Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35, Salem, Oregon 97301-1079
Phone 503-945-5220 | **Fax** 503-947-1119

Month/Year of Review: January 2012
End date of literature search: November 2011
Generic Name: Rivaroxaban
Brand Name (Manufacturer): Xarelto (Janssen Pharmaceuticals)
PDL Class: No current PDL class
Comparator Therapies: Enoxaparin and warfarin
Preferred Anticoagulants: enoxaparin and dalteparin
Non-preferred Anticoagulants: fondiparinux, tinzaparin, rivaroxaban (pending) and dabigatran (pending)
No PDL-status/no restrictions: warfarin

FDA Approved Indications: Rivaroxaban is indicated for the prophylaxis of deep vein thrombosis (DVT) which may lead to pulmonary embolism (PE) in patients undergoing total knee replacement (TKR) or total hip replacement (THR) surgery. Rivaroxaban is also approved to reduce the risk of stroke in patients with non-valvular atrial fibrillation (AF).

Dossier received: Yes

Summary:

- Rivaroxaban is the first oral factor Xa inhibitor. Rivaroxaban differs from warfarin with respect to minimal food and drug interactions, absence of routine laboratory monitoring and quick onset of acton.[1]

Prophylaxis of DVT

- Rivaroxaban is dosed for prophylaxis of DVT as 10mg once daily without regard to food. Use cautiously in moderate renal impairment (CrCl 30-50 ml/min). Do not use in severe renal impairment (CrCl <30 ml/min) due to increased rivaroxaban exposure and pharmacodynamic effects in these patients. Monitor patients with moderate renal impairment (CrCl 30 to 50 mL/min) for signs or symptoms of bleeding. Avoid use in moderate or severe hepatic impairment or in hepatic disease with coagulopathy.

Nonvalvular Atrial Fibrillation

- Rivaroxaban is approved for atrial fibrillation, given as 20mg daily with the evening meal, for patients with CrCl >50 mL/min. For patients with CrCl of 15 to 50 mL/min a dose of 15 mg with the evening meal is recommended. Rivaroxaban is not recommended for a CrCL of <15 mL/min.

Efficacy and Safety Summary on FDA Approved Indications

Surgery Prophylaxis

- Rivaroxaban approval for patients undergoing total hip replacement (THR) or total knee replacement (TKR) surgery was based on three large, prospective, randomized, double blind, double dummy trials.[2,3,4] RECORD 2 and 4 are included in the evidence table, however, they were deemed poor studies based on FDA summaries on the quality of data.
- There was low-strength of evidence from RECORD 1 and 3 that rivaroxaban was similar to enoxaparin in regards to the component outcomes of all-cause mortality, symptomatic venous thromboembolism (VTE) and non-fatal pulmonary embolism. However, the use of the European enoxaparin dosing regimen of 40mg once daily in RECORD 3, limits the applicability of the results to patients in the United States were the recommended dosing regimen for DVT prophylaxis in patients undergoing TKR is 30mg twice daily.
- There was low-strength of evidence to suggest major bleeding rates were slightly higher for rivaroxaban compared to enoxaparin in both RECORD 1 and 3 studies, although not statistically significant.

Atrial Fibrillation

- ROCKET AF was a phase III, DB, DD, RCT in over 14,000 patients in 45 countries with nonvalvular atrial fibrillation who were at moderate to high risk of stroke. Patients were randomly assigned to rivaroxaban 20mg daily or dose-adjusted warfarin (INR 2.0-3.0). The primary efficacy analysis was the composite of stroke (ischemic and hemorrhagic) and systemic embolism.[6]
- There was low-strength of evidence from ROC KET AF that rivaroxaban was noninferior to warfarin for the composite outcome of stroke and systemic embolism (HR 0.88; 95% CI, 0.75 to 1.03; p<0.001 for noninferiority, p=0.12 for superiority). There was low-strength of evidence that major bleeding rates were similar between rivaroxaban and warfarin (HR 1.04; 95% CI, 0.90 to 1.20, p=0.58).
- Concerns over suboptimal warfarin use in ROCKET AF makes conclusions on relative efficacy and safety unknown. The short half-life of rivaroxaban combined with once daily dosing may be problematic if there are adherence concerns. There are concerns on how to best transition patients off of rivaroxaban as there was a noted increase in events after treatment discontinuation (see full prescribing information for transitioning patients from rivaroxaban to other anitcoagulants).

Efficacy and Safety Summary of Off-label Uses

Acute DVT and Continuation Treatment

- Rivaroxaban was studied in two poor quality studies for acute DVT and continuation treatment (EINSTEIN-DVT and EINSTEIN-EXTENSION). Currently, there is insufficient evidence to support rivaroxaban use for this indication and is not recommended until further data becomes available.

Acute Coronary Syndrome

- Most recently rivaroxaban was studied in patients presenting with Acute Coronary Syndrome (ACS) in the ATLAS ACS 2-TIMI 51. Patients were randomized to rivaroxaban 2.5mg twice daily, rivaroxaban 5mg twice daily or placebo, along with standard medical care for ACS.

There is moderate evidence to suggest rivaroxaban is better than placebo for this indication, however, there are no studies comparing the standard of care, aspirin and clopidogrel, to rivaroxaban. Doses used in this study are not currently available and use for this indication will need to be revisited in the future.

Cost Considerations:
Costs will be discussed in the executive session.

PDL Placement Recommendation:
There is low-strength of data to suggest that rivaroxaban is at least as effective as enoxaparin for prophylaxis of DVT in patients undergoing THR and TKR. The RECORD studies demonstrated efficacy favoring rivaroxaban, with the limitation of using the European dosing regimen in the one of the TKR studies, excluding high percentages of patients from analysis, and results being driven by asymptomatic DVTs. It is recommended that rivaroxaban be added to the PDL for this indication, after cost considerations are taken into account, and dose limitations should be applied.

There is one fair quality trial to demonstrating efficacy of rivaroxaban use in AF. Concerns over suboptimal warfarin use in ROCKET AF makes conclusions on relative efficacy and safety unknown. Efficacy relative to dabigatran has not been established. Warfarin is recommended as the first line agent for this indication.

BACKGROUND/CURRENT LANDSCAPE

FDA Approved Indication:Thromboprophylaxis after THR and TKR

For patients undergoing THR or TKR prophylactic anticoagulants are considered standard practice. A recent guideline by the American Academy of Orthopaedic Surgeons gives a moderate recommendation for the use of prophylactic pharmacological agents for VTE prevention in those patients that are not at elevated risk. Due to insufficient evidence they are unable to recommend any particular preventative strategy or treatment duration.[9] The American College of Chest Physicians (ACCP) Evidence-Based Clinical Practice Guidelines (CHEST) on antithrombotic and thrombolytic therapy recommends treatment with warfarin, LMWH, or fondaparinux for at least 10 days and up to 35 days for TKR and THR.[10] Oregon Health Plan (OHP) fee-for-service FFS currently lists LMWHs, enoxaparin and dalteparin, as preferred, and fondaparinux (Arixtra®) and tinzaparin (Innohep®) as not preferred. Desirudin (Iprivask®) is not managed via PDL and currently has no utilization restrictions. In the previous six months approximately 200 patients received short term anticoagulation (<45 days) accounting for almost 200 prescription claims (there were no claims for dabigatran or rivaroxaban).

FDA Approved Indication: Atrial Fibrillation

Patients with AF are at a four to five-fold increased risk of stroke and systemic embolism compared to those without AF.[11] Anticoagulants are a key component to managing patients with AF that are at an increased risk of stroke from cardioembolic events. The $CHADS_2$ risk stratification scheme is recommend to estimate stroke risk in patients with AF based on: presence of heart failure, presence of hypertension, age ≥75 years, presence of diabetes mellitus, and a history of previous stroke or transient ischemic attack (Table 1).[12] The greater the number of risk factors present, the greater the risk of stroke. CHEST guidelines on antithrombotic and thrombolytic therapy recommend anticoagulation for patients with AF and suggest aspirin therapy for patients with up to one risk factor and treatment with a VKA for patients with one or more risk factors or in secondary prevention patients.[10] The guidelines also recommends VKA therapy for patients with a $CHADS_2$ score of ≥2.

Table 1. $CHADS_2$ Classification Scheme for Stroke Risk[12]

	Risk Factor	Points
C	Congestive Heart Failure	1
H	Hypertension	1
A	Age ≥75 years	1
D	Diabetes	1
S_2	History of stroke or TIA	2

Off-label Uses: Acute/Chronic DVT

Acute DVT treatment is an additional indication for anticoagulation. DVT is a serious medical condition that affects 1 in 1000 people and can lead to PE and related risk of morbidity and mortality.[13] CHEST guidelines recommend initial treatment with LMWH, unfractionated heparin (UFH) or fondaparinux for at least 5 days to bridge the patients to effective warfarin therapy, which should begin on the first treatment day.[10] Discontinuation of bridging should occur after the fifth day of therapy, provide the INR has been 2.0 or more for at least 24 hours. For patients with DVT or PE secondary to a reversible risk factor, the guidelines recommend treatment with warfarin for 3 months. Treatment recommendations for patients with unprovoked DVT or PE include warfarin for at least 3 months and up to a year or longer based on clinical judgment.

The VKA, warfarin, has served as the gold standard for oral anticoagulation and is a covered therapy, without restriction for OHP FFS patients. Approximately 350 patients utilized long term anticoagulation (>45 days), representing over 2,000 prescription claims within the last six months within the OHP population.

Off-label Uses: Acute Coronary Syndrome (ACS)

Antiplatelet drugs are used to prevent cardiovascular events and premature death in patients with multiple risk factors and in patients who have experienced Acute Coronary Syndrome (i.e. unstable angina, non-ST segment elevation myocardial infarction, or ST segment elevation myocardial infarction), transient ischemic attacks or thromboembolic stroke, or symptomatic peripheral arterial disease. Aspirin has been considered the gold standard. Aspirin is effective in reducing the occurrence of major cardiovascular events including death, recurrent myocardial infarction, recurrent angina, or progression to severe angina and nonfatal stroke. Several practice guidelines have been published that provide recommendations regarding the role of aspirin.[14,15,16,17,18,19] Limited trials with factor Xa and IIa inhibitors have been studied in patients after an ACS showing promising results in reduction of cardiovascular events.

CLINICAL PHARMACOLOGY

Rivaroxaban selectively blocks the active site of factor Xa, without a cofactor requirement (such as Anti-thrombin III) for activity. Blocking the conversion of factor X to factor Xa (FXa) inhibits intrinsic and extrinsic pathways that play a main role in the blood coagulation cascade.[1]

COMPARATIVE CLINICAL EFFICACY

Relevant Endpoints

All Studies:	All-cause Mortality Major bleeding
DVT:	Recurrent VTE
DVT Prophylaxis:	PE Symptomatic VTE
AF:	Stroke
ACS:	Cardiovascular mortality Stent Thrombosis

Primary Study Endpoint:

RECORD 1-4: Composite of DVT, nonfatal PE and death
ROCKET-AF: Composite of stroke and systemic embolism
EINSTEIN-DVT and EINSTEIN-Extension: Recurrent VTE
ATLAS ACS 2-TIMI 51: Composite of death from cardiovascular causes, MI, or stroke

Evidence Table

Ref./ Study Design[1]	Drug Regimens	Patient Population	N	Duration	Efficacy Results[2]	ARR / NNT[3]	Safety Results^	ARI / NNH[3]	Quality Rating[4]; Comments
RECORD 1[2]									
Eriksson B, et al Phase III, DB, RCT, PG, DD	1. **Rivaroxaban 10mg QD** (started after surgery) 2. **Enoxaparin 40mg SQ QD** (started evening before surgery)	Age: 63 yrs Female: 55% Prior VTE: 2.1-2.5% <u>Inclusion Criteria</u>; Scheduled for THR <u>Exclusion Criteria</u>: Bleeding, contraindications to anticoagulant use, pregnancy, lactation, severe liver or renal impairment, concomitant use of protease inhibitors or	1. n= 2209 2. n= 2224	Mean tx duration: 33 days F/U: 30-42 days after last dose	<u>Composite of DVT, nonfatal PE, or death:</u> R: 18 (1.1%) E: 58 (3.7%) RR 0.30 95% CI 0.12 to 0.51 <u>All-cause Mortality:</u> R: 5 (0.3%) E: 4 (0.3%) RR 1.22 95% CI 0.33 to 4.5 <u>PE:</u> R: 4 (0.3%) E: 1 (0.1%) RR 3.9	ARR 2.6% NNT 38 NS NS	<u>Major Bleeding:</u> R: 6 (0.3%) E: 2 (0.1%) RR 3.0 95% CI 0.61 to 14.9	NS	• Study Rating: Fair • Composite endpoint results driven by asymptomatic findings. • Large number of patients unaccounted for – sensitivity analysis states that missing data didn't effect power estimates • Symptomatic VTE similar in each treatment group (0.3% rivaroxaban and 0.5% enoxaparin) • Primary outcome was a composite endpoint including symptomatic and asymptomatic DVTS. The importance and clinical relevance of asymptomatic DVTs is unknown. • Per-protocol population was used for efficacy outcomes except symptomatic VTE which used mITT population.

		fibrinolytic agents			95% CI 0.44 to 35.0 Symptomatic VTE: R: 7 (0.3%) E: 15 (0.7%) RR 0.47 95% CI 0.19 to 1.15	NS	* Safety population used for above result		
RECORD2									
Kakkar A, et al Phase III, RCT, DB, DD	1. **Rivaroxaban 10 mg daily** (started 6-8 hrs. after wound closure) 2. **Enoxaparin 40mg SQ QD** (started 12 hours before surgery)	Age: 61 years Female: 53.7% Inclusion: Scheduled for THR Exclusion: See RECORD1	1. n= 864 2.n= 869	Rivaroxaban Tx: Mean 33.5 days Enoxaparin Tx: Mean 12.4 days F/U: 30-35 days after last dose of medication	Composite of DVT + nonfatal PE or death R: 17 (2.0%) E: 81 (9.3%) RR 0.21 95% CI 0.13 to 0.35 All-cause Mortality: R: 2 (0.2%) E: 8 (0.7%) RR 0.33 95% CI 0.07 to 1.7 PE: R: 1 (0.1%) E: 4 (0.5%) RR 0.25 95% CI 0.03 to 2.2 Symptomatic VTE: R: 3 (0.2%) E: 15 (1.2%) RR 0.20 95% CI 0.06 to 0.69	ARR 7.3% NNT 14 NS NS ARR 1.0% NNT 100	Major bleeding R: 1 (<0.1%) E: 1 (<0.1%) RR 1.0 95% CI 0.06 to 16.0	NS	• Study Rating: Poor • Composite endpoint results driven by asymptomatic findings • High number of excluded patients from mITT • Compared DVT events for 33 days of rivaroxaban versus 12 days for enoxaparin • Higher than expected invalidity rate for venograms – sensitivity analysis showed that didn't effect power • Increase number of cardiovascular events after rivaroxaban discontinuation

RECORD3[4]									
Lassen M, et al Phase III, RCT DB, DD	**1. Rivaroxaban 10mg QD** (started 6-8 hrs. after wound closure) 2. **Enoxaparin 40mg SQ QD** (started 12 hours before surgery)	Age: 67 years Female: 70% rivaroxaban / 66% enoxaparin Inclusion Criteria: Scheduled for TKR Exclusion Criteria: See RECORD1	1. n= 824 2. n=878	Tx duration: 10-14 days Venography: 11-15 days F/U: 30-35 days after last dose of tx	Composite of DVT, nonfatal PE, or death: R: 79 (9.6%) E: 166 (18.9%) RR 0.51 95% CI 0.39 to 0.65 All-cause Mortality: R: 0 (0%) E: 6 (0.5%) PE: R: 0 (0%) E: 4 (0.3%) Symptomatic VTE: R: 13 (1.1%) E: 27 (2.2%) RR 0.50 95% CI 0.25 to 0.94	ARR 9.2% NNT 11 NS NS NS	Major Bleeds: R: 7 (0.6%) E: 6 (0.5%) RR 1.2 95% CI 0.40 to 3.5	NS	• Study Rating: Fair • Utilized European dosing of enoxaparin 40mg daily for TKR • Anticoagulant allowed during follow-up period • Non-inferiority margin set at 4% • Only 67% of population used in mITT analysis
RECORD 4[5]									
Turpie A, et a Phase III, DB, RCT, DD	1. **Rivaroxaban 10mg QD** (started 6-8 hrs. after wound closure) 2. **Enoxaparin 30mg SQ BID** (started 12 hours postoperatively)	Age: 64 years Female: Rivaroxaban 66% Enoxaparin 64% Inclusion Criteria: Scheduled for TKR Exclusion Criteria: See RECORD1	1. 965 2. 959	Tx Duration: 10-14 days Follow-Up: 30-35 days after last dose	Composite of DVT + nonfatal PE or death: R: 67 (6.9%) E: 97 (10.1%) RR 0.67 95% CI 0.51 to 0.93 All-cause Mortality: R: 6 (0.1%) E: 6 (0.2%) RR 0.99 95% CI 0.32 to 3.1 PE: R: 5 (0.3%) E: 8 (0.5%) RR 0.62 95% CI 0.20 to 1.9	ARR 3.2% NNT 31 NS NS	Major bleeding: R: 10 (0.7%) E: 4 (0.3%) RR 2.5 95% CI 0.78 to 7.9	NS	• Study Rating: Poor • Composite endpoint results driven by asymptomatic findings • Data deemed not reliable by FDA due to compliance deficiencies with study procedures • Only 61% or patients eligible for primary endpoint analysis

					Symptomatic VTE: R: 14 (0.7%) E: 21 (2.0%) RR 0.66 95% CI 0.34 to 1.3	NS			
ROCKET AF[6]									
Patel M, et al Phase III, RCT DB, DD	1. **Rivaroxaban 20mg QD** 2. **Warfarin** (dose-adjusted to INR of 2.0-3.0)	Age: 73 yrs Female: 40% ASA use: 36% Mean $CHADS_2$ Score: 3.5 Coexisting Conditions: 55% Mean TTR for warfarin patients: 55% Inclusion: Nonvalvular a-fib with moderate to high risk of stroke Exclusion: Cardiac related conditions, active bleeding, uncontrolled hypertension, disabling stroke, chronic NSAID, anticoag tx, use of strong CYP3A4 inhibitors , contraindication to warfarin, severe renal or hepatic disease	1. 7081 2. 7090	Median Tx duration: 590 days Follow up: 707 days	Stroke or Systemic Embolism: R: 269 (2.1%) W: 306 (2.4%) HR 0.88 95% CI 0.75 to 1.03 P <0.001 for inferiority p=0.12 for superiority All Cause Mortality: R: 582 (4.5%) W: 632 (4.9%) HR: 0.92 95% CI, 0.82 to 1.03 P= 0.15	NS NS	Major Bleeds: R: 395 (5.6%) W: 386 (5.4%) HR 1.04 95% CI 0.90 to 1.20 P= 0.58	NS	• Study rating: fair • Warfarin INR values were • within the therapeutic range 55% which suggests suboptimal warfarin management • Information on management of INR was not provided • Results shown non-inferiority but unable to claim superiority to warfarin in ITT analysis • Rivaroxaban group had more strokes and embolisms during transition to open-label portion of study (ITT analysis) showing non-inferiority but not superiority • No component endpoint results provided • 32 patients lost to follow-up • 23.7% of patients in rivaroxaban group and 22.2% of patients in warfarin group discontinued treatment prior to an end point event or before the end of study • Concerns over short half-life and once daily dosing.
EINSTEIN-DVT[7]									
The Einstein	1. Rivaroxaban 15mg twice daily X 3 weeks then 20mg	Age: 56 years Female: 43%/44% Inclusion:	1. 1731	Median Tx duration: 3, 6, or 12 months	Recurrent VTE: R: 36 (2.1%) E-VKA: 51 (3.0%) HR 0.68		Major Bleeding: R: 14 (0.8%) E-VKA: 20 (1.2%) HR 0.65	NS	• Study Rating: Poor • Open label design lends results subject to bias • Patients on warfarin in TTR 58%

Investigators Phase III, RCT, Open-label, PG, non-inferiority study	once daily 2. Enoxaparin + either warfarin or acenocoumarol (vitamin K antagonist)	Acute symptomatic DVT Exclusion: Additional VKA indication, CrCl <30 ml/min, significant liver disease, active bleeding uncontrolled HTN, pregnant/breastfeeding concomitant CYP-450 3A4 inhibitors	2. 1718		95% CI 0.44-1.04 p<0.001 PE: R: 3 E-VKA: 6 All-cause mortality: R: 38 (2.2%) E-VKA: 49 (2.9%) HR 0.67 95% CI, 0.33 to 1.30		95% CI 0.33 to 1.30 p=0.21	NS	• 73% in rivaroxaban group and 71% in the warfarin group were pretreated with parenteral anticoagulants • Low dropout rates • Only symptomatic DVTs evaluated
EINSTEIN-Extension[7]									
The Einstein Investigators Phase III, DB, PG	1. Rivaroxaban 20mg daily 2. Placebo	Age: 58 yrs Female: 41%/43% Inclusion: objectively confirmed, symptomatic DVT or PE with 12 month prior treatment with warfarin or acenocoumarol Exclusion: additional VKA indication, CrCl <30 ml/min, significant liver disease, active bleeding, uncontrolled HTN, pregnant/ breastfeeding, concomitant CYP-450 3A4 inhibitors	1. 602 2. 594	Tx duration: 6 or 12 months	Recurrent VTE: R: 8 (1.3%) P: 42 (7.1%) HR 0.18; 95% CI 0.09 to 0.39 p<0.001 PE: R: 1 P: 0 All-cause mortality: R: 1 (0.2%) P: 2 (0.3%)	ARR 5.8% NNT 17	Major Bleeding: R: 4 (0.7%) P: 0 (0.0%) p=0.11	NS	• Study Rating: Poor • 53% of patients from previous studies – bias results to those already able to tolerate therapy • Placebo comparison limits clinical applicability • Lost to follow-up rates low

ATLAS ACS 2-TIMI 51 [8]									
ATLAS ACS 2-TIMI 51 Investigators RCT, DB, PC, Phase III	1. Rivaroxaban 2.5mg or 5mg twice daily 2. Placebo	Mean age: 61 yrs Males: 74-75% <u>Inclusion</u>: patients 18 and over with symptoms of ACS and STEMI, NSTEMI, or unstable angina. Those <55 also had DM or previous MI. NSTEMI: 50% ea.group STEMI: 26% ea. Group Unstable angina: 24% ea. group <u>Exclusion</u>: Reduced platelets and hemoglobin levels, CrC <30ml/min, previous bleeding, previous stroke or TIA on ASA o thienopyridine Also on standard medical therapy including low-dose ASA and thienopyridine	R 2.5mg 5174 R 5 mg 5176 Placebo 5176	Mean tx duration 13.1 months	<u>Composite of death from CV, MI or stroke:</u> R 2.5mg: 9.1% HR 0.84 95% CI 0.72 to 0.97 P= 0.007 P: 10.7% R 5mg: 8.8% HR 0.85 95% CI 0.73 to 0.98 P=0.01 P: 10.7% <u>CV Mortality:</u> R 2.5mg: 2.7% HR 0.66 95% CI, 0.51 to 0.86 P=0.005 P: 4.1% R 5mg: 4.0% HR 0.94 95% CI 0.75 to 1.20 P =0.57 P: 4.1% <u>Stent Thrombosis:</u> R 2.5mg: 2.2% HR 0.65 95% CI 0.45 to 0.94 P= 0.02 R 5mg: 2.3% HR 0.73 95% CI 0.51 to 1.04 P=0.04 P: 2.9%	ARR 1.6% NNT 63 ARR 1.9% NNT 53 ARR 1.4% NNT 71 NS ARR 0.7% NNT 143 ARR 0.6% NNT 166	<u>Major Bleeding:</u> R 2.5mg: 1.8% P: 0.6% HR 3.46 95% CI 2.08 to 5.77 P<0.001 R 5mg: 2.4% P: 0.6% HR 4.47 95% CI 2.71 to 7.36 P<0.001 <u>Intracranial Bleeds:</u> R 2.5mg: 14 (0.4% HR 2.83 95% CI 1.02 to 7.86 P= 0.04 P: 0.2% R 5.0mg: 18 (0.7% HR 3.74 95% CI 1.39 to 10.07 P=0.005 P: 0.2% <u>Fatal Bleeds:</u> R 2.5mg: 6 (0.1%) P: 9 (0.2%) HR 0.67 95% CI 0.24 to 1.89 P=0.45 P: 0.2% R 5mg: 15	ARI 1.2% NNH 83 ARI 1.8% NNH 56 ARI 0.2% NNH 500 ARI 0.5% NNH 200 NS	• Study Rating: Fair • Increased major bleeds and intracranial bleeds but fatal bleeds similar • Younger population studied. Potential for increased risk o bleeding in elderly. • Premature discontinuation i 29.4% of rivaroxaban and 26.4% of placebo

					All-cause mortality: R 2.5mg: 320 (9.3%) P: 153 (4.5%) HR 0.68 95% CI, 0.53 to 0.87 P=0.004 R 5mg: 321 (9.1%) P: 153 (4.5%) HR 0.95 95% CI, 0.76 to 1.19 P=0.89		(0.4%) P: 9 (0.2%) HR 1.72 95% CI 0.75 to 3.92 P= 0.20	NS	

[1]**Study design:** DB = double-blind, RCT = randomized trial, PC = placebo-controlled, PG = parallel -group, XO = crossover, DD = double dummy.
[2]**Results abbreviations**: RRR = relative risk reduction, RR =relative risk, OR= Odds Ratio, HR = Hazard Ratio, ARR = absolute risk reduction, ARI = absolute risk increase
NNT = number needed to treat, NNH = number needed to harm, CI = confidence interval, ITT= intention-to-treat analysis, mITT-modified intention-to-treat analysis
[3]**NNT/NNH** are reported only for statistically significant results
[4]**Quality Rating:** (Good- likely valid, Fair- likely valid/possibly valid, Poor- fatal flaw-not valid)
Clinical Abbreviations: TTR= time in therapeutic range, SQ-subcutaneous, STEMI – ST-segment elevation myocardial infarction, NSTEMI – non-ST-segment elevation myocardial infarction

Trial Details

DVT Prophylaxis

Rivaroxaban was approved for the prophylaxis of DVT and PE in over 9,500 patients undergoing total hip replacement (THR) and total knee replacement (TKR) based on data from four multi-center, RCTs; RECORD 1-4.[2,3,4] RECORD 1 and 2 enrolled patients scheduled for THR and RECORD 3 and 4 included patients scheduled for TKR. Patients were treated for a mean duration of 33 days in RECORD 1 and 2, 10-14 days in RECORD 3 and 4. Patients were randomized to rivaroxaban 10 mg daily, starting after surgery, or enoxaparin, starting on the evening prior to surgery. Enoxaparin doses were 40mg sq daily for RECORD 1-3 and 30mg sq twice daily in RECORD 4. The primary efficacy analysis was the composite of DVT, nonfatal PE and death with the primary safety analysis being major bleeding. The primary efficacy analysis results were based on a Modified Intent to Treat (MITT) population which included 8,512 patients (67%) of the original study population.

There was low to moderate-strength of evidence from RECORD 1 that rivaroxaban was similar to enoxaparin in regards to the component outcomes of all-cause mortality and non-fatal pulmonary embolism. There was also low to moderate-strength of evidence that rivaroxaban was more effective than enoxaparin in regards to incidence of DVTs (ARR -2.7%; 95% CI, -3.7 to -1.7; p<0.001). In RECORD 3 there was also low-moderate strength of evidence for no difference in all-cause mortality and non-fatal pulmonary embolism rates between rivaroxaban and enoxaparin. There was low to moderate-strength of evidence that rivaroxaban was superior to enoxaparin in regards to DVTs (ARR -8.4%; 95% CI, -11.7 to -5.2; p=<0.001). However, the use of the European enoxaparin dosing regimen of 40mg once daily in RECORD 3, limits the applicability of the results to United States patients were the recommended dosing regimen for DVT prophylaxis in patients undergoing TKR is 30mg twice daily. There was moderate-strength of evidence to suggest major bleeding rates were higher for rivaroxaban compared to enoxaparin in both RECORD 1 and 3 studies, although not statistically significant.

The Canadian Agency for Drugs and Technologies in Health (CADTH) recommend rivaroxaban as an effective treatment option for VTE prophylaxis after THR or TKR, as an alternative to enoxaparin, with no compelling evidence to suggest an increased incidence of adverse effects.[21]

RECORD 2 and 4 were deemed poor studies due to FDA analysis stating data was unreliable. RECORD 2 compared rivaroxaban to enoxaparin, using different durations of treatment, which limit the applicability of the efficacy conclusions.[20] One of two clinical investigators confirmed data from RECORD 4 was not considered reliable in support of the New Drug Application (NDA). Two additional clinical investigator inspections were conducted prior to the NDA submission, regarding RECORD 2 and RECORD 4, and found that data from both these sites were unreliable. After an analysis of all the RECORD studies, with removal of questionable data, the FDA found efficacy results favoring rivaroxaban, driven by asymptomatic DVTs detected by venography.

Atrial Fibrillation

ROCKET AF was a phase III, DB, DD, RCT in over 14,000 patients in 45 countries with nonvalvular atrial fibrillation who were at moderate to high risk of stroke. Patients were randomly assigned to rivaroxaban 20mg daily or dose-adjusted warfarin (INR 2.0-3.0). Participants had a median age of 73 years and 60% were male. The mean $CHAD_2$ score was 3.5 and 55% of participants had coexisting conditions. The median treatment duration was 590 days with 707 days of follow-up. The primary efficacy analysis was the composite of stroke (ischemic and hemorrhagic) and systemic embolism. A noninferiority analysis (margin of 1.46) was preformed on the per-protocol population. If noninferiority was achieved then noninferiority and superiority testing would be performed on the ITT population. The major safety endpoint was composite of major and nonmajor clinically relevant bleeding events. Major bleeds is reported as the more clinically relevant safety endpoint.[6]

There was low-strength of evidence from ROC KET AF that rivaroxaban was noninferior to warfarin for the composite outcome of stroke and systemic embolism (HR 0.88; 95% CI, 0.75 to 1.03; p<0.001 for noninferiority, p=0.12 for superiority). There was low-strength of evidence that major bleeding rates were similar between rivaroxaban and warfarin (HR 1.04; 95% CI, 0.90 to 1.20, p=0.58) and intracranial bleeds were less with rivaroxaban. TTR was only 55% for warfarin patients in ROCET-AF. Concerns over suboptimal use of warfarin make conclusions on comparable efficacy and safety difficult. There is insufficient evidence comparing rivaroxaban to well controlled warfarin management. The short half-life of rivaroxaban combined with once daily dosing may be problematic if there are adherence concerns.

Off-label Uses

DVT Treatment

Rivaroxaban was studied in a phase III, parallel group, non-inferiority, open-label, RCT in over 3,400 patients with acute symptomatic DVT without PE in the EINSTEIN-DVT trial. Patients were randomized to rivaroxaban 15mg twice daily for 3 weeks and then 20mg once daily or enoxaparin and a vitamin K antagonist (warfarin or acenocoumarol) for 3, 6, or 12 months.[7]

There was low-strength of evidence that rivaroxaban was non-inferior to standard treatment (enoxaparin plus VKA) for the prevention of recurrent VTE in patients with acute DVT. The primary endpoint was experienced by 2.1% of the rivaroxaban group and 3.0% for the enoxaparin/VKA group (HR 0.68; 95% CI, 0.44-1.04; p<0.001 for noninferiority). There was low-strength of evidence of similar rates of major bleeding ,8.1% in both groups.

The EINSTEIN-EXTENSION study was a PC, double-blind, phase III continuation study in over 1,000 patients with a confirmed symptomatic DVT or PE previously treated with a VKA or rivaroxaban for 6 or 12 months (EINSTEIN-DVT, EINSTEIN-PE(ongoing)), that there was equipoise with respect to the need for continued anticoagulation. Patients were randomly assigned to rivaroxaban 20mg daily or placebo for an additional 6 or 12

months. The average patient was 58 years old with around 40% being female. The primary efficacy analysis was recurrent venous thromboembolism and major bleeding was the primary safety analysis.[7]

There is low-strength of evidence that rivaroxaban is more effective than placebo in preventing VTE with extended treatment (HR 0.18; 95% CI 0.09 to 0.39; p<0.001). There is also low-strength of evidence that rivaroxaban causes more major bleeding than placebo. Extension study design may bias efficacy and safety results based on enrollment of patients already able to tolerate/respond to treatments.

Acute Coronary Syndrome

The ATLAS ACS 2-TIMI 51 study was a DB, PC, RCT involving 15,526 patients in 44 countries presenting with Acute Coronary Syndrome (ACS) and an ST-segment elevation myocardial infarction (NSTEMI), non-ST-segment elevation myocardial infarction (NSTEMI) or unstable angina. Patients were randomized to rivaroxaban 2.5mg twice daily, rivaroxaban 5mg twice daily or placebo, along with standard medical care for ACS. Patients were treated for a mean duration of 13.1 months. The primary efficacy endpoint was a composite of death from cardiovascular causes, myocardial infarction or stroke.[8]

There was moderate-strength of evidence that rivaroxaban 2.5mg decreased cardiovascular death, MI and all-cause mortality rates compared to placebo, being statistically significant for cardiovascular mortality and all-cause mortality. Rivaroxaban 5 mg twice daily decreased cardiovascular mortality and MI compared to placebo with moderate-strength of evidence, with only MI rates being statistically significant. There was moderate-strength of evidence that rivaroxaban 2.5mg and 5mg twice daily increased the risk of stroke, although neither were statistically significant. There was moderate strength of evidence that rivaroxaban increases the risk of major bleeds. There were also noted increases in intracranial bleeds, compared to placebo, in both rivaroxaban treatment groups, with a NNH of 500 and 200 in the 2.5mg and 5mg groups, respectively. The average age of study participant was 62 years old, which makes extrapolating results to a more elderly population difficult.

DRUG SAFETY

Serious (REMS, Black Box Warnings, Contraindications):

As with other anticoagulants, rivaroxaban may cause epidural or spinal hematomas in patients whom are receiving neuraxial anesthesia. Active major bleeding and hypersensitivity are contraindications to rivaroxaban therapy.[1]

Rivaroxaban should be used cautiously in patients with bleeding disorders, severe hypertension, pregnancy and renal and hepatic impairment. Other serious adverse events described in post-marketing reports include cerebral hemorrhage, epidural hematoma, and hypersensitivity reactions including anaphylactic shock, agranulocytosis and Steven-Johnson Syndrome.[1,20]

In patients with AF, discontinuing rivaroxaban treatment has put patients at increased risk of thrombotic events. In ROCKET AF an increased risk of strokes were seen following rivaroxaban discontinuation. Consider continuing patients on another anticoagulant if rivaroxaban is to be discontinued.[1]

Bleeding: Rivaroxaban increases the risk of bleeding and can cause significant or even fatal bleeding in certain patients. The risk for bleeding increases when other drugs that also increase the risk of bleeding are used concurrently and was most common during the first week of surgery. Rivaroxaban should be used with caution in pregnant women due to pregnancy related hemorrhage.[1]

In trials evaluating rivaroxaban for prophylaxis in patients undergoing hip or knee replacement bleeding was the most common adverse event. Major bleeding events were higher with rivaroxaban in the RECORD trials compared to enoxaparin, 0.39% vs. 0.21%, respectively.[20]

Table 2.0 Bleeding Events in Patients Undergoing Hip or Knee Replacement Surgeries[1]

Total Treated Patients in Record 1-3*	Rivaroxaban 10mg N= 4487 (n/%)	Enoxaparin 40mg Daily† 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)

* Data from RECORD 4 excluded from pooled data

** Includes major bleeding events.

† Includes placebo-controlled period for RECORD2

Tolerability (Drop-out rates, management strategies):

Overall rivaroxaban was well tolerated with similar discontinuation rates as enoxaparin, 3.7% and 4.6%, respectively.

Pregnancy/Lactation rating:

Rivaroxaban is rated Pregnancy Category C. Dosing hasn't been studied in pregnant women and it should only be given if the potential benefit outweighs the risk to the mother and fetus.[1] Rivaroxaban was shown to be secreted into milk when studied in rats.

Unanswered safety questions:
The safety of taking rivaroxaban long term is unknown. There is no antidote for rivaroxaban in a bleeding emergency. Bleeding should be managed by holding rivaroxaban treatment and giving recombinant factor VIIa or activated prothrombin complex concentrate could be considered, although not studied. Prothrombin complex concentrate has been shown to be effective in a small population but additional data is needed.[22] Protamine and vitamin K would not be expected to reverse anticoagulant effects of rivaroxaban.[23] Of concern was an increased incidence of cardiovascular events during the follow-up period in ROCET AF in the rivaroxaban group compared to warfarin. This increase was thought to be due to a gap in protective effect during drug transition off of rivaroxaban and to warfarin after study completion.[6]

Dose Index (efficacy/toxic):
DVT Prophylaxis
For most patients the dose of rivaroxaban 10mg daily, without regards to meals is recommended. The initial dose should be taken 6-10 hours post surgery once hemostasis has been established. Treatment should continue for 35 days for patients undergoing hip replacement surgeries and 12 days for patients undergoing knee replacement surgeries.

Nonvalvular Atrial Fibrillation
Rivaroxaban is given as 20 mg with the evening meal, for patients with CrCl >50 mL/min. For patients with CrCl of 15 to 50 mL/min a dose of 15 mg with the evening meal is recommended. Rivaroxaban is not recommended for a CrCL of <15 mL/min.

Increased exposure to rivaroxaban was noted in elderly patients, which may be due to age related changes in renal function. Avoid using rivaroxaban in patients with a CrCl <30 mL/min. Patients with moderate renal failure (CrCl 30-<50 mL/min) should be observed closely for bleeding. Due to significant increases in rivaroxaban concentrations with impaired hepatic function, patients with moderate (Child-Pugh B), severe (Child-Pugh C) hepatic impairment or any hepatic disease associated with coagulopathy should not take rivaroxaban. For patients with renal insufficiency (CrCl 15-50 mL/min) taking rivaroxaban for AF the recommended dose is 15mg once daily, with the evening meal.

Rivaroxaban absorption is dependent upon the site of drug release in the GI tract. Drug delivery directly to the proximal small intestine (e.g., feeding tube) can result in reduced drug absorption.[1]

Monitoring:
Dose –dependent inhibition of Factor Xa and in prothrombin time (PT), activated partial thromboplastin time (aPTT) and HepTest® are prolonged dose-dependently. Rivaroxaban also influences Anti-factor Xa activity.

Look-alike / Sound-alike (LA/SA) Error Risk Potential:
LA/SA names are assessed during the PDL selection of drugs. Based on clinical judgment and an evaluation of LA/SA information from four data sources (Lexi-Comp, USP Online LASA Finder, First Databank, and ISMP Confused Drug Name List), the following drug names may cause LASA confusion:

NME Drug Name	Lexi-Comp	USP Online	MicroMedex	ISMP	Clinical Judgment
LA/SA for rivaroxaban (generic)	None	None	None	None	None
LA/SA for Xarelto (brand)	None	None	None	None	None

Adverse Events Reported in ≥1% of Rivaroxaban Treated Patients in RECORD trials 1-3[1]

Adverse Events (1) (MedDRA System Organ Class and Preferred Term)	Rivaroxaban 10mg n (%)	Enoxaparin 40mg Daily† n (%)
Number of Patients	**n=4487**	**n= 4524**
Injury, poisoning and procedural complications		
Wound secretion	125 (2.8)	89 (2.0))
Musculoskeletal and connective tissue disorders		
Pain in extremity	74 (1.7)	55 (1.2)
Muscle spasm	52 (1.2)	32 (0.7)
Nervous System Disorder		
Syncope	55 (1.2)	32 (0.7)
Skin and subcutaneous tissue disorders		
Pruritus	96 (2.1)	79 (1.8)
Blister	63 (1.4)	40 (0.9)

† Includes placebo-controlled period for RECORD 2

DOSE & AVAILABILITY[1]

STRENGTH	FORM	ROUTE	FREQUENCY	RENAL ADJ	HEPATIC ADJ	Pediatric Dose	Elderly Dose	OTHER DOSING CONSIDERATIONS
Rivaroxaban 10mg for DVT prophylaxis prior to TKR or THR Rivaroxaban 20mg once daily for AF	Tablet	Oral	Once daily	DVT Prophylaxis: Use cautiously in moderate renal impairment (CrCl 30-50 ml/min) Do not use in severe renal impairment (CrCl <30 ml/min) Nonvalvular Atrial Fibrillation: CrCl 15-50 ml/min give 15mg once daily Avoid if CrCl 30-50 ml/min.	Avoid use in moderate or severe hepatic impairment or in hepatic disease with coagulopathy	N/A	Increased rivaroxaban concentrations were seen in elderly patients, perhaps due to age-related changes in renal function. Renal function assessment should be considered in patients ≥65 years old.	- Tx duration of 35 days recommended for hip replacement surgery - Tx duration of 12 days recommended for knee replacement surgery - Absorption is increased with food and is recommended for AF dosing

PHARMACOKINETICS[1]

Parameter	Result
Oral Bioavailability*	10mg dose: 80-100% (not affected by food)
	20mg dose: 66% (fasting), increases with food
Protein Binding	92-95%
Elimination	66% urine, 28% feces
Half-Life	5-9 hours
Metabolism	Oxidative degradation and hydrolysis via CYP3A4/5 and CYP2J2 Substrate of transporter proteins P-gp and ABCG2

* Dose-dependent absolute biovailability

ALLERGIES/INTERACTIONS

Drug-Drug:

Rivaroxaban is a substrate for CYP3A4, CYP2J2, and the P-gp and ATP-binding cassette G2 (ABCG2) transporters. Inhibitors or inducers of these enzymes/transporters may change rivaroxaban exposure. Concomitant use of rivaroxaban with drugs that are combined p-glycoprotein (P-gp) and strong CYP3A4 inducers (carbamazepine, phenytoin, rifampin, St.John's wort) should be avoided. Avoid rivaroxaban use with P-gp and strong CYP3A4 inhibitors (ketoconazole, itraconazole, lopinavir/ritonavir, ritonavir, indinavir/ritonavir and conivaptan) which significant increases in rivaroxaban exposure has been observed, which may increase bleeding risk.[1]

When using rivaroxaban for prophylaxis of DVT, if data suggests a change in exposure is unlikely to affect bleeding risk (e.g., clarithromycin, erythromycin) then no precautions are necessary when using rivaroxaban concomitantly with P-gp and CYP3A4 inhibitors.

Rivaroxaban should not be used with other anticoagulants. Use with clopidogrel should be avoided unless the benefit outweighs the bleeding risk. Promptly evaluate any signs or symptoms of blood loss. No pharmacokinetic or pharmacodynamic interactions have been noted with naproxen or aspirin but safety of coadministration long-term has not been studied.[1]

It is not recommended that rivaroxaban be used with NSAIDS due to an increased risk of bleeding. Caution is advised when treating patients concomitantly with aspirin, other platelet aggregation inhibitors or NSAIDS.[1]

Food-Drug:

No food-drug interactions have been reported.[1]

Allergy/Cross Reactive Substances:

In the RE-LY trial, drug hypersensitivity was reported in <0.1% of patients. No cross-sensitivities have been reported.[1] Postmarketing reports of anaphylaxis to rivaroxaban have occurred. Do not use in patients with severe hypersensitivity reactions to rivaroxaban.

APPENDIX:
Suggested PA Criteria

Oral Direct Factor Xa Inhibitors

Goal(s):

- Promote safe and effective therapies for oral direct factor Xa inhibitors.

Length of Authorization: 1 year

Covered Alternatives: Listed at; http://www.oregon.gov/DHS/healthplan/tools_prov/pdl.shtml

Approval Criteria		
1. Does the patient have a diagnosis requiring short-term (<45 days) anticoagulation (i.e. total knee replacement or total hip replacement)?	**Yes: Yes:** Approve for 12 days for TKR. Approve for 35 days for THR.	**No:** Go to #2
2. Does the patient have a diagnosis of nonvalvular atrial fibrillation?	**Yes**: Go to #3	**No:** Deny. (Medical appropriateness)
3. Will the prescriber consider a change to the preferred oral anticoagulant, warfarin?	**Yes:** Approve. Additional information can be found at: http://www.dhs.state.or.us/policy/healt	**No:** Go to #4

Message: • Preferred products do not require PA for <4 days/week. • Preferred products have received evidence-based reviews for comparative effectiveness and safety by the Health Resources Commission (HRC). http://www.oregon.gov/OHPPR/HRC/Evidence_Based_Reports.shtml	hplan/guides/pharmacy/clinical.html	
4. Is the patient unable to take preferred oral anticoagulants due to one of the following: - unstable INR - allergy - contraindications to therapy - drug-drug interactions - intolerable side effects	**Yes:** Approve for up to 1 yr.	**No:** Deny. Recommend trial of preferred anticoagulants.

References

1. Product Information for Xarelto®. Janssen Pharmaceuticals, Inc. Titusville, NJ. 2011.
2. Eriksson B, Borris L, Friedman R, et al. Rivaroxaban Versus Enoxaparin for Thromboprophylaxis After Hip Arthroplasty. N Engl J Med 2008;358:2765-75.
3. Kakkar A, Brenner B, Dahl O, et al. Extended Duration Rivaroxaban Versus Short-term Enoxaparin For The Prevention of Venous Thromboembolism After Total Hip Arthroplasty: A Double-blind, Randomised, Controlled Trial. Lancet 2008;372:31-39.
4. Lassen M, Ageno W, Borris L, et al. Rivaroxaban Versus Enoxaparin For Thromboprophylaxis After Total Knee Arthroplasty. N Engl J Med 2008;358:2776-86.
5. Turpie A, Lassen M, Davidson B, et al. Rivaroxaban Versus Enoxaparin For Thromboprophylaxis After Total Knee Arthroplasty (RECORD4): A Randomised Trial. Lancet 2009;373:1673-80.
6. Patel M, Mahaffey K, Garg J, et al. Rivaroxaban Versus Warfarin In Nonvalvular Atrial Fibrillation. N Engl J Med 2011;365:883-891.
7. The Einstein Investigators. Oral Rivaroxaban for Symptomatic Venous Thromboembolism. N Engl J Med 2010;363:2499-510.
8. Mega J, Braunwald E, Wiviott S, et al. Rivaroxaban in Patients with a Recent Acute Coronary Syndrome. N Engl J Med 2011; NEJMoa1112277.
9. American Academy of Orthopaedic Surgeons. Preventing Venous Thromboembolic Disease in Patients Undergoing Elective Hip and Knee Arthroplasty Evidence-Based Guideline and Evidence Report, 2011. (Accessed October 27, 2011, at http://www.aaos.org/research/guidelines/VTE/VTE_full_guideline.pdf.)
10. Hirsh J, Guyatt G, Albers G, et al. Executive Summary: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 2008;133;71S-109S.
11. Singer DE, Albers GW, Dalen JE, et al. Antithrombotic therapy in atrial fibrillation. CHEST. 2008;133(6): 546S-592S.

12. Gage BF, Waterman AD, Shannon W, et al. Validation of clinical classification schemes for predicting stroke. Results from the National Registry of Atrial Fibrillation. JAMA. 2001;2864-70.
13. Vardi M, Zittan E, Bitterman H, et al. Subcutaneous unfractionated heparin for the initial treatment of venous thromboembolism. Cochrane Database of Systematic Reviews. 2009, Issue 4.
14. Serebruany VL. Viewpoint: paradoxical excess mortality in PLATO trial should be independently verified. Thromb Haemost 2011; 105: 752-759.
15. Albers GW, Amarenco P, Easton JD, Sacco RL, Teal P. Antithrombotic and Thrombolytic Therapy for Ischemic Stroke: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest.* 2008;133(6 Suppl):630S-669S.
16. Anderson JL, Adams CD, Antman EM, Bridges CR, Califf RM, et al. ACC/AHA 2007 Guidelines for the Management of Patients With Unstable Angina/Non-ST-Elevation Myocardial Infarction: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines for the Management of Patients With Unstable Angina/Non-ST-Elevation Myocardial Infarction). *Circulation.* 2007;116(7):e148-e304
17. King SI, Smith SJ, Hirshfeld JJ, Jacobs A, Morrison D, et al. 2007 Focused Update of the ACC/AHA/SCAI 2005 Guideline Update for Percutaneous Coronary Intervention: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guideline. *Circulation.* 2008;117:261-295.
18. Kushner F, Hand M, Smith SJ, et al. 2009 focused updates: ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction (updating the 2004 guideline and 2007 focused update) and ACC/AHA/SCAI guidelines on percutaneous coronary intervention (updating the 2005 guideline and 2007 focused update): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol.* 2009;54(23):2205-2241.
19. Sobel M, Verhaeghe R, American College of Chest Physicians. Antithrombotic therapy for peripheral artery occlusive disease: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest.* Jun 2008;133(6 Suppl):815S-843S.
20. Rivaroxaban, FDA Center for Drug Evaluation and Research.Medical Review Document. July 1, 2011. Accessed 9/14/11. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/022406Orig1s000TOC.cfm.
21. Ndegwa S, Moulton K, Argáez C. Dabigatran or Rivaroxaban Versus Other Anticoagulants for Thromboprophylaxis After Major Orthopedic Surgery: Systematic Review of Comparative Clinical-Effectiveness and Safety. Ottawa: Canadian Agency for Drugs and Technologies in Health; 2009.
22. Eerenberg ES, Kamphuisen PW, Sijpkens MK, Meijers JC, Buller HR, Levi M. Reversal of rivaroxaban and dabigatran by prothrombin complex concentrate: a randomized, placebo-controlled, crossover study in healthy subjects. Circulation 2011:124: 1573-79.
23. Deloughery TG. Practical Aspects of the Oral New Anticoagulants. Am J Hematol 2011;86:586-90.