

Comparative risk impact of edoxaban in the management of stroke and venous thromboembolism

Katie B Tellor
Joseph S Van Tuyl
Anastasia L Armbruster

Department of Pharmacy Practice, St
Louis College of Pharmacy, St Louis,
MO, USA

Abstract: Edoxaban, a factor Xa inhibitor, was approved by the United States Food and Drug Administration in 2015 for stroke prevention in nonvalvular atrial fibrillation and treatment of venous thromboembolism. It is the fourth target-specific oral anticoagulant to be approved. Edoxaban is noninferior for efficacy compared to warfarin for both approved indications. Edoxaban is superior to warfarin for the first major or clinically relevant nonmajor bleeding event in venous thromboembolism and major bleeding in nonvalvular atrial fibrillation. Edoxaban is dosed once daily for both indications and requires dose adjustment for renal function. In patients with nonvalvular atrial fibrillation, use is not recommended in patients with a creatinine clearance greater than 95 mL/min due to reduced efficacy. Edoxaban offers a new therapeutic alternative to the currently available options in the market.

Keywords: anticoagulation, stroke, deep vein thrombosis, pulmonary embolism, atrial fibrillation, Savaysa™

Introduction

Oral anticoagulation has changed dramatically since 2009. For decades, vitamin K antagonists were the only option available for treatment and prevention of venous thromboembolism (VTE) and prevention of stroke and systemic embolism (SSE) in patients with nonvalvular atrial fibrillation (NVAF). Warfarin has established efficacy in both disease states, but does come with limitations. A narrow therapeutic index, frequent therapeutic drug monitoring, and dietary and medication interactions complicate the management of warfarin.¹

The first target-specific oral anticoagulant (TSOAC) introduced in 2010 was dabigatran, a direct thrombin inhibitor.² There are currently three factor Xa inhibitors approved by the United States Food and Drug Administration (FDA), including, apixaban, rivaroxaban, and edoxaban. Table 1 summarizes the general properties as well as current FDA-approved indications.²⁻⁵ Edoxaban is the most recent factor Xa inhibitor to receive FDA approval. This review summarizes the current evidence for edoxaban in the treatment and prevention of VTE and prevention of SSE in NVAF.

Pharmacodynamics and pharmacokinetics

Edoxaban is an orally active, direct, and specific inhibitor of factor Xa that inhibits thrombin generation and thrombus formation.^{6,7} Edoxaban is associated with dose-dependent prolonged prothrombin time, activated partial thromboplastin time, international normalized ratio (INR) (maximum of 3.5), and antifactor Xa activity.^{7,8}

Correspondence: Anastasia L Armbruster
St Louis College of Pharmacy, 4588
Parkview Place, St Louis, MO 63110, USA
Tel +1 314 446 8522
Email anastasia.armbruster@stlcp.edu



Table 1 Comparison of target-specific oral anticoagulants

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Mechanism of action	Direct thrombin inhibitor	FXa inhibitor	FXa inhibitor	FXa inhibitor
FDA indications	AF, VTE Tx, VTE RR	AF, VTE Px, VTE Tx, VTE RR	AF, VTE Px, VTE Tx, VTE RR	AF, VTE Tx
Bioavailability	3%–7%	10 mg – 80%–100% 20 mg – 66%	50%	62%
Time to C _{max} (hours)	1–2	2–4	3–4	1–2
Protein binding	35%	92%–95%	87%	55%
Half-life (hours)	12–17	5–9	12	10–14
Renal elimination	80%	66%	27%	50%
Metabolism	P-gp	CYP3A4/5, CYP2J2, P-gp, ATP-binding cassette G2 transporters	CYP3A4, P-gp Minor contributions from CYP1A2, 2C8, 2C9, 2C19, and 2J2	P-gp
Dose adjustments	Dabigatran 75 mg bid AF: CrCl 30–50 mL/min with P-gp inhibitors or CrCl 15–30 mL/min	Rivaroxaban 15 mg daily AF: CrCl 15–50 mL/min	Apixaban 2.5 mg bid AF (two of the following): age ≥80 years, body weight ≤60 kg, or SCr ≥1.5 mg/dL	Edoxaban 30 mg daily AF: CrCl 15–50 mL/min; CrCl ≥95 mL/min, avoid use VTE: CrCl 15–50 mL/min, body weight ≤60 kg, or certain P-gp inhibitors
PK drug interactions	P-gp inducers Rifampin P-gp inhibitors Dronedarone Ketoconazole	Combined strong CYP3A4 and P-gp inhibitors Conivaptan Indinavir Itraconazole Ketoconazole Lopinavir/ritonavir Ritonavir Combined strong CYP3A4 and P-gp inducers Carbamazepine Phenytoin Rifampin St John's wort	Combined strong CYP3A4 and P-gp inhibitors Clarithromycin Itraconazole Ketoconazole Ritonavir Combined strong CYP3A4 and P-gp inducers Carbamazepine Phenytoin Rifampin St John's wort	P-gp inducers Rifampin P-gp inhibitors Dronedarone Quinidine Verapamil

Abbreviations: AF, prevention of stroke/systemic embolic event in NVAF; C_{max}, maximum concentration; CrCl, creatinine clearance; FDA, United States Food and Drug Administration; FXa, factor Xa; NVAF, nonvalvular atrial fibrillation; P-gp, P-glycoprotein; PK, pharmacokinetic; SCr, serum creatinine; VTE Px, venous thromboembolism prophylaxis; VTE RR, risk reduction of recurrent venous thromboembolism; VTE Tx, venous thromboembolism treatment.

In healthy adults, edoxaban exhibits dose-dependent and linear pharmacokinetic parameters.⁸ Edoxaban is rapidly absorbed (time of maximum observed plasma concentration of 1–2 hours) with a bioavailability of ~58.3%–61.8%.^{8–10} Edoxaban can be administered with or without food.¹¹ The half-life of edoxaban ranges from 5 to 11 hours.⁸ Edoxaban has 40%–59% plasma protein binding with a volume of distribution of 107 L at steady state.^{8,10} Edoxaban is eliminated through multiple elimination pathways, including renal excretion (35%–55%), biliary excretion, and metabolism.^{8,12}

Edoxaban coadministered with naproxen 500 mg or aspirin 100 or 325 mg demonstrates an additive effect on bleeding time. Edoxaban pharmacokinetics is not affected by naproxen or low-dose aspirin (100 mg); however, high-dose aspirin (325 mg) increases edoxaban bioavailability by 30%. Platelet aggregation is not altered when aspirin or naproxen are coadministered with edoxaban.¹³ Clinical studies included patients

receiving ≤100 mg of aspirin per day, thienopyridines, and nonsteroidal anti-inflammatory therapy. Due to increased rates of clinically relevant bleeding, long-term concomitant therapy with other anticoagulants is not recommended.⁴

Edoxaban is not extensively metabolized by CYP3A; however, edoxaban is a P-glycoprotein substrate. Edoxaban exposure, measured as area under the curve (AUC), is increased when coadministered with quinidine (76.7%), amiodarone (39.8%), verapamil (52.7%), and dronedarone (84.5%).¹⁴ There is also a significant increase in relative bioavailability and decrease in volume of distribution when edoxaban is administered with P-glycoprotein inhibitors (ketoconazole, verapamil, erythromycin, quinidine, and amiodarone).⁹ There is a nonsignificant increase in edoxaban exposure when coadministered with digoxin (9.5%) or atorvastatin (1.7%).¹⁴ Concomitant administration of digoxin and edoxaban does not result in clinically significant

changes in pharmacokinetics, pharmacodynamics, or renal elimination.¹⁵ Coadministration with rifampin should be avoided due to decreased edoxaban serum concentrations.⁴ Edoxaban has minimal effect on cardiac repolarization and does not exhibit clinically significant QTc prolongation and, therefore, it is not necessary to avoid medications that may prolong the QTc interval.¹⁶

Renal function, as estimated by creatinine clearance (CrCl) utilizing the Cockcroft–Gault equation, is the most significant factor influencing edoxaban disposition.¹⁷ A subset of patients from ENGAGE-AF, who were not dose-adjusted, had geometric mean predose edoxaban exposure levels that were 30% less in the normal renal function subgroup, compared to the mild renal impairment subgroup.¹⁸ Patients with low body weight (≤ 60 kg) have a higher incidence of bleeding that is approximately two times greater than patients >60 kg or patients randomized to warfarin.¹⁹

Venous thromboembolism

VTE has an approximate overall incidence of 70–113 cases per 100,000 patients per year. There is approximately a 7% incidence of recurrent VTE within 6 months after an initial acute VTE. The incidence of 30-day mortality after VTE is ~6% after a deep vein thrombosis (DVT) and increases to 12% after a pulmonary embolism (PE).²⁰ Standard treatment for acute VTE consists of parenteral anticoagulation with unfractionated heparin or low molecular weight heparin for a minimum of 5 days and until achievement of an INR greater than 2.0 on warfarin. The duration of anticoagulation is variable and patient-specific but generally consists of 3–12 months of treatment with a goal INR of 2.0–3.0.²¹

The initial 3 months of anticoagulation with warfarin, titrated to a goal INR of 2.0–3.0, has been associated with rates of recurrent VTE and major bleeding events of 6% and 3%, respectively.²² Major bleeding events and intracranial hemorrhage significantly contribute to the mortality of patients receiving anticoagulation for VTE. In a meta-analysis of anticoagulation for the treatment of VTE, warfarin was associated with an overall case-fatality rate due to major bleeding events of 13.4% and a rate of intracranial hemorrhage of 1.15 events per 100 patient-years.²³ Rates of major bleeding and intracranial hemorrhage appear to be greater during the first 3 months of anticoagulation.^{22,23} The TSOACs dabigatran, rivaroxaban, apixaban, and edoxaban have been evaluated in the treatment of acute VTE, including DVT and PE, and have consistently demonstrated comparable clinical efficacy to warfarin with a decreased risk of major bleeding events and intracranial hemorrhage (Table 2).^{24–28}

RE-COVER was a double-blind, noninferiority trial that randomized 2,564 patients with acute DVT (N=1,749) or PE (N=541) to 6 months of anticoagulation with dabigatran 150 mg oral bid or warfarin (goal INR 2.0–3.0).²⁵ Per study protocol, patients in both groups received at least 5 days of parenteral anticoagulation prior to dabigatran initiation or until achievement of a therapeutic INR. Patients assigned to warfarin had an INR in target therapeutic range (TTR) 60% of the time. Dabigatran was noninferior to warfarin for the prevention of symptomatic VTE or VTE-related death (hazard ratio [HR] 1.10, 95% confidence interval [CI] 0.65–1.84). Dabigatran had a significantly lower incidence of any bleeding event (HR 0.71, 95% CI 0.59–0.85; $P<0.001$ for superiority; number needed to treat [NNT] 18) and major or clinically relevant nonmajor bleeding events (HR 0.63,

Table 2 Comparison of outcomes of acute treatment in VTE trials

Trial	RE-COVER ²⁵	EINSTEIN-DVT ²⁶	EINSTEIN-PE ²⁷	AMPLIFY ²⁸	Hokusai-VTE ²⁴
Intervention	Parenteral anticoagulation ≥ 5 days followed by dabigatran 150 mg bid ^a	Rivaroxaban 15 mg bid $\times 3$ weeks, followed by 20 mg daily	Rivaroxaban 15 mg bid $\times 3$ weeks, followed by 20 mg daily	Apixaban 10 mg bid $\times 7$ days, followed by 5 mg bid	Parenteral anticoagulation ≥ 5 days followed by edoxaban 60 mg daily ^a
Comparator	Warfarin, target INR 2.0–3.0	Warfarin, target INR 2.0–3.0	Warfarin, target INR 2.0–3.0	Warfarin, target INR 2.0–3.0	Warfarin, target INR 2.0–3.0
Mean TTR, %	59.9	57.7	62.7	61	63.5
Mean INR <2.0 , %	21	24.4	21.8	23	18.9
Mean INR >3.0 , %	19	16.2	15.5	16	17.6
Recurrent VTE or VTE-related death	Noninferior	Noninferior	Noninferior	Noninferior	Noninferior
Major or clinically relevant nonmajor bleeding, NNT	32	NS	NS	19	56
Major bleeding, NNT	NS	NS	91	84	NS

Note: ^aParenteral anticoagulants included treatment doses of unfractionated heparin or enoxaparin.

Abbreviations: INR, international normalized ratio; NNT, number needed to treat; NS, nonsignificant; TTR, time in therapeutic range; VTE, venous thromboembolism.

95% CI 0.47–0.84; $P=0.002$ for superiority; NNT 32). No significant difference between treatments was demonstrated for the incidence of major bleeding (HR 0.82, 95% CI 0.45–1.48; $P=0.38$ for superiority). However, gastrointestinal (GI) bleeding tended to occur more frequently with dabigatran compared to warfarin ($N=53$ vs $N=35$, respectively), and dabigatran had a significantly higher incidence of dyspepsia (2.9% vs 0.6%; $P<0.001$).

The EINSTEIN-DVT and EINSTEIN-PE trials were double-blind, randomized, noninferiority studies that compared rivaroxaban 15 mg oral bid for 3 weeks followed by 20 mg oral daily and/or treatment with warfarin (goal INR 2.0–3.0) for the acute treatment of DVT ($N=3,449$) and PE ($N=4,833$), respectively.^{26,27} Patients assigned to warfarin received parenteral anticoagulation with enoxaparin 1 mg/kg subcutaneously every 12 hours for at least 5 days and until attainment of a therapeutic INR on two consecutive days. Patients were randomized to receive 3, 6, or 12 months of anticoagulation. Patients assigned to the warfarin group had an INR in TTR 57.7% and 62.7% of the time in the DVT and PE studies, respectively. In EINSTEIN-DVT, rivaroxaban was noninferior to warfarin for the prevention of symptomatic DVT and nonfatal or fatal PE (HR 0.68, 95% CI 0.44–1.04; $P<0.001$ for noninferiority) and demonstrated no significant differences in the incidence of major or clinically relevant nonmajor bleeding (HR 0.97, 95% CI 0.76–1.22; $P=0.77$ for superiority) and major bleeding (HR 0.65, 95% CI 0.33–1.30; $P=0.21$ for superiority).²⁶ Rivaroxaban demonstrated similar efficacy for the acute treatment of PE, as it was noninferior to warfarin for the prevention of fatal or nonfatal PE or DVT (HR 1.12, 95% CI 0.75–1.68, $P=0.003$ for noninferiority). Although rivaroxaban demonstrated no significant difference compared to warfarin for the incidence of the composite of major or clinically relevant nonmajor bleeding (HR 0.90, 95% CI 0.76–1.07; $P=0.23$ for superiority) in EINSTEIN-PE, patients treated with rivaroxaban had a significantly lower incidence of any major bleed (HR 0.49, 95% CI 0.31–0.79; $P=0.003$ for superiority; NNT 91).²⁷

The Apixaban for the Initial Management of Pulmonary Embolism and Deep-Vein Thrombosis as First-Line Therapy (AMPLIFY) trial was a double-blind, noninferiority study that randomized 5,395 patients to apixaban or warfarin for the treatment of acute DVT ($N=3,532$) or PE ($N=1,359$).²⁸ Patients received apixaban 10 mg oral bid for 7 days followed by 5 mg oral bid or warfarin (goal INR 2.0–3.0) for 6 months. Parenteral anticoagulation with enoxaparin 1 mg/kg subcutaneously every 12 hours was administered to patients assigned to warfarin for at least 5 days and until

attainment of a therapeutic INR. Patients in the warfarin group had an INR in TTR 61% of the time. Apixaban was noninferior to warfarin for the prevention of symptomatic VTE or VTE-related death (HR 0.84, 95% CI 0.60–1.18; $P<0.001$ for noninferiority). Apixaban had a lower incidence of major bleeding (HR 0.31, 95% CI 0.17–0.55; $P<0.001$ for superiority; NNT 84), clinically relevant nonmajor bleeding (HR 0.48, 95% CI 0.38–0.60; NNT 24), and the composite endpoint of major bleeding or clinically relevant nonmajor bleeding (HR 0.44, 95% CI 0.36–0.55; $P<0.001$ for superiority; NNT 19).

Hokusai-VTE was a randomized, double-blind, noninferiority study that compared edoxaban and warfarin, adjusted to a goal INR of 2.0–3.0, for the treatment of acute DVT or PE.²⁴ All patients received at least 5 days of anticoagulation with enoxaparin or unfractionated heparin prior to the initiation of edoxaban at a dose of 60 mg oral daily. The dose of edoxaban was decreased to 30 mg oral daily for a calculated CrCl of 30–50 mL/minute, body weight ≤ 60 kg, or concomitant therapy with the strong P-gp inhibitors verapamil or quinidine. Of the 8,240 patients who received study treatment, 3,319 patients were enrolled with a qualifying indication of PE. Patients treated with warfarin had a documented INR in TTR 63.5% of the time. Edoxaban was noninferior to warfarin for the prevention of the primary, composite outcome of recurrent VTE or VTE-related death (HR 0.89, 95% CI 0.70–1.13; $P<0.001$ for noninferiority). Edoxaban was superior to warfarin with a lower incidence of the primary, composite safety outcome of a first major or clinically relevant nonmajor bleeding event (HR 0.81, 95% CI 0.71–0.94; $P=0.004$ for superiority; NNT 56). The difference in the composite safety outcome was primarily due to a significantly lower incidence of clinically relevant nonmajor bleeding events (HR 0.80, 95% CI 0.68–0.93; $P=0.004$ for superiority; NNT 59) in the edoxaban group. Edoxaban also demonstrated a significantly lower incidence of any bleeding event (HR 0.82, 95% CI 0.75–0.90; $P<0.001$ for superiority; NNT 26) in comparison to warfarin. The efficacy and safety of edoxaban were maintained in patients who qualified for a reduced dose of edoxaban 30 mg oral daily, but this analysis is limited by a smaller sample of patients ($N=733$) who received the lower dose during the study.

No studies have directly compared the TSOACs for the treatment of acute VTE. In comparison to warfarin, the TSOACs have demonstrated remarkable consistency for clinical efficacy and safety.^{24–28} A meta-analysis of the five randomized trials of TSOACs in VTE demonstrated a non-significantly lower rate of recurrent VTE (relative risk [RR]

0.88, 95% CI 0.74–1.05) and a significantly lower rate of major bleeding (RR 0.60, 95% CI 0.41–0.88) corresponding to an NNT to prevent one major bleeding event of 149 for the TSOACs compared to warfarin. The incidence of major GI bleeding, however, was not significantly lower for treatment with TSOACs (RR 0.68, 95% CI 0.36–1.30).²⁹ The lack of a significant reduction in the collective risk of major GI bleeding with the TSOACs is due to the greater risk of GI bleeding observed with dabigatran.²⁵ Rivaroxaban and apixaban were not associated with an increased risk of GI bleeding when compared to warfarin, and Hokusai-VTE did not report the incidence of this safety endpoint for edoxaban.^{24,26–28}

Each TSOAC is noninferior for the prevention of recurrent VTE compared to warfarin (goal INR 2.0–3.0), and it can be presumed that edoxaban has comparable efficacy and safety based on these results.^{24–28} Differences in the study populations and safety outcomes may compel providers to choose one TSOAC over another for the treatment of acute VTE. Edoxaban (N=3,319) and rivaroxaban (N=4,832) have been studied more robustly for the treatment of acute PE than apixaban (N=1,836) or dabigatran (N=789). Therefore, despite each TSOAC demonstrating noninferiority for the treatment of acute VTE, the data to support TSOAC treatment for an acute PE are stronger for edoxaban and rivaroxaban than apixaban or dabigatran.

Safety data directly comparing the TSOACs do not exist, which precludes a definitive assertion of the comparative effects of individual TSOACs on bleeding outcomes. The composite outcome of major bleeding or clinically relevant nonmajor bleeding was significantly lower during treatment with dabigatran (NNT 32), apixaban (NNT 19), and edoxaban (NNT 56), while no difference was observed between rivaroxaban and warfarin for the same bleeding outcomes.^{24–28} Dabigatran (NNT 18) and edoxaban (NNT 26) also significantly decreased the incidence of any bleeding event.^{24,25} Both apixaban (NNT 84) and rivaroxaban, when analyzed in EINSTEIN-PE (NNT 91), demonstrated a decreased risk of major bleeding events, but edoxaban failed to significantly decrease the incidence of this safety endpoint.^{24,27,28} The effect of individual TSOACs on bleeding outcomes during the treatment of acute VTE is variable and, at this time, it is not possible to provide a definitive recommendation among the TSOACs on bleeding data alone.

Edoxaban is a noninferior alternative to warfarin, titrated to a goal INR of 2.0–3.0, for the acute treatment of DVT or PE.²⁴ Edoxaban appears to have comparable efficacy for the management of VTE compared to dabigatran, rivaroxaban, or apixaban, and it is the only TSOAC dosed

once daily for the entire duration of therapy. A minimum of 5 days of parenteral anticoagulation is required prior to the initiation of edoxaban for the acute treatment of VTE, a stipulation not required of rivaroxaban or apixaban.^{24,26–28} Dosage adjustments are required for renal impairment (CrCl 15–50 mL/min), low body weight (≤ 60 kg), and concomitant use of P-glycoprotein inhibitors. However, unlike its indication in atrial fibrillation, edoxaban may still be used for patients with a calculated CrCl greater than 95 mL/min.⁴

Prevention of SSE

Atrial fibrillation is the most common cardiac arrhythmia and the prevalence increases with age. It is anticipated that by 2030 the prevalence in the US will reach 12.1 million.³⁰ Prior to 2010, warfarin represented the only oral anticoagulant to reduce the risk of stroke in patients with atrial fibrillation. Four TSOACs have been developed and address many difficulties present with warfarin, including variable dosing, food and drug interactions, long onset of action, and routine monitoring. Reported prescribing rates of warfarin have indicated underutilization in patients at risk for stroke.³¹

Current guidelines recommend oral anticoagulation for patients with NVAF with prior stroke, transient ischemic attack, or CHA₂DS₂-VASc score of 2 or greater. Published in 2014, the guidelines address warfarin in addition to three of the four TSOACs currently on the market. Warfarin, dose-adjusted to an INR of 2.0–3.0, is the only agent with a level IA recommendation. Dabigatran, rivaroxaban, and apixaban are equally recommended with level IB recommendations. Edoxaban was FDA-approved after current guidelines were published.^{4,32}

All four TSOACs were evaluated in large, randomized controlled trials in patients with a mean annual stroke risk of at least 4.0% (Table 3).^{34–37} TSOACs have been compared to warfarin in four landmark trials, including over 71,000 patients to assess the reduction in SSE secondary to NVAF. All four TSOACs currently on the market have demonstrated at least noninferiority to warfarin and with the exception of GI bleeding, lower rates of bleeding. In a recent meta-analysis, TSOACs reduced events by 19% compared with warfarin (RR 0.81, 95% CI 0.73–0.91; $P < 0.0001$), mainly driven by a statistically significant reduction in hemorrhagic stroke.³⁸

Dabigatran was the first TSOAC approved to prevent SSE. The Randomized Evaluation of Long-term Anticoagulation Therapy (RE-LY) trial evaluated 18,113 patients with a mean CHADS₂ score of 2.1.³⁵ Patients were assigned to dabigatran 110 or 150 mg bid compared to open-label warfarin with a goal INR of 2–3. Patients were followed for

Table 3 Reduction in the risk of stroke and systemic embolism secondary to atrial fibrillation

Trial	RE-LY ³⁵	ROCKET-AF ³⁶	ARISTOTLE ³⁷	ENGAGE AF-TIMI 48 ³⁴
Intervention	Dabigatran 150 mg bid or dabigatran 110 mg bid	Rivaroxaban 20 mg daily	Apixaban 5 mg bid	Edoxaban 60 mg daily or edoxaban 30 mg daily
Comparator	Warfarin, target INR 2.0–3.0	Warfarin, target INR 2.0–3.0	Warfarin, target INR 2.0–3.0	Warfarin, target INR 2.0–3.0
Median TTR, %	64	55	62.2	68.4
Mean CHADS ₂ score	2.1	3.5	2.1	2.8
CHADS ₂ 0–1, %	32	0	34	<1
CHADS ₂ 2, %	35	13	36	46
CHADS ₂ 3–6, %	33	87	30	54
Reduction in SEE, NNT	172	NS	303	NS
Major bleeding, NNT	NS	NS	104	147

Abbreviations: INR, international normalized ratio; NNT, number needed to treat; NS, nonsignificant; SEE, systemic embolic event; TTR, time in therapeutic range.

a median of 2 years. Dabigatran 150 mg was superior in efficacy for reduction of SSE (1.11% vs 1.69%) (RR 0.66; 95% CI 0.53–0.82; $P<0.001$; NNT 172). Major bleeding was not statistically significantly different (3.11% vs 3.37%); however, hemorrhagic stroke was significantly reduced in both dabigatran groups compared to warfarin. Dabigatran 150 mg resulted in statistically significant higher GI bleeding compared to warfarin (RR 1.50, 95% CI 1.19–1.89; $P<0.001$).³⁵ This has been confirmed in postmarketing surveillance and is a consideration when selecting anticoagulation therapy.³⁹

Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation (ROCKET-AF) randomized 14,264 patients with a mean CHADS₂ score of 3.5 (a score of at least 2 was required for inclusion).³⁶ The treatment group received rivaroxaban 20 mg daily compared to dose-adjusted warfarin (goal INR 2.0–3.0). Patients with a CrCl of 30–49 mL/min received a dose reduction to 15 mg. Median follow-up was 23 months. Rivaroxaban demonstrated noninferiority to warfarin in the reduction of SSE (1.7% vs 2.2%) (HR 0.79, 95% CI 0.66–0.96; $P<0.001$). There was no statistically significant difference in major and nonmajor clinically relevant bleeding. Similar to dabigatran, a significant reduction was seen in the rate of intracranial bleeding.

Apixaban versus Warfarin in Patients with Atrial Fibrillation (ARISTOTLE) randomized 18,201 patients with a CHADS₂ score of at least 1, resulting in a mean CHADS₂ score of 2.1.³⁷ Apixaban 5 mg bid, or 2.5 mg for selected patients, was compared to dose-adjusted warfarin. Patients were followed for a median of 22 months. Apixaban was superior to warfarin for the reduction of SSE (1.27% vs 1.60%) (HR 0.69, 95% CI 0.60–0.80; $P<0.01$; NNT 303). All bleeding endpoints were significantly lower in the apixaban group. A significant reduction in mortality was also noted for those patients receiving apixaban (3.52% vs 3.94%) (HR 0.89, 95% CI 0.80–0.99; $P=0.047$).

The Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction 48 (ENGAGE AF-TIMI 48) trial randomized 21,105 patients to warfarin or high- or low-dose edoxaban.³⁴ This was a randomized, double-blind, double-dummy trial conducted in 46 different countries. The primary efficacy endpoint was time to first adjudicated stroke, including hemorrhagic stroke, or systemic embolic event and the principal safety endpoint was major bleeding. Enrolled patients had NVAF confirmed within the previous 12 months and a CHADS₂ score of at least 2 at randomization. The high-dose edoxaban group received 60 mg daily, and the low-dose group 30 mg daily. Doses were adjusted by half for any of the following characteristics: CrCl of 30–50 mL/min, a body weight ≤ 60 kg, or concomitant use of verapamil or quinidine. Warfarin patients were dose-adjusted to an INR of 2.0–3.0. The modified intention-to-treat analysis demonstrated noninferiority regarding reduction of SSE for edoxaban 60 mg daily (1.18%) and warfarin (1.50%) (HR 0.79, 95% CI 0.63–0.99; $P<0.001$ for noninferiority). A statistically significant reduction was not demonstrated in the low-dose edoxaban group. Neither group showed a significant reduction in stroke or systemic embolic event (SEE) in the prespecified intention-to-treat superiority analysis. Major bleeding was statistically significantly less in both high- (2.75% vs 3.43%) (HR 0.80, 95% CI 0.71–0.91; $P<0.001$) and low-dose (1.61% vs 3.43%) (HR 0.47, 95% CI 0.41–0.55; $P<0.001$) edoxaban groups compared with warfarin. Risk of major GI bleeding was increased in the high-dose group compared to warfarin (1.51% vs 1.23%) (HR 1.23, 95% CI 1.02–1.50; $P=0.03$).

In a subgroup analysis, a Cox proportional hazard model examined the effect of CrCl on the risk of stroke and SEE. Patients with a CrCl >95 mL/min and treated with warfarin had a lower probability of experiencing a stroke or SEE

(HR 1.02, 95% CI 0.76–1.38). Based on these findings of reduced efficacy, edoxaban has a US Boxed Warning prohibiting use in patients with NVAF and CrCl >95 mL/min.^{4,18}

When selecting oral anticoagulation for patients with NVAF, there are several factors to consider. Currently, no head-to-head trials exist between TSOACs for the reduction in SSE secondary to NVAF; however, general comparisons can be made based on available primary literature. In regard to efficacy, dabigatran and apixaban were able to demonstrate superiority, while rivaroxaban and edoxaban demonstrated noninferiority.^{34–37} Regarding major bleeding risk, dabigatran and rivaroxaban were found to be noninferior to warfarin, while apixaban and edoxaban demonstrated a lower major bleeding risk. GI bleeding was increased compared to warfarin for all agents, except apixaban where no difference was observed in the rate of GI bleeding.

Stroke risk of the study population, as estimated by the CHADS₂ score, provides an estimate of baseline stroke risk.³³ Mean CHADS₂ scores have ranged from 2.1 in the RE-LY trial to 3.5 in ROCKET-AF. Edoxaban patients had a higher stroke risk than those of dabigatran and apixaban. The majority of patients had a CHADS₂ score of at least 3, correlating with an annual stroke risk of at least 5.9%.

Assessing the efficacy of comparator treatment is essential when evaluating TSOACs. For warfarin, the TTR provides a way to compare how well warfarin was managed in the trial. Edoxaban had the highest TTR, 68.4%, compared to other landmark atrial fibrillation trials in which the TTR ranged from 55% to 64%.^{35–37} The INR was between 1.8 and 3.2 for 83.1% of the treatment period, representing an excellent comparator group.³⁴ This statistic was not reported in other studies.

Safety and tolerability

An FDA-approved reversal agent is currently not available; however, several medications are currently in development for the reversal of edoxaban and other TSOACs.^{40–42} Protamine sulfate, vitamin K, and tranexamic acid are not expected to reverse the anticoagulant activity of edoxaban.⁴ Dialysis is not a viable option for reversal as it resulted in only minor decreases in AUC and mean maximum observed plasma concentration values after administration of a single 15 mg dose of edoxaban.⁴³ However, 4-factor prothrombin complex concentrate causes dose-dependent reversal of edoxaban's anticoagulation effect. Complete reversal was achieved with prothrombin complex concentrate 50 IU/kg in regard to bleeding duration, bleeding volume, and endogenous thrombin potential. A complete reversal was not noted for prothrombin time.⁴⁴

Conclusion

All four TSOACs represent favorable characteristics compared to warfarin. Predictable pharmacological profiles negate the need for frequent dose adjustments and monitoring. Rapid onset and offset of action eliminate the need for bridging, which is especially advantageous in the setting of NVAF where clinical necessity is not clear. Reduced food and drug interactions are also advantages for all four agents. When selecting a TSOAC for the treatment of VTE or NVAF, numerous factors, such as drug interactions, renal function, body weight, and patient preference, must all carefully be considered. Based on its favorable safety and efficacy data, edoxaban offers an additional option to consider when selecting an agent for anticoagulation.

Acknowledgment

No financial support was provided for this study.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Gatterlari M, Worthington J, Zwar N, et al. Barriers to the use of anticoagulation for nonvalvular atrial fibrillation: a representative survey of Australian family physicians. *Stroke*. 2008;39:227–230.
2. Pradaxa (dabigatran etexilate mesylate) capsules [prescribing information]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc; 2015.
3. Eliquis (apixaban) tablets [prescribing information]. Princeton, NJ: Bristol-Myers Squibb Company; 2015.
4. Savaysa (edoxaban) tablets [prescribing information]. Parsippany, NJ: Daiichi Sankyo, Inc; 2015.
5. Xarelto (rivaroxaban) tablets [prescribing information]. Titusville, NJ: Janssen Pharmaceuticals, Inc; 2015.
6. Zafar MU, Vorchheimer DA, Gaztanaga J, et al. Antithrombotic effects of factor Xa inhibition with DU-176b: Phase-I study of an oral, direct factor Xa inhibitor using an ex-vivo flow chamber. *Thromb Haemost*. 2007;98(4):883–888.
7. Furugohri T, Isobe K, Honda Y, et al. DU-176b, a potent and orally active factor Xa inhibitor: in vitro and in vivo pharmacological profiles. *J Thromb Haemost*. 2008;6(9):1542–1549.
8. Ogata K, Mendell-Harary J, Tachibana M, et al. Clinical safety, tolerability, pharmacokinetics, and pharmacodynamics of the novel factor Xa inhibitor edoxaban in healthy volunteers. *J Clin Pharmacol*. 2010;50(7):743–753.
9. Yin OQ, Tetsuya K, Miller R. Edoxaban population pharmacokinetics and exposure-response analysis in patients with non-valvular atrial fibrillation. *Eur J Clin Pharmacol*. 2014;70(11):1339–1351.
10. Matsushima N, Lee F, Sato T, Weiss D, Mendell J. Bioavailability and safety of the factor Xa inhibitor edoxaban and the effects of quinidine in healthy subjects. *Clin Pharm Drug Dev*. 2013;2:358–366.
11. Mendell J, Tachibana M, Shi M, Kunitada S. Effects of food on the pharmacokinetics of edoxaban, an oral direct factor Xa inhibitor, in healthy volunteers. *J Clin Pharmacol*. 2011;51(5):687–694.
12. Bathala MS, Masumoto H, Oguma T, He L, Lowrie C, Mendell J. Pharmacokinetics, biotransformation, and mass balance of edoxaban, a selective, direct factor Xa inhibitor, in humans. *Drug Metab Dispos*. 2012;40(12):2250–2255.

13. Mendell J, Lee F, Chen S, Worland V, Shi M, Samama MM. The effects of the antiplatelet agents, aspirin and naproxen, on pharmacokinetics and pharmacodynamics of the anticoagulant edoxaban, a direct factor Xa inhibitor. *J Cardiovasc Pharmacol*. 2013;62(2):212–221.
14. Mendell J, Zahir H, Matsushima N, et al. Drug-drug interaction studies of cardiovascular drugs involving P-glycoprotein, an efflux transporter, on the pharmacokinetics of edoxaban, an oral factor Xa inhibitor. *Am J Cardiovasc Drugs*. 2013;13(5):331–342.
15. Mendell J, Noveck RJ, Shi M. Pharmacokinetics of the direct factor Xa inhibitor edoxaban and digoxin administered alone and in combination. *J Cardiovasc Pharmacol*. 2012;60(4):335–341.
16. Mendell J, Basavapathruni R, Swearingen D, Draves A, Zhang G, Morganroth J. A thorough electrocardiogram study of edoxaban, a novel factor Xa inhibitor. *J Clin Pharmacol*. 2011;51(8):1241–1246.
17. Salazar DE, Mendell J, Kastrissios H, et al. Modelling and simulation of edoxaban exposure and response relationships in patients with atrial fibrillation. *Thromb Haemost*. 2012;107(5):925–936.
18. FDA Draft Briefing Document for the Cardiovascular and Renal Drugs Advisory Committee. ENGAGE AF-TIMI 48; 2014. Available from: <http://www.fda.gov/downloads/AdvisoryCommittees/Committees-MeetingMaterials/Drugs/CardiovascularandRenalDrugsAdvisoryCommittee/UCM420704.pdf>. Accessed March 7, 2016.
19. Yamashita T, Koretsune Y, Yasaka M, et al. Randomized, multicenter, warfarin controlled phase II study of edoxaban in Japanese patients with non-valvular atrial fibrillation. *Circ J*. 2012;76(8):1840–1847.
20. White RH. The epidemiology of venous thromboembolism. *Circulation*. 2003;107(Suppl 1):I-4–I-8.
21. Kearon C, Akl EA, Comerota AJ, et al. Antithrombotic therapy for VTE disease: Antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2012;141(Suppl):e419S–e494S.
22. Douketis JD, Foster GA, Crowther MA, Prins MH, Ginsberg JS. Clinical risk factors and timing of recurrent venous thromboembolism during the initial 3 months of anticoagulant therapy. *Arch Intern Med*. 2000;160:3431–3436.
23. Linkins LA, Choi PT, Douketis JD. Clinical impact of bleeding in patients taking oral anticoagulant therapy for venous thromboembolism: a meta-analysis. *Ann Intern Med*. 2003;139:893–900.
24. Hokusai-VTE Investigators, Büller HR, Décousus H, et al. Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism. *N Engl J Med*. 2013;369:1406–1415.
25. Schulman S, Kearon C, Kakkar AK, et al. Dabigatran versus warfarin in the treatment of acute venous thromboembolism. *N Engl J Med*. 2009;361:2342–2352.
26. EINSTEIN Investigators, Bauersachs R, Berkowitz SD, et al. Oral rivaroxaban for symptomatic venous thromboembolism. *N Engl J Med*. 2010;363:2499–2510.
27. EINSTEIN-PE Investigators, Büller HR, Prins MH, et al. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. *N Engl J Med*. 2012;366:1287–1297.
28. Agnelli G, Büller HR, Cohen A, et al. Oral apixaban for the treatment of acute venous thromboembolism. *N Engl J Med*. 2013;369:799–808.
29. Van der Hulle T, Kooiman J, den Exter PL, Dekkers OM, Klok FA, Huisman MV. Effectiveness and safety of novel oral anticoagulants as compared with vitamin K antagonists in the treatment of acute symptomatic venous thromboembolism: a systematic review and meta-analysis. *J Thromb Haemost*. 2014;12:320–328.
30. Colilla S, Crow A, Petkun W, Singer DE, Simon T, Liu X. Estimates of current and future incidence and prevalence of atrial fibrillation in the U.S. adult population. *Am J Cardiol*. 2013;112:1142–1147.
31. Birman-Deych E, Radford MJ, Nilasena DS, Gage BF. Use and effectiveness of warfarin in Medicare beneficiaries with atrial fibrillation. *Stroke*. 2006;37:1070–1074.
32. January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: Executive summary: A report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the Heart Rhythm Society. *Circulation*. 2014;130:2071–2104.
33. Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. *JAMA*. 2001;285:2864–2870.
34. Giugliano R, Ruff CT, Braunwald E, et al. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2013;369:2093–2104.
35. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2009;361(12):1139–1151.
36. Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med*. 2011;365(10):883–891.
37. Granger CB, Alexander JH, McMurray JJ, et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2011;365(11):981–992.
38. Ruff CT, Giugliano RP, Braunwald E, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. *Lancet*. 2014;383:955–962.
39. US Food and Drug Administration. FDA Drug Safety Communication: FDA study of Medicare patients finds risks lower for stroke and death but higher for gastrointestinal bleeding with Pradaxa (dabigatran) compared to warfarin; 2014. Available from: www.fda.gov/Drugs/DrugSafety/ucm396470.htm. Accessed November 19, 2015.
40. Gold AM, Crowther M, Levy G, et al. ANNEXA-R: a phase 3 randomized, double-blind, placebo-controlled trial, demonstrating reversal of rivaroxaban-induced anticoagulation in older subjects by andexanet alfa (PRT064445), a universal antidote for factor Xa (FXa) inhibitors. *J Am Coll Cardiol*. 2015;65:10S.
41. Siegal DM, Curnutte JT, Connolly SJ, et al. Andexanet alfa for the reversal of factor Xa inhibitor activity. *N Engl J Med*. 2015;373(25):2413–2424.
42. Ansell JE, Bakhrin SH, Laulicht BE, et al. Use of PER977 to reverse the anticoagulant effect of edoxaban. *N Engl J Med*. 2014;371(22):2141–2142.
43. Parasrampur DA, Marbury T, Matsushima N, et al. Pharmacokinetics, safety, and tolerability of edoxaban in end-stage renal disease subjects undergoing haemodialysis. *Thromb Haemost*. 2015;113(4):719–727.
44. Zahir H, Brown KS, Vandell AG, et al. Edoxaban effects on bleeding following punch biopsy and reversal by a 4-factor prothrombin complex concentrate. *Circulation*. 2015;131:82–90.

Therapeutics and Clinical Risk Management

Publish your work in this journal

Therapeutics and Clinical Risk Management is an international, peer-reviewed journal of clinical therapeutics and risk management, focusing on concise rapid reporting of clinical studies in all therapeutic areas, outcomes, safety, and programs for the effective, safe, and sustained use of medicines. This journal is indexed on PubMed Central, CAS,

Submit your manuscript here: <http://www.dovepress.com/therapeutics-and-clinical-risk-management-journal>

Dovepress

EMBASE, Scopus and the Elsevier Bibliographic databases. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.