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Modern Oral Anticoagulants: A Review

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Review Article

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ABSTRACT

Warfarin which was used as an anticoagulant in thrombotic diseases from last few decades were having few drawbacks leads to exigency of new generation anti-coagulation drugs. These drugs were proved to be more effective and overcoming almost all the drawbacks. In this review we would explain these recently developed drugs and their advantages.

INTRODUCTION

Drugs which reduces clotting in blood are known as anticoagulants [1]. Abnormalities in blood coagulation pathway leads to formation of masses of coagulated blood inside blood vessel. These abnormalities lead to blood disorders such as Nonvalvular atrial fibrillation (NVAf)-a most common disorder of cardiac rhythm [2], Venous Thromboembolism (VTE), Pulmonary Embolism (PE) and Deep Vein Thrombosis [3]. Among these disorders Pulmonary Embolism (PE) is third most commonly known cause for vascular disease related death. In order to treat these blood disorders a large amount of research is been done and with the advancements in science and technology new drugs is invented which overcomes drawbacks of previous one.

Since 80's warfarin have been used widely as a major anticoagulant for treatment of blood clots but due its drawbacks such as risk of haemorrhage strokes in old age patients, compliance, achieving a therapeutically optional International Normalised Ratio (INR) and need for regular testing to adjust its dose in blood it faced many challenges in treatment of thrombotic diseases [4-8]. This paves the way for modern anticoagulants to come in light and make a revolutionary effect in field thromboembolic diseases treatment. Our approach in this review is to highlight those modern anticoagulants which proved to be a better medication for clotting blood disorders.

Noval Oral Anticoagulants (NOACs)

As the name depicts these class of drugs that are administered orally and can be used to treat blood clot at a very random rate as compared to the previously used drugs such as warfarin. Warfarin was the most commonly used oral anticoagulant before NOACs [9-11]. Vitamin K plays a vital role in blood coagulation as it regulates the formation of clotting proteins II, VII, IX and X [12,13]. Warfarin acts by inhibiting the recycling of vitamin K in clotting cascade and this leads to the dissociation of clots in blood vessel. But on the dark side, administration of warfarin caused a large number of complications in patients suffering from Thromboembolic diseases. Major problem was related to dose administration of warfarin. If we look at the molecular level SNP (Single Nucleotide Polymorphism) in vitamin K epoxide reductase (VKOR) gene and Cyt P450 2C9 (CYP2C9) have significant effect on dose of warfarin. Genes which are mediating the effect of warfarin don't show any effect on dose administration [14,15]. Due to this wide inter-individual variability in dose requirement which is influenced by environmental as well as

genetic factors, delay in response time and short range of therapeutic index led to discovery of other drugs which can overcome these disadvantages [16-19].

NOACs overcome these bad marks of Warfarin and proved a promising class of drugs which have rapid onset as compared to warfarin. The most important feature of NOACs is their short half-life which helps them to carry out their functions effectively and in a less time. We need not have a regular check at the level of NOACs [20].

Mechanism of action of NOACs

Based on the action mechanism NOACs can be divided into two broad categories:

- a) Direct Thrombin Inhibitor
- b) Factor Xa inhibitor

Direct thrombin inhibitor inhibits thrombin directly and inhibits conversion of fibrinogen to fibrin whereas Factor Xa inhibitor inhibits factor Xa in blood clotting which is responsible for conversion of prothrombin to thrombin [14]. Both these classes of drugs have advantages over previously used warfarin in mode of action as warfarin doesn't act directly in blood coagulation process, irrespective inhibits production of factor II, VII, IX and X (Figure 1) [21,22].

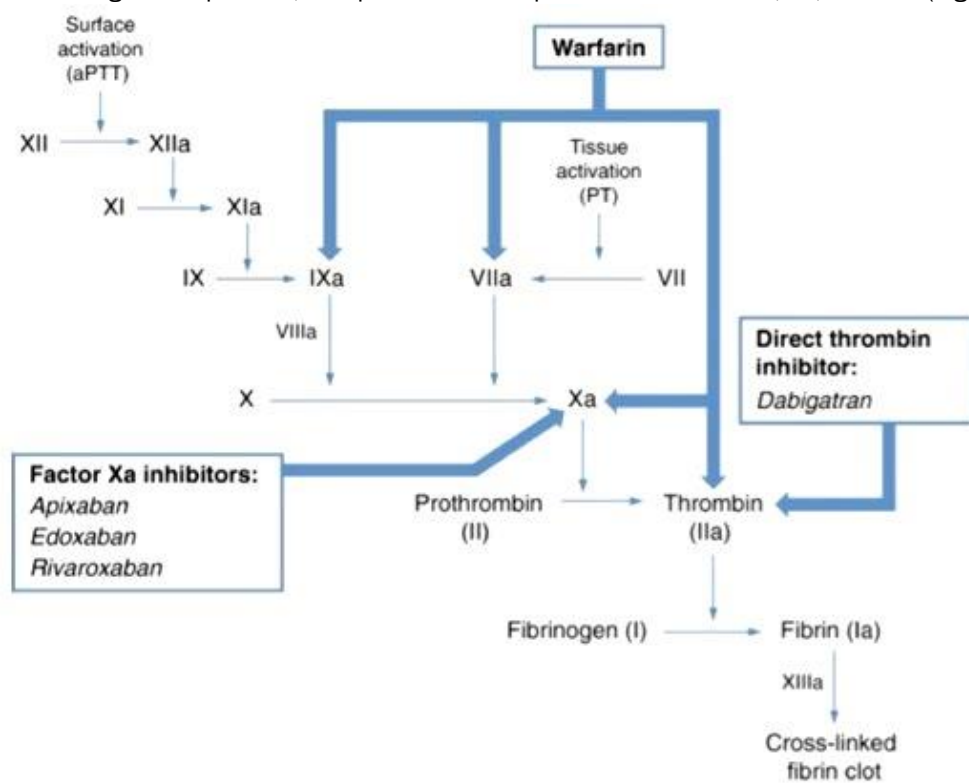


Figure 1: Mode of action of warfarin and direct thrombin inhibitors and Factor Xa inhibitors.

Commonly used NOACs

- a) **Ximelagatran:** Ximelgatran is the first oral NOACs used, which directly inhibits thrombin. Melagatran, active form of Ximelgatran inhibits thrombin. Although due to hepatic complications were diagnosed due to its long term treatment, production of these drugs were stopped but it was a breakthrough in identifying thrombin inhibitor as promising anticoagulant [22-24].
- b) **Dabigatran:** Dabigatran etexilate is one of the most promising alternative to overcome warfarin in anticoagulation therapy for different Thromboembolic diseases. Dabigatran is direct thrombin inhibitor and doesn't require its regular anticoagulation monitoring like warfarin[25]. Dabigatran was non inferior to warfarin in systemic embolism and heart stroke, so approval was given for its production by US Food and

Drug Administration in 2011. It was demonstrated by RE-LY study that, a dose of 150 mg of dabigatran twice in a day is superior to warfarin in comparison to reduce heart stroke, whereas a dose higher than 150 mg can cause gastrointestinal haemorrhage [26-28]. This risk increases with the increase in growing age. An average dose of 150 mg and 75 mg is fixed as higher and lower doses for Dabigatran. Recently it has been reported that dabigatran can also be used to treat left ventricular (LV) thrombus in patients with old Anteroseptal Myocardial Infarction. An oxidative coupling reaction of 3-methyl-2-benzothiazoline hydrazine (MBTH) with MET and DAB in the presence of ferric chloride is at an absorption maxima of 666 nm and 632 nm is used for monitoring higher level of Dabigatran in blood stream [29,30]. Although it has been reported a promising drug and replacement of warfarin but few cases have been reported in which administration of Dabigatran for long term causes severe thrombocytopenia and excessive increase in platelet count up to 16.000 mm³ [26].

- c) **Apixaban:** It is a Xa inhibitor which acts as potential substitute of warfarin. Promising action of apixaban is due to its rapid absorption in its active form. Within 3 hours of its administration apixaban reaches to its peak plasma level [3]. About 56% of the drug administered is excreted through gastrointestinal route and one fourth is excreted renally. As compared to warfarin, administration of Apixaban is associated with lower risk of gastrointestinal bleeding and intracranial bleeding [31]. Apixaban has also been effective in treatment of ischemic strokes and covert embolic-pattern infarction and did not increase the number of microbleeds in patients with atrial fibrillation [32].
- d) **Edoxaban:** Edoxaban is a Xa factor inhibitor class of anticoagulant. Due to its short half-life of 8-10 hours and 50% elimination through kidney it is a good replacement of warfarin [33-35].
- e) **Rivaroxaban:** It is direct factor Xa inhibition protein. Most outstanding property of warfarin is its rapid absorption just after its administration. Its maximum effect is started within 2-3 hours of its administration [36]. A major portion of Rivaroxaban (almost 75%) undergo hepatic metabolism and removed out of body. It is proved to be a potent anticoagulant in orthopaedic surgery and venous thromboembolism [32]. Metabolism of rivaroxaban is via CYP3A4 [36]. Rivaroxaban is a substrate of P-glycoprotein, thus those drugs which are strong inhibitors of P-glycoprotein and CYP3A4 are never advised to use along with rivaroxaban [37]. As in rivaroxaban group gastrointestinal screening is common but there is a reduced risk of intracranial bleeding with comparison to warfarin [38].

Anticoagulants from natural sources

There are few invertebrates whose physiological secretions act as an anticoagulant and are used widely for research and development. Based on their mechanism of action they are divided into five basic groups [39]. Table 1 shows a detailed description of such chemicals having anticoagulatory effects.

Group	Affect	Anticoagulant	Source
I	Antithrombic agents	Hirudin	<i>Hirudo medicinalis</i>
II	Prothrombinase inhibitors	Antistasin	<i>Haementeria officinalis</i>
III	Platelet function	a) Glossina b) Decorsin c) FAGA	a) <i>Glossina morsitans</i> b) <i>Macrobodella decorsa</i> c) <i>Stichopus</i>

			<i>japonicus selenka</i>
IV	Fibrinolytic	d) Hementin e) Hementerin	a) <i>H. officinalis</i> b) <i>Haementeria depressa</i>
V	Multi-activity	f) Destabilase g) Prolixin S	a) <i>H. medicinalis</i> b) <i>Rhodnius prolixus</i>

Table 1: Various anticoagulatory substances present in nature.

Along with this a very promising anticoagulant Batroxobin, a toxin derived from snake venom lyses fibrinogen without effecting platelets functions [40].

Other anticoagulants under trail:

Along with present NOACs there are several other anticoagulants which are still under trails. According to recent studies it is advised to use apibaxam instead of enoxaparin for thromboprophylaxis in patients who have recently gone under hip replacement. Other than apibaxam other agents such as LY-517717, betrixaban (PRT-054021), edoxaban (DU-176b) have also been found. As per new research it was demonstrated that edoxaban was superior to enoxaparin which is in phase III of clinical trials [41]. Betrixaban, which is in its II phase clinical trial is promised to have lower bleeding risk in comparison to that of warfarin by its manufacturers Merck and Portola Pharmaceuticals [42]. Other than Endobaxan and Betrixaban two other Xa inhibitors YM-150 and LY-517717 are also under trails. Data suggest that YM-150 is better for patients with undergoing hip arthroplasty to prevent VTE. Early studies in LY-517717 show non-inferiority at doses of 100 mg to 150 mg daily in comparison to enoxaparin 40 mg dose [3].

Drawbacks for use of modern Novel Oral Anticoagulants

NOACs proved to have great advantages over traditional anticoagulants but still they not in reach of common people. Main reason for this is cost of their medication. At an average medication of Dabigatran for one month costs in a low income country like Pakistan cost thrice than that of Warfarin [43]. For countries having low per capita income widespread use of these drugs can't be implemented on regular basis. A list of NOACs and their cost per dose is given in Table 2.

Drug Name AWP	Cost per dose
Warfarin	\$0.66-\$0.68 per dose
Coumadin	\$0.93 to \$1.50 per dose
Enoxaparin (Lovenox)30mg	\$2.45 per dose
Enoxaparin (Lovenox) 40mg	\$3.27 per dose
Fondaparinox (Arixtra)2.5mg	\$43.50 per dose
Fondaparinox (Arixtra) 5mg	\$118.43 per dose
Dabigatran 75mg and 150mg	\$4.05 per dose

Table 2: Cost per dose for modern anticoagulants.

CONCLUSION

Drugs such as Dabigatran, Apixaban, Edoxaban and other NOACs have played a remarkable role in development of new era of drugs for various blood diseases but in order widespread their use many effective measures are yet to be taken. An approach should be made to develop drugs having same properties as that of NOACs but they should be cost effective so that it would be made feasible for common persons to use them. Steps should be taken by governments not to impose taxes on presently available drugs and provide them at a subsidised rate at government hospitals. Newer drugs under trials need should be made in such a way that they are effective in smaller concentrations and available at a lower cost.

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