The pharmacokinetics of edoxaban for the prevention and treatment of venous thromboembolism

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Introduction: Thromboembolic diseases will become the most important contributors to mortality and morbidity for modern societies. Current antithrombotic strategies using heparins or vitamin K antagonists are inconvenient, with limitations and inherent side effects. A series of new oral anticoagulants with powerful and reliable antithrombotic actions have been developed in the last decade.

Areas covered: Edoxaban is a direct and specific inhibitor of activated factor X, delivered orally. This article reviews literature from PubMed and articles referenced within. The text explores the pharmacological aspects of its antithrombotic action. Pharmacokinetics, metabolism and drug interactions are examined. The review places the results of recent clinical trials that have evaluated the antithrombotic potential of edoxaban versus standard antithrombotic therapies in the prophylaxis and treatment of venous thromboembolism into perspective. The possible relationship between the pharmacokinetic profile of edoxaban and the favorable results in clinical trials is discussed.

Expert opinion: Edoxaban is perceived as a major advance, compared to vitamin K antagonists, in the prevention and treatment of thromboembolic disease given its favorable efficacy, safety, pharmacokinetic profile and renal clearance. The results of ongoing large international trials exploring the prevention of thrombotic complications in patients in different clinical settings should ensure the approval of edoxaban to treat new indications.

Keywords: edoxaban, new oral anticoagulants, pulmonary embolism, venous thrombosis

1. Introduction

Deep vein thrombosis (DVT) and pulmonary embolism (PE), usually referred as venous thromboembolism (VTE), are becoming a major health concern due to their elevated incidence, contribution to disability, mortality and their important burden on health care systems. The global impact of VTE was estimated to cause a total of 900,000 events for the USA population [1]. VTE represents a considerable impact on health care systems. Costs of an initial VTE episode have been estimated $3000 – 9500 in the USA. The total costs related to VTE may rise up to $5000, $10,000 or $33,000 for treatments over 3, 6 or 12 months, respectively [2]. Studies conducted in the European Union indicate lower additional inpatient costs after VTE, though still having a profound economic impact on medical costs. Approximately 10% of all hospital deaths can be attributed, at least in part, to PE. An estimated 60% of cases of VTE are the result of a recent hospitalization suggesting that universal safe and effective prophylaxis could significantly reduce VTE incidence and related mortality [3].
Thrombotic complications are the result of a combination of alterations in the venous vessel, modifications in blood flow and a hypercoagulable condition developing in the circulating blood [4]. The hypercoagulable condition is often multifactorial and may involve genetic or acquired deficiencies of coagulation inhibitors. An imbalance between activators and inhibitors of the coagulation mechanisms is definitely involved in the precipitation of thrombotic events. In contrast with the classic extrinsic and intrinsic pathways of the coagulation, recent models contemplate the coagulation mechanisms as an interaction of cellular and enzymatic mechanisms organized into three differentiated steps: initiation, amplification and propagation [5-6]. As shown in Figure 1, in this modern cell-based model of hemostasis, coagulation is initiated through the tissue factor (TF)/activated factor VII (FVIIa) complex on the surface of a TF-bearing cell [7].

Pharmacological strategies available until recently for the prophylaxis and treatment of VTE were based on parenteral agents working indirectly by potentiating plasma antithrombin (AT) activity (heparins) and vitamin K antagonists inhibiting carboxylation of several coagulation factors. In the last decade, newer anticoagulant therapies have been developed to circumvent the inconveniences of classic therapies requiring parenteral administration with heparins or repeated controls as it is the case of classic oral vitamin K antagonists [8]. The new generation of oral anticoagulants has demonstrated to possess favorable pharmacokinetic profile, rapid onset, predictable action, wider therapeutic range, better safety profile and fewer pharmacological interactions than precedent classic oral anticoagulants [9].

New oral inhibitors of activated factor X (FXa) have shown great promise as anticoagulant therapy without the limitations inherent to traditional vitamin K antagonists 8,10,11. Inhibition of the coagulation steps contributed by FXa has proved a very efficient mechanism to modulate excessive thrombin generation (TG) [12]. Inhibition of FXa during the initiation step reduces the initial generation of thrombin through the activation of the FXa-FVa complex on the cell surface (Figure 1). Moreover, inhibition of FXa during the propagation step prevents TG produced through the assembly of the prothrombinase complex (FVa-FXa and calcium).

Edoxaban tosilate (DU-176b (Daiichi-Sankyo, Inc., Tokyo, Japan) is a new oral anticoagulant with a direct and specific inhibitory action on FXa. The anticoagulant action of edoxaban seems to interfere not only in the activity of FXa generated in the initiation phase, but also in the final propagation phase preventing the action of the prothrombinase complex to generate thrombin on the platelet surface. Interestingly, recent studies have suggested that edoxaban inhibits both free FXa and FXa bound to prothrombinase reducing drastically TG mainly through the propagation phase in which large amounts of thrombin generated during the final step will convert fibrinogen into fibrin.

This review will provide an update on basic information on the pharmacology and pharmacokinetics of edoxaban, and will attempt to place in perspective the results of recent clinical trials that have comparatively evaluated the antithrombotic potential of edoxaban versus standard antithrombotic treatments in the prophylaxis and treatment of VTE.

2. Chemistry

Edoxaban (Figure 2) is the evolution of a prototype molecule initially coded as DX-9065a that was developed through the
Edoxaban tosilate

3. Preclinical pharmacology

3.1 Anticoagulant activity in vitro: mechanism of action and specificity

Edoxaban possess a high specific affinity to competitively inhibit human FXa with a Ki value of 0.561 nM [13], with a very weak direct inhibitory action on thrombin and FIIa, with Ki values of 6.00 and 41.7 µM, respectively; > 10,000-fold greater selectivity for FXa than for thrombin (FIIa) [18]. The antithrombotic effects of edoxaban are independent of plasma levels of AT as demonstrated in studies in AT-deficient mice [19]. Edoxaban prolongs prothrombin time (PT) and activated partial thromboplastin time (aPTT) clotting times of human plasma in a concentration-dependent manner, doubling PT and aPTT at concentrations equivalent to 0.256 and 0.508 µM, respectively. Higher concentrations of edoxaban were required to double the coagulation time for TT indicating that direct AT effect is not the prevalent mechanism for its anticoagulant action. The anticoagulant effects of edoxaban for PT prolongation were similar in human, monkey and rabbit plasma [18].

The inhibitory action of edoxaban on FXa results in the reduction of total thrombin generated during the activation of coagulation mechanisms. Edoxaban inhibits TG in human platelet rich or poor plasma. Comparative studies reveal that the inhibitory activity of edoxaban on TG is greater than that observed with fondaparinux. Table 1 [20] summarizes the most relevant information on the pharmacology of this new anticoagulant.

3.2. Antithrombotic action in animal models and comparative studies

The antithrombotic properties of edoxaban have been confirmed in several models of venous and arterial thrombosis [21-22]. Oral administration of edoxaban significantly inhibited thrombus formation in models of venous stasis in rats and rabbits. Similar results were observed in a platinum wire-induced venous thrombosis model in rats. In the latter case, thrombus formation was significantly reduced by doses of edoxaban-b equivalent to 2.5 mg/kg [18]. Antithrombotic effects elicited by edoxaban paralleled prolongations in PT and anti-FXa activities in the plasma of these animals. Edoxaban also exerted a significant anticoagulant effect in a rat model of TF-induced disseminated intravascular coagulation [23].

The antithrombotic action of edoxaban has been compared with other anticoagulant agents under different experimental conditions. In rats, edoxaban showed antithrombotic effects similar or even superior to fondaparinux (FXa inhibitor) or megalatran (FIIa inhibitor) [24-26]. In other series of animal studies, the antithrombotic effects of edoxaban were compared with those of unfractionated, LMWH, lepirudin and warfarin [27-29]. The safety margins between antithrombotic actions and bleeding-time prolongations of edoxaban in the previous experimental studies were wider than those of unfractionated heparin, dalteparin, lepirudin and warfarin suggesting that antihemostatic actions of edoxaban may be less intense than those of more conventional anticoagulants [29].

4. Pharmacokinetics and metabolism

Clinical safety, tolerability, pharmacokinetics and pharmacodynamics of the novel factor Xa inhibitor edoxaban were explored in healthy volunteers [30]. The pharmacokinetic profile of edoxaban is characterized by a rapid absorption, biphasic elimination and a terminal elimination half-life (t1/2) of 5.8 – 10.7 h with an oral bioavailability of approximately 62%. In pharmacokinetic studies, after single administration at doses ranging from 10 to 150 mg, edoxaban was rapidly absorbed, with a tmax of 1 – 2 h and Cmax from 150 to 300 ng/ml for the 30 and 60 mg doses. Normalized Cmax per body weight and dose demonstrated an increase until 60 mg/day [30]. The mean percentage of plasma protein binding ranged from 40 to 59%. Urine edoxaban amounts
from 0 to 48 h post-dose ranged from 34.7 to 39.0% for all dose levels, the majority of which was excreted within the first 8 h post-administration.

Pharmacokinetics of edoxaban after repeated administration showed a similar profile than that of the single-administration study, the disposition of edoxaban in the multiple-administration study appeared predictable [30]. The \( t_{\text{max}} \) for a 60-mg bid was 2 – 3 h with \( C_{\text{max}} \) of 266 ng/ml on the first day and reached 305 ng/ml after 10 days of continuous treatment. Repeated administration of doses of 90 or 120 mg/day indicated little systemic accumulation after 10 days. Urinary excretion of unchanged edoxaban remained consistent along treatment with the 90 and 120 mg/day doses, ranging from 36 to 45% of the dose administered. Absolute bioavailability of edoxaban in healthy volunteers was 61.8% [31].

Plasma edoxaban concentrations correlated with its pharmacodynamic effects in coagulation parameters (Table 1). Edoxaban exhibited dose-dependent effects on aPTT, PT and anti-factor Xa activities with a twofold increase in PT at the single oral 60-mg dose, similar to that reported in previous pharmacological studies [18]. Edoxaban increased the international normalized ratio (INR) up to a maximum of 3.5, with values returning to normality within 24 – 36 h after
Table 1. Summary of pharmacological, pharmacodynamic and pharmacokinetic characteristics of edoxaban.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reference, molecular weight</td>
<td>DU-176b</td>
</tr>
<tr>
<td>Edoxaban tosilate</td>
<td></td>
</tr>
<tr>
<td>C&lt;sub&gt;31&lt;/sub&gt;H&lt;sub&gt;40&lt;/sub&gt;ClN&lt;sub&gt;7&lt;/sub&gt;O&lt;sub&gt;8&lt;/sub&gt;S&lt;sub&gt;2&lt;/sub&gt;</td>
<td>Molecular weight 738.274</td>
</tr>
<tr>
<td>Commercial name; licenser</td>
<td>LIXIANA&lt;sup&gt;®&lt;/sup&gt;, Daiichi Sankyo</td>
</tr>
<tr>
<td>Mechanism of action; specificity</td>
<td>Anti-Xa; no prodrug, Ki</td>
</tr>
<tr>
<td>Pharmacology</td>
<td>Antithrombotic action in animal models (18,29)</td>
</tr>
<tr>
<td>Alteration in coagulation tests</td>
<td>PT, aPTT (18,30)</td>
</tr>
<tr>
<td>Measurement</td>
<td>Anti-Xa test with appropriate calibrators (30,32)</td>
</tr>
<tr>
<td>Therapeutic dose</td>
<td>15, 30 mg/day (prevention of VTE) (45)</td>
</tr>
<tr>
<td>Pharmacokinetics t&lt;sub&gt;max&lt;/sub&gt;</td>
<td>1 - 2 h</td>
</tr>
<tr>
<td>Half-life t&lt;sub&gt;1/2&lt;/sub&gt;</td>
<td>9 - 11 h (30)</td>
</tr>
<tr>
<td>Pharmacokinetics C&lt;sub&gt;max&lt;/sub&gt;</td>
<td>152 ng/ml after a single dose of 30 mg</td>
</tr>
<tr>
<td></td>
<td>300 ng/ml after repeated daily doses of 60 mg (30)</td>
</tr>
<tr>
<td>Bioavailability</td>
<td>62%</td>
</tr>
<tr>
<td>Elimination</td>
<td>35 - 40 % kidney, 60% feces (30-32)</td>
</tr>
<tr>
<td>Patients who may require special attention</td>
<td>Renal impairment (35-36)</td>
</tr>
<tr>
<td>Interference with cytochromes/P-gp</td>
<td>CYP3A4 (minimal) and P-gp (33)</td>
</tr>
<tr>
<td>Drug interactions</td>
<td>Quinidine, verapamil, amiodarone and dronedarone erythromycin and ketoconazole may alter edoxaban exposure (31,32,35-38).</td>
</tr>
</tbody>
</table>

aPTT: Activated partial thromboplastin time; PT: Prothrombin time; VTE: Venous thromboembolism.

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single administration. Fewer than 8% of subjects had an increase in bleeding time > 9.5 min, and none of the increases appeared to be clinically significant. Bleeding time returned to normal within 12 h in 9 of 10 participants who exhibited prolongation and within 24 h for the remaining subject.

Edoxaban is eliminated through multiple pathways, with a significant proportion of systemically absorbed drug eliminated via renal excretion (32-33). Bathala and cols (32) investigated in detail the biotransformation, and mass balance of radiolabeled edoxaban, after oral administration. The mean recovery of radioactivity was > 97% of the administered radioactive dose, with 62.2% eliminated in feces and 35.4% in urine. Unchanged edoxaban accounted for the majority of radioactivity, with 49.1 and 23.8% of the dose as parent observed in feces and urine, respectively. Unchanged edoxaban was the most abundant species in plasma, with a mean area under the curve (AUC) of 1596 ng h/ml. The next most abundant species was metabolite M4, with a mean AUC (0-infinity) 147 ng/h/ml. Edoxaban, as unchanged parent, is the predominant species circulating in plasma and its minor metabolites are formed primarily through hydrolysis.

Intake of high-fat food did not have an important effect on the pharmacokinetics of edoxaban in Japanese and Caucasian healthy volunteers (34). aPTT were assessed as measures of pharmacodynamic effect. The study demonstrated modest increases ranging from 6 to 22% across pharmacokinetics (PK) parameters for both race cohorts. The disposition was similar in both Japanese and Caucasian matched volunteers with slightly higher AUC values (ranging from 7 to 9%) in Caucasians. The modest effects observed were considered clinically insignificant.

4.1 Interactions of edoxaban with other drugs

As with other new oral anticoagulants acting as direct inhibitors of factor Xa, edoxaban may have potential interactions with other drugs (inhibitors of cytochrome P450 and P-glycoprotein, P-gp). Edoxaban is partially metabolized by cytochrome P450 3A4. Studies using human liver microsomes indicated that edoxaban was metabolized to distinct metabolites mainly by CYP3A4 (35).

Edoxaban is a P-gp substrate, and several cardiovascular drugs have the potential to inhibit P-gp and increase drug exposure (35). The potential pharmacokinetic interactions of edoxaban and six cardiovascular drugs used in the management of atrial fibrillation (AF) and known P-gp substrates/inhibitors were investigated in healthy subjects. Participants received edoxaban 60 mg alone and coadministered with quinidine, verapamil, atorvastatin, dronedarone, amiodarone or digoxin. Edoxaban exposure measured as AUC increased for concomitant administration of edoxaban with quinidine, verapamil and dronedarone, and exposure measured as 24-h concentrations for these drugs did also increase. Administration of edoxaban with amiodarone decreased the 24-h concentration for edoxaban by 25.7%. Concomitant administration with digoxin or atorvastatin had minimal effects on edoxaban exposure.

In another study, Salazar and cols (36) investigated interactions of edoxaban with concomitant administration of strong P-gp inhibitors (amiodarone, erythromycin, ketoconazole, quinidine and verapamil) in patients with AF and simulated possible effects of moderate renal insufficiency. Comparisons were made to edoxaban exposure in a typical patient with non-valvular AF and normal renal function. Results demonstrated that edoxaban exposure in patients with moderate renal impairment receiving strong P-gp inhibitors could potentially increase the exposure to edoxaban.

Interactions of edoxaban with digoxin have been also investigated (37). Edoxaban pharmacokinetic parameters showed mild increases in AUC and peak concentrations of 9.5 and 15.6%, respectively, when coadministered with digoxin. Although digoxin PK parameters demonstrated increased AUC and peak concentrations of 8.3 and 28%, respectively, plasma concentrations were within the established therapeutic range. Edoxaban pharmacodynamics were consistent with
pharmacokinetic parameters. Both drugs were well tolerated alone or in combination. No clinically significant changes in renal elimination were observed with concomitant administration of edoxaban and digoxin.

Effects of the non-steroidal antiinflammatories, aspirin and naproxen, on pharmacokinetics and pharmacodynamics of the anticoagulant edoxaban have been investigated [38]. Modifications in pharmacodynamic and pharmacokinetic interactions of edoxaban 60 mg coadministered with low-dose ASA, high-dose acetylsalicylic acid (ASA) or naproxen (500 mg) were investigated in 126 healthy subjects. Baseline bleeding times ranged from 4.72 to 6.13 min. Edoxaban administered alone prolonged bleeding times by 21 – 35% from baseline. Concomitant administration of edoxaban with a high-dose ASA, low-dose ASA or naproxen prolonged bleeding times approximately twofold. Edoxaban pharmacokinetics were not affected by concomitant low-dose ASA or naproxen, but high-dose ASA increased systemic exposure of edoxaban by approximately 30%. Inhibition of platelet aggregation by high-dose ASA, low-dose ASA or naproxen was not affected by edoxaban.

5. Clinical studies

5.1 Dose finding

A preliminary Phase I study explored the antithrombotic action of edoxaban by measuring modifications in size of ex vivo platelet-rich thrombus generated on a thrombogenic surface using blood pre- and post-drug administration flowing through a well-characterized perfusion chamber. Blood was perfused at different shear rates. Twelve healthy subjects received a single oral dose of 60 mg of edoxaban. Antithrombotic effects were measured at 1.5, 5 and 12 h, along with other biomarkers of coagulation (Table 2). Studies revealed that edoxaban significantly reduced ex vivo thrombus formation at venous and arterial shear rates. The antithrombotic effects in perfusion studies were maximal at 1 h, remained significant at 5 h and disappeared at 12 h. Evolution of clotting parameters, effects on TG and levels of anti-factor Xa activity paralleled findings in perfusion studies [39].

In a randomized, enoxaparin-controlled, multicenter, double-blind parallel group study, a total of 264 patients were randomized to edoxaban 15 or 30 mg once daily or open-label, subcutaneous enoxaparin 20 mg (equivalent to 2000 IU) bid administered for 11 – 14 days [40]. The incidence of thromboembolic events (composite of asymptomatic DVT, symptomatic PE, or symptomatic DVT and safety) were evaluated. Oral administration of edoxaban 15 and 30 mg showed potential efficacy similar to enoxaparin for the prevention of thromboembolic events in patients undergoing total hip arthroplasty. The incidence of major and clinically relevant non-major bleeding for edoxaban was comparable to that of enoxaparin.

Modifications in a panel of biomarkers of blood coagulation and platelet responses induced by edoxaban and other anticoagulants were evaluated in an open-label, randomized, non-treatment and active-controlled multiple dose study, in elderly patients. Patients were randomized to oral edoxaban (60 mg, twice daily, 7 doses), subcutaneous dalteparin (5000 IU, once-daily, 4 doses), oral ximelagatran (24 mg, twice daily, 7 doses) or not exposed to drugs. Blood samples were taken before, and at different intervals from 1.5 to 144 h after the first dose. The primary outcomes were changes in thrombin-AT complex, prothrombin fragment 1+2 and D-dimer, and adverse events. Inhibition of TG lag time, peak and constant velocity index was significantly greater and extended for a longer period of time, following edoxaban administration compared with dalteparin. Changes in coagulation biomarkers following edoxaban administration (including prolongation of PT) reflected inhibition of factor Xa. There were no clinically significant changes in primary outcomes and no serious adverse events were reported. The authors concluded that oral administration of edoxaban resulted in effective FXa and TG inhibition, and was well-tolerated [41].

5.2 Prevention of venous thromboembolism after major orthopedic surgery

Table 2 summarizes information on clinical trials with edoxaban in the prophylaxis and treatment of VTE. The safety, efficacy and pharmacodynamics of edoxaban for the prevention of VTE were assessed in Japanese patients subjected to elective total knee arthroplasty in a randomized, double-blind, placebo-controlled, multicenter study [42]. The study (Studying Thrombosis After Replacement Surgery, STARS J-1, Phase IIb) included 523 patients that received edoxaban 5, 15, 30 or 60 mg once daily or placebo for 11 – 14 days. A placebo control was used as neither LMWH nor fondaparinux had been approved for thromboprophylaxis at the time of the study in Japan. The primary efficacy outcome was the incidence of VTE. The primary safety outcome was the incidence of major and clinically relevant non-major bleeding.

The edoxaban therapy was associated with a significant dose-related reduction in VTE; the incidence of VTE from 29.5 to 9.1% in for edoxaban treatment groups from 5 to 60 mg treatment groups versus 48.3% in the placebo group. The incidence of major and clinically relevant non-major bleeding was similar across all groups without any significant differences among edoxaban doses or between edoxaban and placebo. The authors of the study concluded that edoxaban demonstrated significant dose-dependent reductions in VTE in patients undergoing total knee arthroplasty with a bleeding incidence similar to placebo.

The efficacy and safety of edoxaban in the prevention of VTE was also assessed in a Phase IIb trial in patients undergoing elective total hip replacement (THR) [43]. A total of 903 patients were randomly allocated to receive oral edoxaban 15, 30, 60 or 90 mg once daily or subcutaneous dalteparin once daily (initial dose 2500 IU, subsequent doses ...
5000 IU). Both drugs were begun 6 – 8 h postoperatively and continued for 7 – 10 days, when bilateral venography was performed. The primary efficacy end point was the incidence of total VTE, which included proximal and/or distal DVT by venography or symptomatic, objectively confirmed DVT or PE during the treatment period. The primary safety outcome was the incidence of the composite of major and clinically relevant non-major bleeding. All venograms and bleeding events were reviewed by a central independent adjudication committee blinded as to treatment allocation. Of the 903 patients randomized, 776 were evaluable for the primary efficacy analysis. The incidences of VTE were 28.2, 21.2, 15.2 and 10.6% in patients receiving edoxaban 15, 30, 60 and 90 mg, respectively, compared with 43.8% in the dalteparin group (p < 0.005). There was a statistically significant (p < 0.001) dose-response for efficacy across the edoxaban dose groups for total VTE and for major VTE. The incidence of clinically relevant bleeding was low and similar across the groups. The authors concluded that oral edoxaban once daily is effective for preventing VTE after THR.

Two Phase III clinical trials aimed to assess edoxaban for the prevention of VTE after orthopedic surgery were conducted in Japanese population. The STARS E-3 trial assessed a 30-mg once-daily oral dose of edoxaban versus a twice-daily subcutaneous dose of enoxaparin 20 mg in 716 Japanese patients undergoing total knee arthroplasty [44]. The primary efficacy outcome occurred in 22 of 299 (7.4%) patients receiving edoxaban and 41 of 295 (13.9%) patients receiving enoxaparin indicating non-inferiority (p < 0.001) as well as superiority (p = 0.010) of edoxaban relative to enoxaparin. The incidence of major bleeding events was similar for edoxaban- and enoxaparin-treated groups.

The STARS J-5 trial included 610 patients undergoing THR. Patients received edoxaban 6 – 24 h or 20 mg bid enoxaparin 24 – 36 h after surgery [45]. Both drugs were continued for 11 – 14 days post-surgery. The primary end point was the composite of symptomatic and asymptomatic DVT and PE. The primary safety end point was major and clinically relevant non-major bleeding. In the pooled analysis of both trials, the primary end point occurred in 5.1 versus 10.7% of the edoxaban- versus enoxaparin-treated groups, respectively (p < 0.001). The primary safety end point occurred in 4.6 versus 3.7% of the edoxaban- and enoxaparin-treated patients, respectively (p = 0.427).

The effects of edoxaban on key coagulation biomarkers such as D-dimer, prothrombin fragment F1+2 (F1+2) and soluble fibrin monomer complex (SFMC) were also explored in a pooled analysis of the 1326 patients included in both STARS E-3 and STARS J-V clinical studies [46]. For both treatment groups, D-dimer and SFMC levels were reduced

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### Table 2. Clinical trials with edoxaban in the prophylaxis and treatment of VTE.

<table>
<thead>
<tr>
<th>Objective or clinical condition</th>
<th>Phase</th>
<th># Patients</th>
<th>Duration</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antithrombotic action ex vivo</td>
<td>I</td>
<td>12</td>
<td>12 h</td>
<td>Antithrombotic effects after a single dose (60 mg) were maximal at 1 h, remained significant at 5 h and disappeared at 12 h. PT and TG tests are suitable for the evaluation of FXa inhibitors.</td>
</tr>
<tr>
<td>Modification in a panel of biomarkers in elderly patients subjected to different anti-Xa therapies [62]</td>
<td>I</td>
<td>10</td>
<td>72 h</td>
<td>Dose-dependent alteration of biomarkers of coagulation after edoxaban. Thrombin generation significantly altered versus dalteparin.</td>
</tr>
<tr>
<td>Dose finding for edoxaban versus enoxaparin (20 mg bid) [40] STARS J-2</td>
<td>IIb</td>
<td>264</td>
<td>11 – 14 days</td>
<td>Dose-dependent efficacy observed with doses from 15 to 60 mg/day. Similar incidence of bleeding versus dalteparin. Edoxaban 30 mg/day has efficacy superior to enoxaparin with similar incidence of clinically relevant bleeding events. Edoxaban 30 mg/day similar efficacy and safety than enoxaparin.</td>
</tr>
<tr>
<td>Prevention of VTE after total hip replacement versus dalteparin (2500 IU, followed by 5000 IU daily) [43]</td>
<td>IIb</td>
<td>903</td>
<td>7 – 10 days</td>
<td>Efficacy of edoxaban 30 mg/day superior to enoxaparin without a significant increase in bleeding events. Significant dose-dependent reductions in VTE, 15, 30 or 60 mg once daily versus placebo. Edoxaban 60 mg/day as effective and safer than standard warfarin.</td>
</tr>
<tr>
<td>Prevention of VTE after total hip replacement versus enoxaparin (20 mg bid) STARS J-S [45]</td>
<td>III</td>
<td>610</td>
<td>11 – 14 days</td>
<td>Edoxaban 30 mg/day similar efficacy and safety than enoxaparin.</td>
</tr>
<tr>
<td>Prevention of VTE after hip fracture surgery versus enoxaparin (20 mg bid) [47] STARS J-I</td>
<td>III</td>
<td>92</td>
<td>11 – 14 days</td>
<td>Edoxaban 30 mg/day similar efficacy and safety than enoxaparin.</td>
</tr>
<tr>
<td>Prevention of VTE after total knee arthroplasty versus enoxaparin (20 mg bid) [44] STARS E-3</td>
<td>III</td>
<td>716</td>
<td>11 – 14 days</td>
<td>Efficacy of edoxaban 30 mg/day superior to enoxaparin without a significant increase in bleeding events. Significant dose-dependent reductions in VTE, 15, 30 or 60 mg once daily versus placebo. Edoxaban 60 mg/day as effective and safer than standard warfarin.</td>
</tr>
<tr>
<td>Prevention of VTE after total knee arthroplasty versus placebo [42] STARS J-1, IIb</td>
<td>523</td>
<td>11 – 14 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment of acute DVT/PE and prevention of recurrences versus warfarin [48]</td>
<td>III</td>
<td>8240</td>
<td>3 – 12 months</td>
<td></td>
</tr>
</tbody>
</table>
at day 7 compared to post-operation/pretreatment levels, then increased slightly by day 11 – 14. Levels of F1+2 also decreased by day 7 in both treatment groups and further decreased by day 11 – 14. However, for each coagulation biomarker, levels were significantly lower in the enoxaparin group compared to the edoxaban group at both day 7 and day 11 – 14.

Edoxaban 30 mg/day has demonstrated similar efficacy and safety than enoxaparin in Japanese patients undergoing hip fracture surgery (HFS) [47]. The study, a Phase III, randomized, open-label trial, used subcutaneous enoxaparin 20 mg bid as comparator. The incidence of thromboembolic events was 6.5% (3/46, 95% CI 2.2 – 17.5) in the edoxaban group and 3.7% (1/27, 95% CI 0.7 – 18.3) in the enoxaparin group. All the thromboembolic events were asymptomatic distal DVT. The incidence of adverse events was similar between the treatment groups.

Edoxaban was approved for the prevention of VTE after major orthopedic surgery in Japan in 2011, based on its superiority as evidenced in the STARS trials. However, the 20-mg twice-daily choice of enoxaparin is not commonly used outside Japan and, therefore, the results of the STARS trials may not be extrapolated to other populations [46].

5.3 Treatment of acute venous thromboembolism and prevention of recurrences
Edoxaban 60 mg once daily (or 30 mg once daily in the case of patients with creatinine clearance of 30 – 50 ml/min or a body weight below 60 kg) compared to dose-adjusted warfarin has been assessed in the HOKUSAI-VTE randomized, double-blind, double-dummy Phase III clinical trial [48]. This study evaluated the prevention and treatment of VTE in patients with acute DVT and/or PE after an initial 5-day heparin treatment period (either unfractionated heparin or LMWH). The HOKUSAI-VTE is the largest single clinical trial for the treatment and secondary prevention of acute DVT and/or PE with an enrolment of 8240 patients (4921 with DVT and 3319 with PE). The primary end point was defined as the composite of DVT, non-fatal and fatal PE over a 12-month time frame from randomization. Treatment duration was pre-specified by the patient’s individual risk for either 3, 6 or 12 months. The secondary end point was defined as the composite of symptomatic recurrent DVT, non-fatal symptomatic recurrent PE, all-cause mortality, and major or clinically relevant non-major bleeding during treatment. Among patients receiving warfarin, the time in the therapeutic range was 63.5%. Edoxaban was non-inferior to warfarin with respect to the primary efficacy outcome, which occurred in 130 patients in the edoxaban group (3.2%) and 146 patients in the warfarin group (3.5%) (hazard ratio, 0.89; 95% confidence interval [CI] 0.70 – 1.13; p < 0.001 for non-inferiority). The safety outcome occurred in 349 patients (8.5%) in the edoxaban group and 423 patients (10.3%) in the warfarin group (hazard ratio, 0.81; 95% CI 0.71 – 0.94; p = 0.004 for superiority). The rates of other adverse events were similar in the two groups. Table 3 summarizes main efficacy and safety outcomes in the HOKUSAI study. A total of 938 patients with PE had right ventricular dysfunction, as assessed by measurement of N-terminal pro-brain natriuretic peptide levels; the rate of recurrent VTE in this subgroup was 3.3% in the edoxaban group and 6.2% in the warfarin group (hazard ratio, 0.52; 95% CI 0.28 – 0.98). Results were similar in the subgroup of patients who met the criteria for the 30-mg/day edoxaban dose: 0.73 (95% CI 0.42 – 1.26) for recurrent VTE, 0.62 (95% CI 0.44 – 0.86) for clinically relevant bleeding and 0.50 (95% CI 0.24 – 1.03) for major bleeding.

A remarkable aspect of the HOKUSAI-VTE study was that patients were treated for at least 3 months but were evaluated at 12 months whether or not they remained on randomized therapy. Results demonstrated that the relative efficacy of edoxaban was not limited to patients receiving medication, but it was evident even among those who stopped treatment before 12 months. Patients in the HOKUSAI study were randomized after at least 5 days of open-label enoxaparin or unfractionated heparin indicating that the trial was designed to enroll patients at very high risk. Members of the writing committee concluded that edoxaban administered once daily after initial treatment with heparin was non-inferior to high-quality standard therapy and caused significantly less bleeding in a broad spectrum of patients with VTE, including those with severe PE.

6. Additional therapeutic and safety aspects
6.1 Transitions and bridging with other anticoagulants
Management of patients with thrombotic complications will require a transition from anti-vitamin K anticoagulants or heparin to the newly developed oral drugs. Mendell and cols [49-50] have explored the safety, tolerability and pharmacokinetics of edoxaban in healthy subjects bridging from warfarin therapy. Participants in the study received open-label warfarin titrated to INR 2.0 – 3.0 for 3 days. Twenty-four hours after discontinuation, subjects were randomized to receive edoxaban b 60 mg/day or placebo for 5 days. Administration of edoxaban was associated with a rapid effect on the INR increasing to a peak of 3.8 over 2 h and returning to baseline within 12 h (24 h after warfarin). The study in healthy patients concluded that edoxaban could be safely administered 24 h after the last dose of warfarin.

Pharmacodynamics and safety of enoxaparin 1 mg/kg followed 12 h post-dose by edoxaban 60 mg were explored in a Phase I, open-label, randomized, four-period, four-treatment cross-over study [51]. Treatments were edoxaban alone, enoxaparin alone, edoxaban plus enoxaparin and enoxaparin followed by edoxaban 12 h later. Serial blood samples were collected for pharmacodynamic (TG, anti-FXa) and pharmacokinetic variables (edoxaban and its principal
6.2 Laboratory evaluation of the anticoagulant action of edoxaban

According to pharmacokinetic and pharmacodynamic profile, repeated laboratory monitoring is not necessary during edoxaban treatment. However, occasional evaluation of its anticoagulant effect may be necessary under some circumstances (excessive bleeding or surgical emergencies). As other oral factor Xa inhibitors edoxaban causes a dose-dependent increase in aPTT, PT and one-step prothrombinase-induced clotting time, especially at supratherapeutic doses [30,52]. Edoxaban inhibits TG measured with the calibrated automated thrombogram [20,53]. The magnitude of concentration-dependent increase of PT seems dependent on the thromboplastin reagent. Linear correlations were observed between plasma concentration of edoxaban and anti-FXa activity and results of clotting time assays. In any case, PT and aPTT do not have enough sensitivity to measure plasma levels of edoxaban and TG test are not specific to detect its anticoagulant effect. Measurement of anti-Xa activity with a specific calibrator appears as the more appropriate test to assess plasma concentration of oral factor Xa inhibitors [30,52].

6.3 Reversal of the anticoagulant action of edoxaban in bleeding emergencies

While the hemorrhagic action of excessive treatment with classic vitamin K antagonists can be rapidly reversed with prothrombin complex concentrates (PCCs) [54], there is reasonable concern on the reversion of the antithrombotic action of new oral anticoagulants in life-threatening hemorrhages [55]. Experimental studies indicated that the prolongation of PT induced by edoxaban could be reversed by addition of rFVIIa. Further studies on the reversal of edoxaban using human plasma and rat experimental models of bleeding demonstrated that rFVIIa, PCCs and activated PCCs (Feiba®) have potential to reverse the antithrombotic action of edoxaban [56].

A Phase I study is currently evaluating a specific antidote (PER977) aimed at antagonizing the inhibitory action of edoxaban on FXa [57]. The study explores whether a single dose of PER977 administered alone, and following a single dose of edoxaban PER977 monotherapy and coadministration following 60 mg edoxaban will have an acceptable safety and tolerability profile with no impact on pro-coagulant biomarkers. Other specific antidotes are being developed for a rapid reversal of new oral anticoagulants with an anti-Xa action [58].

6.4 Modeling of edoxaban exposure: predictive value on efficacy and safety clinical outcomes

Pharmacometric analyses are important for understanding the relationship of plasma concentrations of edoxaban to bleeding and to efficacy. A pharmacometric analysis was applied to characterize the population pharmacokinetics of edoxaban and the relationships between edoxaban exposure and clinical outcomes in different studies on surgical patients following THR [59]. A total of 1795 subjects were included. The exposure–response analysis included data from surgical patients assigned to edoxaban in the Phase IIb study. Edoxaban disposition in healthy and post-surgical patients was well described with a linear, two-compartment model. Creatinine clearance correlated significantly with edoxaban clearance and the rate of oral absorption was affected by surgery. The probability of a post-operative VTE was significantly correlated with steady-state metrics of edoxaban exposure estimated for each subject by Bayesian post-hoc methods with age and gender being the significant and expected covariates. Plasma concentration of edoxaban, as either AUC, Cmin or Cmax was a significant predictor of VTE in these patients. These three measures of plasma exposure were all similarly predictive with same order of magnitude of statistical significance (p < 0.005). There were no significant relationships between metrics of edoxaban exposure at steady state and

| Table 3. Summary of main efficacy and safety outcomes for the HOKUSAI-VTE study [48]: hazard ratio (HR) (95% CI) for primary and secondary outcomes, edoxaban (n = 4118) versus warfarin (n = 4122). |
|---|---|---|
| End points | HR (95% CI) | p |
| Primary efficacy outcome* | Non-inferiority | 0.89 (0.70 – 1.13) | < 0.001 |
| 12-months study period | | 0.82 (0.60 – 1.14) | < 0.001 |
| While on treatment† | | 0.82 (0.60 – 1.14) | 0.004 |
| Safety outcomes | | 0.81 (0.71 – 0.94) | 0.004 |
| (on treatment) | | 0.84 (0.59 – 1.21) | 0.35 |
| Primary§ | | 0.80 (0.68 – 0.93) | 0.004 |
| Major bleeding | | 0.82 (0.75 – 0.90) | < 0.001 |
| Clinically relevant bleeding | | 0.82 (0.75 – 0.90) | < 0.001 |
| Any bleeding | | 0.82 (0.75 – 0.90) | < 0.001 |

*First symptomatic recurrent VTE (DVT or fatal or non-fatal PE) or VTE-related death.
†While taking or within 3 days of stopping or interrupting drug.
§First major or clinically relevant non-major bleeding.
DVT: Deep vein thrombosis; PE: Pulmonary embolism; VTE: Venous thromboembolism.
incidences of major bleeding or major plus clinically relevant non-major bleeding events detected by logistic regression analysis.

A similar simulation model was applied to determine possible relationships between edoxaban pharmacokinetics or biomarkers and risk of bleeding in 1281 edoxaban-treated patients with non-valvular AF [36]. Patients analyzed had additional intrinsic factors such as renal impairment or extrinsic factors such as concomitant medications. The study revealed significant effects of renal impairment and concomitant strong P-gp inhibitors on the pharmacokinetics of edoxaban. Exposure-response analysis found that the incidence of bleeding events increased significantly with increasing edoxaban exposure, with steady-state minimum concentration showing the strongest association. Clinical trial simulations of bleeding incidence were used to select 30 and 60 mg once-daily edoxaban with 50% dose reductions for patients with moderate renal impairment or receiving concomitant strong P-gp inhibitors as the treatment regimens.

6.5 Post-marketing safety experience

Edoxaban was approved in Japan for the prevention of VTE following major orthopedic surgery. Data from early post-marketing phase vigilance in Japan after the first 6 months of commercial use of edoxaban for thromboprophylaxis following major orthopedic surgery did not identify any unforeseen safety signals [60]. Adverse drug reactions were spontaneously reported during early post-marketing phase vigilance in Japan. The study was conducted during the initial 6 months after edoxaban commercial launch in July 2011. All adverse drug events that were spontaneously reported were collected and analyzed. The estimated exposure during the initial 6 months was approximately 20,000 patients. The majority of adverse events were bleeding (51 in 42 patients), and serious adverse drug events included cerebral hemorrhage (n = 1), gastric hemorrhage (n = 2) and surgical site hemorrhage (n = 12). Most of these adverse events occurred within the first week of treatment and there were no fatalities. Results of this early post-marketing phase vigilance confirm the safety of edoxaban observed in previous clinical trial and further substantiate the safety profile of edoxaban predicted in models of exposure and clinical outcomes for the prevention of VTE after orthopedic surgery.

7. Expert opinion

Introduction of new oral anticoagulants represents a considerable therapeutic advance over classic parenteral heparins or oral vitamin K antagonists. Edoxaban is a highly specific inhibitor of FXa, a coagulation factor with a key role in the initiation and propagation phases during the cell-based model of the activation of coagulation. The antithrombotic action of edoxaban was confirmed in experimental models of venous and arterial thrombosis. Studies in different animal models predicted a 10-fold dissociation between antithrombotic and bleeding effects.

Edoxaban is well tolerated at doses up to 150 mg in pharmacokinetic studies in humans, with no dose-dependent increase in adverse events. Exposure is proportional to dose. Pharmacokinetic profiles are consistent across dose with rapid absorption, biphasic elimination, with elimination half-life of 8.75 – 10.4 h and mean accumulation of 1.10 – 1.13 after daily dosing and intrasubject variability ranging from 12 to 17% for AUC.

Phase II and III clinical trials have demonstrated that edoxaban is at least as effective as dalteparin or enoxaparin and has a risk of major bleeding similar to that of heparins in the prevention of DVT in patients undergoing major orthopedic surgery. Edoxaban is approved for the prevention of DVT in patients undergoing major orthopedic surgery by a government agency only in Japan.

Some specific limitations of past clinical studies of edoxaban for the prophylaxis of DVT after major orthopedic surgery should be recognized: i) the ethnic distribution of these trials is biased with the majority of patients recruited from Japan or Taiwan; ii) the scale of all studies was small; and iii) treatment with enoxaparin 20 mg twice daily was started according to the standard of care in Japan but is not commonly used in other countries. Consequently, multinational trials are needed to confirm the efficacy and safety as well as the optimal dose of edoxaban for the prevention of VTE after orthopedic surgery in Caucasian populations.

Edoxaban is the fourth agent in a sequence of other new oral anticoagulants (dabigatran, rivaroxaban and apixaban) being approved or seeking approval from regulatory authorities as antithrombotic agents on three main indications: i) prevention of DVT after major orthopedic surgery; ii) treatment of DVT and PE; and iii) prevention of TE in patients with non-valvular AF. Licensing companies have conducted or are developing clinical trials to support these indications. One of the limitations of these clinical trials is that none of them has directly compared one of the new anticoagulant agents with another.

The HOUSAI-VTE Phase III trial represents the largest single clinical study in VTE therapy so far. In this event-driven trial, after initial therapy with open-label enoxaparin or unfractionated heparin, edoxaban or warfarin was administered in a double-blind, double-dummy fashion [48]. As shown in Table 4, HOUSAI-VTE trial included a considerable number of patients with a broad spectrum of venous thromboembolic manifestations as is frequent in clinical diary practice. In addition, the use of once-daily regimen of edoxaban for VTE treatment in comparison with other new oral anticoagulants (dabigatran, rivaroxaban or apixaban) had additional benefits as such more practical and feasible therapy in this setting.

Edoxaban offers the common benefits and limitations of the new oral anticoagulants. Among the benefits: i) rapid onset and offset of action; ii) relative ease of oral
Table 4. Efficacy and safety outcomes of published trials on venous thromboembolism therapy with novel oral anticoagulants.

<table>
<thead>
<tr>
<th>Trials</th>
<th>Patients</th>
<th>Drugs</th>
<th>Dosing schedule</th>
<th>Design</th>
<th>Duration</th>
<th>Recurrent thrombosis</th>
<th>Major bleeding</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>RE-COVER I, 2009 [63]</td>
<td>Acute venous thromboembolism, n = 2539</td>
<td>Dabigatran</td>
<td>Dabigatran 150 mg twice a day</td>
<td>Double blind, double-dummy, randomized, non-inferiority</td>
<td>6 months</td>
<td>2.4 versus 2.1%, p &lt; 0.001 (non-inferiority)</td>
<td>1.6 versus 1.9%, p = 0.38</td>
<td>Initial parenteral heparin anticoagulation. Deep-vein thrombosis only in 68.8%. INR in therapeutic range: 59.9%</td>
</tr>
<tr>
<td>RE-MEDY, 2013 [64]</td>
<td>Acute venous thromboembolism, n = 2866</td>
<td>Dabigatran</td>
<td>Dabigatran 150 mg twice a day</td>
<td>Double-blind, randomized, extended, non-inferiority</td>
<td>6 – 36 months</td>
<td>1.8 versus 1.3%, p = 0.01 (non-inferiority)</td>
<td>0.9 versus 1.8%, p = 0.06</td>
<td>Enrolled patients completed at least 3 months of treatment. Deep-vein thrombosis only in 65.1%. INR in therapeutic range: 65.3% p &lt; 0.001 (superiority)</td>
</tr>
<tr>
<td>RE-SONATE, 2013 [64]</td>
<td>Acute venous thromboembolism, n = 1353</td>
<td>Dabigatran</td>
<td>Dabigatran 150 mg twice a day</td>
<td>Double-blind, randomized, extended, superiority</td>
<td>6 – 12 months</td>
<td>0.4 versus 5.6%,</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EINSTEIN-DVT, 2010 [65]</td>
<td>Deep-vein thrombosis only in 64.9%</td>
<td>Rivaroxaban</td>
<td>Rivaroxaban 15 mg twice daily for 3 weeks, followed by 20 mg once daily Rivaroxaban 20 mg once daily</td>
<td>Open-label, randomized, event-driven, non-inferiority</td>
<td>3, 6 and 12 months</td>
<td>2.1 versus 3.0%, p &lt; 0.001 (non-inferiority)</td>
<td>0.8 versus 1.2%, p = 0.21</td>
<td>Initial anticoagulation with heparin. INR in therapeutic range: 57.7% p &lt; 0.001 (superiority)</td>
</tr>
<tr>
<td>EINSTEIN-Extended, 2010 [65]</td>
<td>Acute venous thromboembolism, n = 1197</td>
<td>Rivaroxaban</td>
<td>Rivaroxaban 15 mg twice daily for 3 weeks, followed by 20 mg once daily Rivaroxaban 20 mg once daily</td>
<td>Double-blind, randomized, event-driven, extended, superiority</td>
<td>6 – 12 months</td>
<td>1.3 versus 7.1%,</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EINSTEIN-PE 2012 [66]</td>
<td>Acute pulmonary embolism, n = 4832</td>
<td>Rivaroxaban</td>
<td>Rivaroxaban 15 mg twice daily for 3 weeks, followed by 20 mg once daily Rivaroxaban 20 mg once daily</td>
<td>Open-label, event-driven, non-inferiority</td>
<td>3 – 12 months</td>
<td>2.1 versus 44%, p = 0.003 (non-inferiority)</td>
<td>1.1 versus 2.2%, p = 0.003</td>
<td>Initial anticoagulation with heparin. INR in therapeutic range: 62.7%</td>
</tr>
<tr>
<td>AMPLIFY-EXT, 2013 [67]</td>
<td>Acute venous thromboembolism, n = 2482</td>
<td>Apixaban</td>
<td>Apixaban 2.5 or 5 mg, twice daily</td>
<td>Double-blind randomized, extended, superiority</td>
<td>12 months</td>
<td>1.7 versus 1.7 versus 8.8%, p &lt; 0.001 for both comparisons (superiority)</td>
<td>0.2 versus 0.1 versus 0.5%, p = 0.11</td>
<td>Enrolled patients completed at least 6-12 months of treatment. Deep-vein thrombosis only in 65.3%. Initial anticoagulation with heparin. Deep-vein thrombosis only in 65.7%. INR in therapeutic range: 63.5%</td>
</tr>
<tr>
<td>HOKUSAI-VTE, 2013 [48]</td>
<td>Acute venous thromboembolism, n = 8292</td>
<td>Edoxaban</td>
<td>Edoxaban 60 mg orally once daily</td>
<td>Double-blind, double-dummy, randomized, non-inferiority</td>
<td>3 – 12 months</td>
<td>3.2 versus 3.5%, p &lt; 0.001 (non-inferiority)</td>
<td>1.4 versus 1.6%, p = 0.35</td>
<td></td>
</tr>
</tbody>
</table>

DVT: Deep vein thrombosis; INR: International normalized ratio; PE: Pulmonary embolism; VTE: Venous thromboembolism.
administration; iii) no need for routine monitoring of anticoagulant effect; and iv) lack of significant drug interactions. Potential limitations for all these new agents are: i) the possible lack of compliance considering their relative short life; ii) technical difficulties for occasional monitoring; and iii) lack of specific antidotes for the reversal of their anticoagulant action in case of emergencies.

Potential advantages of edoxaban are: its favorable pharmacokinetic profile, the reduced rate of accumulation after daily intake, the predictability of the anticoagulant action and the simplicity of the dosing. Efficacy and safety of edoxaban observed in clinical trials have been confirmed in pharmacometric modeling analyses in exposed populations and data seem to be reaffirmed in post-marketing vigilance studies.

Despite the need for some additional studies on dosing of edoxaban for wider ethnic groups, edoxaban can be perceived as a major advance in the prevention and treatment of thromboembolic disease given its favorable efficacy, safety, pharmacokinetic profile and renal clearance. Results of ongoing large international trials in the prevention of thrombotic complications in patients with AF [61] ensure that the licensing company will seek for a wider approval of new indications from regulatory authorities.

Declaration of interest

G Escolar has received honoraria/consultant fees from Bayer, BMS, Boehringer Ingelheim, CSL Behring and NovoNordisk. The other authors declare no relevant conflicts of interest.

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**Dose defining clinical trial.**


**Phase IIb clinical trial on thromboprophylaxis after hip replacement.**


Phase III, pivotal clinical trial comparing edoxaban treatment with standard warfarin.


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