Rivaroxaban: A New Oral Factor Xa Inhibitor

Elisabeth Perzborn, Susanne Roehrig, Alexander Straub, Dagmar Kubitza, Wolfgang Mueck, Volker Laux

Abstract—Rivaroxaban is a direct inhibitor of factor Xa, a coagulation factor at a critical juncture in the blood coagulation pathway leading to thrombin generation and clot formation. It is selective for human factor Xa, for which it has >10 000-fold greater selectivity than for other biologically relevant serine proteases (half-maximal inhibitory concentration [IC50], >20 μmol/L). Rivaroxaban inhibits factor Xa in a concentration-dependent manner (inhibitory constant [Ki], 0.4 nmol/L) and binds rapidly (kinetic association rate constant [kon], 1.7×107 mol/L−1 s−1) and reversibly (kinetic dissociation rate constant [koff], 5×10−3 s−1). By inhibiting prothrombinase complex-bound (IC50, 2.1 nmol/L) and clot-associated factor Xa (IC50, 75 nmol/L), rivaroxaban reduces the thrombin burst during the propagation phase. In animal models of venous and arterial thrombosis, rivaroxaban showed dose-dependent antithrombotic activity. In healthy individuals, rivaroxaban was found to have predictable pharmacokinetics and pharmacodynamics across a 5- to 80-mg total daily dose range, inhibiting factor Xa activity and prolonging plasma clotting time. In phase III clinical trials, rivaroxaban regimens reduced rates of venous thromboembolism in patients after total hip or knee arthroplasty compared with enoxaparin regimens, without significant differences in rates of major bleeding, showing that rivaroxaban has a favorable benefit-risk profile. (Arterioscler Thromb Vasc Biol. 2010;30:376-381.)

Key Words: anticoagulants • blood coagulation • factor Xa • rivaroxaban • venous thromboembolism

Factor Xa is a coagulation factor that acts at the convergence point of the intrinsic and extrinsic pathways in the blood coagulation system. It catalyzes the cleavage of prothrombin and, therefore, is critical for thrombin generation (Figure 1).1,2

Indirect factor Xa inhibitors, such as fondaparinux and biotinylated idraparinux, exert their thrombotic effect by binding to antithrombin; therefore, their efficacy depends on the circulating level of antithrombin. They are parenteral agents and cannot be administered orally.3 Rivaroxaban is the first direct factor Xa inhibitor to be licensed (in the European Union and several other countries) for the prevention of venous thromboembolism (VTE) in adult patients after elective hip or knee arthroplasty. Studies of rivaroxaban in the treatment of VTE, prevention of cardiovascular events in patients with acute coronary syndrome, prevention of stroke in those with atrial fibrillation, and prevention of VTE in hospitalized medically ill patients are ongoing (Supplementary Table I, available at http://atvb.ahajournals.org). Other direct factor Xa inhibitors are also in advanced development: apixaban and edoxaban (DU-176b) are undergoing phase III study, whereas betrixaban and YM150 have passed clinical phase II testing. This review discusses the properties of rivaroxaban and findings from clinical trials.

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Pharmacological Properties

Compound Characteristics

Rivaroxaban (chemical name 5-chloro-N-[[5S]-2-oxo-3-[4-(3-oxomorpholin-4-yl)phenyl]-1,3-oxazolidin-5-yl]methyl]thiophene-2-carboxamide) is a small-molecule factor Xa inhibitor (molecular weight, 436 g/mol). Rivaroxaban is only slightly soluble in organic solvents and is practically insoluble in water.5 Plasma protein binding varies between species (rats, 98.7%; rabbits, 76.6%; and humans, 92%–95%),4 and serum albumin is the main circulating binding component.4,5

Mode of Binding

As a prerequisite for potent activity, factor Xa inhibitors of the first generation, such as DX-9065a, needed a basic arginine-mimic P1 group for direct electrostatic interaction with Asp189 in the S1 pocket of factor Xa. However, those basic groups are also generally critical for oral bioavailability. The X-ray crystal structure of rivaroxaban in complex with human factor Xa6 revealed a different binding mode for the S1 pocket, which no longer requires the P1 group to be basic. Instead, the key interaction in the S1 pocket involves the chlorine substituent of the chlorothiophene moiety, which interacts with the aromatic ring of Tyr228 at the bottom of the S1 pocket (Figure 2). This novel chlorine–Tyr228 interaction enabled the combination of high potency and sufficient oral bioavailability for the nonbasic compound rivaroxaban.

Preclinical In Vitro and In Vivo Pharmacological Profile

In Vitro Studies

Factor Xa Inhibition

Rivaroxaban inhibits factor Xa in a concentration-dependent manner (inhibitory constant [Ki], 0.4 nmol/L), and it is a
competitive inhibitor of the amidolytic activity of factor Xa.\textsuperscript{7} It has a rapid onset of action (kinetic association rate constant \(k_{on}\), 1.7\times10^4 \text{ mol/L}^{-1} \text{s}^{-1}) and is reversible (kinetic dissociation rate constant \(k_{off}\), 5\times10^{-3} \text{ s}^{-1}).\textsuperscript{8} Rivaroxaban inhibits prothrombinase-bound (half-maximal inhibitory concentration [IC\textsubscript{50}], 2.1 \text{ nmol/L})\textsuperscript{7} and clot-associated factor Xa (IC\textsubscript{50}, 75 \text{ nmol/L}).\textsuperscript{9} Rivaroxaban was found to be selective for human factor Xa, for which it has >10 000-fold greater selectivity than for other biologically relevant serine proteases (IC\textsubscript{50}, >20 \text{ \mu mol/L}).\textsuperscript{7} The inhibition of factor Xa is species-dependent, as was shown for a number of factor Xa inhibitors.\textsuperscript{10–12} Rivaroxaban showed a similar affinity to purified human and rabbit factor Xa (IC\textsubscript{50}, 0.7 \text{ nmol/L} and 0.8 \text{ nmol/L}, respectively) but showed lower affinity to rat factor Xa (IC\textsubscript{50}, 3.4 \text{ nmol/L}).

In commercially available chromogenic assays designed for measuring heparins in human plasma, rivaroxaban concentration-dependently inhibited factor Xa activity, with IC\textsubscript{50} values between 21 and 80 ng/mL, depending on the anti-factor Xa assay.\textsuperscript{13}

**Inhibition of Thrombin Generation**

In vitro studies in platelet-poor and platelet-rich plasma demonstrated that rivaroxaban prolonged the initiation phase of thrombin generation and reduced the thrombin burst produced in the propagation phase.\textsuperscript{14,15} In human plasma obtained from healthy volunteers receiving rivaroxaban, rivaroxaban inhibited thrombin generation at clinically relevant plasma concentrations and, thus, the propagation processes of coagulation through the inhibition of factor Xa generated via the intrinsic and extrinsic coagulation pathways.

**Plasma Clotting Times**

Rivaroxaban demonstrated effective anticoagulant effects in human plasma; it prolongs prothrombin time (PT) and activated partial thromboplastin time in a concentration-dependent manner, with greater sensitivity for PT.\textsuperscript{7} However, the prolongation of clotting time varies depending on the PT or activated partial thromboplastin time reagent used because the reactivity of rivaroxaban in the clotting assays is influenced by the composition of the reagents.\textsuperscript{16,17} This variation cannot be reduced by conversion of PT values given in seconds to international normalized ratio values;\textsuperscript{17} therefore, PT and activated partial thromboplastin time are not useful for measuring the pharmacodynamic effects of rivaroxaban.

**Thrombin–Thrombomodulin-Activated Protein C System**

The coagulation pathway comprises negative and positive feedback reactions to regulate hemostasis, and anticoagulants at therapeutic doses ideally should not interfere with the negative feedback mechanisms important in downregulating coagulation. One of the negative feedback reactions is the thrombin–thrombomodulin-activated protein C system, which limits further thrombin generation by inhibiting factor Va and factor VIIIa. In vitro investigations of human plasma from healthy individuals or protein C-deficient plasma, factor Xa inhibitors, such as rivaroxaban, inhibited thrombin generation in a concentration-dependent manner after stimulation by tissue factor and in the presence or absence of thrombomodulin.\textsuperscript{18} This suggests that rivaroxaban does not measurably interfere with the thrombin–thrombomodulin-activated protein C system.\textsuperscript{18}Interestingly, direct thrombin inhibitors, such as melagatran and dabigatran, also showed a concentration-dependent inhibition of thrombin generation over the whole range in the absence of thrombomodulin or in protein C-deficient plasma but increased thrombin generation at low concentrations in the presence of thrombomodulin.\textsuperscript{18,19} This suggests that low concentrations of a direct thrombin inhibitor may partly suppress the negative feedback by activated protein C. However, whether this effect will influence clinical efficacy or safety remains to be investigated.

**Platelet Aggregation**

Rivaroxaban does not affect platelet aggregation induced by collagen, adenosine diphosphate, the selective agonist of prostaglandin H\textsubscript{2}/thromboxane A\textsubscript{2} receptor U46619, or thrombin.\textsuperscript{20,21} However, rivaroxaban effectively and concentration-dependently inhibited tissue factor-induced platelet

Figure 1. Role of factor Xa in the coagulation cascade. Tissue factor/factor VIIa activates factor X and factor IX. Factor IXa also activates factor X. Factor Xa binds factor Va on membrane surfaces. The prothrombinase and tenase trigger the amplified formation of thrombin.\textsuperscript{2,5} Rivaroxaban inhibits factor Xa, free or within the prothrombinase.

Figure 2. The entire X-ray crystal structure of factor Xa (FXa) with a focus on the active site showing the key interaction between rivaroxaban and Tyr228 in the S1 pocket.
aggregation by the inhibition of thrombin generation (IC50, 0.06 μmol/L) in defibrinated plasma. In addition to the anticoagulant effects of a factor Xa inhibitor, this indirect effect on platelet aggregation may be particularly beneficial for the prevention or treatment of arterial thrombosis.

In Vivo Studies

Venous Thrombosis Models
Rivaroxaban reduced thrombus formation7–23 in venous thrombosis models (fibrin-rich and platelet-poor) in which a combination of stasis and an injection of tissue factor was used to induce thrombus formation. In rabbits, rivaroxaban was administered orally, leading to a half-maximal effective dose (ED50) of 1.3 mg/kg;23 in rats, rivaroxaban was administered intravenously, leading to ED50 of 0.1 mg/kg. These findings suggested rivaroxaban might reduce thrombosis formation in humans. In a rabbit thrombosis model, rivaroxaban also inhibited thrombus growth of preformed clots in the jugular vein (assessed by measuring the accretion of radiolabeled fibrinogen),23 which supported further research in VTE treatment.

Arterial Thrombosis Models
Rivaroxaban showed effective dose-dependent antithrombotic activity in arterial (fibrin-poor and platelet-rich) thrombosis models, such as the arteriovenous shunt model in rats and rabbits (ED50, 5.0 mg/kg after oral rivaroxaban in rats; ED50, 0.6 mg/kg after oral administration in rabbits?), and the ferric chloride model in rats and mice (ED50, 2.4 mg/kg after intravenous rivaroxaban in rats; ED50, 1.0 mg/kg after intravenous rivaroxaban in mice24). These results are consistent with a role of the coagulation system in arterial thrombus formation.

Bleeding Models
The antihemostatic effect of rivaroxaban was evaluated in well-characterized bleeding time models in rats (tail transection bleeding time model) and rabbits (ear bleeding time model). Bleeding times were not significantly affected at antithrombotic doses below the ED50 required for antithrombotic efficacy in the bleeding time models. At higher doses in the rat tail-bleeding time model, bleeding times were dose-dependently prolonged.7 Together with the antithrombotic findings, these findings demonstrate that rivaroxaban might have a favorable efficacy-to-bleeding ratio.

Clinical Pharmacology
Rivaroxaban has a favorable safety and tolerability profile in healthy individuals.25,26

Pharmacodynamic and Pharmacokinetic Profiles
Rivaroxaban was found to have predictable pharmacokinetics and pharmacodynamics across a wide range of doses in healthy individuals (5–80 mg total daily doses)25,26 and patients undergoing total hip or total knee arthroplasty (5–60 mg total daily doses).27

The inhibition of factor Xa activity and the prolongation of PT correlated strongly with the plasma concentrations of rivaroxaban in healthy individuals28 and patients undergoing total hip arthroplasty or total knee arthroplasty,27 corroborating the predictability of the pharmacodynamics and pharmacokinetics of rivaroxaban.

Studies in healthy individuals showed that rivaroxaban is rapidly absorbed, with maximum concentrations appearing 2 to 4 hours after tablet intake.4,25,26 Oral bioavailability for the 10-mg dose (which has health regulatory authority approval for thromboprophylaxis after elective hip or knee arthroplasty in adult patients) is high (80%–100%).4 The mean terminal half-life of rivaroxaban is 7 to 11 hours.4

The elimination of rivaroxaban from plasma was rapid, with no major or pharmacologically active circulating metabolites detected in plasma.29 Excretion occurred via renal and fecal/biliary routes. Approximately two-thirds of the administered dose is metabolized to inactive metabolites, with half then being eliminated renally and the other half eliminated by the fecal route. The remaining one-third of the administered dose undergoes direct renal excretion as unchanged active substance in the urine.29

Rivaroxaban is metabolized by a number of independent metabolic pathways involving different classes of enzymes; thus, rivaroxaban should be less prone to drug–drug interactions. The main oxidative metabolic pathway is hydroxylation at the morpholinone moiety and, to a lesser extent, at the oxazolidinone moiety, catalyzed by CYP3A4/3A5 and CYP2J2.30 In addition, hydrolytic pathways were identified, occurring at the morpholinone ring and the chlorothiophene amide moiety.

Effect of Rivaroxaban in Different Populations
Phase I and II clinical studies have investigated the effect of several factors on rivaroxaban pharmacokinetics and pharmacodynamics. The area under the plasma concentration curve was higher in healthy men and women older than age 75 years compared with younger men and women, but maximum plasma concentration was unaffected.31,32 Gender did not affect the area under the plasma concentration curve or maximum plasma concentration of rivaroxaban.31,32 Area under the plasma concentration curve was not affected by extreme body weight (<50 kg or >120 kg), and although maximum plasma concentration was increased by 24% in those weighing ≤50 kg, this increase was not considered to be clinically relevant.32 In patients with mild (creatinine clearance, 50–79 mL/min), moderate (creatinine clearance, 30–49 mL/min), or severe (creatinine clearance <30 mL/min) impairment of renal function, area under the plasma concentration curve was 44%, 52%, and 64% higher, respectively, compared with control subjects, whereas maximum plasma concentration was relatively unaffected.33 In patients with mild (Child–Pugh A) hepatic functional impairment, there were no clinically relevant differences in pharmacokinetics and pharmacodynamics of rivaroxaban.34 Together, these findings suggest that rivaroxaban can be administered to individuals with varying physical characteristics (age, gender, body weight, mild or moderate impairment of renal function, and mild hepatic functional impairment) at a fixed dose, with no requirement for dose adjustment or routine coagulation monitoring.4

Interaction With Food and Drugs
Phase I interaction studies have demonstrated no food interactions and no significant and few clinically relevant drug inter-
actions with rivaroxaban, with the exception of azole antifungal agents or human immunodeficiency virus protease inhibitors. These strong inhibitors of CYP3A4 and P-glycoprotein lead to reduced clearance of rivaroxaban; therefore, rivaroxaban is not recommended in patients receiving these drugs. Strong CYP3A4 inducers may lead to reduced rivaroxaban plasma concentrations and should be coadministered with caution.4

No clinically significant interactions were observed when rivaroxaban was coadministered with the statin atorvastatin (a substrate of CYP3A4 and P-glycoprotein),33 the cardiac glycoside digoxin (a substrate of P-glycoprotein),36 or the benzodiazepine derivative midazolam (a substrate of CYP3A4).4 The histamine H2-receptor antagonist ranitidine (a CYP3A4 inhibitor) and the antacid aluminum–magnesium hydroxide have no significant effect on the pharmacokinetics and pharmacodynamics of rivaroxaban.37

Coadministration of antiplatelet agents, such as the non-steroidal antiinflammatory drugs acetylsalicylic acid38 and naproxen,39 had no significant effect on the pharmacokinetics and pharmacodynamics of rivaroxaban. The antiplatelet agent clopidogrel did not show a pharmacokinetic interaction with rivaroxaban.40

Clinical Trials in the Prevention of Venous Thromboembolism

Phase II Trials

The Oral Direct Factor Xa (ODIXa) program of four phase II dose-finding studies of rivaroxaban for the prevention of VTE in patients undergoing total hip or knee arthroplasty suggested that rivaroxaban 10 mg once daily (compared with approved enoxaparin doses) would provide the best balance between efficacy and safety.41–44

Phase III Trials

In the orthopaedic setting, the phase III Regulation of Coagulation in Orthopaedic surgery to prevent deep vein thrombosis and pulmonary embolism (RECORD) program included >12 700 patients undergoing total hip arthroplasty or total knee arthroplasty.45–48 Patients were randomized to oral rivaroxaban 10 mg once daily administered 6 to 8 hours after wound closure or after adequate hemostasis had been achieved, or subcutaneous enoxaparin 40 mg once daily starting 12 hours before surgery (enoxaparin dose approved in the European Union, North America, and other countries) in RECORD1, 2, and 3 or 30 mg twice daily administered 12 to 24 hours after wound closure (dose approved and more often used in North America) in RECORD4. In RECORD1 and 2, patients undergoing total hip arthroplasty were administered rivaroxaban for 35±4 days. Enoxaparin was administered for 35±4 days in RECORD1 or 12±2 days followed by placebo for up to 35±4 days in RECORD2. In RECORD3 and 4, patients undergoing total knee arthroplasty received prophylaxis for 12±2 days. All patients were followed-up for 30 to 35 days after the last dose of study medication.

The rivaroxaban regimens were significantly more effective than both enoxaparin regimens at reducing the composite of symptomatic and asymptomatic (detected by systematic bilateral venography) deep vein thrombosis, nonfatal pulmonary embolism, and all-cause mortality.45–48 Rates of major bleeding did not differ significantly between rivaroxaban and enoxaparin regimens.45–48 Also, the proportion of patients with elevated liver enzymes (alanine aminotransferase level >3-times the upper limit of the normal range) was low in the rivaroxaban and enoxaparin groups.45–48

In a pooled analysis of the RECORD1–4 data, the composite of symptomatic VTE and death was reduced for the rivaroxaban regimens compared with the enoxaparin regimens at day 12±2 (0.47% vs 0.97%; P=0.001) and in the planned treatment period (rivaroxaban or enoxaparin for 12±2 days [RECORD3 and 4] or 35±4 days [RECORD1 and 2], including the enoxaparin placebo phase in RECORD2; 0.57% vs 1.32%; P<0.001). There were no statistical differences in the rates of major bleeding at any of the time points analyzed. The composite of major and clinically relevant nonmajor bleeding for the rivaroxaban and enoxaparin regimens were 2.85% vs 2.45% (P=0.186) at day 12±2 and 3.19% vs 2.55% (P=0.039) in the planned treatment period.49

Clinical Trials in the Treatment of Venous Thromboembolism

The phase III EINSTEIN EXT study (NCT00439725) showed that in patients who had completed 6 or 12 months of previous therapy for acute VTE, there was a risk reduction of 82% for rivaroxaban vs placebo for recurrent symptomatic VTE.40 Research is ongoing in the EINSTEIN DVT (NCT00440193) and EINSTEIN PE (NCT00439777) studies (Supplementary Table I).

Other Studies

Rivaroxaban is also being studied for the prevention of cardiovascular events in patients with acute coronary syndrome (ATLAS ACS TIMI 51; NCT00809965), stroke prevention in patients with atrial fibrillation (ROCKET AF; NCT00403767), and thromboprophylaxis in hospitalized medically ill patients (MAGELLAN; NCT00571649; Supplementary Table I).

Conclusion

Rivaroxaban was selected as a drug candidate based on its hypothetical therapeutic potential as a direct inhibitor of factor Xa, in vitro potency, demonstrated selectivity against factor Xa,7 anticoagulant activity in clotting assays in human plasma,7 and consistent in vivo antithrombotic activity in venous and arterial thrombosis models.7,23,24 Because of its favorable safety and tolerability profile in healthy individuals and a positive benefit-risk ratio for the prevention of VTE in patients after total hip arthroplasty or total knee arthroplasty,41–44 the 10-mg once-daily dose has been granted health regulatory authority approval for the prevention of VTE after elective hip or knee arthroplasty in adult patients.4 The oral bioavailability of rivaroxaban is an advantage over parenteral anticoagulant agents and could provide better convenience in outpatient settings.

The pharmacodynamic and pharmacokinetic profiles, which were found to be predictable,25–27 together with the low interaction potential with food or other drugs,4,35–40 the wide therapeutic window,7 and the absence of a requirement for routine coagulation monitoring,4 enhance the likelihood that oral factor Xa inhibitors such as rivaroxaban may become an alternative to vitamin K antagonists in patients at risk for thromboembolism.
Use of factor Xa inhibitors might also obviate the drawbacks of vitamin K antagonists, which include unpredictable pharmacodynamics and pharmacokinetics, multiple food–drug and drug–drug interactions, considerable interindividual variability in dose response, and requirement for regular coagulation monitoring. At present, there is a substantial clinical need for an oral anticoagulant to replace vitamin K antagonists for long-term prevention or treatment of patients with venous and arterial thromboembolic events. There is currently a variety of new, promising, oral anticoagulants at various stages of clinical evaluation, with the most advanced being the direct factor Xa inhibitor rivaroxaban and the direct thrombin inhibitor dabigatran (reviewed in this series).

One major focus in the development of drugs targeting factor Xa is factor Xa. Emerging data for rivaroxaban and other potent factor Xa inhibitors, such as apixaban, betrixaban, edoxaban, and YM150, suggest that factor Xa is a highly promising target for new antithrombotic agents for short-term and long-term usage.

Orthopaedic surgery has proved to be a reliable clinical model for assessing the efficacy and safety profile of a new oral anticoagulant. Rivaroxaban has shown superiority over standard therapy with enoxaparin without significantly increasing the major bleeding rate; thus, it might be effective and safe in orthopaedic surgery.

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Disclosures

The authors are employees of Bayer Schering Pharma AG.

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### Table I. Ongoing Rivaroxaban Phase III Trials

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<tr>
<th>Indication</th>
<th>Patient Characteristics</th>
<th>Regimens</th>
<th>Treatment Period</th>
<th>Estimated Enrolment (n)</th>
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</thead>
<tbody>
<tr>
<td><strong>ROCKET AF</strong>&lt;br&gt;(NCT00403767)</td>
<td>Stroke prevention in patients with AF</td>
<td>Non-valvular AF Rivaroxaban 20 mg od (15 mg od in patients with moderate renal impairment (CrCl 30–49 mL/min)) versus warfarin</td>
<td>Event-driven, therefore no minimum; maximum of 4 years(^1)</td>
<td>14,266</td>
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<tr>
<td><strong>EINSTEIN DVT</strong>&lt;br&gt;(NCT00440193)</td>
<td>VTE treatment Acute symptomatic</td>
<td>Rivaroxaban 15 mg</td>
<td>3, 6, or 12 months</td>
<td>3,465</td>
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<tr>
<td>Study</td>
<td>VTE treatment</td>
<td>Disease</td>
<td>Treatment</td>
<td>Duration</td>
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<td>----------------------------</td>
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<tr>
<td><strong>EINSTEIN PE</strong> (NCT00439777)</td>
<td>VTE treatment</td>
<td>Acute symptomatic PE with or without symptomatic DVT</td>
<td>Rivaroxaban 15 mg bid for first 3 weeks, then 20 mg od versus enoxaparin 1.0 mg/kg bid for at least 5 days, followed by warfarin</td>
<td>3, 6, or 12 months</td>
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<tr>
<td><strong>EINSTEIN EXT</strong> (NCT00439725)</td>
<td>VTE treatment</td>
<td>Patients with confirmed</td>
<td>Rivaroxaban 20 mg</td>
<td>6 or 12 months</td>
</tr>
</tbody>
</table>
symptomatic DVT or PE who completed 6 or 12 months of treatment with rivaroxaban or a VKA

**MAGELLAN**
(NCT00571649)
**VTE prevention**
**Hospitalized medically ill patients**
Rivaroxaban 10 mg od for 35±4 days versus subcutaneous enoxaparin 40 mg od for 10±4 days

**ATLAS ACS TIMI 51**
(NCT00809965)
**Prevention of cardiovascular events in patients**
**Patients with recent ACS receiving standard antiplatelet therapy of low-dose**
Rivaroxaban 2.5 mg bid or 5 mg bid or placebo bid

At least 6 months

8,000

16,000
ACS, acute coronary syndrome; AF, atrial fibrillation; bid, twice daily; CrCl, creatinine clearance; DVT, deep vein thrombosis; od, once daily; PE, pulmonary embolism; VKA, vitamin K antagonist; VTE, venous thromboembolism.

Supplemental Material Reference