Factor Xa inhibitors: a novel therapeutic class for the treatment of nonvalvular atrial fibrillation

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***Abstract*:** Atrial fibrillation is the most common cause of stroke. Treatment with anticoagulants in patients with atrial fibrillation reduces embolic complications of the disease including stroke. However, the commonly used anticoagulant has a narrow therapeutic index, requires routine monitoring, and has numerous drug and food interactions leading to less than optimal rates of adherence. Inhibition of clotting factor Xa has been evaluated as a potential target for anticoagulation therapy with the hypothesis that using target-specific therapy will alleviate some of the dosing variability observed with the vitamin K antagonist. Three factor Xa inhibitors are currently indicated for use in nonvalvular atrial fibrillation. Similar to the vitamin K antagonist, warfarin, all of the factor Xa inhibitors are administered orally. Rivaroxaban and edoxaban are dosed once daily while apixaban is dosed twice daily. All three agents have demonstrated noninferiority when compared with current standard treatment with warfarin for efficacy and safety outcomes. The therapeutic dose of factor Xa inhibitors vary based on renal function. Unlike warfarin, there are no currently available antidotes for the factor Xa inhibitors although this is an area of interest for current and future studies. In the event of a life-threatening bleed there are established management strategies to reverse the bleeding effects of the factor Xa inhibitors.

Keywords: anticoagulation, apixaban, edoxaban, factor Xa inhibitor, nonvalvular atrial fibrillation, rivaroxaban, warfarin

Introduction

Atrial fibrillation is the most common cardiac arrhythmia [Mani and Lindhoff-Last, 2014]. It is estimated to affect 0.5–1% of the total population; however, its prevalence increases to 3.7–4.2% for individuals 60–70 years old and to 10–17% in those over 80 years of age [Zoni-Berisso *et al.* 2014]. Stroke occurs in 9–16% of patients with atrial fibrillation and the risk of stroke is five times higher in persons with atrial fibrillation compared with the general population [Zoni-Berisso *et al.* 2014]. Thromboembolic and stroke risk reduction is achieved through the use of anticoagulants. Historically, determination of the need for anticoagulation was done through calculation of a $CHADS_2$ score which estimates stroke risk based on the presence of congestive heart failure, hypertension, age greater than 75, diabetes, and stroke. Each risk factor was awarded one point with the exception of previous stroke, which was worth two points [January *et al.* 2014]. Currently, a new scoring system, CHA_2DS_2-VASc (congestive heart failure, hypertension, age ⩾75 years, diabetes mellitus, stroke, vascular disease, age 65–74 years, sex category), is utilized by the guidelines to quantify stroke risk and subsequent need for anticoagulation. This newer scoring system includes more risk factors associated with stroke than the previously used $CHADS_2$ score thereby identifying a greater number of individuals with an increased risk for stroke development [Camm *et al.* 2012; January *et al.* 2014]. Currently published clinical trials more commonly site $CHADS_2$ in the study protocols [Patel *et al.* 2011; Connolly *et al.* 2011; Granger *et al.* 2011; Giugliano *et al.* 2013]. A score of one or more on either the $CHADS_2$ or CHA_2DS_2-VASc is indicative of anticoagulation need [January *et al.* 2014; Camm *et al.* 2012].

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Warfarin has been widely used as an oral anticoagulant since its approval in 1954 [Bristol-Myers Squibb Company, 2011]. Despite dosing variability, numerous drug and food interactions, and required routine monitoring, warfarin has been the standard of care for systemic thromboembolism and cardioembolic stroke prevention and treatment [Turpie, 2007]. However, a study looking at the prescribing patterns of anticoagulants in Ontario, Canada, reports a greater than 20-fold increase in the prescribing of the non-vitamin K antagonist (non-VKA) anticoagulants over a 24-month period [Xu *et al.* 2013].

Over the past decade, investigators have researched alternative targets in the clotting cascade in attempts to create a safe, efficacious, and less-burdensome alternative to warfarin. The first successful medication approved targeted thrombin in the clotting cascade. Concerns over thrombin's other physiologic properties led investigators to seek out other targets that would more specifically affect coagulation alone. This drove the discovery of the factor Xa (FXa) inhibitors [Turpie, 2007]. A comparison of warfarin and the three available FXa inhibitors is highlighted in Table 1. This manuscript will review the efficacy and safety of the FXa inhibitors for use in patients with nonvalvular atrial fibrillation.

Factor Xa inhibitor therapeutic class

Indications

The FXa inhibitors have several approved indications for use including stroke or systemic embolism risk reduction in patients with nonvalvular atrial fibrillation, treatment and reduction of recurrent deep vein thrombosis and pulmonary embolism, and venous thromboembolism (VTE) prophylaxis following knee or hip replacement surgery [Janssen Pharmaceuticals Inc., 2011; Bristol-Myers Squibb Company, 2012; Daiichi Sankyo Co. Ltd, 2015]. This manuscript will focus primarily on the indication for stroke and systemic thromboembolism in nonvalvular atrial fibrillation. The FXa inhibitors' landmark clinical trials leading to their approval for nonvalvular atrial fibrillation are summarized in Table 2. The class of FXa inhibitors is also under current investigation for use in VTE prophylaxis following abdominal surgery, cardioversion for atrial fibrillation, and acute coronary syndrome.

Pharmacology

The FXa inhibitors have a unique mechanism of action compared with the VKA historically used for oral anticoagulation. FXa is common to both the intrinsic and extrinsic pathways of the clotting cascade making it an excellent target for anticoagulation therapy. It plays a significant role in the formation of thrombin from prothrombin. A single molecule of Xa leads to the creation of 1000 molecules of thrombin. Inhibition of Xa leads to a significant reduction in thrombin and ultimately clot formation [Turpie, 2007].

Contraindications/precautions

All of the currently available FXa inhibitors are contraindicated for use in patients experiencing active bleeding. In addition, they all carry United States (US) Black Boxed Warnings for premature discontinuation and spinal/epidural hematomas. The risk for ischemic events increases when FXa inhibitors are discontinued without an adequate alternative oral or parenteral anticoagulant in place. There is also a risk for the development of spinal/epidural hematomas when FXa inhibitors are used in patients undergoing spinal procedures including neuroaxial anesthesia and spinal puncture [Janssen Pharmaceuticals Inc., 2011; Bristol-Myers Squibb Company, 2012; Daiichi Sankyo Co. Ltd, 2015].

Adverse events and reversal protocols

All of the FXa inhibitors carry similar warnings primarily focused on an increased risk of bleeding. The most serious bleeding event associated with anticoagulation use is intracranial hemorrhage (ICH) due to the high rates of disability and death seen with this specific type of bleed. Patients with atrial fibrillation should have an assessment of their bleeding risk using the HAS-BLED [hypertension, abnormal renal/liver function, stoke, bleeding history or predisposition, labile international normalized ratio (INR), elderly, drugs/alcohol concomitantly] risk score. A high bleeding risk patient is identified by a score of greater than or equal to 3 on the HAS-BLED scale and should receive regular review for bleeding risk factors and active bleeding events [Camm *et al.* 2012].

There are no currently approved antidotes for use in reversal of FXa inhibitors. Due to the short half-lives of the FXa inhibitors, the first step in

Table 1. Comparison of vitamin K antagonist and factor Xa inhibitors.

		Warfarin (Coumadin)*	Rivaroxaban (Xarelto)**	Apixaban (Eliquis)+	Edoxaban (Savaysa)++
Mechanism of action		Vitamin K antagonist	Factor Xa inhibitor	Factor Xa inhibitor	Factor Xa inhibitor
FDA-approved indications		Prophylaxis and treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE); prophylaxis and treatment of thromboembolic complications associated with atrial fibrillation and/or cardiac valve replacement; reduction in the risk of death, recurrent myocardial infarction, and thromboembolic events such as stroke or systemic embolization after myocardial infarction	Reduction of risk of stroke and systemic emboli in nonvalvular atrial fibrillation; prophylaxis of DVT following hip or knee replacement surgery; treatment of DVT and PE; reduction in the risk of recurrence of DVT and PE	Reduction of risk of stroke and systemic emboli in nonvalvular atrial fibrillation; prophylaxis of DVT following hip or knee replacement surgery; treatment of DVT and PE; reduction in the risk of recurrence of DVT and PE	Reduction of risk of stroke and systemic emboli in nonvalvular atrial fibrillation; treatment of DVT and PE
Black box warnings		Coumadin can cause major or fatal bleeding	Premature discontinuation of Xarelto increases the risk of thrombotic events; spinal/epidural hematoma	Premature discontinuation of Eliquis increases the risk of thrombotic events; spinal/epidural hematoma	Reduced efficacy in nonvalvular atrial fibrillation patients with creatinine clearance (CrCl) $>$ 95 ml/min; premature discontinuation of Savaysa increases the risk of ischemic events; spinal/epidural hematoma
Pharmacokinetic properties	Bioavailability	~100%	76% with food	50%	62%
	Half-life	~40 hours	5–9 hours	~12 hours	10–14 hours
	Elimination	Metabolites in the urine (92%)	Unchanged drug in the urine; inactive metabolites in the urine (30%) and feces (21%)	Urine (27%) and feces	Unchanged drug in the urine (50%)

(Continued)

Table 1. (Continued)

		Warfarin (Coumadin)*	Rivaroxaban (Xarelto)**	Apixaban (Eliquis)+	Edoxaban (Savaysa)++
Dose in nonvalvular atrial fibrillation		Individualized dosing adjusted to international normalized ratio (INR) goal	20 mg daily with evening meal	5 mg twice daily	60 mg daily
Dose adjustments	Renal	No dosage adjustment necessary	15 mg daily with evening meal for CrCl 15–50 ml/min	2.5 mg twice daily If the patient has at least two of the following: Age ⩾80 years old; Weight ⩽60 kg; serum creatinine ⩽1.5 mg/dl	30 mg daily for CrCl 15–50 ml/min; CrCl <15 or >95 ml/min: do not use
	Hepatic	Use caution in hepatic impairment	Not recommended in moderate or severe hepatic impairment (Child-Pugh class B or C)	Not recommended in severe hepatic impairment (Child-Pugh class C)	Not recommended in moderate or severe hepatic impairment (Child-Pugh class B or C)
Reversal strategies		Oral or parenteral vitamin K; prothrombin complex concentrate (PCC), fresh frozen plasma, or activated factor VII	PCC	PCC, activated prothrombin complex concentrate, or recombinant factor VIIa, activated oral charcoal	four-factor PCC
Pregnancy category		X; except pregnant women with mechanical heart valves (D)	C	B	C

*Bristol-Myers Squibb Company [2011].
**Janssen Pharmaceuticals Inc. [2011].
+Bristol-Myers Squibb Company [2012].
++Daiichi Sankyo Co. Ltd [2015] and Zahir *et al.* [2015].

Table 2. Landmark atrial fibrillation trials.

Agent	Rivaroxaban	Apixaban	Edoxaban
Trial name	ROCKET AF*	ARISTOTLE**	ENGAGE AF-TIMI 48***
Number of patients	14,264	18,201	21,105
Intervention	20 mg daily *versus* dose adjusted warfarin	5 mg twice daily *versus* dose adjusted warfarin	60 mg high dose or 30 mg low dose *versus* dose adjusted warfarin
Primary outcome	Stroke or systemic embolism: 1.7% per year rivaroxaban; 2.2% per year warfarin ($p < 0.001$ for noninferiority)	Stroke or systemic embolism: 1.27% per year apixaban; 1.60% per year warfarin ($p = 0.01$ for superiority)	Stroke or systemic embolism: 1.18% high dose ($p < 0.001$ noninferiority); 1.16% low dose ($p = 0.005$ noninferiority); 1.50% warfarin
Primary safety outcome	Major and nonmajor clinically relevant bleeding: 14.9% rivaroxaban; 14.5% warfarin ($p = 0.44$)	Major bleeding: 2.13% per year apixaban; 3.09% per year warfarin ($p < 0.001$)	Major bleeding: 2.75% high dose ($p < 0.001$); 1.61% low dose ($p < 0.001$); 3.43% warfarin

*Patel *et al.* [2011].
**Granger *et al.* [2011].
***Giugliano *et al.* [2013].

treating a bleeding event should be discontinuation of the anticoagulant. In nonemergent bleeding situations or times necessitating surgical intervention this may be sufficient enough to mitigate the bleeding risk. Interventions should be delayed at least 12 hours and preferably 24 hours after the last ingested dose of the FXa inhibitor since anticoagulation effects can last at least 24 hours following the last administered dose of the medication [Kovacs *et al.* 2015]. In emergency situations the anticoagulant effects of the FXa inhibitors can be managed through a two-prong approach involving removing the medication from circulation and counteracting the inhibitory effects on the clotting cascade [Kovacs *et al.* 2015]. Gastric lavage or oral administration of activated charcoal may be effective at removing the medication from circulation if the FXa has been recently ingested. Prothrombin complex concentrate (PCC) and activated PCC have demonstrated the ability to reverse the anticoagulant effects of the FXa inhibitors in animal studies and clinical trials conducted in healthy subjects [Kovacs *et al.* 2015; Eerenberg *et al.* 2011; Zahir *et al.* 2015; Perzborn *et al.* 2013].

Concomitant use of the FXa inhibitors with aspirin or other antiplatelet agents, other antithrombotic agents, fibrinolytic therapy, and chronic use of nonsteroidal anti-inflammatory drugs (NSAIDs) further increases the risk for bleeding. Other anticoagulant reversal agents, protamine sulfate and vitamin K, have not shown to be beneficial in reversal of FXa inhibitors [Janssen Pharmaceuticals Inc., 2011; Bristol-Myers Squibb Company, 2012; Daiichi Sankyo Co. Ltd, 2015].

Rivaroxaban

Rivaroxaban has a dose-dependent bioavailability where the bioavailability decreases as the dose increases [Janssen Pharmaceuticals, Inc., 2011]. The 10 mg tablet has a bioavailability of 80–100% and is not affected by food, whereas the 20 mg tablet has only a 66% bioavailability that will increase when taken with food [Mani and Lindhoff-Last, 2014]. After ingestion, rivaroxaban reaches peak concentration within 2–4 hours and has a half-life of 5–9 hours in healthy patients. Rivaroxaban has a plasma protein binding of 92–95% to which it binds mainly to albumin. In addition, 51% of rivaroxaban is metabolized by cytochrome P (CYP)3A4 and CYP2J2 to inactive metabolites and most of the drug is excreted in the urine (one third as unchanged drug) [Janssen Pharmaceuticals, Inc., 2011]. Rivaroxaban does interact with drugs that are dual P-glycoprotein (PGP) and CYP3A4 inhibitors and should be avoided if the patient is taking ketoconazole, ritonavir, clarithromycin, erythromycin, and fluconazole. Rivaroxaban should also be avoided if dual PGP and moderate CYP3A4 inhibitors are being

administered (diltiazem, verapamil, dronedarone) and the patient has a creatinine clearance (CrCl) between 15 and 80 ml/min. Aside from bleeding adverse effects, other adverse effects found in post marketing studies are thrombocytopenia, angioedema, jaundice, and hepatitis [Janssen Pharmaceuticals, Inc., 2011].

Rivaroxaban dosing for nonvalvular atrial fibrillation is a 20 mg daily orally administered dose given with the evening meal for patients with normal renal function (defined as CrCl greater than 50 ml/min) [Janssen Pharmaceuticals, Inc., 2011]. In patients with renal impairment (CrCl between 15–50 ml/min) the recommended dose adjustment is 15 mg daily. Patients with severe renal function (CrCl less than 15 ml/min) should avoid rivaroxaban treatment. Correspondingly, rivaroxaban should be not be used in patients with Child-Pugh B or C hepatic impairment. Rivaroxaban is a pregnancy category C and it is unknown whether rivaroxaban is excreted in breast milk. Lastly, the exposure of rivaroxaban is not affected by extremes of body weight (<50 kg or >120 kg) [Janssen Pharmaceuticals, Inc., 2011].

The major clinical trial with proven efficacy for rivaroxaban in patients with nonvalvular atrial fibrillation is the Rivaroxaban Once Daily, Oral, Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF) trial published in 2011 [Patel *et al.* 2011]. This multicenter, randomized, double-dummy, and double-blind trial included over 14,000 patients assigned to either warfarin (adjusted for an INR goal of 2–3) or rivaroxaban 20 mg (15 mg for patients with a CrCl of 30–40 ml/min). Patients in this study were mostly men (60.3%) in their seventies, with persistent atrial fibrillation (81%), and a mean $CHADS_2$ score of 3.5. For the primary endpoint of composite stroke and systemic embolism, rivaroxaban was noninferior to warfarin with an event rate of 1.7% per year *versus* 2.2% per year respectively in the per-protocol, as treated population ($p < 0.001$). There was no difference in the safety endpoint of composite major and nonmajor clinically relevant bleeding between rivaroxaban and warfarin (14.9% event rate compared with a 14.5% event rate, $p = 0.44$) [Patel *et al.* 2011]. Similarly, in the J-ROCKET AF trial performed solely in Japanese patients, rivaroxaban was noninferior to warfarin for nonvalvular atrial fibrillation at a 15 mg daily dose [Hori *et al.* 2012].

A secondary analysis of the ROCKET AF trial results specific to elderly patients (age 75 and over) was published in 2014 [Halperin *et al.* 2014]. This study illustrated that although elderly patients had higher stroke and bleeding event rates, the overall effect of rivaroxaban was not statistically different from younger patients for both primary efficacy and safety endpoints ($p = 0.3131$ and $p = 0.336$, respectively) [Halperin *et al.* 2014]. Comparable to the ROCKET AF study in elderly patients, the J-ROCKET AF investigators also completed a secondary analysis in elderly patients with atrial fibrillation [Hori *et al.* 2014]. In this study there were more events for the primary safety outcome of major and nonmajor clinically relevant bleeding [hazard ratio (HR) 1.49; 95% confidence interval (CI) 1.02–2.16] for elderly patients receiving rivaroxaban. However, the primary efficacy outcome of stroke and non-central nervous system systemic embolism was favorable to rivaroxaban treatment (HR 0.51; 95% CI 0.20–1.27), leading the authors to conclude that the risks and benefits of rivaroxaban therapy should be weighed in elderly patients prior to use [Hori *et al.* 2014].

A *post hoc* analysis of the ROCKET trial was performed to provide outcomes from patients who received cardioversion or catheter ablation while being treated with rivaroxaban or warfarin [Piccini *et al.* 2013]. The reported incidence of cardioversion or ablation during the study was 1.45 per 100 patient-years (1.44 per 100 patient-years for warfarin and 1.46 per 100 patient-years for rivaroxaban). The primary outcome from ROCKET, stroke or systemic embolism, was comparable for warfarin and rivaroxaban (1.88% *versus* 1.86%) [Piccini *et al.* 2013].

Other secondary analyses were performed to study the relationship between the time in therapeutic range (TTR) of warfarin compared with treatment with rivaroxaban from the ROCKET AF trial [Piccini *et al.* 2014b]. The mean time in therapeutic range for individual patients was 55%, with centers in North America and Western Europe having the highest TTR (65% and 64%, respectively). Excluding patients with interruptions in their warfarin therapy for greater than 7 days, the authors concluded that the effect of rivaroxaban was consistent despite variations in TTR across centers [Piccini *et al.* 2014b].

Lastly, an analysis was performed to determine the rate, outcomes, and predictors of ICH among

patients in the ROCKET AF study [Hankey *et al.* 2014]. At least one ICH event was found in 172 patients (1.2%), with 87 deaths (51%) among subjects with ICH having occurred at 90 days. There were no statistically significant differences in case fatalities between warfarin and rivaroxaban for ICH, however rivaroxaban was found to be a factor that reduced the risk of ICH (HR 0.65; 95% CI 0.44–0.82) [Hankey *et al.* 2014].

The lack of benefit of currently available anticoagulant reversal agents for bleeding events with rivaroxaban use has increased the importance of providing information on bleeding events and their management. The Dresden NOAC (non-VKA oral anticoagulant) registry was a 2-year collection of bleeding events, patterns of bleeding, management of bleeding, and bleeding related mortality in Germany for patients receiving rivaroxaban therapy [Beyer-Westendorf *et al.* 2014]. Of the 1776 patients who received rivaroxaban, 67.5% of them had a diagnosis of atrial fibrillation and 32.4% had a diagnosis of VTE. The rates of major bleeding, as defined by the International Society on Thrombosis and Haemostasis (ISTH), were 3.1 per 100 patient-years for patient with atrial fibrillation compared with 3.4 per 100 patient-years for all rivaroxaban-treated patients. The patients who experienced major bleeding were older than patients without major bleeding and had more impaired renal function ($p = 0.0016$ and $p = 0.0048$, respectively). Most bleeding events were spontaneous (77.4% of all bleeding) and fresh frozen plasma (FFP) or PCC each were used in only 0.6% of all bleeding events (9.1% of major bleeding events) as treatment. Finally, case fatality rates were 5.1% for day 30 and 6.3% at day 90 [Beyer-Westendorf *et al.* 2014]. Results from the analysis for major bleeding events from the ROCKET AF trial were similar to the Dresden registry. Of the 14,143 patients in this analysis, 5.5% had a major bleeding event as defined by the ISTH, with an event rate of 3.52 events per 100 patient-years [Piccini *et al.* 2014a]. The most common major bleeding events reported were in the upper gastrointestinal tract (38.1%). Major bleeding events were managed by packed red blood cells ($n = 176$), other transfusions (whole blood, $n = 14$; platelets, $n = 10$; cryoprecipitate, $n = 2$), FFP ($n = 45$), and PCC ($n = 4$) [Piccini *et al.* 2014a].

Additional observational studies have been performed comparing rivaroxaban to warfarin for reduction in hospitalization days and to compare health care cost for patients with nonvalvular atrial fibrillation [Laliberte *et al.* 2015a, 2015b]. The study by Laliberte and colleagues was a propensity matched cohort using the database of 4506 Humana patients who received rivaroxaban or warfarin prescriptions from 2011 through 2012. For the primary endpoint of total number of hospitalization days, patients receiving rivaroxaban had 2.71 hospitalization days compared to 3.87 for patients receiving warfarin ($p = 0.032$). Results favoring rivaroxaban therapy over warfarin therapy was also seen in the number of atrial fibrillation related hospitalization days (2.11 days compared with 3.02 days, respectively) [Laliberte *et al.* 2015b]. In a similarly designed study using the same patients from the Humana database, Laliberte and colleagues found a significant reduction in all cause health care costs in rivaroxaban patients matched to warfarin patients (US$17,590 *versus* US$18,676, respectively, $p = 0.0468$) [Lalberte *et al.* 2015a]. All cause health care costs was a composite of costs related to hospitalization, ER visits, outpatient visits, and pharmacy. Atrial-fibrillation-related costs were similar between the two agents, however pharmacy related costs were higher for rivaroxaban patients (US$5316 rivaroxaban and US$2620 warfarin, $p < 0.0001$) [Lalberte *et al.* 2015a].

Apixaban

Apixaban achieves a bioavailability of 50% after oral administration and is not affected by food [Bristol-Myers Squibb Company, 2012]. The protein binding is 87% to plasma proteins and apixaban is metabolized mostly through CYP3A4 to inactive metabolites. Apixaban is eliminated by the urine and feces with urine accounting for 27% of the clearance. The half-life for apixaban is 12 hours [Mani and Lindhoff-Last, 2014]. Adverse events and contraindications for apixaban are limited to bleeding events. As a substrate of CYP3A4 and PGP, apixaban does interact with strong inhibitors of both proteins and therefore should be decreased to 2.5 mg twice daily when administered with ketoconazole, itraconazole, ritonavir, or clarithromycin. If the patient is already receiving the 2.5 mg dose when a dual strong inhibitor is administered then apixaban therapy should be avoided. In addition, avoidance of drugs that are strong inducers of both proteins is recommended to avoid decreased exposure to apixaban [Bristol-Myers Squibb Company, 2012].

For nonvalvular atrial fibrillation the recommended dose of apixaban is 5 mg twice daily

[Bristol-Myers Squibb Company, 2012]. In patients with two or more of the following characteristics; age ⩾80 years, body weight ⩽60 kg, or a serum creatinine of ⩾1.5 mg/dl, the dose should be decreased to 2.5 mg twice daily. Patients with the characteristic of low body weight alone have not been found to have differences in apixaban exposure [Upreti *et al.* 2013]. Similarly, geriatric patients with normal body weight and renal function also had normal apixaban exposure [Bristol-Myers Squibb Company, 2012]. Patients with end-stage renal disease who are receiving dialysis are able to remain on the 5 mg twice daily dose, unless they are age ⩾80 years or have body weight of ⩽60 kg, which would require a dose adjustment to 2.5 mg twice daily. Although there is limited data of the use of apixaban in pregnancy or breast-feeding, it is pregnancy category B [Bristol-Myers Squibb Company, 2012].

Apixaban *Versus* Acetylsalicylic Acid to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable or Vitamin K Antagonist Treatment (AVERROES) and Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) are the two clinical trials for apixaban that focus on efficacy in patients with atrial fibrillation [Connolly *et al.* 2011; Granger *et al.* 2011]. The AVERROES trial, published in 2011, was a randomized double-blinded study in over 5000 patients from multiple countries with atrial fibrillation [Connolly *et al.* 2011]. Patients were included if they were over the age of 50 and if they were unable or unwilling to receive therapy with a VKA. Apixaban 5 mg twice daily was studied *versus* aspirin doses ranging from 81 to 324 mg. The patients in this trial had an average age of 70, over half had permanent atrial fibrillation, and the average $CHADS_2$ score was two. Most patients in the trial had multiple reasons indicated for unsuitability for VKA therapy. However the most common reasons reported were assessment of INR could not or was unlikely to be measured at requested intervals (43%), patient refusal of VKA therapy (38%), $CHADS_2$ score of 1 and VKA therapy not recommended by physician (21%), and assessment of INR could not be maintain in therapeutic range (17%). The AVERROES trial was terminated early due to overwhelming evidence of a benefit seen with apixaban therapy. The primary outcome of stroke or systemic embolism was seen in 51 patients receiving apixaban *versus* 113 patients receiving aspirin ($p < 0.001$). There was no significant difference in safety outcomes such as major bleeding (44 events *versus* 39 events for apixaban and aspirin, respectively, $p = 0.57$) [Connolly *et al.* 2011].

In the ARISTOTLE, a randomized double-blind trial, apixaban (5 mg twice daily) was compared with warfarin therapy (target INR goal of 2–3) in patients with atrial fibrillation [Granger *et al.* 2011]. Over 18,000 patients were randomized to one of the aforementioned therapies, and followed for a median duration of 1.8 years. Patients in this study were mostly males (64.5%), with an average age of 70, persistent or permanent atrial fibrillation (84%), and an average $CHADS_2$ score of two. The primary outcome of stroke or systemic embolism was seen in 212 apixaban patients (1.27% event rate) compared to 265 warfarin patients (1.60% event rate) meeting noninferiority and superiority ($p < 0.001$ and $p = 0.01$, respectively). The primary safety outcome of major bleeding occurred more in the warfarin group (3.09% per year *versus* 2.13% per year for apixaban, $p < 0.001$) [Granger *et al.* 2011].

Comparable results in favor of apixaban were seen in a phase II, 12-week trial in Japanese patients with atrial fibrillation [Ogawa *et al.* 2011]. A separate phase III trial in Japanese patients has not been studied, however ARISTOTLE did include Japanese patients. A subanalysis of ARISTOTLE pertaining to East Asian patients, due to the higher risk of ICH in these patients with warfarin use, was performed separately [Goto *et al.* 2014]. The 1993 patients from East Asia (10.9% of the ARISTOTLE population), had similar results compared to the non-East Asian population when comparing apixaban use to warfarin. Apixaban had a significant reduction in major or clinically relevant nonmajor bleeding compared with warfarin (p for interaction = 0.03) however did not reach significance for intracranial bleeding [Goto *et al.* 2014]. Currently, there are no published trials for apixaban use specifically focused on elderly patients.

In a subanalysis of the ARISTOTLE trial, major bleeding events for apixaban and warfarin were studied for predictors of bleeding, characteristics, and outcomes [Hylek *et al.* 2014]. Major bleeding, defined by ISTH, was less common in the apixaban group (2.13% per year) compared with warfarin (3.09% per year). Apixaban-treated patients who had hemorrhages had less hospitalizations (HR 0.72, 95% CI 0.56–0.93), fewer transfusions (HR 0.71, 95% CI 0.57–0.89), and

had 36 deaths at 30 days compared with 71 deaths with warfarin among other adverse consequences (HR 0.50, 95% CI 0.33–0.74). In addition, predictors for bleeding were older age, history of myocardial infarction, impaired renal function, fall within the previous year, and prior hemorrhage [Hylek *et al.* 2014].

A second analysis of the ARISTOTLE results pertaining to bleeding has been conducted using $CHADS_2$, CHA_2DS_2VASc, and HAS-BLED scores to compare apixaban and warfarin [Lopes *et al.* 2012]. The original results from ARISTOTOLE did not report CHA_2DS_2VASc or HAS-BLED scores for patients in the trials; therefore this examination of the data is comparable to newer guidelines that use these scoring systems. Outcomes from this trial confirmed that the reduction in major bleeding reported in apixaban treated patients was consistent across the different scoring systems ($CHADS_2$, p for interaction = 0.4018; CHA_2DS_2VASc, p for interaction = 0.2059; HAS-BLED, p for interaction = 0.7127). Despite these findings the authors concluded the scoring systems may not be relevant when used to determine therapy for individual patients [Lopes *et al.* 2012].

Subgroup analysis of the ARISTOTLE trial exploring differences in the type of atrial fibrillation and time in therapeutic INR range have results supporting the use of apixaban [Al-Khatib *et al.* 2013; Wallentin *et al.* 2013]. Apixaban was comparable to warfarin despite the duration of atrial fibrillation (paroxysmal, persistent, permanent) with a p-value for interaction of >0.13 [Al-Khatib *et al.* 2013]. The comparison of time in therapeutic INR range for warfarin, displayed decreased stroke and systemic embolism events at lower (HR 0.73, 95% CI 0.53–1.00) and higher (HR 0.89, 95% CI 0.57–1.35) INR ranges [Wallentin *et al.* 2013].

In addition, results from ARISTOTLE were examined to compare variations in renal function on the efficacy of apixaban *versus* warfarin therapy [Hohnloser *et al.* 2012]. Using Cockcroft–Gault, Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI), and cystatin C measurements of renal function; the studied reported that apixaban reduced stroke, death, and major bleeding even with various renal function. This study also concluded that the relative risk reduction in major bleeding was higher in patients with impaired renal function [defined as an estimated glomerular filtration rate (eGFR) of $\leq$50 ml/min] with a p for interaction = 0.005 using the Cockcroft–Gault equation and p for interaction = 0.003 for the CKD-EPI equation [Hohnloser *et al.* 2012].

In the subanalysis of the ARISTOTLE trial pertaining to thromboembolic events after cardioversion, there were 743 cardioversions performed in 540 patients taking warfarin or apixaban [Flaker *et al.* 2014]. Among the cardioversion patients, no patient had the primary outcome of stroke or systemic emobli at the 30-day follow up for either drug. Furthermore, both apixaban and warfarin had only two patient deaths each following cardioversion at 30 days [Flaker *et al.* 2014].

Edoxaban

Edoxaban is the most recently approved agent in the FXa inhibitor therapeutic class. It has a quick onset of activity with peak concentrations reached 1–2 hours after dosing and a half-life of 10–14 hours. It has a bioavailability of 62% and may be administered without regards to food. Approximately 50% of exdoxaban is cleared through renal excretion as unchanged drug [Daiichi Sankyo Co. Ltd, 2015].

Edoxaban was not found to be an inhibitor or inducer of the major CYP450 enzymes during *in vitro* trials; however, exdoxaban is a PGP substrate. For nonvalvular atrial fibrillation, the recommended dose is 60 mg once daily. A dose reduction to 30 mg daily is recommended for patients with a creatinine clearance (CrCl) of 15–50 ml/min. Edoxaban use should be avoided in patients with a CrCl of $<$15 ml/min or $>$95 ml/min [Daiichi Sankyo Co. Ltd, 2015].

Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation – Thrombolysis in Myocardial Infarction 48 (ENGAGE AF-TIMI 48) is the landmark trial that led to the approval of exdoxaban for use in patients with atrial fibrillation. The trial was a randomized, double-blind, double-dummy design consisting of 21,105 patients evenly randomized to either high-dose exdoxaban 60 mg, low-dose exdoxaban 30 mg, or warfarin (treated to a goal INR of 2–3) followed for an average of 2.8 years [Giugliano *et al.* 2013]. Patients in this trial were at least 21 years of age with a confirmed diagnosis of atrial fibrillation and a $CHADS_2$ score of two or higher. The primary endpoint of stroke or systemic embolic

event occurred in 232 patients in the warfarin arm, 253 patients in the low-dose exdoxaban arm, and 182 patients in the high-dose edoxaban arm. Differences in the exdoxaban groups were statistically significant with the high-dose edoxaban group meeting superiority ($p = 0.02$) and the low-dose group meeting noninferiority measures ($p = 0.005$) when compared with warfarin. Bleeding rates including life-threatening bleeding, intracranial bleeding, major bleeding, and non-major bleeding were all statistically lower in both of the edoxaban groups compared with warfarin ($p < 0.001$) [Giugliano *et al.* 2013].

A trial conducted by Mendell and colleagues examined the effects of several cardiovascular medications, which are known PGP inhibitors, on the concentrations of edoxaban 60mg. The following medications were evaluated: quinidine, digoxin, amiodarone, dronedarone, verapamil, and atorvastatin. Coadministration with verapamil, quinidine, and dronedarone caused a greater than 50% increase in exposure to exdoxaban leading authors to suggest a 50% reduction in the edoxaban dose when used concomitantly with these agents [Mendell *et al.* 2013]. The dose of edoxaban in both treatment arms was reduced by 50% in the ENGAGE AF-TIMI 48 study if patients had a creatinine clearance of 30–50 mL/min, a bodyweight of 60 kg or less, or were taking a P-glycoprotein inhibitor at time of randomization or at any time during the study [Giugliano *et al.* 2013]. A subgroup analysis was done to evaluate the effects that the dose reduction had on efficacy and safety [Ruff *et al.* 2015]. As expected the overall mean edoxaban concentrations decreased by 29–35% with dose reductions. Similarly, the average anti-FXa activity decreased by 20–25% when the edoxaban dose was reduced. Dose reductions of edoxaban did not alter the efficacy of edoxaban with similar cases of stroke, ischemic stroke, and all-cause mortality observed in patients that had a dose reduction compared with patients that did not have a dose reduction. There were significantly fewer major bleeding events in the group that received a reduction in dose in both the high-dose edoxaban and low-dose edoxaban groups ($p = 0.023$ and $p = 0.002$, respectively) and significantly fewer ICH and fatal bleeds in the edoxaban low-dose patient group that received a reduction to 15 mg ($p = 0.011$ and $p = 0.044$, respectively) [Ruff *et al.* 2015]. However, there was an increase in the primary outcome of stroke and system embolism in the dose reduced PGP inhibitor patient group ($n = 228$) with a HR of 2.17 when compared with warfarin [Ruff *et al.* 2015]. As result of this data, neither the FDA nor the manufacturer of edoxaban recommend dose adjustments when using edoxaban with PGP inhibitors [Daiichi Sankyo Co. Ltd, 2015]. Concurrent use of edoxaban with the PGP inducer, rifampin, should be avoided [Daiichi Sankyo Co. Ltd, 2015]. Further analysis of the ENGAGE AF-TIMI 48 study groups was done to evaluate differences in the specific types of cerebrovascular events between high-dose edoxaban, low-dose edoxaban, and warfarin that occurred during the study [Giugliano *et al.* 2014]. The primary endpoint for this specific analysis was first stroke while secondary endpoints evaluated subtypes of ICH and stroke outcomes. Participants in the high-dose edoxaban treatment arm had fewer first strokes than participants in the warfarin arm, 174 patients *versus* 219 patients, with the difference deemed statistically significant ($p = 0.027$). However, there was no difference seen between the low-dose edoxaban group and the warfarin in patients with first stroke ($p = 0.33$). The upper limits of the confidence intervals were below the pre-specified cutoff of 1.38 for both the high-dose and low-dose exdoxaban groups showing noninferiority to warfarin (95% CI 0.65–0.98 and 0.91–1.32, respectively). The secondary endpoint analysis showed significantly fewer hemorrhagic strokes and fatal ICH in both the high-dose and low-dose exdoxaban groups compared with warfarin ($p < 0.001$ for both outcomes). However, there was no difference seen in the rates of ischemic events when high-dose exdoxaban was compared with warfarin ($p = 0.81$) and a statistically significant increase in ischemic events between low-dose edoxaban and warfarin ($p < 0.001$ in favor of warfarin) [Giugliano *et al.* 2014].

Researchers of the ENGAGE AF-TIMI 48 study conducted a prespecified genetic subgroup analysis to determine whether participants identified as normal, sensitive, or highly sensitive responders to warfarin, through genetic testing for variants in CYP2C9 and VKORC1, had an increased risk for bleeding with warfarin use. Subjects in the warfarin arm that were identified as sensitive or highly sensitive responders spent more time above the therapeutic range compared with normal responders ($p < 0.0001$) [Mega *et al.* 2015]. HAS-BLED scores greater than or equal to three were associated with higher bleeding rates and were observed more often in the highly sensitive responders. Within the first 90 days, both the

high- and low-dose edoxaban arms produced significantly fewer bleeding events than the warfarin group for sensitive and highly sensitive responders ($p = 0.0066$ and $p = 0.0036$, respectively) suggesting that edoxaban has the potential to be a preferred agent for patients at high risk of bleeding with warfarin due to genetic variations [Mega *et al.* 2015].

Conclusion

Research on new FXa inhibitor compounds is ongoing; however, few agents have successfully made it past phase II clinical trials. Clinical practice guidelines for the management of atrial fibrillation have been updated to include newer oral anticoagulants, thrombin inhibitors and FXa inhibitors, as therapeutic alternatives to warfarin in treatment-naïve patients and patients unable to consistently stay in therapeutic range on warfarin [Camm *et al.* 2012; January *et al.* 2014]. Exceptions to the use of newer oral anticoagulants in atrial fibrillation include patients with mechanical heart valves. Warfarin remains the standard of care for this special patient population [January *et al.* 2014]. Currently available FXa inhibitors have been shown to be noninferior to warfarin with regards to efficacy and safety in clinical trials and are viable treatment options for patients with nonvalvular atrial fibrillation.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

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