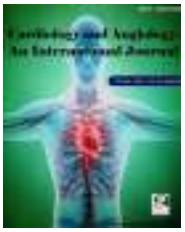

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Analysis of Novel Anticoagulants for Atrial Fibrillation – Pharmacokinetics and Pharmacological Considerations

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Authors' contributions

This work was carried out in collaboration between all authors. Author CC designed the manuscript and wrote the first draft of the manuscript. Authors JDJ and SHJ performed the literature searches and reviewed and revised the manuscript. All authors read and approved the final manuscript.

Review Article

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ABSTRACT

Atrial Fibrillation (AF) is the most common arrhythmia. AF is a major risk factor for stoke. Warfarin has been available for more than 60 years and until recently it was the only oral anticoagulant used for the prevention of stroke. Despite the extensive studies and proven efficacy, its utility is limited by multiple factors. Warfarin interacts with a multitude of drugs and foods, has a delayed onset of action, has a narrow therapeutic range, requires routine lab monitoring and exhibits variable responses in patients. The novel agents dabigatran, rivaroxaban and apixaban have the potential to have some of the limitations of warfarin. This article will discuss the pharmacokinetic and pharmacological considerations and different characteristics of the novel anticoagulants when used for the prevention of AF.

Keywords: Novel anticoagulants; dabigatran; rivaroxaban; apixaban; direct thrombin inhibitor; factor Xa inhibitor.

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1. INTRODUCTION

Atrial Fibrillation (AF) is the most common sustained cardiac arrhythmia and increases in prevalence with age. It has an overall prevalence of 5.5% that increases up to 17.8% in individuals ≥ 85 years of age [1]. As the population ages, the incidence of AF is projected to increase by 2.5 fold in the next 50 years [2]. It is responsible for one-third of the hospitalizations for cardiac rhythm disturbances and is associated with significant morbidity and mortality, including a 4-fold to 5-fold increased risk of stroke and 3-fold increased risk of heart failure, resulting in significant effects on quality of life (QoL) [3]. Stroke is the third leading cause of death and the principal cause of serious, long-term disability in the United States, therefore exerting a high socioeconomic burden [4].

Warfarin is the standard by which all treatments are measured for the prevention of ischemic stroke in AF. However, it has significant limitations which explain its suboptimal use and compliance. It has a slow onset of action, narrow therapeutic window, variable cytochrome P450-dependent metabolism, significant drug-food and drug-drug interactions, and is frequently associated with hemorrhagic complications [5,6,7]. Because of these problems, patients are required to undergo frequent laboratory tests and dosage adjustments, which brings about considerable inconvenience and cost for these patients. These limitations make treatment with warfarin problematic and as a result only about half of all potentially eligible AF patients are treated with warfarin [8]. To address some of the limitations of warfarin, novel oral anticoagulants (NOAC) drugs have been developed. The NOACs include the direct thrombin inhibitor (DTI) dabigatran etexilate and the factor Xa inhibitors (FXaI) rivaroxaban and apixaban. Edoxaban is another FXaI on the horizon for approval. In the completed ENGAGE AF-TIMI 48 phase III study, it was concluded Edoxaban was noninferior to warfarin with respect to prevention of stroke or systemic embolism. Edoxaban was also associated with significantly lower rates of bleeding and death from cardiovascular causes [9].

1.2 Risk Stratification

The risk of stroke is increased in all AF patients. AF leads to blood stasis, causing a thrombus, commonly formed in the left atrial appendage. Mobilization of this thrombus can lead to arterial occlusion, resulting in ischemia, producing a transient ischemic attack (TIA) or stroke [10]. The Framingham Study data indicate that AF is associated with a pro-thrombotic state that increases stroke risk 5-fold [11]. Stroke risk is classified in several risk stratification schemes including CHADS2 (Table 1), CHA2DS2-VASc (Table 2), HAS-BLED (Table 3), AF investigators, Framingham, Birmingham/National Institute for Clinical Excellence (NICE) and The American College of Cardiology (ACC)/American Heart Association (AHA)/ European Society of Cardiology (ESC) guidelines [12,13]. The CHADS2 scoring system is the most widely used to measure AF stroke risk. The system identifies five major risk factors (Congestive heart failure, Hypertension, Age>75 years, Diabetes mellitus, and previous stroke or TIA. Each risk factor is assigned a point, except for prior stroke/TIA which is assigned 2 points [14]. The sum of these points (score 0-6) is reflective of stroke risk [14]. A score of 0 indicates that the risk of stroke is so low that there is no net benefit to anticoagulation. AF patients with a score of ≥2 are considered at high risk for thromboembolic complications and accepted as an indication for anticoagulation. A score of 1 is considered intermediate risk and is more difficult to assess, because some patients have a low risk while others have risks approaching a score of 2. A new risk stratification scheme CHA2DS2 -VASc was created to address the difficult challenge in deciding which patients

with a score of 1 should receive treatment. It also includes new risk factors such as female gender, vascular or heart disease, and age > 65 years, which may provide a more accurate estimation of stroke risk [13]. The HAS-BLED scoring system is used to assess the risk of bleeding in patients with AF being considered for antithrombotic medication. The acronym HAS-BLED represents each of the bleeding risk factors and assigns 1 point for the presence of each of the following: hypertension (uncontrolled systolic blood pressure > 160mmHg), abnormal renal and/or liver function, previous stroke, bleeding history or predisposition, labile international normalized ratios, elderly (>65 years), concomitant drugs and / or alcohol excess [15]. The range is from 0 to 9, with scores of $\geq$ 3 indicating high risk of bleeding [15].

Table 1. $CHADS_2$ risk score [12,13]

$CHADS_2$ risk criteria	**Score**
Congestive heart failure	1
Hypertension	1
Age > 75 years	1
Diabetes mellitus	1
Stroke (prior incidence) or Transient Ischemic Attack	2
Stroke risk based on $CHADS_2$ score	
$CHADS_2$ score	Adjusted stroke rate (% per year)
0	1.9
1	2.8
2	4.0
3	5.9
4	8.5
5	
6	12.5
	18.2

$CHADS_2$ risk score - $CHADS_2$ index to calculate stroke risk in patients with non-valvular atrial fibrillation not treated with anticoagulation

Table 2. CHA_2DS_2 – VASc risk score [12,13]

CHA_2DS_2– VASc risk criteria	**Score**
Congestive heart failure / LV dysfuction (LVEF $\leq$ 40%)	1
Hypertension	1
Age $\geq$ 75 years	2
Diabetes mellitus	1
Stroke/TIA/thromboembolism	2
Vascular disease (prior MI, PAD, or aortic plaque)	1
Age 65-74 years	1
Sex category (female)	1
Maximum score	9

CHA_2DS_2– VASc risk score for predicting stroke and thromboembolism in patients with atrial fribrillation using a novel risk factor-based approach; LV = left ventricular; LVEF = LV ejection fraction; MI = myocardial infarction; PAD = peripheral arterial disease; TIA = transient ischemic attack

Table 3. Bleeding risk (HAS-BLED) scoring system in AF patients [15]

HAS-BLED	Score
Hypertension (systolic blood pressure > 160mmHg	1
Abnormal renal and liver function (1 point each)	1 or 2
Stroke	1
Bleeding tendency/ predisposition	1
Labile INRs (if on warfarin)	1
Elderly (> 65 years)	1
Drugs or alcohol (1 point each)	1 or 2
Maximum Score	9

1.3 Overview of Novel Anticoagulants used in Atrial Fibrillation

1.3.1 Dabigatran etexilate

Dabigatran etexilate is a potent, competitive, reversible DTI [16]. It is a prodrug rapidly and completely converted to the active form dabigatran after oral administration [17]. Dabigatran binds to thrombin inhibiting both free and fibrin-bound thrombin, allowing for effective inhibition of coagulation [17]. Other anticoagulants, such as heparin, indirectly inhibit only free thrombin, allowing fibrin-bound thrombin to continue to activate the coagulation cascade [18]. Dabigatran also inhibits thrombin-mediated effects, including the activation of factors V, VIII, XI and XIII; the cleavage of fibrinogen; and thrombin-induced platelet aggregation [19]. After oral administration, the maximum plasma concentration of dabigatran is reached within 0.5-2 hours [20]. After surgery, the maximum plasma concentrations occurs 6 hours after administration. Delays in peak drug concentration is due to the effects of anesthesia, gastrointestinal paresis, and surgery [17,21]. The delay in absorption usually occurs only on the day of surgery. On subsequent days, rapid absorption of dabigatran etexilate occurs, and maximum plasma dabigatran concentrations are achieved within 2 hours after oral administration [17,21].

1.3.2 Surgery

The number of doses of target specific oral anticoagulants that should be withheld before invasive procedures depends on the type of procedure and the patient's renal function, especially for dabigatran since it is eliminated by the kidney [22]. More doses of dabigatran should be withheld before major surgery than before a minor procedure because of the greater risk of bleeding associated with major surgery (Table 4). In patients with high thrombosis risk in whom adequate hemostasis is achieved shortly after the end of the procedure and postoperative bleeding risk is standard. it may be reasonable to resume anticoagulation within 24 hours after surgery [22]. For surgery, it is recommended to discontinue dabigatran 1 to 2 days (CrCl $\geq$ 50ml/min) or 3 to 5 days (CrCl < 50ml/min) before invasive procedures (Table 4) [23]. Longer discontinuation of dabigatran may be considered in geriatric patients, patients undergoing high risk bleeding or major surgeries, spinal puncture, or placement of a spinal or epidural catheter or port, in whom complete hemostasis may be required [23].

1.3.3 Monitoring

Several methods have been described to monitor the anticoagulant effects of dabigatran, with varying degrees of utility, sensitivity, and precision (Table 5) [16,17,19,24]. The ecarin

clotting time (ECT), is sensitive and precise, and may provide a more accurate measure of dabigatran's anticoagulation compared with other tests [16,19,24]. A drawback is this test is not widely available in the clinical setting [25]. The activated partial thromboplastin time (aPTT) is less precise and sensitive compared to ECT assay [16,17,24]. This test will provide clinicians with a qualitative indication of dabigatran's anticoagulant activity, but not a quantitative anticoagulant effect [16,17,24]. The thrombin time (TT), a measure of the activity of thrombin in plasma, is less useful than the ECT. Prothrombin time (PT) and international normalization ration (INR) are less useful than TT, and all lack appropriate sensitivity making them impractical methods of assessing dabigatran's anticoagulant response.

Table 4. Interruption of target-specific oral anticoagulant therapy for invasive procedure and surgery [39]

Drug (Renal function)	Time of last dose before minor procedure	Time of last dose before major surgery
Dabigatran		
• CrCl > 50 ml/min	1 day (24 hr)	2 days
• CrCl 30-50 ml/min	2 days	4 days
• CrCl ≤ 30 ml/min	4 days	6 days
Rivaroxaban or Apixaban		
• CrCl > 50 ml/min	1 day (24 hr)	2 days
• CrCl 30-50 ml/min	1-2 days	3-4 days
• CrCl ≤ 30 ml/min	2 days	4 days

Therapy should generally be resumed 24-48 hours after a minor procedure and 48-72 hours after major surgery. If un fractioned heparin (UFH) or low-molecular-weight heparin (LMWH) is used as bridging therapy in patients with atrial fibrillation or with thromboembolism who are at high risk for thromboembolism, NOAC should be resumed when the UFH infusion is discontinued and when the next scheduled dose of LMWH would have been given

1.3.4 Dabigatran study

The clinical efficacy and safety of dabigatran versus warfarin for the prevention of stroke or systemic embolism in patients with nonvalvular AF was evaluated in the landmark RE-LY (Randomization Evaluation of Long Term Anticoagulation Therapy) trial. Dabigatran 110mg twice daily or 150mg twice daily were compared with warfarin (target INR 2.0-3.0) [26]. Dabigatran 150mg was superior to warfarin in reducing the incidence of stroke and embolism with no significant difference in major bleeding. The primary outcome measure occurred at a rate of 1.53% per year in the dabigatran 110mg group, 1.11% per year in the dabigatran 150mg group and 1.69% per year in the warfarin group. The 110mg group met the predefined non-inferior criteria; however, the 150mg arm demonstrated superior efficacy compared with warfarin (relative risk [RR] 0.66; 95% confidence interval [CI] 0.53,0.82; $p<0.001$). Rates of major bleeding events were similar between warfarin and the 150mg group, but they were significantly lower than warfarin in the 110mg group (RR 0.80; 95% CI 0.63, 0.93; $p=0.003$). Additionally, life-threatening bleeding events and intracranial bleeding occurred at rates significantly lower, but significantly higher rates of dyspepsia were reported for both dabigatran etexilate groups when compared to warfarin [26].

Table 5. Laboratory test to consider when concerned about bleeding with Warfarin and novel oral anticoagulants [22]

Laboratory test	Warfarin	Dabigatran	Rivaroxaban	Apixaban	Comments
Scr and CBC with platelets	Potentially useful	Potentially useful	Potentially useful	Potentially useful	Monitor serum calcium concentration if transfusing blood
INR or PT	Potentially useful; value increased	Potentially useful; value increased; use central laboratory because point of care test can give much higher values	Potentially useful; value increased	Potentially useful; value increased	PT may be considered because INR may not be calibrated for the NOACs; PT more responsive to factor Xa inhibitors than to dabigatran; limited ability to quantify amount of drug
aPTT	Potentially useful; value somewhat increased	Potentially useful; value increased, but aPTT response flattens at higher serum drug concentration	Potentially useful; value increased	Potentially useful; value increased	aPTT more responsive to dabigatran than FXaI; limited ability to quantify amount of drug
TT	Clinical use limited	Potentially useful; very sensitive at low concentration but not at higher concentrations	Inadequate measure	Inadequate measure	Limited ability to quantify amount of dabigatran
ECT	Clinical use limited	Potentially useful if available; potential ability to quantify amount of drug present	Inadequate measure	Inadequate measure	Limited availability; potential quantitative test
Diluted TT	Clinical use limited	Potentially useful if available; potential ability to quantify amount of drug present	Inadequate measure	Inadequate measure	Lack of standardization and potential differences in measured results among laboratories; may have limitations at low dabigatran concentrations
Chromogenic antifactor Xa assay	Inadequate measure	Inadequate measure	Potentially useful; value increased	Potentially useful; value increased	Limited availability; non standardized; results may vary among laboratories where available

1.4 Pharmacological Considerations

Dabigatran is eliminated primarily unchanged in the urine. After oral administration, dabigatran exposure was approximately 2.7 times high in patients with moderate renal insufficiency and 6 times higher in patients with severe renal insufficiency compared with patients without renal insufficiency [19]. For patients with CrCl > 30ml/min, the recommended dose is 150mg taken orally, twice daily, with or without food. For patients with severe renal impairment (CrCl 15-30ml/min), the recommended dose is 75mg twice daily [24]. This FDA-approved dosage of 75 mg twice a day is based on pharmacokinetic simulations [27]. This regimen has not been investigated for any other indication, including stroke prevention in atrial fibrillation or in patients with stages IV or V chronic kidney disease (CKD) [27]. Dabigatran is not recommended for patients with CrCl < 15ml/min or on dialysis.

When converting from warfarin therapy to dabigatran, discontinue warfarin and start dabigatran when INR is below 2.0. The conversion of dabigatran to warfarin is based on patient's CrCl. For patients with CrCl is > 50ml/min, initiate warfarin 3 days before discontinuation of dabigatran. For patients with CrCl 31-50ml/min, initiate warfarin 2 days before discontinuation of dabigatran. For patients with CrCl 15-30ml/min, initiate warfarin 1 day before discontinuation of dabigatran [23].

When converting from a parenteral anticoagulant, start dabigatran 0 to 2 hours before the time that the next dose of the parenteral anticoagulant is to be administered or at the time of discontinuation of a continuously administered parenteral anticoagulant (e.g., intravenous unfractionated heparin). If converting from dabigatran to a parenteral anticoagulant, it is recommended to wait 12 hours (CrCl $\geq$ 30ml/min) or 24 hours (CrCl < 30ml/min) after the last dose of dabigatran before initiating treatment with a parenteral anticoagulant [23]. To reverse the anticoagulant effect of dabigatran, it is mediated through direct inhibition of the action of thrombin (Table 6). Human data shows no benefit of four-factor prothrombin complex concentrate (PCC) (Cofact) for reversing dabigatran due to limited effects [28]. Recombinant factor VIIa (rFVIIa) and activated prothrombin complex concentrate (aPCC) have also been studied and have shown limited effect. However, aPCC on dabigatran-treated blood had a greater impact than four-factor PCC and rFVIIa [28]. A specific reversal agent for dabigatran is not available. Protamine sulfate and vitamin K are not expected to affect the anticoagulant activity. Hemodialysis can remove dabigatran; however the clinical experience supporting the use of hemodialysis as a treatment for bleeding is limited. The administration of platelet concentrates can be considered in cases where thrombocytopenia is present or long-acting anti-platelets have been used [23].

1.4.1 Rivaroxaban

Rivaroxaban is an orally bioavailable factor Xa inhibitor that selectively blocks the active site of factor Xa and does not require a cofactor (such as Anti-thrombin III) for activity. It is competitively direct, reversible, rapid and dose-dependent inhibitor of FXa [29,30]. It acts at the convergence of the intrinsic and extrinsic pathway, thus inhibiting thrombin production via both pathways. Rivaroxaban inhibits FXa with more than 100,000-fold greater selectivity than other biologically relevant serine proteases, such as thrombin, trypsin, plasmin, factor VIIa, factor IXa, urokinase and activated protein C [29]. In addition to inhibiting free FX, it also inhibits FXa bound to the prothrombinase complex, raising the possibility that it could inhibit clot-bound FXa [29]. The maximum plasma concentrations of rivaroxaban appear 2 to 4 hours after tablet intake.

1.4.2 Surgery

Rivaroxaban should be discontinued at least 24 hours before surgical procedures to reduce the risk of bleeding. It should be restarted as soon as adequate hemostasis has been established, noting that the time to onset of therapeutic effect is short. For surgery rivaroxaban should be held 2 days for major surgery in patients with CrCl >50ml/min, 3-4 days in patients with CrCl of 30-50ml/min and at least 4 days if CrCl is < 30ml/min (Table 3) [22].

Table 6. Therapeutic interventions for reversal of oral anticoagulants based on urgency [39]

Level of urgency	Warfarin	Dabigatran	Rivaroxaban or Apixaban
No rush (> hr)	Withhold warfarin and consider oral phytonadione, with dose based on INR	Withhold drug and monitor clinical status and pertinent laboratory test	Withhold drug and monitor clinical status and pertinent laboratory test
Expected (1-24 hr)	Withhold drug and give oral phytonadione (1-5mg) or low dose IV phytonadione (0.25-5mg), with dose based on initial INR and post reversal INR (checked 24hr after dose)	Withhold drug, give activated charcoal if last dose was taken within past 2hr, and use prolonged hemodialysis (>2hr)	Withhold drug and give activated charcoal if last dose was taken within past 2 hr and repeat 6 hr after the last dose.
Emergent (<1hr)	Withhold drug, consider high-dose IV phytonadione (depending on anticipated need to restart warfarin), and consider clotting factor supplement (listed in order of preference): • PCC4 • Build PCC4 wth PCC3 + rFVIIa • aPCC • PCC3 • rFVIIa • FFP	Withhold drug, give activated charcoal if last dose was taken within past 2hr, use prolonged hemodialysis (>2hr), and consider clotting factor supplement (listed in order of preference): • aPCC • PCC4 • Build PCC4 with PCC3 + rFVIIa	Withhold drug, give activated charcoal if last dose was taken within past 2hr and repeat 6hr after the last dose, and consider clotting factor supplement (listed in order of preference) • PCC4 • aPCC • Build PCC4 with PCC3 plus rFVIIa • PCC3

1.4.3 Monitoring

Based on the pharmacodynamics and pharmacokinetic predictability of rivaroxaban, routine monitoring is unnecessary. However in special situations of surgery, hemorrhage or overdose, measuring the effect of these anticoagulants may be critical and necessary (Table

5). Unlike dabigatran, the ECT is not prolonged in rivaroxaban. It is not sensitive and currently is not useful in monitoring. The effects of rivaroxaban on aPTT are less sensitive than prothrombin time (PT), and PT is more sensitive at higher concentrations. Both laboratory tests are widely available in a hospital setting [31]. The Heptest is a used to measure the inhibition of exogenous FXa, based on the ability of heparin to catalyze to inactivated FXa. This test is sensitive at low and high concentrations, but is not widely available and lacks FDA approval [32,33]. Prothrombinase-inducing clotting time (PiCT) has been evaluated as a way to measure the anticoagulant effect of rivaroxaban, although it is only approved to measure the effects of UFH and LMWH. PiCT has been shown to be sensitive to low concentrations of rivaroxaban [34]. PiCT is not available in all clinical settings, but the high sensitivity of the test and the Heptest provide strong evidence for their use over aPTT and PT in measuring rivaroxaban activity [31]. Chromogenic antifactor FXa assay is accurate and precise and the most promising assay for measuring the direct effects of rivaroxaban. The strategies for reversing rivaroxaban are largely theoretical and based on limited animal and human data (Table 6). The effects of rivaroxaban appears to be reversed by a PCC [28].

1.4.4 Rivaroxaban study

The Rivaroxaban Once Daily Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF) was a double-blinded randomized comparison of once daily rivaroxaban 20mg or 15mg (in patients with CrCl of 30-49ml/min) with warfarin (titrated to achieve an INR 2.0 – 3.0 with target sham INR of 2.5) for the prevention of thromboembolism in patients with AF [35]. The primary efficacy endpoint was the incidence of stroke (hemorrhagic or ischemic) or systemic embolism, and the primary safety endpoint was the composite of major and non-major clinically relevant bleeding events. The study found that rivaroxaban was non-inferior to warfarin when analyzed by intent-to-treat principle (hazard ratio [HR] 0.88, $p=0.117$). Patients in the rivaroxaban group had lower rates of stroke or non-CNS embolism (HR of 0.79, $p<0.001$) with similar rates of major bleeding and adverse events compared with the warfarin group. However, the rates of fatal bleeding and intracranial bleeding occurred at significantly lower rates in the rivaroxaban group. Rates of myocardial infarction (MI) were similar between the groups [35].

1.5 Pharmacological Considerations

For nonvalvular atrial fibrillation in patients with a CrCl >50ml/min, the recommended dose is 20mg taken orally once daily with the evening meal. For patients with CrCl 15 to 50ml/min, the recommended dose is 15mg once daily with the evening meal. Rivaroxaban should be avoided in patients with CrCl < 15ml/min [36]. For patients unable to swallow whole tablets, rivaroxaban may be crushed and mixed with applesauce immediately prior to use. Rivaroxaban can also be administered via nasogastric or gastric feeding tube by crushing the tablet and mixing it with 50ml of water. Avoid administration distal to the stomach, which can result in reduced absorption and reduced drug exposure. When converting from warfarin to rivaroxaban, discontinue warfarin and start rivaroxaban as soon as the INR is below 3 to avoid periods of inadequate anticoagulation [36]. When switching rivaroxaban to warfarin, discontinue rivaroxaban and begin both a parenteral anticoagulant and warfarin at the time the next dose of rivaroxaban would have been administered. Rivaroxaban affects INR, therefore the INR measurement made during co-administration with warfarin may not be useful for determining the appropriate dose of warfarin [36]. The strategy for reversing rivaroxaban are largely theoretical and based on limited animal and human data (Table 6)

[28]. The effects of rivaroxaban appear to be reversed by aPCC [28]. FFP data for reversing the effects of rivaroxaban are not available. Human data on the effects of four-factor PCC and vFVIIa on rivaroxaban – treated patient blood samples were inconsistent in studies. Conversely, aPCC had a consistent impact on thrombin generation in rivaroxaban-treated blood [28].

1.5.1 Apixaban

Apixaban is an oral, reversible, and selective active site inhibitor of FXa. It does not require antithrombin III for antithrombotic activity. It inhibits free and clot bound FXa and prothrombinase activity. It has no direct effect on platelet aggregation, but indirectly inhibits platelet aggregation induced by thrombin. By inhibiting FXa, apixaban decreases thrombin generation and thrombus development [37].

1.5.2 Surgery

Apixaban should be discontinued at least 48 hours prior to elective surgery or invasive procedure with a moderate or high risk of unacceptable or clinically significant bleeding. Apixaban should be discontinued at least 24 hours prior to elective surgery or invasive procedure with low risk of bleeding or where the bleed would be non-critical in location and easily controlled. For minor surgery, apixaban is recommended to be interrupted for 24 hours in patients with CrCl > 50ml/min, 1-2 days CrCl 30-50ml/min and 48 hours CrCl $\leq$ 30ml/min (Table 4). In major surgeries the time of last dose should be 2 days in patients with CrCl >50ml/min, 3 to 4 days CrCl 30 to 50 ml/min and 4 days CrCl $\leq$ 30ml/min [37].

1.5.3 Monitoring

Apixaban does not require routine monitoring because of the pharmacodynamics and pharmacokinetic predictability [25]. Though FXa inhibition, apixaban prolongs clotting test such as PT, INR and aPTT. The changes observed in these tests at the expected therapeutic dose are small, subject to a high degree of variability and not useful in monitoring the anticoagulant effect [37]. The laboratory tests which are potientially useful in monitoring apixaban are INR, PT, aPTT and chromogenic antifactor Xa assay (Table 5). The PT may be considered because INR may not be calibrated for target specific oral anticoagulant. PT is more sensitive to FXa inhibitors than to dabigatran, but is limited in its ability to quantify amount of drug [38]. In contrast to subcutaneous FXa inhibitors which have no effect on PT, oral FXa inhibitors cause prolong PT in a concentration dependent, incremental manner through its inhibition of free and bound FXa in human studies [25]. Activated partial thromboplastin time (aPTT) is useful but has limited ability to quantify amount of drug. It is not as responsive to apixaban as dabigatran. Chromogenic antifactor Xa assay may help measure the direct effects of apixaban. Anti FXa assays are widely available and commonly used in clinical practice. The assay is not standardized and results may vary among laboratories where available [38]. The thrombin time (TT), ECT and diluted TT inadequately measure apixaban effects and are not useful.

1.5.4 Study

Apixaban was evaluated as stroke prevention in AF in two large randomized, double-blinded trials: The Apixaban Versus Acetylsalicylic Acid to Prevent Stroke (AVERROES) and the Apixaban for Reduction in Stroke and other Thromboembolic Events in Arial Fibrillation (ARISTOTLE) trials [39,40]. The AVVEROES trial compared the efficacy of apixaban 5mg

twice daily with aspirin 81mg to 325mg daily for stroke and systemic embolism prevention. Because of favorable outcome, the study was terminated early by the Data and Safety Monitoring Board. The results showed a clinically significant reduction in stroke and systemic embolic rates in the apixaban group (HR 0.45, p<0.001). Specifically, apixaban lowered mortality by 21% and reduced thromboembolic events by 55% compared to ASA [39]. Apixaban did not significantly increase the risk of major bleeding (HR 1.13, p=0.57) or intracranial bleeding (HR 0.85, p=0.69) [39].

Table 7. Comparison of pharmacokinetic and pharmacodynamic properties of NOAC agents [23,36,38,41]

Variable	Dabigatran	Rivaroxaban	Apixaban
Dosage	**150mg twice daily with or without food**	**20mg once daily with evening meal**	**5mg twice daily with or without food**
Dosage adjustments for special populations • Moderate renal impairment (CrCl 30-50ml/min • Severe renal impairment (CrCl of < 30ml/min • CrCl < 15ml/min or on dialysis Moderate hepatic impairment (Child-Pugh class B)	No adjustment 75mg twice daily with or without food Not recommended Use with caution	Reduce dose to: 15mg once daily with evening meal if CrCl 15 to 50ml/min Not recommended Not recommended	Reduce dose to: 2.5mg once daily in patients with 2 of the following characteristics: • Age ≥ 80 years • Weight ≤ 60kg • SCr ≥ 1.5mg/dL No data of patient use No Adjustment
Bioavailability, %	7.2	80	50
Volume of distribution, L	60-70	50	21
Time to peak conc, hr	1.5-3	2-4	1-3
Half-life, hr	12-17	5-9	9-14
Protein binding, %	35	92-95	87
Prodrug	Yes	No	No
Metabolism	Conjugation	Oxidation (CYP3A4 and CYP2J2)	Oxidation (CYP 3A4 and conjugation
Drug interactions • Strong inducers of CYP3A4 and P-gp	Rifampin (avoid concomitant use)	Rifampin, carbamazepine, phenytoin and St. john's wort (avoid concomitant use)	Rifampin carbamazepine, phenytoin and St. John's wort (avoid concomitant use)

• Strong inhibitors of CYP3A4 and P-gp	Dronedrone, systemic ketoconazole (if CrCL 30-50mg/min reduce dabigatran to 75mg bid; if CrCl 15-30mg/min (avoid concomitant use	Ketoconazole,ritonavir, clarithromycin and fluconazole (avoid concomitant use)	Ketoconazole itraconazole, ritonavir or clarithromycin (decrease apixaban to 2.5mg twice daily with concomitant use. Avoid use in patients already taking apixaban at the dose of 2.5mg twice daily

CrCL=creatine clearance, conc=concentration, SCr=serum creatinine, CYP=cytochrome P450 isoenzyme, P-gp=permeability glycoprotein

The ARISTOTLE trial compared apixaban with warfarin. The results demonstrated that apixaban reduced stroke and system embolism by 21% (p=0.01), bleeding by 31% (p<0.001), and lowered mortality by 11% (p=0.047). Apixaban was better tolerated than warfarin, with fewer drug discontinuations [39].

1.6 Pharmacological Considerations

Most of apixaban (>50%) is recovered in feces and about 25% in urine after oral administration. The recommended dose for most patients is 5mg twice daily. Apixaban 2.5mg twice daily is recommended in patients with any 2 of the following characteristics: age $\geq$ 80 years old, body weight $\leq$ 60 kg, serum creatinine $\geq$ 1.5mg/dL [37]. No data information of use in patients with CrCl < 15 ml/min or on dialysis [42]. When converting from warfarin, it should be discontinued and apixaban started when the INR is below 2.39 when switching from apixaban to warfarin, it is imperative to remember that apixaban can affect INR measurements during coadministration with warfarin. Therefore, the INR may not be useful for determining the appropriate dose of warfarin [37]. If continuous anticoagulation is necessary, discontinue apixaban and begin both parenteral anticoagulant and warfarin at the time the next dose of apixaban would have been taken. Discontinue the parenteral anticoagulant when INR is within acceptable range [37]. The reversal strategy for apixaban is similar to rivaroxaban. In patients requiring an emergent intervention, PCC4 is preferred based on limited data and clinical experience (Table 6) [38]. If PCC4 is not available PCC3 may be considered as a potential reversal option [38]. Also a combination of PCC3 plus rFVIIa could be used to build a PCC4. This combination has no specific data available in literature, but this approach may be considered because it has been studied in the setting of warfarin reversal. While these products may aid in the reversal of rivaroxaban and apixaban, none are true antidotes. The ideal reversal agent may be recombinant (r) – antidote, PRT064445, a catalytic inactive form of FXa, which is undergoing development in preclinical trials [41].

2. CONCLUSION

The novel anticoagulants for improving stroke prevention in patients with AF have shown great promise. These agents mitigate many of the management related issues surrounding

warfarin and have demonstrated significantly lower rates of intracranial hemorrhage. Although similar in indication, the NAOCs possess unique characteristics in determining their use in specific patient populations (Table 7). An individualized approach is warranted due to the pharmacological and pharmacokinetic considerations of these medications. The risks for thromboembolism and bleeding in patients needs to be balanced since the novel oral anticoagulants lack specific monitoring options and reversal strategies.

CONSENT

Not applicable.

ETHICAL APPROVAL

Not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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