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RIVAROXABAN: THE FIRST FDA APPROVED ORAL DIRECT FACTOR XA INHIBITOR

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Venous thromboembolism (VTE) is a preventable event associated with significant morbidity and mortality.[1] Patients undergoing total hip or knee arthroplasty are at an increased risk for venous thromboembolism, including deep vein thrombosis (DVT) and pulmonary embolism (PE).[2] Routine prophylactic anticoagulation strategies are recommended to prevent thromboembolic events. After orthopedic surgery, DVT occurs in 40-60% patients and PE occurs in up to 30% of patients not properly anticoagulated.[2] Currently the most effective agents used in VTE prophylaxis include anticoagulants such as low -molecular-weight heparins, fondaparinux, and oral vitamin K antagonists such as warfarin.[2]

Anticoagulant therapy is also used in prophylactic stroke prevention in patients with non-valvular atrial fibrillation (NVAF). Atrial fibrillation is the most common arrhythmia affecting more than 2.3 million people in the US.[3] One of the major complications of this cardiac disorder is a cardiogenic emboli leading to a stroke. Each year in the US atrial fibrillation is responsible for 50,000 strokes in patients who are properly anticoagulated.[4] The CHADS2 algorithm is used to assess for stroke risk factors and stratify risk for a cardiogenic emboli in patients with atrial fibrillation (**Table 1**). Two points are assigned if the patient has had a previous stroke or transient ischemic attack and one point is assigned for each factor: over the age of 75, hypertension, diabetes, or congestive heart failure.[5] The total score is used to guide physicians on what therapeutic options are recommended for anticoagulation (**Table 2**). The American College of Chest Physicians guidelines for atrial fibrillation presents three options for patients with NVAF: no anticoagulation, aspirin 81-325mg daily, or anticoagulant therapy (warfarin, dose adjusted to a target INR 2.5, goal range 2-3, or dabigatran). No anticoagulation is an option only if a patient has a CHADS2 score of less than 1. If a patient has a CHADS 2 score of 1, either aspirin 81-325 mg daily or an anticoagulant are options, but anticoagulant therapy with warfarin is preferred.[5] With a score of 2 or greater, aspirin is no longer recommended and patients should receive anticoagulation therapy with warfarin or dabigatran. For the past 60 years warfarin has been the anticoagulant of choice for at risk patients for stroke prevention. While oral dosing is convenient, warfarin has a delayed onset of action, low bioavailability, and unpredictable pharmacokinetics from drug-drug and drug-food interactions, and requires frequent laboratory monitoring which make it burdensome to use.[6] In the past few years there has been an increased interest in developing oral anticoagulant therapies that offer safe and effective anticoagulation without the need for routine laboratory monitoring.[7]

Inside This Issue:

Table 1 | CHADS 2 risk [5]

	Condition	Points
C	Congestive Heart Failure	1
H	Hypertension (>140/90 mmHg)	1
A	Age >75 years	1
D	Diabetes	1
S	Stroke or Transient ischemic attack	2

Rivaroxaban, a selective factor Xa inhibitor, was FDA approved in July 2011 under the trade name Xarelto® for VTE prophylaxis in patients undergoing elective total hip or knee replacement surgery.[8] In November 2011, rivaroxaban earned a second approval for prophylactic stroke prevention in patients with NVAF. Rivaroxaban was developed and manufactured by Bayer/Johnson & Johnson and is being marketed by Janssen Pharmaceuticals.[8] The objective of this article is to review the pharmacology, pharmacokinetics, safety and efficacy in clinical trial data, drug interactions, dosing and cost of rivaroxaban.

Pharmacology

Rivaroxaban is an orally bioavailable, reversible factor Xa (FXa) inhibitor that selectively blocks the active site of FXa and does not require a cofactor (such as anti-thrombin III). It is an oxazolidinone derivative and structurally similar to the antibiotic linezolid, but contains no antibiotic activity.[9] FXa is the active component of the prothrombinase complex which is responsible for the conversion of prothrombin (factor II) to thrombin (factor IIa). FXa plays a major role in thrombin generation as it is located at the beginning of the common pathway of where the extrinsic and intrinsic coagulation systems merge. Rivaroxaban inhibits FXa whether it is free in the plasma, bound to a clot, or incorporated within the prothrombin complex.[10] Thrombin is a multifunctional factor which converts fibrinogen to fibrin, activates platelets, activates factor XIII (which cross links formed fibrin), and enhances further thrombin production via the activation of factors V and VIII through positive feedback.[11] This pharmacologic property may be an added benefit to using rivaroxaban over some of the alternative anticoagulants, especially with patients with a preexisting clot.[12]

Pharmacokinetics

The absolute bioavailability of rivaroxaban is dose-dependent. At a dose of 10 mg the bioavailability is estimated to be 80% to 100% and is not affected by food.[8] The absolute bioavailability at a dose of 20 mg in the fasted state is approximately 66%. If administered with food the mean area under the curve (AUC) is increased by 39% and the maximum concentration (Cmax) is increased by 76%. Absorption is dependent on the site of drug release in the GI tract. There is a 29% and 56% decrease in AUC and Cmax, respectively, when the drug is released in the proximal small intestine and continues to decrease further through the distal small intestine or ascending colon. Rivaroxaban may be administered via a feeding tube. However, it is important to locate the exact position when placing a feeding tube since intestinal absorption is much lower than gastric absorption. It is recommended that the 15 mg and 20 mg doses should be taken with an evening meal. No dose adjustment was needed for gender or for weight extremes (< 50 kg or > 120 kg).[8]

The time to maximum concentration (Tmax) is achieved in 2 to 4 hours after ingestion. Absorption is not affected by medications that alter gastric pH including proton pump inhibitors and H2-receptor antagonists.[12] Plasma protein binding is 92% to 95%, with albumin being the primary binding protein. The steady-state volume of distribution is approximately 50 liters.[8]

Rivaroxaban undergoes hepatic biotransformation through cytochrome P-450 enzymes (CYP) 3A4/5 and CYP 2J2 and hydrolysis leaving no active circulating metabolites. Excretion has three parts: one third is eliminated as unchanged drug by the kidneys, one third is metabolized by the liver through CYP3A4 dependent and independent pathways with metabolites excreted in the feces, and the final third is metabolized in the liver with metabolites that are eliminated renally.[13] In young, healthy patients the half life is 5-7 hours which increases to 11-13 hours for elderly patients (**Table 3**).

There is no requirement for routine monitoring for rivaroxaban like for warfarin. Rivaroxaban effectively and dose-dependently inhibits FXa activity and prolongs both prothrombin time (PT) and activated partial thromboplastin time (aPTT).[10] However, since the prolongation parameters of PT and aPTT vary signifi-

Table 2 | CHADS 2 assessment [5]

Total score (points)	Risk	CHEST guidelines recommendation
0	Low	None or aspirin 81-325 mg daily; none preferred
1	Moderate	Aspirin 81-325 mg daily or anticoagulation*; anticoagulation preferred
2 or greater	High	Anticoagulation*

*Anticoagulation with either warfarin (goal INR range 2-3) or oral anticoagulant such as dabigatran or rivaroxaban
INR: International normalized ratio

cantly depending on the clotting assays and the substrates used, they are not useful for monitoring the pharmacodynamic effects of rivaroxaban in clinical practice.[14] Chromogenic anti-Xa assays appear to be the most reliable tool for monitoring the anticoagulant activity of rivaroxaban. Currently the standardization of a chromogenic anti-Xa assay and the reagents to use with them is under investigation.[15]

Clinical Trials

The Regulation of Coagulation in Major Orthopedic Surgery Reducing the Risk of DVT and PE (RECORD) trials were a series of four phase III, randomized, double-blind, double-dummy, parallel-group clinical trials involving more than 9000 patients undergoing elective total hip replacement (THR) or total knee replacement (TKR) surgery.[16-19] The RECORD 1[16] and 2 trials[17] involved THR patients, while RECORD 3[18] and 4[19] were conducted in patients undergoing TKR. Efficacy and safety end points were identical in all of the trials. Patients were not eligible for all four trials if they were not at least 18 years of age, pregnant or breastfeeding, at high risk for bleeding, had a contraindication to enoxaparin or rivaroxaban, required dose adjustment of enoxaparin, had significant liver disease or a creatinine clearance < 30 mL/minute, were using protease inhibitors, or if current anticoagulation therapy could not be stopped. However, the RECORD 1 trial[16] was the only trial that included patients whom were concomitantly on fibrinolytic agents.

In all four trials, rivaroxaban was given postoperatively at a fixed dose of 10 mg once daily. In RECORD 1-3[16-18] the dose of enoxaparin was 40 mg subcutaneously once daily, the European dose approved for VTE prevention. In the RECORD 4[19] trial, enoxaparin 30 mg subcutaneously twice daily was used, which is the FDA approved dose for VTE prophylaxis. At the conclusion of therapy, all patients underwent mandatory bilateral venography to assess for the presence of a DVT. The primary end point was the composite of total VTE (any DVT, non-fatal PE) and all-cause mortality. The secondary efficacy outcome was a composite of major VTE, which included proximal DVT, non-fatal PE, symptomatic VTE, or death related to VTE. [16-19] The primary safety end point was major bleeding that was recorded after administration of the first dose until 2 days after the last dose was received. Major bleeding was defined as bleeding that was fatal, involved a critical organ or reoperation, occurred outside the surgical site, or that decreased hemoglobin levels by 2 g/dL, or required an infusion of 2 or more units of blood. Approval of rivaroxaban in orthopedic surgery was based on data from RECORD 1-3 trials (**Table 4**).[8]

Table 3 | Pharmacokinetic Properties of Rivaroxaban [8]

Property	Value
Peak plasma concentration	1-4 hours
Bioavailability	66-80%
Volume of distribution	50L
Protein binding	90% (mainly albumin)
Metabolism	CYP 3A4, CYP2J2 and hydrolysis
Clearance	2/3- renal 1/3 fecal-biliary
Half-life	5-7 hours (average) 9-13 hours (elderly)
Monitoring	No need to monitor. No standardized assay currently

CYP: cytochrome P-450; L: liter

In RECORD 1, the incidence of total VTE was reduced from 3.9% in patients receiving enoxaparin to 1.1% in the rivaroxaban group (relative risk reduction: RRR: 71%, p <0.001) and the incidence of major VTE was reduced from 2.0 to 0.2% respectively (RRR: 88%, p <0.001).[16]

The aim of the RECORD 2 trial was to assess extended thromboprophylaxis with rivaroxaban for 31-39 days compared to a short term, 10-14 day enoxaparin regimen in patients undergoing THR. The American College of Chest Physicians Guidelines recommends up to 35 days of VTE prophylaxis for THR (Grade 1A recommendation).[2] In this trial, the incidence of total VTE was significantly reduced from 9.3% in the group receiving short-term enoxaparin to 2.0% in the long term rivaroxaban group (RRR: 79%, p <0.001). There were 81 events in 869 patients in the short-term prophylactic enoxaparin group and only 17 events in the 864 patients receiving rivaroxaban. The incidence of major VTE also was significantly reduced from 5.1 to 0.6%, respectively (RRR: 88%, p <0.001). However, 10 of the 15 symptomatic DVTs that occurred in the enoxaparin group occurred after day 14 when enoxaparin was discontinued.[17]

The RECORD 3 trial showed a significant reduction in all primary and secondary efficacy end points in the rivaroxaban group. Total VTE was reduced from 18.9% in enoxaparin group to 9.6% in patients on rivaroxaban (RRR: 49%, p <0.001). Major VTE was decreased from 2.6% with enoxaparin to 1.0% in those receiving rivaroxaban (RRR: 62%, p <0.010), and symptomatic VTE was decreased from 2.0% to 0.7%, respectively (RRR: 66%, p =0.005).[18]

Lastly, the RECORD 4 trial demonstrated that riva-

Table 4 | Results of the RECORD Trials

Study	Exclusion criteria	Primary Outcome	Treatment groups	Results
RECORD 1[16] (N = 3,153 in superiority analysis) R, MN, DB, DD, C study, patients >18 yo who underwent THR	Pts who were scheduled to undergo staged THR, were pregnant or breastfeeding, high bleeding risk, CID to either medication, condition requiring dose adjustment of enoxaparin, significant liver disease, CrCl <30 mL/min, use of protease inhibitors or in whom current anticoagulation could not be stopped	Composite of non fatal PE, DVT (symptomatic or detected by bilateral venography if patient was asymptomatic) or all cause mortality at 36 days (range 30-42)	Rivaroxaban 10 mg daily initiated 6-8 hrs after wound closure for 35 days OR SC enoxaparin 40mg daily initiated 12 hrs before surgery and then 6-8 hrs after wound closure and continued for 35 days	Primary outcome occurred in 1.1% of rivaroxaban pts and 3.9% of enoxaparin. pts. • RRR =71% • 95% CI: 50-83% • p <0.001
RECORD 2[17] (N= 1733 in primary efficacy analysis) R, MN,DB, DD, C study, patients >18 yo who underwent THR	Same as RECORD 1 as well as concomitant use of a fibrinolytic agent	Composite of non fatal PE, DVT (symptomatic or detected by bilateral venography if patient was asymptomatic) or all cause mortality at 36 days (range 30-42)	Rivaroxaban 10 mg daily initiated 6-8 hrs after wound closure for 31-39 days OR SC enoxaparin 40mg daily initiated 12 hrs before surgery and then 6-8 hrs after wound closure for 10-14 days	Primary efficacy outcome occurred in 2% of rivaroxaban pts and 9.3% of enoxaparin pts • RRR =79% • 95% CI: 59-86% • p <0.0001
RECORD 3[18] (N =1702 in primary outcome analysis) R,MN, DB,DD, C study, patients >18 yo who underwent TKR	Same as RECORD 2	Composite of any DVT, non-fatal PE or all cause mortality within 13-17 days after surgery	Rivaroxaban 10 mg daily initiated 6-8 hrs after wound closure for 10-14 days OR SC enoxaparin 40mg daily initiated 12 hrs before surgery and then 6-8hrs after wound closure and continued for 10-14	Primary outcome occurred in 9.7% of rivaroxaban pts and 18.8% of enoxaparin pts • RRR =48% • 95% CI:34-60% • p <0.001
RECORD 4[19] (N =1924 in primary outcome analysis) R,MN, DB,DD C study, patients >18 yo who underwent TKR	Same as RECORD 2	Composite of any DVT, non-fatal PE or all cause mortality up to 17 days after surgery	Rivaroxaban 10 mg/ daily initiated 6-8 hrs after wound closure for 10-14 days OR SC enoxaparin 30mg BID initiated 12-24 hrs after wound closure and continued for 10-14 days	In MITT, the primary efficacy outcome occurred in 6.9% of rivaroxaban pts and 10.1% enoxaparin pts • RRR =31.4% • 95% CI: 7.5-49.1% • p =0.0160

BID: twice daily; C: controlled; CI: confidence interval; CID: contraindication; CrCl: creatinine clearance; DB: double blind, DD: double dummy, DVT: deep vein thrombosis; hrs: hours; min: minutes; MITT: modified intention-to-treat; MN: multinational; PE: pulmonary embolism; Pts: patients; R: Randomized; RRR: relative risk reduction; SC: subcutaneous; THR: total hip replacement; TKR: total knee replacement; yo: years old

roxaban was significantly more effective than enoxaparin at the FDA approved dose, 30 mg twice daily, for prevention of VTE in the setting of TKR.[19] In the per-protocol population the primary efficacy outcome occurred in 6.7% of the 864 rivaroxaban patients and 9.3% of the 878 enoxaparin patients (weighted absolute risk reduction 2.71%; p =0.0118 for superiority), indicating not only non-inferiority but also superiority of rivaroxaban over enoxaparin. In the modified intention to treat analysis, the total incidence of VTE decreased from 10.1% in the enoxaparin group to 6.9% in the rivaroxaban group (RRR: 31%, p <0.012).[19]

In the RECORD trials rivaroxaban demonstrated superior efficacy for VTE prevention with no statistical difference in the safety end points when compared with enoxaparin.[16-19] Out of all four trials, the RECORD 2 trial[17] was the only one designed as a superiority trial, while the others were designed as non-inferiority trials.[16,18,19] The RECORD 2 trial specifically showed that extended thromboprophylaxis with rivaroxaban was significantly more effective than short-term enoxaparin plus placebo in the prevention of total, major and symptomatic VTE after THR.[17] Lastly, the RECORD 4 trial[18] proved rivaroxaban is superior to the US approved dose of enoxaparin 30 mg twice daily, which was a different than the off-label dose of 40 mg daily, often used in European countries, used in the previous 3 RECORD trials.

The Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF) was a multi-center, randomized, double-blind, double-dummy study comparing once daily rivaroxaban (20 mg daily or 15 mg daily for patients with a creatinine clearance [CrCl] of 30-49 mL/minute) to dose-adjusted warfarin in patients with NVAF who were at moderate to high risk for stroke.[20] Patients had to have a CHADS2 score of at least 2 to be eligible . Over 54% of the patients had a previous stroke, embolism, or transient attack, 90.5% had hypertension, 62.5% had heart failure, and 40% had diabetes. The mean and median $CHADS_2$ scores were 3.5 and 3.0, respectively. Patients were excluded if they had valvular disease, transient atrial fibrillation caused by a reversible disorder, at an increased hemorrhagic risk, or were to receive planned cardioversion. The primary efficacy outcome was the composite of ischemic or hemorrhagic stroke and systemic embolism. The main safety outcome was the composite of major and nonmajor clinically relevant bleeding events. CNS bleeding was considered a hemorrhagic stroke and included in both the primary efficacy and safety end points.[20]

In the per-protocol population (all the patients included in the primary efficacy analysis), stroke or systemic embolism occurred in 188 patients in the rivaroxaban group (1.7% per year) and in 241 patients in the warfarin group (2.2% per year) (hazard ratio (HR) 0.79%; 95% CI 0.66-0.96; p <0.001 for non-inferiority) (**Table 5**). In the as-treated safety population, 189 patients in the rivaroxaban group (1.7% per year) and 243 warfarin patients (2.2% per year) had a primary event occur (HR 0.79; 95%CI: 0.65-0.95; p =0.01 for superiority). In the intention to treat analysis, which included all the randomized patients, primary events occurred in 269 patients in the rivaroxaban group (2.1% per year) and in 306 patients receiving warfarin (2.4% per year) (HR 0.88; 95% CI, 0.74-1.03; p <0.001 for non-inferiority and p =0.12 for superiority). Rivaroxaban was found to be non-inferior to warfarin but was not statistically superior in reaching the primary end point. However, in the intention to treat analysis, rivaroxaban was superior to warfarin in the safety population. Amongst the patients who stopped taking their assigned medication before the end of the study, 42 primary events occurred in patients originally as-

Table 5 | Rocket AF Primary Endpoint of Stroke or Systemic Embolism§ [20]

Study Population	Rivaroxaban	Warfarin	Hazard Ratio (HR)	p-value	
	Event Rate ¥ (#of events)	Event Rate (#of events)	HR (95% CI)	Non-inferiority	Superiority
Per-protocol, as treated Ⱨ	1.7 (188)	2.2 (241)	0.79 (0.66-0.96)	p <0.001	
Safety, as treated	1.7 (189)	2.2 (243)	0.79 (0.65-0.95)		p =0.02
ITT population£	2.1 (269)	2.4 (306)	0.88 (0.75-1.03)	p <0.001	p =0.12
ITT during treatment	1.7 (188)	2.2 (240)	0.79 (0.66-0.96)		p =0.02
ITT after discontinuation	4.7 (81)	4.3 (63)	1.10 (0.79-1.52)		p =0.58

§ The mean follow up time was 590 days for the per-protocol as treated and safety as treated population. The mean follow up for the intention to treat population was 707 days.
¥ measured in number/100 patient-years
Ⱨ The primary analysis was performed in the as treated per-protocol population
£ Follow up of the intention to treat continued until notification of the study termination
CI: confidence interval; IIT: Intention to treat

Table 6 | Incidence of Adverse Events of RECORD trials [8,16-19]

	RECORD 1 [16]	RECORD 2 [17]	RECORD 3 [18]	RECORD 4 [19]
Major bleeding (primary safety outcome)	0.3% R vs 0.1% E	<0.1% both groups	0.6% R vs 0.5% E	0.7% R vs 0.3% E
Hemorrhagic wound complications (secondary safety outcome)	1.5% R vs 1.7% E	1.6% R vs 1.7% E	2.1% R vs 2% E	1.4% R vs 1.5% E
Other Adverse Reactions[8]		RECORD 1-3 Trials		
Wound secretion		2.8% R; 2% E		
Pain in extremity		1.7% R; 1.2% E		
Muscle Spasm		1.2% R; 0.7% E		
Syncope		1.2% R; 0.7% E		
Pruritus		2.1%R; 1.8% E		
Blister		1.4% R; 0.9% E		
Renal/urinary disorders		<1% both groups		

E: enoxaparin; R: rivaroxaban

signed rivaroxaban and in 36 patients in the warfarin group during the first 30 days after the medication was discontinued. At the completion of the study, 92.5% of the patients in both treatment groups, still on the assigned study drug, were transitioned to warfarin. Patients originally on rivaroxaban experienced more primary events than patients on warfarin (22 vs 7 respectively; p=0.008) This may be attributed to the difficulty in transitioning from a blinded therapy to the open-label use of a vitamin K antagonist when the patient had previously been on rivaroxaban. Patients in the warfarin group would presumably already have had a therapeutic INR. It takes approximately 4-5 days for patients starting warfarin to reach a therapeutic level of anticoagulation. However, the median time to reach therapeutic INR in this study was 13 days for those previously assigned to rivaroxaban and 3 days for patients previously on warfarin.[20]

The time to therapeutic range (TTR) for patients' INR in this trial was lower than other atrial fibrillation trials. In RE-LY, the phase III clinical trial that brought dabigatran to market for stroke prevention in NVAF patients,[21] the TTR for patients on warfarin was 64% but in ROCKET-AF it was only 55%.[20] The low TTR raised concerns over whether patients receiving warfarin were managed effectively and represented an adequate comparator to rivaroxaban to justify its approval.

Adverse Events

With any anticoagulation therapy bleeding is a potential complication. The primary safety outcome of all the RECORD trials was major bleeding, defined as bleeding that resulted in death, occurred in any critical organ, required reoperation, bleeding other than the surgical site associated with a drop in the hemoglobin level of at least 2g/dL or requires a transfusion of 2 more units of packed red blood cells.[16-19] Elevated ALT and AST levels were reported in 1.6% to 3.8% of the patients on rivaroxaban and 1.6% to 7.1% of patients on enoxaparin, with no significant differences between groups. The overall incidence of adverse reactions that lead to the discontinuation of rivaroxaban was 3.7% in the 3 RECORD trials that brought the drug to approval.[16-18] Throughout the four RECORD trials, rivaroxaban demonstrated low and comparable rates of bleeding versus enoxaparin (**Table 6**).[16-19]

In RECORD 1, major bleeding (primary safety outcome) occurred in 6 of the 2209 (0.3%) rivaroxaban patients and 2 of the 2224 enoxaparin patients (0.1%). There was only one fatal bleeding event in the study which occurred in the rivaroxaban group before the first dose was given. The combined incidence of major and non major clinically relevant bleeding was 3.2% in patients receiving rivaroxaban and 2.5% in patients receiving warfarin, which was not statistically significant. The incidence of hemorrhagic wound complications was similar between groups.[16]

Major bleeding occurred in one patient in group in the RECORD 2 trial. Hemorrhagic wound complications were almost identical between the two groups with 1.6% occurring in the rivaroxaban group and 1.7% in the enoxaparin group. The combination of major and clinically relevant non-major bleeding oc-

Table 7 | Rate of Adverse Events in ROCKET-AF [20]

Clinical Events	Rivaroxaban (N=7111)	Warfarin (N=7125)	HR (95% CI)
Principal Safety End point§	20.7% (n=1475) Rate:ℓ 14.9	20.3% (n=1449); Rate: 14.5	1.03 (0.96-1.11) (p=0.44)
Major Bleed ¥	5.6% (n=395) Rate: 3.6	5.4% (n=386) Rate: 3.4	1.04 (0.90-1.20) (p=0.58)
Hemoglobin decrease >2 g/dL	4.3% (n=305) Rate: 2.8	3.6% (n=254) Rate: 2.3	1.22 (1.03-1.44) (p=0.02)
Transfusion	2.6% (n=183) Rate: 1.6	2.1% (n=149) Rate: 1.3	1.25 (1.01-1.55) (p=0.04)
Critical bleeding¶	1.3% (n=91) Rate: 0.8	1.9% (n=133) Rate: 1.2	0.69 (0.53-0.91) (p=0.007)
Fatal bleeding	0.4% (n=27) Rate: 0.2	0.8% (n=55) Rate: 0.5	0.50 (0.31-0.79) (p=0.02)
Intracranial bleed	0.8% (n=55) Rate: 0.5	1.2% (n=84) Rate: 0.7	0.67 (0.47-0.93) (p=0.02)
GI bleed (upper, lower, rectal)	3.2% (n=224)	2.2% (n=154)	p<0.05
Epistaxis	10.1% (n=721)	8.6% (n=609)	p<0.05
Hematuria	4.2% (n=296)	3.4% (n=242)	p<0.05

ℓ event rate measured = #/100 patient-year
§ includes major and non major clinically relevant bleeding
¥ includes Hgb decrease in ≥ 2g/dL, transfusion >2 units or symptomatic bleeding of a critical organ
¶ considered if bleeding events occurred intracranial, intraspinal, intraocular, pericardial, intrarticular, intramuscular or retroperitneal
CI: 95% confidence interval; GI: gastrointestinal tract; HR: hazard ratio

curred in 3.4% of the patients receiving the extended prophylaxis with rivaroxaban and 2.8% in the short term enoxaparin group.[17]

In the RECORD 3 trial, major bleeding occurred in 7 of the 1220 (0.6%) patients on rivaroxaban and in 6 of the 1239 (0.7%) patients receiving enoxaparin. No episodes of fatal bleeding occurred throughout this trial. The combined incidence of major and non-major bleeding occurred in 3.3% of patients on rivaroxaban and in 2.7% of the enoxaparin patients. Bleeding that occurred during or shortly after surgery in the rivaroxaban group was included in the results even though the drug had not been administered.[18]

The RECORD 4 trial showed higher bleeding events than the previous RECORD trials, but although this was not significantly different between groups. Major bleeding occurred in 0.7% of patients receiving rivaroxaban and 0.3% of patients receiving enoxaparin. There was one fatal gastrointestinal bleed in the rivaroxaban group and no fatal bleeding events in the enoxaparin group.[19] Hemorrhagic wound complications were similar to the other trials.[16-19]

In the ROCKET AF trial, major and clinically relevant non-major bleeding occurred in 1475 rivaroxaban patients and 1449 warfarin patients (14.9% and 14.5% per year, respectively; HR for rivaroxaban, 1.03; 95% CI 0.96-1.11; p =0.44). Rates of major bleeding were similar in both groups, occurring in 3.6 % of those receiving rivaroxaban compared to 3.4% in those receiving warfarin (p =0.58). Rates of intracranial hemorrhage were significantly lower in the rivaroxaban group than in the warfarin group (0.5% vs. 0.7% per year respectively; HR 0.67; 95% CI, 0.47 to 0.93; p =0.02) However, major bleeding from a gastrointestinal site was seen more often in the rivaroxaban group compared to the patients taking warfarin (3.2% vs. 2.2%, respectively, p <0.001) (**Table 7**).

Drug Interactions

Rivaroxaban is a substrate for CYP 3A4/5, CYP 2J2, and the P-glycoprotein (P-gp) and ATP-binding cassette G2 (ABCG2) transporters. Because of this, certain drug-drug interactions can occur (**Table 8**). Drugs that are P-gp inhibitors and strong CYP 3A4 inhibitors can increase rivaroxaban concentrations significantly.[8] Patients with renal dysfunction (CrCl <50 mL/minute) taking P-gp inhibitors and weak or moderate CYP 3A4 inhibitors may be at an increased risk for bleeding and should use caution. Rivaroxaban does not induce or inhibit any of the CYP isoforms or the transporters.[11]

Dosing And Administration

For VTE prophylaxis in patients undergoing elective knee or hip arthroplasty the recommended dose of rivaroxaban is 10 mg daily with or without food and it should be started 6-10 hours after surgery.[2,8] For patients undergoing hip replacement surgery, a treat-

Table 8 | Drug Interactions Affecting Rivaroxaban [8]

Effector Drug	Mechanism	Result	Recommendation
Azole-antimycotics: (ketoconazole,voriconazole, posaconazole, itraconazole)	Potent CYP3A4 and P-gp inhibitor	Significant ↑ in Cmax and AUC: ↑ risk of bleeding	Avoid concomitant use
Protease inhibitors	Potent CYP3A4 and P-gp inhibitor	Significant ↑ in Cmax and AUC: ↑ risk of bleeding	Avoid concomitant use
Seizure medication (carbamazepine, phenytoin)	Potent CYP 3A4 and P-gp inducer	Significant ↓ in Cmax and AUC: ↓ in efficacy	Avoid concomitant use
Rifampin, nicardipine and St. John's Wort	Potent CYP 3A4 and P-gp inducer	Significant ↓ in Cmax and AUC: ↓ in efficacy	Avoid concomitant use
Clarithromycin, erythromycin, azithromycin, pantoprazole, tamoxifen, grapefruit, verapamil, diltiazem, quinidine, ranolizine, amiodarone, dronedarone, felodipine	Moderate/weak CYP 3A4 and P-gp inhibitor	May ↑ Cmax and AUC but may not be significant	Use caution especially in patients with renal impairment
Midazolam	Substrate of CYP3A4	No significant interaction	No adjustment necessary
Digoxin	Substrate of P-gp	No significant interaction	No adjustment necessary
Atorvastatin	Substrate of CYP3A4 and P-gp	No significant interaction	No adjustment necessary
Aspirin, NSAIDS, clopidogrel	Platelet aggregation or COX inhibitors	No sig. PK or PD effects (↑bleeding risk)	Evaluate signs or symptoms of blood loss

AUC: area under the curve; Cmax: maximum concentration; COX: cyclooxygenase; CYP: cytochrome P-450; NSAIDS: nonsteriodal anti-inflammatory drugs; P-gp: p-glycoprotein; PD: pharmacodynamic; PK: pharmacokinetic

ment duration of 35 days is recommended and a minimum of 12 days is recommended for patients undergoing knee replacement.[2,8] Due to an expected increase in rivaroxaban exposure and pharmacodynamic effects, patients with a CrCl of <30 mL/minute undergoing orthopedic surgery should not use rivaroxaban for VTE prophylaxis.[8]

Rivaroxaban has a predictable pharmacology profile allowing for a fixed once a day dose without the need for dose adjustments based on gender, weight or age. In patients with NVAF and a CrCl of > 50 mL/minute, the recommended dose is 20 mg once daily with the evening meal.[8] If the CrCl is between 15 and 50 mL/minute the recommended dose is 15 mg daily with an evening meal. Rivaroxaban should not be used in patients with a CrCl of <15 mL/minute.[8] Renal function should be periodically assessed, especially in situations where renal function can decline such as advancing age.

Patients with moderate to severe hepatic impairment (Child Pugh Class B-C) should not receive rivaroxaban. While no dose adjustment is necessary for mild hepatic impairment (Child Pugh Class A), the use of rivaroxaban should be avoided with any degree of hepatic disease associated with coagulopathy.[8]

If patients need to be converted from warfarin, rivaroxaban should be initiated when the INR is less than 3 to avoid a period of inadequate anticoagulation and minimize the risks for bleeding. There is no data to guide a switch from rivaroxaban to warfarin. However, due to rivaroxaban's half life one approach is to start a parenteral anticoagulant and warfarin at the same time as the next dose of rivaroxaban and continue both until a therapeutic INR is established.[8]

There currently is no specific antidote to reverse the anticoagulant effects of rivaroxaban. Reversal requires stopping the medication and possibly administering activated charcoal if the medication was taken very recently. Since rivaroxaban is highly protein bound and has a large volume of distribution dialysis is not likely to be effective. While protamine and vitamin K will have no benefit,[8] prothrombin complex concentrate (PCC) or activated prothrombin complex concentrate may be an option. A randomized, double-blind, placebo-controlled cross-over study was performed in healthy volunteers that were given rivaroxaban 20 mg once daily and/or 150 mg of dabigatran twice daily for 2.5 days. The results demonstrated that PCC immediately and completely reverses the anticoagulant effect of rivaroxaban.[22] This study was done in the Netherlands with a 4 factor PCC (Cofact®) which is not currently available in the US; only 3 factor PCCs are available in the US at this time. Notably, the study was not performed in patients that had supratherapeutic rivaroxaban concentrations or bleeding from either of the two anticoagulants. Therefore, the clinical applicability of the results is unknown. Bebulin® VH

is a freeze-dried concentrate containing the same coagulation factors as Cofact® (IX, II, X and low amounts of Factor VII), which is available in the US but has not yet been studied as a reversal antidote.[23]

Cost

Based on four major retail pharmacies, the average monthly cost for rivaroxaban 10 mg is $266.43, 15 mg is $273.75, and 20 mg is $268.43, with a range between $245.78 and $281.00. Smaller independent pharmacies did not carry the medication at the time of writing due inventory overhead costs.

Summary

Rivaroxaban is the first orally selective factor Xa inhibitor approved by the FDA. Rivaroxaban showed superior efficacy and comparable bleeding in the Phase III RECORD trials when compared with enoxaparin for VTE prophylaxis in patients undergoing total hip or knee replacement surgery. In the ROCKET AF trial, rivaroxaban was comparable to warfarin for stroke prevention in patients with NVAF, with less intracranial bleeding, but had a higher risk for GI bleeding. Although rivaroxaban is a substrate for certain CYP enzymes and P-gp transporters, it still has a lower drug-drug interaction profile compared to warfarin. Predictable pharmacokinetics and pharmacology allows for once daily dosing with no dose adjustment needed based on gender, weight or age. However, caution is advised when using in patients with compromised renal function and the medication should be avoided in patients with moderate to severe hepatic dysfunction. There currently is no standardized antidote for anticoagulation reversal. Lastly, pricing may be an issue for patients at an average of $9.00 a tablet but it would eliminate the monitoring costs for patients who are unable to stay within the therapeutic range on warfarin.

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Drug Update

Plavix—On May 17, 2012 Plavix (clopidogrel, Bristol-Myers Squibb/Sanofi) officially went off-patent [1]and will be available generically once manufacturers and pharmacies are able to ship and obtain the product, respectively.

The FDA has approved two doses of generic clopidogrel: 300 mg and 75 mg; Dr. Reddy's Laboratories was the first manufacturer to gain approval to manufacturer and market generic clopidogrel tablets, and therefore will have 180 days of exclusivity before other generic manufacturers are allowed to produce and market their generic clopidogrel products.

Avanafil—On April 27, 2012 the FDA approved Stendra® (avanafil) for the treatment of erectile dysfunction (ED).[2] Avanafil is a phosphodiesterase-5 inhibitor (PDE5) with a similar mechanism of action to sildenafil (Viagra®), vardenatil (Levitra®), and tadalafil (Cialis®). Avanafil is taken 30 minutes prior to sexual activity without regard to food. Like other PDE5 inhibitors, avanafil has the potential to cause hypotension and is contraindicated when used concomitantly with nitrates, as avanafil may potentiate the vasodilatory and hypotensive effects of nitrates. Be on the lookout for a future PharmaNote to review avanafil and discuss it's role in the treatment of ED.

1. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm304489.htm.
2. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm302140.htm.

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