Edoxaban for Venous Thromboembolism Treatment—The New Kid on The Block for Latin America. A Practical Guide

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Abstract

Edoxaban, a direct factor Xa inhibitor (FXa), is the fourth direct oral anticoagulant (DOAC) approved for clinical use in the treatment of venous thromboembolism (VTE) in Latin America, following global approvals for this indication. Edoxaban features some particular characteristics when compared to the previously approved DOACs. This review summarizes the main properties of edoxaban, the outcomes results of its pivotal global clinical trials and the peculiar clinical features of this compound. This practical guide aims to help Latin America clinicians understand edoxaban, its proper indication and its use for the appropriate patients with VTE.

Keywords

edoxaban, non-vitamin K antagonist oral anticoagulants, oral anticoagulants, venous thromboembolism, vitamin K antagonists

Introduction

Venous thromboembolism (VTE) comprises deep vein thrombosis (DVT) and pulmonary embolism (PE). It is a global prevalent cardiovascular disease, representing a substantial personal and economic burden. Yet it is a preventable cause of long-term morbidity and mortality if properly treated.[1] Although multiple studies have evaluated the epidemiology of VTE in European and American populations, there is limited evidence on the prevalence of VTE and the burden of disease in Latin America. However, its incidence and prevalence is expected to be at least similar to the American population.[2]

The mainstay treatment for VTE is anticoagulation,[3] and non-vitamin K antagonist oral anticoagulants (DOACs) are already approved for its indication, with similar efficacy and less bleeding than the old standard of care, low-molecular-weight heparins (LMWHs) followed by vitamin K antagonists (VKA).[4,5] Latin America clinicians have already incorporated DOACs for the treatment of patients with VTE.[6]

Edoxaban is the fourth DOAC approved for clinical use for the treatment and prevention of recurrences of VTE in Latin America, following its global approval for this indication. It was based on large-scale randomized comparative clinical trials to VKA warfarin for patients with VTE[7] and to the LMWH dalteparin for patients with cancer-associated venous thrombosis (CAT).[8] In addition to demonstrations of efficacy and safety, edoxaban has some peculiar pharmacological properties that make its use an interesting treatment option for patients with VTE requiring anticoagulants.

This article summarizes the main properties of edoxaban, the outcomes results of its pivotal global clinical trials for the VTE treatment indication (particularly the Hokusai-VTE and the Hokusai-VTE cancer trials) and the clinical features of this compound. This practical guide does not aim to make direct comparisons of edoxaban with other DOACs, but to help Latin America clinicians understand edoxaban, its proper indications, its particular features (such as dose adjustments and the need for initial parenteral therapy) and its use for the appropriate patients with VTE.

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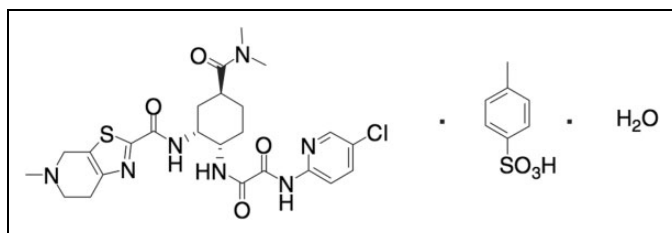Email: eduardoramacciotti@gmail.com

Figure 1. Chemical structure of edoxaban: *N*-(5-chloropyridin-2-yl)-*N'*-[(1S,2R,4S)-4-(*N, N*-dimethylcarbamoyl)-2-(5-methyl-4,5,6,7-tetrahydrothiazol-o[5,4-c]pyridine-2-carboxamido)-cyclohexyl] ethanediamide *p*-toluenesulfonate monohydrate. Adapted from Furugohri, T. et al.[9]

Table 1. Pharmacodynamic Characteristics of Edoxaban.

Parameter	Edoxaban
Target	FXa
Molecular weight (da)	548
Ki (nmol/l)	0.56
Reversible binding to catalytic site	Yes
Concentration for doubling of pt (μmol/l)	0.26
Concentration for doubling of aptt (μmol/l)	0.51

Abbreviation: FXa, factor Xa inhibitor.

Pharmacological Profile of Edoxaban

Edoxaban is a selective, synthetic direct inhibitor of coagulation FXa, such as rivaroxaban, apixaban and betrixaban. Dabigatran is also a DOAC but inhibits directly coagulation factor IIa (FIIa). Edoxaban chemical structure is depicted in Figure 1.

Factor Xa inhibitor plays a central role in the coagulation cascade, and its inhibition leads to decreased thrombin generation with a consequent reduction in thrombus formation and progression. Early investigations with edoxaban assessed *in vitro* pharmacological profiles and *in vivo* effects in animal models of thrombosis and bleeding.[9] Pharmacodynamic characteristics of edoxaban are described in Table 1.

The pharmacokinetics of edoxaban are dose-dependent up to doses of 120 to 150 mg. In healthy patients, 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 to 14 h.[10] Peak plasma concentrations of edoxaban are achieved at ~1.5 hours after oral administration. Systemic exposure is proportional to dose. The PK profiles are consistent across dose with rapid absorption, biphasic elimination, and terminal elimination half-life of 5.8 to 10.7 hours. Single and multiple doses of edoxaban are safe and well tolerated up to 150 mg with predictable pharmacokinetic (PK) and pharmacodynamic (PD) profiles. Figure 2 depicts data from the single-administration study. In general, plasma edoxaban concentrations are linearly correlated with coagulation parameters.

The absolute oral bioavailability of edoxaban in healthy subjects is 62%. Differently from other DOACs such as rivaroxaban, the systemic exposure to edoxaban is not apparently affected by food.[11] Approximately 50% of the drug is eliminated in the urine and approximately 50% in the feces. Renal impairment increases the systemic exposure to the drug. This increase is on average 32% for an estimated creatinine clearance (eCrCl) 51 to 80 mL/min; and 72% for an eCrCl 30 mL/min, in comparison with patients with a normal renal function, therefore eCrCl should be taken in consideration when prescribing edoxaban. No major changes in edoxaban pharmacokinetics have been shown with mild-to-moderate hepatic impairment. Some minimal drug–drug interactions may occur, mainly resulting from interference with the P-glycoprotein efflux transporter, which is responsible for the transport of edoxaban across the intestinal mucosa. P-glycoprotein inhibitors, such as dronedarone, ketoconazole, erythromycin, and cyclosporine, are associated with increased edoxaban plasma concentrations, and the concomitant use of edoxaban with these agents requires dose adjustment (ie, a halving of the dose).[12] The P-glycoprotein inducer rifampin has been shown to significantly decrease edoxaban plasma concentrations and should, therefore, be used with caution. The interaction with cytochrome P3A4 is minimal, decreasing potential drug–drug interactions, mainly or particularly with anticancer drugs. Criteria for dose reduction of edoxaban in relation to clinical and pharmacokinetic variables have been validated in a specific study assessing the blood concentration and factor Xa activity.[13] 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. With these results in mind, ASA ≤ 100 mg once daily was permitted with edoxaban in subsequent phase III clinical studies.[14] Table 2 provides an overview of edoxaban pharmacology compared with other DOACs.

Summary of edoxaban PK/PD profile

Edoxaban is a competitive direct FXa inhibitor

– has a >10 000-fold selectivity for FXa relative to thrombin
– showed no inhibitory effects on other biologically relevant serine proteases
– showed predictable and reversible anticoagulant effects in preclinical studies
– can be given in fixed doses without routine INR monitoring
– demonstrated rapid and sustained inhibition of coagulation up to 24 hours
– it does not need food for absorption

Edoxaban phase III studies for VTE

The Hokusai-VTE Trial

The Hokusai-VTE trial was a global, prospective, double-blind, noninferiority trial that compared the safety and efficacy of edoxaban compared to warfarin in the treatment of VTE.[7]
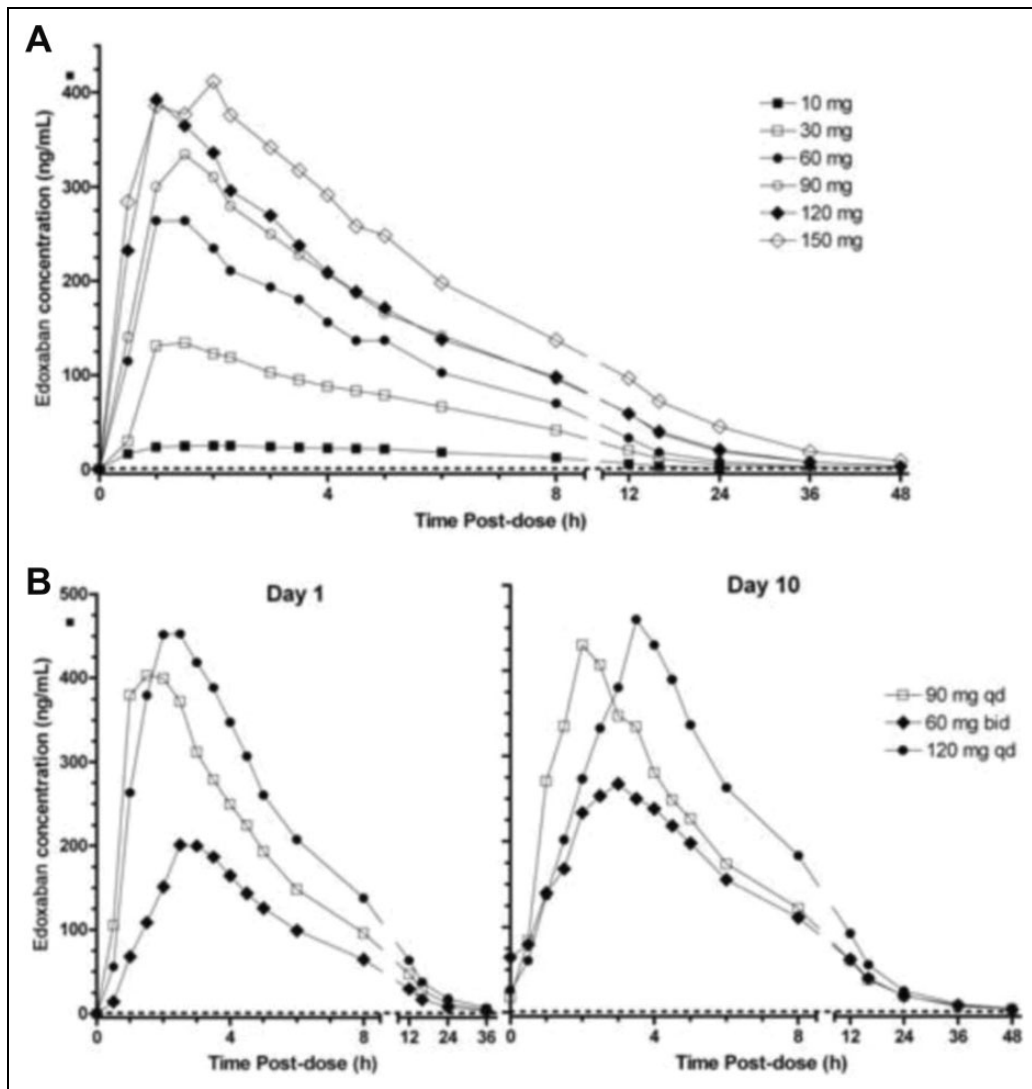
Figure 2. Geometric mean plasma concentrations of edoxaban (ng/mL) after oral dosing. Note that the x-axes are not continuous. Data from the single-administration study. Adapted from Ogata, K. et al.[10]

Table 2. Main Pharmacological Characteristics of the Direct Oral Anticoagulants (DOACs) Used for Stroke Prevention in Atrial Fibrillation and Venous Thromboembolism. (Reproduced from[13]).

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Target	Factor IIa (thrombin)	Factor Xa	Factor Xa	Factor Xa
Prodrug	Yes	No	No	No
Bioavailability	0.06	100% (with food)	0.5	0.62
Plasma protein binding	0.35	0.93	0.87	0.5
Time to peak Elimination	1.5-2 h	2-3 h	2-3 h	1-2 h
Half-life	12-17 h	5-9 h (young), 11-13 h (elderly)	12 hours	10-14 h
Route of clearance	80% renal	35% renal	27% renal	50% renal

The Hokusai-VTE investigators randomized 8292 patients (the largest VTE treatment trial to date) to receive edoxaban 60 or 30 mg (n = 4118) or warfarin (n = 4122). All patients received open-label enoxaparin or unfractionated heparin for at least 5 days prior to randomization (median duration of 7 days).

Differently from rivaroxaban and apixaban studies, where the initial phase is carried out with higher doses of the anti-FXa compounds (rivaroxaban 15 mg bid for 3 weeks, apixaban 10 mg bid for 7 days), on the Hokusai-VTE study parenteral anticoagulation was mandatory. Patients received either edoxaban

Table 3. The Hokusai-VTE Trial, Efficacy Outcomes During Overall Study and On-Treatment Periods. Adapted from The Hokusai Investigators.[7]

Primary Efficacy Outcome: First Recurrent VTE or VTE-Related Death	Edoxaban (n = 4118)	Warfarin (n = 4122)	HR With Edoxaban (95% CI)	P Value
All patients				
Event during overall study period	130/4118 (3.2)	146/4122 (3.5)	0.89 (0.70-1.13)	P < .001
Fatal PE	4/4118 (0.1)	3/4122 (0.1)		
Death with PE not ruled out	20/4118 (0.5)	21/4122 (0.5)		
Nonfatal PE with or without DVT	49/4118 (1.2)	49/4122 (1.4)		
DVT alone	57/4118 (1.4)	63/4122 (1.5)		
Event during on treatment period	66/4118 (1.6)	80/4122 (1.9)	0.82 (0.60-1.14)	P < .001
Patients with index DVT	2468/4188 (59.9)	2453/4122 (59.2)		
Event during overall study period	83/2468 (3.4)	81/2453 (3.3)	1.02 (0.75-1.38)	
Event during on treatment period	48/2468 (1.9)	50/2453 (2.0)	0.96 (0.64-1.42)	
Patients with index PE	1650/4118 (40.1)	1669/4122 (40.5)		
Event during overall study period	47/1650 (2.8)	65/1669 (3.9)	0.73 (0.50-1.06)	
Event during on treatment period	18/1650 (1.1)	30/1669 (1.8)	0.60 (0.34-1.08)	

Abbreviation: HR, hazard ratio; PE, pulmonary embolism; VTE, venous thromboembolism.

60 mg (n = 3385), or edoxaban 30 mg (n = 733) if patients with a CrCl between 30 and 50 mL/min, body weight ≤ 60 kg or concomitant use of P-gp inhibitors. Warfarin was monitored and titrated to a goal INR 2 to 3 for 3 to 12 months; patients in both groups could be treated from 3 to 12 months according to investigator's discretion. Forty percent of patients received the full 12 month treatment.

Patients were considered for inclusion if experienced a DVT (n = 4921) and/or PE (n = 3319). The severity of the index event was similar in the 2 treatment groups. The primary efficacy outcome (VTE recurrence or VTE-related death) occurred in 3.2% of edoxaban patients and 3.5% of warfarin patients (hazard ratio [HR]: 0.89; 95% confidence interval [CI]: 0.70–1.13; P < .001 for noninferiority). No differences were observed with DVT alone, nonfatal PE, or fatal PE. Additionally, no differences in the primary outcome were seen in patients when the index event was a DVT or PE. The noninferiority of edoxaban (noninferiority [NI] margin of 1.5, more astringent than previous trials with rivaroxaban and apixaban whose NI margins were 1.8) was maintained in those patients qualifying for the low dose compared to warfarin (HR: 0.73; 95% CI: 0.42-1.26). The key efficacy results of the Hokusai-VTE trial are listed in Table 3.

The primary safety outcome was the incidence of major (MB) and clinically relevant nonmajor bleeding (CRNMB). The primary safety outcome was significantly lower in the edoxaban group compared to warfarin, 8.5 and 10.3%, respectively (HR: 0.81; 95% CI: 0.71-0.94; P = .004). There were numerically fewer fatal and intracranial bleeding events with edoxaban; however, this was not statistically significant. Major bleeding within this patient group was also numerically lower with the reduced edoxaban dose (1.5% with edoxaban compared with 3.1% with warfarin, HR: 0.50; 95% CI: 0.24-1.03), not statistically significant. Table 4 lists the key safety results of the Hokusai-VTE trial.

Hokusai-VTE Subgroup Analysis

The Hokusai-VTE trial was not designed to address CAT but included relatively large cancer subgroups of 378 (9.2%) patients in the edoxaban arm and 393 (9.5%) patients in the warfarin arm. The primary efficacy outcome occurred in 3.7% of the edoxaban arm and in 7.1% on warfarin arm (HR: 0.53; 95% CI: 0.28-1.00), with significant decrease in major plus clinically relevant non major bleeding, 12.4% versus 18.8%, HR: 0.64; 95% CI: 0.45-0.92) setting the stage for a dedicated CAT trial with edoxaban versus the standard of care for CAT, LMWHs.[7,8]

This trial also included a subset of patients evaluated with biomarkers. In patients with PE with NT-proBNP higher than 500 pg/mL (approximately 28% of the PE population), the primary efficacy outcome was reduced from 6.2% in the warfarin group to 3.3% in the edoxaban group (HR: 0.52; 95% CI: 0.28-0.98).[7]

Among patients who qualified for the 30 mg dose of edoxaban (patients with a eCrCl between 30 and 50 mL/min or a body weight <60 kg, approximately 17% of the entire population), recurrent VTE occurred in 3.0% of edoxaban patients and 4.2% of warfarin patients (HR: 0.73; 95% CI: 0.42-1.26), and the safety outcome in 7.9% and 12.8%, respectively (HR: 0.62; 95% CI: 0.44-0.86). In this population, edoxaban confirmed noninferiority in terms of efficacy and superiority in terms of safety, compared to warfarin.[7]

Hokusai-VTE Trial Summary

Overall, the Hokusai-VTE study showed that a single daily dose of 60 mg of edoxaban is as effective as and safer than warfarin after an initial course of parenteral anticoagulation for the treatment of VTE. Hokusai-VTE was the largest phase III study conducted in this setting to date, the first to assess a flexible dosing regimen, and the first to assess the severity of PE using a biomarker of right ventricular dysfunction. The

Table 4. The Hokusai-VTE Trial, Safety Outcomes During Overall Study and on-Treatment Periods. Adapted From The Hokusai Investigators.[7]

Safety Outcome	Edoxaban (n = 4118)	Warfarin (n = 4122)	HR With Edoxaban (95% CI)	P Value
Principal safety outcome: major or clinically relevant nonmajor bleeding	349 (8.5)	423 (10.3)	0.81 (0.71-0.94)	.004
Major bleeding	56 (1.4)	66 (1.6)	0.84 (0.59-1.21)	.35
Fatal	2 (0.1)	10 (0.2)		
Intracranial	0	6 (0.1)		
Gastrointestinal	1 (0.1)	2 (<0.1)		
Retroperitoneal	0	1 (<0.1)		
Other	1 (<0.1)	1 (<0.1)		
Nonfatal in critical site	13 (0.3)	25 (0.6)		
Intracranial	5 (0.1)	12 (0.3)		
Retroperitoneal	0	3 (0.1)		
Other	8 (0.2)	10 90.2)		
Nonfatal in noncritical site	41 (1.0)	33 (0.8)		
CRNM Bleeding	298 (7.2)	368 (8.9)	0.80 (0.68-0.93)	.004
Any bleeding	895 (21.7)	1056 (25.6)	0.82 (0.75-0.90)	P < .001

Abbreviations: CRNM, clinically relevant nonmajor; HR, hazard ratio; VTE, venous thromboembolism.

favorable efficacy and safety profile of edoxaban was confirmed in the subgroups of patients qualifying for dose reduction and in patients with PE with increased NT-proBNP. In patients at a potential higher risk of bleeding (due to either renal impairment or low body weight), halving the dose of edoxaban to 30 mg significantly reduced bleeding while maintaining efficacy.

The Hokusai-VTE Cancer Trial

The standard care for CAT treatment is LMWH mainly based on the results of the cancer-related clot study (CLOT) trial that compared dalteparin to VKA in this setting, showing 50% risk reductions in LMWH-treated patients.[15] On the subgroup analysis of patients with cancer for all DOAC phase III trials, there was an indication that these drugs might work in this setting.[16] However, straight conclusions could not be drawn because the comparator was warfarin, an inferior option to treat CAT, and patients with cancer were not the focus of these trials.

The Hokusai-VTE cancer trial was a global, prospective, PROBE noninferiority trial that compared the safety and efficacy of edoxaban to dalteparin in the treatment of VTE in patients with CAT for 12 months. The trial assessed for a composite outcome of recurrent VTE or MB. This was an innovative composite primary efficacy end point, based on the idea that VTE recurrence and MB are the 2 most prominent complications expected in anticoagulation therapy for CAT.

Adult patients with CAT (with active cancer) were randomly assigned, in a 1:1 ratio, to receive either edoxaban or dalteparin. Active cancer was defined by any of the following: (1) diagnosis of cancer within the past 6 months, (2) recurrent, regionally advanced or metastatic disease, (3) currently receiving treatment or having received any treatment for cancer during the 6 months prior to randomization, or (4) a hematologic malignancy not in complete remission. Edoxaban was started

after a course of therapeutic dose LMWH (not necessarily dalteparin) was given subcutaneously for at least 5 days. Edoxaban was administered orally at a fixed dose of 60 mg once daily, with the same dose adjustment criteria to 30 mg used on the Hokusai-VTE trial (eCrCl 30-50 mL/min, body weight ≤60 kg or concomitant use of P-gp inhibitors).

Dalteparin was given subcutaneously at a dose of 200 IU per kilogram of body weight once daily for 30 days,[4] with a maximum daily dose of 18 000 IU. Thereafter, dalteparin was given at a dose of 150 IU per kilogram once daily. In all the patients, treatment with edoxaban or dalteparin was to be continued for at least 6 months and up to 12 months.

A total of 1046 patients were included in the modified intention-to-treat analysis. A primary-outcome event (VTE+MB) occurred in 67 (12.8%) of the 522 patients in the edoxaban group as compared with 71 (13.5%) of the 524 patients in the dalteparin group (HR: 0.97; 95% CI: 0.70-1.36; P = .006 for noninferiority; P = .87 for superiority). Recurrent VTE occurred in 41 (7.9%) patients in the edoxaban group and in 59 (11.3%) patients in the dalteparin group (difference in risk, −3.4 percentage points; 95% CI, −7.0 to 0.2). The rate of MB was significantly higher with edoxaban than with dalteparin. Major bleeding occurred in 36 (6.9%) patients in the edoxaban group and in 21 (4.0%) patients in the dalteparin group (difference in risk, 2.9 percentage points; 95% CI, 0.1 to 5.6). This difference was mainly due to the higher rate of upper gastrointestinal bleeding with edoxaban. This finding is consistent with results of previous studies of direct oral anticoagulants.[17,18] The increase in upper gastrointestinal major bleeding occurred mainly in patients who had entered the trial with gastrointestinal cancer. There were no fatal bleeds with edoxaban, and 2 with dalteparin. Severe bleeding at presentation (category 3 or 4) occurred in 10 (1.9%) and 11 (2.1%) patients in the edoxaban and dalteparin groups, respectively. The excess of MB with edoxaban was confined to patients with

Table 5. The Hokusai-VTE cancer Trial, Major Bleeding Outcomes During Overall Study. From Clinical Presentation to Clinical Course. Reproduction from Brekelmans et al.[a,19]

Clinical course	Edoxaban	VKA
Clinical presentation category 2		
Category I	4 (14%)	2 (10%)
Category 2	22 (79%)	17 (85%)
Category 3	2 (7%)	I (5%)
Category 4	0	0
Total	28	20
Clinical presentation category 3		
Category I	I (4%)	4 (11%)
Category 2	14 (56%)	16 (43%)
Category 3	9 (36%)	15 (41%)
Category 4	I (4%)	2 (5%)
Total	25	37

Abbreviations: VTE, venous thromboembolism; VKA, vitamin K antagonists.
[a]Clinical course for major bleeding events classified as clinical presentation 2 (A) and 3 (B), to give an indication of the dynamics in the clinical impact of major bleeding events.

gastrointestinal cancer. However, the frequency of severe major bleeding (category 3 or 4) was similar with edoxaban and dalteparin (table 5), with no fatal or intracranial bleeding.[19,20] Death occurred in 206 (39.5%) patients in the edoxaban group and in 192 (36.6%) patients in the dalteparin group. The majority of deaths were related to cancer with 6 deaths in each group related to either VTE or bleeding.[20]

Hokusai-VTE Cancer Trial Subgroup Analysis

Subgroup analyses for the primary outcome and for recurrent VTE and MB separately were pre-specified. There were no statistically significant interactions between subgroup and treatment, except for the subgroups defined according to whether the patient had gastrointestinal cancer at the time of randomization. When these patients were excluded from the analysis, bleeding rates were similar between both groups.[8]

Hokusai-VTE Cancer Trial Summary

The investigators concluded that in patients with CAT, treatment with a fixed once-daily dose of oral edoxaban for up to 12 months was noninferior to treatment with subcutaneous dalteparin with respect to the composite outcome of recurrent VTE and MB. Edoxaban has the convenience of oral administration in patients were injections are burdensome and expensive and is an attractive alternative to parenteral drugs. Patients with gastrointestinal cancer should be evaluated on an individual basis.

Cost-Effectiveness of Edoxaban for VTE Treatment

Since edoxaban was recently approved, cost-effectiveness (CE) models are not available yet in Latin America. Using US

database and the Hokusai-VTE treatment trial information, CE for edoxaban for VTE treatment was evaluated. The CE model was built using a patient level data entry, clinical event costs from real-world databases, and drug acquisition costs for warfarin of US$0.36 and edoxaban of $9.24 per tablet. From a U.S. health-care delivery system perspective, the incremental cost-effectiveness ratio (ICER) was US$22 057 per quality-adjusted life year (QALY) gained. Probabilistic sensitivity analysis showed that edoxaban had an ICER <US$50 000 per QALY gained relative to warfarin in 67% of model simulations. The result was robust to variation in key model parameters including the cost and disutility of warfarin monitoring. In the USA, despite its higher drug acquisition cost, edoxaban is a cost-effective alternative to warfarin for the treatment of VTE.[21] These calculations are expected to be performed in Latin America, using both the Hokusai-VTE and the Hokusai-VTE cancer trials.

Practical Considerations—Edoxaban for VTE Treatment

Initial, Long-Term, and Extension Treatment

For the initial treatment of VTE, both DVT and PE, in and out-of-hospital, patients should receive an initial course of heparin for at least 5 days prior to treatment with edoxaban. This is not required for the initiation of in patients with NVAF for the prevention of stroke and systemic embolism. Differently from VKA, there is no need for overlapping heparin with the oral anticoagulant. Patients are switched from parenteral anticoagulant to edoxaban 60 mg optical density (OD), for up to 12 months. The long-term treatment is carried out with a daily dose of 60 mg of edoxaban (adjusted to 30 mg OD if eCrCl 15 to 50 mL/min; body weight ≤60 kg or concomitant use of P-gp inhibitors) as well as the extension phase. The Hokusai-VTE program was slightly different from the other DOAC VTE treatment trials. Instead of having a dedicated extension program (after 6 months treatment completion on the long-term phase), investigators could treat patients up to 12 months in a single and more prolonged trial (up to 12 months). The program included patients with both provoked and unprovoked VTE, with different bleeding risks, and treatment durations varied from 3 to 12 months at the discretion of the treating physician. The duration of treatment for VTE and prevention of recurrent VTE should be individualized after assessment of the treatment benefit against the risk for bleeding. Short duration of therapy (at least 3 months) should be based on transient risk factors (eg, recent surgery, trauma, immobilization) and longer durations should be based on permanent risk factors or idiopathic DVT or PE.

The Hokusai-VTE investigators provided an ad hoc analysis of the extended treatment group of patients. Between greater than 6 months and less than 12 months, the incidence of VTE was 0·2% (0.0-0.8; 2 of 896) on the edoxaban-treated group versus 0·8% (0.03–1.7; 7 of 851) on the warfarin-treated group; and at 12 months, <0·1% (0.0--3; 1 of 1661) versus 0·1%

(0·0-0·4; 2 of 1659). The cumulative incidence of clinically relevant bleeding (MB or CRNMB) between 3 and 12 months was 3·9% (95% CI 3.3-4.6; 143 of 3633 patients) in the edoxaban-treated group and 4·1% (3.5–4.8; 147 of 3594 patients) in the warfarin-treated group (HR: 0.97; 95% CI: 0.77-1.22); cumulative incidence of major bleeding was 0.3% (95% CI 0.2-0.5; 11 of 3633 patients) in the edoxaban-treated group and 0·7% (0.4-1.0; 24 of 3594 patients) in the warfarin-treated group (HR: 0.45: 95% CI: 0.22-0.92). The investigators concluded that extended treatment with edoxaban is effective and associated with less major bleeding than warfarin.[22]

The Hokusai-VTE cancer trial is the largest one to date to address VTE treatment in the CAT population. On the Hokusai VTE treatment program, the non-inferiority margin was 1.5, the narrower one for DOACs trials in VTE treatment. From a practical standpoint, the narrower the NI margin, the larger the sample size. Given the fact edoxaban was non-inferior on the composite endpoint of VTE recurrence plus MB, in addition to its oral availability, it will be very convenient for patients undergoing cancer treatment. Most of the time receiving injections for its cancer-related therapies, patients with CAT's adherence to injections are very low. In Latin America, differently from Europe, LMWHs are very expensive with a higher treatment withdrawal on the LMWH group. In that setting, edoxaban is a very attractive and probably a cost-effective anticoagulant strategy.[8]

Dose Adjustment

A dose of 30 mg once daily is required for certain patients who fall into one or more of the following subgroups. These are:

- renal impairment (eCrCl 15-50 mL/min)
- body weight ≤ 60 kg
- concomitant use of potent P-gp inhibitors (dronedarone, erythromycin, ketoconazole, ciclosporin)

Figure 3 depicts a practical guide for the treatment of special populations with edoxaban.

Perioperative Management

The half-life of edoxaban is 10 to 14 hours.[10] As edoxaban is a reversible FXa inhibitor, its anticoagulant activity should lessen within 24 to 48 hours of the last administered dose. In situations where a patient requires a surgical intervention or invasive procedure, edoxaban should be stopped as soon as possible and preferably at least 24 hours beforehand.[23]

In deciding whether a procedure should be delayed until 24 hours after the last dose of edoxaban the increased risk of bleeding should be weighed against the urgency of the intervention. Edoxaban should be restarted after the surgical or other procedures as soon as adequate hemostasis has been established, noting that the time to onset of the edoxaban anticoagulant therapeutic effect is 1 to 2 hours.[9,10,12] In the atrial fibrillation population patients receiving edoxaban, it was observed that more than one-third of patients in a large clinical trial required surgery or an invasive procedure during the 2.8 years of follow-up. Rates of bleeding and thrombotic events were similar between edoxaban and warfarin whether anticoagulant therapy was interrupted for >3 days or not prior to an invasive procedure. Continuation of anticoagulation was associated with higher risks of bleeding than was observed with a strategy of interrupting anticoagulation for at least 3 days prior to an invasive procedure.[24] Regarding neuraxial anesthesia, it is suggest that edoxaban should be discontinued 72 hours prior to procedure. Consider checking edoxaban or anti-factor Xa activity level if less than 72 hours. An acceptable level of residual edoxaban activity to proceed with neuraxial block remains undetermined (grade 2C).[25]

Monitoring Edoxaban

Edoxaban does not require coagulation tests for monitoring its activity.[23] Since it inhibits FXa, it uses prolongs standard clotting tests such as international normalized ratio, prothrombin time, or activated partial thromboplastin time in a dose-dependent manner. However, changes observed in these clotting tests at the expected therapeutic dose are small and subject to a high degree of variability. The use of these tests is misleading and should not be used in clinical practice.

Management of Bleeding Complications

In case of bleeding complications, time is the best reversal agent for edoxaban, given its half-life of approximately 10 to 14 hours. Bleeding events management should be individualized according to the severity and location of the hemorrhage. Appropriate symptomatic treatment could be used as needed, such as mechanical compression, surgical hemostasis with bleeding control procedures, fluid replacement and hemodynamic support, blood products (packed red cells or fresh frozen plasma, depending on associated anemia or coagulopathy) including an infusion of platelets. For life-threatening bleeding that cannot be controlled with the administration of a 4-factor prothrombin complex concentrate (PCC) at 50 IU/kg has been shown to reverse the effects of edoxaban 30 minutes after the infusion.[26] Recombinant factor VIIa (r-FVIIa) can also be considered, with the thrombotic complications associated with the use of r-FVIIa). There is limited clinical experience with the use of this product in individuals receiving edoxaban. Consideration of F-VIIa for reversal is largely preclinical.[27] Protamine sulfate and vitamin K are not expected to affect the anticoagulant activity of edoxaban.[23,26] There is no experience with antifibrinolytic agents such as tranexamic acid, aminocaproic nor with of systemic hemostatic compounds (desmopressin, aprotinin). Given to its high plasma protein binding, hemodialysis does not remove edoxaban from the circulation, therefore not helping bleeding management. Andexanet alfa is approved in the United States for the reversal of rivaroxaban and apixaban (studies with edoxaban are ongoing) but not yet in Latin America.[28] Aripazine is still under investigation and it is not available for clinical use.[29]

Figure 3. Practical guide for the treatment of special populations with edoxaban. Adapted from Brazilian label recommendations.

Antidote for edoxaban

A specific antidote is not yet available for edoxaban (and for other FXa inhibitors) in Latin America. Andexanet alfa, a modified recombinant FX works as an antidote against FXa inhibitors, is now approved by the Food and Drug Administration (FDA) in the Unites States for reversal of its pharmacological action.[28] Andexanet alpha was not tested yet on the landmark trials, but there are data of potential efficacy on edoxaban.[30] The infusion of a PCC at 50 IU/kg has been shown to reverse the effects of edoxaban 30 min after completing its administration.[26] Another promising antidote for edoxaban under

development is aripazine, also called ciraparantag. This small molecule binds noncovalently to and inhibits the activity of both direct and indirect anticoagulants, including both oral and parenteral agents. Specific to edoxaban, a phase 1 trial was conducted in which 80 healthy volunteers received an intravenous bolus dose of 5 to 300 mg aripazine. In the patients who were also pretreated with 60 mg edoxaban, the whole blood clotting time was normalized following a single 300-mg bolus dose of aripazine. The anticoagulant effects of aripazine remained stable over a 24-hour period.[29] An additional phase 2 trial investigating this agent for reversal of edoxaban is currently underway.[29]

Final Considerations

Edoxaban, the new kid on the block for Latin America, is a new alternative for oral anticoagulation for VTE affected patients has been shown to be a safe and effective the treatment of VTE. From a Latin America perspective, some considerations include:

Currently, edoxaban is only approved in Brazil. Considering the burden of the disease (VTE and CAT) both in Brazil and other Latin America countries, edoxaban might have potential positive economic impacts. Future cost-effectiveness regional studies are warranted and planned.

Access to the healthcare system can present a significant barrier to care in general, with World Health Organization estimates indicating that more than 40% of the population of some countries does not have effective access to health care for reasons ranging from language barriers and a lack of education.[2] In that setting, the adherence to LMWH in Latin America is very poor and so it is its compliance.[31] With proper medical education and cost-effectiveness analysis, edoxaban might be very attractive option for CAT management in Latin America.

The guidelines for individual countries in Latin America are generally consistent with those of the American College of Chest Physicians and other American and European guidelines.[2] Given its positive results in CAT management, DOACs has already been incorporated in these guidelines, such as the recent Scientific and Standardization Committee recommendations for the International Society of Thrombosis and Hemostasis and the National Comprehensive Cancer Network, both in 2018.[32,33] Latin America guidelines will probably incorporate these recommendations.

Finally, edoxaban has several clinical advantages including a once-daily regimen, the lack of need routine therapeutic monitoring, and absence of food-drug interactions. Its data on cancer-associated thrombosis are compelling. The need for parenteral anticoagulants in the initial phase of the treatment may not be a barrier in Latin America, where clinicians feel comfortable in initiating VTE therapy with heparins. Proper medical education, as well as new data generation of the upcoming studies with edoxaban might help physicians with their decisions to treat patients with VTE.

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