New Drug Review

Rivaroxaban: An Oral Factor Xa Inhibitor

Tyan F. Thomas, PharmD; Valerie Ganetsky, PharmD; and Sarah A. Spinler, PharmD

Philadelphia College of Pharmacy, University of the Sciences in Philadelphia, Philadelphia, Pennsylvania

ABSTRACT

Background: Currently available anticoagulants utilized for venous thromboembolism (VTE) treatment and prevention and stroke prevention in patients with atrial fibrillation (AF) have proven effectiveness but are not optimally utilized because of barriers such as the need for subcutaneous administration and requisite routine laboratory monitoring. Rivaroxaban, a novel oral Xa inhibitor, is an alternative to standard therapies utilized for VTE prevention after elective orthopedic surgery, primary and secondary stroke prevention in nonvalvular AF, VTE treatment after an acute VTE event, and secondary prevention after the acute coronary syndromes (ACS).

Objective: This article reviews the pharmacology, efficacy, and tolerability of rivaroxaban for VTE prophylaxis in post–orthopedic surgery and medically ill patients, stroke prevention in nonvalvular AF, adjunctive therapy in patients with ACS, and VTE treatment.

Methods: International Pharmaceutical Abstracts and EMBASE were searched for English-only clinical trials and reviews published between 1970 and March 15, 2012. PubMed was searched for articles published between 1970 and June 30, 2012. Additional trials and reviews were identified from the citations of published articles.

Results: Eighty-nine publications were identified: 10 clinical trials and 1 meta-analysis were used to obtain efficacy and tolerability data, and 1 analysis of pooled data from the clinical trials was included; 17 pharmacokinetic, pharmacodynamic, and drug–drug interaction studies were included; and 5 cost-analyses were reviewed. These data showed rivaroxaban to be noninferior to enoxaparin for thromboprophylaxis of VTE after total knee and total hip replacement surgery. It was also shown to be noninferior to vitamin K antagonist therapy for primary and recurrent stroke prevention in nonvalvular AF as well as for the treatment of VTE after an acute deep vein thrombosis or pulmonary embolism. It also showed benefit in lowering the risk for major adverse cardiovascular events after ACS. Differences in major bleeding rates were not statistically significant between rivaroxaban and comparators across the various studies, with the exception of ACS, in which there were higher rates of non–coronary artery bypass graft surgery related bleeding and intracranial hemorrhage.

Conclusions: Based on the findings of the studies reported in this review, rivaroxaban is an effective option for the prevention of VTE after orthopedic surgery, stroke prevention for nonvalvular AF, and treatment of VTE. At this time, rivaroxaban cannot be recommended for secondary risk reduction after ACS because of the increased bleeding risk. (*Clin Ther*. 2013;35:4–27) © 2013 Published by Elsevier HS Journals, Inc.

Key words: anticoagulants, rivaroxaban, venous thromboembolism treatment, venous thromboembolism prophylaxis, atrial fibrillation thromboembolism prophylaxis

INTRODUCTION

For many decades, vitamin K antagonists (VKAs) have been the only oral anticoagulants available for the primary and secondary prevention of venous and arterial thromboembolic events. VKAs have been shown to be highly effective in many settings and are now used by millions of patients worldwide.[1] Despite their efficacy, the management of VKAs is challenging due to their complex pharmacokinetic and pharmacodynamic properties and narrow therapeutic range. Additional limitations to the use of VKAs include their slow onset and offset of action, multiple drug and dietary interactions, and need for frequent monitoring to maintain therapeutic range.[2] To overcome the limitations of

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VKAs, the development of new oral anticoagulants has aimed to find effective treatment options that are more tolerable and more convenient. Among these new classes of anticoagulants are the oral direct thrombin inhibitors (DTIs) and the direct factor Xa inhibitors.

Rivaroxaban is approved by the US Food and Drug Administration (FDA), European Medicines Agency (EMA), and Health Canada for the reduction of the risk for stroke and systemic embolism in patients with nonvalvular atrial fibrillation (AF).[3–5] Rivaroxaban also has approval by the FDA, EMA, and Health Canada for the prevention of venous thromboembolism (VTE) in patients undergoing total knee or hip replacement surgery.[3,5,6] Rivaroxaban has additional approval by Health Canada for treatment of deep vein thrombosis (DVT) without symptomatic pulmonary embolism (PE).[7] The FDA and EMA have approved rivaroxaban for the treatment of DVT and PE and for the reduction in the risk for recurrence of DVT and PE.[3,8]

MATERIALS AND METHODS

PubMed, EMBASE, and International Pharmaceutical Abstracts were searched using the search term *rivaroxaban*. Only English-language clinical trials and systematic reviews published between 1970 and March 15, 2012, and additional trials and reviews referenced in published articles were included. PubMed was searched for studies published between 1970 and June 30, 2012. In addition, cost analyses were identified by searching the terms *rivaroxaban* and *cost analysis* in PubMed.

RESULTS

Eighty-nine publications were identified: 10 clinical trials and 1 meta-analysis were used to obtain efficacy and tolerability data, and 1 analysis of pooled data from the clinical trials were included; 17 pharmacokinetic, pharmacodynamic, and drug–drug interaction studies were included; and 5 cost analyses were reviewed.

Mechanism of Action

VKAs, such as warfarin, produce their anticoagulant effect by targeting the vitamin K conversion cycle and inhibiting vitamin K epoxide reductase (VKOR). Inhibition of this cycle causes hepatic production of coagulation factors (II, VII, IX, and X) with reduced procoagulant activity. In addition to their anticoagulant effect, VKAs inhibit regulatory anticoagulant proteins C and S and therefore have the potential to exert procoagulant effects.[1] Oral direct factor Xa inhibitors, such as rivaroxaban, selectively block the active site of factor Xa.[3] They not only inhibit free factor Xa but also prothrombinase activity and clot-associated factor Xa.[9] This mechanism is unique to small, direct inhibitors because factor Xa that is incorporated in the prothrombinase complex is protected from inhibition by antithrombin and by antithrombin-dependent anticoagulants.[1] Rivaroxaban and other factor Xa inhibitors also inhibit thrombin generation.[10]

Pharmacodynamic and Pharmacokinetic Properties of Rivaroxaban

Rivaroxaban is metabolized in the liver through oxidative and hydrolytic processes catalyzed by cytochrome P450 (CYP) 3A4/5 and 2J2. Rivaroxaban is also a substrate for the P-glycoprotein (P-gp) efflux transporter protein.[3] Approximately 66% of rivaroxaban is excreted in the kidneys (36% as unchanged drug), and the remainder is excreted in the feces as unchanged drug.[11]

Healthy Subjects

In healthy white men aged 19 to 45 years, the administration of a single dose of rivaroxaban 5 to 80 mg resulted in a maximum factor Xa inhibition of 20% to 80% within 1 to 4 hours after administration. After administration of the oral tablets, T_{max} was 2 hours and $t_{1/2}$ was between 6 and 7 hours. Rivaroxaban prolonged the prothrombin time (PT), activated partial thromboplastin time (aPTT), and HepTest (a low-molecular-weight heparin [LMWH] activity assay) but had no effect on thrombin or antithrombin activity.[12] A study that administered multiple doses of rivaroxaban ranging from 5 mg once or twice daily to 30 mg twice daily to healthy men aged 20 to 45 years found that T_{max} was 2 to 4 hours and maximum factor Xa inhibition ranged from 22% (5-mg dose) to 68% (30-mg dose). Similar to the single-dose study, PT, aPTT, and HepTest were prolonged and reached maximum levels after 1 to 4 hours and the $t_{1/2}$ was 5.7 to 9.2 hours at steady state.[13] An analysis of data from the multiple-dose study found that rivaroxaban has predictable, dose-proportional pharmacokinetic (PK) and pharmacodynamic (PD) properties.[14] Similar PK and PD parameters were found in healthy Chinese subjects.[15] See **Table I**[4,11,12,16] for a summary of the characteristics of rivaroxaban in healthy subjects.

Elderly Subjects

The AUC of rivaroxaban is increased by 50% and the $t_{1/2}$ prolonged to between 11 and 13 hours in elderly patients

Table I. Pharmacokinetic characteristics of rivaroxaban in healthy subjects.

Characteristic	Value
C_{max}, h	2–4[12]
T_{max}, h	1–4[11,12]
$t_{1/2}$, h	5–9[11,12]
CYP metabolism	CYP3A4/5, CYP2J2[3]
P-glycoprotein transport	Yes[3]
Renal excretion, %	66[11]

CYP = cytochrome P450.

compared with younger patients.[3] Caucasian subjects >60 years of age (mean age, 65 years) were randomly assigned to receive single oral doses of rivaroxaban ranging between 30 and 50 mg. T_{max} was 4 hours after dosing in all groups and the $t_{1/2}$ ranged between 12 and 13 hours. The PD effects of rivaroxaban (inhibition of factor Xa and prolongation of PT, aPTT, and HepTest) displayed a similar pattern, with maximum inhibition of factor Xa activity ranging from 68% with the 30-mg dose to 75.3% and 74.5% with doses of 40 and 50 mg, respectively. No differences were found between male and female subjects.[17] Elderly Chinese patients were found to have predictable, dose-proportional PK and PD parameters, whereas healthy Japanese subjects had between 20% and 40% increased drug exposure that was mostly corrected by adjusting for lower body weights.[3,18]

Obesity

The effects of extreme body weight on the PK and PD properties of rivaroxaban were evaluated in a study in healthy male and female subjects weighing <50 or >120 kg compared with patients weighing 70 to 80 kg receiving a single dose of 10 mg. C_{max} was 24% greater and the $t_{1/2}$ was increased by 2 hours in the low-body-weight group. Factor Xa inhibition was similar in all groups, with maximum effect occurring at 3 to 4 hours, and slightly lower values reported in patients weighing >120 kg. Based on this study, it is unlikely that rivaroxaban requires dose adjustment for body weight.[19]

Patients Undergoing Orthopedic Surgery

A study was conducted in patients undergoing major orthopedic surgery who were randomly assigned to receive twice-daily doses of rivaroxaban ranging from 2.5 to 30 mg. The study found variability in the PK properties of rivaroxaban on the first postoperative day with all doses. Overall, absorption was rapid, with a T_{max} 1 to 2 hours. The clearance of the drug was consistently affected by renal function and the study found that 1 dose of rivaroxaban could be administered to all patients regardless of covariates such as age or body weight.[20] The second study compared the PK and PD properties of rivaroxaban 10 mg once daily versus twice daily in patients undergoing total hip replacement. The study found that the PK and PD properties of rivaroxaban were predictable when the drug was given either once or twice daily.[21]

Deep Vein Thrombosis

Population PK and PD analyses were conducted in 2 Phase II acute DVT dose-ranging studies. The doses in the studies ranged from 20 to 60 mg/d, with administration once or twice daily. The PK properties of rivaroxaban were found to be predictable across all doses studied.[16]

Acute Coronary Syndrome

A population PK model was developed using blood samples from 2290 patients in the ATLAS ACS–TIMI 46 (Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects with Acute Coronary Syndrome–Thrombolysis in Myocardial Infarction 46) study, which found that the PK and PD parameters in patients with ACS were comparable to those in patients undergoing VTE prevention, DVT treatment, and AF treatment.[22]

Renal Impairment

A study that used modified DVT population demographics to simulate a population of patients with AF demonstrated that moderate renal impairment (CrCl 30–49 mL/min) and increased age led to slight increases in rivaroxaban exposure. The study found that a rivaroxaban dose of 15 mg/d in patients with CrCl 30 to 49 mL/min would achieve a C_{max} similar to that observed with 20 mg/d in patients with normal renal function.[16] In a study evaluating the effects of renal impairment on the PK and PD properties of rivaroxaban, it was found that the increases in the AUC of inhibition of factor Xa activity were 50%, 86%, and 100% for mild, moderate, and severe renal impairment, respectively.[23] In patients being treated for nonvalvular AF, it is recommended to reduce the dose of rivaroxaban to 15 mg once daily if the CrCl is 15 to 50 mL/min.[3]

Hepatic Impairment

It is recommended to avoid the use of rivaroxaban in patients with moderate (Child-Pugh B) and severe (Child-Pugh C) hepatic impairment or with any hepatic disease associated with coagulopathy.[3] These patients were excluded from clinical trials. A small study of 16 patients with severe hepatic disease (Child-Pugh Class A and B) demonstrated significantly increased exposure (127% AUC and 27% C_{max}), factor Xa inhibition, and PT prolongation in patients with Child-Pugh class B liver disease relative to normal values.[3]

Drug Interactions

Drugs that are combined P-gp and CYP3A4 inhibitors result in increases in rivaroxaban exposure and pharmacodynamic effects (ie, factor Xa inhibition). Product labeling recommends avoiding concurrent use of drugs that are combined P-gp inhibitors and strong CYP3A4 inhibitors. These drugs include "-azole" antifungals and HIV protease inhibitors. Combination of rivaroxaban with ketoconazole and ritonavir led to ~2.5-fold and ~1.7-fold increases in AUC and C_{max}, respectively.[3] Drugs that are combined P-gp inducers and strong CYP3A4 inducers should also be avoided with rivaroxaban administration.[3] These drugs include rifampicin (which caused 50% and 22% decreases in AUC and C_{max}, respectively), phenytoin, carbamazepine, and St. John's wort.[3] The PK and PD properties of rivaroxaban were not affected by the coadministration of aspirin, naproxen, ranitidine, omeprazole, or aluminum-magnesium hydroxide.[24–27] Rivaroxaban exposure is reported to be lower in the fed state; the presence of food delayed the T_{max} and increased both C_{max} and AUC at doses >10 mg.[26] It is recommended to take rivaroxaban 15- and 20-mg tablets with the evening meal. The absolute bioavailability of rivaroxaban 10-mg tablets is not affected by food; these tablets can be taken either with or without food.[3]

Reversal of Anticoagulant Effect

There is no specific antidote available for reversal of rivaroxaban. Due to its high plasma protein binding, it is not expected to be dialyzable.[3] Prothrombin complex concentrates (PCCs) may be an option for reversing the anticoagulant effect of rivaroxaban. In a randomized, double-blind, placebo-controlled study, 12 healthy male patients received rivaroxaban 20 mg BID followed by either a 50-IU/kg bolus of PCC or saline. Rivaroxaban caused a significant prolongation of PT, which was immediately and completely reversed by PCC.[28]

In a small study in 10 healthy Caucasian men, patients were randomized to receive rivaroxaban 20 mg or dabigatran 150 mg. Blood samples were collected before drug administration and 2 hours thereafter, and reversal of anticoagulation was tested for in vitro using 4-factor PCC*, activated PCC†, and recombinant factor VIIa (rFVIIa). All three hemostatic agents tested showed inhibitory effects on at least some quantitative (endogenous thrombin potential and maximum thrombin concentration) and kinetic parameters (lag time and time to reach maximum thrombin concentration). Of all of the hemostatic agents studied, activated PCC had at least some effect on all measured hemostatic parameters.[29]

Efficacy and Tolerability

The designs and results of key clinical trials affecting the use of rivaroxaban in clinical practice are described in Table II.[30–39]

Venous Thromboembolism Prophylaxis After Total Knee and Total Hip Arthroplasty

The RECORD (Regulation of Coagulation in Orthopedic Surgery to Prevent Deep Venous Thrombosis and Pulmonary Embolism) investigations are the Phase III double-blinded studies demonstrating efficacy and tolerability of rivaroxaban for VTE prophylaxis after elective total hip and total knee replacement. There were 4 RECORD investigations. RECORD 1 compared rates of VTE and death with rivaroxaban 10 mg given orally once daily for 35 days to enoxaparin 40 mg given subcutaneously once daily for 35 days after elective total hip arthroplasty (THA). RECORD 2 observed rates of VTE and death after elective THA with extended anticoagulation therapy (31–39 days) with rivaroxaban and shorter-duration anticoagulation therapy (10–14 days) with enoxaparin. RECORD 3 compared rates of VTE and death after elective total knee replacement (TKR) with 10 to 14 days of rivaroxaban 10 mg once daily and enoxaparin 40 mg once daily. RECORD 4 compared rates of VTE events and death with the use of shorter treatment durations (10–14 days) of rivaroxaban 10 mg once daily and enoxaparin 30 mg q12h given after elective TKR.[30–33]

*NovoSeven® (Novo Nordisk A/S, Bagsvaerd, Denmark).
†Feiba® (Baxter Healthcare Corp, Westlake Village California).

Table II. Key Rivaroxaban clinical trials.

	Key Criteria		Outcome Measures			
			Efficacy		Tolerability	
Study/Treatment Groups	Inclusion	Exclusion	Primary	Secondary	Primary	Secondary
VTE prevention in total hip replacement						
RECORD 1[30] (Randomized, double-blind, double-dummy, Phase III trial; N = 4541)	Elective THR	Staged bilateral replacement, active bleeding, high risk for bleeding, contraindication to enoxaparin or rivaroxaban, conditions requiring an adjustment of enoxaparin dose, CrCl <30 mL/min, significant liver disease, use of HIV protease inhibitors, other requirement for anticoagulation	Composite of DVT, nonfatal PE, or any mortality up to day 36 (range 30-42)	Major and symptomatic VTE	Major bleeding (as above)	Any on-treatment bleeding
Rivaroxaban 10 mg/d for 35 d	—	—	1.1%	Major, 0.2% Symptomatic, 0.3%	0.3%	6.0%
Enoxaparin 40 mg/d for 35 d	—	—	3.7%	Major, 2.0% Symptomatic, 0.5%	0.1%	5.9%
Statistics	—	—	ARR, 2.6%; 95% CI, 1.5 to 3.7; $P < 0.001$	Major: ARR, 1.7%; 95% CI, 1.0 to 2.5; $P < 0.001$; symptomatic: ARR, 0.2%; 95% CI, −0.1 to 0.6; $P = 0.22$	$P = 0.18$	$P = 0.94$
RECORD 2[31] (Randomized, double-blind, double-dummy, phase III trial; N = 2509)	Elective THR	Staged bilateral replacement, active bleeding, high risk for bleeding, contraindication to enoxaparin or rivaroxaban, or conditions requiring an adjustment of enoxaparin dose, severe renal or hepatic disease, use of HIV protease inhibitors	Composite of DVT, nonfatal PE, and all-cause mortality up to day 30–42	Major VTE (proximal DVT, nonfatal PE, or death from VTE) and symptomatic VTE	Major bleeding (fatal, critical organ, requiring reoperation, overt extracranial bleeding resulting in 2 g/dL hemoglobin drop or 2-U PRBC transfusion) after 1st dose and up to 2 days after last dose	Any on-treatment bleeding
Postoperative rivaroxaban 10 mg/d for 31–39 d	—	—	2.0%	Major, 0.6% Symptomatic, 0.2%	<0.01%	6.6%
Preoperative enoxaparin 40 mg/d for 10–14 d	—	—	9.3%	Major, 5.1% Symptomatic, 1.2%	<0.01%	5.5%

(continued)

Table II. (continued).

	Key Criteria		Outcome Measures			
			Efficacy		Tolerability	
Study/Treatment Groups	Inclusion	Exclusion	Primary	Secondary	Primary	Secondary
Statistics	—	—	ARR, 7.3%; 95% CI, 5.2 to 9.4; $P < 0.0001$	Major: ARR, 4.5%; 95% CI, 3.0 to 6.0; $P < 0.0001$; Symptomatic: ARR, 1.0%; 95% CI, 0.2 to 1.8; $P = 0.004$	NR	$P = 0.25$
VTE prevention in total knee replacement						
RECORD 3[32] (Randomized, double-blind, double-dummy, Phase III trial; N = 2531)	TKR	Active bleeding, high risk for bleeding, contraindication to enoxaparin, or conditions requiring an adjustment of dose, significant liver disease, HIV protease inhibitors, other requirement for anticoagulation	Composite of DVT, nonfatal PE, and all-cause mortality within 13–17 days of surgery	Major and symptomatic VTE, PE	Major bleeding after first dose up to 2 days after discontinuation	Nonmajor bleeding after first dose up to 2 days after discontinuation
Postoperative rivaroxaban 10 mg/d	—	—	9.6%	Major, 1.0%; symptomatic, 0.7%; PE, 0	0.6%	4.3%
Preoperative enoxaparin 40 mg/d for 10–14 d	—	—	18.9%	Major, 2.6%; symptomatic, 2.0%; PE, 0.3%	0.5%	4.4%
Statistics	—	—	ARR, 9.2%; 95% CI, 5.9 to 12.4; $P < 0.001$	Major: ARR: 1.6%; 95% CI, 0.4 to 2.8%; $P = 0.01$; symptomatic: ARR, 1.3%; 95% CI, 0.4 to 2.2; $P = 0.005$; PE: ARR, 0.3%; 95% CI, 0.0 to 0.8; $P = 0.03$	$P = 0.77$	NR
RECORD 4[33] (Randomized, double blind, double dummy, phase III trial; N = 3148)	TKR	Active bleeding/high risk for bleeding, contraindication to enoxaparin or condition requiring dose adjustments of enoxaparin, CrCl <30 mL/min, strong inhibitors of CYP3A4	Composite of DVT, nonfatal PE, and all-cause mortality up to day 17	Major and symptomatic VTE	Major bleeding after 1st dose up to 2 days after last dose	Clinically relevant nonmajor and major bleeding
Postoperative rivaroxaban 10 mg/d for 11–15 d	—	—	6.9%	Major, 1.1%; symptomatic, 0.7%	0.7%	Nonmajor, 2.6%; major, 3.0%
Postoperative enoxaparin 30 mg q12h for 11–15 d	—	—	10.1%	Major, 1.5%; symptomatic, 1.2%	0.3%	Nonmajor, 2.0% major, 2.3%

(continued)

Table II. (continued).

	Key Criteria		Outcome Measures			
			Efficacy		Tolerability	
Study/Treatment Groups	Inclusion	Exclusion	Primary	Secondary	Primary	Secondary
Statistics	—	—	ARR, 3.19% 95% CI, 0.71 to 5.67; $P = 0.0118$	Major: ARR, 0.37%; 95% CI, −0.6 to 1.34%; $P = 0.4556$; symptomatic: ARR, 0.47%; 95% CI, −0.23 to 1.16%; $P = 0.1868$	$P = 0.1096$	Nonmajor, NR; major, $P = 0.1790$
VTE prevention in medically ill patients						
MAGELLAN[34,35] (Randomized, double-blind, double-dummy, Phase III trial; N = 8101)	Hospitalized patients aged ≥40 y with acute medical illness (heart failure, active cancer, acute ischemic stroke, acute infectious disease, acute inflammatory disease, acute respiratory insufficiency) and an additional risk factor for VTE, including decreased mobility	Life expectancy <6 mo, conditions that increase risk for bleeding, or need for drugs or procedures that affect coagulation, severe renal/hepatic disease	Composite of asymptomatic DVT, symptomatic DVT, symptomatic non-fatal PE, and VTE-related death at day 10 (noninferiority) and day 35 (superiority)	all-cause mortality	Composite of major bleeding and nonmajor clinically relevant up to 2 days after study drug discontinuation	Nonmajor clinically relevant bleeding
Rivaroxaban 10 mg/d for 35 ± 6 d	—	—	Day 10, 2.7%; day 35, 4.4%	5.1%	Day 10, 2.8%; day 35, 4.1%	3.0%
Enoxaparin 40 mg/d for 10 d	—	—	Day 10, 2.7%; day 35, 5.7%	4.8%	Day 10, 1.2%; day 35, 1.7%	1.2%
Statistics	—	—	Day 10: HR, 0.968; 95% CI, 0.713 to 1.334; $P = 0.0025$ for noninferiority; day 35: HR, 0.771; 95% CI, 0.618 to 0.962; $P = 0.0211$ for superiority	NR	Day 10, $P < 0.0001$; day 35, $P < 0.0001$	NR

(continued)

Table II. (continued).

	Key Criteria		Outcome Measures: Efficacy		Outcome Measures: Tolerability	
Study/Treatment Groups	Inclusion	Exclusion	Primary	Secondary	Primary	Secondary
Treatment of symptomatic venous thromboembolism						
EINSTEIN-DVT[36] (Randomized open-label Phase III study; N = 3449)	Objectively confirmed proximal DVT without symptomatic PE	LMWH or UFH for >48 h or >1 dose of a VKA before randomization, thrombectomy, vena cava filter, fibrinolytic drug for the presenting episode of thrombosis, concurrent use of strong CYP3A4 inhibitors or inducers, CrCl <30 mL/min, significant liver disease, active bleeding/risk for bleeding, or another indication for a VKA antagonist	Symptomatic recurrent VTE (defined as a composite of DVT and nonfatal or fatal PE)	All-cause mortality; net clinical benefit (composite of primary efficacy and bleeding)	Clinically relevant bleeding (defined as major and clinically relevant nonmajor bleeding during treatment)	Vascular events (eg, ACS, TIA)
Rivaroxaban 15 mg BID for 3 wk, followed by 20 mg/d for 3, 6, or 12 mo	—	—	2.1%	Mortality, 2.2%; benefit, 2.9%	8.1%	0.7%
Enoxaparin 1mg/kg BID bridged to an INR-adjusted VKA regimen (INR, 2.0–3.0) for 3, 6, or 12 mo	—	—	3.0%	Mortality, 2.9%; benefit, 4.2%	8.1%	0.8%
Statistics	—	—	HR, 0.68; 95% CI, 0.44 to 1.04; $P < 0.001$ (1-sided noninferiority)	Mortality: HR, 0.65; 95% CI, 0.33 to 1.30; $P = 0.06$; benefit: HR, 0.67; 95% CI, 0.47 to 0.95; $P = 0.03$	HR, 0.97; 95% CI, 0.76 to 1.22; $P = 0.77$	HR, 0.79; 95% CI, 0.36 to 1.71; $P = 0.55$
EINSTEIN-EXT[36] (Randomized, double-blind Phase III study; N = 1197)	Patients treated for 6-12 mo for symptomatic DVT; objectively confirmed proximal DVT that was treated for 6–12 mo with a VKA or rivaroxaban (inside or outside the EINSTEIN-DVT study)	Concurrent use of a strong CYP3A4 inhibitor or inducer, CrCl <30 mL/min, significant liver disease, active bleeding/ risk for bleeding, or another indication for a VKA antagonist	Symptomatic recurrent VTE (defined above)	All-cause mortality; net clinical benefit (composite of primary efficacy and bleeding during treatment)	Major bleeding; major and clinically relevant nonmajor bleeding	Vascular events (eg, ACS, TIA)

(continued)

Table II. (continued).

			Outcome Measures			
	Key Criteria		Efficacy		Tolerability	
Study/Treatment Groups	Inclusion	Exclusion	Primary	Secondary	Primary	Secondary
Rivaroxaban 20 mg/d for 6 or 12 mo	—	—	1.3%	Mortality, 0.2%; benefit, 2.0%	Major, 0.7%; nonmajor, 0	0.5%
Placebo for 6 or 12 mo	—	—	7.1%	Mortality, 0.3%; benefit, 7.1%	Major, 6.0%; nonmajor, 1.2%	0.7%
Statistics	—	—	HR, 0.18; 95% CI, 0.09 to 0.39; $P < 0.001$	Mortality: NR; benefit: HR, 0.28; 95% CI, 0.15 to 0.53; $P < 0.001$	Major: $P = 0.11$; nonmajor: HR, 5.19; 95% CI, 2.3 to 11.7; $P < 0.001$	HR, 0.74; 95% CI, 0.17 to 3.3; $P = 0.69$
EINSTEIN-PE[37] (Randomized open-label Phase III study; N = 4883)	Objectively confirmed PE with or without symptomatic DVT	LMWH or UFH for >48 h or >1 dose of a VKA before randomization, thrombectomy, vena cava filter or a fibrinolytic drug for the presenting episode of thrombosis, concurrent use of a strong CYP3A4 inhibitor or inducer, CrCl <30 mL/min, significant liver disease, active bleeding/risk for bleeding or another indication for a VKA antagonist	Recurrent symptomatic VTE (defined as composite of DVT and nonfatal or fatal PE)	All-cause mortality; net clinical benefit (composite of primary efficacy and bleeding occurring during treatment)	Clinically relevant bleeding (defined as major and clinically relevant nonmajor bleeding)	Major bleeding; clinically relevant nonmajor bleeding; acute coronary events
Rivaroxaban 15 mg BID for 3 wk followed by 20 mg/d for 3, 6, or 12 mo	—	—	2.1%	Mortality, 2.4%; benefit, 3.4%	10.3%	Major, 1.1%; nonmajor, 9.5%; acute coronary events, 0.6%
Enoxaparin 1 mg/kg BID bridged to an INR-adjusted VKA regimen (INR, 2.0–3.0) for 3, 6, or 12 mo	—	—	1.8%	Mortality, 2.1%; benefit, 4.0%	11.4%	Major, 0.6%; nonmajor, 9.8%; acute coronary events, 0.9%
Statistics	—	—	HR, 1.12; 95% CI, 0.75 to 1.68; $P < 0.003$ for noninferiority; $P = 0.57$ for superiority	Mortality: HR, 1.13; 95% CI, 0.77 to 1.65; $P = 0.53$; benefit: HR, 0.85; 95% CI, 0.63 to 1.14; $P = 0.28$	HR, 0.90; 95% CI, 0.76 to 1.07; $P = 0.23$	Major, HR, 0.49; 95% CI, 0.31 to 0.79; $P = 0.003$; nonmajor, HR, 0.90; 95% CI, 0.76 to 1.07; $P = 0.23$; acute coronary events, NR

(continued)

Table II. (continued).

	Key Criteria		Outcome Measures: Efficacy		Outcome Measures: Tolerability	
Study/Treatment Groups	Inclusion	Exclusion	Primary	Secondary	Primary	Secondary
Treatment of acute coronary syndromes						
ATLAS-ACS 2–TIMI 51[38] (Phase III, randomized, double-blind, event-driven trial; N = 15.526)	Age 18–54 with hospitalization for ACS symptoms (chest discomfort typical of ischemia for ≥10 min at rest occurring within 48 h of hospital presentation) or ACS development during hospitalization for reasons other than ACS; ≥1 of following: STEMI, NSTEMI, and UA with either ST changes or TIMI score ≥4; DM or prior MI in addition to presenting ACS event; taking low-dose aspirin	Increased bleeding risk (eg, active bleeding, clinically significant bleeding, bleeding at a noncompressible place, bleeding diathesis within 30 d of randomization); platelet count $<9 \times 10^3$ cells/μL at screening; ICH; stroke/TIA (in patients taking aspirin plus a thienopyridine); major surgery, parenchymal organ biopsy, or serious trauma within 30 d before randomization; significant GI bleed within previous 12 mo; INR >1.5 at screening; AF requiring anticoagulation, abciximab bolus, or infusion within preceding 8 h; or eptifibatide or tirofiban bolus or infusion within 2 h preceding randomization; HIV infection; significant liver disease; life-expectancy <6 mo; CrCl <30 mL/min; concurrent strong CYP3A4 and P-gp inhibitors	Composite of CV-related mortality, MI, stroke	Composite of all-cause mortality, MI, and stroke; CV-related mortality; all-cause mortality	TIMI major bleeding events (non–CABG surgery related)	TIMI minor bleeding; TIMI bleeding requiring medical attention; ICH; fatal bleeding
Rivaroxaban 2.5 mg BID for up to 31 mo	—	—	9.1%	Composite, 9.3%; CV, 2.7% All-cause, 2.9%	1.8%	TIMI minor, 0.9%; TIMI medical, 12.9%; ICH, 0.4%; fatal bleed, 0.1%
Rivaroxaban 5 mg BID for up to 31 mo	—	—	8.8%	Composite, 9.1%; CV, 4.0% all-cause, 4.4%	2.4%	TIMI minor, 1.6%; TIMI medical, 16.2%; ICH, 0.7%; fatal bleed, 0.4%
Both rivaroxaban groups combined	—	—	8.9%	Composite, 9.2%; CV, 3.3%; All-cause, 3.7%	2.1%	TIMI minor, 1.3%; TIMI medical, 14.5%; ICH, 0.6%; fatal bleed, 0.3%

(continued)

Table II. (continued).

			Outcome Measures			
	Key Criteria		Efficacy		Tolerability	
Study/Treatment Groups	Inclusion	Exclusion	Primary	Secondary	Primary	Secondary
Placebo for up to 31 mo	—	—	10.7%	Composite, 11.0%; CV, 4.1%; All-cause, 4.5%	0.6%	TIMI minor, 0.5%; TIMI medical, 7.5%; ICH, 0.2%; fatal bleed, 0.2%
Statistics	—	—	HR, 0.84; 95% CI, 95% CI, 0.74 to 0.96; $P = 0.008$	Composite: HR, 0.84; 95% CI, 0.74 to 0.95; $P = 0.006$; CV: HR, 0.80; 95% CI, 0.65 to 0.99; $P = 0.04$; All-cause: HR, 0.81; 95% CI, 0.66 to 1.00; $P = 0.04$	HR 3.96 (2.46-6.38), P<0.001	TIMI minor: HR, 2.07; 95% CI, 1.27 to 3.37; $P = 0.003$; TIMI medical: HR, 2.09; 95% CI, 1.83 to 2.38; $P < 0.001$; ICH: HR, 3.28; 95% CI, 1.28 to 8.42; $P = 0.009$; fatal bleed: HR, 1.19; 95% CI, 0.54 to 2.59; $P = 0.66$
Prevention of stroke and systemic thromboembolism in nonvalvular atrial fibrillation						
ROCKET-AF[39] (Randomized, double-blind, double-dummy Phase III trial; N = 14,264)	Age >18 y with AF, history of stroke/TIA, or $CHADS_2$ score ≥2	Cardiac condition such as need for prosthetic heart valve; hemorrhagic risk, recent stroke, anemia, CrCl <30 mL/min	Composite of stroke (ischemic or hemorrhagic) and systemic embolism (PP and ITT)	Composite of stroke, systemic embolism, and CV-related death; composite of stroke, systemic embolism, CV-related death, and MI	Composite of major and nonmajor clinically relevant bleeding	Composite treatment-emergent epistaxis, decrease in hemoglobin ≥2 g/dL, and need for transfusion; composite of critical bleeding, fatal bleeding, and intracranial hemorrhage
Fixed-dose rivaroxaban 20 mg/d (15 mg/d if CrCl 30–<50 mL/min)	—	—	PP, 1.7; ITT, 2.1	Composite without MI, 3.91; Composite with MI, 3.11	14.9	Epistaxis etc, 81.44%; bleed, 10.14%
INR-adjusted warfarin	—	—	PP, 2.2; ITT, 2.4	Composite without MI, 4.62; composite with MI, 3.63	14.5	Epistaxis etc, 81.54%; bleed, 8.55%

(continued)

Table II. (continued).

Study/Treatment Groups	Key Criteria		Outcome Measures			
	Inclusion	Exclusion	Efficacy		Tolerability	
			Primary	Secondary	Primary	Secondary
Statistics	–	–	PP: HR, 0.79; 95% CI, 0.66 to 0.96; $P < 0.001$ for noninferiority; ITT,: HR, 0.88; 95% CI, 0.75 to 1.03; $P < 0.001$ for noninferiority, $P = 0.12$ for superiority	Composite without MI: HR, 0.85; 95% CI, 0.74 to 0.96; $P = 0.010$ for superiority; composite with MI: HR, 0.86; 95% CI, 0.74 to 0.99; $P = 0.034$ for superiority	HR, 1.03; 95% CI, 0.96 to 1.11; $P = 0.44$ for superiority	Epistaxis, NR (significantly favored warfarin); bleed, $P < 0.05$ (significantly favored rivaroxaban)

ACS = acute coronary syndromes; AF = atrial fibrillation; ARR = adjusted risk ratio; ATLAS-ACS = Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects with Acute Coronary Syndrome study; CABG=coronary artery bypass graft; $CHADS_2$ = Scoring system to stratify thromboembolic risk in patients with nonvalvular AF; C = congestive heart failure; H = hypertension; A = age 75 years or older; D = diabetes mellitus; S = stroke; CrCl = creatinine clearance; CV = cardiovascular; CYP = cytochrome P450; DM = diabetes mellitus; DVT = deep vein thrombosis; EINSTEIN = xxx; GI = gastrointestinal; HR = hazard ratio; ICH = intracranial hemorrhage; INR = international normalized ratio; ITT = intent-to-treat; LMWH = low-molecular weight heparin; MAGELLAN = Multicenter, Randomized, Parallel-group Efficacy and Safety Study for the Prevention of VTE in Hospitalized Medically Ill Patients Comparing Rivaroxaban With Enoxaparin; MI = myocardial infarction; NSTEMI = non-ST-segment elevation myocardial infarction; PE = pulmonary embolism; P-gp = P-glycoprotein; PP = per-protocol; PRBC = packed red blood cells; RECORD = Regulation of Coagulation in Orthopedic Surgery to Prevent Deep Venous Thrombosis and Pulmonary Embolism; STEMI = ST-segment elevation myocardial infarction; THR = total hip replacement; TIA = transient ischemic attack; TIMI = Thrombolysis in Myocardial Infarction; TKR = total knee replacement; UA = unstable angina; UFH = unfractionated heparin; VKA = vitamin K antagonist; VTE = venous thromboembolism.

RECORD 1 enrolled 4541 patients from 27 countries who underwent elective THA between February 2006 and March 2007. Patients were randomly selected to receive rivaroxaban 10 mg orally once daily starting 6 to 8 hours after the procedure or enoxaparin 40 mg subcutaneously q12h, with the first dose given 12 hours before surgery and therapy resuming 6 to 8 hours after surgery; therapy was continued for a total of 35 days in both treatment arms. Patients received placebo tablets or injections to maintain blinding. No additional study drug was given after venography, but investigators had the option to continue thromboprophylaxis. Mandatory bilateral venography was performed on day 36 (the day after the last dose of study drug was administered) or sooner in patients with symptoms of VTE. Spiral computed tomography, perfusion-ventilation scintigraphy, or pulmonary angiography, were performed when PE was suspected and the films or images from these studies were interpreted by a central adjudication committee. Additional follow-up was completed 30 to 35 days after the last dose of study drug was administered. Noninferiority analyses were performed in the per-protocol population, and if noninferiority was confirmed, superiority analyses were performed in the modified intent-to-treat population. The per-protocol population included patients who underwent planned surgery, took a study drug, underwent an adequate assessment for VTE within 36 hours after the last dose of study drug for a positive result or >72 hours after the last dose of study drug for a negative result, and they had no major protocol deviations. The modified intent-to-treat population included those patients who underwent planned surgery and took a study drug, but the timing of adequate assessment for thromboembolism did not need to have taken place 36 to 72 hours after the last dose of study drug was administered. Tolerability outcomes were evaluated for all patients receiving ≥1 dose of study drug. Patients with "substantial liver disease," severe renal impairment (defined as CrCl <30 mL/min), or who were using protease inhibitors for HIV infection were excluded from all RECORD studies.

The primary efficacy outcome (composite of any DVT, nonfatal PE, or death from any cause up to 36 days after the procedure) occurred in fewer rivaroxaban-treated patients (0.8% [13/1537] for rivaroxaban vs 3.4% [50/1492] for enoxaparin in the per-protocol population [absolute risk reduction (ARR), 2.6%; 95% CI, 1.5%–3.6%]), which met the prespecified noninferiority

requirements. Moreover, rivaroxaban was shown to be superior to enoxaparin in the modified intent-to-treat group, with 1.1% (18/1595) of rivaroxaban-treated patients having 1 of the primary efficacy events compared with 3.7% (58/1558) of enoxaparin-treated patients (ARR, 2.6%; 95% CI, 1.5%–3.7%). Fewer DVTs appeared to have driven the lower occurrence of the primary efficacy outcome in the modified intent-to-treat population, with 0.1% of rivaroxaban-treated patients compared with 2.0% of enoxaparin-treated patients developing a proximal DVT ($P < 0.001$) and 0.7% and 1.4% of rivaroxaban-treated and enoxaparin-treated patients, respectively, developing a distal DVT ($P = 0.04$). There were no statistically significant differences in the occurrence of nonfatal PEs or death. Finally, there were no statistically significant differences in the occurrence of symptomatic VTE during the 1-month on-treatment period (0.3% [6/2193] in rivaroxaban group and 0.5% [11/2206] in enoxaparin group; $P = 0.22$]) nor during the 1-month post-treatment period (1/2193 vs 4/2206, rivaroxaban and enoxaparin, respectively); these results included all patients who received ≥1 dose of study drug and underwent surgery.

Six of 2209 patients (0.3%) randomly assigned to receive rivaroxaban compared with 2 of 2224 patients (0.1%) assigned to receive enoxaparin had a major bleeding event (defined as bleeding that was fatal, occurred in a critical organ, or required reoperation or extrasurgical-site bleeding that was clinically overt and associated with a minimum 2-g/dL decrease in hemoglobin or required a minimum 2-U blood transfusion) during the on-treatment follow-up period (time of first dose of study drug and up to 2 days after the last dose of study drug). It is important to note that 1 of the 6 bleeding events in the rivaroxaban group occurred during the procedure and before the patient received the first dose of rivaroxaban. The difference in major bleeding rates was not statistically significant ($P = 0.18$). The rate of clinically relevant bleeding (definition was not provided) was slightly higher in the rivaroxaban group (2.9% vs 2.4%), as was the combination of major and clinically relevant bleeding (3.2% vs 2.5%). The rates of non–bleeding-related adverse events were similar, with 12.2% and 11.9% of patients in the rivaroxaban and enoxaparin groups, respectively, having a drug-related adverse effect. Finally, there was no difference in the prevalence of liver enzyme elevations, defined as an increase in alanine aminotransferase (ALT) $>3 \times$ upper limit of the normal range (ULN) (2.0% and 2.7% with rivaroxaban and enoxaparin, respectively); all cases resolved by the end of the follow-up period.

RECORD 2 was designed to evaluate the difference in the rates of the composite of VTE and death between extended-duration anticoagulation therapy with rivaroxaban (total duration, 31–39 days) and shorter duration of anticoagulation with enoxaparin (10–14 days) after THA. Dosing and timing of initiation of study drug were similar to those described in RECORD 1. Patients received placebo injections for days 10 to 14 (if in the rivaroxaban group) or placebo tablets for 31 to 39 days (if in the enoxaparin group) to maintain blinding. Patients underwent venography on the day after the last administration of study drug and additional follow-up 30 to 35 days after the last administration of study drug. Definitions of the primary efficacy outcome and main tolerability outcome were the same as described in RECORD 1. During the 4- to 6-week postsurgery period, there were fewer primary efficacy events in the extended- duration anticoagulation group (ie, rivaroxaban 10 mg administered orally once daily for a mean of 33–34 days) (2.0% [17/864]) compared with that in the shorter-duration anticoagulation group (ie, enoxaparin 40 mg administered subcutaneously once daily for a mean of 12–13 days) (9.3% [81/869]) (AAR, 7.4%, 95% CI, 5.2–9.4; $P < 0.0001$). The lower prevalence of the composite primary outcome appears to have been driven by lower prevalence of proximal and distal DVTs in the rivaroxaban group (1.6% vs 8.2%; $P < 0.001$); the rates of call-cause mortality and nonfatal PE were similar between the 2 treatment groups. These results met the prespecified criteria for superiority. There were fewer symptomatic VTE events during the 1-month on-treatment period in the rivaroxaban group (0.2% [3/1212] vs 1.2% [15/1207]; $P = 0.0040$), but these event rates were similar in the 2 treatment groups during the 1-month post-treatment period (1/1212 vs 2/1207 in the rivaroxaban and enoxaparin groups, respectively). The observed 2.0% prevalence of the primary efficacy outcome with rivaroxaban is similar to the 1.7% prevalence observed with 6-week treatment with the LMWH ardeparin.[40]

There was 1 patient in each group who had a major bleed, but the major bleeding event reported in the enoxaparin group was determined by the independent adjudication committee not to be related to study drug exposure. Although the incidence of major bleeding was similar between the 2 groups, there were more cases of nonmajor bleeding events (6.5% vs 5.5%) and clinically relevant bleeding (3.3% vs 2.7%) in the rivaroxaban

group. Serious, non–bleeding-related adverse event rates were similar between the 2 treatment groups (1.1% with rivaroxaban vs 1.4% with enoxaparin) as were rates of ALT elevations >3 × ULN (0.5% with rivaroxaban vs 0.6% with enoxaparin). It is important to note that the major bleeding rate may have been depressed to be one tenth the rate reported with similar studies because the investigators did not include surgical site bleeding and used the postoperative day 1 hemoglobin level as baseline rather than the preoperative level.[41]

The RECORD 3 investigation demonstrated that a 10- to 14-day (mean duration, 12 days) course of rivaroxaban 10 mg given orally once daily provided a greater reduction in risk for the composite efficacy outcome (defined as DVT, PE, or death occurring 13–17 days after surgery) than the equivalent duration of enoxaparin 40 mg given subcutaneously once daily (9.6% [79/824] vs 18.9% [166/878]; $P < 0.001$) when administered after TKR. This result was driven mostly by the difference in distal DVTs (70/824 vs 140/878; $P < 0.001$). As seen with RECORD 1 and RECORD 2, there was no difference between the 2 treatment groups in major bleeding rates (0.6% and 0.5% for rivaroxaban and enoxaparin, respectively; $P = 0.77$). However, the rate of clinically relevant, nonmajor bleeding was higher in the rivaroxaban arm (2.7%) compared with the rate in the enoxaparin-treated group (2.3%). Also similar to RECORD 1 and RECORD 2, drug-related adverse event rates were similar (12% with rivaroxaban vs 13% with enoxaparin).

A 10- to 14-day (mean, 12 days) duration of rivaroxaban 10 mg given orally once daily was found to be noninferior to a similar duration of enoxaparin 30 mg given subcutaneously q12h in the intent-to-treat population (6.9% [67/965] vs 10.1% [97/959]; ARR, 3.19%; 95% CI, 0.71–5.67; $P = 0.0118$) and superior to enoxaparin in the per-protocol population (6.7% [58/864] vs 9.3% [82/878]; AAR, 2.71%; 95% CI, 0.17–5.25; $P = 0.0362$). The prevalences of symptomatic VTE events were similar between the 2 treatment groups during the on-treatment period (11/1156 with rivaroxaban vs 18/1508 with enoxaparin) and the 1-month post-treatment follow-up period (4/1526 vs 3/1508). These analyses included all patients who received ≥1 dose of study drug. There were more major bleeding events (0.7% [10/1526] vs 0.5% [4/1508]; $P = 0.1096$); clinically relevant, nonmajor bleeding events (2.6% vs 2.0%; *P* not reported); and drug-related adverse events (20.3% vs 19.6%; *P* not reported) in rivaroxaban-treated patients. The relatively smaller risk reduction observed when rivaroxaban was compared to enoxaparin 30 mg BID dose may be reflective of the observed increased effectiveness with higher doses of parenteral LMWH for TKR.[42]

A pooled analysis of the bleeding events observed in RECORD 1 to 4 provided additional information on the efficacy and tolerability of rivaroxaban for VTE prophylaxis after orthopedic surgery.[43] The primary efficacy outcome was the composite of symptomatic VTE and all-cause mortality, and the bleeding outcomes were major bleeding, the composite of major and clinically relevant bleeding, and any bleeding. Any bleeding occurring after the administration of the first dose of study drug and no more than 2 days after the administration of the last dose of study drug was considered treatment emergent. To broaden the study population, any patient who received 1 dose of study drug, regardless of having undergone surgery, was included in this pooled analysis. A total of 12,729 patients from 617 countries were randomly assigned to receive rivaroxaban or enoxaparin. In the 12-day active-treatment pool, the primary outcome occurred in 29/6183 (0.5%) of rivaroxaban-treated patients and 60/6200 (1.0%) in enoxaparin-treated patients (odds ratio [OR], 0.48; 95% CI, 0.30–0.76; $P = 0.001$). There were numerically more bleeding events in the 6183 rivaroxaban-treated patients compared with the 6200 enoxaparin-treated patients, but the differences were not statistically significant. Bleeding rates for rivaroxaban and enoxaparin groups were as follows: major bleeding events, 0.3% versus 0.2% (OR, 1.62; 95% CI, 0.77–3.53; $P = 0.23$); composite of major and clinically relevant bleeding events, 2.8% versus 2.5% (OR, 1.17; 95% CI, 0.93–1.46; $P = 0.19$); any bleeding event, 6.6% versus 6.2% (OR, 1.07; 95% CI, 0.92–1.24; $P = 0.38$). Subgroup analysis did not find bleeding event rates to be influenced by increasing age. There were fewer serious treatment-emergent adverse events (6.6% vs 8.5%; *P* not reported) and fewer cases of ALT elevations (>3 × ULN) in the rivaroxaban group. The definition of *serious adverse event* was not provided.

A meta-analysis of 8 RCTs of including 15,586 patients who underwent elective THA and TKR showed rivaroxaban to lower VTE events and all-cause mortality by an additional 44% (relative risk [RR], 0.56; 95% CI, 0.39–0.80) compared with enoxaparin.[44] Rivaroxaban numerically increased the risk for major bleeding by 65%, but the difference in major bleeding was not statistically significant (RR, 1.65; 95% CI,

0.93–2.93). In addition, clinically relevant bleeding was numerically more frequent in the rivaroxaban group, but again the difference was not statistically significant (RR, 1.21; 95% CI, 0.98–1.50).[44]

The expert panel on the prevention of VTE in orthopedic surgery patients, as part of the ninth edition of the American College of Chest Physicians' Evidence-Based Clinical Practice Guidelines on Antithrombotic Therapy and Prevention of Thrombosis, gives a 1B recommendation for rivaroxaban, given for 10 to 14 days, over no prophylaxis therapy for VTE prophylaxis after elective THR and TKR surgeries. However, the panel preferred the use of LMWH over rivaroxaban because of the concern for increased bleeding and the dearth of long-term safety data with rivaroxaban.[41]

Venous Thromboembolism Prophylaxis for Medically Ill Patients

MAGELLAN (Multicenter, Randomized, Parallel-group Efficacy and Safety Study for the Prevention of VTE in Hospitalized Medically Ill Patients Comparing Rivaroxaban With Enoxaparin) was a multinational Phase III investigation conducted to observe the efficacy and tolerability of standard-duration (10 days) and extended-duration (35 days) VTE prophylaxis using rivaroxaban compared to standard duration using enoxaparin in VTE prophylaxis in acutely ill patients. The primary efficacy outcome was similar to that used in the RECORD trials. The main tolerability outcome varied slightly and was the composite of treatment-emergent major bleeding and clinically relevant nonmajor bleeding.[34]

As of November 2012, the results of this investigation have not been published but were reported at the April 2011 American College of Cardiology meeting.[35] At day 10, rivaroxaban was found to be noninferior to enoxaparin (2.7% event rate in each treatment arm; RR, 0.968; 95% CI, 0.713–1.334; $P = 0.0025$ for noninferiority). At day 35, extended-duration prophylaxis with rivaroxaban was found to be superior to a 10-day duration of enoxaparin, with a 22.9% RR reduction in the occurrence of the primary outcome (4.4% vs 5.7%; RR, 0.771; 95% CI, 0.618–0.962; $P = 0.0211$ for superiority). Major and clinically relevant bleeding rates were higher in rivaroxaban-treated patients during all follow-up periods (days 1–10, 1–35, and 10–35). Overall, more adverse events (composite of VTE and bleeding events) occurred by day 35 in rivaroxaban-treated patients. At this time, rivaroxaban has not been approved in any country for VTE prophylaxis in medically ill patients nor are there guideline recommendations on its use in this population.

Nonvalvular Atrial Fibrillation

The ROCKET-AF (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism) trial was a double-blind study comparing rivaroxaban 20 mg administered once daily orally with an evening meal and warfarin (international normalized ratio [INR], 2.0–3.0) that enrolled 14,264 patients in 45 countries.[39] Key aspects of the study design and results are described in **Table II**. Because the study was double-blind, sham INRs were provided for patients randomized to rivaroxaban. There was no VKA dosing protocol or follow-up appointment timing guidance provided to the study sites. Patients with reduced renal function either received a reduced dose of rivaroxaban of 15 mg (CrCl 30–49 mL/min) or were excluded (CrCl <30 mL/min). Patients were treated for a median of 1.6 years and were at high risk for stroke, with 54.9% of patients having a history of stroke, systemic embolism, or transient ischemic attack (TIA); the median $CHADS_2$ score was 3.0. The primary end point, a per-protocol (on treatment and protocol adherent) analysis of the incidence of stroke or systemic thromboembolism, was 1.7% per year in the rivaroxaban-treated patients and 2.2% per year in the warfarin-treated patients (HR, 0.79; 95% CI, 0.66–0.96; $P < 0.001$ for noninferiority). In the intent-to-treat group, 2.1% of rivaroxaban-treated patients versus 2.4% of warfarin-treated patients experienced a primary event (HR, 0.88; 95% CI, 0.74–1.03; $P < 0.001$ for noninferiority, $P = 0.12$ for superiority). There was no difference in the prevalence of major and clinically relevant nonmajor bleeding or major bleeding. Rivaroxaban significantly decreased the incidence of intracranial hemorrhage by 33% (0.5% vs 0.7% per year; HR, 0.67; 95% CI, 0.47–0.93; $P = 0.02$), whereas the frequency of major gastrointestinal bleeding was more common in rivaroxaban-treated patients (3.2% vs 2.2%; absolute increase 1%; $P < 0.001$).[39]

Most recently, rivaroxaban was recommended in the 2012 American Heart Association (AHA)/American Stroke Association (ASA) guidelines for the prevention of first and recurrent stroke in patients with nonvalvular AF (class IIa recommendation) as were warfarin (class I recommendation), dabigatran (class I recommendation),

and apixaban (class I recommendation).[45] Specifically, rivaroxaban was recommended as an option for patients at moderate- or high-risk for stroke (prior stroke or TIA or at least 2 other risk factors for stroke) based on the patient population enrolled in ROCKET-AF. Because there is no clinical experience in patients with AF and CrCl <15 mL/min, the AHA/ASA guidelines recommend against using rivaroxaban in this patient population. When differentiating between anticoagulants, the AHA/ASA guidelines recommend warfarin anticoagulation without inclusion restrictions, whereas dabigatran is recommended in patients with ≥1 additional risk factor for stroke and who have CrCl ≥15 mL/min. The guidelines recommend reserving rivaroxaban for higher-risk patients (described previously).

Venous Thromboembolism Treatment

The EINSTEIN program is the Phase III clinical trial series that provides efficacy and tolerability data for rivaroxaban use for VTE treatment. The EINSTEIN program consists of 3 randomized trials: the acute DVT treatment trial, the acute PE trial, and the study of extended-duration treatment for DVT and PE.[36,37] The acute DVT study of the EINSTEIN program was a randomized, open-label, event-driven, noninferiority study that included patients with acute, symptomatic, objectively confirmed proximal DVT who were without symptomatic PE.[36] Patients with CrCl <30 mL/min, clinically significant liver disease (including acute hepatitis, chronic active hepatitis, and cirrhosis), ALT ≥3 × ULN, active bleeding or deemed high risk for bleeding, a life expectancy of <3 months, and a systolic blood pressure of >180 mm Hg or diastolic blood pressure >110 mm Hg were excluded from these investigations. Patients on strong CYP3A4 inhibitors (protease inhibitors and systemic ketoconazole) or inducers (rifampin, carbamazepine, or phenytoin) were excluded as well.

Patients who were randomized to the standard-treatment group received enoxaparin 1 mg/kg subcutaneously BID and a VKA (acenocoumerol or warfarin). Enoxaparin was discontinued after there were 2 consecutive days of INRs of 2.0 and the patient received at least 5 days of enoxaparin treatment. VKA was dose adjusted to maintain an INR between 2.0 and 3.0; INR was measured at least once monthly. Patients assigned to the treatment group received rivaroxaban 15 mg BID for 21 days followed by 20 mg once daily. Patients in both treatment arms continued therapy for 3, 6, or 12 months. The primary efficacy end points were recurrence of symptomatic VTE (defined as the composite of DVT and fatal or nonfatal PE), and the primary tolerability end points included clinically relevant bleeding (defined as the composite of major bleeding [bleeding resulting in a 2 g/dL drop in hemoglobin, requiring a transfusion of at least 2 U, occurring in a critical anatomical location, or contributing to death] and clinically relevant, nonsignificant bleeding [overt bleeding not meeting the definition of major bleeding but requiring medical intervention, an unscheduled physician contact, temporary discontinuation of study drug, or causing pain or reduction in the patient's ability to perform activities of daily living]).

Rivaroxaban was found to be noninferior to standard therapy with 36 of the 1731 patients (2.1% event rate) in the rivaroxaban group and 51 of the 1718 patients (3.0% event rate) having a confirmed primary efficacy event (HR, 0.68; 95% CI, 0.44–1.04; $P < 0.001$ for noninferiority). Moreover, the prevalences of the tolerability outcome were similar, with 8.1% of patients in both arms having a major or nonmajor, clinically relevant bleeding event (HR, 0.97; 95% CI, 0.76–1.22; $P = 0.77$). Numerically there were fewer major bleeding events in the rivaroxaban group, but this difference was not statistically significant (0.8% vs 1.2%; HR, 0.65; 95% CI, 0.33–1.30; $P = 0.21$). Overall, the rate of adverse clinical events, defined as the occurrence of a VTE or major bleeding event, was lower in the rivaroxaban treatment group (2.9% vs 4.2%; HR, 0.67; 95% CI, 0.47–0.85). The lower rate of adverse clinical events in the rivaroxaban group seems to have been driven by a lower rate of recurrent VTE events. The rates of nonbleeding adverse events were similar, as shown by similar rates of treatment-emergent adverse events within the 2 treatment arms. Most patients were supposed to be treated for at least 6 months, with 63% of patients expected to complete 6 months and 25% to complete 12 months of therapy. Because the study duration was event driven, the treatment period was shortened in ~5% of patients in each treatment arm because the predetermined number of events had taken place. Prespecified subgroup analyses did not show differences in treatment duration to have affected the rate of VTE recurrence or bleeding.[36]

The EINSTEIN-PE study was similar to the acute DVT study in all respects (design, primary efficacy and tolerability outcomes, and treatment interventions), except that EINSTEIN-PE included patients with an acute symptomatic PE with or without DVT.[37] EIN-

STEIN-PE results showed rivaroxaban to be noninferior to standard treatment in reducing the risk for recurrent VTE (2.1% [50/2419] with rivaroxaban vs 1.8% [44/2413] with standard therapy; HR, 1.12; 95% CI, 0.75–1.68; $P = 0.003$). Moreover, the occurrence of the principal tolerability outcome was similar between the 2 treatment groups (10.3% [249/2419] with rivaroxaban vs 11.4% [274/2413] with standard therapy; HR, 0.90; 95% CI, 0.76–1.07; $P = 0.23$). There were fewer major bleeding events in the rivaroxaban arm (1.1% vs 2.2%; HR, 0.49; 95% CI, 0.31–0.79; $P = 0.003$); interestingly, the difference in major bleeding was nonsignificant in the acute DVT study. Numerically there were fewer adverse clinical events (defined as the occurrence of a VTE or major bleeding event) in the rivaroxaban treatment arm, but this difference was not statistically significant (3.4% with rivaroxaban vs 4.0% with standard therapy; HR, 0.85; 95% CI, 0.63–1.14; $P = 0.28$). Similar to the acute DVT study, the rates of nonbleeding adverse events were similar in the 2 treatment groups. Approximately 57% and 37% of patients were expected to be treated for 6 and 12 months, respectively. Therapy was terminated early for ~5% of patients in both treatment groups because the predetermined number of events for the study had been achieved before these patients completing the intended duration of therapy. Prespecified subgroup analyses did not find VTE recurrence or bleeding to differ by treatment duration.[37]

The findings of the acute DVT and PE EINSTEIN studies demonstrated similar effectiveness with rivaroxaban and standard treatment when patients were treated for 3 to 12 months; however, the EINSTEIN Continued Treatment Study aimed to determine the potential benefits of prolonging anticoagulant therapy by using rivaroxaban for an additional 6 to 12 months.[36] Patients were eligible for the Continued Treatment Study if they had an objectively confirmed, symptomatic DVT or PE and received standard treatment (while in clinical practice or enrolled in the acute DVT or PE EINSTEIN investigations) or rivaroxaban (while enrolled in the acute DVT or PE EINSTEIN investigations) for 6 to 12 months. Unlike the acute DVT and PE investigations, which were open-label, active-comparator, noninferiority studies, the Continued Treatment Study was a double-blind, placebo-controlled, superiority study. Exclusion criteria for the Continued Treatment Study were the same as described for the acute DVT and PE investigations. An additional 6 to 12 months (60% of patients completed additional 6 months of treatment) of anticoagulation with rivaroxaban resulted in an 82% reduction in VTE recurrence (1.3% [8/602] with rivaroxaban vs 7.1% [42/594] with placebo; HR, 0.18, 95% CI, 0.09–0.39; $P < 0.001$), but also caused a 5-fold increase in major and clinically relevant nonmajor bleeding events (6% [36/598] with rivaroxaban vs 1.2% [7/590] with placebo; HR, 5.19, 95% CI, 2.3–11.7; $P < 0.001$). There were 4 major bleeding events in the rivaroxaban group and none in the placebo group ($P = 0.11$).

The expert panel for the American College of Chest Physician's Antithrombotic Guidelines that provided recommendations for VTE treatment gave a grade 1B recommendation for initial therapy with a parenteral anticoagulant or rivaroxaban; however, the panel gave a weak recommendation for warfarin and LMWH over rivaroxaban and dabigatran because of the dearth of published data on effectiveness and tolerability of these agents for VTE treatment at the time the recommendations were drafted (October 2011).[59]

Acute Coronary Syndrome

The ATLAS ACS–TIMI 46 (Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects with Acute Coronary Syndrome–Thrombolysis in Myocardial Infarction 46) trial evaluated rivaroxaban as adjunctive therapy in patients with a recent ACS. This Phase II, randomized, double-blind, placebo-controlled, multicenter, dose-escalation study evaluated rivaroxaban in 3491 patients within 7 days of hospitalization for an ACS. Participants were required to have symptoms suggestive of an ACS that lasted at least 10 minutes at rest, and either a diagnosis of ST-elevation myocardial infarction (STEMI) or a diagnosis of non-STEMI or unstable angina with at least 1 of the following: raised cardiac enzyme markers, 1 mm or more ST-segment deviation, or a TIMI risk score of ≥3. Patients were randomly assigned to receive aspirin only (stratum 1) or aspirin plus a thienopyridine (stratum 2) in addition to rivaroxaban (5 to 20 mg either once or twice daily). Rivaroxaban was associated with a nonsignificant reduction in the primary composite efficacy end point (death, myocardial infarction, stroke, or severe recurrent ischemia requiring revascularization) versus placebo across the entire population (5.6% vs 7%; HR, 0.79; 95% CI, 0.60–1.05; $P = 0.10$). No significant difference was noted between once and twice daily doses for the primary

efficacy end point. Rivaroxaban significantly reduced the secondary end point (death, myocardial infarction, or stroke) compared with placebo (3.9% vs 5.5%; HR, 0.69; 95% CI, 0.50–0.96; $P = 0.027$). The primary safety end point of clinically significant bleeding (TIMI major, TIMI minor, or requiring medical attention) occurred in a dose-dependent manner with rivaroxaban versus placebo (5 mg: HR, 2.21 [95% CI, 1.25–3.91]; 10 mg: HR, 3.35 [95% CI, 2.31–4.87]; 15 mg: HR, 3.60 [95% CI, 2.32–5.58]; and 20 mg: HR, 5.06 [95% CI, 3.45–7.42]; $P < 0.0001$). The increase in bleeding across doses was apparent in both strata 1 and 2 (both, $P < 0.0001$), with absolute rates of clinically significant bleeding being lower in stratum 1 ($P < 0.0001$). On the basis of the graded increase in bleeding across doses of rivaroxaban in both strata 1 and 2 in conjunction with the efficacy noted at lower doses of rivaroxaban, 2.5 and 5 mg of rivaroxaban administered twice daily were selected for further assessment in the Phase III clinical trial.[46]

ATLAS ACS 2–TIMI 51 was a Phase III, randomized, double-blind, placebo-controlled trial that evaluated rivaroxaban 2.5 and 5 mg BID in the same patient population as the Phase II study, for a mean duration of 13 months. The patients enrolled in the study were on background therapy with aspirin (98%) and a thienopyridine (93%). The primary efficacy end point, death from cardiovascular causes, myocardial infarction, or stroke, was significantly reduced compared with placebo (8.9% vs 10.7%; HR, 0.84; 95% CI, 0.74–0.96; $P = 0.008$). The secondary composite efficacy end point of death from any cause, myocardial infarction, or stroke was also significantly reduced as compared with placebo (9.2% vs 11.0%; HR, 0.84; 95% CI, 0.74–0.95; $P = 0.006$). Rivaroxaban 2.5 mg BID, but not 5 mg BID, reduced the rates of cardiovascular death (2.7% vs 4.1%; $P = 0.002$) and death from any cause (2.9% vs 4.5%; $P = 0.002$). Compared with placebo, rivaroxaban increased the rates of TIMI major bleeding not related to coronary artery bypass grafting (2.1% vs 0.6%; $P < 0.001$) and intracranial hemorrhage (0.6% vs 0.2%; $P = 0.009$). Major bleeding was increased in both the 2.5- and the 5-mg BID groups compared with placebo. The 2.5-mg BID dosage resulted in a lower prevalence of fatal bleeding compared with the 5-mg BID dosage (0.1% vs 0.4%; $P = 0.04$), but this prevalence was not statistically different compared with placebo (0.1% vs 0.2%).[38]

The European Society of Cardiology (ESC) Working Group Position Paper recommends the use of newer antiplatelet agents (ie, prasugrel or ticagrelor) in combination with aspirin over the addition of a factor Xa inhibitor in patients with ACS. This recommendation was a result of the increase in major and intracranial bleeding events when factor Xa inhibitors were combined with antiplatelet agents in clinical trials.[47] Rivaroxaban is not currently approved for the treatment of ACS in any country.

Time in Therapeutic Range in Warfarin-Treated Patients in Rivaroxaban Clinical Trials

When comparing an agent to warfarin it is important to consider the percentage of time patients' international normalized ratios (INRs) were within therapeutic range (TTR) in the warfarin-treated group because lower TTRs (<45%) have been associated with an increased risk for recurrent VTE event and bleeding.[48] TTRs were 57.7% in the acute DVT study (subtherapeutic, 24.4%; supratherapeutic, 16.2%) and 62.7% in the acute PE study (subtherapeutic, 15.5% of the follow-up period; and supratherapeutic, 21.8% of the follow-up period). Although some criticize these studies for having TTRs that are lower than seen with contemporary clinical studies and dedicated anticoagulation clinics (64%–66% in both settings), they are better than the TTRs that have been observed in community practice (50%–51%), the setting where most VKA management takes place.[48,49]

Lower TTRs have been shown to reduce the benefit of warfarin for stroke prevention in AF as well. Connolly et al[50] estimated that a TTR of 58% is needed to ensure that patients would benefit from VKA therapy. A criticism of ROCKET-AF findings is that the TTR was 55%, which is below this 58% threshold. However, ROCKET-AF investigators found that rivaroxaban efficacy was favorable across participating centers, regardless of the level of INR control attained at the center, meaning that rivaroxaban efficacy was similar in centers with the best and worst TTRs. Again, it is important to note that although this TTR is below that observed in contemporary clinical trials and dedicated anticoagulation clinics, it is better than those observed in community practice.[48,49]

Laboratory Monitoring for Effectiveness and Toxicity

Rivaroxaban, unlike VKAs, does not require routine coagulation monitoring. Although routine coagu-

lation monitoring is unnecessary, there may be clinical situations in which the measurement of blood levels of rivaroxaban would be useful. Samama et al[51,52] demonstrated the potential for using anti-factor Xa chromogenic and PT assays as a means to quantify plasma rivaroxaban levels. However, another group of investigators observed better correlation between anti-factor Xa activity and apixaban plasma concentrations.[53] The data on this topic continue to emerge.

Periodic assessment of renal function is required to ensure appropriate dosing.[3] Frequency of renal function assessment will vary based on a patient's risk for decline in renal function.

Transitioning From Warfarin to Rivaroxaban

When switching from warfarin to rivaroxaban, warfarin should be discontinued and rivaroxaban initiated when the INR is <3.0. When switching from rivaroxaban to warfarin, treatment a parenteral anticoagulant and warfarin should be initiated when the next dose of rivaroxaban would have been taken.[3]

Holding Rivaroxaban for Invasive Medical Procedures

Rivaroxaban should be stopped at least 24 hours before an invasive medical procedure. In deciding whether a procedure should be delayed until 24 hours after the last dose of rivaroxaban, the increased risk for bleeding should be weighed against the urgency of intervention. Rivaroxaban should be restarted after the surgical or other procedures as soon as adequate hemostasis has been established. If oral medication cannot be taken after surgical intervention, administration of a parenteral anticoagulant should be considered.[3]

Dosing and Administration

For thromboprophylaxis in AF, the recommended dose of rivaroxaban depends on a patient's renal function. Patients with a CrCl >50 mL/min should take 20 mg orally once daily with the evening meal, and patients with a CrCl 15 to 50 mL/min should take 15 mg orally once daily with the evening meal. Rivaroxaban should not be used in patients with a CrCl <15 mL/min. For VTE prophylaxis, rivaroxaban 10 mg once daily should be given. The dose may be administered without regard to timing of meal consumption, and there is no CrCl restriction.[3] For treatment of DVT, PE, and reduction in recurrence of DVT and PE, rivaroxaban should be dosed at 15 mg BID for the first 21 days of treatment and at 20 mg once daily for the duration of therapy. Each dose should be taken with a meal.

Cost-Effectiveness

Studies of the cost-effectiveness of the use of rivaroxaban for post–orthopedic surgery VTE prophylaxis are currently available in the literature. Decision-analytic models using the pooled results from the RECORD 1 and 2 trials showed that the use of rivaroxaban, compared with enoxaparin, provided a cost-savings of US $512 per patient and prevented 14 to 15 additional symptomatic VTE events per 100 patients during the year following THA. This investigation also found that rivaroxaban use was associated with a cost-savings of $466 per person and prevented 19 to 20 additional symptomatic VTE events per 1000 patients during the year following TKA. The cost-savings in the THA population seen with rivaroxaban treatment was due to the lower cost of rivaroxaban and the prevention of more symptomatic VTE events, whereas the cost-savings in the TKR population was due only to the lower cost of rivaroxaban (the investigators used estimated costs of $6.75 per day for rivaroxaban, $25.98 per day for enoxaparin 40 mg once daily, and $38.97 for enoxaparin 30 mg q12h; these cost estimates for enoxaparin were based on data obtained from an online drug-pricing database). Although the models used by the investigators had been previously validated, the assumptions required to complete the model served as a major limitation of the study. Furthermore, it is unclear whether and how the investigators factored into their models the costs associated with increased clinically relevant bleeding events that were observed with rivaroxaban in each RECORD trial.[54]

Duran et al[55] completed a second investigation that also showed rivaroxaban to be less costly than enoxaparin during the 90-day post prophylaxis period. Analysis of the RECORD 1 study findings estimated rivaroxaban given for 35 days to cost $346 and enoxaparin given for 35 days to cost $1041 (cost-savings of $695 for rivaroxaban). While rivaroxaban was less costly, the two regimens appeared to be equally effective as evidenced by similar event rates (2.7 symptomatic VTE events per 1000 patients). Analysis of the RECORD 2 study findings showed the use of rivaroxaban for a 35-day duration, compared with enoxaparin for a 10 to 14-day duration, to have resulted in 9 to 10 fewer symptomatic VTE events per 1000 treated patients, but, not surprisingly, the cost-savings were lower. Again, it is unclear how the higher rate of clinically relevant bleeding events observed with rivaroxaban was factored into these cost models.

Another group of investigators estimated a less-robust cost-savings with rivaroxaban for VTE prophylaxis after elective orthopedic surgery, when both agents were given for 35 days. Friedman et al[56] reported that an analysis of RECORD 1 showed a 31- to 39-day treatment course with rivaroxaban cost $895 and that the same duration of treatment with enoxaparin 40 mg once daily cost $977 (an $82 cost-savings). At the time of these analyses, rivaroxaban was not available in the United States, so it was assumed that the acquisition costs were similar for rivaroxaban and enoxaparin 40 mg once daily; this assumption may have caused the difference in the estimated cost-savings. This model factored in costs associated with major bleeding events. An analysis using cost estimates from Canada also showed rivaroxaban to be more cost-effective than enoxaparin after THR and TKR surgery.[57]

A recent analysis of the ROCKET-AF data suggested that rivaroxaban may be a cost-effective alternative to warfarin for thromboembolism prophylaxis in nonvalvular AF.[58]

DISCUSSION

Rivaroxaban is as an option for VTE thromboprophylaxis after THA and TKR; for the treatment of DVT and PE and reduction in risk for DVT and PE recurrence; and thromboprophylaxis for nonvalvular AF. Its relative ease of use compared with LMWH and fondaparinux, which require subcutaneous administration, and VKAs, which require routine INR monitoring, makes it a good therapeutic option. Also, compared with twice-daily dosing required with dabigatran, once-daily dosing of rivaroxaban may make it a more attractive option for some patients. Because it accumulates with renal impairment, dose adjustments are required in patients with renal impairment. The trend for increased bleeding seen in RECORD, EINSTEIN, and MAGELLAN and the lack of an effective reversal agent may slow widespread use of this agent for these indications.

VTE Prophylaxis After Elective Orthopedic Surgical Procedures

Heparin-induced thrombocytopenia, and the expert panel of The American College of Chest Physicians listed rivaroxaban as a "reasonable choice" for this purpose.[41] Rivaroxaban may be preferred to warfarin in patients with HIT, because of its shorter onset of action relative to warfarin. However, further investigation is needed before rivaroxaban may be recommended for widespread use for this purpose.

Moreover, the authors believe that rivaroxaban will have a role in extended-duration VTE prophylaxis after orthopedic surgery because it does not require routine coagulation monitoring, unlike warfarin, and does not require subcutaneous administration, unlike LMWH and fondaparinux. However, rivaroxaban is not approved in any country for this indication, and it use for this purpose will require additional study before it may be recommended.

VTE Prophylaxis In Medically Ill Patients

Currently, there are no treatment recommendations guiding the use of rivaroxaban for this purpose. However, the MAGELLAN investigation demonstrated the effectiveness of rivaroxaban for this indication, but the benefits were offset by an increased incidence of clinically relevant bleeding. Rivaroxaban is not approved in any country for this indication nor has the manufacturer signaled its intent to seek approval for this indication in the near future. Given the increased bleeding risk relative to LMWH, the authors do not recommend rivaroxaban be routinely used for thromboprophylaxis in medically ill patients, and if a clinician is considering off-label use of this agent for this purpose, that clinician must factor in the patient's bleeding risk during the decision-making process.

Stroke Prevention In Nonvalvular Atrial Fibrillation

The AHA/ASA guidelines for antithrombotic therapy in AF recommend rivaroxaban for primary and recurrent stroke prevention in nonvalvular AF as a first-line option.

The guidelines give preference to warfarin in patients with CKD. However, we feel that the renal substudy of ROCKET-AF provides substantial information documenting the safety of rivaroxaban for its FDA labeled use in patients with CrCl greater or equal to 30 mL/min with a recommended dosing adjustment in patients with CrCl less than 50 mL/min.[60]

Selection between warfarin, rivaroxaban and dabigatran is an individual patient and practitioner decision based on perceived efficacy and safety of the newer agents compared to warfarin, trade-offs between the patient's fear of stroke, ICH and bleeding, the patient's compliance with INR testing for warfarin, potentially interacting drugs, and the patient's acquisition cost.

Warfarin may be favored in patients at higher risk of bleeding until reversal agents become available. Dabigatran should be avoided in patients with significant renal disease. We do not recommend either dabigatran or rivaroxaban in patients with CrCl of less than 30 mL/min and recommend frequent assessment of renal function in patients with CrCl between 30 mL/min and 50 mL/min. Newer agents are preferred in patients who have difficulty complying with PT testing or have fluctuating INRs. While warfarin clearly has the greatest drug and food interactions, both dabigatran and rivaroxaban have selected drug interactions which play a role in selection of which agent to use in an individual patient.

Whether or not patients with stable INRs and no prior history of stroke should switch from warfarin to a newer agent is controversial. Data with rivaroxaban from ROCKET-AF reported a reduction in ICH and fatal bleeding but not in stroke or systemic embolism or major bleeding. Therefore, we do not feel that most practitioners will recommend switching stable patients at this time until more cost data is available.

Venous Thromboembolism Treatment and Prevention of Recurrence

The authors believe that rivaroxaban is currently an option for patients with DVT or PE, especially for patients who are unable to undergo routine coagulation monitoring that is required for warfarin or unable to administer subcutaneous LMWH and fondaparinux. However, because of the lack of reversal with rivaroxaban, bleeding risk needs to be assessed before prescribing this agent. Moreover, systems for ensuring adherence and proper dosing and duration of therapy need to be in place before implementation of rivaroxaban protocols for this indication. Additional data demonstrating reduced length of hospital stay may incentivize hospitals to put systems in place to utilize more rivaroxaban for this indication in eligible patients.

Acute Coronary Syndrome

The reduced rates of primary and secondary outcomes were at the expense of higher rates of TIMI major bleeding and intracranial hemorrhage in the ATLAS ACS 2–TIMI 51 study. Additionally, both Phase II and Phase III ATLAS ACS studies were included in a meta-analysis of 7 studies in patients receiving direct thrombin inhibitors or anti-Xa inhibitors after an ACS. Because 5 of the studies included in the meta-analysis were dose-finding studies, the ATLAS ACS 2–TIMI 51 study comprised 1 of the 2 large Phase III studies included in the analysis. The meta-analysis found a 3-fold increased risk for major bleeding associated with the new oral anticoagulants (OR, 3.03; 95% CI, 2.20–4.16; $P < 0.001$). When the authors looked at the net clinical benefit (calculated as the sum of composite ischemic and TIMI major bleeding events), they found that there was no statistically significant net clinical benefit with any of the agents, including rivaroxaban.[61] Thus, the benefit of rivaroxaban in ACS may not outweigh the risk.

It still remains unknown whether new oral anticoagulants, such as rivaroxaban, would have a place in the adjunctive treatment of ACS in the era of newer and more potent oral antiplatelet therapy. The ESC Working Group currently recommends the use of newer antiplatelet agents over addition of a factor Xa inhibitor in patients with ACS.[47] Additionally, no data are currently available on the addition of factor Xa inhibitors in patients with ACS who have indications for anticoagulation, such as AF and prosthetic heart valves.

CONCLUSIONS

Based on the findings from the studies described in this review, rivaroxaban is a novel direct Xa inhibitor that is an effective alternative for VTE prophylaxis after elective TKR and THR surgery, VTE treatment, secondary risk reduction after acute DVT and PE, and thromboembolism risk reduction in patients with nonvalvular AF. In addition, recently published data suggest that rivaroxaban is more cost-effective than enoxaparin for VTE prophylaxis after elective orthopedic surgery and more cost-effective than warfarin for thromboembolism risk reduction in nonvalvular AF. However, there is a concern of the potential for increased bleeding with rivaroxaban compared with enoxaparin when used for VTE prophylaxis post–orthopedic surgery and in medically ill patients. Rivaroxaban is not recommended for ACS at this time given the increased bleeding risk. Also, more data are needed to determine the long-term tolerability of rivaroxaban. Overall, the currently available data suggest that rivaroxaban is a cost-effective option for patients unwilling or unable to administer subcutaneous injections for VTE prophylaxis after surgery; for VTE treatment; and for patients with nonvalvular AF unable to see a health care provider for routine coagulation monitoring, which is required for warfarin therapy.

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The authors have indicated that they alone contributed to this article. Dr. Thomas was responsible for the abstract, materials and methods, results, clinical efficacy information for VTE prophylaxis and treatment, the section "Time in the Therapeutic Range in Warfarin-Treated Patients in Rivaroxaban Clinical Trials," dosage and administration, cost-effectiveness information, discussion, and conclusion. Dr. Ganetsky was responsible for the introduction, mechanism of action, pharmacokinetics/pharmacodynamics, drug–drug interaction information, reversal, clinical efficacy information for acute coronary syndrome, transitioning from warfarin to rivaroxaban, and information for holding rivaroxaban for medical procedures. Dr. Spinler was responsible for clinical efficacy information for atrial fibrillation and the table summarizing clinical trials. All authors assisted with the literature search and in writing the manuscript. Dr. Thomas revised the manuscript with approval from all coauthors on completions.

CONFLICTS OF INTEREST

Dr. Spinler Is a Paid Consultant for Janssen Pharmaceuticals, Inc. The Authors Have Indicated That They Have No Other Conflicts of Interest With Regard To the Content of This Article.

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Address correspondence to: Tyan F. Thomas, PharmD, BCPS, Philadelphia College of Pharmacy, University of the Sciences in Philadelphia, 600 South 43rd Street, Philadelphia, PA 19104. E-mail: t.thomas@usciences.edu