UCSD Medical Center
Rivaroxaban (Xarelto®) Monograph

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Executive Summary

Background & Indication(s):
Rivaroxaban is an oral Xa inhibitor indicated (1) to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation (AF) and (2) for the prevention of deep vein thrombosis (DVT) in patients undergoing knee or hip replacement surgery.

Atrial Fibrillation

Reason for requesting:
Not yet requested, pre-emptive

Dosing:
For patients with creatinine clearance (CrCl) >50 mL/min, the recommended dose of rivaroxaban is 20 mg taken orally once daily with the evening meal. For patients with CrCl 15 to 50 mL/min, the recommended dose is 15 mg once daily with the evening meal.

Efficacy:
Rivaroxaban is non-inferior to warfarin for the prevention of stroke or systemic embolism in patients with atrial fibrillation. The primary efficacy outcome (stroke or systemic embolism) occurred at a rate of 2.1% per year in patients who received rivaroxaban, compared to 2.4% per year in patients who received warfarin (95% CI, 0.74 to 1.03; $p<0.001$ for non-inferiority, $p=0.12$ for superiority) in the intention-to-treat population.

Safety:
In the ROCKET AF trial, there was no difference in major and non-major clinically relevant bleeding compared to warfarin. Rivaroxaban demonstrated a statistically significant reduction in critical bleeding, fatal bleeding, and intracranial hemorrhage, but an increase in bleeding associated with a drop of ≥2 g/dL in hemoglobin and with transfusion of ≥2 units. The most frequent adverse reactions associated with permanent drug discontinuation were bleeding events, with incidence rates of 4.3% for rivaroxaban compared to 3.1% for warfarin. The incidence of discontinuations for non-bleeding adverse events was similar in both treatment groups.

Pharmacoeconomics:
Rivaroxaban is more expensive than warfarin; the daily cost of rivaroxaban is $6.94, compared to a daily cost of just cents for warfarin (varying depending on the dose and manufacturer). Dabigatran costs $5.40 per day for inpatients, so rivaroxaban is also more expensive than dabigatran. The yearly cost for managing a patient on rivaroxaban is $1898, compared to $1803 for dabigatran and $488 for warfarin (including monitoring).

DVT Prophylaxis

Reason for requesting:
Not yet requested, pre-emptive

Dosing:
Knee replacement therapy: 10 mg daily for 12 days. Hip replacement therapy: 10 mg daily for 35 days. Initial dose should be taken 6-10 hours after surgery or after hemostasis has occurred. Rivaroxaban may be administered without regard to food.

Efficacy:
Rivaroxaban is more effective than enoxaparin for thromboprophylaxis in patients undergoing hip or knee replacement surgery. In patients who underwent hip replacement surgery, the primary efficacy outcome occurred in 1.1% of patients who received rivaroxaban, compared to 3.7% of patients who received enoxaparin (absolute risk reduction (ARR), 2.6%; 95% CI, 1.5 to 3.7; $p<0.001$), with a number needed to treat (NNT) of 39. For patients who underwent knee replacement surgery, the primary efficacy outcome occurred in 9.6% of patients who received rivaroxaban, compared to 18.9% who received enoxaparin (ARR, 9.2%; 95% CI, 5.9 to 12.4; $p<0.001$), with an NNT of 11.

Safety:
Bleeding complications were the most common adverse reactions, occurring in 0.3% of all patients who received rivaroxaban in the RECORD 1-3 trials, compared to 0.2% of enoxaparin patients. Major bleeding events reported in both the hip and knee surgery studies were similar between rivaroxaban and enoxaparin-treated patients. Other adverse events included wound secretion and syncope, which were also similar between rivaroxaban and enoxaparin-treated patients.

Pharmacoeconomics:
Rivaroxaban is less expensive than enoxaparin; the daily cost of rivaroxaban is $5.72, compared to a daily cost of $23.20 for enoxaparin. The oral administration route of this drug decreases medication administration time for nursing. The recent availability of a generic formulation of enoxaparin might impact the pharmacoeconomics assessment of this product in the near future.

The bottom line: Atrial Fibrillation

Arguments for:	Arguments against:
Efficacy: • In a large clinical trial, rivaroxaban was similar in efficacy to warfarin	**Evidence base:** • Indication based on only one clinical trial, where patients with CrCl < 30 mL/min were excluded • Only non-inferior, not superior, to warfarin • No direct comparison with dabigatran
Safety: • No difference in major bleeding compared to warfarin • Lower rate of fatal bleeding and intracranial hemorrhage	**Drug interactions:** • Cannot be used with strong inhibitors and inducers of CYP3A4
Dosing/Administration: Once daily dosing, which should have better compliance compared to twice daily dabigatran	**Dosing/Administration:** • Renal adjustment • Must be taken with food (evening meal) • High rate of noncompliance
Practical issues: • No INR monitoring required • No dietary restrictions	**Practical issues:** • No reversal agent • Black box warning for discontinuation
	Cost: More expensive per day and per year compared to warfarin and dabigatran

The bottom line: DVT Prophylaxis

Arguments for:	Arguments against:
Different route of administration: • Oral administration versus subcutaneous injection	**Evidence base:** • Limited indication • RECORD 1-3 compared to European standard of enoxaparin dosing (40 mg daily)
Cost: • Less expensive than enoxaparin	**Practical issues:** • No antidote
Practical issues: • No monitoring required	

Actions needed if approved:

- Guidelines for how to transition patients on and off rivaroxaban for atrial fibrillation will need to be made available, using the recommendations on the package insert.
- Education regarding administration via feeding tube will be required to ensure that absorption and drug exposure is not reduced due to deposition of drug into the proximal small intestine.
- If rivaroxaban is approved for both indications of atrial fibrillation and VTE prophylaxis, provider education will be needed regarding the different doses used and appropriate renal adjustments.

1. **Introduction**[1]
Rivaroxaban was approved by the FDA in November 2011 to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation, and in July 2011 for prophylaxis of deep vein thrombosis (DVT) in orthopedic patients. It is available as an oral tablet and does not require monitoring of INR or coagulation parameters. Rivaroxaban is the first oral alternative to warfarin that can be given once daily for prevention of stroke in patients with atrial fibrillation.

2. **Therapeutic Classification**
Anticoagulant, factor Xa inhibitor
AHFS Pharmacologic-Therapeutic Classification: 20.12.04.92

3. **FDA Approved Indication(s)**[1]
(1) to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation, and (2) for prophylaxis of deep vein thrombosis (DVT) which may lead to pulmonary embolism (PE) in patients undergoing knee or hip replacement surgery

4. **Non FDA approved (off-label) uses**
Rivaroxaban is currently being investigated for use in acute coronary syndrome (ATLAS-ACS TIMI-51 trial), treatment of VTE (EINSTEIN trial), and VTE prevention in the medically ill (MAGELLAN trial).

5. **Pharmacology/Pharmacokinetics**[2]
Mechanism of action/Pharmacodynamics
Rivaroxaban selectively inhibits factor Xa in a dose-dependent fashion, prolonging neoplastin prothrombin time (PT), activated partial thromboplastin time (aPTT), and HepTest dose-dependently. Binding to and subsequently blocking the active site of factor Xa does not require a cofactor (such as Anti-thrombin III).

Pharmacokinetics
Rivaroxaban is rapidly absorbed, reaching peak serum concentrations 2-4 hours after intake. The pharmacokinetics of rivaroxaban is not affected by food or drugs that alter gastric pH. However, the absorption is dependent on site of drug release in the GI tract, with lower exposure observed when drug is released in the distal small intestine or ascending colon. Therefore, rivaroxaban should not be administered through any method that may deposit the drug directly into the proximal small intestine (e.g., feeding tube) to avoid reduction in absorption and drug exposure. The pharmacokinetic parameters are shown in Table 1.

Table 1: Pharmacokinetics[2]

Bioavailability (Oral)	80-100%
Cmax	2-4 hours
Food Effects	none
Protein Binding (Albumin)	92-95%
Volume of distribution (Vd)	50 L
Enzymes	CYP3A4/5, CYP2J2
Half-life	5-9 hours
Excretion	30% in urine; 21% in feces

6. **Dosage and Administration**[1]
Nonvalvular Atrial Fibrillation
6.1. 20 mg orally once daily with the evening meal
6.2. Renal impairment:
15 mg once daily with the evening meal for patients with CrCl 15 to 50 mL/min

Avoid the use of rivaroxaban in patients with CrCl <15 mL/min

6.3. Transitioning to and from other anticoagulants:

- *Warfarin to rivaroxaban*: discontinue warfarin and start rivaroxaban as soon as the INR is below 3.0 to avoid periods of inadequate anticoagulation.
- *Rivaroxaban to warfarin*: no clinical trial data are available. Rivaroxaban affects INR, so INR measurements made during co-administration with warfarin may not be useful for determining the appropriate dose of warfarin. One approach is to discontinue rivaroxaban and begin both a parenteral anticoagulant and warfarin at the time the next dose of rivaroxaban would have been taken.
- *Other anticoagulant to rivaroxaban*: start rivaroxaban 0 to 2 hours prior to the next scheduled evening administration of the drug (e.g., low molecular weight heparin or non-warfarin oral anticoagulant) and omit administration of the other anticoagulant. For unfractionated heparin being administered by continuous infusion, stop the infusion and start rivaroxaban at the same time.
- *Rivaroxaban to other anticoagulant*: discontinue rivaroxaban and give the first dose of the other anticoagulant (oral or parenteral) at the time that the next rivaroxaban dose would have been taken.

DVT Prophylaxis

6.4. 10 mg orally, once daily with or without food
The initial dose should be taken at least 6 to 10 hours after surgery once hemostasis has been established.

6.5. Treatment duration:
For patients undergoing hip replacement surgery: 35 days
For patients undergoing knee replacement surgery: 12 days

6.6. Renal impairment: Avoid the use of rivaroxaban in patients with CrCl <30 mL/min

7. Safety considerations

7.1. Boxed warnings:[1]

(A) DISCONTINUING IN PATIENTS WITH NONVALVULAR ATRIAL FIBRILLATION INCREASES RISK OF STROKE

Discontinuing rivaroxaban places patients at an increased risk of thrombotic events. An increased rate of stroke was observed following rivaroxaban discontinuation in clinical trials in atrial fibrillation patients. If anticoagulation with rivaroxaban must be discontinued for a reason other than pathological bleeding, consider administering another anticoagulant.

(B) SPINAL/EPIDURAL HEMATOMA

Epidural or spinal hematomas have occurred in patients treated with rivaroxaban who are receiving neuraxial anesthesia or undergoing spinal puncture. These hematomas may result in long-term or permanent paralysis. Consider these risks when scheduling patients for spinal procedures. Factors that can increase the risk of developing epidural or spinal hematomas in these patients include:

- use of indwelling epidural catheters
- concomitant use of other drugs that affect hemostasis, such as nonsteroidal anti-inflammatory drugs (NSAIDs), platelet inhibitors, other anticoagulants
- a history of traumatic or repeated epidural or spinal punctures
- a history of spinal deformity or spinal surgery

Monitor patients frequently for neurological impairment. If neurological compromise is noted, urgent treatment is necessary.
Consider risks/benefits before neuraxial intervention in patients anticoagulated or to be anticoagulated for thromboprophylaxis.

7.2. Adverse Events: The most common adverse reactions were bleeding complications, which were not different from warfarin (Table 2) or enoxaparin (Table 3). The following adverse reactions have also been identified:

- *Blood and lymphatic system disorders*: agranulocytosis
- *Gastrointestinal disorders*: retroperitoneal hemorrhage

- *Hepatobiliary disorders*: jaundice, cholestasis, cytolytic hepatitis
- *Immune system disorders*: hypersensitivity, anaphylactic reaction, anaphylactic shock
- *Nervous system disorders*: cerebral hemorrhage, subdural hematoma, epidural hematoma, hemiparesis
- *Skin and subcutaneous tissue disorders*: Stevens-Johnson syndrome

Table 2: Bleeding Events in ROCKET AF[3]*

Parameter	Rivaroxaban N = 7111 n (%)	Event rate (per 100 pt-yrs)	Warfarin N = 7125 n (%)	Event rate (per 100 pt-yrs)
Major bleeding†	395 (5.6)	3.6	386 (5.4)	3.5
Bleeding into a critical organ‡	91 (1.3)	0.8	133 (1.9)	1.2
Fatal bleeding	27 (0.4)	0.2	55 (0.8)	0.5
Bleeding resulting in transfusion of ≥ 2 units of whole blood or packed red blood cells	183 (2.6)	1.7	149 (2.1)	1.3
Gastrointestinal bleeding	221 (3.1)	2.0	140 (2.0)	1.2

* For all sub-types of major bleeding, single events may be represented in more than one row, and individual patients may have more than one event.
† Defined as clinically overt bleeding associated with a decrease in hemoglobin of ≥ 2 g/dL, transfusion of ≥ 2 units of packed red blood cells or whole blood, bleeding at a critical site, or with a fatal outcome. Hemorrhagic strokes are counted as both bleeding and efficacy events. Major bleeding rates excluding strokes are 3.3 per 100 Pt-yrs for rivaroxaban vs. 2.9 per 100 Pt-yrs for warfarin.
‡ The majority of the events were intracranial, and also included intraspinal, intraocular, pericardial, intraarticular, intramuscular with compartment syndrome, or retroperitoneal.

Table 3: Bleeding Events in Patients Undergoing Hip or Knee Replacement Surgeries (RECORD 1-3)[4,5,6]

	Rivaroxaban 10 mg	Enoxaparin
Total Treated Patients	**N=4487 n (%)**	**N=4524 n (%)**
Major bleeding event	14 (0.3)	9 (0.2)
Fatal bleeding	1 (<0.1)	0
Bleeding into a critical organ	2 (<0.1)	3 (0.1)
Bleeding that required re-operation	7 (0.2)	5 (0.1)
Extra-surgical site bleeding requiring transfusion of > 2 units of whole blood or packed cells	4 (0.1)	1 (<0.1)
Any bleeding event	261 (5.8)	251 (5.6)
Hip Surgery Studies	**N=3281 n (%)**	**N=3298 n (%)**
Major bleeding event	7 (0.2)	3 (0.1)
Fatal bleeding	1 (<0.1)	0
Bleeding into a critical organ	1 (<0.1)	1 (<0.1)
Bleeding that required re-operation	2 (0.1)	1 (<0.1)
Extra-surgical site bleeding requiring transfusion of > 2 units of whole blood or packed cells	3 (0.1)	1 (<0.1)
Any bleeding event	201 (6.1)	191 (5.8)
Knee Surgery Studies	**N=1206 n (%)**	**N=1226 n (%)**
Major bleeding event	7 (0.6)	6 (0.5)
Fatal bleeding	0	0
Bleeding into a critical organ	1 (0.1)	2 (0.2)
Bleeding that required re-operation	5 (0.4)	4 (0.3)
Extra-surgical site bleeding	1 (0.1)	0

requiring transfusion of > 2 units of whole blood or packed cells		
Any bleeding event	60 (5.0)	60 (4.9)

Table 4: Other Adverse Events Reported by ≥1% of Patients in RECORD 1-3 Studies[4,5,6]

Event	Rivaroxaban (N=4487) n (%)	Enoxaparin (N=4524) n (%)
Wound Secretion	125 (2.8)	89 (2.0)
Pain in Extremity	74 (1.7)	55 (1.2)
Muscle Spasm	52 (1.2)	32 (0.7)
Syncope	55 (1.2)	32 (0.7)
Pruritis	96 (2.1)	79 (1.8)
Blister	63 (1.4)	40 (0.9)

7.3. Precautions/Contraindications[1,2]

Precautions

- *Increased Risk of Stroke after Discontinuation in Nonvalvular Atrial Fibrillation*: Discontinuing rivaroxaban in the absence of adequate alternative anticoagulation increases the risk of thrombotic events. An increased rate of stroke was observed during the transition from rivaroxaban to warfarin in clinical trials in atrial fibrillation patients. If rivaroxaban must be discontinued for a reason other than pathological bleeding, consider administering another anticoagulant
- *Risk of bleeding*: Concomitant use of drugs affecting hemostasis increases the risk of bleeding. These include aspirin, P2Y12 platelet inhibitors, other antithrombotic agents, fibrinolytic therapy, and nonsteroidal anti-inflammatory drugs (NSAIDs). Concomitant use of drugs that are combined P-gp and CYP3A4 inhibitors (e.g. ketoconazole and ritonavir) increases rivaroxaban exposure and may increase bleeding risk
- *Spinal/Epidural Anesthesia or Puncture*: When neuraxial anesthesia (spinal/epidural anesthesia) or spinal puncture is employed, patients treated with anticoagulant agents for prevention of thromboembolic complications are at risk of developing an epidural or spinal hematoma which can result in long-term or permanent paralysis. An epidural catheter should not be removed earlier than 18 hours after the last administration of rivaroxaban. The next rivaroxaban dose is not to be administered earlier than 6 hours after the removal of the catheter. If traumatic puncture occurs, the administration of rivaroxaban is to be delayed for 24 hours.
- *Risk of Pregnancy Related Hemorrhage*: Rivaroxaban should be used with caution in pregnant women and only if the potential benefit justifies the potential risk to the mother and fetus. Rivaroxaban dosing in pregnancy has not been studied. The anticoagulant effect of rivaroxaban cannot be monitored with standard laboratory testing nor readily reversed. Promptly evaluate any signs or symptoms suggesting blood loss (e.g., a drop in hemoglobin and/or hematocrit, hypotension, or fetal distress).
- *Severe Hypersensitivity Reactions*: There were postmarketing cases of anaphylaxis in patients treated with rivaroxaban to reduce the risk of DVT. Patients who have a history of a severe hypersensitivity reaction to rivaroxaban should not receive rivaroxaban

Contraindications

- Active pathological bleeding
- Severe hypersensitivity reaction to rivaroxaban

7.4. Considerations for Special Populations[1,2]

7.4.1. Pregnancy: Pregnancy Category C.

There are no adequate or well-controlled studies of rivaroxaban in pregnant women, and dosing for pregnant women has not been established. Use rivaroxaban with caution in pregnant patients because of the potential for pregnancy related hemorrhage and/or emergent delivery with an anticoagulant that is not readily reversible. Rivaroxaban should be used during pregnancy only if the potential benefit justifies the potential risk to mother and fetus. Rivaroxaban crosses the placenta in animals. Animal reproduction studies have shown pronounced maternal hemorrhagic complications in rats and an increased incidence of post-implantation pregnancy loss in rabbits. Rivaroxaban increased fetal toxicity (increased resorptions, decreased number of live fetuses, and decreased fetal body weight) when pregnant rabbits were given oral doses of ≥10 mg/kg rivaroxaban during the period of organogenesis. This dose corresponds to about 4 times the human exposure of unbound drug, based on AUC comparisons at the highest recommended human dose of 20 mg/day. Fetal body weights decreased when pregnant rats were given oral doses of 120 mg/kg. This dose corresponds to about 14 times the human exposure of unbound drug.

7.4.2. **Breastfeeding**: It is not known if rivaroxaban is excreted in human milk. Rivaroxaban and/or its metabolites were excreted into the milk of rats. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from rivaroxaban, a decision should be made whether to discontinue nursing or discontinue rivaroxaban, taking into account the importance of the drug to the mother.

7.4.3. **Pediatrics:** Safety and effectiveness in pediatric patients have not been established.

7.4.4. **Geriatrics:** In ROCKET AF, approximately 77% were 65 years and over and about 38% were >75 years. In clinical trials the efficacy of rivaroxaban in the elderly (65 years or older) was similar to that seen in patients younger than 65 years. Both thrombotic and bleeding event rates were higher in these older patients, but the risk-benefit profile was favorable in all age groups

7.4.5. **Renal impairment**: Avoid the use of rivaroxaban in patients with CrCl <15 mL/min. Periodically assess renal function as clinically indicated and adjust therapy accordingly. Discontinue rivaroxaban in patients who develop acute renal failure while on rivaroxaban.

7.4.6. **Hepatic impairment**: The use of rivaroxaban should be avoided in patients with moderate (Child Pugh B) and severe (Child Pugh C) hepatic impairment or in any patients with hepatic disease associated with coagulopathy.

7.5. Drug Interactions[1,2]

Rivaroxaban is a substrate of CYP3A4/5, CYP2J2, and the P-gp and ATP-binding cassette G2 (ABCG2) transporters.

7.5.1. **Drugs that Inhibit Cytochrome P450 3A4 Enzymes and Drug Transport Systems**

Concurrent administration of rivaroxaban with drugs that are combined strong inhibitors of the CYP3A4 enzyme and P-gp transporter resulted in increases in rivaroxaban exposure, which may increase risk of bleeding. Use with these medications (ketoconazole, itraconazole, lopinavir/ritonavir, ritonavir, indinavir/ritonavir, and conivaptan) should be avoided.

7.5.2. **Drugs that Induce Cytochrome P450 3A4 Enzymes and Transport Systems**

Concurrent administration of rivaroxaban with drugs that are combined strong inducers of the CYP3A4 enzyme and P-gp transporter (carbamazepine, phenytoin, rifampin, St. John's wort) should be avoided due to a decrease in rivaroxaban exposure, which may decrease efficacy.

7.5.3. **Anticoagulants**

Concomitant use of rivaroxaban with other anticoagulants other than for therapeutic transition periods should be avoided due to the increased risk of bleeding. However, due to its quick onset of effect, bridge therapy with heparins or fondaparinux would not be required in situations when immediate anticoagulation is critical. Warfarin did not affect the pharmacokinetics of rivaroxaban

7.5.4. NSAIDs/Aspirin

In ROCKET AF, concomitant aspirin use (almost exclusively at a dose of 100 mg or less) during the double-blind phase was identified as an independent risk factor for major bleeding. NSAIDs are known to increase bleeding, and bleeding risk may be increased when NSAIDs are used concomitantly with rivaroxaban. Patients being treated with both rivaroxaban and NSAIDs and/or platelet aggregation inhibitors should be evaluated for any signs or symptoms of blood loss.

7.5.5. Clopidogrel

Concurrent administration of rivaroxaban with clopidogrel should be avoided unless the benefit outweighs the risk of increased bleeding

7.5.6. Drug-Disease Interaction with Drugs that Inhibit Cytochrome P450 3A4 Enzymes and Drug Transport Systems

In patients with renal impairments receiving rivaroxaban, simulated pharmacokinetic data suggests that there may be significant increases in rivaroxaban exposure if given with combined weak or moderate inhibitors of P-gp and CYP3A4 (erythromycin, azithromycin, diltiazem, verapamil, quinidine, ranolazine, dronedarone, amiodarone, and felodipine). Results from an analysis in the ROCKET AF trial, which allowed concomitant use with combined P-gp and weak or moderate CYP3A4 inhibitors (e.g., amiodarone, diltiazem, verapamil, chloramphenicol, cimetidine, and erythromycin), did not show an increase in bleeding in patients with CrCl 30 to <50 mL/min. Rivaroxaban should be used in patients with CrCl 15 to 50 mL/min who are receiving concomitant combined P-gp and weak or moderate CYP3A4 inhibitors only if the potential benefit justifies the potential risk

7.6. Potential for error

7.6.1. Sound alike/look alike potential

No sound-alike/look-alike combinations have been identified

7.6.2. High-alert medication?

Rivaroxaban is a factor Xa inhibitor which is in a class of high-alert medications – antithrombotic agents (anticoagulants)

7.7. Potential for abuse

None reported to date

7.8. Monitoring requirements / Risk Evaluation and Mitigation Strategy (REMS)

There is a REMS program that consists of a medication guide and communication plan to ensure that the benefits of rivaroxaban outweigh the potential risks in patients with nonvalvular atrial fibrillation. These risks include increased risk of thrombotic events if discontinued without introducing an adequate alternative anticoagulant, and potential decreased efficacy (15 mg and 20 mg) if not taken with the evening meal.

Atrial Fibrillation

8. Efficacy (see attachment 1 for evidence tables)[3]

In ROCKET AF, rivaroxaban was non-inferior to warfarin for the primary composite endpoint of time to first occurrence of stroke (any type) or systemic embolism [HR (95% CI): 0.88 (0.74, 1.03)], but superiority to warfarin was not demonstrated.

9. Current Practice Guidelines[7]

The most recent guidelines for antithrombotic therapy in atrial fibrillation are the 2008 CHEST guidelines, which do not address rivaroxaban or dabigatran since they were not available at that time. According to the CHEST guidelines, long-term anticoagulation with an oral vitamin K antagonist (warfarin) is recommended in patients with AF who have a CHADS2 score of 2 or greater (Grade 1A).

10. Formulary Alternatives[8]

- Coumarins and indanediones: warfarin
- Thrombin inhibitors: dabigatran

11. Pharmacoeconomic analysis

11.1. Budget impact

Table 5 shows a comparison in monthly costs for rivaroxaban, warfarin and dabigatran. Costs are based on outpatient (340B) pricing. Based on an analysis of 6 months of UCSD's anticoagulation clinic data, the typical patient with atrial fibrillation visits the clinic 2-6 times (maximum of one time per month). Assuming one INR measurement, one 1-hour pharmacist appointment and/or one 15 minute follow up appointment, warfarin remains the least costly option.

Table 5. Cost Comparison

	Rivaroxaban 20mg or 15mg	Dabigatran 150 mg	Warfarin 7.5 mg (new start)	Warfarin 7.5 mg (continuation)
Outpatient drug cost per day*	$5.20	$4.94	$0.04	$0.04
Supply cost of INR measurement**			$6.10	$6.10
Initial appointment (1h)			$100.00	
Follow up appt (15 min)			$25.00	$25.00
TOTAL cost per 30 days	$156.00	$148.20	$132.30	$32.30
TOTAL cost per year***	**$1898.00**	**$1803.10**	**$487.60**	

*Cardinal.com. Accessed November 21, 2011
**1 hemocue cuvette, lancet and test strip: $6.10 (Via G. Hagney, December 2010)
***Based on 12 anticoagulation clinic visits annually (1 every month)

Table 6 shows the budget impact for UCSD for varying adoption rates of rivaroxaban. The following assumptions are made:

- Only inpatient drug costs are included
- Only patients with atrial fibrillation are eligible to receive rivaroxaban
- 1634 patients were admitted in FY10 UCSD medical center with a diagnosis of atrial fibrillation
- 642 patients received warfarin (high risk patients) for an average length of stay (LOS) of 3 days

The inpatient cost of the once daily dose of rivaroxaban is $6.94, compared to an average $0.12 per day for the warfarin 7.5mg dose. For an average LOS of 3 days, rivaroxaban expenditure is $20.82 compared to $0.36 for warfarin. As illustrated in Table 6, 100% conversion of patients with atrial fibrillation from warfarin to rivaroxaban for anticoagulation would result in an annual cost-increase of $13,135.

Table 6: Estimated budget impact of rivaroxaban at UCSD

Drug	Dose	Cost/ day*	Cost/ patient/ 3 days LOS	% conversion to RV	No of patients receiving RV†	WF cost	RV cost
Warfarin (WF)	7.5 mg daily	$0.12	$0.36	0%	0	$231	$0
Rivaroxaban (RV)	20 mg daily	$6.94	$20.82	10%	64	$208	$1332
				25%	161	$173	$3352
				50%	321	$116	$6683
				75%	482	$58	$10,035
				100%	642	$0	$13,366

*Based on price info as of November 15, 2011.
†Total number of patients: 642. Average LOS: 3 days
University Health-Consortium database fiscal year 2010: included ICD-9 diagnosis codes atrial fibrillation: 42731

Rivaroxaban is associated with higher drug acquisition costs compared to warfarin, but is potentially cost-effective when evaluating treatment efficacy rates and frequency and cost of monitoring visits to the anticoagulation clinic for warfarin.

12. Pharmacy /nursing issues

12.1. Plan for Shortages:

In the event that rivaroxaban is unavailable, warfarin can be used for prevention of stroke in atrial fibrillation.

12.2. Actions Needed if Approved

- Guidelines for how to transition patients on and off rivaroxaban will need to be made available, using the recommendations on the package insert.
- Education on the boxed warning of increased risk of stroke when rivaroxaban is stopped is needed, with recommendations to provide overlap or early use of another anticoagulant when transitioning patients.
- Education on the lack of a specific reversal agent in the event of bleeding or unplanned major surgery. Options include activated prothrombin complex concentrate (PCC), fresh frozen plasma (FFP), and recombinant activated factor VII.
- If rivaroxaban is approved for both indications of atrial fibrillation and VTE prophylaxis, provider education will be needed regarding the different doses used and appropriate renal adjustments.

13. Conclusions

The ROCKET AF trial demonstrated that rivaroxaban was non-inferior to warfarin for prevention of stroke in patients with atrial fibrillation, without a significant increase in rates of bleeding events.

DVT Prophylaxis

14. Efficacy (see attachment 1 for evidence tables)[4,6]

In all the RECORD trials, rivaroxaban was superior to enoxaparin in preventing deep-vein thrombosis, nonfatal pulmonary embolism, or death from any cause. In patients who underwent hip replacement surgery, the primary efficacy outcome occurred in 1.1% of patients in the rivaroxaban group and 3.7% in enoxaparin group, (absolute risk reduction (ARR), 2.6%; 95% CI, 1.5 to 3.7; p<0.001), and major venous thromboembolism (VTE) occurred in 0.2% of rivaroxaban patients compared to 2.0% of enoxaparin patients, (ARR, 1.7%; 95% CI, 1.0 to 2.5; p<0.001). For patients who underwent knee replacement surgery, the primary efficacy endpoint occurred in 9.6% of rivaroxaban patients versus 18.9% of enoxaparin patients (ARR, 9.2%; 95% CI, 5.9 to 12.4; p<0.001), major VTE occurred in 1.0% of rivaroxaban patients compared to 2.6% of enoxaparin patients, (ARR, 1.6%; 95% CI, 0.4 to 2.8; p=0.01), and symptomatic VTE occurred in 0.7% in the rivaroxaban group versus 2.0% in the enoxaparin group, (ARR, 1.3%; 95% CI, 0.4 to 2.2; p=0.005).

15. Current Practice Guidelines[2,9]

Rivaroxaban is not specifically mentioned in current guidelines. According to the CHEST guidelines, a low-molecular weight heparin (LMWH), fondaparinux, or an adjusted-dose vitamin K antagonist (VKA) should be used for patients undergoing elective total hip or knee replacement, while they recommend against the use of aspirin, low-dose unfractionated heparin (LDUH), or aspirin as monotherapy (Grade 1A recommendation).

Table 7: Guidelines for Anticoagulant Use in Hip or Knee Replacement Surgery

Anticoagulant	FDA-Approved for VTE Prevention	Route	Guidelines Supporting Use in Total Hip or Total Knee Replacement
Aspirin	No	Oral	AAOS; ACCP does not

			recommend for monotherapy
LDUH	Yes	Injection	ACCP does not recommend for monotherapy
LMWH Enoxaparin Dalteparin Tinzaparin	Yes Yes (hip only) No No	Injection Injection Injection	ACCP, AAOS, SCIP
VKAs warfarin	Yes	Oral or Injection	ACCP, AAOS, SCIP
Factor Xa Inhibitors Fondaparinux	Yes	Injection	ACCP, AAOS, SCIP

AAOS = American Academy of Orthopaedic Surgeons; ACCP = American College of CHEST Physicians; SCIP = Surgical Care Improvement Project

16. Formulary Alternatives[8]

Alternative anticoagulants currently on formulary (by class):

- Heparins: enoxaparin, dalteparin, heparin
- Coumarins and indanediones: warfarin
- Factor Xa inhibitors: fondaparinux
- Thrombin inhibitors: argatroban, bivalirudin

17. Pharmacoeconomic analysis

17.1. Budget impact

Over the last four quarters, a total of 434 patients were admitted for elective hip replacement (n=254) and knee replacement (n=180) surgery and received enoxaparin for the prevention of deep-vein thrombosis. The average length of stay (LOS) for these patients was 4 days. The cost of the once daily dose of rivaroxaban is $5.72, compared to $23.20 per day for the twice daily enoxaparin 30 mg dose. For an average LOS of 4 days, rivaroxaban expenditure is $22.88 compared to $92.80 for enoxaparin. As illustrated in Table 8, 100% conversion of patients undergoing hip or knee replacement surgery from enoxaparin to rivaroxaban for DVT prophylaxis would result in an annual cost-savings of $30,345. In other words, if no patients were to be converted from enoxaparin to rivaroxaban, the cost for a year would be $40,275 versus $9,930 if all patients were converted to rivaroxaban.

Table 8: Estimated budget impact of rivaroxaban at UCSD

Drug	Dose	Cost/ Dose	Cost/ Patient / 4 day LOS	% conversion to RV	No of patients receiving RV	EX cost	RV cost
Rivaroxaban (RV)	10 mg daily	$5.72	$22.88	0%	0	$40,275	$0
Enoxaparin (EX)	30 mg BID	$11.60	$92.80	10%	44	$36,248	$993
				25%	109	$30,206	$2,482
				50%	217	$20,138	$4,965
				75%	326	$10,069	$7,447
				100%	434	$0	$9,930
Total LESS expenditure (range)			**$0 to $30,345**				

** Total number of patients: 434 (254 hip, 180 knee). Average LOS: 4 days*
University Health-Consortium database Fiscal year 2010
Based on current orthopedic patients matching the FDA approved prescribing criteria: total of 434 eligible patients with average LOS of 4 days

18. Pharmacy /nursing issues

18.1. Plan for Shortages: In the event that rivaroxaban is unavailable, enoxaparin can be used for DVT prophylaxis.

18.2. Actions Needed if Approved *(i.e., CPOE build, provider education, guidelines, infusion pump settings, patient education materials, periodic evaluation):* Education regarding administration via feeding tube will be required to ensure that absorption and drug exposure is not reduced due to deposition of drug into the proximal small intestine. Since rivaroxaban absorption is dependent on the site of drug release in the GI tract, gastric placement of the tube should be confirmed prior to administration via feeding tube. When rivaroxaban granulate is released in the proximal small intestine, there was a 29% and 56% decrease in AUC and C_{max}, and an even greater reduction was reported when drug was released in the distal small intestine or ascending colon. In other words, NG and G-tube administration of rivaroxaban is acceptable once proper tube placement has been confirmed, but J-tube administration should be avoided.

19. Conclusions

The RECORD 1-4 trials demonstrated that rivaroxaban was superior to enoxaparin for thromboprophylaxis in patients undergoing hip or knee replacement surgery, without a significant increase in rates of bleeding events.

20. References

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Attachment 1

Evidence Tables

ROCKET AF[2,3]: **R**ivaroxaban, **O**nce-daily, oral, direct Factor Xa inhibition **C**ompared with vitamin **K** antagonism for prevention of stroke and **E**mbolism **T**rial in **A**trial **F**ibrillation

This study was a randomized, double-blind, double-dummy, active-controlled, parallel-group, multi-center, event-driven, noninferiority study to evaluate the efficacy and safety of oral fixed-dose rivaroxaban 20 mg once daily (15 mg for patients with CrCl 30-49 ml/min) and dose-adjusted warfarin (target INR: 2.0 to 3.0) for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation at moderate-to-high risk for stroke.

Common inclusion criteria:

Patients aged ≥18 years with documented nonvalvular atrial fibrillation (AF) and one or more of the following additional risk factors for stroke:

- A prior stroke (ischemic or unknown type), transient ischemic attack (TIA) or non-CNS systemic embolism, or
- 2 or more of the following risk factors:
    - age ≥75 years,
    - hypertension,
    - heart failure or left ventricular ejection fraction ≤35%, or
    - diabetes mellitus

Common exclusion criteria:

- Cardiac-Related Conditions: hemodynamically significant mitral stenosis, any valve prosthesis, atrial fibrillation due to reversible disorders, planned cardioversion, active endocarditis, atrial myxoma or left ventricular thrombus
- Hemorrhage Risk-Related Criteria: active internal bleeding, any prior or current condition associated with an increased risk of bleeding, platelet count <90,000
- Concomitant Conditions: severe, disabling stroke within 3 months or any stroke within 14 days of randomization, TIA within three days of randomization, required anticoagulation for conditions other than atrial fibrillation, anemia, pregnancy or lactation, contraindication to warfarin, HIV infection, CrCl <30 mL/min, significant hepatic impairment or ALT >3x the ULN
- Concomitant Therapies: aspirin >100 mg per day, aspirin in combination with thienopyridines or use of IV antiplatelets within five days of randomization, fibrinolytics within 10 days of randomization, long-term NSAID use, strong CYP450 3A4 inhibitors or inducers within four days of randomization or during the study

Of the 14,264 patients randomized in the study, 13,962 (rivaroxaban, n=6958; warfarin, n=7004) were included in the per-protocol (PP) as-treated population; 14,143 (rivaroxaban, n=7061, warfarin, n=7072); were included in the safety as-treated population and 14,171 (rivaroxaban, n=7081; warfarin, n=7,090) were included in the intention-to-treat (ITT) population. The primary efficacy endpoint was the composite of stroke (ischemic or hemorrhagic) and systemic embolism. The primary safety endpoint was the composite of major bleeding and non-major clinically relevant bleeding.

Efficacy:

Rivaroxaban was non-inferior to warfarin for prevention of stroke or systemic embolism (primary efficacy outcome) in the PP as-treated population and ITT population. In the safety as-treated population, the primary efficacy event rate was 1.7% per year with rivaroxaban compared to 2.2% per year with warfarin (hazard ratio, 0.79; 95% CI, 0.65 to 0.95; p=0.02 for superiority). During treatment in the ITT population, patients in the rivaroxaban group had lower event rates

rates than those in the warfarin group (1.7% per year vs. 2.2% per year; p=0.02). Significantly more patients that transitioned from rivaroxaban than from warfarin developed primary events during the first month after discontinuing randomized treatment (22 vs. 7; p=0.008).

Safety:
The event rates of the composite of major and non-major clinically relevant bleeding events (principal safety endpoint) were comparable between rivaroxaban and warfarin (14.9% per year vs. 14.5% per year, respectively; p=0.44). Major bleeding rates were comparable between the two groups (rivaroxaban: 3.6% per year vs. warfarin: 3.4% per year; p=0.58). Intracranial hemorrhage rates were significantly lower with rivaroxaban than with warfarin (0.5% per year vs. 0.7% per year, respectively; p=0.02). Major bleeding from a gastrointestinal site was significantly greater with rivaroxaban compared to warfarin (3.2% vs. 2.2%, respectively; p<0.001).

Conclusion:
Rivaroxaban was demonstrated non-inferior to warfarin for the primary composite endpoint of time to first occurrence of stroke (any type) or non-CNS systemic embolism [HR (95% CI): 0.88 (0.74, 1.03)], but superiority to warfarin was not demonstrated. There is insufficient experience to determine how rivaroxaban and warfarin compare when warfarin therapy is well-controlled.

Table 9: Study Design, Adverse Events and Comments[2,3]

Study	Patient Population	Treatment Groups	Primary Endpoint	Statistical Methods	Results
ROCKET AF	Patients with non-valvular atrial fibrillation at moderate-to-high risk for stroke (CHADS2 score of 2 or greater)	Rivaroxaban 20 mg orally once daily; 15 mg once daily for patients with CrCl 30 – 49 mL/min Adjusted-dose warfarin orally once daily titrated to a target INR of 2.0 to 3.0	Efficacy: Composite of stroke and systemic embolism Safety: Composite of major and non-major clinically relevant bleeding	PP population for analysis of non-inferiority; ITT population for analysis of superiority for primary efficacy endpoints; safety as-treated population for analysis of secondary efficacy endpoints Safety on-treatment population for analysis of safety endpoints	Primary efficacy (per 100 pt-years): PP as-treated population: Rivaroxaban: 1.7% Warfarin: 2.2% HR (95% CI): 0.79 (0.66 to 0.96; p<0.001 for non-inferiority) ITT population: Rivaroxaban: 2.1% Warfarin: 2.4% HR (95% CI): 0.88 (0.74 to 1.03; p<0.001 for non-inferiority, p=0.12 for superiority) Primary safety (per 100 pt-years): Rivaroxaban: 14.9% Warfarin: 14.5% HR (95% CI): 1.03 (0.96 to 1.11; p=0.44)

Attachment 2

Evidence Tables

RECORD 1 and 2[4,5]

Both studies were phase III, randomized, double-blind trials.

Common inclusion criteria were:
- Male or female patients greater than 18 years of age
- Patients scheduled to undergo elective total hip arthroplasty

Common exclusion criteria were:
- Patients scheduled to undergo staged bilateral hip arthroplasty, had active bleeding or a high risk of bleeding, or had any condition contraindicating the use of enoxaparin or a condition that might require an adjusted dose of enoxaparin
- Patients with conditions preventing bilateral venography, substantial liver disease, severe renal impairment (CrCl < 30 mL/min), concomitant use of HIV protease inhibitors, planned intermittent pneumatic compression, or requirement for anticoagulant therapy that could not be discontinued

Both clinical trials had similar study protocols. Patients were randomized using permutated blocks and stratified by center to receive either rivaroxaban 10 mg orally once daily plus placebo injection or enoxaparin 40 mg subcutaneously once daily plus placebo tablet. Rivaroxaban was started 6-8 hours after wound closure for 31-39 days along with placebo injection for 10-14 days starting 12 hours before surgery, and enoxaparin was initiated 12 hours before surgery and restarted 6-8 hours after wound closure along with placebo tablets given for 31-39 days starting 6-8 hours after wound closure. After the last dose of study medication, patients underwent mandatory bilateral venography after which no further study medication was given. However, further thromboprophylaxis given at the investigator's discretion. Patients were followed up 30-35 days after the last dose of study medication.

The primary efficacy outcome of these studies was the composite of deep-vein thrombosis (either symptomatic or detected by bilateral venography), nonfatal pulmonary embolism, or all-cause mortality up to day 30-42 (day 1 defined as day of surgery). The main secondary efficacy outcome was major venous thromboembolism, which was a composite of proximal deep-vein thrombosis, nonfatal pulmonary embolism, and death due to venous thromboembolism). The primary safety outcome was major bleeding.

RECORD 3[6]

This study was a multicenter, randomized, double-blind trial.

Inclusion criteria:
- Male of female patients greater than 18 years of age
- Patients scheduled for total knee arthroplasty

Exclusion criteria:
- Patients with active bleeding or a high risk of bleeding that contraindicated the use of low-molecular-weight heparin

- Patients with any contraindication to the use of enoxaparin or a condition that might require an adjusted dose
- Patients with conditions preventing bilateral venography, significant liver disease, concomitant use of HIV protease inhibitors or fibrinolytic agents, planned intermittent pneumatic compression, requirement of ongoing anticoagulant therapy, and pregnancy or breast-feeding

Patients were randomly via a central telephone system to receive either rivaroxaban 10 mg orally once daily or a once-daily injection of enoxaparin 40 mg. Rivaroxaban was initiated 6-8 hours after wound closure, and enoxaparin was initiated 12 hours prior to surgery and restarted 6-8 hours after wound closure. Study medications were continued until at least day 10 and up to day 14. After the last dose of study medication, patients underwent mandatory bilateral venography between day 11 and 15, after which no further study medication was given. However, further thromboprophylaxis was given at the investigator's discretion. Patients were followed up for 30-35 days after the last dose of study medication.

The primary outcome of this study was the composite of any deep-vein thrombosis, nonfatal pulmonary embolism, or all-cause mortality within 13-17 days after surgery. The main secondary outcome was major venous thromboembolism (proximal deep-vein thrombosis, nonfatal pulmonary embolism, or death related to venous thromboembolism). Other efficacy outcomes included the incidence of any, proximal, or distal deep-vein thrombosis, symptomatic venous thromboembolism occurring during the treatment period of follow-up period, and death during the follow-up period.

RECORD 4[10]

This study was a multicenter, randomized, double-blind trial.

Inclusion criteria:
- Male or female patients greater than 18 years of age
- Patients scheduled for total knee arthroplasty

Exclusion criteria:
- Patients with active bleeding or a high risk of bleeding, or any condition contraindicating the use of enoxaparin or that would require an adjusted dose
- Patients with conditions preventing bilateral venography, significant liver disease, severe renal impairment (CrCl < 30 mL/min), concomitant use of medications that strongly inhibit CYP450 such as protease inhibitors or ketoconazole, planned intermittent pneumatic compression, requirement of ongoing anticoagulant therapy, and pregnancy or breast-feeding

Patients were randomly assigned to study drug prior to surgery via a central telephone system and were stratified by center with permuted blocks on a double-blind, double-dummy basis. Patients in the rivaroxaban arm received 10 mg orally once daily along with placebo injections, while patients in the enoxaparin arm received enoxaparin 30 mg subcutaneously every 12 hours along with placebo tablets. Rivaroxaban was initiated 6-8 hours after wound closure or after hemostasis was achieved, and enoxaparin was started 12-24 hours after wound closure. Mandatory bilateral venography occurred between day 11 and 15, after which no further study drug was given. However, use of thromboprophylaxis after the study period was at the investigator's discretion. Patients were followed up for 30-35 days after the last dose of study medication.

The primary efficacy outcome of this study was the composite of any deep-vein thrombosis, nonfatal pulmonary embolism, or all-cause mortality up to day 17 after surgery. The main secondary outcome was major venous thromboembolism (proximal deep-vein thrombosis, nonfatal pulmonary embolism, or venous thromboembolism-related death). Some other efficacy outcomes that were also included were the incidence of asymptomatic deep-vein thrombosis (any, any proximal, and distal only), symptomatic venous thromboembolism that occurred during treatment and follow-up periods, and death during the follow-up period.

Table 10: Study Design, Adverse Events and Comments

Study	Patient Population	Treatment Groups	Primary Endpoint	Statistical Methods	Results
RECORD 1	Patients undergoing total hip arthroplasty	Rivaroxaban 10 mg orally once daily plus placebo injection (n=1595) Enoxaparin 40 mg subcutaneously once daily plus placebo tablet (n=1558)	Efficacy: composite of deep-vein thrombosis (either symptomatic or detected by bilateral venography), nonfatal pulmonary embolism, or all-cause mortality up to day 30-42 Safety: major bleeding	Per protocol analysis for noninferiority, modified intention-to-treat analysis for superiority	Primary efficacy: 1.1% in rivaroxaban group (R), 3.7% in enoxaparin group (E), (absolute risk reduction (ARR), 2.6%; 95% CI, 1.5 to 3.7; p<0.001) Major VTE: 0.2%(R), 2.0%(E), (ARR, 1.7%; 95% CI, 1.0 to 2.5; p<0.001) Primary safety: 0.3%(R), 0.1%(E), p=0.18
RECORD 2	Patients undergoing total hip arthroplasty	Rivaroxaban 10 mg orally once daily plus placebo injection (n=1252) Enoxaparin 40 mg subcutaneously once daily plus placebo tablet (n=1257)	Efficacy: composite of deep-vein thrombosis (either symptomatic or detected by bilateral venography), nonfatal pulmonary embolism, or all-cause mortality up to day 30-42 Safety: incidence of major bleeding events after first intake and up to 2 days after last intake of study medication	Modified intention-to-treat, Fisher's exact test	Primary efficacy: 2.0%(R), 9.3%(E), (ARR, 7.3%; 95% CI, 2 to 9.4; p<0.0001) Primary safety: 6.6%(R), 5.5% (E), p=0.25
RECORD 3	Patients undergoing total knee arthroplasty	Rivaroxaban 10 mg orally once daily plus placebo injection (n=908) Enoxaparin 40 mg subcutaneously once daily plus placebo tablet (n=925)	Efficacy: composite of any deep-vein thrombosis, nonfatal pulmonary embolism, or all-cause mortality within 13-17 days after surgery Safety: major bleeding	Per protocol analysis for noninferiority, modified intention-to-treat analysis for superiority	Primary efficacy: 9.6%(R), 18.9%(E), (ARR, 9.2%; 95% CI, 5.9 to 12.4; p<0.001) Major VTE: 1.0%(R), 2.6%(E), (ARR, 1.6%; 95% CI, 0.4 to 2.8; p=0.01) Symptomatic VTE: 0.7%(R), 2.0%(E), (ARR, 1.3%; 95% CI, 0.4 to 2.2; p=0.005) Primary safety: 0.6%(R), 0.5%(E), p=0.77

RECORD 4	Patients undergoing total knee arthroplasty	Rivaroxaban 10 mg orally once daily plus placebo injection Enoxaparin 30 mg subcutaneously twice daily plus placebo tablet	Efficacy: composite of any deep-vein thrombosis, nonfatal pulmonary embolism, or all-cause mortality up to day 17 after surgery Safety: major bleeding	Per protocol analysis for noninferiority, modified intention-to-treat analysis for superiority	Primary efficacy: 6.9%(R), 10.1%(E), (ARR, 3.19%; 95% CI, 0.71 to 5.67; p=0.0118) Primary safety: 0.7%(R), 0.3%(E), p=0.1096