Efficacy and safety of novel anticoagulants compared with established agents

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***Abstract*:** Dabigatran, rivaroxaban, and apixaban are novel oral anticoagulants that offer major advantages over existing agents. The onset of the anticoagulant effect of these agents is rapid. Each agent has a predictable anticoagulant response that eliminates the need for monitoring. Clinical trials have been completed with all three agents in the prevention and treatment of the three leading causes of cardiovascular death: myocardial infarction, stroke, and venous thromboembolism (VTE). Novel agents have shown reduced or similar rates of thrombosis, major bleeding, and adverse events when weighed against either low molecular weight heparin or warfarin. Additional trials are underway and more agents are in development. As a result, novel anticoagulants may impact physician prescribing practices and warrant consideration in patients requiring thrombosis management.

***Keywords*:** acute coronary syndromes, anticoagulation, apixaban, atrial fibrillation, dabigatran, prophylaxis, rivaroxaban, venous thromboembolism, warfarin

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Introduction

Dabigatran, rivaroxaban, and apixaban are novel oral anticoagulants that offer major advances in the prevention and treatment of both venous and arterial thrombosis. They feature a wider therapeutic index, a more predictable therapeutic response without the need for monitoring, and fewer drug–drug and drug–food interactions when compared with warfarin [Garcia *et al.* 2010]. A rapid onset of action may eliminate the need for unfractionated heparin (UFH) or low molecular weight heparin (LMWH) administration. Moreover, studies with all of these agents have shown reduced or comparable rates of thrombosis, bleeding, and other adverse events when weighed against commercially available anticoagulants [Piccini *et al.* 2010]. As a result, novel anticoagulants figure to significantly impact physician prescribing practices, change consensus guidelines, and generate clinical debate on the optimum choice for medical management of thrombosis.

Dabigatran

Dabigatran etexilate is a prodrug. After oral administration, nonspecific plasma and hepatic esterases hydrolyze the compound into the active anticoagulant, dabigatran [Boehringer Ingelheim, 2011]. Dabigatran is a univalent direct thrombin inhibitor (DTI), exerting its action through reversible, competitive binding to the active site on thrombin, without binding to the exosite domains [Baetz and Spinler, 2008; Stangier *et al.* 2008b; Di Nisio *et al.* 2005]. Similar to other DTIs, dabigatran inactivates both fibrin-bound and circulating thrombin consequently interrupting thrombin's role in thrombogenesis. With limited ability to bind to extraneous plasma proteins, dabigatran provides a more predictable anticoagulation response compared with UFH [Baetz and Spinler, 2008]. Furthermore, dabigatran indirectly exerts an antiplatelet effect by reducing thrombin's impact on promoting platelet activation and aggregation [Baetz and Spinler, 2008; Di Nisio *et al.* 2005; Xiao and Theroux, 1998].

Pharmacokinetics

Dabigatran has low bioavailability (6.5%) following oral administration (Table 1) [Boehringer Ingelheim, 2011]. Dabigatran has a rapid onset of anticoagulant action with peak plasma concentrations occurring 1–2 hours after administration. While food delays dabigatran's absorption by 2–4 hours [Stangier *et al.* 2005], there are no dietary restrictions or food interactions [Boehringer Ingelheim, 2011]. There is no

Table 1. Pharmacokinetic features of novel anticoagulants.

Parameter	Dabigatran etexilate	Rivaroxaban	Apixaban
Target	Thrombin	Factor Xa	Factor Xa
Prodrug	Yes	No	No
Dosing	Fixed	Fixed	Fixed
Bioavailability (%)	6.5	80	90
Food Effects	Delay Tmax 2–4 hours	Delays Tmax	Not reported
Half-life (hours)	12–17	5-9	12
Renal excretion (%)	80	65	25
Coagulation Monitoring	No	No	No
Antidote	None	None	None
Interactions	P-gp inhibitors*	Combined P-gp and CYP 3A4 inhibitors**	Potent 3CYP3A4 inhibitors**

*P-glycoprotein (P-gp) inhibitors include verapamil, clarithromycin, and quinidine.
**Cytochrome (CYP) P450 3A4 inhibitors include but are not limited to ketoconazole, macrolide antibiotics, and protease inhibitors.

antidote available to reverse or attenuate dabigatran's anticoagulant effect. Dabigatran is eliminated through renal filtration with up to 80% of the dose excreted unchanged in urine [Boehringer Ingelheim, 2011; Baetz and Spinler, 2008; Stangier *et al.* 2010]. Dabigatran's mean terminal elimination half-life is prolonged in patients with severe renal dysfunction. The recommended dabigatran dose for prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation is 150 mg twice daily. For patients with a creatinine clearance of 15-30 ml/min, the manufacturer recommends decreasing the dose to 75 mg twice daily [Boehringer Ingelheim, 2011; Stangier *et al.* 2010]. The cytochrome P450 system is not involved in dabigatran metabolism and several trials have failed to identify clinically significant drug interactions [Boehringer Ingelheim, 2011; Baetz and Spinler, 2008; Stangier *et al.* 2008b, 2007a, 2007b, 2007c]. Since patients with moderate and severe hepatic impairment were excluded from dabigatran clinical studies, no dosing adjustment recommendations exist in hepatic dysfunction [Eriksson *et al.* 2010, 2007a, 2007b, 2005, 2004; Ginsberg *et al.* 2009; Hirsh *et al.* 2008].

Dabigatran acts as a substrate to the efflux transporter P-glycoprotein (P-gp), a system responsible for the transport of various molecules across extracellular and intracellular membranes.

Dabigatran therapy should be avoided with P-gp inducers, such as rifampin, that can reduce its absorption by as much as two thirds. It should be used cautiously with P-gp inhibitors (e.g. ketoconazole, verapamil, amiodarone or quinidine) which may produce fluctuations in dabigatran, increasing plasma concentrations from 50% to as much as 200%.

A study in healthy volunteers treated with the proton-pump inhibitor pantoprazole showed a reduction in dabigatran absorption by 22% and a decrease in the mean maximum serum concentration by almost one third [Stangier *et al.* 2008a]. However, recent data from clinical trials suggests the concomitant use of proton-pump inhibitors or H_2 antagonists does not result in markedly lower serum concentrations of dabigatran [Boehringer Ingelheim, 2011].

Multiple dose ranging studies have shown a fixed-dose dabigatran regimen does not require routine coagulation monitoring of activated partial thromboplastin time (aPTT), thrombin clotting time (TT), international normalized ratio (INR), or ecarin clotting time (ECT) [Van Ryn *et al.* 2010; Stangier *et al.* 2007a, 2007b, 2007c; Eriksson *et al.* 2004]. ECT and TT can be used to assess anticoagulant status in patients receiving dabigatran [van Ryn *et al.* 2010]. With a predictable pharmacokinetic profile, phase III clinical studies were completed without routine coagulation monitoring [Eriksson *et al.* 2010, 2008, 2007b, 2005, 2004; Ginsberg *et al.* 2009; Schulman *et al.* 2009; Hirsh *et al.* 2008; Stangier *et al.* 2008a, 2007a, 2007b].

The most common adverse events reported with dabigatran include dyspepsia, dizziness, headache, dyspnea, peripheral edema, diarrhea, and joint, back, and extremity pain. Hypersensitivity

reactions are rare. Abdominal pain and gastritis-like symptoms are related to the capsule formulation which contains tartaric acid, and can be combated by taking the medication with food. Reversing the anticoagulant effect of dabigatran in hemorrhagic complications is a challenge. In the event of overdose, the early use of activated charcoal has been successful in reducing gastrointestinal absorption [van Ryn *et al.* 2010]. Dabigatran is removed by dialysis and may be an option for renally impaired patients. Limited data exists supporting the use of activated prothrombin complex concentrates or recombinant factor VIIa for the treatment of life-threatening bleeding [Boehringer Ingelheim, 2011; van Ryn *et al.* 2010].

Clinical evidence

Dabigatran has been compared with enoxaparin for venous thromboembolism (VTE) prophylaxis, with warfarin in acute VTE treatment and secondary VTE prevention (Table 2), and for stroke prevention in atrial fibrillation (AF) [Eriksson *et al.* 2010, 2007a, 2007b, 2005, 2004; Ginsberg *et al.* 2009; Schulman *et al.* 2009; Hirsh *et al.* 2008]. Dabigatran has been combined with the standard dual antiplatelet treatment (aspirin and clopidogrel) for the secondary prevention of cardiac events in acute coronary syndrome (ACS) patients [Oldgren *et al.* 2009].

Prophylaxis of venous thromboembolism

The dose-ranging BISTRO I and BISTRO II trials determined the optimal dabigatran dosing for prevention of VTE [Baetz and Spinler, 2008; Eriksson *et al.* 2005, 2004].

The RE-MODEL and RE-MOBILIZE noninferiority trials compared oral dabigatran with subcutaneous enoxaparin for VTE prophylaxis in patients undergoing total knee replacement surgery (Table 2) [Ginsberg *et al.* 2009; Eriksson *et al.* 2007a]. The RE-NOVATE and the RE-NOVATE II trials were similar studies, enrolling patients undergoing total hip replacement surgery [Eriksson *et al.* 2007b]. Across all four trials, the primary efficacy, safety endpoints, and methods of detection were the same. The primary endpoints for all four trials was the composite of total VTE events, including symptomatic and venographically identified deep vein thrombosis (DVT) and/or symptomatic pulmonary embolism (PE), and all-cause mortality during treatment. DVT was detected using bilateral venography. Spiral computed tomography, perfusion–ventilation lung scintigraphy, or pulmonary angiography were used to detect PE. Lastly, an autopsy was performed for patients who died during the study. The primary safety outcome of all four trials was the occurrence of major bleeding, clinically relevant nonmajor bleeding, and minor bleeding. Major bleeding was defined as fatal, clinically overt and associated with a 20 g/l fall in hemoglobin, requiring more than 2 units of packed cells or whole blood, bleeding into a critical area (retroperitoneal, intracranial, intraocular, or intraspinal), or bleeding that required treatment cessation or operation. Clinically relevant nonmajor bleeding was defined by the occurrence of spontaneous skin hematoma, hematuria, nasal, rectal or gingival bleeding, bleeding leading to hospitalization or surgical treatment, bleeding leading to a transfusion of less than 2 units of whole blood or red cells or any other bleeding event considered clinically relevant by the investigator.

The dabigatran dosing regimens were similar across the four trials. In RE-MOBILIZE, RE-MODEL, and RE-NOVATE, the first dose of dabigatran started at 75 or 110 mg. All subsequent doses were either 150 or 220 mg daily. In the RE-NOVATE trial, only the dabigatran 220 mg once-daily dose was evaluated *versus* enoxaparin. In both the RE-MODEL and RE-NOVATE studies, the first dabigatran dose was administered 1–4 hours after the surgery. In the RE-MOBILIZE study, the first dose of dabigatran was given 6–12 hours after surgery. While enoxaparin 40 mg once daily was initiated in the evening before surgery in the RE-MODEL and RE-NOVATE studies, in the RE-MOBILIZE study enoxaparin was given 30 mg twice daily starting 6–12 hours after the surgical procedure. The overall duration for VTE prophylaxis varied to reflect the current guideline recommendations for the population studied [Hirsh *et al.* 2008].

In the RE-MODEL trial, both the 150 mg and 220 mg regimens of dabigatran were statistically noninferior to enoxaparin for the primary endpoint of total VTE events and all-cause mortality (40.5%, $p = 0.017$; 36.4%, $p = 0.0003$; and 37.7%, respectively) [Eriksson *et al.* 2007a]. Symptomatic VTE during the treatment period was similar across the three groups. There was no difference in major bleeding rates between the doses of dabigatran 150 mg (1.3%), dabigatran

Table 2. Summary of clinical trials of dabigatran in thromboembolism prevention and treatment.

Name	Population	Number of patients	Design	Treatment regimen	Duration	Primary efficacy endpoint	Primary safety endpoint
RE-MODEL	TKR	2076	Randomized, Double Blind	Dabigatran 150 mg QD Dabigatran 220 mg QD Enoxaparin 40 mg SC QD	6–10 days	Total VTE events and all-cause mortality: 40.5% ($p = 0.017$) 36.4% ($p = 0.0003$) 37.7%	Major Bleeding 1.3% (NS) 1.5% (NS) 1.3%
RE-MOBILIZE	TKR	2615	Randomized, Double Blind	Dabigatran 150 mg QD Dabigatran 220 mg QD Enoxaparin 30 mg SC BID	12–15 days	33.7% ($p = 0.0009$) 31.1% ($p = 0.02$) 25.3%	0.6% (NS) 0.6% (NS) 1.4%
RE-NOVATE	THR	3494	Randomized, Double Blind	Dabigatran 150 mg QD Dabigatran 220 mg QD Enoxaparin 40 mg SC QD	28–35 days	8.6% ($p = 0.0001$) 6.0% ($p = 0.0001$) 6.7%	1.3% (NS) 2.0% (NS) 1.6%
RE-NOVATE 2	THR	2055	Randomized, Double Blind	Dabigatran 220 mg QD Enoxaparin 40 mg SC QD	28–35 days	7.7% ($p = 0.0001$) 8.8%	1.4% (NS) 0.9%
RE-COVER	Acute VTE (proximal DVT or PE)	2539	Randomized, Double Blind	Dabigatran150 mg BID Warfarin (INR goal 2-3)	6 months	Symptomatic VTE and VTE-associated death 2.4% ($p < 0.001$) 2.1%	Major Bleeding 1.6% (NS) 1.9%
RE-LY†	Non-valvular AF	18113	Blinded Dabigatran	Dabigatran 110 mg BID Dabigatran 150 mg BID Warfarin (INR 2-3)	2 years	Stroke or Systemic Embolism 1.54%/year ($p < 0.001$) 1.11%/year ($p < 0.001$) 1.71%/year	Major bleeding 2.87%/year ($p < 0.003$) 3.32%/year (NS) 3.57%/year

† Results represent revised study results.
AF, atrial fibrillation; BID, twice daily; DVT, deep vein thrombosis; INR, international normalized ratio; NS, nonsignificant; PE, pulmonary embolism; QD, once daily; SC, subcutaneous; THR, total hip replacement; TKR, total knee replacement; VTE, venous thromboembolism.

220 mg group (1.5%) and enoxaparin (1.3%). Clinically relevant nonmajor bleeding did not differ, and ranged from 5.3% to 6.8% in the three groups. Similarly, the rate of minor bleeding events ranged 8.4% to 9.9% of patients across the three groups and was not statistically different.

In the RE-MOBILIZE trial, the primary efficacy composite endpoint of total VTE events and all-cause mortality occurred in 33.7% of patients in the 150 mg dabigatran group ($p = 0.0009$), 31.1% in the 220 mg dabigatran group ($p = 0.02$), and in 25.3% of the enoxaparin group. Both dabigatran doses were statistically inferior to the enoxaparin regimen [Ginsberg *et al.* 2009]. Symptomatic VTE or death during the follow up period was similar across the three groups. Both major bleeding and clinically relevant nonmajor bleeding were not statistically different during treatment and ranged from 0.6% to 1.4% and 2.4% to 2.7%, respectively, across the three groups.

Patients undergoing total hip replacement surgery were evaluated in the RE-NOVATE and RE-NOVATE II studies [Eriksson *et al.* 2010, 2007b]. In RENOVATE trial, the rate of the primary efficacy endpoint in dabigatran 150 mg (8.6%) and 220 mg (6.0%) treated patients was statistically noninferior to the enoxaparin (6.7%, $p < 0.0001$) treated patients. Symptomatic VTE was rare during the treatment period and ranged from 0.4% to 0.9% across the three groups. There was no statistical difference between either dabigatran group with respect to major bleeding events, ranging from 1.3% to 2.0%, when compared with patients in the enoxaparin group. Clinically relevant nonmajor bleeding was not different and ranged from 3.5% to 4.7% across the three groups.

In the RE-NOVATE II trial, only dabigatran 220 mg once daily was compared with enoxaparin 40 mg once daily. The primary efficacy endpoint of total VTE events and all-cause mortality occurred in 7.7% of dabigatran-treated patients *versus* 8.8% of enoxaparin-treated patients, meeting the noninferiority criteria ($p < 0.0001$). Major bleeding events were similar between the two groups, and not statistically significant. These events occurred in 1.4% and 0.9% of patients in the dabigatran and enoxaparin groups, respectively.

Given the occurrence of adverse events seen in patients on another oral DTI, ximelagatran, patients who were receiving dabigatran were closely monitored for hepatic injury. In the orthopedic VTE prevention studies, there was no incidence of isolated liver enzyme elevations associated with either dabigatran dose as compared with enoxaparin [Ufer, 2010]. Benign elevations were noted in transaminase values. These changes were associated with either anesthesia or the surgical procedure itself. The incidence of ACS events was also low among dabigatran doses and enoxaparin. The low incidence of adverse events may support prolonged dabigatran regimens for VTE prevention [Eriksson *et al.* 2007b].

Acute venous thromboembolism treatment

The RE-COVER study compared dabigatran 150 mg twice daily with warfarin (dosed to achieve a target INR 2.0–3.0) in the early treatment of acute symptomatic VTE. Both study arms were preceded by at least 5 days of intravenous UFH or subcutaneous LMWH (Table 2) [Schulman *et al.* 2009]. Patients were assessed at 7 days and then monthly for the following 6 months. If symptoms of recurrent VTE occurred, patients were evaluated with compression ultrasonography or venography of the leg veins and ventilation–perfusion lung scanning, angiography, or spiral computed tomography of pulmonary arteries. The 6-month follow up occurred in 92% of dabigatran-treated and 92% of warfarin-treated patients.

Patients in the warfarin group were maintained within a therapeutic INR range 60% of the time during the study. The primary efficacy endpoint, defined as the composite of symptomatic VTE or VTE-associated death, occurred in 2.4% of dabigatran-treated patients *versus* 2.1% of warfarin-treated patients, meeting the criteria for noninferiority ($p < 0.001$). There were no differences between the two groups in the incidence of symptomatic VTE. While major bleeding was not statistically different between dabigatran and warfarin (1.6% *versus* 1.9%, respectively), clinically relevant nonmajor bleeding when combined with major bleeding was reduced in dabigatran patients (5.6% *versus* 8.8%; $p = 0.002$). Gastrointestinal hemorrhage was the only form of bleeding that showed an increased trend in the dabigatran group. The number of deaths and ACS events were similar in the two treatment groups. There was no evidence of liver toxicity associated with dabigatran.

Stroke prevention in atrial fibrillation

The PETRO dose-ranging trial identified two optimal dabigatran doses for patients with AF [Ezekowitz *et al*. 2007].

Following this dose-ranging trial, the RE-LY trial was a noninferiority trial designed to determine the long-term safety and efficacy of dabigatran 110 and 150 mg administered twice daily as compared with warfarin (INR goal 2.0-3.0) in patients with nonvalvular AF [Connolly *et al.* 2009] (Table 2). In addition, enrolled patients were required to have at least one addition thromboembolism risk factor of prior stroke, left ventricular ejection of less than 40%, New York Class II or higher heart failure, 75 years of age or older, or be aged 65 to 75 with diabetes mellitus, hypertension, or coronary artery disease. Dabigatran regimens were blinded to the investigators and patients while warfarin was managed in an open-label fashion. Patients in the warfarin group were maintained within a therapeutic INR range 64% of the time during the study. Patients were followed for a median of 2 years. The primary efficacy outcome was defined as the occurrence of stroke or systemic embolism. Stroke was defined as a sudden onset of focal neurologic deficit. Systemic embolism was defined as an acute vascular occlusion of an extremity or organ documented during surgery, autopsy, or with an objective imaging study. The dabigatran 150 mg twice daily regimen was statistically superior to warfarin in reducing the rate of stroke and systemic embolism, 1.11% per year *versus* 1.69% per year, respectively ($p < 0.001$). The dabigatran 110 mg twice-daily regimen was noninferior to warfarin with the primary endpoint occurring in 1.53% of patients per year ($p < 0.001$). The primary safety outcome was major bleeding defined as a reduction in the hemoglobin level of at least 20 g/l, transfusion of at least 2 units of blood, or symptomatic bleeding in a critical area or organ. The rate of major bleeding was statistically lower in the dabigatran 110 mg group (2.71% per year) compared with the warfarin group (3.36% per year, $p < 0.001$). There was no difference in the rate of major bleeding in the dabigatran 150 mg group (3.11% per year) compared with the warfarin group.

The RE-LY trial results were revised after the identification of additional primary efficacy and safety outcome events were discovered during routine clinical site closure. The revised results report the incidence of stroke or systemic embolism in 110 mg dabigatran-treated patients as 1.54% per year. The primary efficacy endpoint in 150 mg dabigatran-treated patients was unchanged. Warfarin-treated patients developed a stroke or systemic embolism at a rate of 1.71% per year. In addition, the rate of major bleeding was revised in 110 and 150 mg dabigatran-treated patients to 2.87% and 3.32% per year, respectively. In warfarin-treated patients the revised major bleeding rate was 3.57% per year [Connolly *et al*. 2010].

In a substudy of patients with previous stroke or transient ischemic attack, the rates of stroke or systemic embolism in dabigatran-treated patients were similar to warfarin-treated patients and not significantly different. The rate of major bleeding was significantly lower in patients on 110 mg (2.74%) of dabigatran and similar in those on 150 mg (4.15%) of dabigatran compared with those on warfarin (4.15%) [Diener *et al.* 2010].

The RE-LY trial outcomes were evaluated in relationship to each trial center's mean time in therapeutic range in warfarin-treated patients. The advantages of dabigatran in reducing vascular events, nonhemorrhagic events, and mortality were greater at sites with poor INR control than in those with good INR control [Wallentin *et al.* 2010].

Secondary prevention of cardiac events in acute coronary syndrome patients

The RE-DEEM trial was a phase II dose-finding trial combining dabigatran (50–150 mg twice daily) with dual antiplatelet therapy for the secondary prevention of ischemic events in patients stricken with ACS. RE-DEEM was designed as a safety study, evaluating the primary safety endpoint of major bleeding or clinically relevant minor bleeding episodes over 6 months. A dose-related bleeding risk was evident with the primary endpoint occurring in 3.5% (50 mg twice daily), 4.3% (75 mg twice daily), 7.9% (110 mg twice daily), and 7.8% (150 mg twice daily) of patients in the dabigatran groups as compared with 2.4% in the placebo group [Oldgren *et al*. 2009].

Rivaroxaban

Rivaroxaban is an oral, highly selective, direct, competitive inhibitor of factor Xa [Tersteegen and Burkhardt, 2007; Perzborn *et al*. 2005]. Inhibition of factor Xa leads to interruption of

the both intrinsic and extrinsic coagulation pathways, thus preventing thrombin generation and subsequent thrombus formation [Gulseth *et al.* 2008]. Rivaroxaban inhibits both free and fibrin-bound factor Xa which differentiates its action from LMWH or fondaparinux [Perzborn, 2009; Gerotziafas *et al.* 2005; Kubitza *et al.* 2005b]. Rivaroxaban exerts minimal effect on platelet function [Kubitza *et al.* 2006a, 2005a].

Pharmacokinetics

Rivaroxaban is absorbed rapidly after oral ingestion with a bioavailability of 80–100% (Table 1) [Kubitza *et al.* 2007c, 2006a, 2006b]. Maximum plasma levels are achieved 3 hours after administration, occurring in a dose-dependent manner [Kubitza *et al.* 2006a, 2005b, 2003]. Rivaroxaban has a low potential for drug-food interactions [Bayer Healthcare, 2009]. There is a slightly delayed and clinically insignificant higher maximum serum concentration in patients receiving rivaroxaban with meals or within 2 hours of eating [Gulseth *et al.* 2008; Kubitza *et al.* 2006b]. There is no specific antidote to antagonize the anticoagulant effect of rivaroxaban. Rivaroxaban undergoes both hepatic and renal elimination. Two thirds of the active compound is metabolized by the liver via the cytochrome P450 (CYP) 3A4 system and the remainder is excreted unchanged in urine via active secretion [Kubitza *et al.* 2006a; Weinz *et al.* 2004].

Rivaroxaban acts as a substrate of the transporter protein P-gp. Avoidance of strong CYP 3A4 and P-gp inhibitors (azole-antimyotics such as ketoconazole) and cautious use with concomitant CYP 3A4 and P-gp inducers is recommended due to the potential for changes in rivaroxaban serum concentration [Bayer Healthcare, 2009].

Rivaroxaban did not affect the inhibition of platelet aggregation associated with clopidogrel [Kubitza *et al.* 2007b]. Conversely, the combination of rivaroxaban and aspirin doubled bleeding time, as defined as the time taken for a standardized skin cut of fixed depth and length to stop bleeding [Kubitza *et al.* 2006a; Mielke, 1984].

There are no specific recommendations for dose adjustments in patients with mild, moderate, or severe renal or hepatic impairments. The manufacturer does not recommend the use of rivaroxaban in patients with an estimated creatinine clearance of less than 15 ml/min [Bayer Healthcare, 2009]. No dose adjustments are required in obese or underweight patients [Bayer Healthcare, 2009; Gulseth *et al.* 2008; Kubitza *et al.* 2007a]. In phase II dose-ranging studies, rivaroxaban showed a dose-dependent response with both aPTT and prothrombin time (PT) being prolonged. PT was found to be more sensitive and correlated closely with rivaroxaban's plasma concentrations [Kubitza *et al.* 2005c; Perzborn *et al.* 2005]. Coagulation monitoring is not recommended in clinical practice [Mahaffey, 2010; Bayer Healthcare, 2009; Turpie *et al.* 2009b; Eriksson *et al.* 2008; Gulseth *et al.* 2008; Kakkar *et al.* 2008; Lassen *et al.* 2008].

The most common adverse events associated with rivaroxaban included constipation, nausea, vomiting, pyrexia, anemia, wound secretion, decreased hemoglobin, dizziness, and insomnia. No specific antidote is available to antagonize the anticoagulant effect of rivaroxaban. Similar to dabigatran, the early use of activated charcoal is recommended for rivaroxaban overdose. In the event of bleeding, discontinuation of rivaroxaban and symptomatic treatment of the hemorrhage should be initiated [Bayer Healthcare, 2009].

Clinical evidence

Clinical studies have been designed to evaluate the efficacy and safety of rivaroxaban for VTE prophylaxis in hospitalized medically ill patients and in those undergoing major orthopedic surgeries. Rivaroxaban has also been studied in VTE treatment, thromboembolism prevention in AF patients, and as an adjunctive treatment with antiplatelet therapy in ACS (Table 3).

Venous thromboembolism prophylaxis

RECORD 1 and RECORD 2 evaluated rivaroxaban for VTE prophylaxis in total hip replacement surgery, while RECORD 3 and RECORD 4 enrolled patients requiring total knee replacement surgery [Turpie *et al.* 2009b; Eriksson *et al.* 2008; Kakkar *et al.* 2008; Lassen *et al.* 2008] (Table 3). In the RECORD trials, rivaroxaban 10 mg once daily, initiated 6–8 hours after surgery, was compared with enoxaparin either 40 mg once daily or 30 mg twice daily. In RECORD 1–3, enoxaparin was given the evening before surgery. In RECORD 4, enoxaparin was given 12–24 hours after wound closure. Total hip replacement patients were continued on thromboprophylaxis for 31–39 days in both treatment arms in RECORD 1. In RECORD 2, patients

Table 3. Summary of clinical trials of rivaroxaban in thromboembolism prevention and treatment.

Name	Population	Number of patients	Design	Treatment regimen/ duration	Duration	Primary efficacy endpoint	Primary safety endpoint
RECORD 1	THR	4433	Randomized, double-blind	Rivaroxaban 10 mg QD Enoxaparin 40 mg SC QD	31–39 days	DVT, Non-fatal PE, all-cause mortality 1.1% ($p < 0.001$) 3.7%	Major bleeding 0.3%(NS) 0.1%
RECORD 2	THR	2509	Randomized, double-blind	Rivaroxaban 10 mg QD Enoxaparin 40 mg SC QD	31–39 days 10–14 days	2.0% ($p < 0.0001$) 9.3%	<0.1%(NS) <0.1%
RECORD 3	TKR	2531	Randomized, double-blind	Rivaroxaban 10 mg QD Enoxaparin 40 mg SC QD	10–14 days	9.6% ($p < 0.001$) 18.9%	0.6%(NS) 0.5%
RECORD 4	TKR	3148	Randomized, double-blind	Rivaroxaban 10 mg QD Enoxaparin 30 mg SC BID	10–14 days	6.9% ($p < 0.0118$) 10.1%	0.7%(NS) 0.3%
EINSTEIN DVT	Acute symptomatic DVT	3449	Randomized, open label	Rivaroxaban 15 mg BID followed by 20 mg QD Warfarin (INR 2–3)	3, 6, or 12 months	Symptomatic, recurrent VTE 2.1% ($p < 0.001$) 3.0%	Major, clinically relevant non-major bleeding 8.1%(NS) 8.1%
EINSTEIN EXTENSION	Acute VTE; extended treatment (after initial 6–12 months of anticoagulation therapy)	1197	Randomized, double-blind	Rivaroxaban 20 mg QD Placebo	6 or 12 months	1.3% ($p < 0.001$) 7.1%	Major Bleeding 0.7%(NS) 0%
ROCKET AF	Nonvalvular AF	14264	Randomized, double-blind, double dummy, sham INR	Rivaroxaban 20 mg QD (15 mg QD if CrCl 30–49 ml/min) Warfarin (INR 2-3)	up to 4 years	Stroke or non-CNS systemic embolism 1.71% ($p < 0.001$) 2.16%	Major, clinically relevant non-major bleeding 14.91%(NS) 14.52%

AF, atrial fibrillation; ACS, acute coronary syndrome; BID, twice daily; CNS, central nervous system; CrCl, estimated creatinine clearance; DVT, deep vein thrombosis; INR, international normalized ratio; QD, once daily, NS, nonsignificant; SC, subcutaneous; THR, total hip replacement; TKR, total knee replacement; VTE, venous thromboembolism.

received rivaroxaban for 31–39 days while enoxaparin-treated patients received prophylaxis for only 10–14 days. Patients enrolled in RECORD 3 and RECORD 4 received prophylaxis for 10–14 days. The primary efficacy endpoint evaluated across these trials was the composite endpoint of any DVT, nonfatal PE, or all-cause mortality. The primary efficacy endpoint of DVT was detected using mandatory, bilateral venography. PE was detected with spiral computed tomography, perfusion–ventilation lung scintigraphy or pulmonary angiography. Autopsy was ordered for patients who died during the trial. The main safety outcome was the incidence of major bleeding during treatment period. Major bleeding was defined as fatal bleeding, bleeding into a critical organ, bleeding requiring re-operation or blood transfusion of 2 or more units of whole or packed cells, or clinically overt extra-surgical-site bleeding associated with a fall in hemoglobin of 20 g/l or more.

In the RECORD 1 trial intention-to-treat population, rivaroxaban was superior to enoxaparin for the primary efficacy endpoint of DVT, nonfatal PE, and all-cause mortality (1.1% *versus* 3.7%; $p < 0.001$). Symptomatic VTE during the treatment period and during the follow-up period was similar across both groups. The major bleeding rate was not statistically different in the rivaroxaban group *versus* the enoxaparin group (0.3% *versus* 0.1%; $p = 0.18$).

The RECORD 2 trial showed that extended rivaroxaban prophylaxis was more effective than short-term enoxaparin in lowering the primary efficacy endpoint (2.0% *versus* 9.3%; $p < 0.0001$) in the modified intention-to-treat population analysis. Symptomatic VTE was statistically reduced in rivaroxaban-treated patients (0.2%) compared with enoxaparin-treated patients (1.2%) during the treatment period ($p < 0.004$). Mean duration of rivaroxaban was 33.5 days and 12.4 days with enoxaparin. In both groups there was only one patient that experienced a major bleeding event.

The RECORD 3 clinical trial evaluated rivaroxaban VTE prophylaxis in total knee replacement patients. The primary composite efficacy endpoint of all DVT, nonfatal PE, and all-cause mortality in the modified intention-to-treat population was lower in rivaroxaban patients (9.6%) *versus* enoxaparin patients (18.9%), a statistically significant reduction ($p < 0.001$). Symptomatic VTE was reduced in the rivaroxaban group (0.7%) compared to the enoxaparin group (2.0%) during the treatment period ($p = 0.005$). The primary safety endpoint of major bleeding occurred infrequently in both rivaroxaban patients (0.6%) and enoxaparin-treated patients (0.5%), with the rates not statistically different ($p = 0.77$).

In the RECORD 4 modified intention-to-treat population, 6.9% of rivaroxaban patients developed the primary composite efficacy endpoint of DVT, nonfatal PE, and all-cause mortality *versus* 10.1% of enoxaparin patients ($p = 0.0118$). Symptomatic VTE during the treatment period and during the follow-up period did not differ between the two groups. The primary safety endpoint of major bleeding was similar in the two groups, occurring in 0.7% of rivaroxaban-treated patients compared with 0.3% of enoxaparin-treated patients ($p = 0.11$).

Liver function tests were closely monitored for signs of hepatic toxicity in all clinical trials. Both rivaroxaban- and enoxaparin-treated patients developed mild elevations in aspartate aminotransferase (AST) and alanine aminotransferase (ALT). ALT elevations reached three times the upper limit of normal in 1.3–2% of rivaroxaban-treated patients in the combined RECORD trials. This adverse effect did not appear to be dose-related [Turpie *et al.* 2009b; Eriksson *et al.* 2008; Kakkar *et al.* 2008; Lassen *et al.* 2008].

Acute venous thromboembolism treatment

Two phase III clinical studies investigated the efficacy and safety of rivaroxaban in patients with acute, symptomatic DVT (EINSTEIN-DVT) or PE (EINSTEIN-PE) [Einstein Investigators 2010; ClinicalTrials.gov identifier: NCT00439777] (Table 3). The EINSTEIN-PE trial is not yet completed. In the acute DVT study, rivaroxaban was initiated at 15 mg twice daily for 3 weeks followed by a fixed dose of 20 mg once daily for 3, 6, or 12 months. The comparator arm initiated enoxaparin 1 mg/kg twice daily followed by an oral vitamin K antagonist (VKA). The primary efficacy outcome was symptomatic recurrent VTE, defined as the composite of DVT and all PE. DVT was detected using either ultrasound or venography. PE was detected using a computed tomography scan or pulmonary angiography. The main safety outcome was the composite of major and clinically relevant nonmajor bleeding. Major bleeding was

clinically overt and associated with a fall in the hemoglobin level of 20 g/l or more, led to transfusion of two or more units of red cells, occurred in a critical site (retroperitoneal, intracranial), or contributed to death. Clinically relevant nonmajor bleeding was defined as overt bleeding not meeting the criteria for major bleeding but associated with medical intervention, unscheduled contact with a physician, interruption or discontinuation of study treatment, or associated with any other discomfort such as pain or impairment of activities of daily life [Einstein Investigators, 2010]. In the EINSTEIN-DVT trial analysis rivaroxaban was noninferior with respect to the primary efficacy outcome when compared with enoxaparin (2.1% *versus* 3.0%; $p < 0.001$). The rate of major and clinically relevant nonmajor bleeding in both groups (8.1%) was not statistically different ($p = 0.77$). In the rivaroxaban-treated patients, 73% of patients received pretreatment with UFH, LMWH, or fondaparinux for less than 2 days.

The EINSTEIN-EXTENSION trial, a secondary prevention study of recurrent symptomatic VTE, evaluated the relative efficacy and safety of rivaroxaban compared with placebo [Einstein Investigators, 2010]. Patients who completed 6–12 months of anticoagulation therapy in EINSTEIN-DVT or EINSTEIN-PE continued on rivaroxaban 20 mg daily or placebo for another 6–12 months. The primary efficacy outcome was symptomatic recurrent DVT and all fatal and nonfatal PE. The primary efficacy outcome occurred in 1.3% of rivaroxaban patients and 7.1% of placebo patients ($p < 0.001$). The primary safety outcome of major bleeding was not statistically different ($p = 0.11$), occurring in 0.7% of rivaroxaban-treated patients and not observed in placebo patients.

Stroke prevention in atrial fibrillation

The ROCKET AF trial enrolled patients with nonvalvular atrial fibrillation, comparing rivaroxaban 20 mg once daily with dose-adjusted warfarin (INR 2.0–3.0) [Mahaffey, 2010] (Table 3). Patients were eligible if they had AF with at least two additional risk factors for thromboembolism. The risk factors included a prior history of stroke, transient ischemic attack, or thromboembolus, congestive heart failure, hypertension, diabetes, or age 75 years or greater. Both rivaroxaban and warfarin regimens were blinded to patients and investigators. Rivaroxaban doses were reduced to 15 mg daily for patients with an estimated creatinine clearance between 30 and 49 ml/min. Patients receiving warfarin were within the desired INR range 57.8% of the time during the study. Patients were followed for 15 months. The primary endpoint of this study was the prevention of stroke and non-CNS (central nervous system) systemic embolism. Stroke was defined as any sudden, focal, idiopathic neurologic deficit resulting from a cerebrovascular cause and not reversible within 24 hours. Stroke was diagnosed using advanced brain imaging [Patel *et al*. 2010]. Non-CNS embolism was defined as an abrupt, vascular insufficiency associated with arterial occlusion not due to other likely causes [Patel *et al.* 2010].

In the predetermined statistical analysis rivaroxaban was evaluated for noninferiority using patients that were protocol compliant and considered to be on treatment. For patients on treatment, rivaroxaban was noninferior to warfarin in reducing the primary endpoint of stroke and systemic embolism, 1.71% per year *versus* 2.16% per year ($p < 0.001$). For the superiority analysis, rivaroxaban was evaluated using an intent-to-treat approach, which included all patients originally enrolled in the study. In the intent-to-treat population, rivaroxaban failed to show superiority over warfarin, with stroke or systemic embolism occurring 2.12% per year in rivaroxaban-treated patients compared with 2.42% per year in warfarin-treated patients ($p = 0.117$).

The primary safety endpoint included major and nonmajor clinically relevant bleeding. Major bleeding was defined as clinically overt bleeding leading to death, involving a critical organ, a fall in hemoglobin concentration of 20 g/l or more, or a transfusion of 2 or more units of packed red blood cells or whole blood. There were no differences in the rates of major and nonmajor clinically relevant bleeding between rivaroxaban (14.91%) and warfarin (14.52%) ($p = 0.442$).

Secondary prevention of cardiac events in acute coronary syndrome patients

The safety and efficacy of rivaroxaban in patients after an ACS was initially assessed in the ATLAS ACS-TIMI 46 clinical trial [Mega *et al*. 2009]. In this dose-ranging study the primary efficacy endpoint was death, myocardial infarction (MI), stroke, or severe recurrent ischemia requiring revascularization. Rivaroxaban total daily doses ranged from 5 to 20 mg. Rivaroxaban therapy was associated with a trend towards a reduction

Table 4. Pharmacokinetic features of drugs in development.

Parameter	Edoxaban	Betrixaban	LY517717	YM150	TAK-442
Target	Direct Factor Xa Inhibitor	Direct Factor Xa Inhibitor	Direct Factor Xa Inhibitor	Direct Factor Xa Inhibitor	Direct Factor Xa Inhibitor
Prodrug	No	No	No	No	No
Dosing	Oral once or twice daily	Oral twice daily	5–20 mg daily	Not reported	20–160 mg
Bioavailability (%)	50%	47%	82%	25–82%	Not reported
Food Effects	Low potential	Not reported	Not reported	Not reported	Not reported
Half-life (hours)	9–11 hours	19 hours	25 hours	Not reported	Not reported
Renal excretion (%)	35%	5–10%	Gastrointestinal	Not reported	Not reported
Coagulation Monitoring	None	None	None	None	Not reported
Antidote	None	None	None	None	Not reported
Interactions	Potent CYP3A4 Inhibitors**	Not reported	Not reported	Not reported	Not reported

**Cytochrome (CYP) P450 3A4 inhibitors include but are not limited to: ketoconazole, macrolide antibiotics, and protease inhibitors.
ACS, acute coronary syndrome; AF, atrial fibrillation; BID, twice daily; CV, cardiovascular; DVT, deep vein thrombosis; INR, international normalized ratio; MI, myocardial infarction; PE, pulmonary embolism; QD, once daily; VTE, venous thromboembolism.

in the composite efficacy endpoint supporting the hypothesis that oral anticoagulant therapy may be beneficial in the long-term management of ACS patients. The 2.5 and 5 mg twice-daily rivaroxaban dosing regimens emerged as the more favorable dosing regimens to combine with aspirin or aspirin and a thienopyridine.

Apixaban

Apixaban is a potent oral, reversible, direct factor Xa inhibitor. Apixaban inhibits both free and clot-bound factor Xa without significantly affecting platelet aggregation [Ufer *et al.* 2010; Wong *et al.* 2008]. Apixaban is a follow-up compound to razaxaban but with a more favorable safety profile.

Pharmacokinetics

Apixaban has a rapid onset of action with peak plasma concentrations occurring within 30 minutes to 2 hours of ingestion (Table 1) [Raghavan *et al.* 2009]. Approximately 66% of an oral apixaban dose is bioavailable. Apixaban is eliminated in a biphasic manner, with approximately 30% of an oral dose excreted in the urine with the remaining 70% excreted in the feces. Consequently, apixaban has a half-life of 8–15 hours. Plasma steady state is typically reached within 3 days of oral dosing. Apixaban's pharmacokinetics are not significantly affected by co-administration with digoxin [Frost *et al.* 2007].

Adverse events reported with apixaban in orthopedic patients include nausea, vomiting, and constipation. Adverse events reported with apixaban in atrial fibrillation patients include cardiac arrhythmias, heart failure, gastrointestinal, and respiratory disorders. There have been no reported organ toxicities or liver function test abnormalities associated with its use. Currently, there is no antidote available to reverse the effects of apixaban.

Clinical evidence

Apixaban has been evaluated in thromboprophylaxis following orthopedic surgery, secondary prevention of VTE, ACS, and stroke prevention in atrial fibrillation (Table 5).

Prophylaxis of venous thromboembolism

The APROPOS trial investigated apixaban dosing for VTE prophylaxis following total knee replacement surgery [Lassen *et al.* 2007]. APROPOS was a multicenter trial evaluating once-daily and twice-daily apixaban dosing (5, 10, or 20 mg total daily doses) compared with enoxaparin (30 mg twice daily) or open-label warfarin (titrated to an INR of 1.8–3.0). Both apixaban and enoxaparin were given 12–24 hours after surgery, while warfarin was given the night of surgery. The primary efficacy endpoint was the incidence of total VTE and all-cause mortality, with VTE detected using bilateral venography. In apixaban-treated patients, the primary efficacy outcome was not statistically different from those treated with enoxaparin or warfarin. The primary safety endpoint, major bleeding, was rare and ranged from

0.0% to 3.3% in the apixaban groups. The authors concluded that apixaban 2.5 mg twice daily 12–24 hours after surgery offered the most promising benefit–risk profile to move forward into phase III trials.

ADVANCE-1, ADVANCE-2, and ADVANCE-3 were double-blind clinical trials evaluating apixaban for VTE prophylaxis in orthopedic surgery patients [Lassen *et al.* 2010a, 2010b, 2009] (Table 5). In ADVANCE-1 patients received either apixaban 2.5 mg twice daily or enoxaparin 30 mg twice daily over 10–14 days with both drugs initiated 12–24 hours after total knee replacement surgery. In the ADVANCE-2 trial apixaban 2.5 mg twice daily 12–24 hours after wound closure was compared with enoxaparin 40 mg initiated 12 hours before surgery and continuing once daily for 10–14 days after total knee replacement surgery. In ADVANCE-3 patients requiring thromboprophylaxis after hip replacement surgery received either apixaban 2.5 mg twice daily or enoxaparin 40 mg once daily, initiated 12 hours before surgery, for 35 days.

In these trials the primary efficacy outcome was a composite of asymptomatic and symptomatic VTE or all-cause death. Clinically suspected DVT was detected using ultrasonography or venography. Asymptomatic DVT was assessed using bilateral venography. PE was detected using ventilation–perfusion scanning, spiral computed tomography, or pulmonary angiography. The primary safety outcome was the composite of major bleeding and clinically relevant nonmajor bleeding. Major bleeding was defined as clinically overt bleeding with a decrease in hemoglobin of 20 g/l or more, requiring a transfusion of 2 or more units of packed red cells, occurring in a critical site, into an operated joint, intramuscular with compartment syndrome, or requiring operation or intervention, or fatal. Nonmajor clinically relevant bleeding was defined as acute clinically overt bleeding that included epistaxis that required physician visit or intervention, gastrointestinal bleeding, hematuria, unusual bruising/ecchymosis, hematoma associated with a surgical wound, or hemoptysis.

In ADVANCE-1 the composite endpoint of asymptomatic and symptomatic VTE or all-cause death occurred in 9.0% and 8.8% of patients treated with apixaban and enoxaparin, respectively. While the incidence of the primary

Table 5. Summary of clinical trials of apixaban in thromboembolism prevention and treatment.

Name	Population	Number of patients	Design	Treatment regimen	Duration	Primary efficacy endpoint	Primary safety endpoint
ADVANCE 1	TKR	3195	Randomized, double-blind	Apixaban 2.5 mg BID Enoxaparin 30 mg SC BID	10–14 days	Symptomatic and asymptomatic VTE and all-cause mortality 9.0% ($p = 0.06$) 8.8%	Major bleeding, clinically relevant nonmajor 2.9% ($p = 0.03$) 4.3%
ADVANCE 2	TKR	3057	Randomized, double-blind	Apixaban 2.5 mg BID Enoxaparin 40 mg QD	10–14 days	15.1% ($p < 0.0001$) 24.4%	3.5% ($p = 0.09$) 4.8%
ADVANCE 3	THR	5407	Randomized, double-blind	Apixaban 2.5 mg BID Enoxaparin 40 mg QD	35 days	1.4% ($p < 0.001$) 3.9%	4.8% (NS) 5.0%
AVERROES	Nonvalvular AF	5600	Randomized, double-blind	Apixaban 2.5–5 mg BID Aspirin 81–324 mg QD	36 months	1.6% per year (NS) 3.6% per year	1.4% per year 1.2% per year

efficacy outcome was similar in both groups, events were lower than anticipated with apixaban failing to meet the predefined criteria for noninferiority ($p = 0.06$). Symptomatic VTE occurred with equal frequency between the groups. The rate of combined major and nonmajor clinically relevant bleeding events was significantly lower in apixaban-treated patients (2.9%) when compared with enoxaparin-treated patients (4.3%) ($p = 0.03$).

In ADVANCE-2 apixaban significantly reduced the primary efficacy endpoint of asymptomatic and symptomatic VTE or all-cause death (15.1%) compared with the enoxaparin group (24.4%), meeting the statistical criteria for superiority ($p < 0.0001$). Symptomatic VTE was similar between the groups. The combined safety endpoint of major and nonmajor clinically relevant bleeding was not statistically significant between apixaban-treated (3.5%) and enoxaparin-treated (4.7%) patients.

In ADVANCE-3, the rate of the primary efficacy endpoint was reduced in apixaban-treated patients (1.4%) compared with enoxaparin-treated patients (3.9%), meeting the criteria for superiority ($p < 0.001$). Symptomatic VTE occurred infrequently during the treatment period, occurring in 0.1% and 0.4% of patients in the apixaban and enoxaparin groups, respectively. There was no statistical difference between the apixaban (4.8%) and the enoxaparin group (5.0%) with respect to the combined endpoint of major bleeding and clinically relevant nonmajor bleeding events.

In ADVANCE-1, ADVANCE-2, and ADVANCE-3, liver function tests were closely monitored for signs of hepatic toxicity. During treatment ALT/AST elevations greater than three times the upper limit of normal ranged from 0.3% to 1.3% of apixaban-treated patients, across the three trials. Enoxaparin-treated patients developed similar elevation rates ranging from 1% to 1.6%, across the three trials [Lassen *et al.* 2010a, 2010b, 2009].

Acute venous thromboembolism treatment

The BOTTICELLI DVT study was a dose-ranging trial examining the safety and efficacy of apixaban for DVT treatment [Büller, 2008]. Patients were randomized to treatment with apixaban or LMWH followed by a VKA. Apixaban treatment was divided into 5 mg twice daily, 10 mg twice daily, and 20 mg once daily subgroups. Tinzaparin, enoxaparin once daily or twice daily, and fondaparinux were considered acceptable LWMHs and given at a fixed dose until two INR measurements greater than 2.0 were observed at least 24 hours apart. Acceptable VKAs were warfarin, acenocoumarol, and phenprocoumon. VKA doses were titrated to an INR within a range of 2–3. The primary efficacy outcome was the rate of symptomatic recurrent VTE or asymptomatic VTE. Symptomatic recurrent VTE included all recurrent DVT and all fatal and nonfatal PE, detected using objective testing. Asymptomatic VTE was defined as deterioration in thromboembolism burden resulting in an increase in the residual diameter of at least one vein after compression ultrasonography or a decrease in an individual lung lobe after perfusion lung scan when compared with baseline.

The primary efficacy outcome occurred in 4.7% of all three apixaban-treated groups compared with 4.2% in the LMWH/VKA group. The primary safety endpoint was the composite of major and clinically relevant nonmajor bleeding. The primary safety outcome occurred in 7.3% of patients treated with apixaban *versus* 7.9% of LMWH/VKA treated patients. The authors concluded that apixaban 10 mg twice daily would be appropriate for acute VTE treatment while 5 mg twice daily would more appropriate for long-term VTE management.

Stroke prevention in atrial fibrillation

The AVERROES trial evaluated the efficacy and safety of apixaban for secondary thromboembolism prevention in AF patients (Table 5). Patients enrolled were over 50 years, had at least one additional thromboembolism risk factor, and were unable to take, were intolerant, or unable to adhere to warfarin therapy [Connolly *et al.* 2011; Eikelboom *et al.* 2009]. Patients received apixaban 5 mg twice daily or aspirin 81–324 mg once daily. The apixaban dose was reduced to 2.5 mg twice daily in patients who met two of the following criteria: age (80 years or older), low body weight (less than 60 kg), or a serum creatinine indicative of renal dysfunction (greater than 1.5 mg/dl).

The primary efficacy outcome of stroke or systemic embolism occurred in 1.6% per year of apixaban-treated patients compared with 3.6% per year of aspirin-treated patients. This risk reduction (54%) was statistically significant and

occurred without a corresponding increase in major bleeding, clinically relevant nonmajor bleeding, or intracranial hemorrhage. The data and safety monitoring board determined a significant benefit with apixaban *versus* aspirin and the trial was ended prematurely.

Secondary prevention of cardiac events in acute coronary syndrome patients

The APPRAISE trial was a dose-ranging study evaluating apixaban for prevention of recurrent ischemic events after ST-elevation myocardial infarction (STEMI) and non-ST elevation myocardial infarction (NSTEMI) [APPRAISE steering committee and investigators, 2009]. Patients were eligible for enrollment if they experienced either STEMI or NSTEMI within the previous 7 days. Then acute management patients received one of four apixaban doses (2.5 mg twice daily, 10 mg twice daily, 10 mg once daily, or 20 mg once daily) over 6 months. Nearly all patients received concurrent treatment with aspirin and over 75% received additional clopidogrel. The primary efficacy endpoint consisted of cardiovascular death, MI, severe recurrent ischemia, or ischemic stroke. Although more placebo-treated patients developed the primary efficacy outcome (8.0%) *versus* either apixaban 2.5 mg twice daily (7.6%) or apixaban 10 mg twice daily (6.0%), the result was not statistically significant. The primary safety endpoint was the incidence of major or clinically relevant nonmajor bleeding. Major bleeding included those events that were fatal, occurred in a critical location (intracranial, intraspinal, intraocular, retroperitoneal, intraarticular, intramuscular with compartment syndrome, or pericardial), or were associated with a fall in hemoglobin of 2 g/dl, or a transfusion of 2 or more units of packed red blood cells. Clinically relevant nonmajor bleeding was defined as bleeding that required medical or surgical intervention. An interim analysis showed a dose-dependent increase in bleeding risk that forced the discontinuation of the groups receiving a total daily apixaban dose of 20 mg. The primary safety endpoint of major or clinically relevant nonmajor bleeding occurred in 5.7% of the apixaban 2.5 mg twice-daily group, 7.9% of the 10 mg once-daily apixaban group, and 3.0% in the placebo group.

The APPRAISE 2 trial was a follow-up study intended to evaluate apixaban 5 mg twice daily *versus* placebo in ACS patients already receiving mono or dual antiplatelet therapy. The primary efficacy outcome was the time to the first occurrence of cardiovascular death, nonfatal MI, or ischemic stroke. The trial was discontinued due to a significant increase in bleeding seen in patients taking apixaban. Evaluation of the data is pending completion. The increased bleeding risk was not offset by a decrease in ischemic events.

Ongoing trials with novel agents

There are ongoing clinical trials with dabigatran, rivaroxaban, and apixaban in assorted indications and in various stages of development and completion (Table 6).

Dabigatran in being evaluated in acute VTE treatment (RE-COVER II) and in secondary prevention of acute VTE in patients who have completed 6 months of dabigatran or warfarin therapy (RE-MEDY and RE-SONATE). RE-COVER II duplicates the RE-COVER trial. RE-MEDY will evaluate 18 months of extended dabigatran treatment in reducing recurrent VTE and VTE related death in patients who have received an initial 3-6 months of approved therapy. RE-SONATE will evaluate 6 months of extended dabigatran treatment in reducing symptomatic recurrent VTE in patients who have received an initial 6-18 months of VKA therapy [RE-COVER, 2010, ClinicalTrials.gov identifier: NCT00680186; RE-MEDY, 2010, ClinicalTrials.gov identifier: NCT00329238; RE-SONATE, 2010, ClinicalTrials.gov identifier: NCT00558259].

Rivaroxaban is being evaluated in a large phase III clinical trial (ATLAS ACS 2-TIMI 51) for secondary prevention of ACS in patients who are treated concurrently with aspirin and thienopyridine. Rivaroxaban 2.5 and 5 mg administered twice daily is being compared with placebo for at least 6 months [ATLAS ACS 2-TIMI 51, 2010, ClinicalTrials.gov identifier: NCT00809965].

The MAGELLAN phase III clinical trial is designed to compare the efficacy and safety of oral rivaroxaban extended thromboprophylaxis (up to 39 days) with short-term (up to 14 days) enoxaparin therapy in hospitalized, medically ill patients [MAGELLAN, ClinicalTrials.gov identifier: NCT00571649]. The primary efficacy outcome measured is the composite of any VTE and death up to day 35. The primary safety outcome is the composite of major and nonmajor clinically relevant bleeding rates. Patient enrollment in this

Table 6. Ongoing clinical trials with novel agents.

Name	Population	Design	Treatment regimen	Duration	Primary efficacy endpoint
RE-COVER-2	Acute, symptomatic DVT/PE	Randomized, double-blind	Dabigatran 150 mg BID Warfarin (INR 2–3)	6 months	Recurrent symptomatic VTE and VTE-associated death
RE-MEDY	3–6 months of anticoagulant therapy	Randomized, double-blind	Dabigatran 150 mg BID Warfarin (INR 2–3)	6–36 months	VTE and VTE-associated death
RE-SONATE	Extended VTE prevention after 6–18 months of VKA therapy	Randomized, double-blind	Dabigatran 150 mg BID Placebo	6 months	Recurrent DVT and all-PE
EINSTEIN PE	Acute symptomatic PE	Randomized, double-blind	Rivaroxaban 15 mg BID/20 mg QD Enoxaparin/VKA	3, 6, or 12 months	Recurrent symptomatic VTE
ATLAS ACS 2-TIMI 51	Recent ACS	Randomized, double-blind	Rivaroxaban 2.5 or 5 mg BID Placebo	6 months	CV death, MI, or stroke
MAGELLAN	VTE prophylaxis in acute medical illness	Randomized, double-blind	Rivaroxaban 10 mg QD Duration: 31–39 days Enoxaparin 40 mg SC QD	6–14 days	Total VTE and death
AMPLIFY	Acute DVT/PE treatment	Randomized, double-blind	Apixaban 10 mg BID/ 5 mg BID Enoxaparin/Warfarin	6 months	VTE recurrence or death
AMPLIFY-EXT	VTE secondary prevention after initial anticoagulant therapy	Randomized, double-blind	Apixaban 5 mg BID/ 2.5 mg BID Placebo	12 months	VTE recurrence or death
ADOPT	VTE prophylaxis in acute medical illness	Randomized, double-blind	Apixaban 2.5 mg BID Enoxaparin 40 mg QD/Placebo	30 days	Composite VTE and VTE-related death
ARISTOTLE	Non-valvular AF	Randomized, double-blind	Apixaban 5 mg BID Warfarin (INR 2–3)	Up to 39 months	Ischemic, hemorrhagic stroke, or systemic embolism

AF, atrial fibrillation; ACS, acute coronary syndrome; BID, twice daily; CV, cardiovascular; DVT, deep vein thrombosis; INR, international normalized ratio; PE, pulmonary embolism; QD, once daily; VTE, venous thromboembolism.

study, targeting over 8000 patients, has been completed.

The AMPLIFY and AMPLIFY-EXT trials are currently recruiting patients [AMPLIFY, 2010, ClinicalTrials.gov identifier: NCT00643201; AMPLIFY-EXT, 2010, ClinicalTrials.gov identifier: NCT00633893]. AMPLIFY will compare apixaban 10 mg twice daily followed by 5 mg twice daily to enoxaparin 1 mg/kg twice daily with concurrent warfarin (INR 2.0–3.0) for 6 months duration in the acute management of VTE. AMPLIFY-EXT will enroll patients who have completed an intended treatment of DVT or PE. Patients will be randomized to apixaban 2.5 mg twice daily, 5 mg twice daily, or placebo for 12 months. Both studies will evaluate patients for the primary endpoint of VTE recurrence or death.

ARISTOTLE is an ongoing, head-to-head comparison of apixaban 5 mg twice daily *versus* warfarin in patients with atrial fibrillation [Lopes *et al*. 2010]. The primary efficacy endpoint is the composite of ischemic or hemorrhagic stroke and systemic embolism. Eligible patients have a history of AF and at least one other prespecified risk factor for stroke. Warfarin doses are titrated to an INR range 2.0–3.0. The trial is scheduled to finish in April 2011 [ARISTOTLE, 2010, ClinicalTrials.gov identifier: NCT00412984].

Apixaban for the prevention of thrombosis-related events in patients with acute medical illness (The ADOPT trial) is currently enrolling patients [ADOPT, 2010, ClinicalTrials.gov identifier: NCT00457002]. This phase III clinical trial is designed to establish the difference between apixiban dosed 2.5 mg twice daily for 30 days and 40 mg enoxaparin daily for 6–14 days in preventing DVT and PE in patients hospitalized for acute medical illness. The primary efficacy outcome measured is the composite of VTE and VTE-related death. The primary safety endpoint includes the occurrence of all-cause mortality, major bleeding and clinically relevant nonmajor bleeding.

Other novel agents

There are several factor Xa inhibitors still in clinical development and include edoxaban, betrixaban, YM150, LY517717, and TAK-442 (Table 4).

The ENGAGE AF-TIMI 48 trial is investigating edoxaban (Daiichi Sankyo, LTD) safety and efficacy *versus* warfarin in approximately 20,000 patients with AF. The primary efficacy endpoint is the composite of stroke and systemic embolism. The primary safety endpoint is the occurrence of major bleeding. Patients will receive treatment for 24 months [ENGAGE AF-TIMI 48, 2010, ClinicalTrials.gov identifier: NCT00781391]. The HOKUSAI VTE trial is evaluating edoxaban's safety and efficacy in patients with DVT or PE. Patients will receive initial treatment with either UFH or enoxaparin, followed by treatment with either warfarin or edoxaban. The primary efficacy endpoint is the composite of symptomatic recurrent DVT, and nonfatal and fatal PE. The primary safety endpoint is the composite of major and clinically relevant nonmajor bleeding. Treatment will last 12 months [HOKUSAI VTE, 2010, ClinicalTrials.gov identifier: NCT00986154].

The EXPERT trial evaluated betrixaban (Portola, Inc.) safety and efficacy compared with enoxaparin in patients undergoing total knee replacement [Turpie *et al*. 2009a]. The primary efficacy outcome was the composite of venography evaluated DVT, systemic proximal DVT, or PE. The incidence of primary efficacy endpoint was comparable across patients receiving betrixaban 15 mg (20%), betrixaban 40 mg (15%), or enoxaparin patients (10%). The primary safety endpoint was the composite of major and clinically relevant nonmajor bleeding and increased in a dose-related fashion, betrixaban 15 mg (0%), 40 mg (2.3%), when compared with enoxaparin (4.6%). The EXPLORE Xa trial evaluated the safety of oral betrixaban therapy in patients with nonvalvular atrial fibrillation and at least one additional risk factor for stroke [Ezekowitz, 2010]. Patients received betrixaban 40, 60, or 80 mg once daily or dose-adjusted warfarin. The incidence of major or clinically relevant nonmajor bleeding was dose dependant occurring in 0.8%, 3.9%, 3.9%, and 5.5 % of patients in the betrixaban 40, 60, and 80 mg and warfarin groups, respectively. There are studies planned to investigate betrixaban in VTE treatment [Turpie, 2010].

YM150 (Astellas, Inc.) was compared with enoxaparin for efficacy and safety in preventing VTE after total hip replacement surgery [Eriksson *et al.* 2007c]. The primary efficacy endpoint

was the occurrence of VTE detected using bilateral venography. YM150 treated patients developed VTE at rates ranging from 19% to 52% across the four dose regimens. Enoxaparin-treated patients developed VTE at a rate of 39%. There were no major bleeding events reported in either YM150 or enoxaparin- treated patients. YM continues to be evaluated for VTE prophylaxis in patient with medical illness, orthopedic and abdominal surgery as well as for prevention of stroke and recurrent ischemic events in patients with AF and ACS.

A phase II study compared six LY517717 (Eli Lilly, Inc.) doses with enoxaparin in acute VTE [Agnelli *et al*. 2005]. The composite endpoint of proximal, distal DVT, and PE ranged from 17.1% to 24% in patients treated with the three highest LY517717 doses. The primary safety endpoint was the composite of major and minor bleeding and ranged from 0.9% to 1.0%. LY517717 will be evaluated for VTE prophylaxis in orthopedic surgery.

TAK-442 (Takeda, LTD) has been compared in a range of daily doses (20–160 mg) with enoxaparin for thromboprophylaxis after total knee replacement [Weitz *et al.* 2009]. TAK-442 is being investigated in a dose-ranging trial in patients with ACS receiving standard antiplatelet therapy.

Summary

Dabigatran, rivaroxaban, and apixaban have performed comparably, and in some instances, better than current anticoagulant options in the management of MI, stroke, and VTE, the three leading causes of cardiovascular death [Anderson and Wheeler, 1992]. Other agents such as edoxaban, betrixaban, YM150, LY517717, and TAK-442 offer similar future promise. These medications have the important advantages of oral administration which is more convenient and likely to improve patient compliance compared with parenteral anticoagulants. Meticulous blood parameter monitoring is no longer required. Carefully considered anticoagulant dose adjustments can be eliminated, saving both patient and clinician time. Patients' lifestyles can be unshackled since these agents have fewer adverse events and are free from many food and drug interactions. Novel anticoagulants have generated a great deal of excitement among practitioners who have been burdened with the limitations of UFH, LMWH, and warfarin.

There are, however, important limitations with these new agents. They do not eliminate or remove the underlying causes generating thrombosis. Questions remain regarding appropriate dosing in the elderly, in organ dysfunction, and with concomitant antiplatelet therapy. There is lack of an antidote to the anticoagulant effect of these newer orally bioavailable agents. Controversy and debate may ensue when prescribed in patient populations, such as those with mechanical heart valves and thrombophilias, where no study data exist. Surgical and invasive procedures add additional levels of complexity where therapy may be continued, interrupted, or replaced with short-term parenteral or 'bridge' therapy.

The cost of these novel agents will be greater than the cost of current anticoagulants and associated monitoring. For an uninsured patient the out of pocket expense for dabigatran and rivaroxaban ranges from approximately US$250 to US$500 for a 30-day supply, respectively. However, the reduction in adverse outcomes may reduce the total cost of patient care. A recent cost-effectiveness analysis of 10,000 atrial fibrillation patients found that dabigatran 150 mg twice daily yields an additional 0.56 quality-adjusted life years compared with warfarin [Freeman *et al.* 2011]. The incremental cost effectiveness ratio was US$45,372 per quality-adjusted life year with dabigatran when compared with warfarin. This satisfies the threshold of US$50,000 per quality-adjusted life year that most policymakers use as a reasonable measure of the value of an intervention. Therapy, therefore, may require a value judgment for patient and physician. Those patients already on warfarin with excellent INR control may not have much to gain by switching to a novel agent.

The efficacy and safety benefits of novel anticoagulants have been confirmed in small populations and within the narrow structure of clinical trial eligibility. Performance now must be translated to the more complex patients seen in routine practice.

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Conflict of interest statement

The authors declare that they have no conflicts of interest.

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