

Risk impact of edoxaban in the management of stroke and venous thromboembolism

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Abstract: The new generation of target-specific oral anticoagulants is being prescribed for increasing numbers of patients at risk of stroke or venous thromboembolism (VTE). These drugs offer valuable benefits due to fast onset anticoagulation, a fixed anticoagulation effect (allowing administration of specified doses), and no requirement for routine monitoring. Edoxaban is a fast-acting oral anticoagulant, approved for use in the prevention of stroke in patients with nonvalvular atrial fibrillation (AF) and in the treatment of acute VTE. Like many of the new oral anticoagulants, it selectively inhibits factor Xa, in a concentration-dependent manner. Multiple Phase II clinical trials have shown edoxaban to be noninferior to vitamin K antagonists in the prevention of stroke and VTE, with a good safety profile. To date, the pivotal studies to endorse edoxaban's clinical use have been ENGAGE AF-TIMI and Hokusai-VTE, both of which have compared its efficacy to standard warfarin treatment. This paper aims at reviewing the use of edoxaban in the management of stroke and thromboembolic disease, highlighting the key study results that have led to its current license.

Keywords: edoxaban, stroke management, venous thromboembolism, atrial fibrillation, randomized controlled trials, new oral anticoagulants

History and development

Patients are prescribed oral anticoagulants for a variety of medical conditions, including, but not limited to, atrial fibrillation (AF), acute venous thromboembolism (VTE), secondary prevention of stroke and myocardial infarction, and VTE prophylaxis. Warfarin (an antagonist of vitamin K-dependent clotting factors, VKA) had previously been the mainstay for long-term anticoagulation as its effect could be easily quantified, it could be reversed if required, and its long-term sequelae were well understood. VKAs, however, have multiple limitations due to their delayed anticoagulation effects, variability in dosing, drug and food interactions, and requirement for frequent monitoring.^{1,2} Several studies have also shown VKAs to be ineffective in up to half the patients for the treatment of VTE, due to their unreliability, slow onset of action, and need for stringent patient cooperation.³

Since 2008, new oral anticoagulants (NOACs) have been increasingly used in clinical settings. Their fixed anticoagulation response and regular dosing regimens are fast becoming favored by clinicians.^{4,5}

The majority of NOACs work by selectively targeting factor Xa, a molecule responsible for the activation of thrombin in the clotting cascade. The exception to this is dabigatran, which acts on thrombin directly.

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Multiple randomized controlled trials (RCTs) have shown all NOACs to be equivalent to standard warfarin therapy, with equivocal or reduced rates of stroke^{6,7} and comparable rates of arterial embolism.^{8,9}

Bleeding complications have been shown to be similar between the two medications but significantly reduced rates of intracerebral hemorrhage and overall mortality have been documented following the use of NOACs.^{2,10,11}

Consequently, after many years with only one treatment option available, the NOACs now provide a safe alternative to warfarin. Listed below are the current NOAC licenses (UK):

- Dabigatran: for stroke prevention in patients with AF + one CHADS (congestive heart failure, hypertension, age =75 years, diabetes mellitus, stroke) risk factor (150 mg twice daily [BD]), the treatment of deep vein thrombosis (DVT) or pulmonary embolism (PE) after parenteral anticoagulation for 5–10 days (150 mg BD), and prevention of VTE in elective hip/knee surgery (110 mg 1–4 hours after surgery, then 220 mg once daily [OD] 9/7).
- Rivaroxaban: for prevention of VTE in elective hip/knee surgery (10 mg OD), stroke prevention in patients with AF + one CHADS risk factor (20 mg OD), and treatment of DVT and PE (15 mg BD), or prophylaxis after recurrent DVT/PE (20 mg OD).
- Apixaban: for prevention of VTE in elective hip/knee surgery (2.5 mg) and stroke prevention in patients with AF + one CHADS risk factor (5 mg).

The European Society of Cardiology and the American Heart Association (AHA) updated their guidelines in 2012 and 2014, respectively, to include NOACs in the management of AF.^{12,13} The American College of Chest Physicians followed in 2012 by advising the use of NOACs for the treatment for VTE,¹⁴ and licenses for all the aforementioned have been approved by the National Institute of Clinical Excellence (NICE).

Edoxaban is the newest inhibitor of factor Xa to complete Phase III trials. It was developed by Daiichi Sankyo, and gained its first license in Japan in 2011 for the prevention of VTE after lower limb surgery.¹⁵ Following the clinical license of dabigatran, rivaroxaban, and apixaban, both the US and the UK have more recently approved edoxaban for the prevention of AF-related strokes and VTE.

Phase I studies concluded that single doses from 10 up to 150 mg, and multiple doses up to 120 mg, were safe and well tolerated. Following multiple Phase II studies, the two key Phase III studies, ENGAGE F-TIMI¹⁶ and Hokusai VTE,¹⁷ have been key in the introduction of edoxaban into clinical practice.

Pharmacokinetics

Edoxaban is a direct factor Xa inhibitor, with a predictable anticoagulation profile. Its peak effects are seen within 1–2 hours, and studies have shown elevated baseline levels for up to 24 hours after administration (half-life 10–14 hours).¹⁸ Although once-daily and twice-daily dosing regimens have been trialed, greater bleeding risks were associated with twice-daily prescriptions.¹⁹

Edoxaban is predominantly eliminated in feces and urine, but renal elimination ranges from 35% to 50%.¹⁸ In patients with renal impairment, dose reduction should also be considered.²⁰ Table 1 provides summary information of edoxaban.

Table 1 Edoxaban: summary information

Mode of action	Direct inhibitor of factor Xa
Indication/license	Treatment of DVT or PE and prevention of recurrence of symptomatic VTE Prevention of stroke and systemic embolic events in patients with AF
Dosage	30–60 mg
Dose regimen	Once daily
Reversal	Specific reversal not available. Consider prothrombin complex concentrate in emergency setting
Monitoring	No routine monitoring required
Periprocedure management	Edoxaban should be discontinued a minimum of 12 hours prior to procedure, and enoxaparin commenced at the same time as the next scheduled NOAC dose
Prodrug	None; edoxaban is a direct factor Xa inhibitor and active upon administration
Half-life	10–14 hours
Peak serum levels	1–2 hours
Excretion	Excretion predominantly in feces and urine Approximately 35% renal elimination
Use in pregnancy	Not recommended. Risks cannot be ruled out at present
Reduces efficacy of edoxaban, risk of stroke/embolism	CYP3A4 and P-gp inhibitors: HIV protease inhibitors, itraconazole, ketoconazole, clarithromycin
Increases edoxaban serum levels, risk of bleeding	CYP3A4 and P-gp inducers: carbamazepine, phenytoin, rifampicin
Dose in renal impairment	Avoid edoxaban administration 50% dose reduction if GFR is 15–29 mL/min Do not use if GFR <15 mL/min
Bridging	Edoxaban should be discontinued and enoxaparin commenced at the same time as the next scheduled NOAC dose For conversion to warfarin, edoxaban should be discontinued once the patient's INR is in therapeutic range
Monitoring	aPTT and PT and anti-factor Xa are all sensitive to edoxaban concentrations

Abbreviations: DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism; P-gp, p-glycoprotein; AF, atrial fibrillation; GFR, glomerular filtration rate; NOAC, new oral anticoagulant; INR, international normalized ratio; aPTT, activated partial thromboplastin time; PT, prothrombin time.

Although edoxaban has minimal drug and food interactions, it is affected by drugs that inhibit the p-glycoprotein (P-gp) transport protein. Consequently, when taken in combination with such drugs, a dose reduction of 50% is recommended.²¹

Efficacy in stroke prevention

AF is one of the most prevalent cardiac conditions, associated with a four to five times increased relative risk of ischemic stroke.²² Consequently, oral anticoagulant

therapies have been used in patients with nonvalvular AF for many years, and they are recommended in all those who have had a prior stroke or transient ischemic attack, or have an increased risk of ischemic event determined by the CHAD₂S₂-VASc score.²³

There have been four major RCTs comparing edoxaban to warfarin in the prevention of stroke in nonvalvular AF. Results of these studies are summarized in Tables 2 and 3. All the RCTs included patients with nonvalvular AF and CHAD₂S₂-VASc score of >1.

Table 2 RCT comparing edoxaban to warfarin therapy in the prevention of AF-related ischemic strokes

Study	Study information	Jadad score	Key outcomes (numbers expressed as %)
Weitz et al ¹⁹	Number of participants; 1,146 Randomized open-label drug, double blinded 3-month follow-up Comparison: Edoxaban 30 mg OD (N: 235) Edoxaban 30 mg BD (N: 245) Edoxaban 60 mg OD (N: 235) Edoxaban 60 mg BD (N: 180) and standardized warfarin therapy INR 2–3 (N: 251)	5	Edoxaban OD noninferior to warfarin. Bleeding: 30 mg OD; 5.5 (P=0.367) 30 mg BD; 12.7 (P=0.104) 60 mg OD; 3.9 (P=0.864) 60 mg BD; 18.3 (P=0.002) Warfarin; 8.0 Major bleeding: 30 mg OD; 3.0 (P=1.0) 30 mg BD; 7.8 (P=0.029) 60 mg OD; 3.9 (P=0.807) 60 mg BD; 10.6 (P=0.002) Warfarin; 3.2 Major cardiovascular event: 30 mg OD; 1.7 30 mg BD; 2.5 60 mg OD; 4.3 60 mg BD; 1.1 Warfarin; 2.4
Chung et al ²⁴	Number of participants; 234 Randomized open-label, double-blinded dose. 3-month follow-up Comparison: Edoxaban 30 mg OD Edoxaban 60 mg OD to warfarin (INR 2–3)	5	Edoxaban noninferior to warfarin. Bleeding: 30 mg OD; 20.3 60 mg OD; 23.8 Warfarin; 29.3 Major bleeding: 30 mg OD; 0 60 mg OD; 7.5 Warfarin; 6.6 Major cardiovascular event: 30 mg OD; 2.5 60 mg OD; 3.8 Warfarin; 1.3
Yamashita et al ²⁵	Number of participants; 546 Randomized, double-blinded trial. 3-month follow-up Comparison: Edoxaban 30 mg OD Edoxaban 45 mg OD Edoxaban 60 mg OD with warfarin treatment (INR 2–3)	5	Edoxaban noninferior to warfarin. Bleeding: 30 mg OD; 18.5 45 mg OD; 22.4 60 mg OD; 27.7 Warfarin; 20 Major bleeding: 30 mg OD; 1.5 45 mg OD; 5.2 60 mg OD; 5.4 Warfarin; 3.2

Abbreviations: BD, twice daily; OD, once daily; RCTs, randomized controlled trials; AF, atrial fibrillation; INR, international normalized ratio.

Weitz et al¹⁹ followed 1,146 patients over a 3-month period. Both 30 and 60 mg doses were trialed in once- and twice-daily regimens, and were compared to a group of patients on standard warfarin treatment (international normalized ratio: 2–3). The study was double blinded to the dose of edoxaban but open label to those on edoxaban and warfarin. Results showed that once-daily dosing regimens were of the same efficacy and safety as warfarin (major bleeding 60 mg; 3.0 [$P=0.807$], 30 mg; 3.0 [$P=1.0$] warfarin 3.2), but twice-daily regimens were associated with an increased risk of bleeding (10.6%, $P=0.002$ for 60 mg and 7.8%, $P=0.029$ for 30 mg).

Both Chung et al and Yamashita et al showed edoxaban to be noninferior to warfarin at 30 mg OD, 45 mg OD, and 60 mg OD dosing regimens.^{24,25}

However, the key study so far assessing the use of edoxaban in AF-related stroke prevention is the ENGAGE-AF

Table 3 The key outcomes of the ENGAGE-AF TIMI 48 trial,¹⁶ comparing edoxaban 30 and 60 mg to warfarin treatment

Complications	Low-dose edoxaban (30 mg)	High-dose edoxaban (60 mg)	Warfarin (therapeutic)	Outcome
Stroke and embolism prevention	1.61% ($P=0.005$)	1.18% ($P=0.001$)	1.50%	Reduced by up to 0.32%
Bleeding rates	1.61% ($P=0.001$)	2.75% ($P=0.001$)	3.43%	Reduced by up to 1.82%
Intracranial hemorrhage	0.26% ($P=0.001$)	0.39% ($P=0.001$)	0.85%	Reduced by up to 0.59%
Cardiovascular death	2.71% ($P=0.008$)	2.74% ($P=0.013$)	3.17%	Reduced by up to 0.46%

Table 4 Evidence for edoxaban in the prevention of VTE, including RCTs and meta-analysis

Study	Study information	Jadad score	Key outcomes (numbers expressed as %)
Robertson et al ³¹	Number of participants: 27,945 11 RCTs Three studies on direct thrombin inhibitors, eight studies on oral factor Xa inhibitors; (four rivaroxaban, two apixaban, and two edoxaban)	n/a	Oral factor Xa inhibitors demonstrated a similar rate of recurrent VTE compared to warfarin (OR 0.89; 95% CI 0.73–1.07) and a lower rate of recurrent DVT (OR 0.75; 95% CI 0.57–0.98)
Fuji et al (STARS E-3) ²⁹	Number of participants: 716 RCT. All patients undergoing unilateral total knee arthroscopy Comparison: edoxaban 30 mg and subcutaneous enoxaparin 20 mg BD	5	Edoxiban superior when compared to enoxaparin in the prevention of VTE. Absolute risk reduction of 6.5% Efficacy: 7.4 vs 13.0 ($P<0.001$) Safety: 6.2 vs 3.7 ($P=0.129$)
Fuji et al (STARS J-4) ³²	Number of participants: 92 RCT. Patients undergoing surgery for trochanteric or subtrochanteric fractures Edoxaban 30 mg compared to subcutaneous enoxaparin 20 mg BD	5	Rates of VTE with edoxaban and enoxaparin were 6.5% and 3.7%, respectively, and bleeding rates were 3.4% and 6.9%, respectively
Fuji et al (STARS J-V) ³⁰	Number of participants: 610 Phase III, double-blinded study. Patients undergoing elective, unilateral total knee arthroplasty Edoxaban 30 mg OD or enoxaparin 2,000 IU twice daily for 11–14 days.	5	Edoxaban superior to subcutaneous enoxaparin in the prevention of VTE; 2.4 vs 6.9 ($P=0.0157$). Major or clinically relevant nonmajor bleeding: 2.6 vs 3.7 (0.465)

Abbreviations: BD, twice daily; CI, confidence interval; DVT, deep vein thrombosis; OD, once daily; OR, odds ratio; RCTs, randomized controlled trials; VTE, venous thromboembolism; n/a, not applicable; IU, international units.

TIMI 48 trial.¹⁶ This study included 21,105 patients who were randomized to 30 or 60 mg edoxaban OD, compared to standardized warfarin therapy, for 3–12 months. The study was randomized, double blinded, and included patients with a moderate-to-high risk of stroke (CHADS₂ score ≥ 2). Results showed that both 30 and 60 mg doses of edoxaban were noninferior to warfarin in the prevention of stroke and systemic embolism. Study outcomes are tabulated in Table 3.

In light of these results, the ENGAGE-AF TIMI 48 trial conclusions recommended edoxaban 60 mg for the prevention of AF-related strokes and 30 mg for those patients with high bleeding risk.

Efficacy in prevention of VTE

VTE most commonly presents as either a DVT or PE and has an estimated mortality of up to 25,000 deaths annually in the UK.²⁶ It also costs the National Health Service approximately £640 million per year.²⁷ In light of this, prophylactic subcutaneous low-molecular-weight heparin has been recommended by the National Institute of Clinical Excellence for the prevention of VTE in all those at risk.²⁸

Three Phase III clinical trials have evaluated the use of edoxaban in the prevention of VTE, including a combined total of 1,418 patients (Table 4). STARS E-3, STARS J-4, and STARS J-V were all randomized, double-blinded studies in patients undergoing orthopedic surgery, and they compared edoxaban 30 mg once daily to enoxaparin 20 mg twice daily. All three RCTs showed no significant difference in bleeding rates between the two treatments, and both STARS E-3 and

STARS J-V proved edoxaban to be superior in the prevention of VTE.^{29,30}

Robertson et al³¹ reviewed a total of 27,945 patients (from eleven RCTs) and demonstrated a similar rate of recurrent DVT with the use of edoxaban compared to enoxaparin. A lower rate of recurrent DVT was also observed.

The results of the RCT STARS E-3²⁹ compared 716 patients following knee arthroscopy and showed edoxaban to be superior to enoxaparin in the prevention of DVT (overall risk reduction of 6.5%).

STARS J-4 compared edoxaban to enoxaparin following trochanteric and subtrochanteric fractures.³² Rates of VTE with edoxaban and enoxaparin were 6.5% and 3.7%, respectively, and bleeding rates were 3.4% and 6.9%.

Patients undergoing elective, unilateral total knee arthroplasty were compared in the STARS J-V RCT.³⁰ Six hundred and ten patients were randomized, and outcomes showed edoxaban to be superior to enoxaparin in both prevention of DVT and major bleeding risk.

Efficacy in treatment of VTE

For the treatment of VTE, the largest randomized, double-blinded Phase III clinical trial is the Hokusai VTE study.¹⁷ This study evaluated whether 5 days of heparin treatment followed by 60 mg once-daily edoxaban would be a superior alternative to warfarin therapy for the prevention of recurrent thromboembolism.

In patients with VTE (including PE with right ventricular dysfunction), treatment with heparin followed by oral edoxaban 60 mg once daily was shown to be noninferior to the standard treatment. With respect to bleeding, results were superior for edoxaban: 8.5% vs 10.3% ($P=0.004$).

Hokusai VTE also showed that a reduced dose (30 mg OD) of edoxaban is safe in patients with renal impairment and low body weight. Results are summarized in Table 5.

Safety

As described earlier, the clinical trials of edoxaban efficacy have also reported on the drug safety profile. In combination with the results of large meta-analyses (Table 6), edoxaban has been shown to be safe in the current recommended doses.

Because of the pharmacokinetics of NOACs, there are no suitable reversal therapies in the setting of acute bleeding.^{33,34} Thus, the same protocol as for major bleeding in warfarin must be adhered to: discontinue the drug, apply manual compression, maintain blood pressure, surgical/radiological intervention if appropriate, and replace blood products \pm prothrombin complex concentrate.³⁵ It is possible

Table 5 Trial information for Nakamura et al – the only RCT comparing edoxaban to enoxaparin and warfarin therapy in the treatment of VTE

Study name	Number of participants	Jadad score	Key outcomes (numbers expressed as %)
Nakamura et al ³⁷	8,292 patients from 439 centers worldwide RCT, double blinded of patients with DVT \pm PE Edoxaban 60 mg OD compared to warfarin therapy. (For patients with CrCl 30–50 mL or weight <60 kg 50% dose reduction in edoxaban)	5	Edoxaban noninferior in efficacy to warfarin but superior when comparing bleeding complications VTE: Edoxaban 3.2 Warfarin 3.5 Bleeding: Edoxaban 8.5 Warfarin 10.3

Abbreviations: RCT, randomized controlled trial; VTE, venous thromboembolism; DVT, deep vein thrombosis; OD, once daily; PE, pulmonary embolism.

Table 6 Meta-analyses reporting on the safety of edoxaban in comparison to alternative oral anticoagulants

Study	Trial information	Comparators	Key outcomes
Caldeira et al ³⁸	Meta-analysis of eleven Phase III RCTs	Comparison of NOACs with VKAs or low-molecular-weight heparin followed by VKAs	NOACs decrease the risk of fatality in cases related to major bleeding events, particularly in AF patients Results support the safety profile of NOACs even without having a widely available drug-specific antidote
Loffredo et al ³⁹	Meta-analysis of eleven RCTs (29,482 patients)	Comparison of 30 and 60 mg doses of edoxaban with warfarin, for rates of recurrent VTE and death	Treatment with NOACs in patients with acute VTE is noninferior to conventional therapy with warfarin for recurrent VTE or death, but there might be an increased incidence of myocardial infarction
Sardar et al ⁴⁰	Meta-analysis of 50 RCTs (155,537 patients)	Comparison of NOACs (rivaroxaban, dabigatran, apixaban, edoxaban, and darexaban) with VKAs	No significant difference between NOACs and comparators in the treatment of AF and extended treatment of VTE NOACs caused significantly less major bleeding compared to VKAs. Risk of major bleeding varied with indication for use NOACs may increase the risk of major bleeding after hip surgery, ACS and acute medically ill patients, but may be associated with less bleeding in treatment of acute VTE/PE

Abbreviations: RCTs, randomized controlled trials; VTE, venous thromboembolism; PE, pulmonary embolism; VKAs, vitamin K antagonists; NOACs, new oral anticoagulants; AF, atrial fibrillation; ACS, acute coronary syndromes.

to administer activated charcoal orally if the anticoagulant was taken within 2 hours. Tranexamic acid should also be considered following the result of the CRASH-2 trial.^{35,36}

Conclusion

The NOACs are quickly becoming the preferred treatment in the prevention and management of thromboembolic disease. Edoxaban is a once-daily oral factor Xa inhibitor with fast onset and the added benefit of fixed anticoagulation profiling without routine monitoring. Phase III clinical trials for its use in AF-related strokes (ENGAGE AF-TIMI 48) and VTE treatment (Hokusai VTE) have shown noninferior efficacy compared to standard therapy, as well as reduced rates of bleeding and cardiovascular death. Further studies have also confirmed safe use in both 30 and 60 mg doses.

From the results of multiple RCTs and systematic reviews, edoxaban appears to be a safe and effective alternative treatment to oral coagulation in the clinical setting. However, further developments are always pending. In October 2015, we saw the introduction of the first reversal agent for dabigatran “Praxbind” (idarucizumab; Boehringer Ingelheim, Ingelheim, Germany), and pharmaceutical companies are trialing reversal agents for the factor Xa inhibitors. There are now multiple new options for the management of acute and chronic medical conditions for which we previously could only realistically recommend warfarin in the long term. The focus of clinical trials on both safety and efficacy has facilitated the expansion of edoxaban in clinical practice.

Of the NOACs, edoxaban appears to have the best evidence base for efficacy and safety. The NOACs are here to stay, and physicians and surgeons alike need to learn how to use them optimally for patient safety and benefit.

Disclosure

The authors report no conflicts of interest in this work.

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