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Novel Oral Anticoagulants in Atrial Fibrillation: Update on Apixaban



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Abstract: Almost 800,000 new or recurrent strokes occur every year. Atrial fibrillation, the most common cardiac arrhythmia, is a major risk factor for stroke, accounting for 15-20% of ischemic strokes. Apixaban is a direct inhibitor of Factor Xa that was approved in December 2012 by the US Food and Drug Administration (FDA) for the prevention of stroke in patients with non-valvular atrial fibrillation. It is part of a family of novel oral anticoagulants (NOACs) which has advantage over warfarin of less dosing variability, rapid onset of action and no INR monitoring required. Apixaban showed superiority to warfarin in both primary efficacy and primary safety outcomes by simultaneously showing both significantly lower rates of strokes and systemic embolism and a reduced risk of major clinical bleeding in clinical trials. Warfarin remains the anticoagulant of choice for patients with prosthetic heart valves and significant mitral stenosis. There are currently no head-to-head studies that directly compare the different NOACs with one another, but it is expected that there will be more trials in the future that will explore this comparison. Dabigatran is the only NOAC with an FDA approved reversal agent. However, a reversal agent for apixaban is being developed and was successful in recent clinical trials. This review summarizes the clinical trial data on apixaban for atrial fibrillation, compares apixaban to other NOACs and discusses apixaban use in clinical practice.

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INTRODUCTION

More than 2,150 Americans die of cardiovascular diseases (CVD) each day, with an average of one death every 40 seconds. It is estimated that 795,000 new or recurrent strokes (ischemic or hemorrhagic) occur yearly and of those, one person has a stroke every 40 seconds and one person dies every 4 minutes [1]. Atrial fibrillation (AF), the most common cardiac arrhythmia, is a major risk factor for heart failure, cardiovascular deaths, and stroke, accounting for 15-20% of ischemic strokes [2-6].

The standard treatment for thrombosis had been warfarin and heparin; however, these agents have numerous limitations [7]. For instance, the warfarin dose needs to be titrated due to extensive pharmacodynamic (variations of epoxide reductase in the population) and pharmacokinetic (cytochrome P450 polymorphisms) variability and drug interaction. Several Novel Oral Anticoagulants (NOACs) have been

approved for the treatment of AF. They have a fast and reliable onset of action, and unlike warfarin do not require dose-response monitoring [8]. The NOACs including dabigatran, rivaroxaban, and apixaban, were introduced respectively in the United States in the order listed. The RE-LY [9], ROCKET-AF [10] and ARISTOTLE [11] were landmark trials which ushered in and guided the use of dabigatran, rivaroxaban and apixaban in clinical practice (Table 1). In all studies of the NOACs, patients with significant valvular heart disease have been excluded, and warfarin is still the only FDA-approved oral anticoagulant for valvular AF (Table 3).

Apixaban: A Direct Factor Xa Inhibitor

Apixaban use in the United States was approved in December 2012 by the Food and Drug Administration (FDA), and it is indicated for the prevention of stroke and systemic thromboembolism in patients with Non-Valvular Atrial Fibrillation (NVAf).

Apixaban is an oral, reversible, direct competitive inhibitor of factor Xa, with a half-life of 9 – 12 hours. It has a bioavailability of 50%, is rapidly absorbed (within 3 hours), and excretion is mainly through the hepatobiliary system (75% liver, 25% kidneys) [12] (Table 2). The CYP3A4

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Table 1. Comparison of the NOACs in Clinical Trials for Atrial Fibrillation.

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Clinical trial	RE-LY Open-label trial	ROCKET-AF Double-blind	ARISTOTLE Double-blind	ENGAGE AF-TIMI 48 Double-blind
Sample Size	18, 113	14,264	18,201	21,105
Intervention and Comparison	150mg or 110mg twice daily compared with warfarin (INR 2-3)	20mg once daily compared with warfarin (INR 2-3)	5mg twice daily compared with warfarin (INR 2-3)	60mg or 30mg once daily compared with warfarin (INR 2-3)
Baseline CHADS2	2.1	3.6	2.1	2.8
Median Follow Up	1.9 years	1.9 years	1.8 years	2.8 years
Primary Outcome (Composite of all strokes and systemic embolism)	150mg RR 0.66 (CI 0.53 to 0.82, p < 0.001) 110mg RR 0.91 (CI 0.74 to 1.11, p < 0.001)	HR 0.79 (CI 0.66 to 0.96, p < .001)	HR 0.79 (CI 0.66 to 0.95, p = 0.01)	60mg HR 0.79 (CI 0.63 to 0.99, p < 0.001) 30mg HR 1.07 (CI 0.87 to 1.31, p = 0.005)
All-Cause Mortality	150mg RR 0.88 (CI 0.77 to 1.00, p = 0.051) 110mg RR 0.91 (CI 0.80 to 1.03, p = 0.13)	HR 0.85 (CI 0.70–1.02, p = 0.07)	HR 0.89 (CI 0.80 to 0.99, p = 0.047)	60mg HR 0.92 (CI 0.83 to 1.01, p = 0.08) 30mg HR 0.87 (CI 0.79 to 0.96, p = 0.006)
Major Clinical Bleeding	150mg RR 0.93 (CI 0.81 to 1.07, p = 0.31) 110mg RR 0.80 (CI 0.69 to 0.93, p = 0.003)	HR 1.03 (CI 0.96 to 1.11, p = 0.44)	HR 0.69 (CI 0.60 to 0.80, p < 0.001)	60mg HR 0.80 (CI 0.71 to 0.91, p < 0.001) 30mg HR 0.47 (CI 0.41 to 0.55, p < 0.001)

CI, 95% Confidence intervals; RR, Relative Risk; HR, Hazard Ratio.

enzyme metabolizes apixaban. Therefore clinicians should be careful when using inhibitors and inducers of this enzyme pathway [13]. Even though apixaban like the other NOACs has no antidote, administration of activated charcoal within 6 hours of apixaban intake reduces exposure and facilitates elimination [14].

Apixaban in Clinical Trials for Atrial Fibrillation

In AF, apixaban's effectiveness was demonstrated in two international, randomized controlled trials – ARISTOTLE [11] and AVERROES [15]. The ARISTOTLE trial (n=18,201) compared apixaban with warfarin to prevent strokes in patients with AF, while AVERROES (n=5,598) compared apixaban with aspirin in AF patients who were unable to take warfarin.

ARISTOTLE showed that the composite primary outcome (hemorrhagic or ischemic stroke or systemic embolism) was lower in the apixaban group than warfarin (1.27% per year in apixaban group versus 1.6% per year in warfarin group, hazard ratio [HR] 0.79, 95% confidence interval [CI] 0.66 to 0.95, p=0.01) [11]. Apixaban was also superior for the primary safety outcome of major bleeding with fewer bleeding events than warfarin (2.13 % per year vs 3.09 % per year) for all the major bleed types (intracranial major bleeding HR 0.42, 95% CI 0.30 to 0.58, p < 0.001; other location major bleeding HR 0.79, 95% CI 0.68 to 0.93, p=0.004) [11]. The only sub-category of bleeding where there was no statistically significant difference compared to warfarin was for major gastrointestinal bleeding (HR 0.89, 95% CI 0.70 to 1.15, p=0.37). All-cause mortality was also

lower in the apixaban group compared with warfarin (3.52% versus 3.94 %, HR 0.89, 95% CI 0.80 to 0.99, p=0.047) [11].

AVERROES showed that apixaban reduced the rate of stroke or systemic embolism compared with aspirin (1.6% per year versus 3.7% per year, HR 0.45, 95% CI 0.32 to 0.62, p<0.001). A sub-analysis of the composite outcome showed that apixaban significantly reduced the rates of ischemic stroke compared with aspirin (1.1% per year versus 3.0% per year HR 0.37, 95% CI 0.25 to 0.55, p<0.001), but the results for hemorrhagic stroke were not significant (0.2 % per year versus 0.3% per year, HR 0.67, 95% CI 0.24 to 1.88, p=0.45). This is probably because aspirin caused less intracranial bleeding than apixaban. Apixaban was associated with higher rates of major bleeding than aspirin, but this was not statistically significant (1.4% per year versus 1.2% per year, HR 1.54, 95% CI 0.96 to 2.45, p=0.07) [15]. This study was discontinued prematurely as the safety committee found that apixaban was better than aspirin for the primary outcome of preventing stroke or systemic embolism [16].

Apixaban Compared to the other NOACs

Dabigatran is a direct thrombin inhibitor, while rivaroxaban and apixaban are direct Factor Xa inhibitors (Table 2). There have been no head-to-head clinical trials comparing the NOACs to each other, but there is available data on how they individually compare to warfarin.

Rivaroxaban has the highest bioavailability (>80%), while dabigatran has a very low bioavailability (6.5%). Apixaban has a bioavailability in-between both at 50%. Ri-

Table 2. Comparison of the NOACs – Pharmacokinetics.

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Mechanism of action	Reversible thrombin inhibitor	Reversible Factor Xa inhibitor	Reversible Factor Xa inhibitor	Reversible Factor Xa inhibitor
Prodrug	Yes	No	No	No
Pharmacokinetics	Bioavailability 6.5% Time to peak effect in 1-2 hours Half-life 12-17 hours Plasma protein binding 35% Metabolism - Serum esterases and non-CYP hepatic enzymes Excretion - urine 80%, feces 20%	Bioavailability > 90% Time to peak effect in 2-4 hours Half-life 5-9 hours Plasma protein binding > 80% Metabolism - CYP 3A4/5, CYP2J2 hydrolysis Excretion - urine 70%, feces 30%	Bioavailability 50% Time to peak effect in 3-4 hours Half-life 9-11 hours Plasma protein binding 87% Metabolism - CYP 3A4/5 (major) Excretion - urine 25%, feces 75%	Bioavailability 62% Time to peak effect in 1.5 hours Half-life 10-14 hours Plasma protein binding 55% Metabolism - CYP < 4%, Hydrolysis (major) Excretion - urine 35% feces 65%
PT/INR	Not used	Prolonged: suggests excessive bleeding risk	Not used	Not used
aPTT	>2x ULN suggests excessive bleeding risk	Not used	Not used	Not used
Absorption with food	No effect	+39% more; mandatory intake with food	No effect	No effect
Renal/Hepatic Monitoring	Renal function	Renal and hepatic function	Renal and hepatic function	Renal function
Dosing	CrCl > 30 mL/min 150 mg PO twice daily CrCl < 30 mL/min Not recommended	CrCl > 50 mL/min 20 mg PO Daily CrCl 30-50 mL/min 15 mg PO Daily CrCl < 30 mL/min Not recommended	5 mg PO twice daily 2.5 mg PO twice daily if 2 or more of the following > 80 years, < 60 kg, Serum Creatinine > 1.5 mg/dL CrCl < 30 mL/min Not recommended	CrCl 50 - 95 mL/min 60 mg PO once daily CrCl 15 - 50 mL/min 30 mg PO once daily CrCl > 95 mL/min Not recommended CrCl < 15 mL/min Not recommended

PT, prothrombin time; INR, international normalized ratio; aPTT, activated partial thromboplastin time; ULN, upper limit of normal; CrCl, creatinine clearance; PO, per oral.

varoxaban can be dosed once daily, and this is very helpful for compliance compared to the other NOACs which require at least two doses a day. Only 25% of apixaban is excreted through the kidneys - the lowest among all the NOACs compared to 33% for rivaroxaban and 80% for dabigatran [17-20]. A sub-study of the ARISTOTLE trial provides evidence that this might make apixaban the best choice for AF patients with renal impairment; however more data is needed to establish this [21-23].

Comparing the NOACs regarding the primary efficacy outcome of stroke and systemic embolism prevention, clinical trials show that both high-dose dabigatran (150 mg) and apixaban are superior to warfarin while low-dose dabigatran (110 mg) and rivaroxaban are non-inferior to warfarin.

There are some differences in the side effect profiles of the NOACs. There was no significant difference in the

incidence of major clinical bleeding between rivaroxaban/high-dose dabigatran and warfarin. However, apixaban holds an advantage here as the drug leads to less clinical bleeding (major) compared to warfarin. Dabigatran causes severe dyspepsia and in RE-LY, 11.8% of patients taking 110-mg and 11.3% of patients taking 150-mg dabigatran had dyspepsia compared to 5.8% in the warfarin group [19]. This side effect was so severe that 21% of patients had to discontinue therapy [19]. This might be due to the tartaric acid component of the drug needed to create a low pH for the drug's absorption [23].

Management of Patients on Apixaban

It would be pertinent to note that before starting apixaban, an assessment of the hepatic and renal function should be done. The usual dose of apixaban is 5 mg twice daily, but

Table 3. Indications for the different NOACs and Warfarin.

Clinical Indication	Dabigatran	Rivaroxaban	Apixaban	Edoxaban	Warfarin
VTE prophylaxis after elective hip or knee surgery	Yes	Yes	Yes	No	Yes
VTE treatment	Yes	Yes	Yes	Yes	Yes
Anticoagulation for NVAf	Yes	Yes	Yes	Yes	Yes
Anticoagulation for significant mitral stenosis or Prosthetic heart valves	No	No	No	No	Yes

VTE, venous thromboembolism; NVAf, nonvalvular atrial fibrillation.

2.5 mg twice daily is recommended for patients with at least 2 of the following conditions: age > 80 years, body weight ≤ 60 kg, or serum creatinine > 1.5 mg/dl [9]. In the ARISTOTLE trial, there was an increased risk of cardiovascular events in patients with creatinine clearance ≤ 80 ml/min; with a correlation of major bleeding with worsening renal function [22].

Drug-Drug Interactions

Apixaban is metabolized by the CYP3A4 enzyme pathway. Its use with strong inhibitors of the CYP3A4 enzyme (HIV protease inhibitors, ketoconazole, etc.) is contraindicated. Dose adjustments are not needed when used together with less potent CYP3A4 inhibitors (diltiazem, amiodarone, verapamil), and CYP3A4 inducers (phenytoin, rifampin) [12]. Gastric acid modifying agents such as famotidine do not affect absorption of apixaban because of its lack of an ionizable group and pH-independent solubility [23].

Apixaban and Prior Anticoagulant Use

It is recommended that the INR should be < 2.0 after discontinuing warfarin before using apixaban at therapeutic doses. Likewise, when changing from apixaban to warfarin, ensure that INR ≥ 2.0, before discontinuing apixaban. This means that daily INR checks should be done and an interval of 48 – 72 hours allowed to elapse when switching to warfarin [12, 24]. On the other hand, apixaban has the same onset of action and half-life as LMWH such as enoxaparin. Therefore doses can easily be interchanged when needed.

Bleeding while on Apixaban

Spontaneous bleeding can happen in patients on anticoagulants. The ARISTOTLE trial showed that there was a statistically significant reduced risk of all major bleeding with apixaban compared to warfarin [11]. However, in the event of bleeding, it is pertinent to establish the time of the last dose, the source of bleeding, measure baseline coagulation parameters (though they are insensitive to apixaban). If bleeding is clinically significant, local hemostasis can be started, and the dose can be withheld; if major bleeding ensues, activated charcoal can be given if the last dose was less than six hours ago and volume replacement with crystalloids or blood transfusion can be instituted. With refractory bleeding, prothrombin concentrate complex (PCC) at 25-50 U/kg can be used and a hematology consult obtained. In the event of superficial or mucosal bleeding, tranexamic acid can be used. As at this time, there is no evidence that fresh frozen

plasma is effective in reversing bleeding caused by apixaban [25, 26]. It should be noted that apixaban is not dialyzable as it is mainly protein-bound.

Perioperative Management of Patients on Apixaban

Apixaban is recommended to be discontinued 2 to 3 days before surgery depending on whether surgery has a high or low bleeding risk. In patients with renal or hepatic impairment, it is advisable to withhold apixaban starting five days before the procedure. LMWH or heparin could be used in the interval for patients with a high risk of thrombosis [25, 27, 28].

In the immediate post-operative period, adequate hemostasis should be ensured before starting apixaban. Caution should be exercised in the first 48 hours, however, if the risk of thrombosis is high and bleeding risk is high, low dose prophylactic apixaban 2.5 mg BID can be given [25, 26].

Monitoring Drug Activity

Apixaban does not require routine laboratory monitoring. In the rare cases where drug activity needs to be quantified, anti-Factor Xa activity can be measured and shows a strong linear relationship with apixaban over a wide range of drug levels [29]. Undetectable anti-Xa activity likely excludes clinically relevant drug concentrations of apixaban. Prothrombin time (PT) and activated partial thromboplastin time (APTT) are less sensitive are not useful in quantifying drug activity.

OTHER INDICATIONS FOR APIXABAN

In March 2014, the US FDA approved Apixaban for postoperative thromboprophylaxis after hip and knee replacement surgery [30]. This approval was supported by findings from the ADVANCE 1, ADVANCE 2, and ADVANCE 3 clinical trials [31-33]. Apixaban was also approved by the FDA for the treatment of DVT or pulmonary embolism in August 2014, thereby joining other NOACs like rivaroxaban and dabigatran already approved for treatment of the same (Table 3).

NEW DEVELOPMENTS AND FUTURE DIRECTIONS

The next direct Factor Xa inhibitor recently approved by the FDA is edoxaban. The ENGAGE AF – TIMI 48 study (The Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation—Thrombolysis in Myocardial Infarction 48) [34] showed that once-daily dosing of edoxaban

at either 60 mg or 30 mg resulted in less major bleeding, and was noninferior to warfarin in preventing stroke or systemic embolism. Edoxaban, however, comes with a boxed warning that it is less effective in patients with normal (high) creatinine clearance ($\text{CrCl} > 95 \text{ ml/min}$) as the patients in the clinical trial with normal (high) creatinine clearance had an increased risk of stroke compared to warfarin as lower levels of the drug were maintained in the blood. This pharmacokinetic property will likely limit the acceptability of the drug in the marketplace.

The FDA recently approved an antidote (Idarucizumab) for Dabigatran, the first reversal agent approved for a NOAC. Idarucizumab is an antibody fragment that was shown in the REVERSE-AD trial to completely reverse the anticoagulant effects of Dabigatran within minutes [35]. Recent phase 1 trials (ANNEXA-R and ANNEXA-A trials) showed that the recombinant modified human Factor Xa decoy protein, Andexanet, rapidly restored factor Xa activity and thrombin generation and reduced unbound factor Xa inhibitor concentrations in apixaban-treated and rivaroxaban-treated study participants [36]. This is welcome news as one of the common argued disadvantages of the NOAC is the lack of reversal agents in cases of severe bleeding (unlike heparin which has protamine as antidote and warfarin which has vitamin K and fresh frozen plasma).

Future research will be needed to develop reversal agents for the other NOACs and develop better NOACs with better dosing schedules such as weekly dosing. Research in this direction will ultimately aid in reducing the morbidity and mortality associated with thromboembolism in AF and enable patients with AF to have a better quality of life.

CONCLUSION

Either a NOAC or warfarin is recommended for NVAF patients with a CHA₂DS₂-VASc score ≥ 2 , unless contraindicated [24]. Apixaban is a reversible direct Factor Xa Inhibitor which when compared to warfarin showed a reduced incidence of stroke, systemic embolism, and major bleeding. In the US, apixaban has been approved for use in patients with NVAF at risk for thromboembolic events, postoperative thromboprophylaxis in patients after hip or knee replacement surgery and treatment of venous thromboembolisms. The NOACs have not been compared head-to-head. However, clinicians should tailor their selection of NOACs based upon the patient's clinical history, renal and hepatic function, bleeding risk, and anticipated compliance. Clinicians should emphasize strict compliance since the short half-life of NOACs could limit stroke prevention.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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