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Edoxaban

A New Oral Direct Factor Xa Inhibitor

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Abstract

Edoxaban is an oral direct factor Xa inhibitor that is currently undergoing investigation in phase III clinical trials for the prevention of stroke in patients with atrial fibrillation (AF) and for the prevention and treatment of venous thromboembolic events (VTE).

Factor Xa is an attractive target for anticoagulant treatment, as it is the primary and rate-limiting source of amplification in the coagulation cascade. Edoxaban is a competitive inhibitor of factor Xa and has >10 000-fold greater selectivity for factor Xa relative to thrombin. In phase I clinical trials, the anticoagulant effects of edoxaban included dose-dependent increases in activated partial thromboplastin time and prothrombin time following single edoxaban doses of 10–150 mg and after multiple ascending doses (60 mg twice daily, 90 mg daily and 120 mg daily). The anticoagulant effects of edoxaban were rapid in onset (time to peak plasma concentration 1–2 hours) and sustained for up to 24 hours. Prolongation of bleeding time in 8% of subjects was >9.5 minutes (none of which appeared to be clinically significant) 2 hours after initial dosing, and was independent of edoxaban dose, formulation or dietary state. In general, plasma edoxaban concentrations were linearly correlated with coagulation parameters. Phase II clinical trials in patients with AF and VTE suggest that the edoxaban 30 mg once-daily and 60 mg once-daily regimens had a similar or better safety profile compared with dose-adjusted warfarin (international normalized ratio 2.0–3.0) in terms of bleeding events, and that edoxaban was not associated with hepatotoxicity. In addition, edoxaban was associated with statistically significant dose-dependent reductions in VTE after orthopaedic surgery compared with placebo or dalteparin sodium. Further clinical investigation of the efficacy and safety of once-daily edoxaban is being conducted in phase III clinical trials in comparison with warfarin in patients with AF in the phase III ENGAGE AF-TIMI 48 trial (NCT00781391), and in comparison with low-molecular weight heparin/warfarin in the prevention of recurrent VTE in patients with symptomatic deep vein thrombosis and/or pulmonary embolism in the HOKUSAI VTE trial (NCT00986154).

1. Introduction

Parenteral agents such as unfractionated heparin, low-molecular weight heparin (LMWH) or

fondaparinux sodium and oral vitamin K antagonists (VKAs), such as warfarin, acenocoumarol and phenprocoumon, have been the cornerstones of anticoagulant therapy for decades.

Oral anticoagulant therapy with a VKA is recommended in a dose-adjusted regimen for the prevention of stroke and systemic embolization in patients with non-valvular atrial fibrillation (AF) with more than one moderate risk factor for stroke in the American College of Cardiology (ACC), American Heart Association (AHA) and European Society of Cardiology (ESC) 2006 AF practice guidelines,^[1] and also in patients with "at least one clinically relevant non-major risk factor for stroke". The CHADS₂ (Cardiac failure, Hypertension, Age, Diabetes, Stroke doubled) stratification scheme is recommended for initial assessment of stroke risk, with oral anticoagulant treatment indicated for patients with a CHADS₂ score ≥ 2 , and a more detailed risk evaluation (including age, gender and the presence of vascular disease) recommended to determine whether those with a score of 0–1 should receive no antithrombotic therapy, aspirin or oral anticoagulant treatment.^[2] Recent changes to the ESC AF guidelines include refinement of CHADS₂ into the slightly more sensitive CHA₂DS₂-VASc (congestive heart failure, hypertension, age ≥ 75 [doubled], diabetes, stroke [doubled], vascular disease, age 65–74, and sex category [female]) system, which allows assessment of who may benefit from the anticipated introduction of new-generation oral anticoagulants for stroke prevention.^[3]

Current guidelines also note that warfarin is effective and recommended for use in the primary and secondary prevention of venous thromboembolic events (VTEs).^[4–7] However, warfarin is challenging to use in clinical practice because of a range of significant limitations, including (i) a slow onset of action; (ii) a narrow therapeutic margin requiring frequent laboratory monitoring of international normalized ratio (INR) with often complex dose adjustment, and an increased risk of bleeding, particularly in elderly patients; (iii) considerable variability in dose response among subjects; and (iv) multiple drug-drug and drug-food interactions. Laboratory control can also be difficult to standardize, and problems in dosing may occur as a result of a lack of patient adherence and miscommunication between patients and physicians.^[6,8,9] In addition, discontinuation rates are high and many patients still have in-

adequate anticoagulation.^[10] For example, in clinical practice, <60% of patients with AF who do not have contraindications to warfarin therapy are actually receiving it, and less than half of those are consistently within therapeutic targets.^[10–17] As a consequence, warfarin is under-prescribed in clinical practice for stroke prevention in AF.

Warfarin also acts nonspecifically, impacting upon the coagulation cascade (figure 1) at various steps. The anticoagulant effects of warfarin are produced by interference with the cyclic inter-conversion of vitamin K and its 2,3 epoxide, which modulates the γ -carboxylation of glutamate residues on the N-terminal regions of vitamin K-dependent proteins.^[6] The four vitamin K-dependent coagulation factors II (prothrombin), VII, IX and X all require γ -carboxylation for their procoagulant activity, and warfarin treatment leads to hepatic production of partially carboxylated and decarboxylated proteins with reduced coagulant activity.^[6] Thus, the limitations of warfarin therapy point to a need for new orally active anticoagulant agents that are safer, effective and more convenient to use.

Factor Xa is a serine protease that plays a key role in the coagulation pathways and binds to factor Va on the surface of activated platelets to form the prothrombinase complex, which in turn converts prothrombin to thrombin (figure 1). Indeed, factor Xa is the primary site of amplification, and one molecule of factor Xa can activate approximately 1000 prothrombin molecules.^[18] Thus, factor Xa is an attractive target for anticoagulant treatment as it is the primary and rate-limiting source of amplification in the coagulation cascade.^[21] Inhibitors of factor Xa attenuate thrombin generation and prevent conversion of fibrinogen to fibrin in the final stage of the coagulation cascade,^[22,23] and may block factor Xa either directly or indirectly.^[22] The oral factor Xa inhibitors in particular bind directly to the active site of factor Xa and block the interaction with its substrate.^[23]

A range of new oral anticoagulants that act on the two key serine protease enzymes that drive clot formation and fibrin deposition are currently being introduced or are in late-stage clinical development for the prevention of stroke in patients

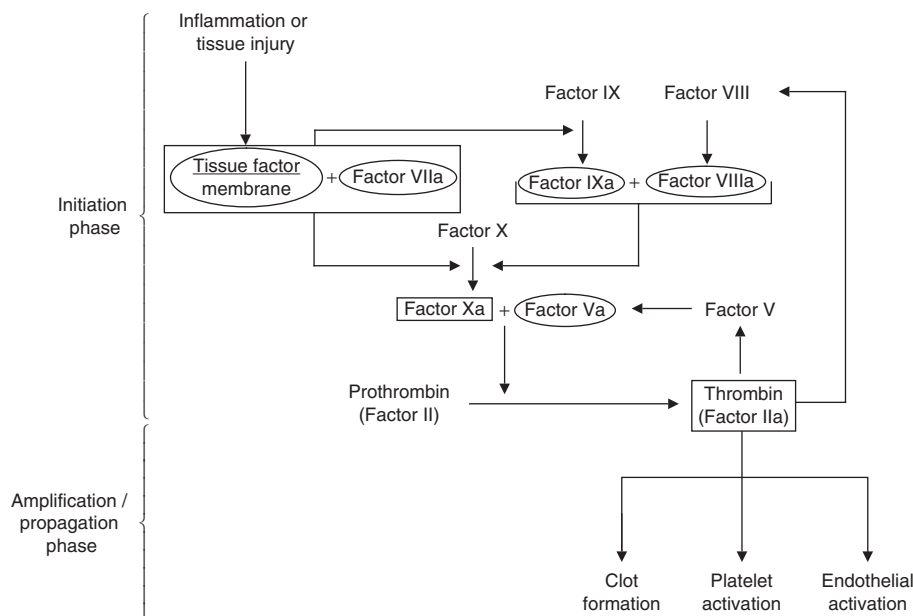


Fig. 1. The coagulation cascade. Ovals denote potential targets for an anticoagulant; rectangles denote components of the cascade with inhibition that would provide the most effective anticoagulation.^[18–20]

with AF and the prevention and treatment of VTE, including the factor Xa inhibitors edoxaban,^[24–26] apixaban^[27–29] and rivaroxaban,^[30–34] and the direct thrombin inhibitor dabigatran.^[23,35,36]

The novel oral factor Xa inhibitor edoxaban (supplementary figure 1 can be found in the Supplemental Digital Content 1, <http://links.adisonline.com/DGZ/A8>) is one of several oral anticoagulants currently in development.^[20] The aim of this review is to examine the clinical pharmacology, efficacy and safety of edoxaban, which has recently been licensed for the prevention of VTE after major orthopaedic surgery in Japan and entered phase III clinical trials for the prevention of stroke in patients with AF and for the prevention of VTE.

2. Pharmacokinetic Properties

The pharmacokinetic characteristics of oral factor Xa and direct thrombin inhibitors in late-stage clinical development are summarized and compared in table I. In particular, the low inter-subject variability and dose linearity observed in both single- and multiple-dose studies in healthy

subjects suggest that edoxaban has a predictable and consistent pharmacokinetic profile.^[38] After oral administration of single doses in the range 10–150 mg, edoxaban was rapidly absorbed (time to peak plasma concentration 1–2 hours) and plasma concentrations of edoxaban were dose proportional (figure 2).^[38] The mean apparent volume of distribution of edoxaban during the terminal elimination phase was generally >300 L, due to relatively low protein binding and distribution to extravascular tissues. The mean elimination half-life of edoxaban is in the range of 5.8–10.7 hours (single doses 10–150 mg) or 8.75–10.4 hours (multiple doses 90–120 mg daily), indicating reasonably consistent terminal elimination.^[38] Mean renal clearance rates for edoxaban exceeded the glomerular filtration rate, which suggested the involvement of active secretion. In addition, there was little systemic accumulation of edoxaban after 10 days of administration.^[38] Moreover, the time to achievement of steady-state plasma concentrations of edoxaban was consistent with the half-life after a single dose, and trough concentrations reached maximal levels by day 2.

Table I. Comparison of the pharmacokinetic properties of oral factor Xa and direct thrombin inhibitors in clinical development. Reproduced from Eriksson et al.^[23] with permission from Adis, a Wolters Kluwer business (© Adis Data Information BV 2009. All rights reserved)

Parameter	Edoxaban	Rivaroxaban	Apixaban	Dabigatran etexilate
F _{abs} (%)	50 in monkeys ^[37]	57–86 in animals	~66 in humans	6.5 in humans
F _{rel} (%)	NR	60–80 in humans	NR	~85 in humans
t _{max} (h)	1–2 ^[38,39]	2–4	1–3	1.25–3
Vd (L)	>300 ^{a [38]}	~50	Reported as low	60–70
Protein binding (%)	40–59 ^[38]	92–95	87	35
t _{1/2} (h)	5.8–10.7 (single doses 10–150 mg) or 8.75–10.4 (multiple doses 90–120 mg daily) ^[38]	9–13	8–15	12–14
CL/F (L/h)	30.2 (30 mg) to 33.7 (60 mg) ^[38]	~10	5	70–140
Renal excretion (%)	35–39 ^[38,39]	66 (but only 33% as active metabolites)	~25	80
Accumulation	Negligible ^{b [38]}	None	NR	None
Food effect	No ^[38,40]	Absorption delayed but not reduced with food ^[41]	NR	Absorption delayed but not reduced with food ^[42]
Age effect	NR	No	NR	No
Bodyweight effect	NR	No	NR	No
Gender effect	NR	No	NR	No
Drug interactions	Substrate for P-gp ^[43] Edoxaban dosage reduction may be needed when coadministered with strong P-gp inhibitors (e.g. verapamil, quinidine, amiodarone ^[43] and dronedarone) Concomitant administration of NSAIDs or clopidogrel may increase bleeding time	Potent inhibitor of CYP3A4 and P-gp Coadministration of rivaroxaban with strong CYP3A4 and P-gp inhibitors (e.g. azole antifungals or HIV protease inhibitors) is contraindicated Coadministration of rivaroxaban with strong CYP3A4 inducers (e.g. rifampicin, phenytoin, carbamazepine, phenobarbital or St John's Wort) may reduce rivaroxaban plasma concentrations ^[44] Concomitant administration of NSAIDs or clopidogrel may increase bleeding time ^[44]	Metabolized by CYP3A4 A similar interaction profile to rivaroxaban is likely ^[45] Concomitant administration of NSAIDs or clopidogrel may increase bleeding time ^[45]	Dabigatran etexilate (but not dabigatran [active drug]) is a substrate for P-gp Coadministration with P-gp inhibitors (e.g. verapamil, quinidine, amiodarone) increases exposure to dabigatran Coadministration with P-gp inducers (e.g. rifampicin) reduces exposure to dabigatran and should generally be avoided Concomitant administration of NSAIDs or clopidogrel may increase bleeding time ^[46]
Involvement of CYP	CYP3A4 ^[47]	CYP3A4	CYP3A4	No
Safe in pregnancy	No	No	No	No

a Vd during the elimination phase.

b At daily doses.

CL/F = apparent total oral clearance; C_{max} = peak plasma concentration; CYP = cytochrome P450; F_{abs} = absolute bioavailability; F_{rel} = relative bioavailability; NR = not reported; P-gp = P-glycoprotein; t_{1/2} = terminal elimination half-life; t_{max} = time to reach C_{max}; Vd = apparent volume of distribution.

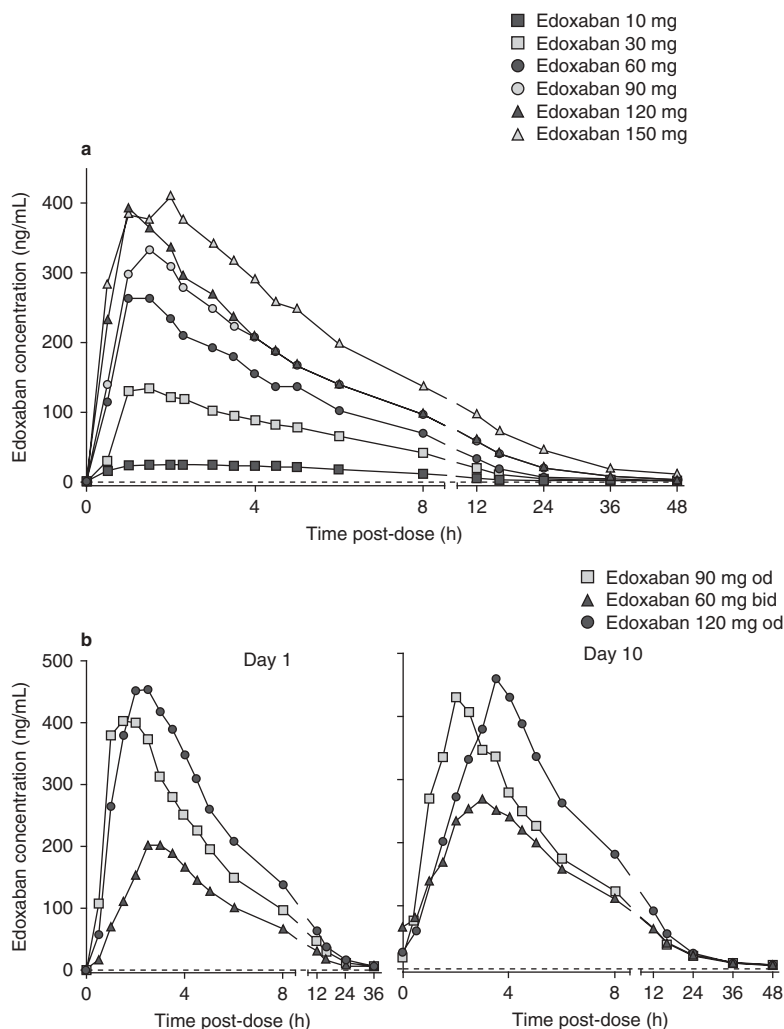


Fig. 2. Geometric mean plasma concentrations (ng/mL) of edoxaban after oral administration. Note that the x-axes are not continuous. (a) Data from the single-administration study. The 60 mg results were from the subjects in the fasted portion of the fed/fasting crossover study. (b) Data from day 1 and day 10 (study end) of the ascending multiple-administration study. Dotted line indicates lower limit of quantitation (1 ng/mL). Reproduced from Ogata et al.,^[38] with permission from SAGE Publications © 2010. **bid**=twice daily; **od**=once daily.

Studies in healthy volunteers have also noted that the formulation of edoxaban 60 mg as either tablet or oral solution had no effect on bioavailability, and administration with a high-fat meal had only modest and clinically insignificant effects on bioavailability, which demonstrated that edoxaban can be administered without regard to food.^[38,40]

Single doses of edoxaban in the range 10–150 mg in healthy volunteers demonstrated a consistent and proportional relationship for peak

plasma concentration and area under the plasma concentration-time curve from time 0 to the last quantifiable concentration.^[38] These results were consistent with blood coagulation parameters (activated partial thromboplastin time [aPTT] and prothrombin time [PT]), which showed a linear relationship to edoxaban concentration.^[38] However, edoxaban is a substrate for the efflux transporter P-glycoprotein (P-gp), which is primarily located in the intestine, and which acts

to pump drugs back into the intestinal lumen thereby limiting systemic absorption of xenobiotics. Consequently, in the phase III ENGAGE AF-TIMI 48 (Effective aNticoagulation with factor Xa next GEneration in Atrial Fibrillation – Thrombolysis In Myocardial Infarction) study,^[48] reduction of edoxaban dosage by 50% is required if increased drug exposure is anticipated, because of concomitant administration of strong P-gp inhibitors (e.g. verapamil, quinidine). Other factors such as creatinine clearance 30–50 mL/min or bodyweight ≤60 kg may also have a role.^[43] Potential drug interactions of edoxaban and other oral factor Xa and direct thrombin inhibitors in clinical development are also summarized in table I.

3. Pharmacodynamic Properties

The pharmacodynamic characteristics of oral factor Xa and direct thrombin inhibitors in late-stage clinical development are summarized and compared in table II.

3.1 Factor Xa Inhibition

Edoxaban is a competitive direct inhibitor of factor Xa and inhibits human factor Xa *in vitro*

with inhibition constant (Ki) values of 0.561 nmol/L with free factor Xa compared with 2.98 nmol/L for factor Xa bound to the prothrombinase complex. Edoxaban exhibited >10 000-fold selectivity for factor Xa relative to thrombin and had no inhibitory effects on other biologically relevant serine proteases.^[49] Edoxaban has been shown to have a rapid onset of action *in vivo*. For example, in rats, edoxaban 2.5 and 5 mg/kg produced significant inhibition of factor Xa activity in plasma (86% and 94% inhibition, respectively) 0.5 hour after oral administration, which was maintained for up to 4 hours.^[49] Similarly, in cynomolgus monkeys, edoxaban treatment also led to a rapid onset of anti-factor Xa activity, which reached a peak at 4 hours (93%) and persisted for 24 hours (11%) after administration.^[49]

In healthy human volunteers, anti-factor Xa activity increased dose dependently following single edoxaban doses of 10–150 mg. The maximum anti-factor Xa activity was 0.4, 2.1, 3.8, 8.1, 9.1 and 10.7 IU/mL at the edoxaban 10, 30, 60, 90, 120 and 150 mg doses, respectively. Recovery was also dose dependent and similar effects on anti-factor Xa activity were noted with multiple ascending doses (60 mg twice daily, 90 mg once daily and 120 mg once daily) over 10 days.^[38]

Table II. Comparison of the pharmacodynamic properties of oral factor Xa and direct thrombin inhibitors. Reproduced from Eriksson et al.^[23] with permission from Adis, a Wolters Kluwer business (© Adis Data Information BV 2009. All rights reserved)

Parameter	Edoxaban	Rivaroxaban	Apixaban	Dabigatran etexilate ^a
Target	FXa ^[49]	FXa	FXa	FIIa ^b
Molecular weight (Da)	548	436	460	628 (prodrug)/472 (active)
Ki (nmol/L)	0.56 ^[49]	0.4	0.08	4.5 ^b
Reversible binding to catalytic site	Yes ^[49]	Yes	Yes	Yes ^b
Concentration for doubling of PT (μmol/L) ^c	0.26 ^[49]	0.23	3.6	0.8 ^b
Concentration for doubling of aPTT (μmol/L) ^c	0.51 ^[49]	0.69	7.4	0.23 ^b
Concentration for doubling of ECT (μmol/L) ^c	NR	NR	NR	0.18 ^b
Concentration for doubling of HepTest (μmol/L) ^c	NR	NR	0.4	NR
Reversal of antithrombotic effect	APCC, rFVIII, FIX, ^[50] rFVIIa ^[51]	rFVIIa	NR	rFVIIa, APCC

a Approved for the prevention of venous thromboembolic events after hip- and knee-replacement surgery (and stroke prevention in AF in the USA). Phase III trials are ongoing in other indications.

b The data refer to dabigatran, the active metabolite of dabigatran etexilate.

c In human plasma.

APCC=activated prothrombin complex concentrate; **aPTT**=activated partial thromboplastin time; **ECT**=ecarin clotting time; **FIIa**=activated factor II (thrombin); **FIX**=factor IX (Christmassin-MTM); **FXa**=activated factor X; **Ki**=inhibition constant; **NR**=not reported; **PT**=prothrombin time; **rFVIIa**=recombinant activated factor VII (Novoseven[®]); **rFVIII**=recombinant factor VIII (Kogenate[®] FS).

3.2 Anticoagulant Activity

In human plasma *in vitro*, edoxaban doubled PT and aPTT values at concentrations of 0.256 and 0.508 $\mu\text{mol/L}$, respectively. *In vivo*, edoxaban dose-dependently inhibited thrombus formation in rat and rabbit thrombosis models (supplementary figure 2 can be found in the Supplemental Digital Content 1, <http://links.adisonline.com/DGZ/A8>). In addition, in the tail-bleeding model in rats, edoxaban did not significantly affect bleeding time at the 3 mg/kg dose level.^[49]

However, in the rat model of template bleeding, edoxaban significantly prolonged bleeding time and PT at a supratherapeutic dose (1 mg/kg intravenously), and also inhibited thrombin generation. Recombinant factor VIIa (rFVIIa; 0.3, 1 and 3 mg/kg, intravenously) reversed the edoxaban-induced prolongation of bleeding time in a dose-dependent manner and significant shortening of bleeding time was observed with rFVIIa doses of 1 and 3 mg/kg. The dose-response relationship for the increase in peak thrombin concentration with rFVIIa corresponded well with that for suppression of bleeding time and suggested that the peak concentration of thrombin generation may be a marker for the haemostatic effect of rFVIIa when used as an antidote in case of accidental haemorrhage by overdoses of direct factor Xa inhibitors.^[52]

In healthy human volunteers, aPTT and PT increased dose dependently following single edoxaban doses of 10–150 mg and after multiple ascending doses (60 mg twice daily, 90 mg once daily and 120 mg once daily) over 10 days (see figure 3 for PT concentrations over time).^[38] Prolongation of bleeding time in 8% of healthy volunteers was >9.5 minutes (none of which appeared to be clinically significant) 2 hours after initial dosing, and was independent of edoxaban dosage, formulation or dietary state. As a prolongation of bleeding time was seen in only 8% of healthy volunteers, this supports the available evidence that anticoagulants, in contrast to antiplatelet agents, do not influence bleeding time. However, at high doses, anticoagulants in general may enhance secondary bleeding if the primary platelet clot is removed. In general,

plasma edoxaban concentrations were linearly correlated with coagulation parameters (supplementary figure 3 can be found in the Supplemental Digital Content 1, <http://links.adisonline.com/DGZ/A8>).^[38]

Edoxaban was approximately 3-fold more active than the synthetic pentasaccharide indirect factor Xa inhibitor fondaparinux sodium in inhibiting thrombin generation parameters *in vitro*, with the exception of endogenous thrombin potential.^[53] In addition, the effects of oral edoxaban 30, 60 or 120 mg on markers of coagulation in shed and venous blood have been compared with placebo and fondaparinux sodium in 100 healthy male volunteers. Treatment with edoxaban led to rapid and sustained reductions for up to 24 hours in markers of coagulation (prothrombin fragment 1 + 2 [F_{1+2}]; thrombin-antithrombin [TAT]; and platelet activation [β -thromboglobulin]), which were significantly greater than with fondaparinux sodium, in the shed blood model.^[54]

In vitro, adenosine diphosphate-, collagen- and U46619-induced platelet aggregation were not inhibited by edoxaban, although a high concentration (concentration for 50% inhibition [IC_{50}] 2.90 $\mu\text{mol/L}$) did inhibit thrombin-induced platelet aggregation, reflecting the weak antithrombin activity of edoxaban.^[49]

3.3 Safety Margin

The safety margin of edoxaban has also been evaluated by comparing its antithrombotic effects with those of the thrombin inhibitor melagatran in a rat model of intracerebral haemorrhage (ICH).^[55] Edoxaban 3 mg/kg/h had no effect on ICH volume, while PT was doubled. Higher doses of edoxaban (6 and 18 mg/kg/h) significantly increased ICH volume in a dose-dependent manner (180% and 230%, respectively) and PT was prolonged 2.8- and 6.5-fold, respectively. No deaths were observed in the edoxaban groups. Melagatran at 0.3 mg/kg/h did not affect ICH but enlarged ICH volume at 1 mg/kg/h (280%), with approximately 6-fold prolongation of PT. At a higher dose of melagatran (3 mg/kg/h), all treated rats died, probably due to severe ICH damage.

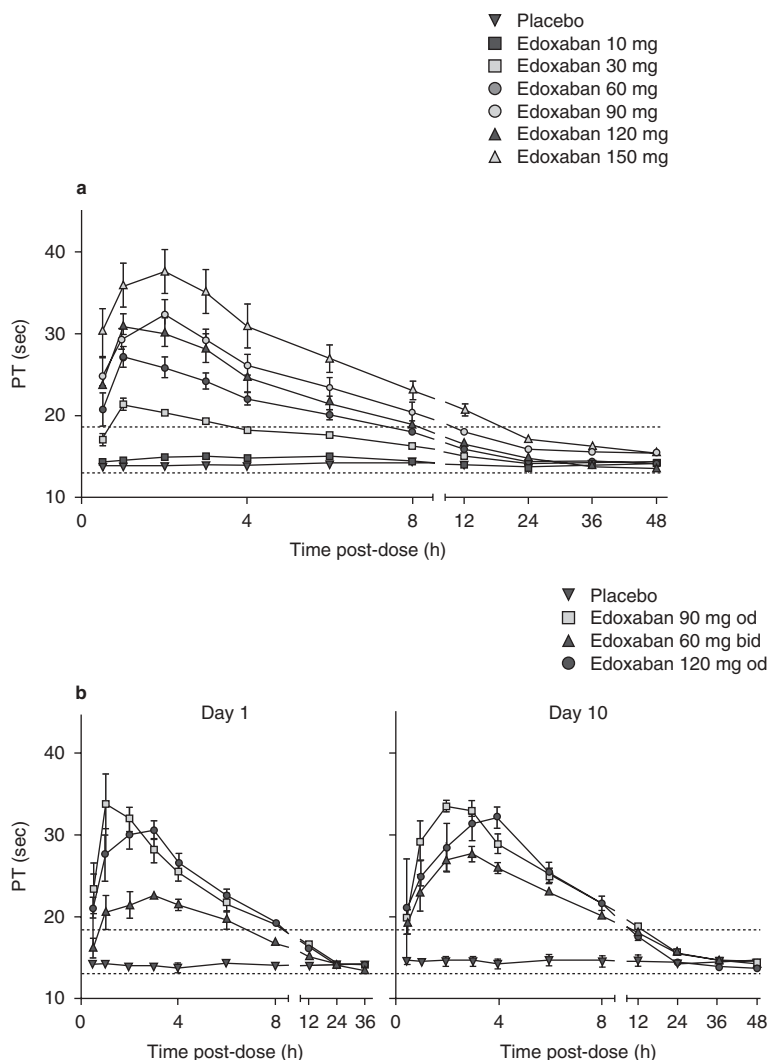


Fig. 3. Mean \pm SEM effects of edoxaban on prothrombin time (PT) after oral dosing. Note that the x-axes are not continuous. **(a)** Data from the single-administration study. The 60 mg results were from subjects in the fasted portion of the fed/fasting crossover study. **(b)** Data from day 1 and day 10 (study end) of the ascending multiple-administration study. Dotted lines represent the reference range for the analysis (reproduced from Ogata et al.,^[38] with permission from SAGE Publications © 2010). **bid** = twice daily; **od** = once daily; **SEM** = standard error of the mean.

Edoxaban and melagatran had no effects on physiological parameters at these doses. The edoxaban and melagatran effective dose (ED_{50}) values for 50% inhibition of thrombosis were 0.045 and 0.12 mg/kg/h, respectively, with safety margins of 133 and 8, respectively.^[55]

In summary, edoxaban and other novel oral anticoagulants in development have shown pre-

dictable and reversible anticoagulant effects in pre-clinical studies, which suggests they can be given in fixed doses without routine INR monitoring.^[23] Edoxaban has been shown to be a potent and selective factor Xa inhibitor in preclinical studies^[49] and, in healthy volunteers, edoxaban demonstrated rapid and sustained inhibition of coagulation up to 24 hours.^[54]

4. Clinical Trials

4.1 Phase I Clinical Trials

4.1.1 Effects on Thrombus Formation and Coagulation Parameters

The antithrombotic effects of a single dose of edoxaban 60 mg have been investigated in a phase I study in 12 healthy volunteers. Edoxaban treatment significantly reduced *ex vivo* thrombus formation in both venous and arterial flow conditions, up to 5 hours post-dose.^[39] The onset of action of edoxaban was rapid, and under venous flow conditions (low shear rate) after 1.5 and 5 hours the thrombus size was 28% and 21% smaller versus baseline, respectively ($p < 0.01$). Under arterial flow conditions (high shear rate), the corresponding reductions versus baseline were 26% and 17%, respectively ($p < 0.01$). Endogenous thrombin potential decreased by 28% at 1.5 hours and 10% at 5 hours ($p < 0.01$ in both cases) and then increased to return to baseline levels at 12 hours. Changes in PT and INR correlated well with plasma edoxaban concentrations ($R^2 = 0.80$ and 0.78 , respectively).^[39] The antithrombotic activity of edoxaban paralleled the changes in clotting parameters, suggesting the possibility of their use for monitoring purposes, and the reduction in the generation of thrombin was associated with a decrease in size of the acute platelet-rich thrombus.^[39]

In phase I single ascending dose and multiple ascending dose studies, edoxaban had dose-dependent effects on INR (up to a maximum value of 3.5), which were reversible within 24 to 36 hours. After single doses of edoxaban, the maximum INR increased dose dependently from an 85% increase relative to baseline (1.1–2.04) at 60 mg to a 189% increase relative to baseline (1.2–3.47) at 150 mg.^[38] After multiple doses of edoxaban, the maximum INR increased 209% from baseline (1.0–3.09) to 240% from baseline (0.9–3.41) for edoxaban 90 mg daily and 120 mg daily, respectively, at day 10. The maximum INR values achieved with edoxaban 60 mg twice-daily dosing were lower than those for 90 mg daily and 120 mg daily doses.^[38]

4.1.2 Safety

Single doses of edoxaban up to 150 mg and multiple doses up to 120 mg/day for 10 days were well

tolerated, with no dose-dependent increase in drug-related adverse events in the phase I study reported by Ogata et al.^[38] After single doses of edoxaban, treatment-emergent adverse events (TEAEs) were reported by 17.4% of subjects compared with 9.5% in the placebo group. Most TEAEs were mild (76.7%) and none were considered serious. The most commonly reported TEAEs included headache, dizziness, sweating, diarrhoea, dyspepsia and prolongation of bleeding following venipuncture.^[38] Similarly, in the multiple-administration study, 10/27 edoxaban-treated subjects (37.0%) experienced a TEAE compared with 9/9 subjects (100.0%) who were on placebo. Most of the TEAEs were mild (77.0%) and none were considered severe. There were no serious adverse events (AEs), and the most common TEAEs in the multiple-dose study included abdominal discomfort, diarrhoea, upper abdominal pain, constipation, gingival bleeding and myalgia. Eight percent of subjects exhibited a bleeding time of >9.5 minutes and none of the increases appeared to be clinically significant. Bleeding time returned to normal within 12 hours in 9/10 individuals who exhibited prolongation and within 24 hours for the remaining subject. No adverse effects of edoxaban on clinical safety parameters (12-lead ECG, bodyweight and vital signs) were noted, and there were no apparent trends or clinically relevant changes in serum biochemistry, haematology laboratory values, creatinine clearance, urinalysis or any positive faecal occult blood tests for the duration of the studies.^[38]

In addition, the lack of effect of a single supra-therapeutic (180 mg) dose of edoxaban on corrected QT (QTc) interval duration in a phase I, randomized, placebo-controlled study in healthy volunteers ($n = 64$) has indicated that it has a low potential liability for inducing cardiac arrhythmias related to QT prolongation.^[56]

4.2 Phase II Clinical Trials

4.2.1 Prevention of Venous Thromboembolism in Orthopaedic Surgery

Patients undergoing major orthopaedic surgery are at a high risk of postoperative venous thromboembolism and, without the use of thrombopro-

phylaxis, objectively confirmed hospital-acquired deep vein thrombosis (DVT) occurs in approximately 40–60% of patients.^[4] Suggested thromboprophylaxis options for patients undergoing hip or knee arthroplasty that are recommended in current guidelines include LMWH, the indirect factor Xa inhibitor fondaparinux sodium or warfarin.^[4] However, LMWH and fondaparinux sodium both require subcutaneous administration and, in view of the additional limitations of warfarin, oral anticoagulants are also in development for use in patients undergoing orthopaedic surgery.^[20]

Total Knee Arthroplasty

A randomized, double-blind, placebo-controlled, multicentre, phase II dose-ranging study of the efficacy and safety of edoxaban has been conducted in 523 Japanese patients undergoing total knee arthroplasty who were assigned to receive edoxaban 5, 15, 30 or 60 mg once daily or placebo for 11–14 days.^[25] A placebo control was used in this study, as neither a LMWH nor fondaparinux sodium had been approved for prevention of VTE in Japan at the time of study initiation. Edoxaban treatment led to statistically significant dose-dependent reductions in VTE (lower extremity DVT, symptomatic pulmonary embolism [PE] or symptomatic DVT) compared with placebo. The incidence of major and clinically relevant non-major bleeding was similar across all groups: 1.9–4.7% in the edoxaban groups versus 3.9% in the placebo group. Frequently reported ($\geq 5\%$) AEs included wound haemorrhage, erythema, subcutaneous haemorrhage, pruritus, haematuria, decreased haemoglobin and increased platelets, but edoxaban was well tolerated overall. Severe AEs occurred in only 0.9% of patients in the edoxaban 60 mg once-daily group compared with 2.9% in the placebo group. Pharmacokinetic and pharmacodynamic observations in this study were consistent with those in healthy volunteers, which suggested that the surgical setting did not significantly alter the exposure metrics of edoxaban.^[25]

Thus, once-daily administration of edoxaban produced significant dose-dependent reductions

in VTE in patients undergoing total knee arthroplasty, with a bleeding incidence similar to placebo.^[25] Phase III clinical trials in this indication have been conducted and completed in Japan.

Total Hip Arthroplasty

A randomized, parallel-group, active-controlled, double-blind, multicentre phase II dose-response study with a double dummy design has been conducted in which 903 patients undergoing elective total hip arthroplasty were assigned to treatment with edoxaban 15, 30, 60 or 90 mg once daily or subcutaneous dalteparin sodium once daily (initial dose 2500 IU, subsequently increased to 5000 IU).^[57] Anticoagulant therapy was started 6–8 hours postoperatively and continued for 7–10 days. The incidence of total VTE in the edoxaban 15, 30, 60 and 90 mg once-daily groups was 28.2%, 21.2%, 15.2% and 10.6%, respectively, versus 43.8% in the dalteparin sodium group ($p < 0.005$) [figure 4]. There were also statistically significant trends for dose-response for efficacy across the edoxaban dose groups for total VTE ($p < 0.001$), major VTE ($p < 0.01$) and any proximal DVT ($p < 0.01$). The incidence of major and clinically relevant non-major bleeding was low and similar across the groups (1.6%, 1.8%, 2.2% and 2.3% in the edoxaban 15, 30, 60 and 90 mg once-daily groups, respectively, vs 0% in the dalteparin sodium group). An edoxaban dose-response relationship for bleeding outcomes was not detected. Overall, edoxaban appeared to be well tolerated and the incidence of TEAEs with edoxaban (35.4%, 28.2%, 36.2% and 39.0% in the 15 mg, 30 mg, 60 mg and 90 mg groups, respectively) was similar to that observed in the dalteparin sodium group (34.9%), and no indications of hepatotoxicity were noted.^[57]

In addition, oral administration of edoxaban 15 mg and 30 mg once daily showed potential efficacy similar to subcutaneous enoxaparin sodium 20 mg twice daily for the prevention of VTE in a randomized, multicentre, parallel group phase IIb study in 264 patients undergoing total hip arthroplasty. The incidence of VTE was 3.8%, 2.8% and 4.1% in the edoxaban 15 mg, 30 mg

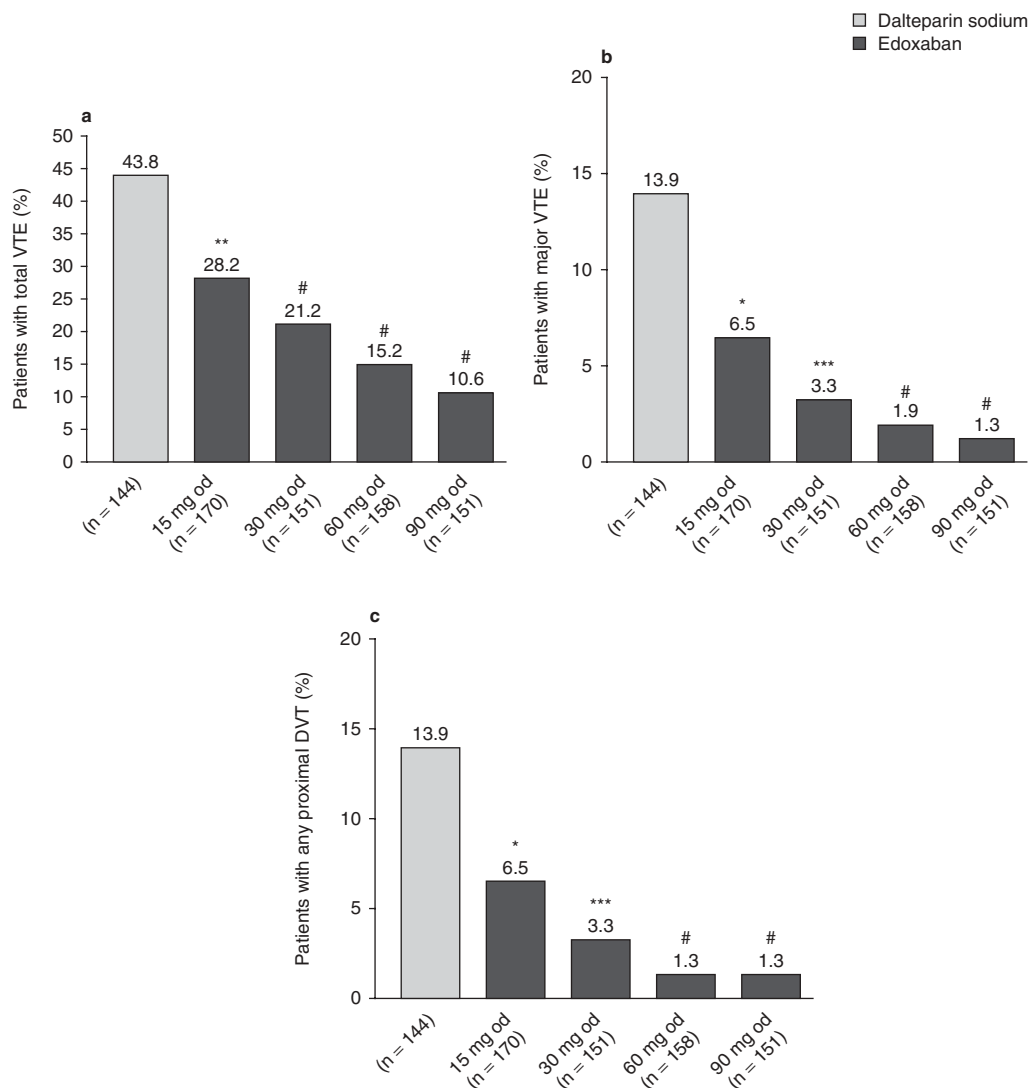


Fig. 4. Incidences of (a) total venous thromboembolic events (VTEs), (b) major VTE and (c) any proximal deep vein thrombosis (DVT) in patients undergoing elective total hip arthroplasty. p-Values vs dalteparin sodium.^[57] od=once daily; * p=0.036, ** p=0.005, *** p=0.001, # p<0.001.

and enoxaparin sodium groups, respectively. The incidence of major and clinically relevant non-major bleeding with edoxaban was also comparable to that of enoxaparin sodium.^[58]

In summary, oral administration of edoxaban once daily is effective for preventing VTE after total hip arthroplasty.

4.2.2 Atrial Fibrillation

AF is the most commonly occurring significant cardiac arrhythmia (1–2% of the general population), and it affects up to 6 million people in Europe and more than 3 million people in the US.^[1,2,59] AF is a major cause of morbidity, mortality and hospitalization.^[1,2,60,61] In particular,

AF is associated with increased rates of death, stroke and other thromboembolic events, heart failure and hospitalizations, degraded quality of life, reduced exercise capacity and left ventricular dysfunction.^[2] The risk of stroke is increased 5-fold by AF,^[2] death rates are doubled, independently of other known predictors of mortality,^[61,62] and only antithrombotic therapy has been shown to reduce AF-related mortality.^[63]

The safety of antithrombotic therapy with fixed doses of edoxaban (30 mg once daily, 30 mg twice daily, 60 mg once daily or 60 mg twice daily; double-blind) has been compared with that of open-label warfarin (INR 2.0–3.0) in 1146 patients with non-valvular AF and risk of stroke (CHADS₂ score ≥ 2) in a 12-week, parallel-group, multicentre, multinational, phase II dose-finding study.^[24] Overall, the edoxaban 30 mg once-daily and 60 mg once-daily regimens had a similar safety profile to that of dose-adjusted warfarin, but the 60 mg once-daily regimen was safer than the 30 mg twice daily regimen in terms of the incidence of bleeding events (figure 5).^[24] The ex-

planation for this unexpected finding was that the bleeding incidence may have been due to the higher trough plasma concentrations of edoxaban seen with twice-daily dosing. The incidence of stroke/transient ischaemic attacks was comparable across all edoxaban treatment groups (0.4–1.1%) and was highest in the warfarin group (1.6%). The rates of myocardial infarction (0.0–0.9%) and cardiovascular death (0.0–1.6%) were also low across the edoxaban groups, and in the warfarin group (0.0 and 0.8%, respectively). In general, few events were reported and the study was not powered to detect differences in major cardiovascular events. Overall, 40.4%, 39.8%, 42.3%, 45.6% and 46.0% in the edoxaban 30 mg once daily, 30 mg twice daily, 60 mg once daily, 60 mg twice daily and warfarin treatment groups reported TEAEs, respectively. There were no significant differences in hepatic enzyme elevations or bilirubin values among the groups.^[24]

In addition, a 3-month, randomized, parallel-group, multicentre, double-blind study of edoxaban (30 mg once daily and 60 mg once daily) and

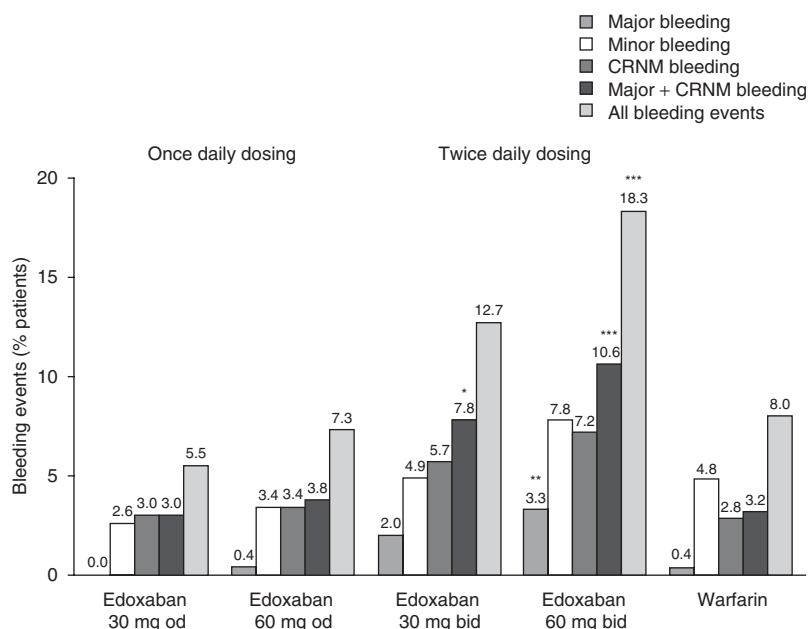


Fig. 5. Bleeding events during long-term treatment with edoxaban or warfarin in patients with atrial fibrillation (safety population). Patients were counted only once under the most severe event. p-Values vs warfarin. **bid** = twice daily; **CRNM** = clinically relevant non-major; **od** = once daily; * $p = 0.029$, ** $p = 0.023$, *** $p = 0.002$.^[24]

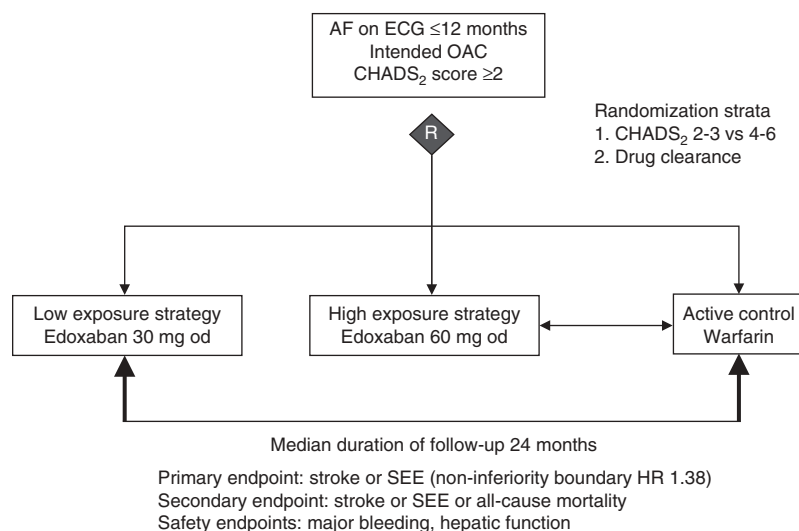


Fig. 6. Design of the randomized, double-blind ENGAGE AF-TIMI 48 study of edoxaban vs warfarin in patients with moderate-high risk atrial fibrillation (AF). **CHADS₂** = Cardiac failure, Hypertension, Age, Diabetes, Stroke doubled stratification scheme; **HR** = hazard ratio; **OAC** = oral anticoagulant; **od** = once daily; **R** = randomization **SEE** = systemic embolic event; ↔ indicates primary analyses of the study.

open-label warfarin (INR 2.0–3.0) in 235 Asian patients with non-valvular AF has also shown a trend towards a lower incidence of bleeding with edoxaban compared with dose-adjusted warfarin. However, dose adjustment of edoxaban may be required in patients with low bodyweight (≤ 60 kg).^[64]

A trend towards dose-dependent increases in bleeding events was noted in a 12-week, randomized, controlled, parallel group, multicentre study of edoxaban (30, 45 or 60 mg once daily) or open-label warfarin (INR 2.0–3.0 for age <70 years or 1.6–2.6 for age ≥ 70 years) in 536 Japanese patients with non-valvular AF. The mean incidences of all bleeding for edoxaban 30 mg, 45 mg and 60 mg once daily and warfarin were 18.5%, 22.4%, 27.7% and 20.0%, respectively, but no statistically significant differences were noted between any edoxaban doses and warfarin.^[65]

Open-label phase II studies of edoxaban titrated from 5–30 mg once daily (low dose, $n=24$) and from 30–60 mg twice daily (high dose, $n=32$) in Japanese warfarin-naïve patients with AF have confirmed the linear relationship between plasma edoxaban concentrations and pharmacodynamic variables, including reductions in biomarkers of coagulation activation (D-dimer, TAT and F_{1+2}).^[66]

In summary, phase II trials in AF have indicated the rates of bleeding with edoxaban 30 mg or 60 mg once daily were similar to or less than with warfarin,^[24,64] and bleeding rates with edoxaban twice daily were approximately double those with edoxaban once daily. Therefore, these once-daily edoxaban doses were selected for further investigation and comparison with warfarin for stroke prevention in patients with AF in the phase III ENGAGE AF-TIMI 48 trial^[48] (figure 6).

4.3 Phase III Trial Programmes

A range of new oral anticoagulant drugs are currently in late-stage clinical development, including oral factor Xa inhibitors and an oral direct thrombin inhibitor. The research programmes for agents that are either currently approved or undergoing investigation in large-scale, phase III clinical trials (edoxaban, rivaroxaban, apixaban and dabigatran) are summarized in tables III and IV for stroke prevention in AF and prevention and treatment of VTE, respectively. In particular, recently completed landmark phase III trials of new oral anticoagulants include the RE-LY (Randomized Evaluation of Long-term anticoagulant therapy with dabigatran etexilate) study,^[35] the

Table III. Summary of phase III trials of factor Xa and oral direct thrombin inhibitors in development for prevention of stroke in patients with atrial fibrillation (AF) [sources: www.clinicaltrials.gov (Accessed 2011 Jun 20); Ahrens et al.;^[19] Mavrakanas and Bounameaux^[20]]

Product/trial	Interventions	Design	Patient number	Primary endpoint	Outcome/status
Edoxaban					
ENGAGE AF-TIMI 48 (NCT00781391) ^[48]	Edoxaban 30 or 60 mg od vs warfarin ^a	r, db, dd	21 107 (CHADS ₂ score ≥2)	Composite primary endpoint of stroke and SEE Expected duration 24 mo	Ongoing (estimated primary completion 2012)
Rivaroxaban					
ROCKET-AF (NCT00403767) ^[32-34,67]	Rivaroxaban 20 mg od vs warfarin ^a	r, db, dd, Noninf	14 264 (CHADS ₂ score ≥2)	Any stroke or non-CNS systemic embolism Composite of major and CRNM bleeding events Follow-up 4 years	Completed Rates of the primary efficacy outcome (PP, Noninf) were: warfarin 2.16 per 100 patient-years; rivaroxaban 1.71 per 100 patient-years (HR 0.79; p < 0.001) Rates of major and CRNM bleeding were similar: warfarin 14.52 per 100 patient-years; rivaroxaban 14.91 per 100 patient-years (HR1.03; p = 0.442)
J-ROCKET AF (NCT00494871)	Rivaroxaban 15 mg od vs warfarin ^a	r, db	1 280	The composite of major and CRNM bleeding events (safety) The composite of stroke and non-CNS systemic embolism (efficacy)	Completed
Apixaban					
AVERROES (NCT00496769) ^[68,69]	Apixaban 5 mg bid ^b vs aspirin 81–324 mg od	r, db ^c	5 600 ^d (CHADS ₂ score ≥1)	Time to first occurrence of unrefuted ischaemic stroke, haemorrhagic stroke or systemic embolism	Study terminated early as interim analysis showed that stroke rates were: aspirin 3.3%, apixaban 1.5% (RR 0.48) Rates of major and CRNM bleeding were similar
ARISTOTLE (NCT00412984)	Apixaban 5 mg bid vs warfarin ^a	r, db, dd, Noninf	15 000 (CHADS ₂ score ≥1)	Confirmed stroke or systemic embolism	Completed
Dabigatran					
RE-LY (NCT00262600) ^[35]	Dabigatran 110 or 150 mg bid vs warfarin ^a	r, db, Noninf	18 113 (mean CHADS ₂ score 2.1)	Incidence of stroke (including haemorrhagic) and systemic embolism Median duration of follow-up 2.0 y	Completed Rates of the primary outcome were: warfarin group 1.69% per year dabigatran 110 mg 1.53% per year (RR 0.91; p < 0.001 for non-inferiority) dabigatran 150 mg 1.11% per year (RR 0.66; p < 0.001 for superiority) Rates of major haemorrhage were similar
RELY-ABLE (NCT00808067)	Dabigatran low vs high dose bid	r, db	6 200 ^e	Major bleeding (up to 28 mo)	Ongoing (estimated primary completion 2011)

a INR 2.0–3.0.

b Apixaban 2.5 mg bid in selected patients.

c Optional long-term open-label extension phase.

d Patients unsuitable for warfarin treatment.

e Patients who completed the RE-LY trial.

bid = twice-daily; **CHADS₂** = Congestive heart failure, Hypertension, Age, Diabetes, Stroke or transient ischaemic attack doubled; **CRNM** = clinically relevant non-major; **db** = double-blind; **dd** = double-dummy; **DVT** = deep vein thrombosis; **HR** = hazard ratio; **INR** = international normalized ratio; **ITT** = intention-to-treat analysis; **Noninf** = non-inferiority study; **od** = once-daily; **PE** = pulmonary embolism; **PP** = per-protocol analysis; **r** = randomized; **RR** = relative risk; **SEE** = systemic embolic event.

AVERROES (Apixaban VERSus acetylsalicylic acid to pRevent strOkES) study,^[68,69] in patients with AF, and the ROCKET AF (Rivaroxaban Once daily, oral, direct Factor Xa inhibition Compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation) study,^[32-34,67] as well as the secondary prevention RE-COVER trial of dabigatran in patients with acute VTE.

4.3.1 Dabigatran, Apixaban and Rivaroxaban

In the RE-LY study in patients with AF and a risk of stroke, comparison of two doses of the oral direct thrombin inhibitor dabigatran (110 mg and 150 mg) was double-blinded, whereas adjusted-dose warfarin was open label. Dabigatran 110 mg twice daily was non-inferior to warfarin for the prevention of stroke and systemic embolism with lower rates of major bleeding, whilst dabigatran 150 mg twice daily was associated with lower rates of stroke and systemic embolism with similar rates of major haemorrhage, compared with warfarin (table III). In addition, both dabigatran doses were associated with a lower rate of ICH compared with warfarin.^[35] Similarly, in the ROCKET-AF study, rivaroxaban was non-inferior to warfarin for prevention of stroke and non-CNS embolism in the intention-to-treat analysis, but achieved superiority in the less stringent on-treatment analysis (i.e. while taking study drug). Similar rates of bleeding and AEs were also noted with rivaroxaban compared with warfarin; however, there was less ICH and fatal bleeding with rivaroxaban (table III).^[34,67] The AVERROES study in patients with AF was terminated early because of a reduction in stroke and systemic embolism with the oral factor Xa inhibitor apixaban 5 mg twice daily compared with aspirin 81–324 mg once daily in warfarin-ineligible patients (table III).^[68,69]

In addition, in the RE-COVER trial, dabigatran 150 mg twice daily was as effective as warfarin in the secondary prevention of VTE in patients with DVT or PE, with similar levels of bleeding risk, but with a significantly greater risk of discontinuation due to AEs.^[73] Rivaroxaban (20, 30 and 40 mg) was shown to have similar efficacy to warfarin/LMWH, on a composite

endpoint that included symptomatic DVT and PE, in the EINSTEIN-DVT dose ranging study.^[74] Treatment with rivaroxaban 20 mg once daily (following an initial 3 weeks of 15 mg twice daily) for up to 12 months is now being investigated in the randomized, open-label, non-inferiority EINSTEIN-DVT and EINSTEIN-PE studies in patients with acute symptomatic DVT and in patients with acute symptomatic PE, respectively. In addition, the EINSTEIN-Extension study is a double-blind, randomized, event-driven superiority study that compared rivaroxaban alone (20 mg once daily) with placebo for an additional 6 or 12 months in patients who had completed 6–12 months of treatment for VTE.^[70] The EINSTEIN-DVT study showed that rivaroxaban had non-inferior efficacy versus enoxaparin sodium-VKA therapy with respect to symptomatic recurrent VTE (36 events [2.1%] vs 51 events [3.0%], respectively; hazard ratio 0.68 [$p < 0.001$]). Major or clinically relevant non-major bleeding occurred in 8.1% of the patients in each group.^[70] In the EINSTEIN-Extension study, rivaroxaban had superior efficacy to placebo with no statistically significant increase in major bleeding.^[70]

4.3.2 Edoxaban

In the completed ROCKET-AF and ongoing ARISTOTLE (Apixaban for Reduction In STroke and Other ThromboemboLic Events in atrial fibrillation)^[75] phase III studies in patients with AF, single doses of rivaroxaban (20 mg once daily) and apixaban (5 mg twice daily) have been investigated, and it should be noted that neither dose was based upon phase II studies. In contrast, the phase III study of edoxaban is using two doses that were selected on the basis of phase I and phase II study results in patients with AF and in patients undergoing major orthopaedic surgery. The evaluation of two doses of an anticoagulant increases the chance of a successful trial outcome but may produce results that are difficult to interpret or translate into regulatory approval. The edoxaban 30 mg once-daily and 60 mg once-daily regimens were found to have a safety profile similar to dose-adjusted warfarin in phase II trials. Each of these doses has been carried forward into a large-scale, randomized, double-blind,

Table IV. Summary of phase III trials of oral direct thrombin and factor Xa inhibitors in development for prevention and treatment of venous thromboembolic events (VTEs) [sources: www.clinicaltrials.gov (Accessed 2011 Feb 3); Ahrens et al.^[19] Mavrakanas and Bounameaux^[20]]

Product/trial/setting	Interventions	Design	Patient number	Primary endpoint	Outcome/status
Edoxaban					
HOKUSAI VTE (NCT00986154) Treatment and prevention of recurrent VTE in patients with acute DVT and/or PE	Edoxaban 30 or 60 mg od vs warfarin after initial LMWH 1 mg/kg bid or 1.5 mg/kg od SC	r, db	7 500	Composite clinical outcome of symptomatic recurrent DVT, non-fatal symptomatic recurrent PE and all-cause mortality	Recruiting/ongoing (estimated primary completion 2012)
Rivaroxaban					
EINSTEIN-DVT (NCT00440193) ^[70] Secondary prevention of VTE	Rivaroxaban 15 mg bid (3 wks) then 20 mg od (3, 6 or 12 mo) vs enoxaparin 1 mg bid switched to warfarin within 48 h ^a	r, sb ^b , Noninf	2 900	Symptomatic recurrent VTE	Completed Rivaroxaban non-inferior to warfarin with trend for superiority
EINSTEIN-PE (NCT00439777) Secondary prevention of VTE	As for EINSTEIN-DVT	r, sb ^b , Noninf	4 000	Symptomatic recurrent VTE	Completed
EINSTEIN-Extension (NCT00439725) ^[70] Secondary prevention of VTE	Rivaroxaban 20 mg od vs placebo	r, db, Sup	1 197	Symptomatic recurrent VTE (composite of recurrent DVT, non-fatal and fatal PE)	Completed Extended OAC with rivaroxaban superior to placebo
MAGELLAN (NCT00571649) Primary prevention of VTE in hospitalized, medically ill patients	Rivaroxaban 10 mg od (31–39 days) vs enoxaparin 40 mg od (6–14 days)	r, db	8 000	Composite of VTE (DVT and/or PE) and death up to day 35	Completed
ATLAS 2 TIMI 51 (NCT00809965) ^[71] Secondary prevention of CV events in ACS	Rivaroxaban 2.5 or 5 mg bid vs placebo	r, db	15 527	Risk of the composite endpoint of CV death, MI, or stroke	Recruiting/ongoing (estimated primary completion 2011)
Apixaban					
AMPLIFY Prevention of recurrent VTE study (NCT00643201)	Apixaban 10 mg bid (7 days) followed by 5 mg bid (6 mo) vs enoxaparin 1 mg/kg bid then warfarin	r, db, dd	4 816	VTE recurrence or death	Recruiting/ongoing (estimated primary completion 2012)
AMPLIFY-Extension Prevention of recurrent VTE or death (NCT00633893)	Apixaban 2.5 or 5 mg bid vs placebo (12 mo)	r, db,	2 430	VTE recurrence or death	Recruiting (estimated primary completion 2013)
APPRAISE-2 (NCT00831441) ^[72] Prevention of acute ischaemic events in patients with recent ACS	Apixaban 5 mg bid	r, db, Sup	10 800	Time to first occurrence of CV death, MI or ischaemic stroke	Study terminated early due to increased bleeding risk with apixaban
ADOPT (NCT00457002) Primary prevention of VTE in hospitalized, medically ill patients	Apixaban 2.5 mg bid vs enoxaparin 40 mg od	r, db, dd	6 524	Composite of VTE and VTE-related death during 30 days sb treatment	Recruiting/ongoing (estimated primary completion 2011)
Dabigatran					
RE-COVER (NCT00291330) ^[73] Treatment of acute VTE	Dabigatran 150 mg od vs warfarin ^a	r, db, Noninf	2 564	Composite of recurrent symptomatic VTE and deaths related to VTE within 6 mo	Completed Dabigatran non-inferior to warfarin

Continued next page

Table IV. Contd

Product/trial/setting	Interventions	Design	Patient number	Primary endpoint	Outcome/status
RE-COVER II Treatment of acute VTE study (NCT00680186)	Dabigatran 150 mg bid vs warfarin ^a	r, db	2 554	Composite of recurrent symptomatic VTE and deaths related to VTE within 6 mo	Ongoing (estimated primary completion 2011)
RE-MEDY Secondary prevention of VTE (NCT00329238)	Dabigatran 150 mg bid vs warfarin ^a	r, db	2 700	Composite of recurrent symptomatic VTE and deaths related to VTE during the treatment period	Completed
RE-SONATE Long-term prevention of recurrent symptomatic VTE (NCT00558259)	Dabigatran 150 mg bid vs placebo ^c	r, db, Sup	1 412	Composite of recurrent DVT or fatal or non-fatal PE during the treatment period	Ongoing (estimated primary completion 2011)

a INR guided.
b Open-label (assessor blinded).
c Patients had completed 6–18 mo treatment with VKA.

ACS = acute coronary syndrome; **bid** = twice-daily; **CV** = cardiovascular; **db** = double-blind; **dd** = double-dummy; **DVT** = deep vein thrombosis; **INR** = international normalized ratio; **LMWH** = low molecular weight heparin; **MI** = myocardial infarction; **Noninf** = non-inferiority study; **OAC** = oral anticoagulation; **od** = once-daily; **ol** = open-label; **PE** = pulmonary embolism; **r** = randomized; **sb** = single-blind; **SC** = subcutaneous; **Sup** = superiority study; **VKA** = vitamin K antagonist.

double-dummy phase III trial (ENGAGE AF-TIMI 48) in which they are being compared with the current standard of care with dose-adjusted warfarin for stroke prevention (figure 6; table III). A total of 21 107 patients with AF who are at moderate to high risk of stroke (CHADS₂ score ≥2), have been enrolled, from over 1400 sites worldwide, making ENGAGE AF-TIMI 48 the largest AF trial so far. Patients eligible for inclusion in this trial will be randomly assigned, on a double-blind, double-dummy basis, to one of three treatment groups: edoxaban 30 mg once daily, edoxaban 60 mg once daily or warfarin. The trial will involve administration of edoxaban at fixed doses without coagulation monitoring, while warfarin dosage will be adjusted to maintain an INR in the range 2.0–3.0. The primary objective of ENGAGE AF-TIMI 48 is to compare edoxaban versus warfarin with regard to the composite primary endpoint of stroke and systemic embolic events, while the primary safety endpoint is major bleeding. The study was initiated in December 2008, the expected median duration of follow-up is 24 months and the trial is scheduled to be completed in 2012.^[43,48] As edoxaban and rivaroxaban are being directly compared with warfarin and apixaban with aspirin and warfarin separately, network meta-analyses and indirect comparisons may be needed to compare edoxaban with placebo and aspirin, which would prove cost-effective and has already been published for dabigatran.^[76]

Edoxaban 60 mg once daily is also being compared with warfarin after initial heparin (unfractionated and LMWH) once daily in the HOKUSAI VTE study (table IV; figure 7). HOKUSAI VTE (NCT00986154) is a randomized, double-blind, double-dummy study comparing edoxaban with warfarin after an initial 5-day period with a heparin-based treatment in both arms. In contrast, EINSTEIN DVT and EINSTEIN PE are randomized open studies comparing rivaroxaban with the conventional regimen of LMWH overlapped and followed by a vitamin K antagonist. Also, AMPLIFY (Apixaban after the initial Management of Pulmonary embolism and deep vein thrombosis with First-line therapy) is a randomized, double-blind, triple-dummy study comparing

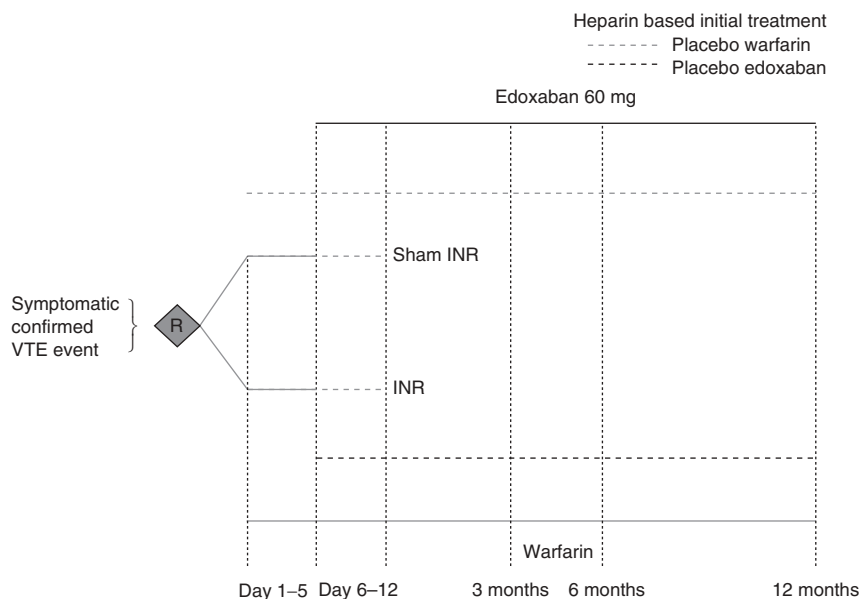


Fig. 7. Design of the randomized, double-blind, multinational phase III HOKUSAI-VTE trial of edoxaban vs warfarin for the treatment and prevention of recurrent venous thromboembolic events (VTEs). **INR**=international normalized ratio; **R**=randomization.

apixaban with LMWH overlapped and followed by warfarin. HOKUSAI VTE is currently the largest, single, randomized, double-blind, multinational phase III trial for the treatment and prevention of recurrent VTE in approximately 7500 patients with acute symptomatic proximal DVT and/or symptomatic PE confirmed by diagnostic imaging. The primary outcome measure is symptomatic recurrent VTE (i.e. the composite of DVT, non-fatal PE and fatal PE) over a 12-month time frame from randomization. The treatment duration depends on the individual patient's risk profile requiring anticoagulation for 3, 6 or 12 months. Secondary outcome measures include the composite clinical outcome of symptomatic recurrent DVT, non-fatal symptomatic recurrent PE, and all-cause mortality and clinically relevant bleeding (i.e. major or clinically relevant non-major bleeding) occurring during treatment. HOKUSAI VTE commenced in October 2009 and is scheduled to be completed in 2012.^[77,78]

Phase III clinical trials looking at VTE prevention following orthopaedic surgery are summarized in table V. The STARS (Studying Thrombosis After Replacement) E-3 trial (NCT01181102)

looked at 716 Japanese patients who had undergone total knee arthroplasty and found that edoxaban 30 mg once daily was superior to subcutaneous enoxaparin sodium 20 mg twice daily in reducing a composite endpoint of symptomatic PE and symptomatic and asymptomatic DVT detected by routine venography. There was no statistically significant difference in bleeding events; however, the study was not powered to detect small differences in bleeding rates.^[79] In STARS E-3 in particular, the primary efficacy outcome occurred in 7.4% of patients in the edoxaban group and 13.9% of patients in the enoxaparin sodium group (relative risk reduction 46.8%), indicating non-inferiority ($p < 0.001$) as well as superiority ($p = 0.010$) of edoxaban relative to enoxaparin sodium. There were no cases of PE, ICH or deaths. Major and clinically relevant non-major bleeding occurred in 6.2% versus 3.7% of the edoxaban and enoxaparin sodium groups, respectively ($p = 0.129$). Elevations of serum aminotransferase levels of ≥ 3 times the upper limit of normal (ULN) were noted in only 1.4% of the edoxaban group versus 8.0% of the enoxaparin sodium group.^[79] Similarly, in the STARS J-5 trial in 610

Table V. Summary of phase III trials of oral direct thrombin and factor Xa inhibitors in development for the prevention of venous thromboembolic events (VTEs) after orthopaedic surgery (sources: www.clinicaltrials.gov [Accessed 2011 Jun 20]; Ahrens et al.^[19])

Product/trial/setting	Interventions	Design	Patient number	Primary endpoint	Outcome/status
Edoxaban					
STARS E-3 (NCT01181102) ^[79] Thromboprophylaxis after knee surgery	Edoxaban 30 mg od vs enoxaparin 20 mg bid	r, db, dd, Noninf	716	Composite of symptomatic PE and symptomatic and asymptomatic DVT	Completed Edoxaban superior to enoxaparin
STARS J-4 (NCT01181141) ^[80] Thromboprophylaxis after hip surgery	Edoxaban 30 mg od vs enoxaparin 20 mg bid	r, ol	92	Bleeding events	Completed Edoxaban similar to enoxaparin
STARS J-5 (NCT01181167) ^[81] Thromboprophylaxis after hip surgery	Edoxaban 30 mg od vs enoxaparin 20 mg bid	r, db, dd	610	Composite of symptomatic PE and symptomatic and asymptomatic DVT	Completed Edoxaban superior to enoxaparin
Rivaroxaban					
RECORD 1 (NCT00329628) ^[82] Thromboprophylaxis after hip surgery	Rivaroxaban 10 mg od vs enoxaparin 40 mg od SC	r, db, dd	4541	Composite of DVT, nonfatal PE, or death from any cause at 36 days	Completed Rivaroxaban superior to enoxaparin
RECORD 2 (NCT00332020) ^[83] Thromboprophylaxis after hip surgery	Rivaroxaban 10 mg od vs enoxaparin 40 mg od SC	r, db, dd	2509	Composite of DVT, nonfatal PE, or death from any cause up to day 30–42	Completed Rivaroxaban superior to enoxaparin
RECORD 3 (NCT00361894) ^[84] Thromboprophylaxis after knee surgery	Rivaroxaban 10 mg od vs enoxaparin 40 mg od SC	r, db, dd	2531	Composite of DVT, nonfatal PE, or death from any cause up to day 13–17	Completed Rivaroxaban superior to enoxaparin
RECORD 4 (NCT00362232) ^[85] Thromboprophylaxis after knee surgery	Rivaroxaban 10 mg od vs enoxaparin 30 mg bid SC	r, db, Noninf	3148	Composite of DVT, nonfatal PE, or death from any cause up to day 17	Completed Rivaroxaban superior to enoxaparin
Apixaban					
ADVANCE-1 (NCT00371683) ^[29] Thromboprophylaxis after knee surgery	Apixaban 2.5 mg bid vs enoxaparin 30 mg SC	r, db, dd, Noninf	3195	Composite of DVT, nonfatal PE, or death from any cause during treatment	Completed Apixaban failed to show non-inferiority to enoxaparin
ADVANCE-2 (NCT00452530) ^[28] Thromboprophylaxis after knee surgery	Apixaban 2.5 mg bid vs enoxaparin 40 mg od	r, db, Noninf	3057	Composite of DVT, nonfatal PE, or death from any cause during treatment	Completed Apixaban superior to enoxaparin
Dabigatran					
RE-NOVATE (NCT00168818) ^[86] Thromboprophylaxis after hip surgery	Dabigatran 150 or 220 mg od vs enoxaparin 40 mg od	r, db, dd, Noninf	3505	Composite of total VTE and all-cause mortality during the treatment period	Completed Dabigatran non-inferior to enoxaparin
RE-NOVATE II (NCT00657150) Thromboprophylaxis after hip surgery	Dabigatran 220 mg od vs enoxaparin 40 mg od	r, db, Noninf	2055	Composite of total VTE and all-cause mortality during the treatment period	Completed Dabigatran non-inferior to enoxaparin
RE-MODEL (NCT00168805) Thromboprophylaxis after knee surgery	Dabigatran 150 or 220 mg od vs enoxaparin 40 mg od	r, db	2076	Composite of total VTE and all-cause mortality during the treatment period	Completed Dabigatran non-inferior to enoxaparin
RE-MOBILIZE (NCT00152971) Thromboprophylaxis after knee surgery	Dabigatran 150 or 220 mg od vs enoxaparin 30 mg bid	r, db	2610	Composite of total VTE and all-cause mortality during the treatment period	Completed Dabigatran inferior to enoxaparin
bid = twice-daily; CV = cardiovascular; db = double-blind; dd = double-dummy; DVT = deep vein thrombosis; od = once-daily; Noninf = non-inferiority study; PE = pulmonary embolism; r = randomized; SC = subcutaneous; VTE = venous thromboembolic event.					

Japanese patients who had total hip arthroplasty (NCT01181167), edoxaban 30 mg once daily was also superior to subcutaneous enoxaparin sodium 20 mg twice daily in reducing a composite endpoint of symptomatic PE and symptomatic and asymptomatic DVT detected by routine venography, with no statistically significant difference in major and clinically relevant non-major bleeding events.^[81] The smaller STARS J-4 trial (NCT01181141) also found no statistically significant difference in the incidence of bleeding events after hip fracture surgery (table V); however, the study was not large enough to detect small differences in bleeding rates.^[80] The choice of an enoxaparin sodium 20 mg control group in the STARS studies for DVT prevention was appropriate in a Japanese population, but this protocol is not commonly used outside of Japan. The results of these studies may therefore not extrapolate to other regions. Registration for this purpose may therefore remain limited to Japan due to this choice of comparator.

5. Discussion

Although warfarin is very effective in preventing thromboembolic events, it has a narrow therapeutic window and its effects are subject to significant interindividual and intraindividual variability, which imposes the need for regular anticoagulation monitoring. Warfarin is also affected by significant drug, food and alcohol interactions, and many patients may be below the optimal INR range of 2.0–3.0 for significant periods.^[2,20]

Novel anticoagulants like thrombin and factor Xa inhibitors reduce the risk of thrombus formation through mechanisms that are more selective than those of warfarin, and potentially offer greater safety as well as more convenience. Inhibition of factor Xa is a particularly attractive strategy due to the rate-limiting common role that this factor plays in the extrinsic and intrinsic coagulation pathways. Furthermore, factor Xa has relatively few functions outside the coagulation cascade, which limits the potential for adverse effects compared with direct thrombin inhibition.

The oral factor Xa inhibitor edoxaban is more convenient to use than warfarin because it has predictable and consistent pharmacokinetic and

pharmacodynamic profiles across doses, as demonstrated by low intersubject variability and dose linearity. Edoxaban is administered once daily, unlike apixaban and dabigatran, and its absorption is unaffected by food. But, like rivaroxaban, which should be used with caution in patients with moderate renal impairment, edoxaban is largely excreted via the kidneys.^[23,38,40,44] Edoxaban exhibits less protein binding than apixaban or rivaroxaban, and this may prove to be an advantage of edoxaban over apixaban and rivaroxaban during removal of the substance, e.g. during dialysis treatment.

Edoxaban and other new oral anticoagulants share some common features in that they are direct-acting, reversible, small molecules that do not require routine therapeutic monitoring of INR and dose adjustment.^[20] In addition, hepatotoxicity has not been noted in phase II or phase III clinical trials of edoxaban,^[24,79] dabigatran,^[35] rivaroxaban^[67] or apixaban.^[29,69]

Phase II clinical trials of edoxaban have indicated that rates of bleeding events were not significantly different to dose-adjusted warfarin with the edoxaban 30 mg or 60 mg once-daily regimens in patients with AF,^[24] which is similar to enoxaparin sodium and placebo in patients after knee surgery,^[25,79] and similar to dalteparin sodium after hip surgery.^[57] Higher rates of bleeding events have been reported with edoxaban twice daily dosing regimens than with the once-daily regimen, which suggests that there is a threshold level of anticoagulant activity with edoxaban that can lead to bleeding if it is exceeded.^[24] Though edoxaban concentrations are higher with twice daily regimens and, thus, the putative threshold for bleeding events may be only temporarily exceeded with once-daily dosing of edoxaban, in comparison with agents such as dabigatran or apixaban, which are administered in a twice-daily regimen. However, it should be noted that in the ROCKET-AF trial, once-daily treatment with rivaroxaban was not shown to be superior to warfarin in terms of major and clinically relevant non-major bleeding events.^[34,67]

On the basis of these findings, edoxaban 30 mg and 60 mg once-daily regimens are being compared with dose-adjusted warfarin in the ongoing

phase III trial ENGAGE AF-TIMI 48 and edoxaban 60 mg once daily is being tested in HOKUSAI VTE.

6. Conclusions

The choice of treatment options for oral anticoagulant therapy has been limited to the use of VKAs for over 60 years, but their limitations have prompted efforts to develop a range of new oral anticoagulants which target pathways central to the coagulation system such as factor Xa or thrombin. The evidence to support the safety of once-daily administration of the novel oral factor Xa inhibitor edoxaban, and the initial efficacy indications from phase II clinical trials, make edoxaban a potentially attractive alternative antithrombotic agent to warfarin or oral direct thrombin inhibitors for the prevention of stroke in patients with AF and/or the treatment and prevention of embolic events. However, the results of ongoing phase III clinical trials will be required in order to determine the place of edoxaban in antithrombotic therapy.

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