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REVIEW ARTICLE

Prophylaxis of Stroke and a Therapeutic Approach to Venous Thromboembolism Using Novel Oral Anticoagulants (NOAC's)

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ABSTRACT

In the prophylaxis of stroke in Non valvular Atrial Fibrillation (NVAF) as well as Deep Vein Thrombosis (DVT) and Pulmonary Embolism (PE) treatment, the Novel Oral Anticoagulants are becoming popular management option. These NOACs have efficacy similar to that of Warfarin along with non inferior safety profiles. Though Warfarin has been widely used because of its anticoagulant effect and also has a probable reversibility in terms of bleeding, it may also be disadvantageous sometimes in few cases such as food interactions, drug and drug interaction, having a poor and unpredictable therapeutic response. The use of Novel Oral Anticoagulants (NOACs), approved by U.S Food and Drug Administration (FDA) rendered a new hope in patients who needed anticoagulant therapy. There are about four Novel Oral Anticoagulants approved by FDA, which includes Dabigatran (direct thrombin inhibitor), Rivaroxaban, Apixaban and Edoxaban (selective factor Xa Inhibitors). The predictable pharmacokinetics and minimal drug interactions of apixaban should allow for safe anticoagulation in the majority of patients, including temporary interruption for elective procedures. The main aim is to provide better treatment and prophylaxis of stroke, venous thromboembolism and Pulmonary Embolism using Novel Oral Anticoagulants (NOACs) as they exhibit minimal adverse effects when compared to Warfarin.

KEYWORDS

Stroke, Non valvular Atrial Fibrillation (NVAF), Deep Vein Thrombosis (DVT), Warfarin, Dabigatran, Rivaroxaban, Apixaban, Edoxaban

INTRODUCTION

For many years, in the prevention of stroke in setting of atrial fibrillation, Deep Vein Thrombosis (DVT) and in prevention of Pulmonary Embolism (PE), the vitamin K antagonist, Warfarin was only used as an oral anticoagulant. Though Warfarin has been widely used because of its anticoagulant effect and also has a probable reversibility in terms of bleeding, it may also be disadvantageous sometimes in few cases such as food interactions, drug and drug interaction, having a poor and unpredictable therapeutic response etc. Over the past few decades, Enoxaparin, Dalteparin and Fondaparinux, the anticoagulants which were injected subcutaneously have probably shown a good response when compared to Warfarin without any monitoring. These drugs can be used as a monotherapy for anticoagulation in the settings of Warfarin failure, cancer and in prophylaxis of short or long term Venous Thromboembolism (VTE). However, these

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anticoagulants which were used subcutaneously were found to be insignificant by the patients due to their cost, transportation and less readily reversible nature. These anticoagulants had to be injected once in a day and thereby were considered to be suboptimal by the patients. The use of Novel Oral Anticoagulants (NOACs), approved by U.S Food and Drug Administration (FDA) rendered a new hope in patients who needed anticoagulant therapy. There are about four Novel Oral Anticoagulants approved by FDA, which includes Dabigatran (direct thrombin inhibitor), Rivaroxaban, Apixaban and Edoxaban (selective factor Xa Inhibitors). These Novel Oral Anticoagulants offer a new hope for the patients who need anticoagulant therapy because these are beneficial in having less drug and drug as well as food and drug interactions. Also, these are predictable oral anticoagulants showing a probable therapeutic response without any monitoring. In this review, the characteristics, mechanism of action, indications, contraindications, and dosing recommendations of these four Novel Oral Anticoagulants are discussed.

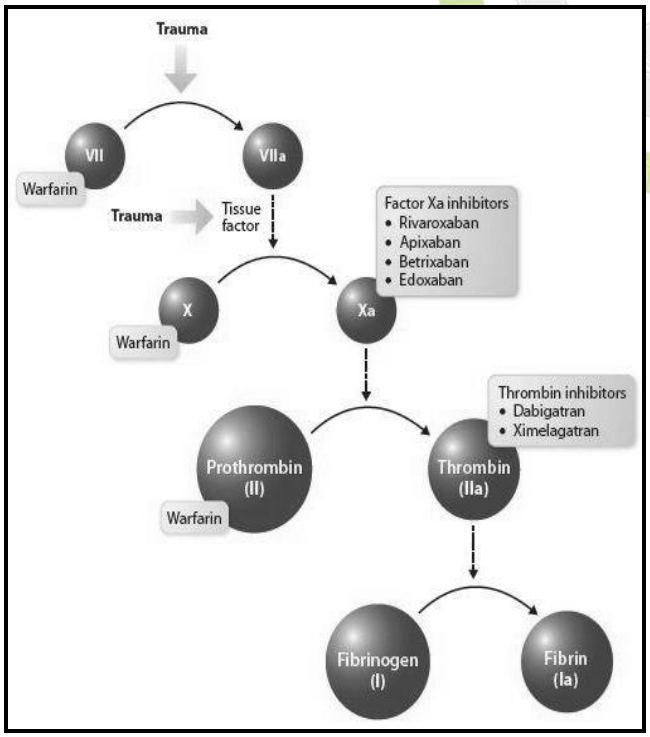

Figure 1: Cascade of coagulation along the tissue factor pathway and thrombin inhibitors, direct factor Xa targets[24]

Dabigatran Etexilate

Mechanism of Action/ Pharmacodynamics

Dabigatran is an oral anticoagulant and a competitive direct thrombin inhibitor which helps in preventing the formation of thrombus by obstructing the thrombin which is free and clot-bound. It also inhibits the aggregation of platelets which is induced by thrombin. This oral anticoagulant extends the thrombin time and coagulation markers activated partial thromboplastin time. APTT provides an approximate anticoagulant effect, with a median of 52 seconds (range: 40–76 seconds) in patients receiving the 150-mg dose[1]. Although routine monitoring is not required, an aPTT ≥ 2.5 times that of control may suggest supra-therapeutic anticoagulation. INR is typically insensitive to dabigatran exposure. The drug is metabolized in the liver, where the prodrug is converted to dabigatran. It is excreted mostly renally and has a half-life of 12–17 hours[2].

Indications

- Reduction in risk of stroke and systemic embolism in NVAF.
- Treatment of DVT and PE following 5-10 days of parenteral anticoagulation.
- Reduction in risk of recurrence of DVT and Pulmonary Embolism in previously treated patients[1].

Contraindications

- Active pathological bleeding (i.e. clinically significant bleeding secondary to a disease process or injury).
- Known serious hypersensitivity reaction to dabigatran (e.g. Anaphylaxis).
- Mechanical prosthetic heart valve[3].

Dosing

Dabigatran's 110-mg dose is not available in the United States. The FDA approved the 150-mg dose but not the 110-mg dose due to its inability to identify any subgroup in which the use of the lower dose would not represent a substantial disadvantage[4].

Dosing guidelines1 is as follows:

- For stroke and systemic embolism prophylaxis in patients with nonvalvular atrial fibrillation (NVAF): 150 mg orally twice a day. For renal dosing in those with creatinine clearance (CrCl) of 15–30: 75 mg orally twice a day (dosing is based on pharmacokinetic rather than clinical trial data). For those with CrCl < 15 or in hemodialysis, dosing is not defined.
- For recurrent DVT/PE prophylaxis: 150 mg orally twice a day. For those with CrCl < 30 or in hemodialysis, dosing is not defined.
- For DVT/PE treatment: 150 mg orally twice a day. For those with CrCl < 30 or in hemodialysis, dosing is not defined.
- Dosing for hepatic impairment is not defined.

Dabigatran vs. Warfarin

Dabigatran has been studied in multiple clinical trials and compared to Warfarin in most of them. In the RE-LY trial, dabigatran was non inferior to Warfarin in stroke and systemic embolism prophylaxis in NVAF patients at a dose of 110 mg and was superior to Warfarin in stroke and systemic embolism prophylaxis in NVAF patients at a dose of 150 mg[5]. In the RE-COVER and RE-COVER II trials, dabigatran was shown to have similar efficacy to Warfarin in the treatment of VTE[6,7]. In the REMEDY (vs. Warfarin) and RESONATE (vs. placebo) trials, dabigatran was found to be effective in the extended treatment of VTE[8]. The risk of major bleeding was similar with dabigatran 150 mg and Warfarin except for patients 75 years or older, in whom there was a trend toward higher incidence of major bleeding on dabigatran (hazard ratio [HR]: 1.2, 95% confidence interval [CI]: 1.0–1.4). There also was a higher rate of major gastrointestinal bleeding in patients taking dabigatran 150 mg than in patients taking Warfarin (1.6% vs. 1.1%, respectively) and a higher rate of any gastrointestinal bleeding as per the study (5.7% vs. 3.9%, respectively)[1].

Rivaroxaban

Mechanism of Action/ Pharmacodynamics

Rivaroxaban is a selective factor Xa inhibitor. It doesn't require antithrombin for activity, but it inhibits both free and clot-bound factor Xa and prothrombinase activity. It has no direct effect on platelet aggregation, but indirectly inhibits platelet aggregation induced by thrombin. By inhibiting factor Xa, rivaroxaban decreases thrombin generation.

Rivaroxaban reaches maximum plasma concentrations and inhibits factor Xa activity at 2–4 hours. The half-life of rivaroxaban is 5–9 hours in healthy subjects 20–45 years of age and 11–13 hours in the elderly. Coagulation markers, including aPTT, thrombin time and INR, are typically not used to monitor its anticoagulant effects. [9] The drug is metabolized in the liver by the cytochrome P450 enzyme's 2J2, 3A4/5 Substrate. Excretion is 66% renal and 28% fecal[2].

Indications

- Stroke risk reduction in NVAF.
- DVT and PE treatment.
- Reduction in risk of DVT and PE recurrence.
- DVT prophylaxis after knee and hip replacement surgery.

Contraindications

- Active pathological bleeding.
- Severe hypersensitivity reaction to rivaroxaban (e.g. anaphylactic reactions).
- Mechanical heart valves[9].

Dosing

Dosing guidelines for rivaroxaban are as follows:

- For stroke reduction in NVAF: 20 mg once daily with dinner. For renal dosing in those with CrCl 15–50: 15 mg once daily. Avoid use in patients with CrCl < 15 ml/min.
- For DVT and PE treatment: 15 mg twice daily with food for the first 21 days; on day 22, transition to 20 mg once daily with food at the same time each day. Avoid use in patients with CrCl < 30 ml/min.

- For reduction in the risk of recurrence of DVT and PE: 20 mg once daily with food at the same time each day. Avoid use in patients with CrCl < 30 ml/ min.
- For DVT prophylaxis after knee or hip replacement surgery: 10 mg once daily. Avoid use in patients with CrCl < 30 ml/min.
- Avoid use in patients with moderate and severe hepatic impairment or with any hepatic disease associated with coagulopathy[9].

Rivaroxaban vs. Warfarin

Rivaroxaban was compared to Warfarin in the ROCKET AF trial, where it showed efficacy in the reduction of stroke and non-central nervous system embolism in patients with NVAF at moderate or high risk for stroke. Major bleeding rates were comparable to Warfarin[10]. In a pooled analysis of the EINSTEIN-DVT and EINSTEIN-PE studies, the single-drug approach with rivaroxaban resulted in similar efficacy to standard therapy (enoxaparin 1 mg/kg twice daily and Warfarin) and was associated with a lower rate of major bleeding (46% relative risk reduction, 0.7% absolute risk reduction)[11-13].

In EINSTEIN-EXT, patients on placebo had a significantly greater rate of recurrent VTE than patients on rivaroxaban (42 events vs. 8 events, HR [95% CI]: 0.18 [0.09–0.39], P<0.0001)[11]. In the RECORD trials, patients taking rivaroxaban 10 mg daily had significantly lower rates of postoperative VTE than patients taking enoxaparin 40 mg daily, with comparable bleeding events[14-16].

Apixaban

Mechanism of Action/ Pharmacodynamics

Apixaban is a selective factor Xa inhibitor. It does not require antithrombin to exert its antithrombotic activity. The drug inhibits free and clot-bound factor Xa as well as prothrombinase activity. It has no direct effect on platelet aggregation but indirectly inhibits platelet aggregation induced by thrombin. By inhibiting factor Xa, apixaban decreases thrombin generation and thrombus development. As a result of factor Xa inhibition, apixaban prolongs clotting tests such as prothrombin time, INR and aPTT. However, changes observed in these clotting tests at the expected therapeutic dose are small, subject to a high degree of variability and not useful in monitoring the anticoagulation effect of apixaban[17]. The drug is metabolized in the liver by the cytochrome P450 enzyme's 1A2, 2C8, 2C9, 2C19, 2J2 and 3A4 (primary) substrates. Excretion is 27% renal and the rest fecal. The half-life of apixaban is 12 hours[2].

Indications

- Stroke risk reduction in NVAF.
- DVT/PE treatment and reduction in risk of recurrence.
- Prophylaxis of DVT after hip or knee replacement surgery.

Contraindications

- Active pathological bleeding
- Severe hypersensitivity reaction to apixaban (e.g. anaphylactic reactions).
- Mechanical heart valves[18]

Dosing

- For stroke reduction in NVAF: 5 mg twice daily in most patients; 2.5 mg twice daily in patients with at least two of the following — age ≥ 80 years, body weight ≤ 60 kg, serum creatinine ≥ 1.5 mg/dL, or in patients taking drugs that are strong dual inhibitors of cytochrome P450 3A4 (CYP3A4) and P-glycoprotein (e.g. ketoconazole, itraconazole, ritonavir and clarithromycin).
- No dose adjustment is required for patients with mild, moderate or severe renal impairment alone. There is also no dose adjustment in NVAF patients with end-stage renal disease maintained on hemodialysis, unless they satisfy two of the aforementioned dose-reduction criteria.
- For prophylaxis of DVT after hip or knee replacement surgery: 2.5 mg twice daily, 12 to 24 hours after surgery, for 35 days after

hip replacement or for 12 days after knee replacement surgery. No dose adjustment is needed in patients with renal impairment.

- No dose adjustment is required in mild hepatic impairment (Child-Pugh A). Dosing recommendations cannot be provided in patients with moderate hepatic impairment (Child-Pugh B). Apixaban is not recommended in patients with severe hepatic impairment (Child-Pugh C).

Apixaban (vs) Warfarin

In the ARISTOTLE study, Apixaban was found to be superior to Warfarin (21%/year relative risk reduction, 0.33%/year absolute risk reduction) in reducing the risk of stroke and systemic embolism in the setting of NVAF.

Purely ischemic strokes occurred with similar rates on both drugs. Major bleeding rates were less with Apixaban than with Warfarin (31%/year relative risk reduction, 0.96%/year absolute risk reduction)[19].

Edoxaban

Mechanism of Action/ Pharmacodynamics

Edoxaban is an oral anticoagulant that reversibly and directly inhibits factor Xa[20]. By inhibiting factor Xa, edoxaban decreases thrombin generation and thrombus development. The drug also indirectly inhibits platelet aggregation. Edoxaban is minimally metabolized in the liver by the cytochrome P450 enzyme's 3A4 substrate. Its half-life is 10–14 hours, with 50% of the drug being renally excreted[2].

Indications

- Reduction in the risk of stroke and systematic embolism in patients with Non Valvular Atrial Fibrillation (NVAF).

Contraindications

- Patients with active pathological bleeding.
- Mechanical heart valves.
- Mitral stenosis- Moderate to severe[21]

Dosing

- For stroke prophylaxis in NVAF: 60 mg once daily in patients with CrCl > 50 to ≤ 95 ml/min. Edoxaban should not be used in patients with a CrCl > 95 ml/ min, as the higher rate of drug metabolism in such patients was associated with an increased rate of ischemic stroke compared to patients treated with Warfarin. Reduce the dose to 30 mg once daily in patients with CrCl of 15–50 ml/min. Avoid use in patients with a CrCl < 15 ml/min. There is no data regarding the use of edoxaban in hemodialysis patients.
- For treatment of DVT and PE: 60 mg once daily. The dose is reduced to 30 mg once daily in patients with CrCl of 15–50 ml/min or body weight ≤ 60 kg or who use certain P-glycoprotein inhibitors[22].

Edoxaban (vs.) Warfarin

- In the ENGAGE AF-TIMI 48 study, edoxaban was noninferior to Warfarin for the primary efficacy endpoint of stroke or systemic embolization in the setting of NVAF (HR: 0.68, 95% CI: 0.55–0.84), and the rates of cardiovascular death with edoxaban and Warfarin were 2.95% per year versus 3.59% per year, respectively. Edoxaban also was associated with less major bleeding in NVAF patients compared to Warfarin (HR: 0.80, 95% CI: 0.70–0.91, P<0.001). In the same study population, edoxaban was associated with lower rates of intracranial hemorrhage (0.5% vs. 1% per year) but with a higher rate of gastrointestinal bleeding events (1.8% vs. 1.3% per year) compared to Warfarin, respectively. In patients with CrCl > 95 ml/min, the use of edoxaban was associated with an increased risk of ischemic stroke compared to Warfarin[23].

Andexanet, Idarucizumab, Aripazine are specific antidotes for these agents and there clinical use will be seen in the near future.

Table 1: Characteristics of FDA approved Novel Oral Anticoagulants (NOACs) and their comparison with Warfarin[24]

Characteristics	**Warfarin**	**Dabigatran**	**Rivaroxaban**	**Apixaban**	**Edoxaban**
Site of Action	Vitamin K Antagonist	Direct Thrombin Inhibitor (IIa)	Factor Xa inhibitor	Factor Xa inhibitor	Direct Factor Xa inhibitor.
Maximum onset time	2-5 days	2 hours	2.5-4hours	3 hours	1-2 hours
Half-life	2-5 days	14-17 hours	5-9 hours in healthy patients, 9-12 hours in elder patients.	8-15 hours	10-14 hours
Drug Interactions	Acetaminophen, Aspirin, NSAIDs, anti-infectives, Phenytoin, SSRIs, etc.	Dronedarone, Ketokonazole, Aspirin, NSAIDs, Clopidogrel etc.	Strong Inhibitors and inducers of CYP3A4 and P-glycoprotein, Aspirin, NSAIDs, Clopidogrel.	Aspirin, Clopidogrel, Potentially strong Inhibitors and inducers of CYP3A4 and P-glycoprotein.	Potent CYP3A4 inhibitors and P-glycoprotein inhibitors.
Prodrug	No	Yes	No	No	No
Oral Bioavailability	>95%	6.5%	80%	~66%	50%
Monitoring	INR-adjusted	None	None	None	None
Metabolism and elimination	CYP 2C9, 3A4,1A2	80% renal, 20% fecal.	CYP3A4; 66% renal, 33% fecal	CYP3A4; 75% fecal, 25% renal.	CYP3A4; 65% fecal, 35% renal.
Dosing	Once Daily	Fixed, Once/twice daily	Fixed, Once/twice daily	Fixed, twice daily	Fixed, Once daily

CONCLUSION

In the setting of Non Valvular Atrial Fibrillation (NVAF), Deep Vein Thrombosis (DVT) and Pulmonary Embolism (PE) treatment, the Novel Oral Anticoagulants (NOACs) offered physicians and patients multiple new options for Anticoagulation. In comparison, Warfarin has many drawbacks. The current lack of approved, standardized "NOAC level" tests makes use in some populations, such the morbidly obese or the extremely underweight, quite challenging. Although there are no strong data to suggest NOAC dose adjustments or recommendations against NOAC use in morbidly obese patients, the use of Warfarin in this population is likely safer and more predictable. The ability to readily check International Normalized Ratio (INR) in patients on Warfarin anticoagulation provides valuable information about the patient's status and, thus, risk of thrombosis versus bleeding. Several attempts are been made to understand the action of these Novel Oral Anticoagulants in the management of Stroke as well as DVT and PE treatment. The advent of reliable reversal agents and potential "NOAC level" laboratory tests would certainly make their use more attractive in the foreseeable future.

ABBREVIATIONS

NOACs- Novel Oral Anticoagulants.

VTE- Venous Thromboembolism (VTE)

NVAF- Non valvular Atrial Fibrillation.

DVT- Deep Vein Thrombosis.

PE- Pulmonary Embolism.

FDA- Food and Drug Administration.

aPTT- activated Partial Thromboplastin Time.

INR- International Normalized Ratio.

CrCl- Creatinine Clearance.

HR- Hazard Ratio

CI- Confidence Interval.

NSAIDs- Non Steroidal Anti-Inflammatory Drugs

SSRIs- Selective Serotonin Reuptake Inhibitors.

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