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Novel Oral Factor Xa and Thrombin Inhibitors in the Management of Thromboembolism

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Keywords

anticoagulants, factor IIa inhibitors, factor Xa inhibitors, thrombin inhibitors

Abstract

The last decade has seen the evaluation of several new oral anticoagulants that directly target thrombin or activated factor X (FXa). All demonstrate a rapid onset of action, a low potential for food and drug interactions, and a predictable anticoagulant effect that obviates the need for routine coagulation monitoring. Those agents at the most advanced stages of clinical development are a direct thrombin inhibitor, dabigatran, and direct FXa inhibitors, rivaroxaban and apixaban. Dabigatran and rivaroxaban are approved in more than 70 countries for prevention of venous thromboembolism in patients undergoing elective hip or knee arthroplasty, and apixaban is being considered for approval by regulatory agencies for this indication. Dabigatran was shown in a large phase III trial to be more effective and safer than warfarin for the prevention of stroke or systemic embolism in patients with atrial fibrillation and has recently been approved for this indication. Edoxaban, an oral FXa inhibitor, is also being evaluated in phase III clinical trials. This review summarizes the pharmacology, clinical trial results, and future role of the new oral anticoagulants in clinical practice.

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VKA: vitamin K antagonist

FIIa: activated factor II

FXa: activated factor X

DTI: direct thrombin inhibitor

VTE: venous thrombocmbolism

AF: atrial fibrillation

INTRODUCTION

Unfractionated heparin and warfarin have been available for more than 50 years but have important limitations. Several new parenteral anticoagulants, including low-molecular-weight heparins and the synthetic pentasaccharide fondaparinux, have been introduced as replacements for unfractionated heparin, but the development of new oral agents to replace warfarin and other vitamin K antagonists (VKAs) has been much slower. Efforts to find a replacement for VKAs have focused on the development of nonpeptidic, orally available, small molecules that directly inhibit one of two key serine proteases in the coagulation cascade, thrombin [activated factor II (FIIa)] and activated factor X (FXa). Dabigatran etexilate, a direct thrombin inhibitor (DTI), and rivaroxaban, a selective FXa inhibitor, are approved in more than 70 countries for the prevention of venous thromboembolism (VTE) in patients undergoing hip or knee arthroplasty. In addition, the recently reported RE-LY and RE-COVER trials comparing dabigatran with warfarin for stroke prevention in atrial fibrillation (AF) and for the treatment and secondary prevention of VTE (1, 2), respectively, and the EINSTEIN trials comparing rivaroxaban with warfarin for the treatment and secondary prevention of VTE (3, 4), demonstrate the potential of the new oral anticoagulants to replace VKAs for long-term treatment. Two other oral factor Xa inhibitors, apixaban and edoxaban, are in advanced stages of clinical development but neither has yet been approved for use.

In this article, we review the limitations of the VKAs that prompted the development of new oral agents, summarize the pharmacological characteristics of the new oral anticoagulants, critically review the results of phase III randomized controlled trials that have evaluated their effectiveness, and evaluate the opportunities for new oral anticoagulants in different clinical indications.

LIMITATIONS OF VITAMIN K ANTAGONISTS

VKAs, such as warfarin, are the only orally active anticoagulants that are licensed for long-term use, but they have important limitations. VKAs have a slow onset of action, a narrow therapeutic window, and an unpredictable anticoagulant effect resulting from multiple food and drug interactions and genetic polymorphisms that affect drug metabolism (CYP2C9) and vitamin K turnover (VKORC1). Because VKAs have a slow onset of action, patients who require an immediate anticoagulant effect require bridging therapy with a rapidly acting agent (e.g., heparin). Because VKAs interact with food and drugs, patients must take dietary precautions, and prescribers must take special care when modifying concomitant drug therapy. Because of their unpredictable anticoagulant effects, VKAs require routine coagulation monitoring and dose adjustment to maintain the international normalized ratio (INR) within the target range (5).

The need for bridging anticoagulation, dietary and drug restrictions, and routine coagulation monitoring is inconvenient for patients and costly for the health care system, and so it has contributed to the underuse of VKAs. Even when VKAs are appropriately used for stroke prevention in patients with AF, the INR is frequently outside of the therapeutic range, leading to ineffective anticoagulation or increased bleeding risk (6). Poor anticoagulant control in patients with AF receiving VKA therapy for stroke prevention (where "poor" control is defined as <60% of the time in a target INR range of 2–3) doubles the frequencies of stroke, major bleeding, and death compared with those achieving good control (>75% of the time with an INR of 2–3) (7). An effective and safe replacement for VKAs with a more rapid onset of action, a low potential for food and drug interactions, and a predictable anticoagulant effect that obviates the need for routine coagulation monitoring is urgently required.

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FEATURES OF NOVEL ORAL ANTICOAGULANTS

The new oral anticoagulants in the most advanced stages of development inhibit either thrombin or FXa (**Figure 1**).

Thrombin plays a central role in blood coagulation and thrombus (clot) formation by converting fibrinogen to fibrin and amplifying its own generation by feedback activation of factors V, VIII, and XI. Thrombin also is the most potent platelet agonist. DTIs directly neutralize thrombin by occupying the catalytic binding site, fibrinogen binding site, or both. DTIs also inhibit both fluid-phase and fibrin-bound thrombin. Clinical results with parenteral DTIs (e.g., hirudin, bivalirudin, argatroban) and a previously developed oral DTI (ximelagatran) validate thrombin as a target for new oral anticoagulants (8, 9).

FXa, which is located at the junction of the intrinsic and extrinsic pathways, is another target for new oral anticoagulants. FXa binds to FVa on the surface of activated platelets to form the prothrombinase complex, which converts prothrombin to thrombin. Inhibitors of FXa attenuate thrombin generation, thereby preventing the conversion of fibrinogen to fibrin. Oral FXa inhibitors bind directly to the active site of FXa and block the interaction with its substrate. In contrast to indirect FXa inhibitors, such as fondaparinux, direct FXa inhibitors inactivate free FXa and FXa incorporated within the prothrombinase complex equally well. Clinical results with the parenteral agent, fondaparinux, validate FXa as a target for new oral anticoagulants (10, 11).

Advantages of the new oral anticoagulants over VKAs include a rapid onset of action, no significant food interactions, low potential for drug interactions, and a predictable anticoagulant effect that obviates the need for routine coagulation monitoring (**Table 1**). Because of their rapid onset of action, the new oral anticoagulants have the potential to be used both in acute and chronic settings. The pharmacological characteristics of the new oral anticoagulants that are most advanced in clinical development are compared in **Table 2**.

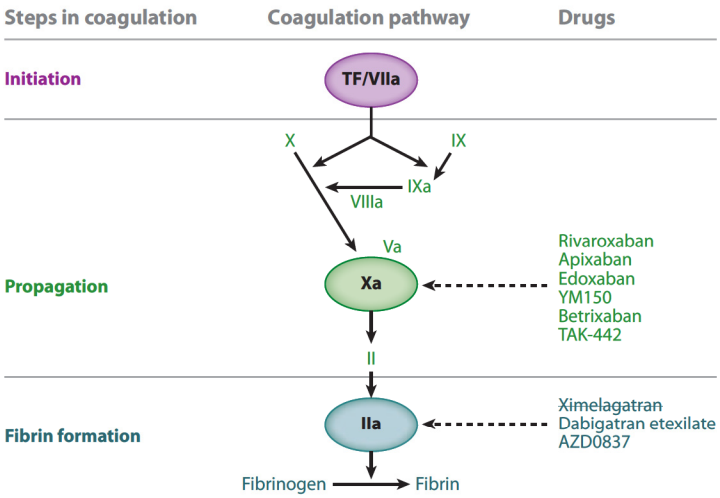

Figure 1

New oral anticoagulants and their targets in the coagulation pathway.

DIRECT THROMBIN INHIBITORS

Ximelagatran, the prodrug of melagatran, was the first orally available small-molecule reversible DTI to undergo clinical evaluation. Although ximelagatran proved to be an effective oral anticoagulant, prolonged therapy with ximelagatran resulted in idiosyncratic hepatic

Table 1 Advantages of new oral anticoagulants compared with vitamin K antagonists

Advantage	Clinical implications
Rapid onset of action	No need for bridging
Predictable anticoagulant effect	No need for routine coagulation monitoring
Specific coagulation enzyme target	Low risk of off-target adverse effects
Low potential for food interactions	No dietary precautions
Low potential for drug interactions	Few drug restrictions

Table 2 Comparison of the pharmacological characteristics of new oral direct thrombin and FXa inhibitors in late-stage clinical development[a]

Parameter	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Target	Thrombin	Factor Xa	Factor Xa	Factor Xa
Oral bioavailability	6.5%	80%	~66%	50%
Dosing	Fixed, once or twice daily	Fixed, once or twice daily	Fixed, twice daily	Fixed, once daily
Pro-drug	Yes	No	No	No
Half-life (h)	12–14	7–13	8–13	9–11
Routine coagulation monitoring	No	No	No	No
Renal clearance	80%	66%; half is inactive drug	~25%	35%
Potential drug interactions	Rifampicin, quinidine, amiodarone, potent P-gp inhibitors	Potent inhibitors of CYP3A4 and P-gp[b]	Potent CYP3A4 inhibitors[b]	Potent inhibitors of CYP3A4 and P-gp
Involvement of CYP	No	CYP3A4	CYP3A4	CYP3A4
Clinical status	Approved in >70 countries[c]	Approved in >70 countries[c]	Phase III	Phase III

[a]The table does not include data for AZD0837, betrixaban, YM150, and TAK-442, which remain in early stages of clinical development.
[b]CYP, cytochrome P-450 isoenzymes; P-gp, P-glycoprotein. Strong inhibitors of both CYP3A4 and P-gp include azole antifungals (e.g., ketoconazole, itraconazole, voriconazole, posaconazole) and protease inhibitors, such as ritonavir. Potent CYP3A4 inhibitors include azole antifungals, macrolide antibiotics (e.g., clarithromycin), and protease inhibitors (e.g., atanazavir).
[c]Approved for the prevention of venous thromboembolism after hip and knee arthroplasty. Dabigatran is also approved in the U.S. and Canada for stroke prevention in patients with AF. Phase III trials are ongoing in other clinical indications.

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toxicity, and it was subsequently withdrawn from the market in 2006. Ximelagatran did however have many desirable properties, and experience with the drug demonstrated that an oral anticoagulant specifically targeting thrombin without routine monitoring could be as effective as VKAs in the prevention and treatment of VTE and stroke prevention in patients with AF, with no increase in bleeding. Confirmation of the suitability of thrombin as a target comes from subsequent studies with dabigatran, which, unlike ximelagatran, is not hepatotoxic.

Dabigatran Etexilate

Dabigatran etexilate is the prodrug of dabigatran, which reversibly inhibits the active site of thrombin. Oral bioavailability is ~6%. Following oral administration, dabigatran etexilate is rapidly converted to dabigatran by esterases in the blood and liver with peak plasma concentrations achieved 2–3 h after oral administration. Dabigatran is not metabolized and does not inhibit cytochrome P-450 (CYP) isoenzymes (12). About 80% of the drug is excreted unchanged via the kidneys with the remainder conjugated and excreted via the biliary system. Dabigatran is contraindicated in patients with severe renal impairment [creatinine clearance (CL_{CR}) <30 mL/min]. For patients undergoing hip or knee arthroplasty who have moderate renal impairment (CL_{CR} 30–50 mL/min), a lower dose (150 mg once daily) is recommended in place of the usual dose of 220 mg once daily (13). The half-life of dabigatran is 12–14 h, which permits once- or twice-daily dosing (12).

Dabigatran etexilate is a substrate for the efflux transporter P-glycoprotein (P-gp) in the intestine, and coadministration of a P-gp inhibitor increases blood levels of dabigatran by decreasing efflux of the prodrug. Amiodarone and verapamil are moderately potent inhibitors of P-gp and increase blood levels of dabigatran by ~50%. Consequently, a lower dose of dabigatran (150 mg once daily) is recommended for VTE prevention in patients taking amiodarone or verapamil. Quinidine is a strong P-gp inhibitor and should not be used in conjunction with dabigatran (13).

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Based on promising results in phase II trials, dabigatran was investigated in four large phase III trials for prevention of VTE after total hip arthroplasty [RE-NOVATE (14), $n = 3{,}494$; RE-NOVATE II (15), $n = 2{,}055$] and total knee arthroplasty [RE-MODEL (16), $n = 2076$; RE-MOBILIZE (17), $n = 2{,}615$]. RE-NOVATE and RE-MODEL were conducted mainly in Europe and used the European approved dose of enoxaparin (40 mg once daily with the first dose given in the evening before surgery) as the comparator, whereas RE-MOBILIZE was conducted predominantly in the United States and Canada and used the North American–approved dose of enoxaparin (30 mg twice daily starting 12 to 24 h after surgery) as the comparator. RE-NOVATE II is the most recently completed trial and involved patients from both Europe and North America. In the first three trials, two doses, 220 mg and 150 mg once daily, were compared with enoxaparin. Both RE-MODEL and RE-NOVATE demonstrated noninferiority for the primary outcome, which was a composite of symptomatic or asymptomatic deep vein thrombosis (DVT), nonfatal pulmonary embolus (PE) (hereafter called total VTE), and all-cause mortality, with p-values of 0.0003 and <0.0001, respectively (**Figure 2*a***). These data formed the basis for approval of the drug by European and Canadian regulators in 2008. The third trial, RE-MOBILIZE, did not demonstrate

DVT: deep vein thrombosis

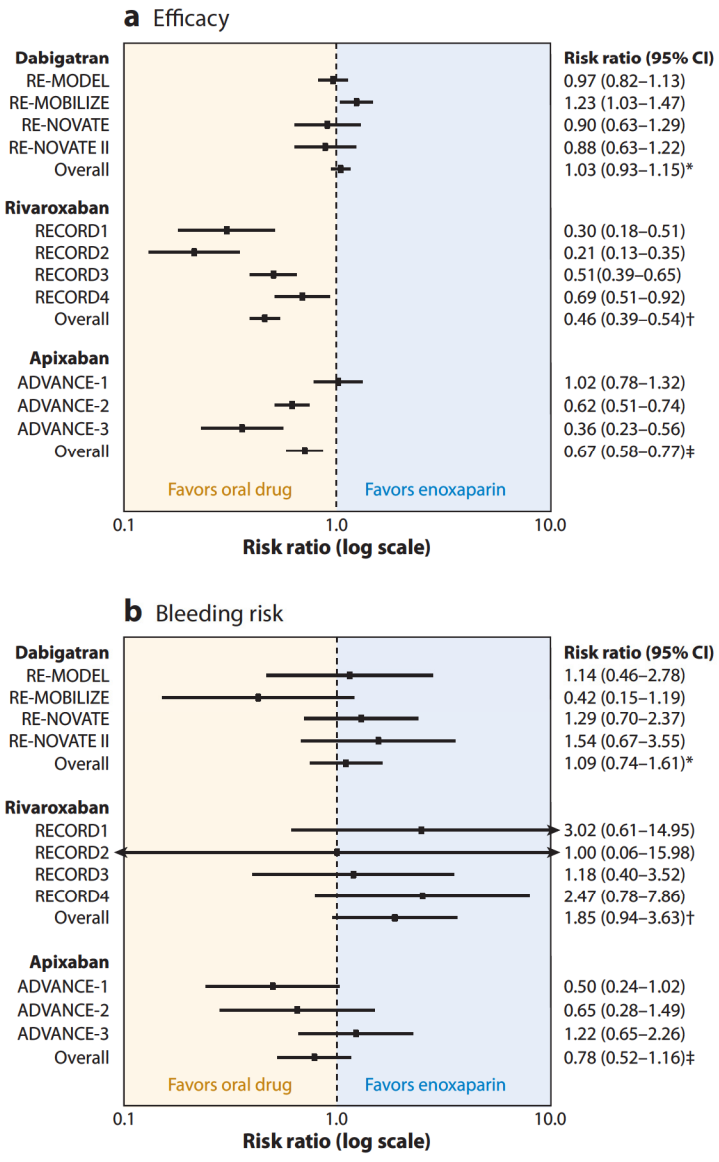

Figure 2

Pooled estimates of the results of randomized controlled trials comparing the effects of new oral anticoagulants versus enoxaparin on total venous thromboembolism (VTE) and all-cause mortality, and major bleeding among patients undergoing hip or knee arthroplasty. The new anticoagulant regimens evaluated in the trials were dabigatran 220 mg once daily (14–17), rivaroxaban 10 mg once daily (18–21), and apixaban 2.5 mg twice daily (22–24) and the comparator regimens were enoxaparin 40 mg once daily or 30 mg twice daily. Effect estimates were calculated using the Mantel–Haenszel method under a fixed-effects model and are presented as risk ratios and 95% CIs (log scale). In panel *a*, "efficacy" refers to total VTE and all-cause mortality. *Heterogeneity: $p = 0.12$, $I^2 = 49\%$; overall effect: $p = 0.58$. †Heterogeneity: $p = 0.0003$, $I^2 = 84\%$; overall effect: $p < 0.00001$. ‡Heterogeneity: $p = 0.0001$, $I^2 = 89\%$; overall effect: $p < 0.00001$. In panel *b*, "bleeding risk" refers to major bleeding as defined in the individual trials. *Heterogeneity: $p = 0.24$, $I^2 = 28\%$; overall effect: $p = 0.66$. †Heterogeneity: $p = 0.70$, $I^2 = 0\%$; overall effect: $p = 0.07$. ‡Heterogeneity: $p = 0.16$, $I^2 = 45\%$; overall effect: $p = 0.21$.

PE: pulmonary embolus

ACS: acute coronary syndrome

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noninferiority for the primary outcome (25.3% for enoxaparin versus 31.1% for 220 mg, risk difference +5.8%, 95% CI, 0.8–10.8; $p = 0.02$ and 33.7% for 150 mg, risk difference +8.4%, 95% CI, 3.4–13.3; $p = 0.0009$). However, both treatments were similar for the secondary composite outcome, major VTE (symptomatic or asymptomatic proximal DVT, nonfatal or fatal PE) plus VTE-related mortality (3.4% with 220 mg, 3.0% with 150 mg, and 2.2% with enoxaparin) and symptomatic DVT (0.8%, 0.7%, and 0.6%). There were no differences in bleeding rates (**Figure 2b**), hepatic enzyme elevations, or acute coronary syndrome (ACS) events between the two treatments. The RE-NOVATE II trial showed that five weeks of treatment with dabigatran 220 mg once daily was as effective as enoxaparin 40 mg once daily for prevention of total VTE events and all-cause mortality ($p < 0.0001$ for noninferiority) in patients undergoing hip arthroplasty with a similar risk of bleeding (15). Treatment with dabigatran was, however, superior to enoxaparin for the secondary composite outcome of major VTE plus VTE-related mortality (2.2% for dabigatran versus 4.2% for enoxaparin, $p = 0.029$).

The long-term use of dabigatran for the prevention of stroke in patients with AF, as a replacement for VKAs, was investigated in RE-LY, a prospective randomized multinational phase III trial with blinded evaluation of all outcomes (1). Two blinded doses of dabigatran (110 mg or 150 mg twice daily) were compared with open-label warfarin (targeted INR 2–3) in 18,113 patients with nonvalvular AF and at least one other major risk factor for thromboembolism. The minimum follow-up was one year.

After a median follow-up of two years, the rate of stroke or systemic embolism (including hemorrhagic stroke) was similar in the warfarin group (1.69% per year) and the group that received dabigatran 110 mg twice daily (1.53% per year, $p < 0.001$ for noninferiority), and significantly lower in the group given dabigatran 150 mg twice daily (1.11% per year, $p < 0.001$ for both noninferiority and superiority) (**Figure 3**). The major bleeding risk associated with dabigatran 150 mg twice daily was comparable to that observed with warfarin (3.1% per year versus 3.4% per year, $p - 0.31$), whereas dabigatran 110 mg twice daily was associated with a significantly lower rate of major bleeding than warfarin (2.7% per year, $p = 0.003$) (1). For both doses of dabigatran, the rates of intracranial, life-threatening, minor, and total bleeding were significantly lower than with warfarin. Dabigatran 150 mg twice daily significantly increased gastrointestinal bleeding compared with warfarin, and both doses of dabigatran were associated with higher rates of myocardial infarction (MI) than warfarin [dabigatran 110 mg twice daily: 0.72% ($p = 0.07$); dabigatran 150 mg twice daily: 0.74% ($p = 0.048$); warfarin 0.53%]. The mechanism of increased MI remains uncertain. The mortality rate was 4.13% per year in the warfarin group compared with 3.75% per year with 110 mg of dabigatran ($p = 0.13$) and 3.64% per year with 150 mg of dabigatran ($p = 0.051$). There was no signal for liver toxicity or other adverse events with dabigatran except for an increase in dyspepsia compared with warfarin. In contrast to previous trials, in which the vast majority of patients were on VKAs at the time of trial entry, RE-LY included a balanced representation of warfarin-naive (<2 months of VKA) and warfarin-experienced patients. Consistent benefits of dabigatran were seen whether patients were warfarin-naive or experienced. Patients in the dabigatran groups who completed RE-LY were offered the possibility of continuing in the open-label long-term safety extension trial, RELY-ABLE. More than 6,000 patients have been enrolled for up to 28 months of treatment, with results expected in 2011.

The use of dabigatran for treatment and secondary prevention of VTE, as a replacement for VKAs, has been studied in RE-COVER, which compared six months of dabigatran 150 mg twice daily with warfarin (dosed to achieve a target INR of 2–3) preceded by initial treatment (5–10 days) with an approved parenteral anticoagulant for treatment of acute symptomatic VTE (2). Rates of the primary efficacy outcome,

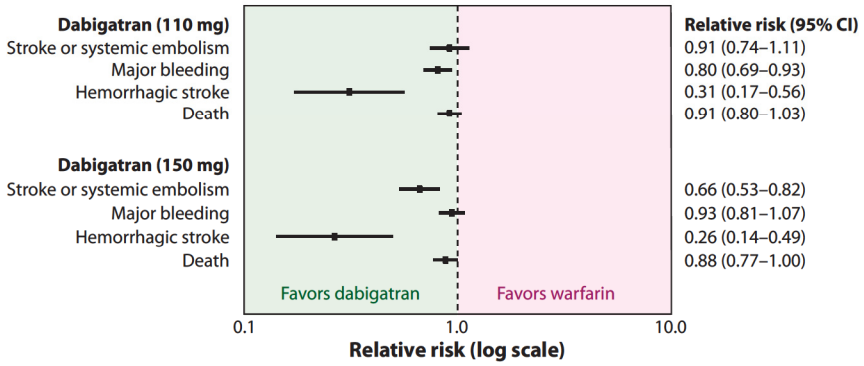

Figure 3

Results of the RE-LY trial for the primary outcome event of stroke or systemic embolism, major bleeding and important safety endpoints (hemorrhagic stroke), and death (1). Point estimates and 95% CIs are shown.

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recurrent symptomatic VTE and VTE-related death, were 2.4% and 2.1% in the dabigatran and warfarin groups, respectively ($p < 0.001$ for noninferiority). Rates of major bleeding were 1.6% and 1.9% in the dabigatran and warfarin groups, respectively; rates of any bleeding were 16.1% and 21.9%, respectively ($p < 0.05$). The results of additional phase III trials in VTE treatment (RE-COVER II, $n = 2,550$) and secondary prevention of VTE (two trials, $n = 4,095$) will be available in 2011 (**Table 3**).

A phase II dose-ranging trial assessing the safety and efficacy of dabigatran in the prevention of ischemic events in subjects with ACS has been reported (26). Dabigatran was associated with low rates of major bleeding, the primary outcome of the study, but it is unclear whether a phase III trial will be performed for this indication.

AZD0837

AZD0837 is the prodrug of AR-H067637, with oral bioavailability of 22% to 55%. It has superior pharmacological properties compared with its predecessor, ximelagatran, and appears to be devoid of liver toxicity. Plasma levels of AR-H067637 peak 0.7–1.5 h after oral administration, and the mean half-life is 9 h after single oral doses (15–750 mg) of AZD0837 in solution (12). An extended-release formulation has been developed, potentially enabling once-daily dosing without significant peak-to-trough variability.

Limited phase II trials evaluating AZD0837 have been completed (12), exposing >900 patients to at least three months of treatment (longest exposure ~16 months). ASSURE, a phase III trial comparing AZD0837 (175 mg once daily) to warfarin for the prevention of stroke or systemic embolism in patients with AF, was halted in 2008 because of stability problems with the oral formulation. Although this issue was subsequently resolved, it is unclear whether there will be further development of AZD0837.

ORAL FACTOR Xa INHIBITORS

Rivaroxaban

Rivaroxaban is an orally active FXa inhibitor with oral bioavailability reported to be >80% (12). Absorption is rapid with maximal anticoagulant effects achieved 2–4 h after oral dosing. Rivaroxaban has a dual mechanism of excretion; one third is cleared as unchanged drug via the kidneys, one third is metabolized by the liver via CYP3A4-dependent and -independent pathways with the metabolites then excreted in the feces, and one third is metabolized in the liver with the inactive metabolites then eliminated via the kidneys. Rivaroxaban has a half-life of 5–9 h in young subjects, increasing to

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Table 3 Completed and ongoing phase III clinical trials (August 2010)[a]

	Dabigatran		Rivaroxaban		Apixaban		Edoxaban	
Indication	**Completed**	**Ongoing**	**Completed**	**Ongoing**	**Completed**	**Ongoing**	**Completed**	**Ongoing**
Total hip arthroplasty	RE-NOVATE (14), RE-NOVATE II (15)	–	RECORD1 (18), RECORD2 (19)	–	ADVANCE-3 (24)	–	–	–
Total knee arthroplasty	RE-MODEL (16), RE-MOBILIZE (17)	–	RECORD3 (20), RECORD4 (21)	–	ADVANCE-1 (22), ADVANCE-2 (23)	–	–	–
Acute medical illness	–	–	–	MAGELLAN	–	ADOPT	–	–
Acute VTE treatment	RE-COVER (2)	RE-COVER II	EINSTEIN-DVT (4)	EINSTEIN-PE	–	AMPLIFY	–	The Edoxaban Hokusai-VTE
Secondary prevention of VTE	–	RE-MEDY, RE-SONATE	EINSTEIN-EXT (3)	–	–	AMPLIFY-EXT	–	–
Atrial fibrillation	RE-LY (1)	RE-LYABLE	ROCKET-AF[b]	–	AVERROES (25), ARISTOTLE[b]	–	–	ENGAGE-AF
Acute coronary syndromes	–	–	–	ATLAS ACS-TIMI 51	APPRAISE-2	–	–	–

[a] Data obtained from **http://www.clinicaltrials.org**.
[b] Completed trials that have finished enrollment but have not yet reported trial results.

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11–13 h in elderly subjects. In subjects with moderate renal impairment, overall exposure is 50% higher than that in controls (12). Rivaroxaban is generally administered once daily, although the drug is given twice daily for the initial treatment of patients with VTE and in patients with ACS.

Intestinal excretion of rivaroxaban is mediated in part by P-gp, because potent P-gp inhibitors increase drug levels (12). Concomitant administration of potent inhibitors of both P-gp and CYP3A4, such as ketoconazole and ritonavir, is contraindicated because they substantially increase plasma drug levels (27).

Based on promising results in phase II trials, rivaroxaban was investigated in four large phase III trials for prevention of VTE after total hip arthroplasty [RECORD1 (18), $n = 4{,}541$; RECORD2 (19), $n = 2{,}509$] and total knee arthroplasty [RECORD3 (20), $n = 2{,}531$; RECORD4 (21), $n = 3{,}148$]. The RECORD1, -2, and -3 trials used enoxaparin 40 mg once daily as the comparator, whereas RECORD4 used enoxaparin 30 mg twice daily as the comparator. RECORD1, -3, and -4 compared equivalent durations of treatment with both drugs; the RECORD2 trial compared a 31- to 39-day course of rivaroxaban versus a 10- to 14-day course of enoxaparin followed by 21 to 25 days of placebo. In all four trials, the dose of rivaroxaban was 10 mg once daily, started 6–8 h after wound closure. All four trials demonstrated superiority for rivaroxaban over enoxaparin for the primary outcome, a composite of total VTE and all-cause mortality (**Figure 2*a***). There were no significant differences in the rates of major bleeding (**Figure 2*b***) or hepatic enzyme elevations between the two treatments. In both the RECORD2 and -3 trials, rivaroxaban significantly reduced the incidence of symptomatic VTE compared with enoxaparin. Pooled analyses of the RECORD trials revealed a small but significant increase in major plus clinically relevant nonmajor bleeding with rivaroxaban (28). The phase III trial data formed the basis for European and Canadian approval in 2008. Approval by the U.S. Food and Drug Administration (FDA) was deferred pending long-term safety data.

The use of rivaroxaban for the secondary prevention of VTE, as a replacement for VKAs, has been studied in EINSTEIN-EXT, which compared rivaroxaban 20 mg once daily versus placebo in patients who had completed 6–12 months of anticoagulant treatment for their acute episode of VTE (3). Rates of the primary efficacy outcome after a median of six months treatment, recurrent symptomatic VTE, were 1.3% and 7.1% in the rivaroxaban and placebo groups, respectively (risk reduction 82%, $p < 0.0001$). Rates of major bleeding were 0.7% and 0% in the rivaroxaban and placebo groups, respectively, and the composite of major and clinically relevant nonmajor bleeding were 6.0% and 1.2%, respectively ($p < 0.001$).

Phase II dose-ranging trials assessing the safety and efficacy of rivaroxaban in the prevention of ischemic events in subjects with ACS (29) and patients with symptomatic DVT (30) have been reported. A large phase III trial ($n = 14{,}266$) comparing rivaroxaban (20 mg once daily) versus warfarin for prevention of stroke or systemic embolism in patients with AF (31) completed enrollment in May 2010, and the results are expected to be presented in November 2010. A phase III trial comparing rivaroxaban (15 mg twice daily for 3 weeks followed by 20 mg once daily for 3–12 months) versus enoxaparin followed by VKA for the treatment of acute symptomatic DVT without symptoms of PE (EINSTEIN-DVT, $n = 3{,}465$) demonstrated that patients treated with rivaroxaban had a similar rate of symptomatic recurrent VTE (fatal or nonfatal, 2.1% versus 3.0%, $p < 0.0001$ for non-inferiority) and bleeding (defined as the composite of major and clinically relevant nonmajor bleeding, 8.1% in both treatment groups, $p = 0.77$) as those treated with standard therapy (4). Ongoing phase III trials (**Table 2**) are investigating rivaroxaban in PE treatment ($n = 4{,}000$), primary prevention of VTE in acutely ill medical patients ($n = 8{,}000$), and the prevention of recurrent ischemia in patients with ACS ($n = 16{,}000$).

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Apixaban

Apixaban is an orally active, reversible inhibitor of FXa. Absorption is rapid with maximal plasma concentrations achieved 1–3 h after oral administration (12). Lower peak-to-trough concentration ratios are observed with twice-daily versus once-daily dosing regimens, resulting in a preference for twice-daily dosing. The drug has a mean half-life of 8–15 h in healthy young subjects.

Apixaban and its metabolites are excreted by multiple elimination pathways, including renal excretion (25%), hepatic metabolism via CYP3A4-dependent mechanisms, and intestinal excretion (~55%). The multiple elimination pathways raise the possibility that patients with hepatic or renal impairment can be treated with apixaban. Concomitant treatment with potent inhibitors of CYP3A4 such as ketoconazole is contraindicated in apixaban-treated patients (12).

Based on promising results observed in a phase II study in patients undergoing knee arthroplasty, apixaban was investigated in three large phase III trials for prevention of VTE after total knee arthroplasty [ADVANCE-1 (22), $n = 3{,}195$; ADVANCE-2 (23), $n = 3{,}057$] and hip arthroplasty [ADVANCE-3, $n = 5{,}407$ (24)]. ADVANCE-1 used enoxaparin 30 mg twice daily as the comparator, whereas ADVANCE-2 and -3 used enoxaparin 40 mg once daily as the comparator. In all three trials, the dose of apixaban was 2.5 mg twice daily, started in the morning of the day after surgery. In ADVANCE-1, a 12-day course of apixaban had efficacy similar to an equal duration of treatment with enoxaparin with total VTE plus all-cause mortality rates of 9.0% and 8.8%, respectively. Major bleeding rates were 0.7% with apixaban and 1.4% with enoxaparin ($p = 0.053$). Despite similar efficacy, apixaban did not meet the prespecified noninferiority goal because the event rates in the control group were much lower than expected. In ADVANCE-2, the same apixaban regimen significantly reduced total VTE plus all-cause mortality compared with enoxaparin (15.1% and 24.4%, respectively; $p < 0.0001$) and was associated with a similar risk of bleeding (major bleeding, 0.6% and 0.9%, respectively; $p = 0.30$). In ADVANCE-3, five weeks of treatment with apixaban in patients undergoing hip arthroplasty significantly reduced total VTE and all-cause death compared with enoxaparin (1.4% and 3.9%, respectively; $p < 0.0001$) and was associated with a similar risk of bleeding (major bleeding, 0.8% and 0.7%, respectively; $p = 0.54$). In ADVANCE-2 and -3, major VTE was significantly lower with apixaban versus enoxaparin. Taken together, the results of these three trials suggest that apixaban offers a favorable efficacy-safety balance in patients undergoing hip or knee arthroplasty (**Figure 2**).

Phase II dose-ranging trials assessing the safety and efficacy of apixaban in the prevention of ischemic events in patients with ACS (32) and patients with symptomatic DVT (33) have been reported. A phase III trial comparing apixaban (5 mg twice daily) to aspirin for the prevention of stroke or systemic embolism in patients with AF who have failed or are unsuitable for VKA (AVERROES) was stopped early in May 2010 (5,600 patients enrolled) for efficacy after a predefined interim analysis revealed clear evidence of a clinically important reduction in stroke and systemic embolism (preliminary results showing a 3.6% rate per year on aspirin and 1.8% per year on apixaban; relative risk 0.46, $p < 0.001$) and an acceptable safety profile for apixaban (25). Preliminary safety results showed a major bleeding rate of 1.2% per year on aspirin and 1.4% per year on apixaban, relative risk 1.14, $p = 0.56$. The rate of intracranial bleeding was 0.3% per year on aspirin and 0.4% per year on apixaban. There was no evidence of hepatic toxicity or other major adverse events. A large phase III trial ($n = 18{,}183$) comparing apixaban (5 mg twice daily) versus warfarin for prevention of stroke or systemic embolism in patients with AF (34) completed enrollment in 2010 and the results are expected in 2011. Additional phase III trials are evaluating the use of apixaban for VTE prevention in acutely ill medical patients ($n = 6{,}500$), initial and

long-term VTE treatment ($n > 5{,}000$), and prevention of recurrent ischemia in patients with ACS ($n = 10{,}800$).

Edoxaban

Edoxaban is an orally active FXa inhibitor that reaches peak plasma concentrations approximately 1–3 h after oral administration. Edoxaban has a half-life of 9–11 h and has a dual mechanism of elimination; approximately one third is eliminated via the kidney, and the remainder is excreted in the feces (35).

In phase II studies, edoxaban has been evaluated for VTE prevention in patients undergoing elective total hip arthroplasty (36) and for stroke prevention in AF (37). The AF study (37) showed that once-daily dosing was associated with less bleeding than twice-daily dosing. Phase III trials are comparing two doses of edoxaban (30 or 60 mg once daily) to warfarin for prevention of stroke or systemic embolism in patients with AF ($n = 16{,}500$), and for initial and long-term treatment of VTE ($n = 7{,}500$).

Other Agents in Development

Other FXa inhibitors in earlier stages of clinical development include YM150, betrixaban, and TAK-442. Phase II trials have evaluated various doses of these agents in patients undergoing hip or knee arthroplasty, in patients with AF at risk of stroke or systemic embolism, and/or in subjects with ACS.

CLINICAL INDICATIONS AND DEVELOPMENT ISSUES

Potential target indications for the new oral anticoagulants are discussed in more detail below.

Prophylaxis of Venous Thromboembolism

Current guidelines recommend that patients undergoing knee or hip arthroplasty should receive thromboprophylaxis such as low-molecular-weight heparins, VKAs, or a pentasaccharide for at least 10 days after surgery, and continuing up to 28–35 days after hip arthroplasty (38). However, VKA therapy is often discontinued following hospital discharge because of the need for routine coagulation monitoring and concerns about the risk of bleeding, and parenteral agents are often stopped because of the inconvenience of subcutaneous injections. In some countries, patients remain hospitalized for only 3–4 days after hip or knee arthroplasty (39), so that the longest period of recommended prophylaxis in both hip and knee arthroplasty patients occurs out-of-hospital. Oral agents that are effective and safe and do not require routine coagulation monitoring or parenteral administration could play an important role in increasing uptake of prophylaxis beyond hospital discharge.

On the basis of the results of the phase III studies, dabigatran and rivaroxaban have been approved for the prevention of VTE after hip or knee arthroplasty in more than 70 countries. Both drugs have the potential to streamline out-of-hospital prophylaxis. Apixaban has been submitted for European regulatory approval for the same indication in early 2010.

Stroke Prevention in Atrial Fibrillation

Long-term anticoagulation therapy with VKAs such as warfarin is recommended for individuals with nonvalvular AF who are considered at moderate to high risk of stroke but is grossly underutilized and often relatively ineffective (40). The favorable results of the RE-LY trial are likely to dramatically change the approach to long-term anticoagulant therapy for stroke prevention in patients with AF. With fewer strokes and less intracranial bleeding with the higher-dose 150-mg dabigatran regimen compared with warfarin, and less bleeding yet similar efficacy with the lower-dose 110-mg regimen, the opportunity exists to tailor anticoagulant treatment according to the patient's risk of stroke and bleeding (41). In addition, the availability of simple, fixed-dose, unmonitored therapy should increase the uptake of anticoagulant therapy in patients with

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AF at risk for stroke. Several questions remain, however, concerning the use of dabigatran in clinical practice if and when it is approved for use (42). These include (*a*) the optimal dosing regimen to use in different patient groups according to risk profile, renal function, and concomitant medications; (*b*) the cost-effectiveness for different risk groups; and (*c*) which patients currently receiving VKA treatment for stroke prevention should be switched to dabigatran. The more efficacious 150-mg dose is likely to be appropriate for patients at high risk of stroke and the safer 110-mg dose for those at high risk of bleeding or associated drug interactions. Dabigatran was submitted for FDA and European regulatory approval for this indication in early 2010. Promising preliminary results from the AVERROES trial suggest that apixaban is also an effective anticoagulant for stroke prevention in patients with AF. Phase III results for rivaroxaban are expected in late 2010 and, together with results of a second phase III trial of apixaban expected in 2011, should provide additional information on the benefits of these agents in this clinical setting.[1]

Treatment of Venous Thromboembolism

Therapy for VTE is aimed at limiting or preventing extension of the thrombus, as well as preventing recurrence of VTE and (fatal) PE. Current management strategies involve initial treatment with heparins or pentasaccharide for at least five days followed by long-term oral anticoagulation with VKAs (43). Previous studies involving the oral DTI ximelagatran showed that the use of fixed dosing without coagulation was effective for six months' treatment of DVT with or without PE (44), with a low rate of major bleeding events. Since the greatest risk of recurrent DVT or PE occurs within the first 5–10 days after diagnosis, and initial treatment is currently well served by parenteral low-molecular-weight heparin and fondaparinux, several new oral anticoagulants were not started until after at least five days of treatment with a parenteral agent. Dabigatran was shown to be as effective as warfarin for six months' treatment of DVT and PE after an initial 5–10 days' treatment with a parenteral anticoagulant in all patients (2). Treatment trials of rivaroxaban and apixaban compared higher anticoagulant doses during the initial one week (apixaban) and three weeks (rivaroxaban) with a parenteral agent after an acute VTE event, followed by longer-duration anticoagulation with a lower dose of the oral agent compared with a VKA for an additional 6–12 months. These contrasting approaches will further define the optimal strategy for the initial and long-term treatment of acute VTE.

Most physicians have been reluctant to continue anticoagulant treatment beyond three or six months after a first episode of VTE because of the inconvenience and bleeding risks associated with VKAs. Due to the absence of laboratory monitoring requirements with the new anticoagulants, there is an increased interest in extension of secondary prophylaxis beyond the first six months. Rivaroxaban reduced the risk of recurrent symptomatic VTE by 80% compared to placebo, with no increase in the rate of major bleeding but with a significant increase in clinically relevant nonmajor bleeding, when continued for a further 6 months among patients who already had completed 6–12 months of anticoagulant treatment (3). Similarly designed phase III trials are under way with dabigatran and apixaban, and their results may further refine the duration of secondary prophylaxis following an acute VTE event.

[1]Since this review went to press, the U.S. FDA and Health Canada have approved dabigatran for reduction in the risk of stroke in patients with non-valvular AF (**http://www.pradaxa.com/**). In addition, the phase III ROCKET-AF trial showed that in patients with non-valvular AF, rivaroxaban was non-inferior to dose-adjusted warfarin with regard to the primary endpoint of all-cause stroke and non-central nervous system embolism. The rates of the composite of major and non-major clinically relevant bleeding were comparable in the rivaroxaban- and warfarin-treatment arms, with less fatal bleeding and intracranial haemorrhage observed among those treated with rivaroxaban (**http://www.theheart.org/article/1148785.do**) (accessed December 9, 2010).

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Acute Coronary Syndromes

The use of anticoagulants in patients post ACS remains controversial. Oral anticoagulation with VKAs has been shown to prevent recurrent ischemic events after ACS; however, there is a clear risk of bleeding (45). For post-ACS patients, aspirin plus warfarin at INR values of 2–3 doubles the risk of major bleeding but is superior to aspirin alone in preventing major cardiac events (all-cause death, nonfatal MI, and nonfatal thrombo-embolic stroke) (45). However, uncertainty remains about the safety (bleeding risk) of combining oral anticoagulation with dual antiplatelet therapy (e.g., aspirin plus clopidogrel) as used in contemporary clinical practice or in ACS patients, particularly those with coexisting conditions, such as AF or a mechanical valve prosthesis. Several of the new anticoagulants are undergoing evaluation in this clinical setting. Phase III results for rivaroxaban and apixaban versus placebo are expected in 2011 or 2012 and should help to clarify the benefits of oral anticoagulation in post-ACS patients who routinely receive concomitant dual antiplatelet therapy.[2]

CONCLUSIONS AND FUTURE DIRECTIONS

The new oral anticoagulants under evaluation for the prevention and management of venous and arterial thromboembolism have important advantages over VKAs, including a rapid onset of action, predictable anticoagulant effects that obviate the need for routine coagulation monitoring, and a low propensity for drug interactions. The superior pharmacological properties and convenience of the new oral anticoagulants compared with existing anticoagulants have translated into improvements in efficacy and safety in initial randomized trials.

Dabigatran, rivaroxaban, and apixaban are the agents most advanced in development. Both dabigatran and rivaroxaban have been approved in more than 70 countries for prevention of VTE in patients undergoing hip and knee arthroplasty, with apixaban likely to be the next agent approved for clinical use. Several other new oral anticoagulants will also likely reach the market over the next few years and thereby improve the management of thromboembolic disorders.

Dabigatran, which was found superior to warfarin with a lower bleeding risk in the RE-LY trial, so far offers the greatest promise and opportunity for the replacement of VKAs. Phase III results for rivaroxaban are also promising and provide additional information of the benefits of this agent in this clinical setting. Given the growing burden of AF and valvular heart disease and the lack of resources and infrastructure to monitor VKAs in substantial numbers of patients, the arrival of these new agents is anticipated with optimism.

The withdrawal of oral ximelagatran in 2006 due to hepatic toxicity has heightened awareness about potential side effects of these new agents, particularly hepatotoxicity, cardiovascular adverse events, and associated drug interactions. None of the new oral anticoagulants in advanced stages of development has demonstrated evidence of liver toxicity, but long-term data are still required. Recognition that bleeding is associated with adverse outcomes in patients with cardiovascular disease and concern about the lack of antidotes have focused attention on the risk of bleeding with all of the new oral anticoagulants. In particular, the potential bleeding risks incurred by combining some of the specific platelet aggregation inhibitors with the new oral anticoagulants will require further evaluation.

Although speculation still remains that the drug target (e.g., inhibition of thrombin versus inhibition of FXa) is a critical element in differentiating the efficacy and safety profile of an anticoagulant, the pharmacokinetic

[2]Since this review went to press, the phase III APPRAISE-2 trial of apixaban in high-risk patients with recent ACS was stopped early because of increased bleeding that would not be offset by reductions in ischemic events (**http://www.theheart.org/article/1154633.do**, accessed December 9, 2010).

characteristics, dosing strategies and side effects profiles may be more clinically relevant. Key characteristics include their renal elimination, which is of particular importance in elderly patients and in those with renal dysfunction; their frequency of administration, which could affect drug adherence; and selection of the optimal dose of an anticoagulant drug. Uncertainties about the relative importance of these factors will persist without head-to-head comparisons, which are unlikely owing to the commercial nature of the different treatments in development.

SUMMARY POINTS

1. Recent efforts to find a replacement for vitamin K antagonists (VKAs) have focused on the development of nonpeptidic, orally available, small molecules that directly inhibit thrombin and activated factor X (FXa).
2. The new agents are direct-acting, reversible, small molecules with predictable pharmacodynamic profiles allowing once- or twice-daily fixed dosing regimens without the need for routine monitoring of their respective anticoagulant effects.
3. The direct thrombin inhibitor dabigatran and the selective FXa inhibitor rivaroxaban are most advanced in clinical development and are approved in more than 70 countries for the prevention of venous thromboembolism in patients undergoing hip or knee arthroplasty.
4. The recently reported RE-LY trial compared dabigatran to warfarin for stroke prevention in atrial fibrillation. The RE-LY results demonstrated the potential of the new oral anticoagulants to replace VKAs for long-term treatment.
5. It is likely that several of the new orally available anticoagulants, targeting direct inhibition of thrombin and the direct inhibition of factor Xa, will replace VKAs for long-term thrombosis management.

FUTURE ISSUES

1. The pharmacological properties of the new oral drugs, especially metabolism and route of elimination, might be important in determining the future preferred usage of particular drugs in different patient groups (e.g., patients with impaired liver or renal function, adolescents, the elderly).
2. Studies will be needed to examine the potential role of the novel oral anticoagulants in other clinical settings (e.g., prosthetic heart valves, cerebrovascular disease, and peripheral artery disease).

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1. Landmark phase III megatrial that showed dabigatran to be more effective and safer than warfarin for the prevention of stroke or systemic embolism in patients with atrial fibrillation.

2. Phase III trial demonstrating that dabigatran is noninferior to warfarin in the treatment of acute venous thromboembolism.

12. A comprehensive summary of the pharmacodynamic and pharmacokinetic characteristics of the new oral anticoagulants mentioned in this article.

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