New drugs

Edoxaban: a focused review of its clinical pharmacology

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Long-term anticoagulation treatment with warfarin has been associated with a number of limitations in clinical practice and there is a need for more convenient long-term anticoagulation treatment. One of the non-vitamin K oral anticoagulants in development is edoxaban, a factor Xa inhibitor that is administered once daily. The pharmacological properties of edoxaban have various advantages in anticoagulant therapy. Edoxaban quickly reaches peak plasma concentrations in 1.5 h, has a half-life of 10–14 h, has relatively high bioavailability of 62% and exhibits highly selective, competitive, concentration-dependent inhibition of human factor Xa. The plasma concentrations of edoxaban are also closely correlated with suppression of thrombin generation and a range of platelet activation parameters (fragment 1+2, thrombin–antithrombin complex, and β-thromboglobulin), which edoxaban has been shown to rapidly inhibit. The anticoagulant activity of edoxaban is not affected by food intake or ethnicity and a number of drug–drug interaction studies have been performed. Co-administration of edoxaban with strong P-glycoprotein inhibitors, such as dronedarone, quinidine, and verapamil requires edoxaban dose-reduction by 50% to avoid the risk of over-exposure. The exposure of edoxaban may also increase in patients with a body weight ≤ 60 kg and moderate renal impairment. This meant a dose-reduction strategy in patients at risk of over-exposure was utilized in Phase III clinical studies. In conclusion, the pharmacological properties of edoxaban provide rapid and specific inhibition of factor Xa, which is closely related to plasma concentrations. Given the limitations with long-term warfarin therapy, once-daily edoxaban may provide a convenient long-term alternative for patients.

Keywords  Edoxaban • Oral anticoagulant • Pharmacokinetics • Pharmacodynamics • Coagulation factors

Introduction

Dose-adjusted oral anticoagulant (OAC) therapy with warfarin is currently recommended for the prevention of stroke in patients with atrial fibrillation (AF).1,2 Oral anticoagulant therapy overlapped with parenteral heparin is also recommended for the prevention of recurrent venous thromboembolism (VTE).3,4

Warfarin therapy is low cost, its use is long established and well understood, and it can be administered once-daily. However, warfarin is subject to a range of limitations in clinical practice. These include: a slow onset of action; a narrow therapeutic margin; inadequate anticoagulation; high discontinuation rates; frequent, complex dose adjustments; increased risk of bleeding, particularly in the elderly; variability in dose response; drug and food interactions; and lack of laboratory standardization in coagulation monitoring.5

Non-vitamin K oral anticoagulants (NOACs, previously referred to as new or novel OACs) are now available in two broad classes, which act on the two key serine protease enzymes that drive clot formation and fibrin deposition, the oral factor Xa (FXa) inhibitors (rivaroxaban, apixaban, and edoxaban [DU-176b]), and the oral direct thrombin inhibitor dabigatran etexilate have recently been introduced, or are in clinical development, for stroke prevention in AF, and prevention of recurrence of VTE.6,7

Potential advantages of the new OACs over once-daily warfarin include a rapid onset of action, no significant food interactions, lower potential for drug interactions, and a predictable anticoagulant effect that obviates the need for routine coagulation monitoring. However, there are pharmacodynamic and pharmacokinetic differences between the new OACs, which may also have implications for their clinical use.5

The objective of this review was to focus specifically on the pharmacology of the direct FXa inhibitor, edoxaban. PubMed was searched for original primary and secondary research publications with ‘edoxaban’ OR ‘DU-176b’ OR ‘DU 176b’ OR ‘DU176b’ in any field. Original primary and secondary congress research abstracts were also searched on BIOSIS from 2010 to January 2014 using the...
same search terms. The results of all searches were reconciled to remove duplicate entries and all manuscripts and abstracts with original research on the pharmacokinetics or pharmacodynamics of edoxaban were assessed for inclusion in this review article (Figure 1).

Pre-clinical pharmacological analyses with edoxaban

Effects on coagulation parameters

Studies in vitro

Early investigations with edoxaban assessed in vitro pharmacological profiles and in vivo effects of edoxaban in animal models of thrombosis and bleeding. Edoxaban inhibited FXa with Ki values of 0.561 nM for free FXa, 2.98 nM for prothrombinase and exhibited >10 000-fold selectivity for FXa. Inhibition of human FXa by edoxaban was concentration-dependent and competitive (Figure 2).8 In human plasma, edoxaban doubled prothrombin time (PT) and activated partial thromboplastin time (aPTT) at concentrations of 0.256 and 0.508 μM, respectively.8

Edoxaban has also been analysed in an in vitro thrombin generation (TG) assay in human plasma. In this assay, edoxaban suppressed TG in a concentration-dependent manner, suppressed TG peak height and prolonged lag time.9 The effects of edoxaban on TG have also been compared with the indirect FXa inhibitor fondaparinux. In the study by Samama et al.,10 edoxaban exhibited a three-fold greater concentration-dependent effect than fondaparinux across TG lag time, peak thrombin, and time to peak, but this was not observed with endogenous thrombin potential; also, edoxaban produced a concentration-dependent prolongation of the PT ratio and aPTT.10

An analysis of the effects of edoxaban on human platelet aggregation induced by tissue factor and clot-bound FXa in vitro found that edoxaban, a direct FXa inhibitor, was a more potent inhibitor of tissue factor-induced platelet aggregation and clot-bound FXa than fondaparinux, an indirect FXa inhibitor. These findings suggest that direct inhibition of FXa may provide additional benefits over indirect FXa inhibition.11

Studies in animals

Edoxaban dose-dependently inhibited thrombus formation in rat and rabbit thrombosis models in vivo. Orally administered edoxaban in rats and rabbits significantly and dose-dependently reduced

Figure 1 Flowchart of edoxaban manuscript and abstract selection process.

Figure 2 Lineweaver–Burk kinetic analysis of the activity of human FXa in the absence or presence of edoxaban (DU-176b). Data represent means ± SEM of triplicate assays. Reproduced from Furugohri et al.8
thrombus formation and prolonged PT.8 Also, plasma samples derived from edoxaban-treated rats inhibited exogenous FXa activity and, in rabbits, edoxaban exerted a dose-dependent antithrombotic effect on venous thrombus weight (Figure 3). Moreover, edoxaban 10 and 30 mg/kg significantly prolonged rat tail bleeding time by 1.9-fold, compared with control.8

In addition, edoxaban has also been compared with fondaparinux in venous and arterial thrombosis models and in an ex vivo perfusion-chamber thrombosis model under low- and high-shear rates, which simulated conditions in veins and stenosed arteries in rats. Effective doses of edoxaban that reduced thrombus formation by 50% (ED50) in venous and arterial thrombosis models were 0.076 and 0.093 mg/kg/h, respectively.12 In contrast, the ED50 of fondaparinux in the arterial thrombosis model (>10 mg/kg/h) was markedly higher compared with the venous thrombosis model (0.021 mg/kg/h).12

Edoxaban also inhibited the formation of fibrin under both high- and low-shear rate conditions, whereby edoxaban 3 mg/kg/h reduced thrombus weight by 88% under the low-shear rate (venous model) and by 70% under the high-shear rate (arterial model), respectively. In contrast, fondaparinux inhibited fibrin deposition by 84% under low-shear rate and only showed a slight reduction under the high-shear rate.12

The potential of edoxaban to influence tissue factor-induced coagulation and coagulation pathways in rats has been compared with the direct thrombin inhibitor, melagatran.13 Edoxaban dose-dependently inhibited platelet consumption and thrombin–antithrombin (TAT) complex generation. Also, in a hypercoagulation model, edoxaban did not exert any deleterious effects on platelet counts and inhibited the rapid pattern of platelet consumption observed with the direct thrombin inhibitor melagatran. This observation of a lower possibility of coagulation pathway activation points to a potential mechanistic benefit with anticoagulation using a factor Xa inhibitor such as edoxaban, rather than a direct thrombin inhibitor.13

**Effects on bleeding in animal models**

The risks of bleeding with edoxaban have been compared with those associated with warfarin and the low-molecular-weight heparin (LMWH), enoxaparin, in rat models of thrombosis and haemorrhage. The dose–response curves of the antithrombotic effects and bleeding time prolongation of edoxaban, warfarin, and enoxaparin from Morishima et al.14 are shown in Figure 4. In this study, the therapeutic index of edoxaban was >10.5, whereas that of warfarin and enoxaparin were 1.3 and 3.4, respectively, indicating a wider therapeutic window with edoxaban compared with warfarin or enoxaparin treatment.14

**Combination therapy in animal models**

The combined effects of edoxaban with the antiplatelet agents, aspirin and clopidogrel have been investigated following oral administration in fasted rats, 0.5, 1, and 2 h before thrombus induction.15 In the study by Morishima et al.,15 the combination of submaximal doses of edoxaban 1 mg/kg and aspirin 50 mg/kg, or edoxaban 1 mg/kg and clopidogrel 10 mg/kg showed additive antithrombotic effects. Edoxaban 1 mg/kg or aspirin 50 mg/kg alone had no effect on bleeding time, but combining both these agents induced less than two-fold bleeding prolongation. Clopidogrel 10 mg/kg also

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**Figure 3** Antithrombotic effect of edoxaban in venous stasis thrombosis models in rats (n = 8, A–C) and rabbits (n = 8, D). (A) thrombus weight, (B) PT, (C) exogenous FXa activity and (D) thrombus weight in rabbits. In the rat model, edoxaban was orally administered 30 min before thrombus induction. Blood samples were drawn 29 min after dosing. In rabbits, edoxaban was orally administered 45 min before thrombus induction. Data represent the means ± SEM. ***p < 0.01, ****p < 0.0001 vs. control. Data represent means ± SEM of triplicate assays. PT, prothrombin time. Reproduced from Furugohri et al.8
prolonged bleeding time 2.1-fold and the addition of edoxaban 1 mg/kg had no effect on the prolongation of bleeding time by clopidogrel. Thus, perhaps unsurprisingly, edoxaban potentiates the effects of antiplatelet therapy in pre-clinical models.15

Clinical pharmacokinetics of edoxaban

Absorption, distribution, metabolism, and excretion of edoxaban

The clinical pharmacokinetic studies with edoxaban are summarized in Table 1. In healthy subjects, the pharmacokinetics of edoxaban are characterized by rapid absorption (1–3 h) and the elimination half-life of edoxaban 60 mg once daily is 10–14 h.16,17 Peak plasma concentrations of edoxaban are achieved at ~1.5 h after oral administration (Figure 5A).16,18 The absolute oral bioavailability of edoxaban in healthy subjects is 62% (Table 1).17

Edoxaban pharmacokinetics is also linearly correlated with coagulation parameters within its therapeutic dose range in healthy subjects. Accordingly, from 1 to 3 h post-dose, edoxaban 60 mg has been observed to produce plasma concentrations approximately double those achieved after administration of edoxaban 30 mg (Figure 5B).19 In a study by Fuji et al.,20 the profile of coagulation biomarkers with edoxaban 30 mg once daily compared with enoxaparin 20 mg twice daily treatment, was assessed in VTE patients from the STARS E-3 and STARS J-V trials. The investigators found that edoxaban reduced d-dimer, prothrombin fragment 1 + 2 (F1+2), and the soluble fibrin monomer complex all to a significantly greater extent than enoxaparin by 7 and 11–14 days of treatment ($P < 0.001$ for edoxaban vs. enoxaparin in all comparisons).20

The elimination profile of radiolabelled [14C]edoxaban has been investigated in healthy subjects and ~60% of edoxaban is eliminated in faeces, with ~35% in urine. Edoxaban undergoes biotransformation to various metabolites, the most abundant of which [M4] is formed through hydrolysis.21,22 In addition, over 70% of an edoxaban dose is excreted unchanged.22 Gender has a minimal clinical effect on the pharmacokinetics of edoxaban.23

In view of the role of the kidneys in the elimination of edoxaban, its pharmacokinetics has been assessed in patients with renal impairment. An initial 8-week study in 93 AF patients found that the use of edoxaban 15 mg once daily in patients with severe renal impairment resulted in similar safety outcomes and plasma levels 1–8 h post-dose as edoxaban 30 or 60 mg once daily in patients with mild renal impairment or normal renal function.24 A similar study has been performed in 80 VTE patients undergoing lower-limb orthopaedic surgery, with edoxaban 15 mg in patients with severe renal impairment compared with edoxaban 30 mg in patients with mild renal impairment and fondaparinux 1.5 mg in patients with severe renal impairment.25 By Day 7 of treatment, edoxaban plasma concentrations overlapped between patients with severe and mild renal impairment and similar bleeding outcomes and adverse events were observed in the edoxaban 15 and 30 mg groups. These two initial studies suggest that edoxaban 15 mg once daily may be a suitable dosing regimen for both AF and orthopaedic surgery VTE patients with severe renal impairment.25 In patients with end-stage renal disease (ESRD) with or without haemodialysis treatment, it has also been shown that haemodialysis had minimal effects on the clearance of edoxaban and that additional edoxaban dose adjustment may not be necessary when ESRD patients are undergoing haemodialysis.26

Relationship between edoxaban pharmacokinetics and bleeding

The pharmacokinetics of various doses of edoxaban were also assessed in a Phase II dose-finding study in patients with AF, which showed that edoxaban exposure parameters (minimum steady-state concentration $[C_{\text{minss}}]$, area under the plasma concentration-time curve from 0 to 24 h at steady-state $[AUC_{\text{ss}}]$, and maximum steady-state plasma concentration $[C_{\text{maxss}}]$) increased with higher total daily doses of edoxaban.27 With the same total daily dose of
<table>
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<th>Study</th>
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<th>Design</th>
<th>Principal findings</th>
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<tbody>
<tr>
<td>Ogata et al.16</td>
<td>Healthy adult males (n = 121)</td>
<td>SD group: edoxaban 10, 30, 60, 90, 120, and 150 mg q.d.</td>
<td>Phase I, single-blind, randomized, placebo-controlled, ascending single and multiple oral dose study</td>
<td>Edoxaban plasma levels were proportional to dose, consistently peaked 1.5 h post-dose and correlated with coagulation parameters.</td>
<td>Edoxaban 10 mg q.d. to 150 mg q.d. were safe and well tolerated, with predictable pharmacology</td>
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<td>Matsushima et al.17</td>
<td>Healthy adults (n = 35)</td>
<td>Edoxaban 60 mg or 30 mg IV over 30 min</td>
<td>Randomized, two-arm study assessing bioavailability of oral and IV edoxaban</td>
<td>The ratios of geometric LSM of the dose-adjusted AUC_{0-\infty} between oral and IV edoxaban indicated bioavailability of 61.80% (95% CI: 57.70, 66.19). Edoxaban 60 mg half-life was 11.3 ± 5.63 h</td>
<td>Edoxaban has a relatively high bioavailability of 62%</td>
</tr>
<tr>
<td>Mendell et al.15</td>
<td>Healthy Japanese and Caucasian adults (n = 32)</td>
<td>Edoxaban 60 mg with or without food, then an alternative diet</td>
<td>Open-label, randomized, food effect study</td>
<td>Edoxaban plasma concentration, elimination, changes in PT and aPTT were not affected by race or food intake</td>
<td>Edoxaban can be administered without regard to food</td>
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<tr>
<td>Bathala et al.22</td>
<td>Healthy males (n = 6)</td>
<td>[^{14}C]Edoxaban 60 mg</td>
<td>Open-label study</td>
<td>Over 97% of the administered radioactive [^{14}C]Edoxaban dose was recovered, with 62.2% eliminated in faeces and 35.4% in urine</td>
<td>A substantial proportion of edoxaban is excreted by the renal system in urine</td>
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<td>Raskob et al.29</td>
<td>VTE patients following orthopaedic surgery (n = 903)</td>
<td>Edoxaban 15, 30, 60, or 90 mg q.d. or dalteparin q.d., 6–8 h post-operatively for 7–10 days</td>
<td>Parallel-group, multinational, active-controlled, 12-week study</td>
<td>Incidences of VTE were 28.2, 21.2, 15.2, and 10.6% in the edoxaban 15, 30, 60, or 90 mg groups, respectively, vs. 43.8% in the dalteparin group</td>
<td>Edoxaban 15, 30, 60, or 90 mg is more effective than dalteparin in preventing VTE, with a dose-response relationship observed</td>
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<tr>
<td>Fuji et al.25</td>
<td>Japanese VTE, orthopaedic surgery patients (n = 80)</td>
<td>Edoxaban 15 mg (CrCl \geq 15 to \leq 20 mL/min), edoxaban 15 mg or fondaparinux 1.5 mg (CrCl \geq 20 to &lt; 30 mL/min), edoxaban 30 mg (CrCl \geq 50 to &lt; 80 mL/min)</td>
<td>Open-label study</td>
<td>Bleeding events occurred in 6 (20.7%), 8 (40.0%), and 10 (33.3%) and CRNM bleeding in 1 (3.4%), 1 (5.0%), and 2 (6.7%) patients in the edoxaban 15 mg, fondaparinux 1.5 mg, and edoxaban 30 mg groups</td>
<td>Edoxaban 15 mg may be a suitable dose in VTE, orthopaedic surgery patients with severe renal impairment</td>
</tr>
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<td>Weitz et al.27</td>
<td>AF patients with CHADS\textsubscript{2} \geq 2 (n = 1,146)</td>
<td>Edoxaban 30 mg q.d., 30 mg b.i.d., 60 mg q.d., or 60 mg b.i.d. or open-label, dose-adjusted warfarin</td>
<td>Parallel-group, multinational, active-controlled, 12-week study</td>
<td>Major and CRNM bleeding in 3.1% of warfarin, 10.6% of edoxaban 60 mg b.i.d. (P = 0.002 vs. warfarin), 7.8% of 30 mg b.i.d. (P = 0.029 vs. warfarin), 3.8% of 60 mg q.d., 3.0% of 30 mg q.d. treatment groups. Bleeding frequency and C_{\text{cr}} were higher in the 30 mg b.i.d. group than in the 60 mg q.d. group</td>
<td>Edoxaban 30 or 60 mg q.d. resulted in similar bleeding outcomes as warfarin in AF patients, both q.d. doses were well tolerated and bleeding with edoxaban is related to C_{\text{cr}}</td>
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<tr>
<td>Fuji et al.20</td>
<td>VTE patients in STARS E-3 and J-V</td>
<td>Edoxaban 30 mg q.d., enoxaparin 20 mg b.i.d.</td>
<td>Pooled post hoc analysis</td>
<td>Edoxaban 30 mg reduced D-dimer, F_{1+2}, and SFMC significantly more than enoxaparin</td>
<td>Edoxaban is more effective at reducing blood coagulation markers than enoxaparin</td>
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<td>Yamashita et al.28</td>
<td>Japanese AF patients with CHADS\textsubscript{2} \geq 1 (n = 536)</td>
<td>Edoxaban 30, 45, or 60 mg q.d. or open-label, dose-adjusted warfarin</td>
<td>Multicentre, randomized, dose-ranging, 12-week study</td>
<td>All bleeding events increased with increasing edoxaban doses, but a significant dose response was not found with edoxaban for all major, major or major and CRNM bleeding. Edoxaban C_{\text{cr}} in the \leq 60 kg subgroup was higher than the C_{\text{cr}} in the \geq 60 kg subgroup with all doses</td>
<td>Edoxaban 30, 45, or 60 mg are safe and well tolerated in AF patients, and patients &lt; 60 kg are at risk of edoxaban under-exposure</td>
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edoxaban 60 mg, Cminss and bleeding rates were higher with the 30 mg twice-daily regimen than with the 60 mg once-daily regimen (Figure 6). This was a surprising finding as it may have been thought that peak edoxaban concentrations, and not trough concentrations, would be more closely associated with bleeding rates. A study by Yamashita et al. in Japanese AF patients found that the Cmin of edoxaban also increased with increasing once-daily doses. However, body weight had an effect on edoxaban Cmin, and when patients were stratified by body weight, Cmin in the ≤60 kg subgroup was higher than the Cmin in the >60 kg subgroup. Another study in 235 Asian AF patients found that edoxaban 60 mg was higher than the edoxaban 30 mg regimen in the >60 kg subgroup, with dose in the target interval. The effect of edoxaban was stronger in Asian patients than in Caucasian patients, which may explain the differences in bleeding rates observed. In a study by authors of an Asian AF study, edoxaban 60 mg was associated with lower bleeding rates than the 30 mg once-daily regimen. Edoxaban 60 mg Cmin and bleeding rates were higher with the edoxaban 60 mg Cminss regimen, and bleeding rates were lower with the edoxaban 30 mg Cminss regimen.

Figure 5

Arithmetic mean (SD) plasma concentrations vs. time
(A) Oral edoxaban 30, 60, and 120 mg (measured by high performance liquid chromatography); (B) plasma concentration vs. time for edoxaban 30 and 120 mg in Asian atrial fibrillation patients. Reproduced from Wolzt et al.18 and Chung et al.19
doses for subsequent Phase III studies. Dose reduction by 50% in patients with moderate renal impairment (creatinine clearance 30–50 mL/min) or who required strong P-glycoprotein (P-gp) inhibitors was also suggested by the modelling observations. These findings, together with those regarding body weight by Yamashita et al., meant that in Phase III studies with edoxaban, body weight ≤60 kg, moderate renal impairment or concomitant treatment with strong P-gp inhibitors were criteria for dose reduction. A large proportion of patients (17.5%) met the criteria for dose adjustment in Hokusai-VTE and analogous results to the overall population were reported in this group. The rate of recurrent VTE was 3.0% in the dose-adjusted edoxaban group vs. 4.3% in the warfarin group (hazard ratio 0.73 [95% confidence interval] 0.42–1.26).

Clinical pharmacodynamics of edoxaban

The clinical pharmacodynamic studies with edoxaban are summarized in Table 2. In healthy subjects, edoxaban 60 mg once daily has been shown to inhibit TG for over 24 h (Figure 7), providing further support that once-daily dosing provides suitable anticoagulation efficacy with once-daily dosing (Table 2). The antithrombotic effects of edoxaban have been investigated under arterial and venous flow conditions. Under venous flow conditions 1.5 and 5 h post-edoxaban, thrombus size was reduced by 28 and 21%, respectively (P < 0.05 vs. baseline). Under arterial conditions, the reduction was 26 and 17% at 1.5 and 5 h post-edoxaban, respectively (P < 0.05 vs. baseline), which was also statistically significant. Changes in INR, PT and anti-FXa activity also correlated closely with edoxaban plasma concentrations, and the strongest correlation among these clotting parameters was observed with PT changes (R² = 0.79), followed closely by INR changes (R² = 0.78). The correlation with aPTT, whilst statistically significant, was less close (R² = 0.40). In addition, a study of the effects of edoxaban on PT and aPTT in Japanese and Caucasian patients has shown that ethnicity does not influence the anticoagulant activity of edoxaban (Figure 8).

Compared with fondaparinux 2.5 mg, edoxaban 30 mg, 60 and 120 mg once-daily causes significantly larger reductions in the TG and platelet activation parameters, F₁+₂, the thrombin-antithrombin (TAT) complex and platelet activation marker β-thromboglobulin (β-TG). This analysis also found a direct linear correlation between the observed range of plasma concentrations of edoxaban during the dosing interval and the blood coagulation parameters aPTT and PT, with correlation coefficients of 0.738 and 0.957, respectively. When compared with the LMWH dalteparin and direct thrombin inhibitor ximelagatran, edoxaban 60 mg twice-daily also caused a larger reduction in PT activity compared with ximelagatran, but did not for TAT, F₁+₂ or D-dimer.

The clinical pharmacodynamics of edoxaban have also been investigated 24 h post-warfarin therapy, with edoxaban causing a significant increase in PT within 2 h (from 27.0 to 43.9 s; P < 0.001 vs. placebo). PT values returned to near post-warfarin baseline.
Table 2  Clinical pharmacodynamic studies with edoxaban

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<th>Study</th>
<th>Patients</th>
<th>Treatment groups</th>
<th>Design</th>
<th>Principal findings</th>
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<tbody>
<tr>
<td>Woltz et al.18</td>
<td>Healthy adult males</td>
<td>Edoxaban 30, 60, or 120 mg, fondaparinux 2.5 mg or placebo</td>
<td>Open-label, randomized, study of blood coagulation markers F1+2, TAT and β-TG in venous and shed blood</td>
<td>All edoxaban doses inhibited F1+2, TAT and β-TG in shed blood samples significantly more than fondaparinux</td>
<td>Single oral doses of edoxaban 30, 60, or 120 mg cause rapid and sustained inhibition of coagulation for up to 24 h</td>
</tr>
<tr>
<td>Mendell et al.7</td>
<td>Healthy adults</td>
<td>Edoxaban 60 mg q.d. or placebo, followed by warfarin</td>
<td>Randomized, placebo-controlled, safety study of edoxaban post-warfarin therapy</td>
<td>Edoxaban 60 mg administered 24 h post-warfarin appeared to be safe and well tolerated. Adverse events were similar across treatments.</td>
<td>Edoxaban causes transient increases in coagulation parameters, when administered 24 h post-warfarin therapy</td>
</tr>
<tr>
<td>Samama et al.36</td>
<td>Healthy elderly males</td>
<td>Edoxaban 60 mg b.i.d., dalteparin 5000 IU or ximelagatran 24 mg</td>
<td>Open-label, randomized, study of blood coagulation markers F1+2, TAT, dimer and adverse events</td>
<td>There were no differences in TAT, F1+2 and dimer levels post-edoxaban and post-ximelagatran dosing. Edoxaban caused a greater change in TAT and F1+2 levels than dalteparin. Edoxaban reduced PT more rapidly and for longer than ximelagatran and dalteparin. Edoxaban did not affect platelet activation, tissue factor pathway inhibition or endothelial breakdown</td>
<td>This was the first study to compared a FXa inhibitor; DTI and LMWH, and showed edoxaban inhibits TG and FXa</td>
</tr>
<tr>
<td>Zahir et al.33</td>
<td>Healthy adults aged 18–45 years</td>
<td>Edoxaban, enoxaparin, edoxaban plus enoxaparin, enoxaparin plus edoxaban 12 h later</td>
<td>Phase I, open-label, randomized, four-period, four-treatment, cross-over study of enoxaparin 1 mg/kg followed by edoxaban 60 mg 12 h later</td>
<td>Edoxaban alone and combined with enoxaparin inhibited TG for over 24 h. No adverse events were reported in any group and changes in drug pharmacology were not observed</td>
<td>Edoxaban 60 mg can be safely administered 12 h after enoxaparin 1 mg/kg</td>
</tr>
<tr>
<td>Zafar et al.34</td>
<td>Healthy adults</td>
<td>Edoxaban 60 mg</td>
<td>Phase I, open-label, single-arm pharmacology study</td>
<td>Peak plasma edoxaban concentrations observed 1.5 h after dosing. TG was significantly reduced under venous and arterial conditions 1.5 and 3 h post-dosing. Correlation of plasma edoxaban with FXa activity R² = 0.85, INR R² = 0.78, PT R² = 0.79, aPTT R² = 0.40</td>
<td>Plasma edoxaban levels closely correlated with reductions in TG and changes in clotting parameters</td>
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β-TG, β-thromboglobulin; b.i.d., twice daily; DTI, direct thrombin inhibitor; FXa, factor Xa; F1+2, fragment 1+2; INR, international normalized ratio; LMWH, low-molecular-weight heparin; PT, prothrombin time; q.d., once daily; TAT, thrombin-antithrombin; TG, thrombin generation.

levels (26.3 s) at 12 h post-edoxaban dose and remained higher than with placebo at all measured time points between 1 and 12 h. Warfarin treatment increased aPTT values from 35.6 to 50.8 s, and edoxaban also increased aPTT further to 67.4 s at 1 h post-dose, demonstrating that edoxaban has a bigger effect on aPTT than warfarin. Also, anti-FXa activity was mostly undetectable during warfarin treatment (<0.10 IU/mL), but increased following edoxaban administration, reaching peak levels of 2.68 IU/mL at 1 to 2 h post dose, and then declining to approximately baseline levels by 24 h post dose (Figure 9). The transient increases in various coagulation parameters returned to baseline levels 24-h after edoxaban dosing.

Edoxaban metabolism, drug, and food interactions

A study in healthy, fasted or fed Japanese and Caucasian volunteers showed that the absorption, mean plasma concentration and a wide range of other PK characteristics of edoxaban are not affected by food. Also, food does not affect edoxaban absorption, elimination, peak concentrations, half-life or the influence of edoxaban on aPTT and PT (Figure 8).

The drug–drug interaction studies with edoxaban are summarized in Table 3. No effect on edoxaban absorption has been observed in co-administration with digoxin, atorvastatin or esomeprazole.
The pharmacokinetics of edoxaban are not affected by enoxaparin, whether they are administered concomitantly or 12 h apart. When co-administered with the P-gp inhibitor digoxin, the extent of exposure to edoxaban (AUC_{0-tau}) was similar vs. edoxaban administered alone and edoxaban C_{max} increased by ~16% in combination with digoxin. Overall, there was a minimal effect on the PK profile of either edoxaban or digoxin during co-administration.

With regard to concomitant administration of amiodarone with edoxaban, an increase of 39.8% in edoxaban exposure and reduction of 25.7% in the 24-h concentration for edoxaban was observed. In combination with a strong P-gp inhibitor quinidine, edoxaban C_{max} and AUC_{0–24} increased substantially by 85.4 and 76.7%, respectively. Moreover, peak increases from baseline in PT, INR, and aPTT with edoxaban were augmented by 73, 70, and 46%, respectively, by quinidine. The pharmacokinetics of edoxaban is influenced by co-administration with dronedarone, which increases AUC_{0–inf} and C_{max} by 84.5 and 45.8%, respectively. Co-administration of dronedarone also increased 24-h edoxaban concentration by 157.6%. A similar strong P-gp inhibitor, verapamil, caused reductions of 41, 44 and 29%, in PT, INR, and aPTT, respectively, consistent with increased edoxaban exposure. Verapamil also substantially increased edoxaban C_{max} and AUC_{0–24} by 53.3 and 52.7%, respectively. These findings meant that in Phase III studies with edoxaban, co-administration with a strong P-gp inhibitor such as dronedarone, or verapamil was a criteria for edoxaban dose reduction (Table 3).

In addition, there are restrictions on the co-administration of edoxaban with certain macrolide antibiotics (erythromycin, azithromycin, and clarithromycin) and azole antifungals (ketoconazole and itraconazole) were also prohibited in the Phase III trials. However, edoxaban metabolism by cytochrome P450 isozymes is <4% of parent exposure and they play an insignificant role in the metabolism of edoxaban.

Regarding co-administration of edoxaban with acetylsalicylic acid (ASA) 100 or 325 mg once daily, combining treatments increased bleeding time to a larger extent than observed with either monotherapy. Also, co-administration with ASA 325 mg affected edoxaban pharmacokinetics, and geometric mean ratios (90% CI) for AUC and C_{max} were 129.9 (122.6, 137.7) and 134.6 (123.8, 146.3), respectively. However, the coagulation markers PT, aPTT and change in
anti-FXa activity were similar in combination therapy with both ASA doses compared with monotherapy. With these results in mind, ASA ≤ 100 mg once daily was permitted with edoxaban in subsequent Phase III clinical studies. The effects of co-administration of the platelet aggregation inhibitor naproxen on the pharmacodynamics of edoxaban have also been evaluated. Combining both treatments increased PT and did not substantially change the area under the curve or maximum plasma concentrations compared with either monotherapy.

The effects of warfarin and edoxaban on the serum concentration of total, gamma-carboxylated (Gla-osteocalcin), and under-carboxylated osteocalcin (uc-osteocalcin) in rats have been assessed because osteocalcin plays a role in bone homeostasis. This study found that warfarin impaired the carboxylation of osteocalcin in rats. In contrast, edoxaban at doses needed for an antithrombotic effect or higher sustained circulating Gla-osteocalcin levels. Thus, edoxaban had no significant effect on the production of Gla-osteocalcin; therefore, it may potentially have a lower risk of adverse effects on bone health in humans.

Reversal of edoxaban anticoagulant effects

Increased risk of haemorrhage is the principal side-effect of anticoagulation and the ability to reverse excessive anticoagulation is an important option in certain clinical situations. Potential reversal agents for edoxaban have been investigated in pre-clinical studies. Recombinant human factor VIIa (rhFVIIa), anti-inhibitor coagulant complex (FEIBA), and prothrombin complex concentrate (PPSB-HT) are all able to significantly reduce the changes in PT caused by edoxaban in a concentration-dependent manner. Compared with edoxaban alone, rhFVIIa (1 and 3 mg/kg), and FEIBA (100 U/kg) reversed edoxaban-induced prolongation of bleeding time in rats to a significant extent. Also, rhFVIIa significantly increased thrombus formation when combined with edoxaban.

An ex vivo study has also been performed with human plasma samples, to determine the effective doses and time course required for either rhFVIIa or FEIBA to reverse anticoagulation by supratherapeutic doses of edoxaban. A TG assay indicated both rhFVIIa and FEIBA reversed 45 and 20% of the effect of edoxaban at 500 and 1000 ng/mL, respectively, 4 h after adding the reversal agents. With the exception of one baseline sample, levels of d-dimer did not show significant changes with the addition of edoxaban or with its subsequent reversal by either rhFVIIa or FEIBA. Therefore, low therapeutic concentrations of rhFVIIa and FEIBA induced significant and rapid reversal of supratherapeutic concentrations of edoxaban.

These were promising initial pre-clinical results and they did not include comparisons with the reversal of anticoagulation after dabigatran administration. Further studies may help clarify the clinical efficacy of rhFVIIa, FEIBA, and PPSB-HT.

The recombinant factor Xa protein andexanet alpha (PRT4445) is catalytically inactive, does not inhibit factor Xa, and may be a potential reversal agent for factor Xa inhibition. A Phase II proof-of-concept study in healthy volunteers to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of andexanet alfa after

### Table 3

Clinical drug–drug interaction studies with edoxaban

<table>
<thead>
<tr>
<th>Study</th>
<th>Drug tested</th>
<th>Potential interaction</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mendell et al.38</td>
<td>Esomeprazole</td>
<td>No influence on edoxaban AUCO&lt;sub&gt;1&lt;/sub&gt; or C&lt;sub&gt;max&lt;/sub&gt;</td>
<td></td>
</tr>
<tr>
<td>Mendell et al.39</td>
<td>Atorvastatin</td>
<td>No influence on edoxaban absorption</td>
<td></td>
</tr>
<tr>
<td>Mendell et al.39,40</td>
<td>Digoxin</td>
<td>No influence on edoxaban absorption</td>
<td></td>
</tr>
<tr>
<td>Mendell et al.39</td>
<td>Amiodarone</td>
<td>Increased edoxaban exposure by 39.8%</td>
<td>Dose-adjustment recommended</td>
</tr>
<tr>
<td>Mendell et al.39</td>
<td>Quinidine</td>
<td>Increased edoxaban exposure by 76.7%; reduced peak increases in PT, INR, and aPTT</td>
<td>Dose-adjustment recommended</td>
</tr>
<tr>
<td>Mendell et al.39</td>
<td>Verapamil</td>
<td>Increased edoxaban exposure by 52.9%; reduced peak increases in PT, INR, and aPTT</td>
<td>Dose-adjustment recommended</td>
</tr>
<tr>
<td>Mendell et al.39</td>
<td>Dronedarone</td>
<td>Increased edoxaban exposure by 84.5%</td>
<td>Dose-adjustment recommended</td>
</tr>
<tr>
<td>Zahir et al.33</td>
<td>Enoxaparin</td>
<td>No significant changes in edoxaban pharmacokinetics</td>
<td></td>
</tr>
<tr>
<td>Mendell-Harary et al.44</td>
<td>Naproxen</td>
<td>No significant changes in edoxaban pharmacokinetics</td>
<td>Concomitant ASA limited to ≤ 100 mg/day</td>
</tr>
<tr>
<td>Mendell-Harary et al.43</td>
<td>ASA</td>
<td>No significant changes in edoxaban pharmacokinetics with ASA 100 mg</td>
<td></td>
</tr>
</tbody>
</table>

AUC, area under the plasma concentration-time curve; aPTT, activated partial thromboplastin time; ASA, acetylsalicylic acid; C<sub>max</sub>, maximum concentration; INR, international normalized ratio; PT, prothrombin time.
dosing of a direct or indirect factor Xa inhibitor is currently ongoing (NCT01758432). Recent results from this ongoing clinical trial showed that andexanet alpha is able to dose-dependently, partially reverse the anticoagulant effects of rivaroxaban and apixaban, as assessed by pharmacodynamic markers. In addition, a novel, synthetic small molecule (PER977) has been designed and synthesized for the reversal of anticoagulation with NOACs. Preliminary studies with PER977 in vitro and assessment of rat tail bleeding models have shown that it directly and specifically binds the NOACs to reverse anticoagulant activity. PER977 exhibits no binding to any human plasma coagulation factors or albumin and has shown no pro-coagulant properties. It reverses the anticoagulant effects of edoxaban within 20 min after administration. A first-in-human clinical trial to assess the safety and efficacy of PER977 3 h after administration of edoxaban 60 mg in healthy human volunteers is ongoing (NCT01826266).

There may also be other potential options for the reversal of anticoagulation, such as tranexamic acid or desmopressin, which utilize different approaches to induce a pro-coagulant response compared with the antidotes in development. However, studies with these agents following administration of edoxaban have not been performed.

**Discussion**

Anticoagulation treatment with warfarin is associated with a number of limitations in clinical practice. Therefore, new OACs have been developed for a number of indications, such as acute VTE treatment and stroke prevention in AF patients. Extensive pharmacological studies have been performed with edoxaban, with important insights into the drug, and these have also influenced the design of subsequent clinical studies. Importantly, in healthy subjects edoxaban has been shown to maintain adequate anticoagulant activity and appeared well tolerated when administered 24 h after the last dose of warfarin.

Edoxaban has various properties that may be advantageous in anticoagulant therapy. It is rapidly absorbed, has relatively high bioavailability, quickly reaches peak plasma concentrations, and exhibits highly selective, competitive, concentration-dependent inhibition of FXa. Edoxaban quickly induces anticoagulant activity and has a wider therapeutic window than warfarin. The plasma concentrations of edoxaban are also closely correlated with its anticoagulant activity.

Two large Phase III clinical studies with edoxaban have recently been completed. The Hokusai-VTE study in patients with acute symptomatic VTE (n = 8292) demonstrated that LMWH/edoxaban 60 mg once daily was non-inferior to the standard therapy with LMWH/warfarin in the treatment and prevention of recurrent VTE. In terms of safety, patients in the edoxaban 60 mg once daily group had a significantly lower rate of major or clinically relevant non-major bleeding events than the conventional therapy group.

In addition, the ENGAGE AF-TIMI 48 study showed that in patients with AF (n = 21 105), the high-dose edoxaban strategy (60 mg once daily, reduced to 30 mg based on patient characteristics) and low-dose edoxaban strategy (30 mg once-daily, reduced to 15 mg based on patient characteristics) were both non-inferior to warfarin for the prevention of stroke or systemic embolism, and were also associated with significantly lower rates of bleeding and cardiovascular death than warfarin. On the basis of these Phase III study results, marketing authorization for edoxaban 60 mg once daily (with adjustment to 30 mg if required) for both stroke prevention in AF and the treatment and prevention of recurrence of VTE in the USA and EU was requested in January 2014.

The clinical pharmacology studies with edoxaban provided important insights that influenced the design of the Phase III edoxaban studies. Drug interaction studies with edoxaban showed that co-administration with strong P-gp inhibitors and body weight < 60 kg may lead to increased exposure, and a reduced dose of edoxaban should be utilized in such situations. They also showed that the optimum balance between stroke prevention and bleeding risk is achieved with edoxaban once daily dosing, rather than twice daily. An edoxaban once daily regimen was therefore utilized in the Phase III Hokusai-VTE and ENGAGE AF-TIMI 48 trials. Edoxaban was also safe when co-administered with ASA ≤ 100 mg and this was the limit permitted in Phase III studies. The food and drug interaction profile of warfarin poses numerous restrictions on physicians and patients. As edoxaban can be administered without regard to food, this drug (as well as other new OACs) may provide a more convenient long-term anticoagulant treatment for patients. The other potential advantages with edoxaban treatment are a lack of routine laboratory monitoring, reliable pharmacology, reliable dose response and a simplified once-daily dosing schedule that may help promote patient adherence.

It has also been observed that inhibition of FXa with edoxaban does not stimulate coagulation pathways, as is observed with direct-thrombin inhibition. This may prove to be a significant theoretical advantage with anticoagulation by FXa inhibition rather than thrombin inhibition. Edoxaban is also a more effective anticoagulant than fondaparinux, the direct-thrombin inhibitor ximelagatran and LMWH dalteparin.

The pharmacological properties of edoxaban allow it to provide rapid and specific inhibition of FXa, which has been shown to closely relate to edoxaban plasma concentration. Preliminary pharmacology studies with edoxaban identified the optimum dosing regimen to provide adequate anticoagulant efficacy with minimal bleeding risk in VTE and AF patients.

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