongly needed. This overview focuses on the most advanced oral direct inhibitors of factor Xa, rivaroxaban.
Rivaroxaban, an oral oxazolidinone-based anticoagulant, is a potent, selective direct inhibitor of factor Xa that is used in the prevention of venous thrombo embolism in adult patients after total hip replacement (THR) or total knee replacement (TKR) surgery. In four large, clinical trials, oral rivaroxaban was more effective than subcutaneous enoxaparin in preventing postoperative VTE in patients undergoing total hip replacement or total knee replacement surgery. Notably, the superior efficacy of rivaroxaban was achieved with a low but not significant increase in the incidence of major bleeding episodes. In addition, preliminary pharma co-economic analyses in several countries indicate that rivaroxaban is a cost-effective treatment strategy versus enoxaparin. Although the position of rivaroxaban relative to other therapies remains to be fully determined, it is an effective emerging option for the prevention of venous thrombo embolism following total hip replacement and total knee replacement.
KEY WORDS: Direct factor Xa inhibitor, oral anticoagulant, thrombin generation, rivaroxaban

INTRODUCTION

The activation of factor X to factor Xa (FXa) plays a central role in blood coagulation—it converts prothrombin (factor II) to thrombin (factor IIa), which leads to the conversion of fibrinogen to fibrin and the formation of a clot. In vivo, this process is initiated by tissue factor (TF), which, in conjunction with factor VIIa (FVIIa), activates FXa directly or via propagation of the tenase complex (factor VIIIa + IXa) on an activated platelet membrane. The prothrombinase complex is then formed on the platelet surface by FXa and platelet-derived factor Va (Figure. 1). Incorporation of FXa into the prothrombinase complex increases the rate of thrombin generation by several orders of magnitude—the prothrombinase complex is 300 000 fold more efficient at catalyzing the conversion of prothrombin (factor II) to thrombin (factor IIa) than free FXa, emphasizing the importance of platelet function for thrombin generation. In vitro studies demonstrated that although heparins inhibit free FXa, FXa incorporated into the prothrombinase complex is protected from inhibition by antithrombin and by antithrombin-dependent heparins (independent of their molecular size). Selective inhibition of FXa should terminate this burst of thrombin generation and result in potent antithrombotic activity and small-molecule direct FXa inhibitors are capable of inhibiting prothrombinase activity.[1]

Currently available anticoagulants include both parenteral and oral agents. Low-molecular-weight heparins (LMWHs) have now replaced unfractionated heparin because they are more convenient to administer, and meta-analyses of clinical trials comparing LMWHs with unfractionated heparin indicate that they are more effective and safe.[2] To date, the vitamin K antagonists are the oral anticoagulants most frequently used for daily clinical practice. However, these drugs have certain limitations, such as a narrow therapeutic window and interaction with other drugs and food, and require regular coagulation monitoring and dose titration.[3] It is clear that a more effective and convenient alternative to these traditional methods of anticoagulation is needed. A number of new oral antithrombotic therapies targeting different steps in the coagulation cascade have been investigated, including the direct thrombin (factor IIa) inhibitors and the selective factor Xa inhibitors.[4] The inhibition of factor Xa, and in particular its direct

inhibition, seems to satisfy the still unmet need of an oral, safe and easily manageable anticoagulant drug. The rationale of the direct inhibition of factor Xa has recently been reviewed[5]: (1) Factor Xa is common to the intrinsic and the extrinsic activation pathways, its inhibition providing a more effective anticoagulation. (2) Factor Xa is the primary site of amplification, as one molecule gives origin to approximately 1,000 molecules of thrombin. (3) The functions of factor Xa seem to be restricted to promoting coagulation and inflammation. Finally, small molecules of direct factor Xa inhibitors are able to inhibit both free and prothrombinase-bound factor Xa, and eventually even clot-associated factor Xa.

INTRODUCTION OF RIVAROXABAN

Rivaroxaban is a potent oral direct inhibitor of the serine endopeptidase factor Xa and inhibits both free factor Xa and factor Xa bound in the prothrombinase complex. The potency of factor Xa inhibition occurs primarily as a result of rivaroxaban binding with high selectivity to the S1 and S4 pockets of the serine endopeptidase.[6]

The chemical name for Rivaroxaban, a direct inhibitor of Factor Xa, is 5-Chloro-N-({(5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophene-carboxamide. The empirical formula is $C_{19}H_{18}ClN_3O_5S$ and the molecular weight is 435.89.[3, 4, 5] The structural formula is shown in figure 2.[7]

PHARMACOLOGY / MECHANISM OF ACTION

Rivaroxaban (BAY 59-7939) is an oral direct, reversible, competitive, rapid, and dose-dependent inhibitor of FXa.[8] Activation of factor X to factor Xa (FXa) via the intrinsic and extrinsic pathway plays a central role in the cascade of blood coagulation. FXa directly converts prothrombin to thrombin through the prothrombinase complex and, ultimately, this reaction leads to fibrin clot formation and activation of platelets by thrombin. One molecule of FXa is able to generate more than 1000 molecules of thrombin due to the amplification nature of the coagulation cascade. In addition, the reaction rate of prothrombinase-bound FXa increases 300,000-fold compared to that of free FXa and causes an explosive burst of thrombin generation. Selective inhibitors of FXa can terminate the amplified burst of thrombin generation, thereby diminishing thrombin-mediated activation of coagulation.[7]

PHARMACOKINETICS

Rivaroxaban is a non basic compound that is absorbed rapidly with 60–80% bioavailability after oral administration. Its pharmacokinetics is dose dependent, with peak plasma concentrations (C_{max}) occurring 2.5–4 hours after an oral tablet dose.[9] Rivaroxaban is bound extensively (≈90%) to plasma proteins.[8]

Studies in healthy individuals showed that rivaroxaban is rapidly absorbed, with maximum concentrations appearing 2 to 4 hours after tablet intake.[7, 10] Oral bioavailability for the 10-mg dose (which has health regulatory authority approval for thrombo prophylaxis after elective hip or knee arthroplasty in adult patients) is high (80%–100%).[8] The mean terminal half-life of rivaroxaban is 7 to 11 hours.[7, 10, 11] The elimination of rivaroxaban from plasma was rapid, with no major or pharmacologically active circulating metabolites detected in plasma. Excretion occurred via renal and fecal/biliary routes. Approximately two-thirds of the administered dose is metabolized to inactive metabolites, with half then being eliminated renally and the other half eliminated by the fecal route. The remaining one-third of the administered dose undergoes direct renal excretion as unchanged active substance in the urine.[10]

Rivaroxaban is metabolized by a number of independent metabolic pathways involving different classes of enzymes; thus, rivaroxaban should be less prone to drug–drug interactions. The main oxidative metabolic pathway is hydroxylation at the morpholinone moiety and, to a lesser extent, at the oxazolidinone moiety, catalyzed by CYP3A4/3A5 and CYP2J2.[7, 11]

CLINICAL TRIALS

In studies in healthy adult volunteers (n=43–108) and pooled analyses of trials in adult total hip replacement or total knee replacement patients (n=758 and 1009), rivaroxaban dose-dependently inhibited factor Xa and prolonged PT and aPTT. For example, in a dose-escalation study, plasma concentrations of rivaroxaban following multiple 5–30mg doses correlated with both factor Xa inhibition and PT, following a maximum effect (E_{max}) and linear model, respectively. The concentration that produced a 50% effective response (EC_{50}) for factor Xa inhibition with rivaroxaban was 220 mg/mL..[6]

In healthy male volunteers (n = 12), single doses of rivaroxaban (5 and 30 mg) dose dependently inhibited collagen- and tissue factor induced thrombin generation by ≤95% and ≤66%, respectively, demonstrating the downstream effect of rivaroxaban on thrombin generation. Similarly, in whole blood and platelet-rich plasma taken from healthy volunteers (n = 16), nano molar concentrations of rivaroxaban (5–100 nmol/L) were shown to dose dependently reduce the initiation and propagation phases of thrombo plastin-induced thrombin generation. Taken together, these data demonstrate that rivaroxaban inhibits thrombin generation by both the intrinsic and the tissue factor pathways, and that rivaroxaban may have activity towards prothrombinase-bound factor Xa.[6]

Phase I Trials

Phase I clinical studies showed that rivaroxaban is well tolerated in healthy human subjects, with a predictable, dose-proportional pharmacokinetic and pharmacodynamic profile. It is absorbed in the gastrointestinal tract, is primarily renally excreted and has a bioavailability of more than 80%. Plasma levels of the drug peak after 3–4 h, with a half-life ranging from 5 to 9 h in young individuals and from 11 to 13 h in the elderly. Like other direct factor Xa inhibitors, rivaroxaban prolongs prothrombin time and activated partial thrombo plastin time; however, the effect of the drug on these tests is short-lived, with prolongation only seen at peak drug levels.[9]

Phase II Trials

Phase II randomized, double-blind, active comparator-controlled, dose-ranging studies evaluated

the efficacy of oral rivaroxaban 2.5–30mg twice daily or 5–40mg once-daily compared with subcutaneous enoxaparin 40mg once-daily in patients undergoing total hip replacement (per-protocol populations; n = 548 and n = 618) or total knee replacement (n= 366). The primary efficacy endpoint in these studies was the incidence of the composite of any venous thrombo embolism and all cause mortality during treatment. Across the phase II studies, a relatively flat efficacy dose response was observed in patients who had received a rivaroxaban dosage regimen of 2.5, 5, 10, 20 or 30 mg twice daily or 5, 10, 20, 30 or 40 mg once daily, according to the incidence of the primary endpoint. For example, in the largest dose-ranging study in adult patients undergoing THR who received once-daily rivaroxaban 5–40 mg , no significant dose response relationship was observed (p=0.0852). However, significant dose-response relationships were observed with major postoperative bleeding events in the phase II trials. The rivaroxaban dosage that represented the optimal balance between efficacy and safety was 10 mg once daily. This dosage was selected for the phase III studies.[6]

Phase III Trials

The RECORD program comprised four phase III studies investigating the efficacy and safety of rivaroxaban in 12,500 patients undergoing total hip and knee arthroplasties. All patients received rivaroxaban 10mg once daily 6–8 hours after surgery, and there was no upper age or weight limit for participation. The primary efficacy endpoint was the composite of DVT, nonfatal PE and all-cause mortality up to day 30–42 after surgery for RECORD1 and RECORD2, up to day 13–17 for RECORD3 and up to day 17 for RECORD4. The main safety endpoint was the incidence of treatment-emergent (observed no later than 2 days after the last dose of the study drug) major bleeding events. Other safety outcomes (for example, non major bleeding and postoperative wound infection) were also reported.[6, 12]

RECORD1 showed that 5 weeks of extended-duration rivaroxaban (10 mg once daily for 31–39 days after surgery) was significantly more effective than enoxaparin (40 mg once daily for 31–39 days) for extended-duration prophylaxis in patients undergoing total hip arthroplasties (1.1% versus 3.7% for the primary efficacy endpoint, $P < 0.001$). Major bleeding events did not differ significantly between the groups (0.3% versus 0.1% of patients, p=0.18). Clinically relevant non major bleeding occurred in 2.9% of the rivaroxaban group versus 2.4% of the enoxaparin group; haemorrhagic wound complications in 1.5% versus 1.7% of patients; and postoperative wound infections in 0.4% of patients in both groups. The incidence of symptomatic VTE during treatment was not significantly different between the groups (0.3% versus 0.5%, p=0.22).

RECORD2 demonstrated that extended-duration rivaroxaban prophylaxis (10mg once daily for 31–39 days after surgery) was significantly more effective than short-duration prophylaxis with enoxaparin (40 mg once daily for 10–14 days) followed by placebo in patients undergoing total hip arthroplasties (2.0% versus 9.3% for the primary efficacy endpoint, $P < .0001$). The incidence of bleeding was comparable between extended-regimen rivaroxaban and short-duration enoxaparin. Major bleeding events occurred in <0.1% of patients in both groups. Clinically relevant non major bleeding was recorded in 3.3% of the rivaroxaban group versus 2.7% of the enoxaparin group; haemorrhagic wound complications in 1.6% versus 1.7% of patients; and postoperative wound infections in 0.7% versus 0.5% of patients, respectively. Significantly fewer patients in the rivaroxaban group had symptomatic venous thrombo embolism (0.2%) than in the enoxaparin group (1.2%, p=0.004) during the active study period.

In RECORD3, rivaroxaban prophylaxis (10mg once daily for 10–14 days) was significantly more effective than the European enoxaparin regimen for prophylaxis (40 mg once daily) in patients undergoing total knee arthroplasties (9.6% versus 18.9% for the primary efficacy endpoint, $P < .001$), with a similar safety profile. Rates of major bleeding were similar in the rivaroxaban and enoxaparin groups (0.6% versus 0.5%, p=0.77); clinically relevant non major bleeding occurred in 2.7% versus 2.3% of patients; haemorrhagic wound complications in 2.0% versus 1.9% of patients; and postoperative wound infections in 0.6% versus 0.9% of

patients. There was a significant reduction in the number of symptomatic venous thrombo embolic events in the rivaroxaban group (0.7% versus 2.0%, p=0.005).

In RECORD4, rivaroxaban showed significantly better efficacy than the enoxaparin regimen (30 mg every 12 hours) commonly used in North America for short-term prophylaxis after total knee arthroplasties (6.9% versus 10.1%, respectively, for the primary efficacy endpoint, p=0.0118) . The rates of major bleeding were 0.7% versus 0.3% (p=0.1096), respectively; clinically relevant non major bleeding occurred in 2.6% versus 2.0% of patients; haemorrhagic wound complications in 1.4% versus 1.5% of patients; and postoperative wound infections in 0.3% versus 0.2% of patients, respectively. The observed incidences of symptomatic venous thrombo embolism in those receiving rivaroxaban or enoxaparin were 0.7% versus 1.2% (p=0.187), respectively.

In the four studies comparing rivaroxaban with enoxaparin, rivaroxaban demonstrated superior efficacy compared with enoxaparin. In addition, extended thrombo prophylaxis with rivaroxaban was significantly more effective than short term enoxaparin plus placebo in the prevention of total, major and symptomatic venous thrombo embolism after total hip arthroplasties. Furthermore, the incidence of treatment-emergent major and clinically relevant non major bleeding was low for rivaroxaban and enoxaparin (p= 0.21 [data on file] for RECORD1, p=0.39 [data on file] for RECORD2, p=0.44 for RECORD3 and p=0.18 for RECORD4). There was no evidence of compromised liver function or rebound cardiovascular events associated with rivaroxaban.

In a pooled analysis of the RECORD1, 2 and 3 studies (which compared rivaroxaban with enoxaparin 40 mg once daily after total hip and knee arthroplasties) , the prespecified primary efficacy outcome (the composite of symptomatic venous thrombo embolism and all-cause mortality at 2 weeks) was 0.4% and 0.8%, respectively (p=0.005). The rates were 0.5% and 1.3%, respectively, at the end of the planned medication period ($P < .001$). Rates of on-treatment major bleeding were 0.2% for both drugs at 2 weeks (p=0.662), and 0.3% for rivaroxaban and 0.2% for enoxaparin at the end of the planned medication period (p=0.305). Rates of clinically relevant non major bleeding were 2.6% for rivaroxaban and 2.3% for enoxaparin at 2 weeks, and 3.0% and 2.5%, respectively, at the end of the planned medication period (*P* values not reported). In a pooled analysis of all four RECORD studies, the primary efficacy endpoint (the composite of symptomatic venous thrombo embolism and death) was significantly reduced for the rivaroxaban regimens compared with enoxaparin regimens at day 12 ± 2 (0.5% versus 1.0%, p=0.001), in the planned treatment period (0.6% versus 1.3%, p<0.001), and in a post hoc analysis of the treatment and follow-up period (0.8% versus 1.6%, p<0.001). Rates of treatment emergent major bleeding were not significantly different between groups at any of the time points analysed. The composite of major and clinically relevant non major bleeding did not differ at day 12 ± 2 (p=0.186), but was significantly higher for rivaroxaban in the planned medication period (p=0.039). Rates of the composite of pulmonary embolism and death were lower for rivaroxaban compared with enoxaparin in the planned treatment period and follow-up (0.5% versus 0.8%, p=0.039).

ADVERSE DRUG REACTIONS

The most common ADEs were nausea, anemia, post procedural hemorrhage, increase in transaminases, gamma-glyamyltransferase.[7]

The safety of rivaroxaban 10 mg has been evaluated in three randomized, double-blind, active control phase III studies (RECORD 1, RECORD 2, and RECORD 3). In the phase III studies, 4657 patients undergoing total hip replacement or total knee replacement surgery were randomized to rivaroxaban, with 4571 patients actually receiving rivaroxaban.[7]

In RECORD 1 and 2, a total of 2209 and 1228 total hip replacement patients, respectively, were randomized to rivaroxaban 10 mg od. In RECORD 1, the treatment period for both groups was 35±4 days postoperatively. In RECORD 2, patients randomized to rivaroxaban were treated for 35 ±4 days postoperatively, and patients randomized to enoxaparin received placebo after day 12±2 until day 35±4 postoperatively. In RECORD 3, a total of 1220 total knee replacement patients were randomized to rivaroxaban 10 mg od, and both groups received study drug until day 12±2 postoperatively. The safety profile of rivaroxaban with regard to adverse events (AE) and serious adverse events (SAE) is similar to that of the active comparator in the RECORD 1, 2, and 3studies.[7]

The most common adverse events (apart from bleeding) during rivaroxaban treatment across the RECORD trials were pyrexia, vomiting, nausea and constipation, and these events occurred at a similar frequency to that with enoxaparin treatment. Generally similar incidences of elevated liver enzymes were observed in rivaroxaban recipients compared with enoxaparin recipients across the four RECORD trials.[6]

DRUG INTERACTIONS

Several randomized studies in healthy volunteers have examined the pharmacokinetic interactions between rivaroxaban and other agents. These studies are fully published or are available as abstracts. No clinically relevant pharmacokinetic interactions occurred when rivaroxaban was coadministered with agents that interfere with platelet function and homeostasis, such as aspirin, enoxaparin or clopidogrel.[13]

There were also no pharmacokinetic interactions when rivaroxaban was coadministered with the NSAID naproxen or the cardiac glycoside digoxin. However, there is an increased risk of bleeding with concurrent administration of rivaroxaban with NSAIDs, aspirin and platelet aggregation inhibitors (e.g. clopidogrel); therefore, caution is advised when these agents are coadministered.[11]

Coadministration of rivaroxaban with strong CYP3A4 and P-glycoprotein inhibitors such as azole antifungal agents (e.g. ketoconazole) or HIV protease inhibitors may increase plasma rivaroxaban concentrations to a clinically relevant degree, which may lead to an increased bleeding risk. For example, concomitant administration of rivaroxaban with ketoconazole (400 mg once daily) or ritonavir (600 mg twice daily) increased the mean AUC of rivaroxaban by 2.6- and 2.5-fold and increased mean C_{max} of rivaroxaban by 1.7- and 1.6-fold, with corresponding increases in pharmacodynamic effects, potentially increasing the bleeding risk. The use of rivaroxaban is, therefore, not recommended in patients receiving these agents.[12] In some countries (EU and Canada), the manufacturer's SPC advises caution if rivaroxaban is coadministered with strong inducers of CYP3A4 (e.g. rifampicin (rifampin), phenytoin, hypericum and carbamazapine), because this can result in reduced plasma rivaroxaban concentrations.[7,11]

PRECAUTIONS AND WARNINGS

Appropriate precautions required because as with rivaroxaban, like other anticoagulants, should be used with caution in patients with an increased bleeding risk such as congenital or acquired bleeding disorders, uncontrolled severe arterial hypertension, vascular retinopathy, or concomitant use of drugs affecting hemostasis. Due to the pharmacological mode of action, rivaroxaban may be associated with an increased risk of occult or overt bleeding which may result in post hemorrhagic anemia. The signs, symptoms, and severity will vary according to the location and degree, or extent, of the bleeding.[7,11]

The use of rivaroxaban is contraindicated in patients receiving concomitant systemic treatment

with strong inhibitors of both *CYP3A4* and P-gp such as ketoconazole, itraconazole, voriconazole, posaconazole, or ritonavir). These drugs may increase rivaroxaban plasma concentrations to a clinically relevant degree, which may lead to an increased bleeding risk. Strong *CYP3A4* inducers should be administered with caution in combination with rivaroxaban Care should be taken if patients are treated concomitantly with drugs affecting hemostasis such

as nonsteroidal anti-inflammatory drugs (NSAIDs) and platelet aggregation inhibitors. Coadministration of rivaroxaban with other anticoagulants or antithrombotic therapy has not been adequately studied in clinical trials and is not recommended, as it may lead to an increased bleeding risk. Any unexplained fall in hemoglobin or blood pressure should lead to a search for a bleeding site.[7,11]

DOSAGE AND ADMINISTRATION

Rivaroxaban has been approved in the EU, Canada and several other countries for the prevention of venous thrombo embolism in adult patients undergoing total hip replacement or total knee replacement surgery. A new drug application is under review and is pending in the US.

The recommended dose of rivaroxaban is 10 mg taken orally once daily with the initial dose taken 6–10 hours after surgery, provided that haemostasis has been established. The duration of prophylaxis depends on the type of orthopaedic surgery. For patients undergoing THR, prophylaxis for 5 weeks is recommended; for those undergoing major knee surgery, the recommended duration is 2 weeks.[13,35] Rivaroxaban 10 mg once-daily can be taken with or without food.[7,11]

In patients with mild (CLCR 50–80mL/min [3.0–4.8 L/h]) or moderate (CLCR 30–49mL/min [1.8–2.9 L/h]) renal impairment, no dose adjustment is necessary. Patients with severe renal impairment (CLCR <30mL/min [<1.8 L/h]) were excluded from the RECORD studies; however limited clinical data for these patients indicate that plasma rivaroxaban concentrations are significantly increased in this patient population, therefore, the EU and Canadian manufacturers' summary product characteristic recommend that rivaroxaban be used with caution in these patients.

Rivaroxaban is contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk. In the EU, it is recommended that rivaroxaban be used with caution in cirrhotic patients

with moderate hepatic impairment (Child-Pugh B) if it is not associated with coagulopathy.

Tolerability

Generally similar bleeding events were observed in the individual RECORD trials, with no significant between-group differences in major bleeding events, on treatment non-major bleeding events and any on-treatment, bleeding events with rivaroxaban and enoxaparin treatments. Bleeding events were the most frequently reported adverse events associated with rivaroxaban prophylaxis across the four RECORD trials.[6]

CONCLUSION

Oral factor Xa inhibitors are undoubtedly a further improvement in anticoagulation therapy

and appear to be a very promising strategy for thrombo prophylaxis in orthopedic surgery. Rivaroxaban is a direct FXa inhibitor that appears to offer promise for the prevention and treatment of venous thrombo embolism and for stroke prevention in atrial fibrillation; it offers once-daily oral administration without the need for frequent monitoring. Because of its favorable safety and tolerability profile in healthy individuals and a positive benefit to- risk ratio for the prevention of venous thrombo embolism in patients after total hip arthroplasty or total knee arthroplasty,the 10-mg once-daily dose has been granted health regulatory authority approval for the prevention of venous thrombo embolism after elective hip or knee arthroplasty in adult patients. The oral bioavailability of rivaroxaban is an advantage over parenteral anticoagulant agents and could provide better convenience in outpatient settings. The pharmacodynamic and pharmacokinetic profiles, which were found to be predictable, together with the low interaction potential with food or other drugs, the wide therapeutic window, and the absence of a requirement for routine coagulation monitoring, enhance the likelihood that oral factor Xa inhibitors such as rivaroxaban may become an alternative to vitamin K antagonists in patients at risk for thrombo embolism.

REFERENCES

1. Graff J, Hentig N, Misselwitz F, Kubitza D, Becka M, Breddin HK and Harder S. Effects of the Oral, Direct Factor Xa Inhibitor Rivaroxaban on Platelet-Induced Thrombin Generation and Prothrombinase Activity. J Clin Pharmacol 2007; 47:1398-1407.
2. Weitz JI, Hirsh J, Samama MM: New antithrombotic drug. American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th edition). Chest 2008; 133: 234S–256S.
3. Furie B, Furie BC: Molecular basis of vitamin K-dependent γ-carboxylation. Blood 1990; 75: 1753–1762.
4. Harenberg J: Indirect and direct anticoagulants predominantly inhibiting factor Xa. Therapy 2008; 5: 177–192.
5. Turpie AG: Oral, direct factor Xa inhibitors in development for the prevention and treatment of thromboembolic diseases. Arterioscler Thromb Vasc Biol 2007; 27: 1238–1247.
6. Duggan ST, Scott LJ and Plosker GL. Rivaroxaban- a review of its use for the prevention of venous thromboembolism after total hip or knee replacement surgery. Drugs 2009; 69 (13): 1829-1851.
7. Product Monograph of [Pr] Xarelto™ Rivaroxaban Tablets 10 mg. Anticoagulant. Bayer Inc. 77 Belfield Road, Toronto, Ontario, Canada. Date of Preparation: September 10, 2008.
8. Misnetti P, Laporte S. Rivaroxaban : données pharmaco-cliniques Rivaroxaban: clinical pharmacology. French annals of Anaesthesia and Intensive Care, 2008; 27: S16-S21.
9. Imberti D, Prisco D. Oral factor Xa inhibitors for venous thromboembolism prevention in major orthopedic surgery: A Review. Pathophysiol Haemost Thromb 2007–08; 36: 217–226.
10. Perzborn E, Roehrig S, Straub A, Kubitza D, Mueck W and Laux V. Rivaroxaban: A new oral factor Xa inhibitor. Arterioscler Thromb Vasc Biol 2010; 30; 376-381.
11. Summary Product Characteristic of Xarelto 10 mg Tablets.
12. Friedman RJ. New oral anticoagulants for thromboprophylaxis after elective total hip and knee arthroplasty. Thrombosis 2010; 1-9.
13. Kubitza D, Becka M, Mueck W, Zuehlsdorf M. Safety, tolerability, pharmacodynamics, and pharmacokinetics of rivaroxaban- an oral, direct factor Xa inhibitor- are not affected by aspirin. J Clin Pharmacol. 2006 Sep; 46(9):981-90.

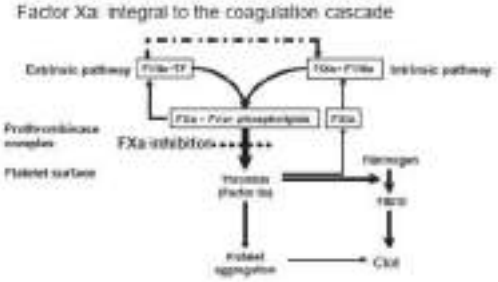


Figure 1: Thrombin generation cascade at the interface between endothelium, plasmatic coagulation, and platelet membrane [5]

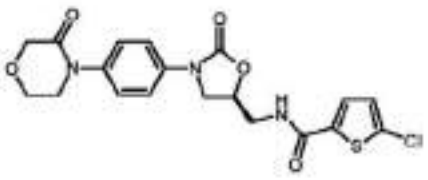


Figure 2: Chemical Structure of Rivaroxaban [7]