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REVIEW

Edoxaban in Atrial Fibrillation and Venous Thromboembolism—Ten Key Questions and Answers: A Practical Guide

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ABSTRACT

Edoxaban is the fourth non-vitamin K antagonist oral anticoagulant now available for clinical use in the prevention of stroke/systemic embolism in atrial fibrillation (AF) and in the treatment of venous thromboembolism (VTE), after the completion of large-scale randomized comparative clinical trials with the vitamin K antagonist warfarin. Edoxaban has some peculiar pharmacological properties and outcome data. Here a group of experts in AF and VTE answers a set of questions on its practical use, trying to define the profile of patients that would be most appropriate for its use.

Keywords: Atrial fibrillation; Edoxaban; Non-vitamin K antagonist oral anticoagulants; Oral anticoagulants; Venous thromboembolism; Vitamin K antagonists

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INTRODUCTION

Edoxaban is the fourth non-vitamin K antagonist oral anticoagulant (NOAC) approved for clinical use for prevention of stroke/systemic embolism in atrial fibrillation (AF) and for the treatment of venous thromboembolism (VTE) after the completion of large-scale randomized comparative clinical trials with the vitamin K antagonists (VKA) warfarin. In addition to demonstrations of efficacy and safety, edoxaban has some peculiar pharmacological properties that make its use an interesting treatment option for patients requiring anticoagulant treatment.

This manuscript, written by a group cardiologists, hematologists, and internists with a specific interest in antithrombotic therapies, summarizes the main properties of edoxaban; formulates a set of practical questions selected by the group, with an eye to profiles of patients in whom the use of the drug appears to be particularly suitable; and provides answers to such questions with the aim of helping physicians to properly administer this agent in the appropriate patients. This paper does not aim to make direct comparisons of edoxaban with other NOACs, but is intended to help delineate reasons supporting the use of this specific drugs in specific patient categories, highlighting possible advantages in specific patient subsets or therapeutic areas where the use of the drug is supported by scientific evidence. References to other NOACs are therefore done only when opportune to delineate the specificity of this drug.

Compliance with Ethics Guidelines

This article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors.

PHARMACOLOGICAL PROFILE OF EDOXABAN IN COMPARISON WITH OTHER NOACS

Like rivaroxaban and apixaban, edoxaban is a selective, direct inhibitor of coagulation factor Xa, whereas dabigatran selectively inhibits factor IIa (thrombin). Factor Xa inhibition in the coagulation cascade leads to decreased thrombin generation, and therefore a reduction in thrombus formation and progression. The pharmacokinetics of edoxaban is dose-dependent up to doses of 120–150 mg [1]. Peak plasma concentrations are reached after 1–2 h from the administration [1]. The bioavailability is approximately 62%. At variance from rivaroxaban, the systemic exposure to edoxaban is not apparently affected by food [1]. In plasma, edoxaban primarily circulates in an unchanged form, with minimal metabolism [1]. Approximately 50% of the drug is eliminated in the urine, and approximately 50% in the feces [1]. Over 70% of edoxaban is cleared unchanged, with an elimination half-life of 10–14 h [1]. Renal impairment increases the systemic exposure to the drug. This increase is on average 32% for an estimated creatinine clearance (eCrCl) 51–80 mL/min; and >72% for an eCrCl <30 mL/min, in comparison with subjects with a normal renal function [1]. No major changes in edoxaban pharmacokinetics have been shown with mild-to-moderate hepatic impairment [1]. Albeit limited in number, some 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 [1]. P-glycoprotein inhibitors, such as dronedarone, ketoconazole, erithromycin, and cyclosporine, are associated with increased edoxaban plasma concentrations, and the concomitant use of edoxaban with these agents requires dose adjustment (i.e., a halving of the dose) [2]. Amiodarone, however, had no effect on the relative efficacy and safety of edoxaban 60 mg [3]. Conversely, 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. 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 [4].

An overview of edoxaban pharmacology compared with other NOACs is provided in

Table 1 Main pharmacological characteristics of the non-vitamin K-antagonist oral anticoagulants (NOACs) used in atrial fibrillation and venous thromboembolism

	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	1.5–2 h	2–3 h	2–3 h	1–2 h
Elimination half-life	12–17 h	5–9 h (young), 11–13 h (elderly)	12 h	10–14 h
Route of clearance	80% renal	35% renal	27% renal	50% renal

Table 1. Because of the better safety profile compared with VKAs, leading to a consistent saving in direct healthcare costs, all NOACs are likely cost-effective. This is probably also true with edoxaban [5]. Edoxaban price conditions in Europe will be similar to that of other NOACs.

A specific antidote is not yet available for edoxaban, as well as for the other Xa inhibitors. Andexanet alfa, an antidote against factor Xa inhibitors, is currently under review by the European Medicinal Agency (EMA) for reversal of its pharmacological action [6]. The infusion of a 4-factor prothrombinase complex concentrate (PCC) at 50 IU/kg has been shown to reverse the effects of edoxaban 30 min after completing its administration [7].

THE REGISTRATION STUDIES

ENGAGE AF-TIMI 48

In the ENGAGE AF-TIMI 48 trial [8], edoxaban, at the initial doses of 60 and 30 mg once daily (OD), was compared with adjusted-dose warfarin, targeted to an international normalized ratio (INR) of 2.0–3.0, for the prevention of stroke/systemic embolism in patients with non-valvular atrial fibrillation (NVAF). The choice for the OD administration regimen for edoxaban derives from a randomized, dose-ranging, warfarin-controlled, phase II study involving 1146 patients with AF. In this study, the OD regimen was shown to be safer (with less bleeding) than the twice-daily (BID) regimen [9].

The ENGAGE AF-TIMI 48 trial [8] was a randomized, double-blind, multicenter, placebo-controlled trial. The population enrolled was of 21,105 patients, followed up for a median of 2.8 years, making ENGAGE AF-TIMI 48 the study with the largest population and the longest follow-up in comparison with other registration trials with NOACs in NVAF [10–12]. The median time in therapeutic range (TTR) in the warfarin arm was 68.4%, which was the highest among the studies with NOACs in NVAF [8, 10–12]. The stroke risk profile of the ENGAGE AF-TIMI 48 population was intermediate between the relatively lower risk of RE-LY [10] and ARISTOTLE [12] and the relatively higher risk of ROCKET-AF [11], as shown by a mean $CHADS_2$ score of 2.8 [8]. The study protocol demanded the halving of the edoxaban dose when factors known to increase plasma concentrations, and therefore conceivably the risk of bleeding, were present. These included an eCrCl 30–50 mL/min; or a body weight $\leq$60 kg; or the concomitant use of potent P-glycoprotein inhibitors (such as verapamil, quinidine, or dronedarone). At variance from the other registration trials, such a dose adjustment could be done both at randomization and during the study, and was reversible in case of a reversal of the conditions that had demanded the dose reduction [8].

For the primary efficacy endpoint of stroke/systemic embolism, the statistical analysis

tested the non-inferiority of edoxaban versus warfarin [8]. Table 2 reports the results of the comparison versus warfarin of the edoxaban daily dose of 60 mg, reduced to 30 mg in the selected populations specified above; this—herein indicated as 60/30 mg—is now the recommended dose approved by American and European regulatory authorities. Edoxaban 60/30 mg proved to be non-inferior to warfarin in the prevention of stroke and systemic embolism, with a trend towards superiority [rate of 1.50% per year in the warfarin group vs 1.18% in the edoxaban 60/30 group; hazard ratio (HR) vs warfarin, 0.79; 97.5% confidence interval (CI) 0.63–0.99; $P < 0.001$ for noninferiority]. Edoxaban 60/30 mg also significantly reduced cardiovascular death. As to the primary safety endpoint of major bleeding, edoxaban 60/30 mg proved significantly superior to warfarin (rate of 3.43% per year with warfarin vs 2.75 with edoxaban 60/30; HR vs warfarin, 0.80; 95% CI 0.71–0.91; $P < 0.001$).

Table 2 Main efficacy and safety outcomes with edoxaban 60/30 mg vs warfarin in ENGAGE AF-TIMI 48

	HR (95% CI)	*P* value
Stroke/SEE		
mITT	0.79 (0.63–0.99)	<0.001[b]
ITT	0.87 (0.73–1.04)[a]	0.08[b]
Stroke	0.88 (0.75–1.03)	0.11
Hemorrhagic	0.54 (0.38–0.77)	<0.001
Ischemic	1.00 (0.83–1.19)	0.97
Death		
All-cause	0.92 (0.83–1.01)	0.08
CV	0.86 (0.77–0.97)	0.013
Myocardial infarction	0.94 (0.74–1.19)	0.60
Bleeding		
Major	0.80 (0.71–0.91)	<0.001
Life-threatening	0.51 (0.38–0.70)	<0.001
Major or CRNM	0.86 (0.80–0.92)	<0.001

SEE systemic embolic event, *mITT* modified intention-to-treat, *ITT* intention-to-treat, *HR* hazard ratio, *CI* confidence intervals, *CV* cardiovascular, *CRNM* clinically relevant non-major

[a] 97.5% CI

[b] Non-inferiority

Hokusai-VTE

The Hokusai-VTE study [13] was a randomized, double-blind, non-inferiority trial, aimed at assessing the efficacy and safety of edoxaban for the treatment of VTE. In this study, patients with objectively diagnosed deep vein thrombosis (DVT) and/or pulmonary embolism (PE) received an initial therapy with open-label enoxaparin or unfractionated heparin for at least 5 days. Edoxaban or warfarin were administered in a double-blind, double-dummy fashion. Edoxaban or placebo was started after the discontinuation of initial heparin. Warfarin or placebo was started concurrently with the study regimen of heparin, with adjustment of the dose to maintain the INR between 2.0 and 3.0. The standard edoxaban 60 mg OD dose was reduced to 30 mg OD in patients with eCrCl between 30 and 50 mL/min or a body weight <60 kg, or the concomitant use of potent P-glycoprotein inhibitors, as for ENGAGE AF-TIMI 48. The anticoagulant treatment was given for at least 3 months and up to 12 months, at the discretion of the investigators.

The primary study outcome was the recurrence of symptomatic VTE at 12 months; the primary safety outcome was the incidence of major and clinically relevant non-major bleeding. A total of 8292 patients were enrolled in the study, of whom 3319 had PE. The median duration of heparin treatment was 7 days, the INR was in the therapeutic range for 63.5% of the time, and 40% of patients were treated for 12 months. At 12 months, recurrent VTE occurred in 3.2% of the edoxaban patients and in 3.5% of the warfarin patients (HR 0.89; 95% CI 0.70–1.13; *P* for non-inferiority <0.001). The safety outcome occurred in 8.5% and in 10.3% of patients, respectively (HR 0.81; 95% CI 0.71–0.94; *P* for superiority 0.004). In PE patients 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).

Among patients who qualified for the 30 mg dose of edoxaban (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) (Fig. 1). In summary, Hokusai-VTE showed that a single daily dose of edoxaban is as effective as and safer than warfarin after an initial course of heparin for the treatment of VTE. Hokusai-VTE was the largest phase III study conducted in this setting, 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 favorable efficacy and safety profile of edoxaban was confirmed in the subgroups of patients qualifying for dose reduction and in PE patients with increased NT-proBNP.

TEN SELECTED QUESTIONS AND ANSWERS

Once Daily Administration: Which Patients Might Benefit Most From It?

The NOAC dosing regimen, specifically whether OD or BID, is part of the decision-making to select the most appropriate drug for the specific patient. For all NOACs, because of their short half-life, non-adherence is a more serious problem than for warfarin—see the higher rate of thromboembolic events that occurred in the

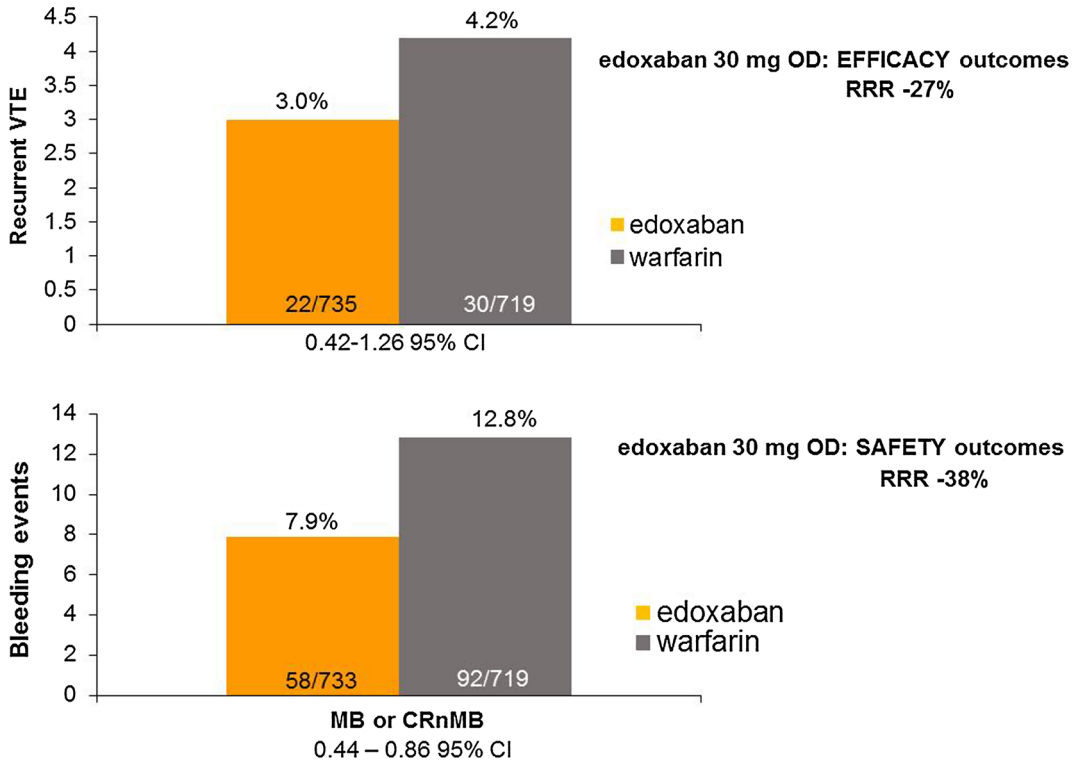

Fig. 1 Efficacy and safety outcomes in patients who qualified for the 30 mg dose of edoxaban. In the Hokusai-VTE study edoxaban was administered at the 60 mg once daily dose, reduced to 30 mg once daily in patients with a creatinine clearance between 30 and 50 mL/min or a body weight ≤60 kg. In patients requiring dose reduction, edoxaban confirmed non-inferiority in terms of efficacy and superiority in terms of safety, compared with warfarin. *VTE* venous thromboembolism, *OD* once daily, *RRR* relative risk reduction, *MB* major bleeding, *CRNMB* clinically relevant non-major bleeding

discontinuation phase of rivaroxaban in the ROCKET-AF trial [11]. Therefore, all measures maximizing adherence should be welcome and of advantage to the patients. In cardiovascular patients, the OD administration has been demonstrated to be associated with a greater adherence compared with BID dosing in patients with diabetes and hypertension [14] and, specifically, in patients with AF [15]. This is likely to be true also for the NOACs, provided that OD regimens ensure efficacy and safety at least similar to BID regimens [16]. Among the NOACs, edoxaban has been tested in a phase II dose-finding trial in AF, demonstrating lower bleeding rates (i.e., superior safety) with the OD regimen than with the BID regimen with the same total daily dose [9]. OD administration is also used for all VKAs: therefore, having a NOAC that can be given OD like VKAs eliminates a possible reservation bias in the patient already used to anticoagulation with a VKA. OD dosing in AF patients and for the management of most durations of VTE treatment is also possible for rivaroxaban. With these premises, the results of phase III registration trials [8, 13] indicate that the clinical efficacy of edoxaban is not compromised by OD dosing.

Skipping one pill of an OD drug for NOACs, all with a half-life of approximately 12 h, might, on the other hand be of greater detrimental effect than for a BID drug. Recent results, however, have not in general lent much support to the hypothesis that skipping one pill with an OD drug has a greater detrimental effect than for a BID drug [17]. In summary, although the issue of OD vs BID should be seen in its complexity [16] (see also the higher possible risk of overdosing with the accidental overingestion of one or several pills of an OD vs a BID drug), the authors concluded that the advantages of achieving better adherence with an OD drug outweigh the higher theoretical risks deriving from skipping doses or overdosing.

From everyday practice, several patient categories would appear to probably benefit from an OD administration. These include [16]

- Patients with comorbidities, needing to take many tablets per day
- Elderly people, commonly using complex drugs regimens with multiple drugs, which can negatively affect medication adherence
- Patients with suspected low adherence
- Young active workers, reluctant to take medications

Few Interactions with Other Drugs: A Particular Advantage for Edoxaban?

As detailed in the general section above, edoxaban has a very minor (<4%) proportion of metabolism through the cytochrome P450 system compared with the other Xa factor inhibitors [18, 19], suggesting that it may have fewer drug–drug interactions compared with other NOACs. Indeed, a CYP3A4-dependent elimination is involved in the hepatic clearance of rivaroxaban and apixaban [20]. This means that strong CYP3A4 inhibition or induction may affect plasma concentrations of these two NOACs. When strong inhibitors of both CYP3A4 and P-glycoprotein (dronedarone or azole antimycotics, such as itraconazole, ketoconazole, posaconazole, voriconazole) are administered, plasma levels of rivaroxaban and apixaban can increase [21]. In patients needing these drugs, edoxaban is the only FXa inhibitor not contraindicated, although a dose reduction from 60 to 30 mg/day is suggested. Similarly, rivaroxaban and apixaban are contraindicated in combination with strong inducers of P-glycoprotein and CYP3A4 (such as rifampicin, carbamazepine, phenobarbital, phenytoin, St John's wort), which strongly reduce plasma levels [22]. The need for using such drugs may represent a contraindication to the simultaneous use of those NOACs (Table 3). Conversely, the edoxaban label mentions that co-administration is possible for edoxaban in such cases, despite expected slightly decreased plasma level. Minor interactions of edoxaban have been noted with amiodarone, verapamil, and quinidine; however, after the analysis of phase III clinical trial data, this interaction was considered not clinically relevant, and no dose reduction is thus recommended in the label.

Table 3 Interaction between NOACs and strong inhibitor/inducers of both CYP3A4 and P-glycoprotein Modified from [16]

Inhibitors	via	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Antiarrhythmics drugs					
Dronedarone	P-gp competition and CYP3A4 inhibition	Contraindicated/ not recommended	Moderate effect but no PK or PD data: caution and try to avoid	No PK or PD data: caution	Reduce from 60 mg to 30 mg
Fungostatics					
Itraconazole, ketoconazole, posaconazole, voriconazole	Potent P-gp and BCRP competition; CYP3A4 inhibition	Contraindicated/ not recommended	Contraindicated/ not recommended	Contraindicated/ not recommended	Reduce from 60 mg to 30 mg
Inducers					
Carbamazepine, phenobarbital, phenytoin, St John's wort	P-gp/BCRP and CYP3A4/ CYP2 J inducers	Contraindication for simultaneous use	Contraindication for simultaneous use	Contraindication for simultaneous use	Co-administration is possible

P-gp P-glycoprotein, *PK* pharmacokinetic, *PD* pharmacodynamic, *BCRP* breast cancer resistance protein

Association with Antiplatelet Drugs: How Safe is Edoxaban?

Because of their impact on hemostasis, the association of NOACs with other anticoagulants, platelet inhibitors (aspirin, clopidogrel, ticlopidine, and others), and non-steroidal anti-inflammatory drugs increases the bleeding risk by at least 60% [23–25]. This estimate is similar to what was previously described for the association of these drugs with VKAs [26]. Therefore, the need for such associations needs to be carefully assessed, balancing benefits and risks in each individual patient. In the ENGAGE AF-TIMI 48 trial, the concomitant use of single antiplatelet therapy (SAPT), when judged necessary by the prescribing physicians, did not alter the relative efficacy of edoxaban compared with warfarin [edoxaban vs warfarin without SAPT: HR 0.94, 95% CI 0.77–1.15, with SAPT: HR 0.70, 95% CI 0.50–0.98, *P* for interaction (P_{int}) 0.14]. Notably, when compared with warfarin, edoxaban 60/30 mg OD featured less overall bleeding, including intracranial hemorrhage and life-threatening bleeding, both in patients receiving aspirin or other antiplatelet agents (HR 0.46, 95% CI 0.27–0.79; and HR 0.56, 95% CI 0.35–0.88, respectively) and in patients who were not receiving these drugs (HR 0.47, 95% CI 0.31–0.71 and HR 0.56, 95% CI 0.39–0.79, respectively). The concurrent use of aspirin increased the risk of having major bleeding events in all treatment groups, but did not change the relative risk compared with warfarin; major bleeding was lower with edoxaban than warfarin both without SAPT (HR 0.80, 95% CI 0.68–0.95) and with SAPT (HR 0.82, 95% CI 0.65–1.03, P_{int} 0.91) [27]. In patients taking aspirin, a similar benefit of edoxaban compared with warfarin was observed

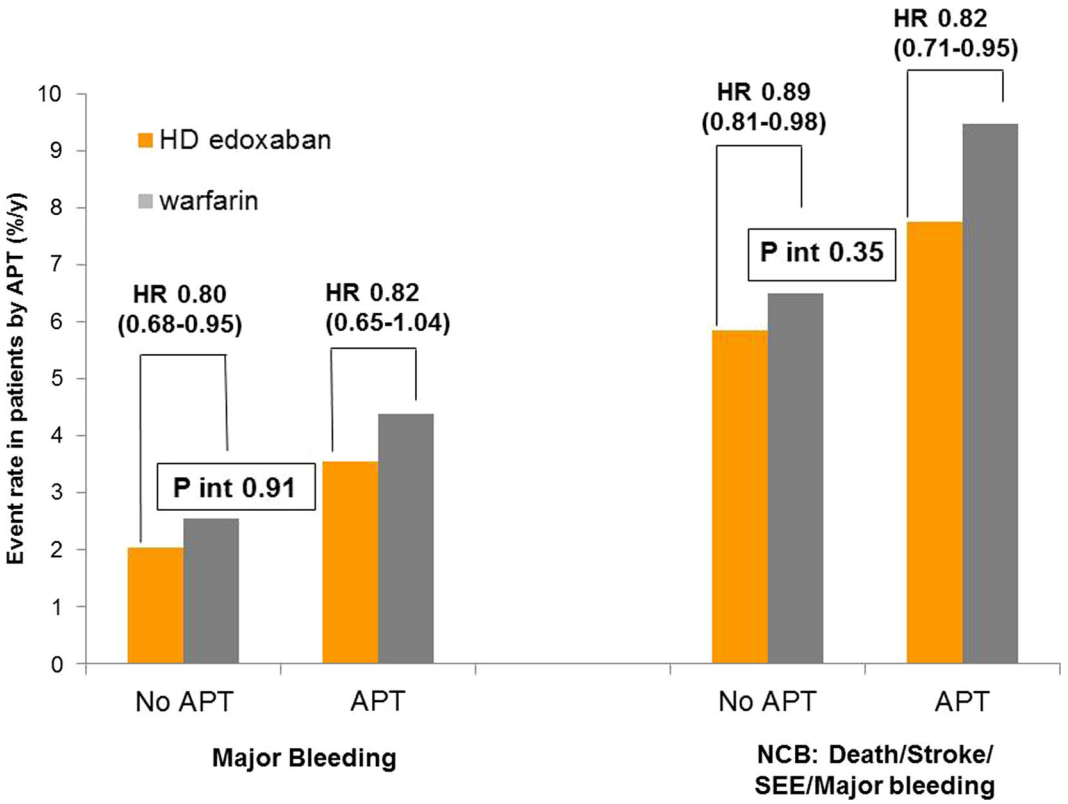

Fig. 2 Major bleeding and net clinical outcomes of HD edoxaban vs warfarin in patients with and without antiplatelet therapy. Patients taking aspirin in the higher dose edoxaban once daily regimen group had a lower rate of major bleeding and a net clinical benefit (NCB), compared with those treated with warfarin. High dose refers to edoxaban 60 mg, reduced to 30 mg in patients specifically qualifying for dose reduction (otherwise designated high-dose edoxaban regimen, HDER). *HD* high dose, *APT* antiplatelet therapy, *SEE* systemic embolic event, *HR* hazard ratio, *P int P* for interaction

for all the efficacy endpoints, all the safety endpoints, and for the net clinical benefit evaluation, which combined death, stroke, systemic embolic events, and major bleeding (edoxaban 60/30 mg without SAPT HR 0.82, 95% CI 0.71–0.95 and with SAPT HR 0.89, 95% CI 0.81–0.98, P_{int} 0.35). A lower occurrence of bleeding was observed in the edoxaban 60/30 mg group, without significant excess in all type strokes or ischemic strokes compared with warfarin [27] (Fig. 2). These data broadly confirm the safety profile of NOACs compared with warfarin when administered together with antiplatelet drugs, and inform physicians that, when the dangerous coadministration of antiplatelet drugs and an anticoagulant is deemed necessary, then NOACs, including edoxaban, are overall a safer choice than warfarin.

Is Edoxaban Attractive in Patients with Atrial Fibrillation and Chronic Kidney Disease?

Chronic kidney disease (CKD) is common in patients with AF, even if clinically not overt [28], with 11–23% of AF patients presenting an impairment in renal function, of variable degree [29]. In the ENGAGE AF-TIMI 48 trial, patients with an eCrCl <30 mL/min (assessed with the Cockcroft–Gault formula) were not enrolled [8], similarly to the other trials on NOACs in AF [10–12]. The labeling and the summary of product characteristics (SmPc) of edoxaban [2] report a non-indication for this drug if the eCrCl is <15 mL/min; this may allow a window of safety should the eCrCl fall below the 30 mL/min threshold during treatment [22], similar to

what is possible for rivaroxaban and apixaban [22]. For edoxaban, a reduction of the standard dose of 60 mg OD (the dose approved by regulatory agencies) to 30 mg OD is indicated when at least one of the following criteria is satisfied: eCrCl from 30 to 50 mL/min; or body weight ≤60 kg; or the concomitant use of potent P-glycoprotein inhibitors (such as verapamil, quinidine, or dronedarone) [8]. Similar to apixaban, but at variance from rivaroxaban and dabigatran, the application of the dose reduction criterion implies a more considerable (50%)—and therefore possibly safer—reduction of the dose than that occurring with rivaroxaban and dabigatran (for which the dose reduction is 25% and 27% (from 20 to 15 mg OD and from 150 to 110 mg BID, respectively).

The ENGAGE AF-TIMI 48 trial enrolled 4074 patients (1306 patients in the edoxaban 60/30 mg group) [4] with an eCrCl between 30 and 50 mL/min (19.3% of the trial population), and this constitutes the largest group of patients with renal insufficiency ever enrolled in a trial with a NOAC [4, 8]. Patients eligible for the edoxaban dose reduction had a complex clinical profile, with a much higher risk of stroke/systemic embolism, as well as of major bleeding, compared with normal patients (1.7-fold increased risk of stroke and 1.6 increased risk of bleeding in the warfarin arm) [4]. It is noteworthy that dose reduction did not alter the efficacy of edoxaban compared with warfarin (HR 0.81, 95% CI 0.58–1.13, $P = 0.85$), while the risk of major bleeding was significantly reduced (HR 0.63, 95% CI 0.50–0.81, $P = 0.023$) with the higher-dose regimen (60/30 mg OD) of edoxaban as compared with warfarin [4] (Fig. 3). Direct comparisons between different NOACs are not available, but a meta-regression analysis, with all its intrinsic limitations [30], found that in patients with moderate renal impairment the risk of major bleeding with edoxaban 60/30 mg OD was lower than that of dabigatran 150 mg BID, dabigatran 110 mg BID, or rivaroxaban 20 mg OD, with no significant differences compared with apixaban 5 mg BID. With regard to efficacy (prevention of stroke/systemic embolic events), no significant differences could be detected between edoxaban 60/30 mg OD and dabigatran 110 mg BID, dabigatran 150 mg BID, apixaban 5 mg BID, or rivaroxaban 20 mg OD [30]. In view of the data from ENGAGE AF-TIMI 48, edoxaban, with the appropriate dose reduction from 60 to 30 mg OD, appears to be a quite reasonable option in patients with NVAF and CKD with an eCrCl between 30 and 50 mL/min.

Can Edoxaban be Suitable for Frail Elderly Patients?

Most AF patients are elderly (≥75 years old), and increasing age is consistently a strong independent risk factor for AF-associated stroke [31]. However, elderly patients are often underrepresented in randomized clinical trials.

Edoxaban might be a first-choice NOAC for frail elderly patients for the following reasons:

- Edoxaban was widely tested in elderly patients at both dosages. The ENGAGE AF-TIMI 48 trial provides relevant data with respect to the use of edoxaban in elderly patients. Indeed [8], more than 8000 of the enrolled patients were 75 years or older, accounting for 40% of the 21,105 patients at moderate-to-high thromboembolic risk enrolled in the trial. The 60/30 mg edoxaban regimen was non-inferior to warfarin in preventing stroke/systemic embolism and was associated with significantly less overall major bleeding and intracranial hemorrhage (ICH). Results were consistent in different age and thromboembolic risk subgroups. Notably, edoxaban 60/30 mg also reduced the risk of ischemic stroke in the older group, in whom a risk reduction with edoxaban 60/30 mg compared with warfarin for ISTH major bleeding (event rate %/year edoxaban = 4; warfarin = 4.8; HR 0.83; 95% CI 0.70–0.99) and for ICH (event rate %/year edoxaban = 0.5 warfarin = 1.2; HR 0.40; 95% CI 0.26–0.62) was particularly evident in patients aged ≥75 years. Furthermore, only 18% and 41% of patients aged ≥65 and ≥75 years, respectively, received the reduced dose in each randomization arm, thus demonstrating that age alone does not demand a dose reduction. A recent post hoc

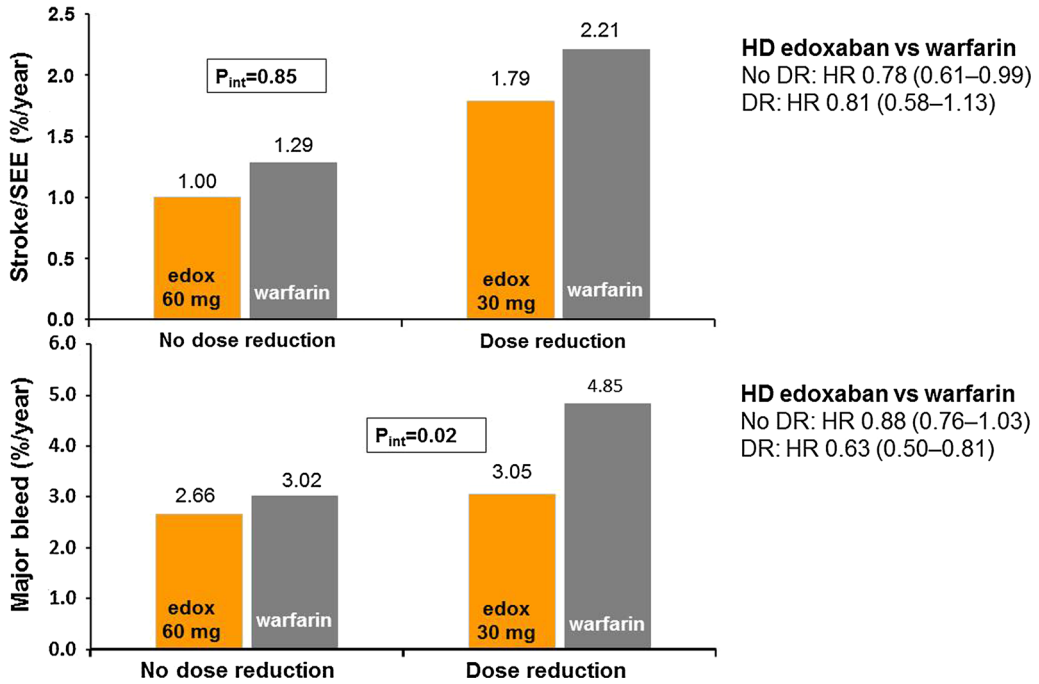

Fig. 3 Efficacy and safety outcome with edoxaban dose reduction. No dose reduction refers to the full dosage—60 mg—for all patients who did not meet any criteria for reducing the dosage, regardless of the randomization group (warfarin or edoxaban). Conversely, dose reduction refers to the halved dosage, 30 mg, for patients who met at least one criteria for reducing the dosage (eCrCl 50–30 mL/min, body weight ≤60 kg, concomitant use of P-gp inhibitors), regardless of the randomization group (warfarin or edoxaban). The dose reduction did not alter the efficacy of edoxaban compared with warfarin in the prevention of stroke or systemic embolic event (HR 0.81, 95% CI 0.58–1.13, *P* int = 0.85), while the risk of major bleeding was significantly reduced (HR 0.63, 95% CI 0.50–0.81, *P* int = 0. 023). *HD* high dose, *HR* hazard ratio, *Edox* edoxaban, *SEE* systemic embolic event, *P int* *P* for interaction

analysis of very elderly patients (age ≥80 and age ≥85) showed that there were no significant treatment interactions between age groups and treatment for all major outcomes, demonstrating the robustness of the findings with edoxaban in the elderly. It should be highlighted that this post hoc analysis included a considerable number of very old patients, being 3591 patients (17.0%) aged ≥80 and 899 (4.3%) aged ≥85, thus reinforcing the perception of edoxaban safety even in very elderly patients [32] (Table 4).

- Edoxaban is safer than warfarin in patients at risk of falls. An increased risk of falls and associated neuropsychiatric disease is—besides age—a risk factor for ICH in the elderly [33, 34]. Patients with AF at high risk of falls are at substantially increased risk of ICH, especially traumatic ICH. However, because of their high stroke rate, they still appear to benefit from anticoagulant therapy if they have multiple stroke risk factors [33, 34]. Indeed, while the risks of fall and ICH with warfarin are often quoted as reasons to avoid anticoagulation, it has been estimated that if a patient has a 5% annual risk of stroke from AF, he/she would need to fall at least 295 times to offset the benefit of oral anticoagulation [35]. A subgroup analysis of the ENGAGE AF-TIMI 48 trial demonstrated that, in patients at increased risk of falls [defined by any of the following eight criteria at randomization: (1) prior history of falls; (2) lower extremity weakness; (3) poor balance; (4) cognitive impairment; (5) orthostatic hypotension; (6) use of psychotropic

Table 4 Efficacy and safety outcomes for edoxaban in patients aged >80 and >85

	Warfarin Event rate (%/years)	Edoxaban 60/30 mg Event rate (%/years)	Edoxaban 60/30 mg vs warfarin HR (95% CI)	P_{int}
Stroke/SSE (years)				
<80	1.6	1.4	0.87 (0.73–1.04)	0.97
≥80	2.9	2.5	0.88 (0.64–1.20)	
<85	1.7	1.5	0.88 (0.75–1.03)	0.56
≥85	3.5	2.5	0.73 (0.40–1.33)	
Ischemic stroke (years)				
<80	1.1	1.1	1.03 (0.84–1.27)	0.54
≥80	2.1	1.8	0.90 (0.63–1.30)	
<85	1.2	1.2	1.01 (0.84–1.22)	0.5
≥85	2.4	1.9	0.79 (0.39–1.60)	
Hemorrhagic stroke (years)				
<80	0.4	0.2	0.55 (0.37–0.82)	0.93
≥80	0.8	0.4	0.53 (0.26–1.06)	
<85	0.5	0.3	0.53 (0.37–0.76)	0.78
≥85	0.8	0.5	0.64 (0.18–2.28)	
Major bleeding (years)				
<80	3	2.5	0.83 (0.71–0.96)	0.54
≥80	6.2	4.6	0.75 (0.58–0.98)	
<85	3.3	2.7	0.82 (0.72–0.94)	0.17
≥85	8.8	5	0.58 (0.35–0.94)	
ICH (years)				
<80	0.7	0.4	0.49 (0.34–0.69)	0.64
≥80	1.6	0.6	0.41 (0.22–0.77)	
<85	0.8	0.4	0.46 (0.33–0.62)	0.62
≥85	1.6	0.9	0.61 (0.20–1.88)	
Fatal bleeding (years)				
<80	0.3	0.2	0.57 (0.35–0.94)	0.79
≥80	0.8	0.4	0.50 (0.21–1.15)	
<85	0.4	0.2	0.52 (0.33–0.82)	0.45
≥85	0.6	0.6	0.99 (0.20–4.91)	

HR hazard ratio, *CI* confidence interval, P_{int} *P* for interaction, *ICH* intracranial hemorrhage, *SEE* systemic embolic events

drugs; (7) severe arthritis; or (8) dizziness], edoxaban was associated with a sixfold lower risk of ICH and fatal bleeds [36].
- Edoxaban dosage can be safely modified when necessary. In the ENGAGE AF-TIMI 48 trial, dose adjustments were permitted after randomization [8]. Since factors that affect drug clearance may vary over time, especially in the elderly, thus requiring a dose reduction, the possibility of a dynamic dose adjustment (meaning increase or decrease of the daily dose in the presence of changing body weight and eCrCl, besides age), uniquely tested prospectively in the ENGAGE AF-TIMI 48 trial, is a relevant factor in the choice of the drug.
- Edoxaban can be administered relatively safely in patients on aspirin. See Section "Association with Antiplatelet Drugs: How Safe is Edoxaban?"
- Edoxaban administration OD enhances patients' compliance compared with the BID dosing necessary with two other NOACs (see Section "Once Daily Administration: Which Patients Might Benefit Most From It?").

Can Edoxaban be Suitable for Patients with Heart Failure?

The occurrence of AF may complicate the clinical course of patients with heart failure (HF). HF patients with concomitant AF have a poorer outcome compared with HF patients without AF [37]. Thus, prevention of AF-related complications may improve prognosis in this setting. In the ENGAGE AF-TIMI 48 trial, the prevalence of HF was 58% ($n = 12{,}124$), accounting for the largest number of HF patients enrolled in the phase III trials with NOACs [38]. In ENGAGE AF-TIMI 48, HF patients had a higher risk profile, with a higher $CHADS_2$ score and increased prevalence of prior myocardial infarction versus those without HF [38]. This translated into higher rates of adverse events, including cardiovascular death and hospitalization for cardiovascular causes.

Similarly to what was observed in randomized trials with the other NOACs, in ENGAGE AF-TIMI 48 there was no interaction between treatment assignment and the presence/absence of HF. In particular, in patients with HF and New York Heart Association (NYHA) class III–IV, the use of edoxaban instead of warfarin led to a 17% relative risk reduction of stroke/systemic embolism (HR 0.83, 95% CI 0.55–1.25), as well as to a 21% (HR 0.79, 95% CI 0.54–1.17) and 65% (HR 0.35, 95% CI 0.14–0.88) lower risk of major bleeding and ICH, respectively [38]. Because of the higher incidence of stroke/systemic embolism in HF patients, the absolute reduction of this endpoint by edoxaban was more pronounced in this subgroup, with more events prevented during the follow-up (3.5/1000 patients/year vs 2.3/1000 patients/year in patients without HF).

Edoxaban may thus represent a reasonable option for patients with HF inasmuch as such patients usually
- Have important frailty
- Are treated with multiple drugs, and their compliance to treatment may thus be improved with a NOAC given once daily
- Derive—for the same reason—advantages from an anticoagulant agent having low interference with other drugs frequently used in the presence of HF, such as amiodarone
- Have frequent fluctuations of creatinine clearance, with the ENGAGE AF-TIMI 48 trial specifically demonstrating the safety of edoxaban dynamic dose adjustments after randomization

Are There Concerns About Edoxaban in Patients with a Creatinine Clearance ≥95 mL/min?

In a post-hoc, exploratory analysis of the results of the ENGAGE AF-TIMI 48 trial [8], a trend towards decreased relative efficacy for ischemic stroke prevention was observed in those patients with an eCrCl >95 mL/min, with

numerically higher rates in the edoxaban 60/30 mg group [39]. Rates of bleeding were on the other hand lower with edoxaban 60/30 mg OD in comparison to warfarin at all levels of eCrCl [39]. Since about 50% of edoxaban is excreted through the kidney, lower plasma concentrations, and—as a consequence—a lower anticoagulant effect, are conceivable in such patients. On this basis, although absolute event rates were very low in those with an eCrCl >95 mL/min in both treatment groups, the American Food and Drug Administration (FDA) recommended to exclude patients with an eCrCl >95 mL/min from edoxaban treatment [40]. This decision did not take into account the exploratory nature of the subgroup analysis performed here; the lack of randomization for classes of renal function; and—most importantly—the particularly good and outlying performance of warfarin in the normal renal function subgroup in only this specific trial, downsizing the effect of edoxaban [39]. Contrary to the FDA, the European Medicines Agency (EMA) has not prohibited the use of edoxaban in any classes of high creatinine clearance. The phrasing has here been "edoxaban should only be used in patients with NVAF and high creatinine clearance after a careful evaluation of the individual thromboembolic and bleeding risk" [4]. There should be therefore no limitation to edoxaban use in patients with normal renal function, also in the light of the preserved safety on major bleeding observed in this category [39]. In addition, the net clinical outcome (stroke/systemic embolism, ISTH major bleeding, and the primary net clinical outcome of stroke/systemic embolism, major bleeding, and all-cause death) showed no significant difference between edoxaban and warfarin at higher levels of renal function, owing to the preserved effect on bleeding and mortality [39] (Fig. 4). The inconsistent interpretations of the findings with edoxaban point, however, to a need for further investigation into the efficacy of all oral anticoagulants that are renally cleared, with a focus on patients with normal or super-normal renal clearance [39]. For edoxaban, this will be done within the setting of a formal post-authorization safety study (PASS) now in a phase of advanced planning.

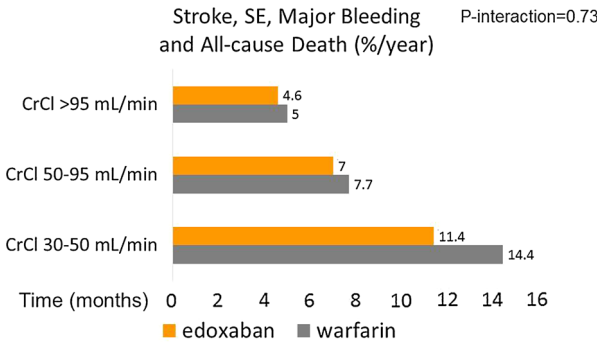

Fig. 4 Net clinical outcome endpoints by exploratory estimated creatinine clearance (eCrCl) subgroups. CrCl (mL/min) at randomization was estimated with the Cockcroft–Gault equation. *P* for interaction for treatment by eCrCl is shown for the endpoint. *CI* confidence interval, *HDER* higher-dose edoxaban regimen, *HR* hazard ratio. *Asterisk* HDER of 60 mg daily or 30 mg daily if dose reduced for eCrCl ≤50 mL/min, weight ≤60 kg, or potent P-glycoprotein inhibitor use

What are the Main Strengths of Edoxaban in Patients with Acute Pulmonary Embolism?

In the Hokusai-VTE study [13], edoxaban was evaluated for the treatment of VTE patients. Edoxaban was non-inferior to warfarin with respect to efficacy and superior with respect to safety, with fewer clinically significant bleeding events (defined as major bleeding and clinically relevant non-major bleeding). In all PE patients, NT-proBNP was measured at baseline, and right ventricular dysfunction was defined by levels of 500 pg/mL or higher. In this large subgroup of patients with PE and right ventricular dysfunction the rate of recurrent VTE was 3.3% in the edoxaban group ($n = 454$) and 6.2% in the warfarin group ($n = 484$) (hazard ratio 0.52; 95% CI 0.28–0.98), with a significant reduction in recurrent VTE (Fig. 5).

The main strengths of edoxaban in the treatment of VTE can be summarized as follows:

- Edoxaban is a once daily dose regimen drug (60/30 mg OD).
- In frail patients, with renal impairment (eCrCL 15–50 mL/min) or low body weight (≤60 kg), the dose can be safely adapted to 30 mg OD.

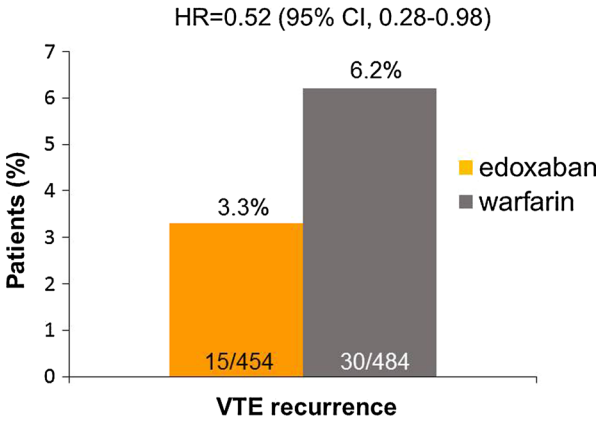

Fig. 5 Subgroup analysis in pulmonary embolism patients with NT-proBNP ≥500 pg/mL. In 90% of Hokusai-VTE patients with PE, NT-proBNP was measured at baseline. Right ventricular (RV) dysfunction was defined as a level of ≥500 pg/mL. In PE patients with NT-proBNP levels ≥500 pg/mL recurrent VTE occurred in 15 of 454 patients (3.3%) who received edoxaban and in 30 of 484 patients (6.2%) given warfarin [HR 0.52 (0.28–0.98)]. *HR* hazard ratio, *CI* confidence interval, *VTE* venous thromboembolism, *PE* pulmonary embolism, *NT-proBNP* N-terminal prohormone of the brain natriuretic peptide

- The drug is effective and safe in patients with PE and right ventricular dysfunction.

It must be emphasized that treatment should be initiated with standard dose of parenteral heparin.

In conclusion, edoxaban is an attractive regimen in a broad spectrum of PE patients and can be a recommended approach, as it further facilitates tailored treatment.

Is There a Clinical Benefit of the Heparin Lead-In, as Indicated for Edoxaban, in Patients with Pulmonary Embolism?

The first 5–10 days following the onset of a DVT or PE account for the "acute phase" of the disease. In this period, patients are at risk of thrombosis extension, recurrence, hemodynamic failure, and death [41]. Failure to rapidly achieve therapeutic levels of anticoagulation appears to be an independent risk factor for recurrence [42], which is about threefold more likely to be PE after an initial PE than after an initial episode of DVT [43]. This observation may justify an initial intensive anticoagulant therapy and a more aggressive treatment of PE. Guidelines recommend starting treatment of PE with parenteral anticoagulation [a low molecular weight heparin (LMWH), or fondaparinux], concomitant initiation of a VKA, and continuation of the parenteral drug for at least 5 days until the INR is ≥2.0 [44]. A recently published update of such guidelines recommends anticoagulation with one of the NOACs instead of VKAs, in the light of extensive documentation of comparable efficacy and better safety [45]. Edoxaban and dabigatran require an anticoagulation lead-in with a LMWH for at least 5 days, whereas a single-drug approach may be used with apixaban and rivaroxaban (with dose adjustment in the first or 3 weeks of treatment, respectively). Hokusai VTE in the only trial that identified a subset of PE patients with right ventricular (RV) dysfunction, defined as a level of NT-proBNP >500 pg/mL. In these patients edoxaban demonstrated a reduction of recurrent VTE by 48% [13]. Edoxaban requires a short course of LMWH and has the distinguished feature of being given once a day during the entire course of treatment. Thus, the heparin lead-in associated with edoxaban can be seen as an effective and safe treatment in a wide spectrum of patients with PE, including those with right ventricle dysfunction. In these patients, the initial lead-in with heparin facilitated the use of rescue thrombolysis.

Does the Hokusai Study Provide Data for the Extended Treatment with Edoxaban in VTE Patients?

All patients with VTE should receive anticoagulant treatment for a minimum of 3 months. At this time, patients at increased risk of recurrence, such as those with unprovoked VTE or previous VTE, should be considered for extended treatment duration [44]. A number of "extension" studies have suggested that dabigatran, rivaroxaban, and apixaban are valid alternatives to warfarin in this setting.

In the Hokusai-VTE study, all patients were treated for a minimum of 3 months and were followed for 12 months regardless of the

intended or actual duration of therapy. The decision on treatment duration beyond 3 months was left to the discretion of the investigators, to simulate clinical practice. Thus, although no formal "extension study" was planned for edoxaban, the design of the Hokusai study provided the opportunity to compare edoxaban with warfarin for a prolonged treatment of VTE. In a post-hoc analysis of the study [46], the risk–benefit of anticoagulation with edoxaban compared with warfarin was evaluated in those patients who continued therapy beyond 3 months. Among patients who received edoxaban or warfarin, 88.2% ($n = 3633$) and 87.2% ($n = 3594$), respectively, continued treatment beyond 3 months; and 45.7% ($n = 1661$) and 46.2% ($n = 1659$), respectively, were treated for 12 months. The baseline characteristics of the two subgroups who received extended therapy were comparable. At 12 months, the cumulative incidence rates of recurrent VTE were 1.8% in the edoxaban group and 1.9% in the warfarin group (HR 0.97; 95% CI 0.69–1.37). The cumulative incidences of major or non-major bleeding were 3.9% and 4.1%, respectively (HR 0.97; 95% CI 0.77–1.22); and the cumulative incidences of major bleeding were 0.3% and 0.7%, respectively (HR 0.45; 95% CI 0.22–0.92). These results provide additional evidence that edoxaban, administered OD, is an effective and safe alternative to warfarin for VTE patients who require anticoagulant treatment beyond 3 months.

EXPERT OPINION

In spite of the predictable anticoagulant effect of NOACs, attention has been paid to the possibility that vulnerable patients might be exposed to excess drug concentrations, which might significantly increase the bleeding risk. These concerns may have several implications in the management of AF and VTE patients who require an anticoagulation therapy, which might lead to an inappropriate dose reduction of NOACs, with a subsequent increase of thromboembolic events.

The ENGAGE AF-TIMI 48 and the Hokusai VTE are the largest trials ever conducted, with the longest duration, in their setting, and both considered reducing the dosage in patients with high bleeding risk. Results demonstrating that dose reduction provided an even greater difference in major bleeding with edoxaban versus warfarin, while not altering its efficacy, suggest that edoxaban might overcome these concerns. The criteria adopted for dose reduction, based on purely clinical information, allowed a proper tailoring of the dose of edoxaban optimizing the balance between the risks of thromboembolic and bleeding events. Thus, a clear dose strategy, together with the ease of use (owing to the OD administration, few drug–drug interactions, and no impact of food), might support the use of edoxaban in a large spectrum of patients, including the most vulnerable ones.

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Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors.

Data Availability. Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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