Novel Oral Anticoagulants in Atrial Fibrillation: Update on Apixaban

Kenechukwu Mezue1*, Chukwudi Obiagwu2, Jinu John3, Abhishek Sharma4, Felix Yang3 and Jacob Shani3

1Department of Medicine, Einstein Medical Center, Philadelphia, PA, USA; 2Department of Medicine, Maimonides Medical Center, Brooklyn, NY, USA; 3Department of Cardiology, Maimonides Medical Center, Brooklyn, NY, USA; 4Department of Cardiology, SUNY Downstate Medical Center, Brooklyn, NY, USA

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.

Keywords: Apixaban, atrial fibrillation, new oral anticoagulants, stroke risk, bleeding risk, factor Xa inhibitor.

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
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-
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
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

| Table 3. Indications for the different NOACs and Warfarin. | 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.
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 (CrCl > 95 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 disadvantage 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 thromboembolism. 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.

ACKNOWLEDGEMENTS

Declared none.

REFERENCES

[1] Go AS, Mozaffarian D, Roger VL, et al. Heart disease and stroke statistics–2014 update: a report from the American Heart Association. Circulation 2014; 129(3): e28-e292.

[2] Benjamin EJ, Wolf PA, D’Agostino RB, et al. Impact of atrial fibrillation on the risk of death: the Framingham Heart Study. Circulation 1998; 98: 946-52.

[3] Stewart S, Hart CL, Hole DJ, McMurray JJ. A population-based study of the long-term risks associated with atrial fibrillation: 20-year follow-up of the Renfrew/Paisley study. Am J Med 2002; 113: 359-64.

[4] Kannel WB, Abbott RD, Savage DD, McNamara PM. Epidemiologic features of chronic atrial fibrillation: the Framingham study. N Engl J Med 1982; 306: 1018-22.

[5] Singer DE, Chang Y, Fang MC, et al. The net clinical benefit of warfarin anticoagulation in atrial fibrillation. Ann Intern Med 2009; 151: 297-305.

[6] Goto S, Bhatt DL, Röther J, et al. Prevalence, clinical profile, and cardiovascular outcomes of atrial fibrillation patients with atrial fibrillation. Am Heart J 2008; 156: 855-63.

[7] Eikelboom JW, Weitz JI. New anticoagulants. Circulation 2010; 121: 1523-32.

[8] Augustevides JG. Breakthroughs in anticoagulation: Advent of the oral direct factor Xa inhibitors. J Cardiothorac Vasc Anesth 2012; 26: 740–5.

[9] Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation: a randomised trial. N Engl J Med 2009; 361: 1139-51.

[10] Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med 2011; 365: 883-91.

[11] Granger CB, Alexander JH, McMurray JJ, et al; for the ARISTOTLE Committees and Investigators. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2011; 365(11): 981-92.

[12] ELIQUIIS® (Apixaban) Approved Product Information. Bristol-Myers Squibb Australia Pty Ltd and Pfizer Pty Ltd; 2013. http://www.bmsa.com.au/products/pages/Home.aspx.

[13] Wang L, Zhang D, Raghavan N, et al. In vitro assessment of metabolic drug-drug interaction potential of apixaban through cytochrome P450 phenotyping, inhibition, and induction studies. Drug Metab Dispos 2010; 38: 448-58.

[14] Wang X, Mondal S, Wang J, et al. Effect of activated charcoal on apixaban pharmacokinetics in healthy subjects. Am J Cardiovasc Drugs 2014; 14(2): 147-54.

[15] Connolly SJ, Eikelboom J, Joyner C, et al; for the AVERROES Steering Committee and Investigators. Apixaban in patients with atrial fibrillation. N Engl J Med 2011; 364(9): 806-17.

[16] European Society of Cardiology. AVERROES trial terminated early: apixaban associated with “important” relative risk reduction for stroke and systemic embolism in AF. Aug 31, 2010.

[17] Weitz JI. New oral anticoagulants in development. Thromb Haemost 2010; 103(1): 62-70.

[18] Davis EM, Packard KA, Knezevich JT, Campbell JA. New and emerging anticoagulant therapy for atrial fibrillation and acute coronary syndrome. Pharmacotherapy 2011; 31(10): 975-1016.

[19] Hohnloser SH, Oldgren J, Yang S, et al. Myocardial ischemic events in patients with atrial fibrillation treated with dabigatran or warfarin in the RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy) trial. Circulation 2012; 125(5): 669-76.

[20] Gonsalves WL, Puthri RK and Pamaik MM. The new oral anticoagulants in clinical practice. Mayo Clin Proc 2013; 88(5): 495-511.

[21] Steffel J, Hindricks G. Apixaban in renal insufficiency: successful navigation between the Scylla and Charybdis. Eur Heart J 2012; 33(22): 2766-8.

[22] Hohnloser SH, Hijazi Z, Thomas L, et al. Efficacy of apixaban when compared with warfarin in relation to renal function in patients with atrial fibrillation: insights from the ARISTOTLE trial. Eur Heart J 2012; 33: 2821-30.

[23] Upeti VV, Song Y, Wang J, et al. Effect of famotidine on the pharmacokinetics of apixaban, an oral direct factor Xa inhibitor. Clin Pharmacol 2013; 5: 59-66.

[24] Ward C, Conner G, Donnan G, et al. Practical management of patients on apixaban: a consensus guide. Thromb J 2013; 11(1): 27.

[25] Eerenberg ES, Kamphuisen PW, Sijpkens MK, et al. Reversal of rivaroxaban and dabigatran by prothrombin complex concentrate: a randomized, placebo-controlled, crossover study in healthy subjects. Circulation 2011; 124: 1573-9.
[26] Ferrandis R, Castillo J, de Andrés J, et al. The perioperative management of new direct oral anticoagulants: a question without answers. Thromb Haemost 2013; 110: 515-22.

[27] Baron TH, Kamath PS, McBane RD. Antithrombotic therapy and invasive procedures. New Engl J Med 2013; 368: 1079-80.

[28] Douketis JD. Pharmacologic properties of the new oral anticoagu-lants: a clinician-oriented review with a focus on perioperative management. Curr Pharm Des 2010; 16: 3436-41.

[29] Cuker A, Siegal DM, Crowther MA, Garcia DA. Laboratory measurement of the anticoagulant activity of the non-vitamin K oral anticoagulants. J Am Coll Cardiol 2014; 64(11): 1128-39.

[30] Bristol-Myers Squibb. US FDA approves Eliquis (apixaban) to reduce the risk of blood clots following hip or knee replacement surgery [press release]. March 14, 2014.

[31] Lassen MR, Raskob GE, Gallus A, et al. Apixaban or Enoxaparin for Thromboprophylaxis after Knee Replacement. N Engl J Med 2009; 361: 594-604.

[32] Lassen MR, Raskob GE, Gallus A, et al. Apixaban versus enoxa-parin for thromboprophylaxis after knee replacement (ADVANCE-2): A randomized, double-blind trial. Lancet 2010; 375: 807-15.

[33] Lassen MR, Gallus A, Raskob GE, et al. Apixaban versus enoxa-parin for thromboprophylaxis after hip replacement. N Engl J Med 2010; 363: 2487-98.

[34] Giugliano RP, Ruff CT, Braunwald E, et al. for the ENGAGE AF-TIMI 48 Investigators. Edoxaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2013; 369(22): 2093-104.

[35] Pollack CV, Reilly PA, Eikelboom J, et al. Idarucizumab for Dabigatran Reversal. N Engl J Med 2015; 373(6): 511-20.

[36] Siegal DM, Curnutte JT, Connolly SJ, et al. Andexanet alfa for the reversal of factor Xa inhibitor activity. N Engl J Med 2015; 373: 2413-24.