

## Edoxaban: a new oral direct factor Xa inhibitor for the prevention and treatment of thromboembolic disorders

Anticoagulants have a key role in the treatment of arterial and venous thromboembolic disorders. The recently introduced novel oral anticoagulants target a single coagulation factor (factor Xa or thrombin) and address several of the limitations associated with traditional agents. Edoxaban is an oral direct factor Xa inhibitor that inhibits free and clot bound factor Xa and has been investigated in an extensive clinical development program. This article provides an overview of the mechanism of action, pharmacokinetics and pharmacodynamics of edoxaban. Phase III studies have evaluated edoxaban versus conventional therapy to prevent stroke in patients with atrial fibrillation (ENGAGE AF-TIMI 48) and in the treatment and prevention of recurrent venous thromboembolism in patients with deep vein thrombosis and/or pulmonary embolism (Hokusai-VTE).

**Keywords:** atrial fibrillation • direct factor Xa inhibitor • edoxaban • novel oral anticoagulant • pharmacodynamics • pharmacokinetics • stroke prevention • thromboembolic disorders • venous thromboembolism

Activation of the plasma coagulation cascade is central to thrombus formation in the pathogenesis of thromboembolic disorders in several cardiovascular diseases. Anticoagulants have long been the mainstay for the long-term treatment and prophylaxis of thromboembolic diseases such as venous thromboembolism (VTE), as well as stroke prevention in patients with atrial fibrillation (AF). For several decades, conventional antithrombotic therapy comprised unfractionated heparin, the low-molecular-weight heparins (LMWHs), the synthetic pentasaccharide fondaparinux and the oral vitamin K antagonists (VKAs), such as warfarin. Indeed, warfarin remains one of the most widely used anticoagulants as it is low cost, can be administered once-daily (QD) and its use is well established, with meta-analyses having shown warfarin to be highly effective in prevention of stroke and recurrent VTE under optimal conditions [1,2].

However, these agents are associated with a number of limitations that make achieving

optimal conditions difficult and which consequently impact on patient care. Both VKAs and heparin require frequent laboratory monitoring. Although LMWH enabled once-daily administration without the need for coagulation monitoring, it is inconvenient due to daily subcutaneous administration and may cause heparin-induced thrombocytopenia [3,4]. In addition, the VKAs are associated with a slow onset of action, multiple food and drug interactions, variable anticoagulant effect and a narrow therapeutic window; this necessitates close monitoring to achieve a target international normalized ratio (INR) of 2.5 (range: 2.0–3.0). This constitutes the background for a 40-fold range in dosing (0.5–20 mg/day) to achieve the same therapeutic effect, but increases the risk for bleeding or recurrent thrombotic event (from excessive or insufficient anticoagulation, respectively) [3,5,6]. In view of these limitations, VKAs are significantly underutilized, with an analysis of over 183,000 patients with AF showing no antithrombotic protection by

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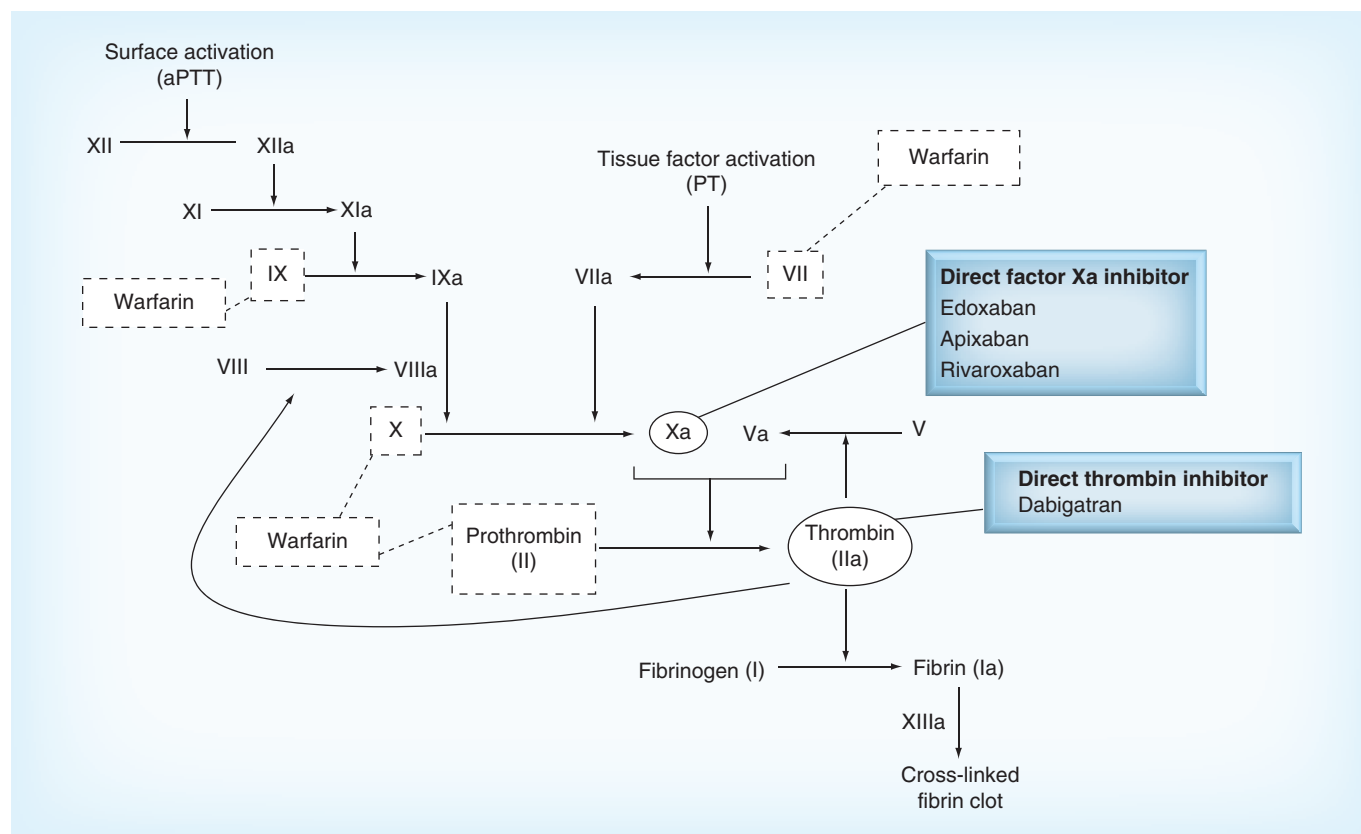
anticoagulant of nearly 50% of the observed patient-days [7]. In addition, a systematic review found nearly 90% of studies reported under-treatment with oral anticoagulant [8].

These limitations highlight the need for new anticoagulants that are at least as effective but safer and more convenient to use. Knowledge of the various factors in the coagulation cascade and targeted drug design has led to the development of novel/non-VKA oral anticoagulants (NOACs). A key step in the formation of a thrombus is the conversion of fibrinogen to fibrin, which is mediated by thrombin (factor IIa [FIIa]) and plays a central role in the coagulation cascade (Figure 1). Heparins and fondaparinux act indirectly by binding to the natural anticoagulant antithrombin, thereby accelerating inactivation of thrombin and several other activated coagulation factors. VKAs act indirectly by blocking a step in the biosynthesis of several coagulation factors. Specifically, VKAs prevent the  $\gamma$ -carboxylation of FII (prothrombin), FVII, FIX and FX, as well as anticoagulant protein C ( $\gamma$ -carboxylation is required for the activity of coagulation factors) leading to the production of

nonfunctional enzymes following coagulation factor activation [5,6,9].

In contrast, the NOACs have been designed to act via direct (antithrombin-independent) inhibition of a specific coagulation factor (Figure 1). Direct oral thrombin inhibitors (dabigatran) bind directly to the thrombin active site thereby suppressing its activity and preventing formation of fibrin and activation of platelets. FXa is an attractive target for anticoagulation as it is the primary and rate-limiting source of amplification in the coagulation cascade. It is a serine protease that binds to FVa, with the resulting prothrombinase (FXa/FVa) complex assembled on the membrane surface efficiently converting prothrombin to thrombin; one molecule of FXa (in the prothrombinase complex) can activate approximately 1000 prothrombin molecules. Direct FXa inhibitors (apixaban, rivaroxaban and edoxaban) bind directly to the active site of free and clot-bound FXa, blocking the interaction with its substrate [5,6].

The NOACs have a number of potential advantages over warfarin, including a rapid onset of action, no significant food interactions, lower potential for drug



**Figure 1. The coagulation cascade and anticoagulant sites of action.** Warfarin acts indirectly by blocking a step in the biosynthesis of FII (prothrombin), FVII, FIX and FX (dashed lines and rectangles). The nonvitamin K antagonist oral anticoagulants are direct inhibitors of thrombin (FIIa; dabigatran) or FXa (edoxaban, apixaban, rivaroxaban) (solid lines and ovals).

aPTT: Activated partial thromboplastin time; PT: Prothrombin time.

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interactions and a predictable anticoagulant effect, obviating the need for routine monitoring of anticoagulation parameters [6]. Based on the results of Phase III clinical studies, dabigatran, apixaban, rivaroxaban and edoxaban have gained approval for the prevention and treatment of several thromboembolic disorders in adult patients [10–14], while several agents are in various stages of development.

Results from Phase III studies of edoxaban in VTE and stroke prevention in AF have also recently become available. In addition, the manufacturers of edoxaban have recently submitted applications to the US FDA and the EMA for the approval of edoxaban for use in these conditions. The objective of this review is to provide an overview of the pharmacokinetics and pharmacodynamics of edoxaban, and discuss the findings from the recent clinical studies in VTE and patients with AF.

### Pharmacokinetic & pharmacodynamic properties of edoxaban

#### Pharmacokinetics, metabolism & excretion, & drug–drug interactions

Studies in healthy subjects using single and multiple doses have shown that edoxaban demonstrates predictable and consistent pharmacokinetics, with dose linearity and low intrasubject variability (summarized in Table 1). Edoxaban is characterized by rapid absorption ( $t_{\max}$  of 1–2 h), dose proportional increases in plasma concentrations (Figure 2) and total exposure, and limited accumulation consistent with a half-life of approximately 10–14 h. [15–17]. The absolute bioavailability of edoxaban following a single 60 mg dose is 61.8% [18]; mean apparent volume of distribution was generally >300 l due to relatively low protein binding and distribution to extravascular tissues [15]. Studies have shown that the pharmacokinetics of edoxaban are not influenced by gender, age, ethnicity or food intake; only small but clinically insignificant changes in pharmacokinetic parameters are detected in elderly subjects or following a high fat meal [15,19].

A key interaction mechanism for several NOACs is secretion via P-glycoprotein (P-gp) transporters, which modulate absorption and excretion of drugs, thereby influencing their systemic exposure, as well as renal and biliary excretion. Edoxaban is a substrate for P-gp, which may account for the majority (62%) of the drug being detected unchanged in the feces. Approximately 35% of edoxaban is eliminated in the urine, indicating the importance of renal secretion in elimination. Hydrolysis of the parent compound is the predominant route of metabolism for edoxaban. In contrast, CYP450 enzymes appear to have an insignificant role in the metabolism of edoxaban [20,21].

Given the importance of renal excretion in the elimination of edoxaban, studies have evaluated the drug in patients with normal renal function or mild renal impairment (creatinine clearance [ClCr]  $\geq 50$  ml/min) compared with severe renal impairment (ClCr  $\leq 30$  ml/min), suggesting that edoxaban exposure increases in patients with renal impairment, and that a lower dose (15 mg QD) seems appropriate [22,23]. However, in patients with end-stage renal disease, hemodialysis had minimal effects on the clearance of edoxaban and further dose adjustment may not be necessary [24]. This is likely due to the plasma protein binding of 40–59% for edoxaban [15] and therefore hemodialysis is not an effective means for removing edoxaban from the blood.

With edoxaban being a substrate for P-gp, practitioners need to be aware of potential interactions with inhibitors or inducers of this transporter, particularly as some drugs used in patients with AF are also P-gp substrates. Strong P-gp inhibitors may increase systemic absorption and decrease drug elimination (increasing bleeding risk due to increased exposure), while P-gp inducers may increase drug elimination and reduce systemic exposure (increasing risk of thromboembolic events due to insufficient anticoagulation). As such, the FDA now recommends that all investigational drugs be evaluated for potential effect on P-gp activity.

A number of drug–drug interaction studies have evaluated the pharmacokinetics of edoxaban when administered with, or following, various P-gp inhibitors (Table 2). Co-administration of edoxaban with the strong P-gp inhibitors quinidine, verapamil and dronedarone increased edoxaban exposure, and so dose reductions of edoxaban are necessary when co-administered with these drugs. In contrast, modest or minimal effects on edoxaban exposure were observed when co-administered with amiodarone, atorvastatin and digoxin, and no dose adjustment is required [25,26].

Esomeprazole, a proton-pump inhibitor, reduces gastric acid secretion, and may therefore impact the absorption of orally administered drugs, particularly where absorption is pH sensitive. Co-administration of esomeprazole with edoxaban did not affect edoxaban absorption and had no clinically significant effect on its pharmacokinetics (Table 2) [28].

Aspirin and naproxen inhibit platelet aggregation, and co-administration with an anticoagulant may potentiate bleeding. Co-administration of naproxen and edoxaban had no effect on either drug's pharmacokinetics, but prolonged bleeding time shortly after administration; although this returned to near baseline values by 24 h, the authors concluded that although co-administration was safe and well tolerated, long-term concomitant use could potentiate bleeding (Table 2) [27].

Table 1. Pharmacokinetic properties of edoxaban.		
Parameter	Edoxaban pharmacokinetics	
	Single dosing (10–150 mg)	Multiple daily dosing (90–120 mg)
AUC <sub>0–∞</sub> (ng·h/ml) <sup>†</sup>	1873–2563	2048–2296
C <sub>max</sub> (ng/ml) <sup>†</sup>	248–416	347–451
C <sub>trough</sub> (ng/ml) <sup>†</sup>	–	10.2–80.3
t <sub>max</sub> (h)	1.0–1.5	1.0–3.5
t <sub>1/2</sub> (h)	5.8–10.7	8.8–10.4
Apparent total plasma clearance (ml/min)	504–717	535–636
Apparent volume of distribution during terminal phase (l)	322–536	415–576
Ae <sub>0–48</sub> (μg)	3472–46,627	21,910–44,093
fe <sub>0–48</sub> (%)	34.7–39.0	36.1–50.2
CL <sub>R0–48</sub> (ml/min)	194–283	184–227

<sup>†</sup>Normalized for dose and body weight.  
Ae<sub>0–48</sub>: Amount of drug excreted in urine from 0 to 48 h; AUC<sub>0–∞</sub>: Area under the curve from 0 to infinity; CL<sub>R0–48</sub>: Renal clearance from 0 to 48 h; C<sub>max</sub>: Maximum observed plasma concentration; C<sub>trough</sub>: Plasma concentration at the end of the dosing interval; fe<sub>0–48</sub>: Fraction of dose excreted in urine from 0 to 48 h; t<sub>1/2</sub>: Apparent plasma terminal elimination half-life; t<sub>max</sub>: Time of maximum observed plasma concentration.  
Data taken from [15].

Similar observations were made with the co-administration of aspirin and edoxaban, and it was concluded that the dose of aspirin should be limited to 100 mg when co-administered with edoxaban (Table 2) [27].

In line with guidelines, LMWHs, such as enoxaparin, are often used in clinical practice for initial

treatment before a patient is started on an oral anticoagulant (such as the VKA warfarin), or for rescue following failure of a VKA. This approach was the basis for the design of the Phase III study of edoxaban in the treatment of VTE, and so a study was conducted to provide guidance on initiating edoxaban following

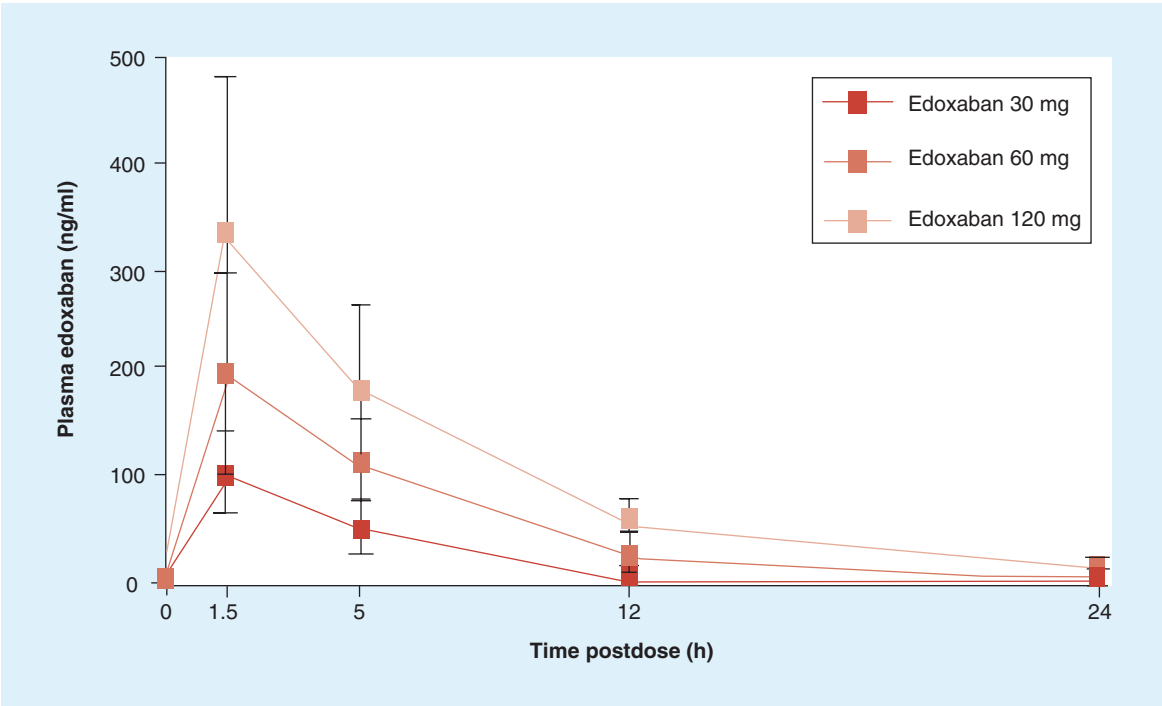


Figure 2. Plasma concentrations of edoxaban after oral administration. Adapted with permission from [16].

Table 2. Drug–drug interaction studies with edoxaban.

Drug tested	Drug effect	Interaction outcome	Additional information	Ref.
Amiodarone	Strong P-gp inhibitor	Total exposure increased 39.8% 24-h edoxaban concentration decreased 25.7%	Modest increase in edoxaban exposure; no dose adjustment required	[25]
Aspirin (ASA)	COX-1 and -2 inhibitor; may potentiate bleeding	Bleeding time increased; no change in edoxaban pharmacokinetics	Co-administration of ASA limited to ≤100 mg/day	[27]
Atorvastatin	P-gp substrate; CYP3A4 inhibitor	Total exposure increased 1.7% 24-h edoxaban concentration increased 7.9%	Minor effects; no dose adjustment required	[25]
Digoxin	P-gp substrate	Total exposure increased 9.5% 24-h edoxaban concentration decreased 9.4%	Minor effects; no dose adjustment required	[25]
Dronedarone	Strong P-gp inhibitor; CYP3A4 inhibitor	Total exposure increased 84.5% 24-h edoxaban concentration increased 57.6%	Reduce edoxaban dose by 50%	[25]
Esomeprazole	May affect absorption of pH sensitive drugs; CYP2C19/2C9 inhibitor	Slight increase (<3%) in exposure and maximum plasma concentration of edoxaban tablet formulation	Minor effects; no dose adjustment required	[28]
Naproxen	Platelet aggregation inhibitor; may potentiate bleeding	Bleeding time increased 4 h postdose, returning to near baseline 24 h postdose; no change in edoxaban pharmacokinetics	Long-term co-administration likely to potentiate bleeding	[27]
Quinidine	Strong P-gp inhibitor	Total exposure increased 76.7% 24-h edoxaban concentration increased 11.8%	Reduce edoxaban dose by 50%	[25]
Rifampicin	P-gp, CYP3A4 and CYP2J2 inducer	Reduction in edoxaban plasma levels by 35%	Consider dose adjustment if co-administering with another inhibitor	[29]
Verapamil	Strong P-gp inhibitor; weak CYP3A4 inhibitor	Total exposure increased 52.7% 24-h edoxaban concentration increased 29.1%	Reduce edoxaban dose by 50%	[25]

P-gp: P-glycoprotein.

enoxaparin. This open-label study evaluated the pharmacokinetics, pharmacodynamics and safety of enoxaparin 1 mg/kg followed 12 h postdose by edoxaban 60 mg. Neither edoxaban nor enoxaparin significantly altered the pharmacokinetics of either drug, nor the ability to anticoagulate, with the data supporting the initiation of edoxaban after discontinuation of subcutaneous enoxaparin [30].

### Pharmacodynamics

Edoxaban is a potent and highly selective direct inhibitor of FXa (Figure 1). Preclinical studies show that edoxaban inhibits FXa in a dose-dependent manner *in vitro*, with inhibition constant ( $K_i$ ) values of 0.561 nM for free FXa and 2.98 nM for FXa bound to the prothrombinase complex. Edoxaban is a weak inhibitor of other coagulation factors, exhibiting

>10,000-fold selectivity for FXa relative to thrombin and other biologically relevant serine proteases [31]. The potent inhibition of both free FXa and FXa complexed in prothrombinase has important implications for the anticoagulant effects of edoxaban, as the prothrombinase complex is responsible for conversion of prothrombin to thrombin. *In vitro* studies with edoxaban on anticoagulation parameters in human plasma have shown a prolongation of prothrombin time (PT) and activated partial thromboplastin time (aPTT), with a doubling of these parameters at concentrations of 0.256 and 0.508 mM, respectively [31].

There is evidence to suggest that antithrombin-independent thrombin inhibitors (e.g., melagatran) exert a rebound coagulation effect and increase thrombin generation (TG), particularly at subtherapeutic concentrations. Assessment of TG provides a global

measure of anticoagulant effect by measuring the inhibition of thrombin formation, and is a more sensitive evaluation of the pharmacodynamics of new anticoagulants [30]. An *in vitro* analysis of TG in human plasma showed a concentration-dependent suppression of TG, TG peak height suppression and lag time prolongation by edoxaban, suggesting that direct FXa inhibitors are less prone to induce activation of coagulation [32]. Furthermore, direct FXa inhibition may provide additional benefits over indirect FXa inhibition. Compared with the indirect FXa inhibitor fondaparinux, edoxaban was found to be a more potent inhibitor of tissue factor-induced platelet aggregation and clot-bound FXa. Both edoxaban and fondaparinux exhibited concentration-dependent inhibition of TG, but edoxaban exhibited a threefold greater concentration-dependent effect [33,34]. This may be related to the broader inhibition activity of edoxaban (free and bound FXa) in contrast to fondaparinux (free FXa only).

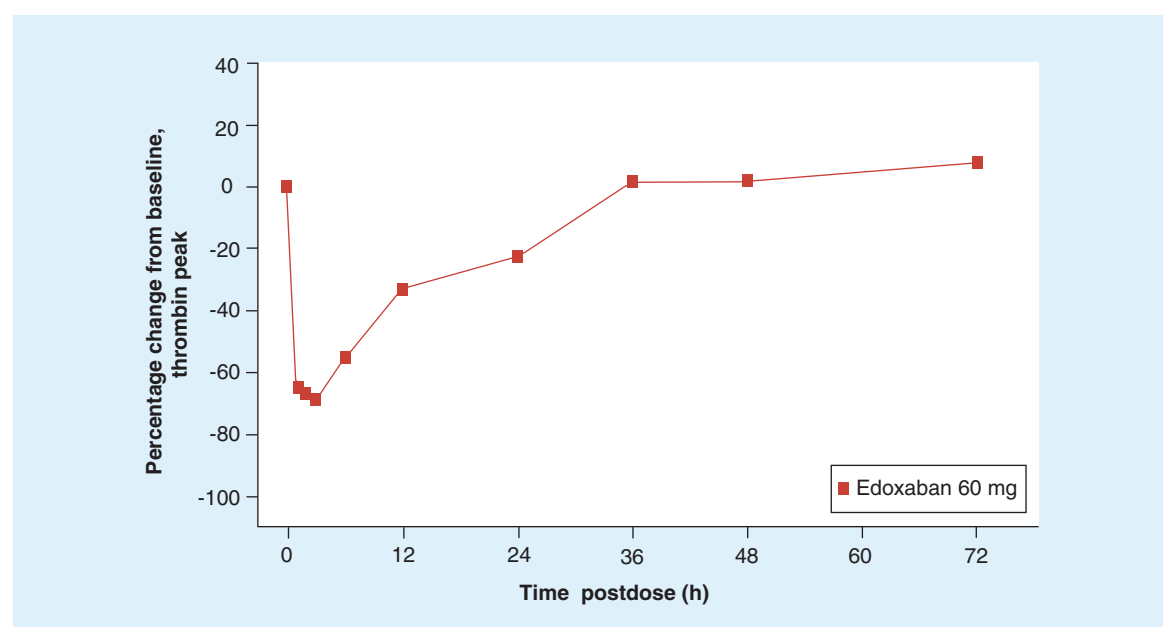
The changes in clotting parameters are reflected by significant reductions in thrombus formation under flow conditions typical of venous and moderately stenosed arterial vessels (low and high shear rates, respectively) [35]. Using an *ex-vivo* flow chamber, the antithrombotic effect of edoxaban was assessed by measuring the size of thrombus formed post-treatment and comparing it with pretreatment thrombus. Edoxaban demonstrated strong antithrombotic properties: under low shear rate conditions (venous thrombosis), thrombus formed at 1.5 h postdose was smaller than the baseline thrombus by an average of 28% ( $p < 0.01$ );

at 5 h, the thrombus size was 21% smaller ( $p < 0.01$ ). The thrombi formed at high-shear rate were more than twofold greater in size compared with low-shear rate, but the effect of FXa inhibition followed the same pattern [35].

These findings are supported by clinical pharmacodynamic studies with edoxaban in healthy subjects. The plasma concentration of edoxaban shows a linear relationship with coagulation parameters (aPTT and PT) within the therapeutic range in healthy subjects [15,35]. Indeed, a single oral 60-mg dose (the dose to be evaluated in clinical trials) of edoxaban produced an approximate twofold increase in PT, consistent with previous preclinical results. These findings are reagent independent.

Using blood samples from healthy subjects to assess the effect on TG assay parameters, edoxaban 60 mg decreased the endogenous thrombin potential and thrombin (peak), and increased the TG lag time and thrombin time to peak. The inhibition of TG for >24 h by edoxaban 60 mg QD (Figure 3) reinforced the anticoagulation efficacy of once-daily dosing with edoxaban [30].

Compared with fondaparinux 2.5 mg, edoxaban 30, 60 and 120 mg QD caused rapid and significantly larger reductions in several blood coagulation biomarkers (prothrombin fragment 1+2 [ $F_{1+2}$ ], the thrombin–antithrombin [TAT] complex and platelet activation marker  $\beta$ -thromboglobulin [ $\beta$ -TG]), indicating inhibition of thrombin generation and platelet activation [16]. In a comparison of LMWH dalteparin,



**Figure 3. Thrombin generation in healthy subjects following edoxaban 60 mg.** Percentage change from baseline in thrombin peak over time. Adapted with permission from [30].



the direct thrombin inhibitor ximelagatran, and edoxaban 60 mg twice-daily (BID), all three drugs produced similar reductions in TAT complex and  $F_{1+2}$ ; however, edoxaban caused a larger reduction in PT activity compared with ximelagatran [36]. This finding may be a result of the mechanism of action of direct FXa inhibitors, which inhibit both free FXa, as well as FXa in the prothrombinase complex.

The clinical pharmacodynamics of edoxaban 60 mg QD have been investigated 24-h post-warfarin therapy, to determine if patients could be safely transitioned from warfarin to edoxaban. Edoxaban 60 mg 24-h after warfarin cessation maintained anticoagulation, as shown by significant, but transient increases in PT and aPTT. Edoxaban was also shown to have a bigger effect on aPTT than warfarin. Anti-FXa activity was mostly undetectable during warfarin treatment, but increased following edoxaban administration, before declining to approximately baseline levels by 24-h postdose; this suggests edoxaban maintains its anticoagulant effect without presenting a prolonged risk for over-anticoagulation [37].

These Phase I studies also demonstrated that edoxaban was well tolerated in healthy subjects. Once-daily doses of 10–150 mg, and edoxaban 60 mg BID did not result in any dose-dependent increase in drug-related adverse events [15]. Single doses of edoxaban 60 mg did not cause serious adverse events and only few bleeding events [16,30,37]. The International Conference on Harmonisation E14 Guideline requires that all new drugs with systemic bioavailability undergo a thorough electrocardiogram study (a 'thorough QT/QTc' study). A single supratherapeutic dose of edoxaban (180 mg; the highest single dose that could be safely administered posing minimal bleeding risk) in healthy subjects showed that the placebo-corrected QT interval did not exceed the predefined limit of 10 ms, suggesting minimal potential for inducing cardiac arrhythmias [38].

### Atrial fibrillation

AF, a common cardiac arrhythmia, is a growing public health concern. It is currently estimated to affect 1.5–2% of the general population of the developed world, but with the prevalence increasing with age (the average age of people with the condition is 75–85 years) [39], it is expected to rise dramatically over the next 50 years, from approximately 3 million people in the US in 2010 to as many as 12 million people by 2050 [11,40,41].

The risk of stroke is increased in patients with AF, with 20–30% of strokes associated with AF [42], while strokes caused by AF are often more severe compared with those without AF and are associated with worst

survival [42]. Hospitalization of patients with AF is common (one-third of hospitalizations for cardiac rhythm disturbances), and the condition is associated with considerable morbidity and mortality [11,43,44]. Consequently, AF represents a major cardiovascular challenge in modern society with the medical, social and economic aspects set to worsen over the coming decades.

Fortunately, a number of interventions are available to patients. In addition to pharmacological and nonpharmacological options to control heart rate and rhythm, anticoagulant prophylaxis to reduce the risk of stroke is recommended for patients with AF and other risk factors [11]. Chronic treatment with VKAs remains the mainstay of anticoagulation, having been shown to significantly reduce the risk of AF-related stroke by 64% and mortality by 26% [1,2]. However, with the limitations and underutilization associated with VKA, research has led to the recent approval of the NOACs dabigatran, rivaroxaban and apixaban for the prevention of stroke and systemic embolism in adult patients with nonvalvular AF [11,13].

The efficacy and safety of edoxaban in AF has been evaluated in Phase II and Phase III trials. Several Phase II trials have investigated different doses of edoxaban to identify the optimal doses to be safely carried forward into Phase III. A 12-week, randomized, parallel group trial evaluated double-blind edoxaban 30, 45 or 60 mg QD versus open-label warfarin in 536 Japanese patients with nonvalvular AF [45]. There was a trend towards dose-dependent increases in bleeding events with edoxaban (mean incidence of all bleeding was 18.5, 22.4 and 27.7% with edoxaban 30, 45 and 60 mg, versus 20.0% with warfarin), although the differences were not statistically significant. A separate 3-month randomized, parallel-group study of double-blind edoxaban 30 or 60 mg QD versus open-label warfarin in 235 Asian patients showed a trend toward a lower incidence of all bleeding events with edoxaban (20.3 and 23.8% for 30 and 60 mg QD, respectively) versus warfarin (29.3%) [46]. Subgroup analyses in both studies suggested that lower body weight ( $\leq 60$  kg) was associated with a higher bleeding risk, due to the increased exposure of edoxaban [45,46].

A key Phase II study randomized 1146 patients with AF to 12 weeks' treatment with one of four fixed doses of edoxaban (30 mg QD, 30 mg BID, 60 mg QD and 60 mg BID) or open-label warfarin titrated to an INR of 2.0–3.0 [47]. QD regimens were associated with less bleeding than BID regimens, and had a safety profile similar to that of warfarin. Although this was unexpected, a correlation was found between higher trough plasma concentrations ( $C_{\min}$ ) of edoxaban and the frequency of bleeding. The  $C_{\min}$  were higher with

twice-daily dosing than once-daily regimens, so that with the same total daily dose of 60 mg, both  $C_{min}$  and bleeding rates were higher with edoxaban 30 mg BID than 60 mg QD. The incidence of stroke/transient ischemic attacks were similar across edoxaban groups (0.4–1.1%) and lower than with warfarin (1.6%) [47].

The findings from these studies were supported by a pooled analysis of Phase I and II studies using a range of edoxaban doses [48]. Exposure–response analyses confirmed the association between bleeding events and  $C_{min}$ . In addition, clinical trial simulations of bleeding incidence confirmed that edoxaban 30 mg and 60 mg QD were the most suitable doses for further evaluation. Moreover, it was recommended that a 50% dose reduction should be performed in selected patients with criteria that would result in increased edoxaban exposure (patients with moderate renal impairment, receiving concomitant strong P-gp inhibitors, or body weight  $\leq 60$  kg) [48]. These studies enabled the selection of edoxaban 30 mg and 60 mg QD for investigation in the Phase III ENGAGE AF-TIMI 48 trial [49,50].

ENGAGE AF-TIMI 48 was a randomized, double-blind, double-dummy trial that compared two dose regimens of edoxaban with the current standard of care (dose-adjusted warfarin) for stroke prevention. A total of 21,105 patients with AF (documented on an electrical recording within the past 12 months) and a moderate-to-high risk of stroke (CHADS<sub>2</sub> score  $\geq 2$ ) were enrolled from 1393 centers in 46 countries, with a median follow-up of 2.8 years, making ENGAGE AF-TIMI 48 the largest trial of NOACs in AF to date. Patients were randomized to edoxaban high exposure (60 mg QD or dose adjusted to 30 mg QD to avoid excessive exposure), edoxaban low exposure (30 mg QD or dose adjusted to 15 mg to avoid excessive exposure) or warfarin titrated to an INR of 2.0–3.0 (Figure 4). The primary study objective was to determine whether edoxaban was noninferior to warfarin in the prevention of a composite of stroke and systemic embolic events (SEE), while the principal safety end point was major bleeding (ISTH definition). The study design benefited from a number of features that helped simulate clinical practice (dose adjustment after randomization, rigorous monitoring of warfarin to achieve appropriate levels of time in therapeutic range [TTR], and an extensive transition strategy to open-label anticoagulation at study end) [49,50].

During the treatment period, both high-dose and low-dose edoxaban regimens were noninferior to warfarin treatment in patients with AF with respect to the primary end point. In the modified intention-to-treat population in the on-treatment analysis, stroke or SEE occurred at a rate of 1.50% per year with warfarin, 1.18% per year with high-dose edoxaban

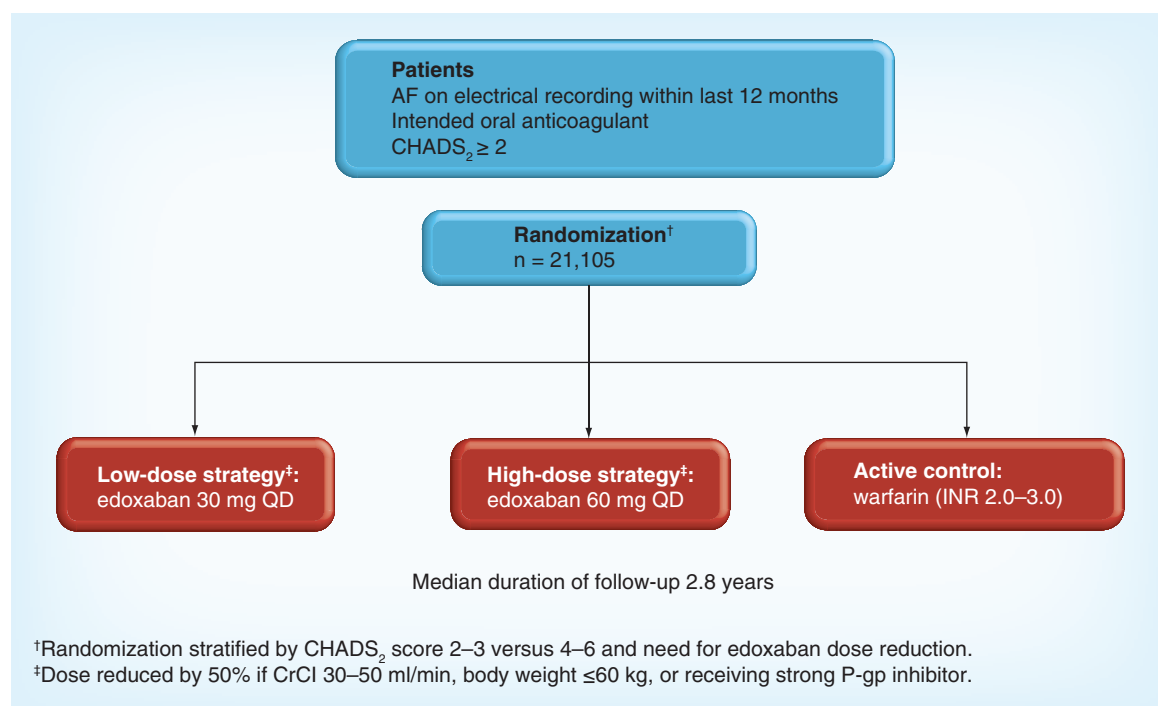
regimen (hazard ratio [HR] vs warfarin: 0.79; 97.5% CI: 0.63–0.99;  $p < 0.001$  for noninferiority;  $p = 0.02$  for superiority) and 1.61% per year with low-dose edoxaban regimen (HR vs warfarin: 1.07; 97.5% CI: 0.87–1.31;  $p = 0.005$  for noninferiority;  $p = 0.44$  for superiority). The median TTR of the warfarin group was 68.4%, indicating well-controlled patients. In the overall intention-to-treat superiority analysis performed with data from the overall study period, there was a trend favoring high-dose edoxaban versus warfarin (1.57 vs 1.80%; HR: 0.87; 97.5% CI: 0.73–1.04;  $p = 0.08$  for superiority), but not for low-dose edoxaban (2.04 vs 1.80%; HR: 1.13; 97.5% CI: 0.96–1.34;  $p = 0.10$ ) (Figure 5A). The incidence of hemorrhagic stroke and the rate of death from cardiovascular causes were significantly lower with both edoxaban regimens than with warfarin. At the end of the trial during the transition from blinded study drug to open-label anticoagulant, there was a low and evenly distributed number of events, making it unlikely that there is a rebound activation of coagulation after the discontinuation of edoxaban [50].

Compared with warfarin, both edoxaban dosing regimens were associated with consistently lower rates of nearly all types of bleeding. Major bleeding occurred at a rate of 3.43% per year in the warfarin group, 2.75% per year with the high-dose edoxaban regimen (HR: 0.80; 95% CI: 0.71–0.91;  $p < 0.001$ ) and 1.61% per year with the low-dose edoxaban regimen (HR: 0.47; 95% CI: 0.41–0.55;  $p < 0.001$ ) (Figure 5B). Treatment with edoxaban also led to a significantly reduced rate of intracranial hemorrhage, fatal bleeding, life-threatening bleeding, major or clinically relevant nonmajor bleeding and any overt bleeding versus warfarin. The single exception was gastrointestinal bleeding, which occurred more frequently with high-dose edoxaban but less frequently with low-dose edoxaban than with warfarin [50].

Based on these data, a Marketing Authorization Application for edoxaban has been submitted to the EMA for the prevention of stroke and SEE in patients with nonvalvular AF, and a new drug application to the FDA for the reduction in risk of stroke and SEE in patients with nonvalvular AF [51,52].

A recent meta-analysis of results from all four NOACs (dabigatran, rivaroxaban, apixaban and edoxaban) in their Phase III trials for stroke prevention in AF (71,683 patients; 42,411 of which received NOAC and 29,272 received warfarin) found a favorable risk–benefit profile for the NOACs. Compared with warfarin the NOACs significantly reduced stroke or SEE by 19% (relative risk [RR]: 0.81; 95% CI: 0.73–0.91;  $p < 0.0001$ ) and reduced major bleeding by 14% (RR: 0.86; 95% CI: 0.73–1.00;  $p = 0.06$ ). There





**Figure 4. Study design of ENGAGE AF-TIMI 48.**

AF: Atrial fibrillation; CrCl: Creatinine clearance; INR: International normalized ratio; P-gp: P-glycoprotein; QD: Once daily.

Adapted with permission from [49].

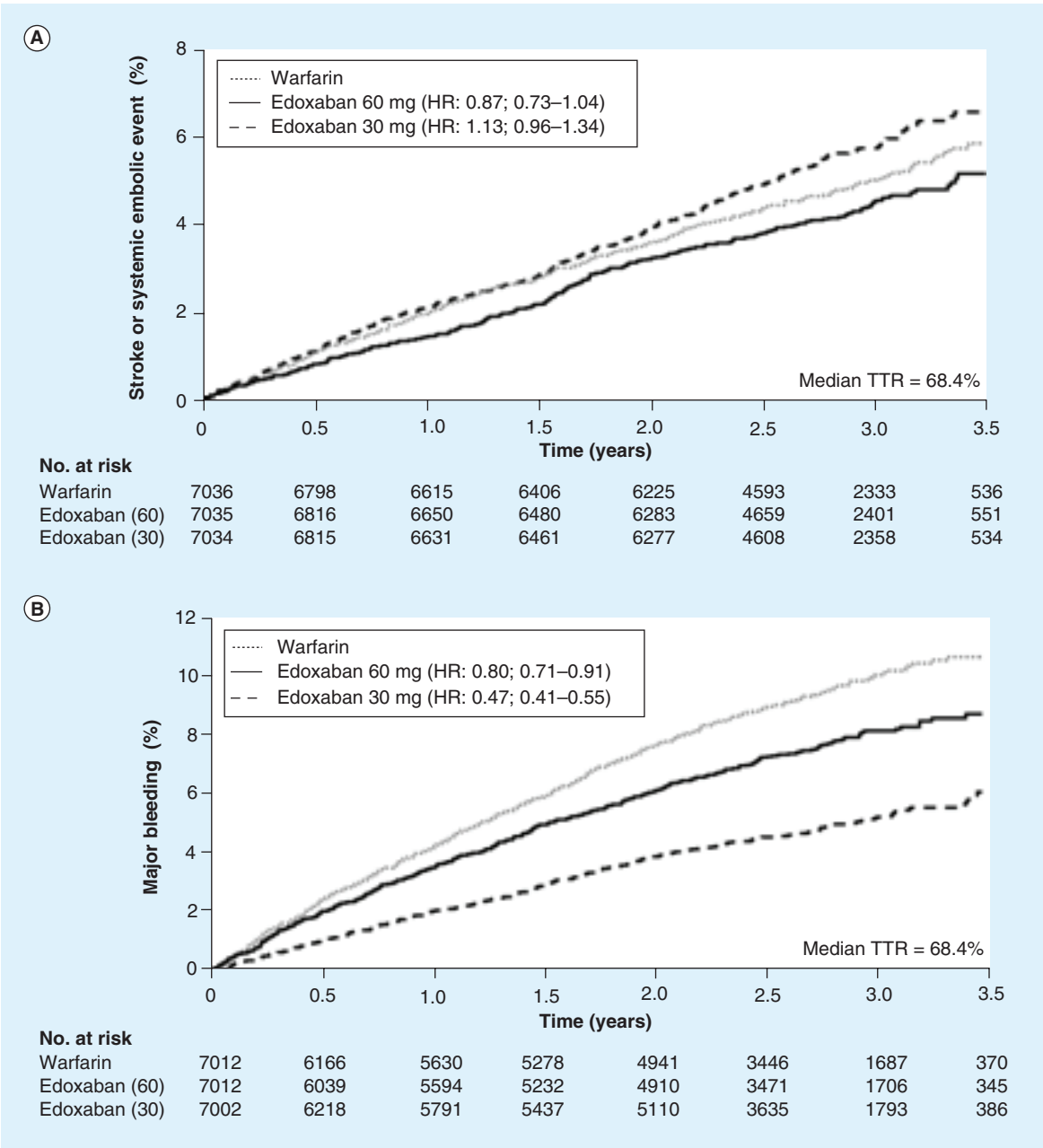
were also significant reductions in intracranial hemorrhage and mortality. The relative efficacy and safety of the anticoagulants was consistent across a wide range of patients with AF [53]. However, it is important to acknowledge some limitations with this meta-analysis. The study pooled data for the FXa inhibitors and the thrombin inhibitor, two different drug classes that inhibit different steps in the coagulation cascade. In addition, the analysis was done at study level and not with individual patient data, while there may be important differences in patient demographics and trial characteristics.

### VTE following orthopedic surgery

The frequency of major orthopedic surgery is increasing, and the risk for postoperative VTE is among the highest among all surgical procedures; without thromboprophylaxis, DVT occurs in 40–60% of patients [54,55]. Practice guidelines recommend anticoagulant prophylaxis with LMWH, fondaparinux, aspirin or warfarin for a minimum of 10 days and up to 35 days following surgery [54,55]. The efficacy and safety of edoxaban in the prevention of VTE after orthopedic surgery has been established from several Phase II and III studies, summarized in Table 3. Currently, edoxaban is approved in Japan as a 30-mg QD dose for the prevention of VTE following total knee arthroplasty, total hip arthroplasty and hip fracture surgery [14].

A Phase II, randomized, placebo-controlled study after total knee replacement in Japanese patients found dose-dependent and significant reductions in VTE with edoxaban, without significant increases in major or clinically relevant nonmajor bleeding [56]. A separate randomized, active (dalteparin)-controlled study after total hip replacement in US patients found edoxaban significantly reduced VTE incidence compared with dalteparin, with comparable rates of clinically relevant bleeding in all edoxaban and dalteparin groups [57]. The Phase III trial program comprised the STARS E-3, STARS J-4 and STARS J-5 studies to evaluate the efficacy and safety of edoxaban 30 mg QD compared with enoxaparin in Japanese patients following knee or hip surgery. Edoxaban was found to be superior to subcutaneous enoxaparin for preventing symptomatic pulmonary embolism (PE) and symptomatic and asymptomatic deep vein thrombosis (DVT) in patients following knee (STARS E-3) and hip (STARS J-5) surgery. In the smaller STARS J-4 study, there were no differences between treatments in bleeding events, although the study was not large enough to detect small differences in bleeding rates [58–60].

More recently, a retrospective analysis of 300 patients undergoing total knee arthroplasty suggested that edoxaban 15 mg QD was more effective in terms of the incidence of DVT (22%) than enoxaparin



**Figure 5. Outcomes from the ENGAGE AF-TIMI 48 study. (A)** Efficacy and **(B)** safety. HR: Hazard ratio; TTR: Time in therapeutic range. Adapted with permission from [50].

2000 IU BID (28%) and fondaparinux 1.5 mg QD (28%), with a lower incidence of bleeding (although the difference was not significant) [61]. These results suggest that a lower dose of edoxaban was effective and safe in preventing DVT.

To better understand the safety profile of a drug following its approval, it is important to monitor adverse reactions. A postmarketing safety analysis of edoxaban in approximately 20,000 Japanese patients who received edoxaban 30 mg during the first 6 months following its launch did not identify any additional safety

signals beyond those reported in the clinical studies. A total of 67 adverse events were observed in 56 patients (including 51 bleeding events in 42 patients), with only 15 serious events [62].

These studies show that edoxaban is effective for preventing VTE after orthopedic surgery compared with enoxaparin; however, because enoxaparin 2000 IU BID is not widely used outside Japan in orthopedic surgery, these results could not be extrapolated to patient populations in other geographic regions and further studies would be required [57].

## Treatment of VTE

VTE, which comprises DVT and PE, is the third most common cardiovascular disease after myocardial infarction and stroke, affecting an estimated 1 million people in the EU and >600,000 people in the USA, with approximately 540,000 and 300,000 deaths each year in the EU and USA, respectively [63,64]. Furthermore, VTE is the second most common cause of extended hospital stay. In addition to the trauma and risks associated with acute VTE, VTE is considered a chronic disease because of the high risk of recurrence after an acute event. The hazard of recurrence is highest within the first 6–12 months of the first event, and approximately 30% of patients develop recurrence within the next 10 years [64]. Recurrent VTE is itself associated with several potentially life-threatening acute and long-term complications, including post-thrombotic syndrome and chronic thromboembolic pulmonary hypertension [63,65].

Anticoagulation is the standard of care that has been shown to effectively treat the acute event and decrease the risk of recurrence. The treatment of VTE can be divided into three phases. The initial (or acute) phase aims to prevent thrombus extension and involves approximately 5–7 days of parenteral therapy (heparin,

LMWH, fondaparinux). The intermediate phase of treatment aims to complete the treatment of the acute episode of VTE and involves VKAs, such as warfarin, for at least 3 months. The goal of long-term treatment is the prevention of new episodes of VTE that are not directly related to the acute event, requiring months to years of therapy [12,65]. Patients with unprovoked VTE have a high risk of recurrent disease, and are candidates for treatment beyond 3 months. The effectiveness of anticoagulation in reducing the risk of recurrent VTE is well established, with warfarin having been shown to produce a 90% risk reduction [66–68]. Unfortunately, patients and physicians are often reluctant to consider long-term treatment with VKA due to the risk of bleeding, and the need for regular monitoring and lifestyle changes for as long as treatment is continued [69]. Treatment of VTE must therefore be tailored to an individual patient's needs, which primarily depend on the risks of having a recurrent VTE event or a bleed. A number of studies have shown that NOACs are effective alternatives to warfarin (with or without initial heparin) for the treatment of acute VTE, but with a lower risk of bleeding events [12,70–75].

The most recent of these studies, the Hokusai-VTE study, was a randomized, double-blind trial of edoxaban

**Table 3. Summary of the Phase II and Phase III clinical trials of edoxaban for the prevention of venous thromboembolism after orthopedic surgery.**

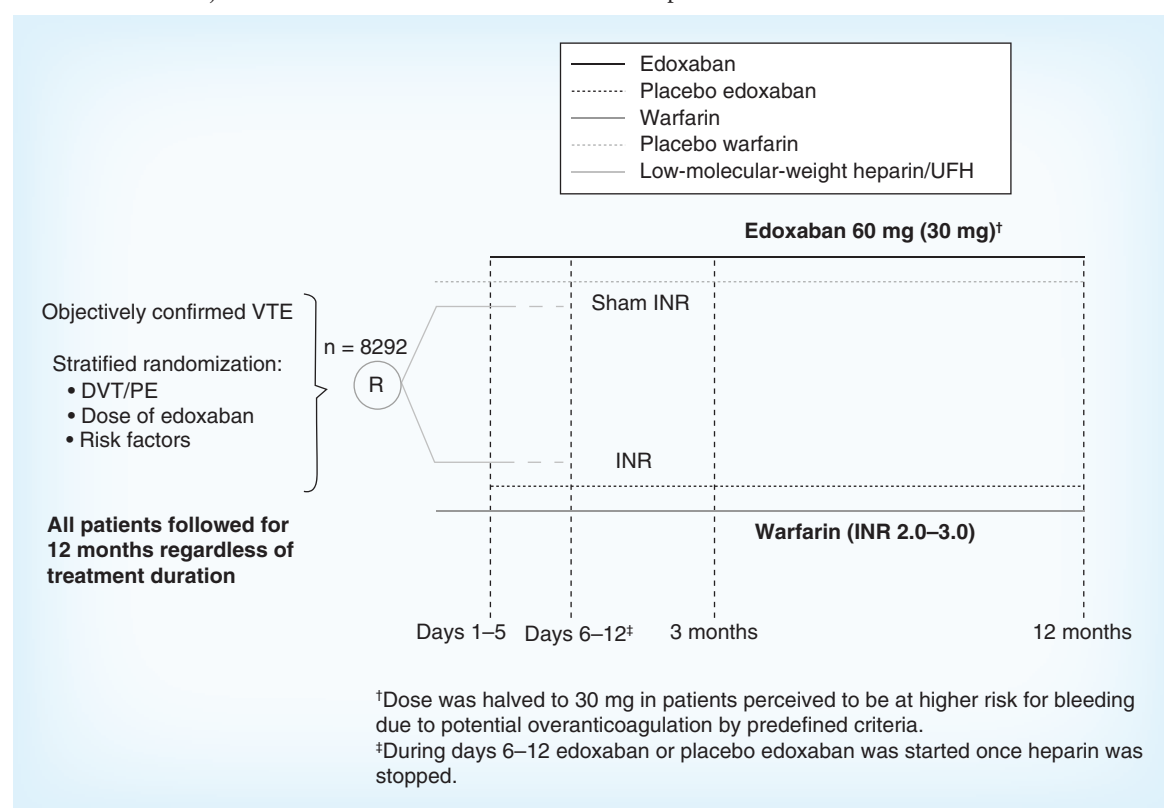
	<b>Study J04</b> [56]	<b>Study 011</b> [57]	<b>STARS E-III</b> [58]	<b>STARS J-4</b> [59]	<b>STARS J-5</b> [60]
Phase	II	II	III	III	III
Indication	Total knee replacement	Total hip replacement	Total knee replacement	Hip fracture surgery	Total hip replacement
Patients (n)	523	774	716	92	610
Design	Randomized, double-blind, placebo-controlled, dose-ranging	Randomized, double-blind, active-controlled, dose-response	Randomized, double-blind, double-dummy, active-controlled	Randomized, open-label	Randomized, double-blind, double-dummy, active-controlled
Edoxaban doses	5, 15, 30, 60 mg QD	15, 30, 60, 90 mg QD	30 mg QD	30 mg QD	30 mg QD
Comparator	Placebo	Dalteparin 2500 IU increased to 5000 IU	Enoxaparin 2000 IU (every 12 h)	Enoxaparin 2000 IU (every 12 h)	Enoxaparin 2000 IU BID (equivalent to 20 mg)
Main findings	Dose-related reduction in VTE vs placebo (VTE incidence 29.5, 26.1, 12.5, 9.1 and 48.3% for edoxaban 5, 15, 30, 60 mg and placebo, respectively); comparable bleeding	Significant dose-related reduction in VTE vs dalteparin (VTE incidence 28.2, 21.2, 15.2, 10.6 and 43.8% for edoxaban 15, 30, 60, 90 mg and dalteparin, respectively); comparable bleeding	Significantly less VTE vs enoxaparin (7.4 vs 13.9%); comparable bleeding	Comparable efficacy (VTE incidence 6.5% for edoxaban vs 3.7% for enoxaparin) and bleeding	Significantly less VTE vs enoxaparin (2.4 vs 6.9%); comparable bleeding

BID: Twice daily; QD: Once daily; VTE: Venous thromboembolism.

for the treatment of acute VTE, and is, to date, the largest single Phase III study ever initiated in this patient population, with a total of 8292 patients randomized across 439 sites in 37 countries [75,76]. Patients with objectively diagnosed, acute, symptomatic DVT (involving the popliteal, femoral, or iliac veins) or acute, symptomatic PE (with or without DVT) were randomized to receive initial therapy with open-label LMWH or unfractionated heparin (as determined by the investigator) for at least 5 days followed by either edoxaban 60 mg QD daily or warfarin (adjusted to an INR 2.0–3.0) (Figure 6). Warfarin therapy was started after randomization and the initial heparin regimen was continued for at least 5 days after randomization and until the INR (real or sham) was  $\geq 2.0$  on two measurements at least 1 day apart. Edoxaban was started after discontinuing initial heparin. By initiating treatment with the proven, global standard of parenteral heparin, the study design was more applicable to real-world clinical practice than the designs of previous clinical trials, and also encouraged investigators to enroll a high proportion of patients with more extensive grades of VTE, particularly more severe PE. Furthermore, the study featured flexibility with regards to treatment duration in that physicians were allowed to adjust the duration of treatment after

3 months according to their judgement, with treatment continued for up to 12 months. This flexibility is in line with clinical practice, but uncommon in clinical trials. Regardless of the total duration of treatment actually received, efficacy and safety data were collected on all subjects during the entire 12-month period following randomization in order to compare clinical outcomes of the two treatment regimens. Another unique feature of the Hokusai-VTE study was the ability to adjust the dose of edoxaban (from 60 to 30 mg QD) at randomization and at any point during the study in patients perceived to be at higher risk of bleeding (renal impairment [ $\text{CrCl}$  30–50 ml/min], body weight  $\leq 60$  kg or who were receiving select P-gp inhibitors) [75,76].

The primary objective of the study was to demonstrate noninferiority of edoxaban versus warfarin for the incidence of adjudicated symptomatic recurrent VTE (a composite of DVT or nonfatal or fatal PE). The principal safety outcome was the incidence of adjudicated clinically relevant bleeding (a composite of major or clinically relevant nonmajor bleeding). In total, 25 and 27 patients did not receive treatment in the edoxaban and warfarin groups, respectively, with the edoxaban group comprising 4118 patients, the warfarin group 4122 patients [75].



**Figure 6. Study design of Hokusai-VTE.**

DVT: Deep vein thrombosis; INR: International normalized ratio; PE: Pulmonary embolism; UFH: Unfractionated heparin; VTE: Venous thromboembolism.

Reproduced with permission from [76].

Edoxaban was shown to be noninferior to warfarin in a broad range of patients with VTE. In the overall study population (12 months), recurrent VTE occurred in 130 of 4118 patients (event rate of 3.2%/year) in the edoxaban group and 146 of 4122 patients (3.5%/year) in the warfarin group (HR: 0.89; 95% CI: 0.70–1.13;  $p < 0.001$  for noninferiority). The time course for recurrent VTE is shown in [Figure 7A](#). With the flexible duration study design, >61% of patients remained on-treatment for >6 months, and approximately 40% remained on-treatment for 12 months; in these patients (the on-treatment population), recurrent VTE occurred in 1.6% of the edoxaban group versus 1.9% of the warfarin group (HR: 0.82; 95% CI: 0.60–1.14;  $p < 0.001$  for noninferiority). The results with edoxaban not only highlight the importance of maintaining treatment to prevent recurrence, but also indicate that efficacy was evident among those who stopped treatment before 12 months, without evidence of a rebound effect. It is also worth noting that these results with edoxaban were obtained compared with a group of patients who were very well controlled on warfarin, with an overall time in therapeutic range of 63.5% [75].

The results of the safety outcomes demonstrated that treatment with edoxaban caused significantly lower rates of nearly all bleeding types than treatment with warfarin. The incidence of adjudicated clinically relevant bleeding (principal safety outcome) occurred in 349 of 4118 patients (8.5%) in the edoxaban group and in 423 of 4122 patients (10.3%) in the warfarin group (HR: 0.81; 95% CI: 0.71–0.94;  $p = 0.004$  for superiority) ([Figure 7B](#)). Clinically relevant nonmajor bleeding occurred in 298 (7.2%) patients in the edoxaban group and 368 (8.9%) patients in the warfarin group (HR: 0.80; 95% CI: 0.68–0.93;  $p = 0.004$  for superiority). Any bleeding occurred in 895 (21.7%) patients in the edoxaban group and 1056 (25.6%) patients in the warfarin group (HR: 0.82; 95% CI: 0.75–0.90;  $p < 0.001$  for superiority). The incidence of major bleeding was similar in the edoxaban (1.4%) and warfarin (1.6%) groups (HR: 0.84; 95% CI: 0.59–1.21;  $p = 0.35$  for superiority) [75].

In total, 17.8% of patients qualified for the edoxaban 30 mg QD dose at randomization. In these patients, patient-specific dosing with edoxaban maintained overall safety and efficacy benefits. Fewer clinically relevant bleeding events occurred in the edoxaban 30 mg than warfarin group (7.9 vs 12.8%; HR: 0.62; 95% CI: 0.44–0.86) and efficacy was maintained (3.0 vs 4.2%; HR: 0.73; 95% CI: 0.42–1.26) [75].

Analyses of the primary outcome were also performed in patients according to the presenting diagnosis (DVT or PE [with/without DVT]). In these patients, recurrence rates were similar with edoxaban

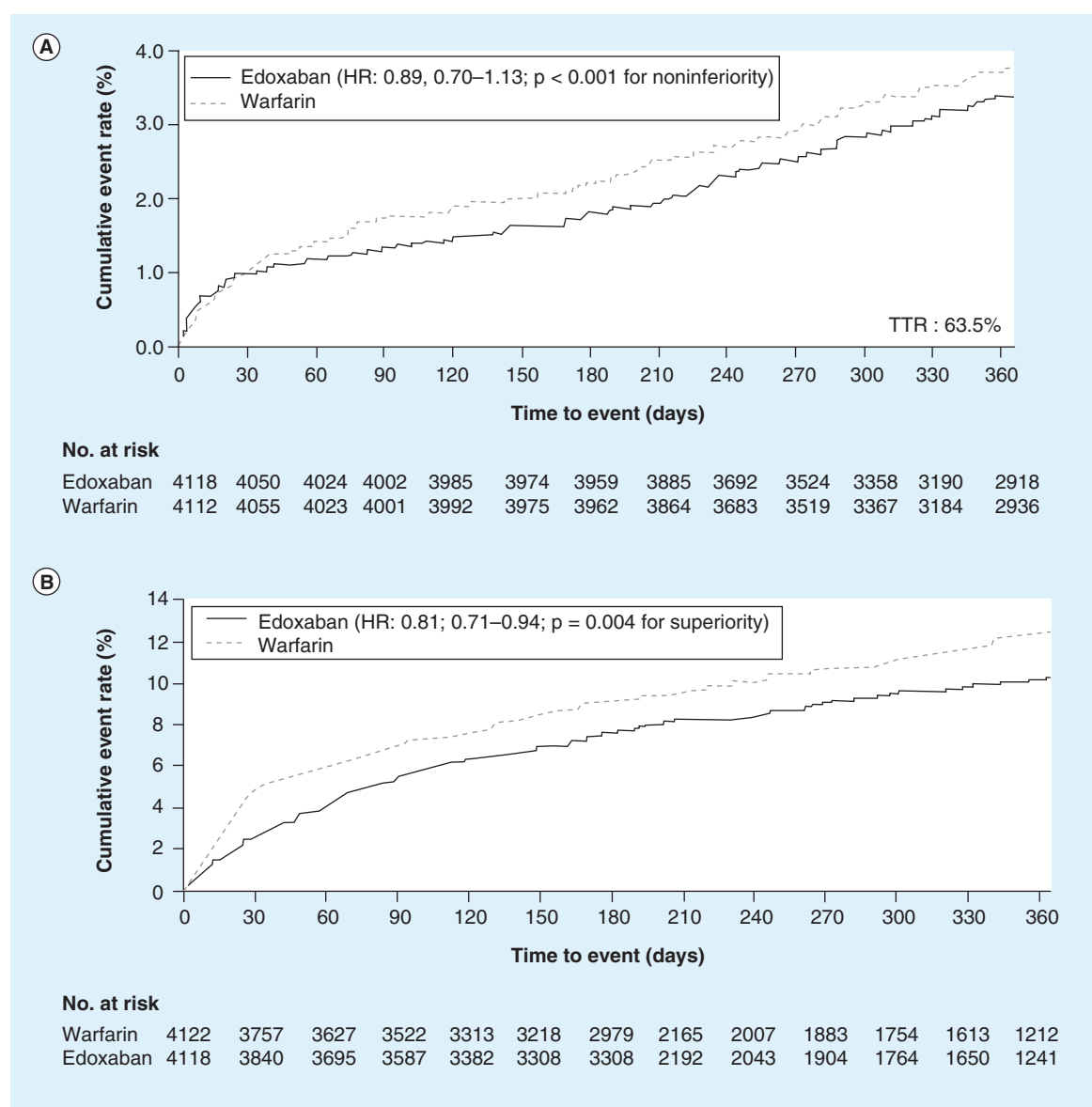
and warfarin, with the upper limits of the 95% CI of the hazard ratios not exceeding the margin of 1.5 (index DVT, 3.4 vs 3.3%; HR: 1.02; 95% CI: 0.75–1.38; index PE, 2.8 vs 3.9%; HR: 0.73; 95% CI: 0.50–1.06). In all patients with PE, N-terminal pro-brain natriuretic peptide (NT-proBNP) levels were measured at baseline to determine right ventricular dysfunction and extensive disease. Approximately one-third of patients had extensive disease, defined as an NT-proBNP level of  $\geq 500$  pg/ml. Edoxaban demonstrated robust efficacy in this high-risk group of PE patients compared with warfarin with an incidence of recurrent VTE of 3.3 versus 6.2% per year (HR: 0.52; 95% CI: 0.28–0.98). In addition to this criteria for extensive disease, right ventricular dysfunction was determined in a random sample of 1002 patients using a computed tomographic scan (defined as a ratio of the right ventricular diameter to the left ventricular diameter of  $\geq 0.9$ ). Similar results were observed among these patients (HR: 0.42; 95% CI: 0.15–1.20) [75].

The Hokusai-VTE study delivered consistent results across all subgroups, including cancer patients ( $n = 771$ ), moderate renal impairment ( $n = 541$ ) and fragile patients ( $n = 1421$ ; aged >75 years, body weight <50 kg, CrCl <50 ml/min), compared with high-quality treatment in the standard of care group (mean TTR for warfarin was 63.5%). Further analysis of patients with cancer (active cancer or a history of cancer) enrolled in Hokusai-VTE ( $n = 771$ ) suggested that edoxaban was at least as effective as warfarin, and may reduce the incidence of bleeding. The authors recommended additional studies of edoxaban for initial and long-term therapy of VTE in patients with cancer with LMWH as the comparator, as LMWH is the anticoagulant recommended for long-term therapy in patients with cancer and VTE [77].

Based on the Hokusai-VTE results, a marketing authorization application and a new drug application have been submitted to the EMA and the FDA, respectively, for the approval of edoxaban for the treatment of DVT or PE and for the prevention of recurrence of symptomatic VTE [51,52].

A recent meta-analysis evaluated the efficacy and safety of all four NOACs in patients with acute VTE. The risk ratio for recurrent VTE, fatal PE and overall mortality for NOACs versus VKA were 0.88 (95% CI: 0.74–1.05), 1.02 (95% CI: 0.39–5.96) and 0.97 (95% CI: 0.83–1.14), respectively, while the risk ratio of major bleeding and for fatal bleeding were 0.60 (95% CI: 0.41–0.88) and 0.36 (95% CI: 0.15–0.87), respectively. These results indicate the NOACs had comparable efficacy to VKA, but with a significantly lower risk of bleeding complications; furthermore, there were no significant differences between individual NOACs [78].





**Figure 7. Outcomes from the Hokusai-VTE study. (A)** Efficacy and **(B)** safety.

HR: Hazard ratio; TTR: Time in therapeutic range.

Adapted with permission from [75].

### Practical aspects for consideration with the NOACs

#### Monitoring the anticoagulant effect

An advantage of the NOACs over traditional treatments, such as VKAs, is the lack of need for routine monitoring of coagulation. This is because the NOACs directly inhibit specific coagulation factors, and their predictable pharmacokinetic and pharmacodynamic profiles directly determine the time course of inhibition, so that neither the dose nor the dosing intervals need altering to changes in coagulation parameters. However, certain emergency situations may require the quantitative assessment of the anticoagulant effect, including serious bleeding and thrombotic events as

well as for patients requiring urgently needed surgery. In addition, quantitative assessment of drug exposure may be needed for special clinical situations, such as in patients who present with renal or hepatic insufficiency (in case of potential drug–drug interactions), or where drug adherence remains doubtful or drug overdose is suspected [3,29].

Available coagulation tests can be divided into those that measure general clot formation and those that directly quantify specific clotting factor inhibition (chromogenic assays for anti-FXa). An overview of the interpretation of several of these coagulation tests for edoxaban is presented in Table 4. When interpreting a coagulation assay with a NOAC, it is important

to know exactly when the NOAC was administered relative to the time of blood sampling, as the maximum effect of the NOAC on the clotting test occurs at its maximal plasma concentration (~2–3 h after intake) [29].

The most commonly available clot-based assays (PT, aPTT, diluted thrombin time, ecarin clotting time), measure the time taken for plasma to clot in the presence of anticoagulant, but do not mirror the overall hemostatic balance. PT and aPTT are dose-dependently prolonged with edoxaban, but cannot be correlated with bleeding risk. Furthermore, these tests are not very sensitive for measuring the anticoagulant effect of edoxaban, since therapeutic doses of the drug produced results at the lower limits of discrimination. In addition, conversion of PT (in seconds) to INR, which is defined for stable VKA patients only, did not correct the variation in results due to differences in sensitivity of edoxaban to various thromboplastin reagents; therefore, INR measurements are not appropriate for monitoring the anticoagulant effect of direct FXa inhibitors such as edoxaban. Modified tests for PT could assist in measuring the degree of anticoagulation with edoxaban [33].

Both PiCT and HepTest are clot-based anti-FXa assays in which edoxaban produced a concentration-dependent prolongation of clot formation. Both these tests could be used for monitoring edoxaban, but require suppression or reduction of the incubation phase to increase sensitivity [33].

Chromogenic assays measure a specific reaction between a clotting factor and its substrate which is inhibited by the presence of anticoagulant. Such assays are more specific than clot-based assays and have proved suitable for the quantitative measurement of edoxaban

using the Hyphen BioMed and a modified version of the Rotachrom® HBPM assay (which is specific for LMWH) [33]. Some of these chromogenic assays have received European authorization for commercial distribution, but these tests may not be routinely available in most hospitals [3,29].

### Management of bleeding complications

At present, the lack of specific antidotes or reversal agents to counter the effect of the NOACs is considered as a drawback to their widespread use, and such agents would offer a number of advantages. For example, in patients undergoing elective surgical procedures, an efficacious reversal agent for NOACs minimize the time patients are off the anticoagulant before surgery and provide confidence when restarting anticoagulant therapy following surgery. In addition, the ability to reverse the effect of the NOACs would allow for rapid emergency responses in cases of overdose or trauma.

Strategies for reversal of the anticoagulant effects are limited, with recommendations on bleeding management reflecting experts' opinions or laboratory end points, rather than clinical experience [29]. Guidance on the emergency reversal of the anticoagulant effects of the new agents has recently been published, and recommend supportive care and discontinuation of therapy for patients experiencing major bleeding while on anticoagulant therapy [79]. In case of drug overdose, activated charcoal may be given within 3 h of oral anticoagulant intake to reduce gastrointestinal absorption. In healthy volunteers, administration of prothrombin complex concentrates (PCC) completely reversed rivaroxaban-induced prolongation of the PT. *In vitro* testing using blood samples from volunteers taking rivaroxaban, dabigatran or apixaban, showed

Table 4. Interpretation of coagulation assays in patients treated with edoxaban.

Coagulation assay	Edoxaban outcome
Prothrombin time	Prolonged, but no known relation with bleeding risk; effect varies with different assays
International normalized ratio	Cannot be used
Activated partial thromboplastin time	Prolonged, but no known relation with bleeding risk; effect varies with different assays
Diluted thrombin time	Cannot be used
Prothrombinase-induced clotting time	Concentration-dependent prolongation; sensitive if incubation suppressed or reduced
HepTest	Concentration-dependent prolongation; sensitive if incubation suppressed
Anti-factor Xa chromogenic assays	Quantitative; no data on threshold values for bleeding or thrombosis
Ecarin clotting time assay	Not affected

Data taken from [15,29,31,33].

that activated prothrombin complex concentrates (aPCC; i.e., similar to PCC but with activated factor VIIa) corrected more coagulation parameters than PCC alone [29,79].

Preclinical studies have evaluated the effects of several commercially available hemostatic agents on coagulation activity of edoxaban. Using human plasma *in vitro*, PCC (PPSB®-HT), aPCC (Feiba®) and recombinant FVIIa (rFVIIa; NovoSeven®) significantly and dose-dependently reversed the anticoagulant effect of therapeutic and higher concentrations of edoxaban as shown by a reduction in PT. In addition, rFVIIa and aPCC significantly reversed edoxaban-induced prolongation of bleeding time in rats; plasma TAT levels and bleeding time were negatively correlated, suggesting that plasma TAT concentration could be a better biomarker rather than PT [80]. Practical guides on the use of NOACs highlight, in cases of bleeding complications, the importance of determining the dosing regimen and time of last dose, as restoration of hemostasis can be expected within 12–24 h after cessation of treatment. Local hemostatic measures should be undertaken, while fluid replacement, red blood cell and platelet substitution (in case of thrombocytopenia  $\leq 60 \times 10^9/l$  or thrombopathy) should be considered. Fresh frozen plasma should be used as plasma expander, but not as a reversal agent. The anti-fibrinolytic agent tranexamic acid can be considered as an adjuvant, particularly in hyperfibrinolytic or mucosal bleedings, and desmopressin can be considered in special cases (coagulopathy or thrombopathy). In life-threatening bleeds, PCC 25 U/kg can be used and may be repeated once or twice, although clinical evidence is lacking. aPCC 50 IE/kg (maximum 200 IE/kg/day), is also recommended but it is not as readily available and data for additional benefit over PCC are not convincing. The same applies to rFVIIa (90 mg/kg), where only data from animal studies are available [29].

A number of other options for reversal agents are also in development and being investigated. A modified recombinant FXa (r-Antidote) has been developed as a potential antidote to FXa inhibitors. r-Antidote is a catalytically inactive molecule that retains the ability of native FXa to bind to, with high affinity, FXa inhibitors and LMWH-activated antithrombin. This molecule has been shown to dose-dependently reverse the inhibitory activity of several FXa inhibitors (rivaroxaban, apixaban, betrixaban); in animal models, it restored hemostasis following treatment with rivaroxaban and corrected increases in blood loss following treatment with enoxaparin and fondaparinux [81].

A synthetic small molecule, PER977, has been designed and synthesized with the aim of reversing

the anticoagulant effects of the NOACs. Modeling and *in vitro* studies to characterize the mechanism of action and binding specificity of PER977 indicate the formation of strong physical, noncovalent complexes between PER977 and NOACs and heparins (enoxaparin). Importantly, PER977 has shown no procoagulant properties as measured by thromboelastography (TEG), PT and aPTT in rat and human whole blood. Preclinical studies have shown that intravenous administration of PER977 significantly decreased bleeding in rats treated with edoxaban, rivaroxaban, apixaban and dabigatran. In addition, treatment with PER977 restored coagulation parameters (PT for edoxaban, rivaroxaban, and apixaban; aPTT for dabigatran; TEG for edoxaban) to baseline values within 20 min of administration [82,83]. The first Phase I in-human clinical trial to evaluate safety and efficacy of PER977 is currently underway and recruiting patients (NCT01826266).

### Perioperative management

Patients receiving long-term anticoagulation may be exposed to elective or emergency surgery or invasive procedures that carry a bleeding risk and require the temporary discontinuation of the anticoagulant. Proposals for perioperative management for optimal safety regarding the risk of bleeding and thrombosis have been made [29,84]. These proposals differ depending on whether the situation is scheduled or is an emergency, with scheduled surgical procedures ranked according to the potential for bleeding and the thrombotic risk to which the patient would be exposed following interruption of anticoagulation.

For procedures with low hemorrhagic risk (e.g., endoscopy, prostate or bladder biopsy, angiography, radiofrequency catheter ablation or pacemaker implantation), bleeding will be of low abundance, noncritical and could be managed with mechanical hemostasis. A therapeutic window of 48 h is proposed, with last administration of anticoagulant 24 h before, and restarted 24 h after, surgery. Procedures with medium or high hemorrhagic risk include those that would produce clinically significant bleeding, surgery that is hemorrhagic, or where the risk of bleeding would be unacceptable (e.g., complex left-sided ablation, thoracic, abdominal or major orthopedic surgery, liver or kidney biopsy). The anticoagulant should be stopped at least 48 h and up to 4 days before surgery depending on the half-life of the drug to ensure complete elimination in all patients, and resumed only when the risk of bleeding has been controlled. In an emergency, the procedure should be postponed for as long as possible (minimum 1–2 half-lives) and nonspecific anti-hemorrhagic agents, such as rFVIIa or PCC should not

be given for prophylactic reversal due to their uncertain benefit–risk [29,84].

Patient characteristics such as renal function can play an important role in deciding when to discontinue the NOAC. For patients on VKA undergoing invasive procedures, a HAS-BLED score  $\geq 3$  has been shown to be predictive of bleedings [85]. For patients with a CrCl  $>30$  ml/min (i.e., moderate renal function or better) taking FXa inhibitor (apixaban or rivaroxaban), last intake of drug should be  $\geq 24$  and  $\geq 48$  h for those at low and high risk of bleeding, respectively. In those with CrCl of 15–30 ml/min (severe renal function), discontinuation should be  $\geq 36$  and  $\geq 48$  h. When the label of edoxaban is finalized, specific advice for this NOAC will be formulated [29].

## Conclusion

The VKAs have been widely prescribed for over 60 years, and will remain an important anticoagulation option for venous and thromboembolic diseases. However, the scope for the effective management of these conditions has been enhanced with the advent of the NOACs, which, given the advantages they convey

over current standards of care, provide clinicians with further options and enable treatment to be tailored to meet individual patient needs.

The direct FXa inhibitor edoxaban is the latest NOAC to be investigated for stroke prevention in patients with AF (ENGAGE AF-TIMI 48), and treatment of VTE (Hokusai-VTE), in Phase III clinical trials which, to date, are the largest conducted in these indications. The design of these studies simulate aspects of real-world clinical practice. The ability to adjust the dose based on certain patient criteria ensures patients can be administered edoxaban without unduly increasing drug exposure or aggravating the risk of bleeding events while maintaining efficacy. In addition, the oral QD fixed dose provides a simplified regimen for thromboprophylaxis, and provides added convenience for patients which may help ensure long-term treatment adherence. In these studies, edoxaban was at least as effective as the current optimized standard of care, warfarin. Moreover, edoxaban demonstrated an improved safety profile, with reduced rates of bleeding events compared with warfarin. Edoxaban has now been submitted for regulatory approval in these

## Executive summary

### Background

- Although oral anticoagulants such as the vitamin K antagonist warfarin are the standard of care for the management of thromboembolic diseases, they are associated with a number of limitations.
- This has led to the development of the novel oral anticoagulants (NOACs) designed to act via direct (antithrombin-independent) inhibition of a specific coagulation factor.
- Edoxaban has recently been submitted to the US FDA and EMA for approval for use in thromboembolic diseases.

### Edoxaban pharmacokinetics & pharmacodynamics

- Edoxaban is a potent and highly selective direct inhibitor of free and clot-bound factor Xa.
- Edoxaban demonstrates predictable and consistent pharmacokinetics, characterized by rapid absorption and onset of action, and which are not influenced by gender, age, ethnicity or food intake.
- Plasma concentration of edoxaban shows a linear relationship with prolongation of coagulation parameters and reduction in thrombus formation within the therapeutic range in healthy subjects.

### Atrial fibrillation & clinical studies with edoxaban

- Atrial fibrillation (AF) is a common cardiac arrhythmia, the most serious and feared complication of which is thromboembolic stroke; the risk of stroke is increased three- to five-times in patients with AF.
- Several Phase II studies in patients with AF demonstrated the efficacy and tolerability of edoxaban, and identified edoxaban 30 mg and 60 mg once daily as the most suitable doses for Phase III evaluation.
- The Phase III ENGAGE AF-TIMI 48 study, the largest trial of NOACs in AF to date, randomized 21,105 patients with a moderate-to-high risk of stroke.
- Edoxaban was noninferior to warfarin for the incidence of stroke or systemic embolic events, and was associated with a significantly lower rate of nearly all types of bleed.

### Venous thromboembolism & clinical studies with edoxaban

- Venous thromboembolism (VTE) comprises deep vein thrombosis and pulmonary embolism and is the third most common cardiovascular disease affecting 1 million people and causing 540,000 deaths in the EU.
- The Phase III Hokusai-VTE study randomized 8292 patients with acute VTE, making it the largest study of the NOACs for the treatment of acute VTE to date.
- Edoxaban was shown to be noninferior to warfarin for the incidence of adjudicated symptomatic recurrent VTE in a broad range of patients with VTE, and caused significantly lower rates of nearly all bleeding types than warfarin.
- Robust efficacy was demonstrated in a subgroup of patients with extensive disease.

indications, which would provide clinicians with an effective, well tolerated and convenient once-daily option for treating patients.

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