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NOACS FOR STROKE PREVENTION IN PATIENTS WITH AF AND VTE: A SYSTEMATIC REVIEW AND META ANALYSIS

Nabila Unnisa Begum and Sathish Kumar Mittapalli*

IV B.Pharm, Deccan School of Pharmacy, Nampally, Hyderabad.

***Corresponding Author: Sathish Kumar Mittapalli**
IV B.Pharm, Deccan School of Pharmacy, Nampally, Hyderabad.

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ABSTRACT
The long term anticoagulation with warfarin has black box warning from Food and Drug Administration (FDA) bleeding problems warning, pregnancy warning, calciphylaxis warnings associated with various bleeding risks and drug-drug interactions and act by blocking vitamin K epoxide reductase (VKORC1) enzyme complex which led to development of novel drugs. The non-vitamin K antagonist oral anticoagulants (NOACs) are replacing warfarin for many indications. These agents include dabigatran, which inhibits thrombin, and rivaroxaban, apixaban, and edoxaban, which inhibit factor Xa for treatment of venous thromboembolism and rivaroxaban and apixaban are approved for thromboprophylaxis after elective hip or knee arthroplasty. The NOACs are effective as warfarin in reducing stroke and systemic embolism through anticoagulation with in fixed doses without routine coagulation monitoring but also are safer because they are associated with less intracranial bleeding, notably have prophylaxis for VTE after an orthopediac surgery and to prevent stroke in AF patient,a decreased risk of significant bleeding and other secondary adverse events. This review aims that beneficial effects of NOACs, pharmacokinetic and pharmacodynamic properties, mode of activities, common drug-drug interactions, pharmacological and identifies the doses of each approved indication, provides an overview on ongoing studies, the emerging real-world data and highlights the potential opportunities to identifies the remaining challenges.

KEYWORDS: warfarin, AF, novel oral anticoagulant, stroke, VTE, vitamin k antagonist, rivaroxaban, apixaban, edoxaban, dabigatran.

INTRODUCTION
The major cause of death in United States and other Western countries includes various Thromboembolic condition, including Acute Myocardial Infarction, Unstable Angina, Deep Vein Thrombosis, Pulmonary Embolism, and Ischemic Stroke.[1] Currently, the stroke incidence in India is much higher than Western industrialized countries due to patients with Atrial Fibrillation, Venous Thromboembolism, Stroke requiring constant anticoagulation, warfarin was considered as the mainstay of treatment for such patients. The available drugs for these conditions remain only at sub-optimal levels. Moreover, their narrow therapeutic index, unpredictable drug-drug interactions and need for continuous close monitoring also uncontrolled bleeding do mask VKA's (Vitamin K Antagonist) beneficial properties of preventing propagation. This situation changed with the recent introduction of the non-vitamin K antagonist oral anticoagulants (NOACs), which include dabigatran, rivaroxaban, apixaban, and edoxaban. The drugs were revolutionized oral anticoagulants because they are effective as warfarin, and more convenient administration, can be given in fixed doses without routine coagulation monitoring without adverse effects of warfarin, Moreover, the drugs are associated with significantly less intracranial bleeding than warfarin. This is an important advantage because bleeding into the brain is the most feared complication of anticoagulation therapy. In the United States, rivaroxaban and apixaban are licensed for prevention of venous thromboembolism (VTE) after elective hip or knee replacement surgery and dabigatran, rivaroxaban, apixaban, and edoxaban are approved for treatment of VTE and for stroke prevention in patients with atrial fibrillation (AF).[2]

Initially LMWH (Low Molecular Weight Heparin) and Fondaparinaux were introduced, accepted as they require less drug monitoring and even gave the choice of subcutaneous administration. Then the limitation was highlighted as the need for frequent administration through the subcutaneous route, thereby it reduced their long term efficiency. To add on the misery, these drugs had lower renal clearance, no known antidotes and at times posed threat in the form of Catheter Thrombosis to the patients receiving Percutaneous Coronary Intervention (PCI). Bivalirudin is the best choice of drug in PCI undergoing patients. Nonetheless, its lack of

antidote and shorter half life it is contra-indicated in Renal impaired patients.[3]

In this brief review, the pharmacology of these, non-vitamin K antagonist, novel oral anticoagulants (NOACs), their applications in total hip and knee replacement, the treatment of venous thromboembolic disorders, stroke prevention in arterial fibrillation (AF), and their advantages over vitamin K antagonists (VKAs) will be discussed.

MECHANISM OF ACTION

Anticoagulants include a variety of agents that inhibit one or more steps in the coagulation cascade. In recent years, the search for new anticoagulants has generated novel agents for preventing and managing thromboembolic disorders. Specifically, anticoagulants that directly target the enzymatic activity of thrombin and factor Xa have been developed. These direct thrombin inhibitors and direct factor Xa inhibitors block major procoagulant activities involved in the generation of a fibrin clot.[4]

Thrombin is the final enzyme in the clotting cascade that produces fibrin; it is formed by the proteolytic cleavage of prothrombin by factor Xa. Factor Xa acts immediately upstream of thrombin in the clotting cascade, and direct factor Xa inhibitors bind to the active site of factor Xa and inhibit its activity without requiring cofactors. Both thrombin and factor Xa are active in circulating and clot-bound forms.[5]

Direct Thrombin Inhibitors: These agents prevent thrombin from cleaving fibrinogen to form fibrin. They bind to thrombin directly, rather than enhancing the activity of antithrombins, as is done by heparin. The only oral drug in this group is dabigatran (Pradaxa).[4]

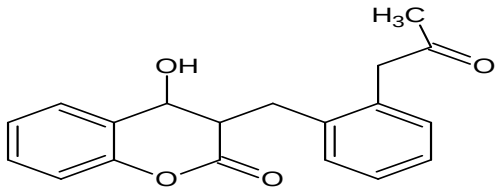
Direct Factor Xa Inhibitors: Factor Xa is a trypsin-like serine protease that plays a key role in the blood coagulation cascade. It holds a central position that links the intrinsic and extrinsic pathways to the final common coagulation pathway. Factor Xa converts the prothrombin to its active form, thrombin. These agents prevent factor Xa from cleaving prothrombin to form thrombin and bind directly to factor Xa, rather than enhancing the activity of antithrombin. There are no parenteral direct factor Xa inhibitors in clinical use. The drugs include rivaroxaban (Xarelto), apixaban (Eliquis), edoxaban (Lixiana), and betrixaban (Bevyxxa). Of note, the generic names for these agents all end in "Xa-ban."[5]

Recommendations for each agent are based largely on the efficacy and safety in specific patient populations and clinical indications. Dabigatran was the first of the direct oral anticoagulants to become clinically available (2010). The direct factor Xa inhibitors became available in subsequent years. Many clinicians, however, are still unfamiliar with appropriate dosing of these drugs. Pharmacokinetic differences may make one medication a better choice compared to another for a given patient.[2,4]

Premature discontinuation of rivaroxaban and other direct factor Xa inhibitors increase the risk of thrombotic events in the absence of adequate alternative anticoagulants. Also, epidural spinal hematomas have occurred in patients treated with rivaroxaban who are receiving neuraxial anesthesia or undergoing spinal puncture. These hematomas may result in long-term or permanent paralysis. These patients, therefore, must be monitored for signs and symptoms of neurologic impairment.[2,5]

DIRECT THROMBIN INHIBITORS

Warfarin (Coumadin) is a synthetic oral anticoagulant, chemically 4-hydroxy-3-(3-oxo-1-phenylbutyl)chromen-2-one [Fig: 1]. It inhibits the regeneration of vitamin K1 epoxide and so the synthesis of vitamin K dependent clotting factors, which include Factors II, VII, IX and X, and the anticoagulant proteins C and S. This inhibition results in a sequential depression of Factors VII, IX, X and II activities. Vitamin K is an essential cofactor for the post ribosomal synthesis of the vitamin K dependent clotting factors. The vitamin promotes the biosynthesis of gamma-carboxyglutamic acid residues in these proteins which are essential for biological activity. It is a racemic mixture of two optically active isomers (R and S) in equal pro-portion. Its pharmacokinetic and pharmacodynamic (PK/PD) properties are shown in Tables 1 and 2. Common drug-drug interactions are shown in Table 3. In vitamin K epoxide reductase gene and cytochrome P450 type 2C9 (CYP2C9) are not race specific, and they account for 25% and 10%, respectively, of the interindividual variability in warfarin dosing.[6]



Warfarin

Fig: 1.

A literature search was conducted on PubMed, EMBASE and Web of Science using the search terms 'anticoagulants', 'oral', 'renal impairment', 'dabigatran', 'rivaroxaban', 'apixaban', 'betrixaban' and 'edoxaban' (date limits 2000 to Feb 2012). In the absence of peer-reviewed publications, some information on the drugs and dosing issues was obtained from the Summary of Product Character-istics (SPC) for the individual drugs mentioned and, in some cases, unpublished data. The content of the SPCs was retrieved from the websites of the European Medicines Agency (EMA) and US Food and Drug Administration (FDA).

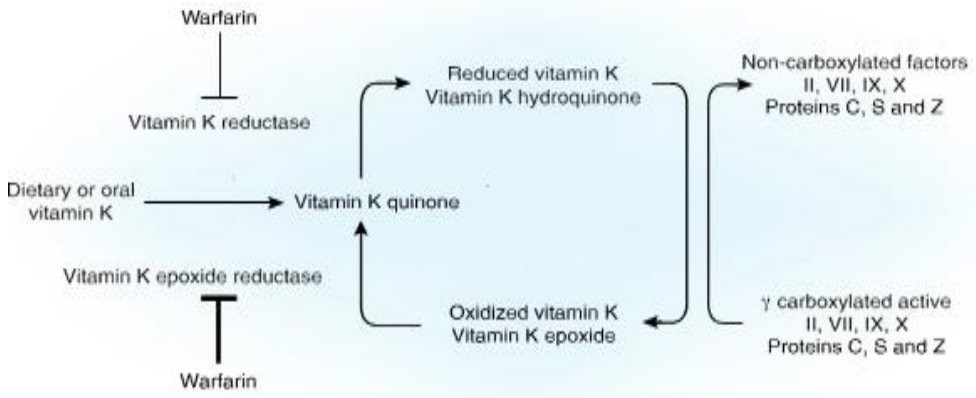


Figure 1: Carboxylation of vitamin K–dependent proteins requires the reduced form of vitamin K, g- glutamyl carboxylase enzyme, molecular oxygen, and carbon dioxide. Because body stores of vitamin K are low, the oxidized (inactive) form of vitamin K is recycled to the reduced (active) form by vitamin K epoxide reductase, which is inhibited by warfarin. Inhibition results in reduced hepatic synthesis of these clotting factors and reduction in their activities by 40%–50%.

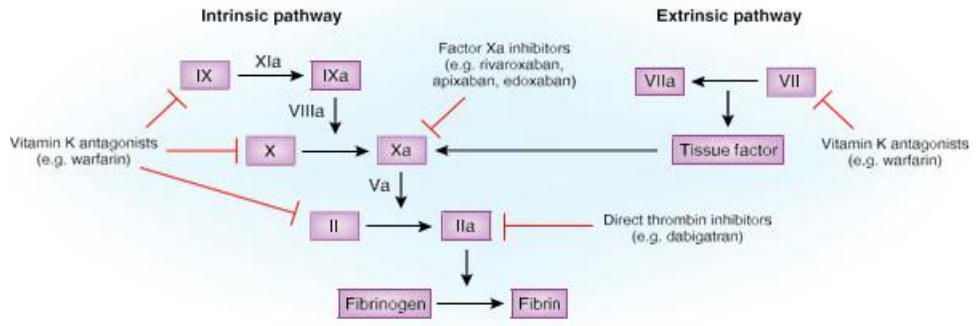


Figure 2: Oral anticoagulants act at different sites in the coagulation cascade for their anticoagulant effects.

Table 1: Summary of pharmacokinetic and pharmacodynamic properties of commonly used oral anticoagulants

OAC	Type	Prodrug	Pharmacokinetics		Dialyzable	Pharmacodynamics: Binding to Effector
			Metabolism	Renal Dose Adjustment		
Warfarin	Vitamin K–dependent factor inhibitor	No	Extensive metabolism by CYP2C9	No	No	Irreversible
Dabigatran	Direct thrombin inhibitor	Yes	Metabolized by esterases, 80% excreted by kidney	Yes	Yes	Reversible
Apixaban	Free and clot-bound Xa inhibitor	No	Metabolized in liver by CYP3A4, then excreted in feces and kidney (25%), no active metabolite	No	Small	Reversible
Rivaroxaban	Free and clot-bound Xa inhibitor	No		Yes	No	Reversible
Edoxaban	Free Xa inhibitor	No	66% Excreted by kidney, 36% unchanged, minimal in feces 50% Excreted unchanged by the kidney, 10% hydrolyzed by carboxyesterase 1	Yes	No	Reversible

OAC, oral anticoagulant; CYP2C9, cytochrome P450 type 2C9; Xa, factor Xa; CYP3A4, cytochrome P450 type 3A4.

Table 2: Additional pharmacokinetic properties in those with normal kidney function.						
OAC	**Cmax,**	**h**	**$t_{1/2}$, h**	**Protein binding, %**	**V_D, L**	**Bioavailability, %**
Warfarin	2–6	42		97–99	10	99
Dabigatran	1–2	12–14		38	50–70	3–7
Apixaban	3–4	12		87	21	50
Rivaroxaban	2–4	6–13		.90	50	66–100
Edoxaban	1–2	10–14		55	107	62
OAC, oral anticoagulant; Cmax, peak concentration; V_D, volume of distribution.						

Table 3. Common drug-drug interactions of oral anticoagulants		
Drug	Increase Anticoagulant Effects	Decrease Anticoagulant Effects
Warfarin	Amiodarone, fluconazole, tigecycline, voriconazole, fluoroquinolones, verapamil, diltiazem,	Rifampin, phenobarbital,
	anticoagulants, antiplatelet drugs, NSAIDs, and SSRIs	carbamazepine, cigarette
Dabigatran	Amiodarone, verapamil, ketoconazole, dronaderone, clopidogrel,	Rifampin
	enoxaparin, anticoagulants, antiplatelet drugs	
Apixaban	Ketoconazole, anticoagulants, antiplatelet drugs	Rifampin
Rivaroxaban	anticoagulants, antiplatelet drugs, fluconazole, ketoconazole,	Rifampin, phenytoin,
	erythromycin, and clarithromycin	carbamazepine, St. John's Wort
Edoxaban	Other anticoagulant, antiplatelet drugs,	Rifampin
NSAID, nonsteroidal anti-inflammatory drug; SSRI, serotonin reuptake inhibitor.		

Direct Thrombin Inhibitor: Dabigatran

Dabigatran etexilate, 5-chloro-*N*-[[(5*S*)-2-oxo-3-[4-(3-oxomorpholin-4-yl)phenyl]-1,3-oxazolidin-5-yl]methyl] thiophene -2-carboxamide[Fig: 2], is FDA approved to prevent stroke or systemic embolism in patients with AF. It is an anticoagulant and the first orally active direct factor Xa inhibitor. Unlike warfarin, routine lab monitoring of INR is not necessary. It is a prodrug that is converted in the liver to dabigatran, an active direct thrombin inhibitor that inhibits both free and bound thrombin. The half-life of this medication is 12 to 17 hours in patients with normal renal function.[6] However there is no antidote available in the event of a major bleed. Only the 10 mg tablet can be taken without regard to food. The 15 mg and 20 mg tablet should be taken with food. FDA approved on July 1, 2011. Nonspecific, ubiquitous esterases rapidly convert this nonpeptide prodrug into a potent, direct, and selective inhibitor of free and fibrin-bound thrombin (Table 1).[7] In general, dabigatran etexilate is well tolerated, although it is associated with a higher rate of dyspepsia than warfarin. Major bleeding was as common in recipients of the higher dosage as, and less common in recipients of the lower dosage of dabigatran etexilate than, that in recipients of warfarin. In conclusion, dabigatran etexilate is more effective than warfarin for the prevention of stroke and systemic embolism in patients with atrial fibrillation, and generally well tolerated, particularly with regard to bleeding endpoints compared with warfarin.[8]

Dosing: Dabitagran etexilate is available as 75-mg, 110-mg, and 150-mg capsules. It is given as a fixed dose without monitoring, and the maximum effect is achieved within 3 hours of ingestion. Renal excretion of unchanged drug is the predominant elimination pathway, with 80% excreting in the urine.[6]

Reversal of Antithrombotic Effects

There are patient reports using fresh frozen plasma and prothrombin complex concentrate to reverse dabigitran's effects in patients with major bleeding. A recent randomized, controlled trial (RCT) in subjects with normal kidney function raised questions about the efficacy of prothrombin complex concentrate as an effective reversal agent. In another study in subjects with normal kidney function, nonspecific anti-inhibitor coagulant complex (*e.g.*, factor VIII inhibitor bypass activity) but not recombinant factor VIIa reversed dabigatran's anticoagulant effects.[9]

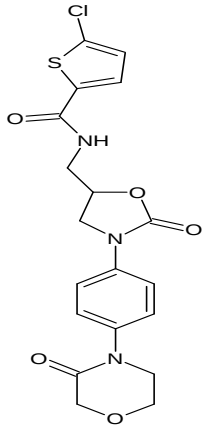
Dabigatran Reversal: Idarucizumab (Praxbind) is a humanized antidabigatran monoclonal antibody fragment that may be used for emergency reversal of the anticoagulant effect of dabigatran. This agent should be administered in patients for whom more conservative bleeding management measures have been ineffective. It should be administered only to patients with convincing evidence of significant dabigatran levels based on clinical history of ingestion or laboratory testing. Idarucizumab should not be administered to patients with a normal thrombin time. The dose is 5 g (two 2.5-g vials), which can be administered either as two consecutive infusions or as a bolus (i.e., injecting both vials consecutively via syringe).[10]

DIRECT FACTOR Xa INHIBITORS

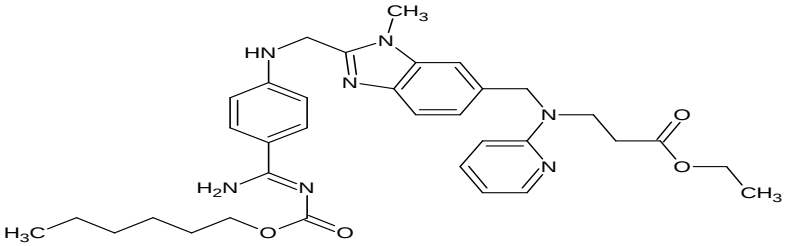
Rivaroxaban, 5-chloro-N-[[(5S)-2-oxo-3-[4-(3-oxomorpholin-4-yl) phenyl]-1, 3-oxazolidin-5-yl] methyl] thiophene-2-carboxamide[Fig:2] is FDA approved in patients with AF to prevent stroke. It is also FDA approved for deep venous thrombosis (DVT) and

pulmonary embolism (PE) prophylaxis after knee and hip replacement.[11] These drugs inactivate the free and bound factor Xa. Several are clinically available as oral agents, but there are no parenteral drugs available in this group. Otamixaban was developed as an intravenous drug but discontinued owing to excessive bleeding and bioavailability varies with dosing strength: 80%–100% with a 10-mg dose and 66% with a 20-mg dose.[12]

This drug should not be used in patients with CrCl <15 mL/min or with CYP3A4 and P-glycoprotein dual inhibitors, such as ketoconazole, itraconazole, voriconazole, posaconazole, or ritonavir. Routine monitoring of coagulation time is not necessary because drug levels are relatively predictable for a given dose.[13] Concomitant use of other drugs that impair hemostasis increases the risk of bleeding. These include aspirin, platelet inhibitors, fibrinolytic therapy, nonsteroidal anti-inflammatory drugs, selective serotonin reuptake inhibitors, and serotonin norepinephrine reuptake inhibitors. They must be used with caution in patients with CrCl <30 mL/min. This drug should be used during pregnancy only if the potential benefits justify the potential risk to mother and fetus and there is no antidote available for overdose.[14]



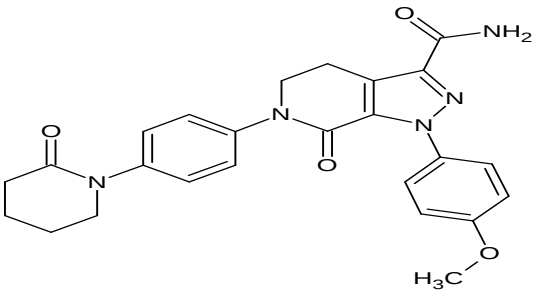
Rivoraxaban



Dabigatran etexilate

Figure: 2.

Apixaban is a pyrazolopyridine, a lactam and an aromatic ether, 7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxamide[Fig: 3] substituted at position 1 by a 4-methoxyphenyl group and at position 6 by a 4-(2-oxopiperidin-1-yl)phenyl group. It is used for the prevention and treatment of thromboembolic diseases.[15] It is a oral anticoagulant and direct inhibitor of factor Xa which is used to decrease the risk of venous thromboses, systemic embolization and stroke in patients with aeterial fibrillation, and lower the risk of deep vein thrombosis and pulmonary embolism. It has been linked to a low rate of serum aminotransferase elevations during therapy and to rare instances of clinically apparent liver injury.[16]

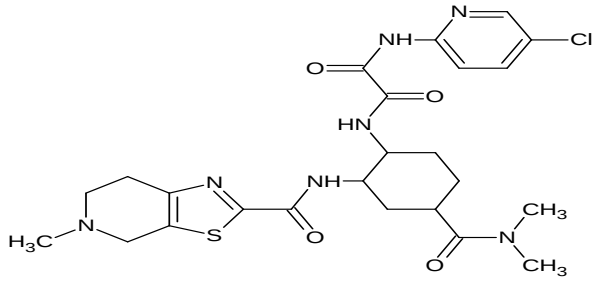


Apixaban

Figure: 3.

Dosing for VTE prophylaxis is 2.5 mg twice daily for 35 days (hip replacement) or 12 days (knee replacement) and prevention and treatment of VTE, 10 mg is administered twice daily for 7 days, followed by 5 mg twice daily. For stroke prevention in AF, 5 mg is given twice daily (CrCl >50 mL/min) or 2.5 mg twice daily.

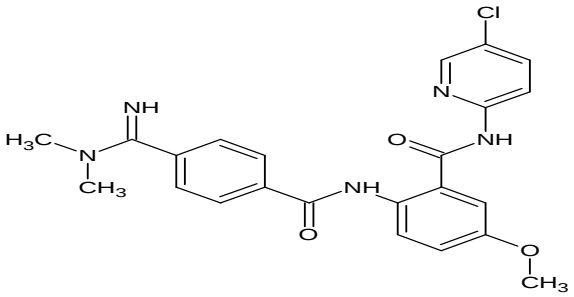
Edoxaban is a monocarboxylic acid amide, a chloropyridine, a thiazolopyridine and a tertiary amino compound, *N*'-(5-chloropyridin-2-yl)-*N*-[(1*S*,2*R*,4*S*)-4-(dimethylcarbamoyl)-2-[(5-methyl-6,7-dihydro-4*H*-[1,3]thiazolo[5,4-c]pyridine-2-carbonyl)amino] cyclohexyl]oxamide[Fig:4], direct oral anticoagulant, specific inhibitor of factor Xa with an approximate 10,000-fold selectivity for factor Xa over thrombin. Edoxaban was approved by the FDA in January 2015 for the prevention of stroke, to decrease the risk of venous thromboses, systemic embolization and stroke in patients with arterial fibrillation. The drug reported to a low rate of serum aminotransferase elevations during therapy, but has not been implicated in cases of clinically apparent acute liver injury and it is given at a fixed rate with no monitoring. The typical dosage is 30 or 60 mg once daily. Edoxaban is renally excreted and is a substrate for P-glycoprotein.[17]



Edoxaban

Fig: 4.

Betrixaban is a secondary carboxamide obtained by formal condensation of the carboxy group of 4-(N,N-dimethylcarbamimidoyl)benzoic acid with the amino group of 2-amino-N-(5-chloropyridin-2-yl)-5-methoxybenzamide. A synthetic anticoagulant compound that targets activated factor Xa in the coagulation cascade. It has a role as an anticoagulant (coagulation factor Xa) inhibitor. The drug reported that low rate of serum aminotransferase elevations during therapy, but has not been linked to instances of clinically apparent liver injury.[18] This is a long-acting inhibitor with a half-life of 19 to 27 hours and used in the prevention of VTE. The typical dosage is 160 mg on the first day followed by 80 mg once daily. Doses are given at the same time with food. For individuals with CrCl <30 mL/min, 80 mg is given on the first day, followed by 40 mg daily. For VTE prophylaxis, the duration of therapy is 35 to 42 days.[19]



Batrixaban

Fig: 5.

Reversal of Rivaroxaban, Apixaban, Edoxaban, Betrixaban: There is no specific antidote for the direct factor Xa inhibitors. The following may be helpful, although evidence from randomized trials is lacking regarding these strategies.[20] For patients with major bleeding (including life-threatening bleeding), administering an antifibrinolytic agent (e.g., tranexamic acid) is suggested. The use of this agent may also be appropriate in individuals with less serious bleeding if the patient has ongoing bleeding or other comorbidities that increase bleeding risk.[21]

ADVANTAGES OF NOACs OVER VKAs

NOACs have various advantages in the prevention and treatment of patients with a predisposition toward AF, deep venous thrombosis, pulmonary embolism, stroke, and other conditions that are related to inherited or acquired thrombophilia. The following are the main advantages of NOACs compared with VKAs in preventing various factors that are responsible for thromboembolic disorders and in the treatment of thromboembolic diseases: absence of food interactions; few strong drug interactions; predictable pharmacokinetic and pharmacodynamic profiles; rapid onset and offset of action; short half-life; and absence of the need for laboratory monitoring. Routine monitoring is not required, regardless of body weight, age, sex, race, and demographic variations. Additional advantages of NOACs over VKAs include wide therapeutic windows, greater efficacy in AF, and lower risk of intracranial hemorrhage, except for dabigatran, which has an intracranial hemorrhage rate equal to that of warfarin at doses of 150 mg.

SUMMARY

Anticoagulants are used frequently to treat and prevent thromboembolism. Historically, vitamin K antagonists (VKAs; warfarin) have been the standard of care and only oral option. Many limitations are associated with warfarin despite its widespread use. Warfarin has a narrow therapeutic window, requires frequent laboratory monitoring, and is affected by diet, genetics, and illnesses. Medications that do not require frequent monitoring and have less inter and intra patient variability could offer great potential. Novel oral anticoagulants (NOACs) are NOACs are direct thrombin inhibitors and direct factor Xa inhibitors. Dabigatran (Pradaxa) is currently the only direct thrombin inhibitor. Factor Xa inhibitors include rivaroxaban, apixaban, and edoxaban. Dabigatran and rivaroxaban have rates of major bleeding similar to that of warfarin. Apixaban and edoxaban have a reduced risk of bleeding compared with warfarin.

CONCLUSION

Long-term use of oral anticoagulant therapy with VKAs presented several problems related to major indications like pregnancy warning, calciphylaxis warnings associated with various bleeding risks and drug-drug interactions and act by blocking vitamin K epoxide reductase (VKORC1) and the need for continuous monitoring. The advantages of NOACs over VKAs are their high efficacy in preventing stroke in AF, nonvalvular AF and VTE, lower incidence of major bleeding, convenience of use, minor drug and food interactions, rapid onset and offset of action, short half-life, and lack of the need for laboratory monitoring. Disadvantages of NOACs, such as their higher cost, absence of specific antidotes, and limited experience and dosing, however, should be taken into consideration. In addition, NOACs should not be used in patients with severe renal and hepatic disease, patients with mechanical heart valves, patients younger than age 18 years, and the elderly.

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REFERENCES

1. FDA approves new antiplatelet drug used during heart procedure. Food and Drug Administration Website, June 22, 2015. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm452172.htm Accessed August 21, 2015.
2. FDA Briefing Document: Kengreal® NDA 204-958. Food and Drug Administration Web site, April15, 2015. Accessed September 25, 2015.
3. Dey S, Lo HJ, Wong CH. An Efficient Modular One-Pot Synthesis of Heparin-Based Anticoagulant Idraparinux. Journal of the American Chemical Society, 2019 Jun 3; 141(26): 10309-14.
4. Di Nisio M, Middeldorp S, Büller HR. Direct thrombin inhibitors. *N Engl J Med*, 2005; 353: 1028.
5. Samama MM. The mechanism of action of rivaroxaban—an oral, direct Factor Xa inhibitor—compared with other anticoagulants. *Thromb Res*, 2011; 127: 497.
6. Poulsen BK, Grove EL, Husted SE. New oral anticoagulants: a review of the literature with particular emphasis on patients with impaired renal function. *Drugs*, 2012; 72: 1739.
7. Kengreal™ [package insert]. Parsippany, NJ: The Medicines Company; Updated July 2015.
8. Kengreal. Micromedex [online database]. Greenwood Village, CO: Truven Health Analytics. Updated June 30, 2015.
9. Van Ryn J, Stangier J, Haertter S, et al. Dabigatran etexilate—a novel, reversible, oral direct thrombin inhibitor: interpretation of coagulation assays and reversal of anticoagulant activity. *Thromb Haemost*, 2010; 103: 1116.
10. Reilly PA, van Ryn J, Grottke O, Glund S, Stangier J. Idarucizumab, a specific reversal agent for dabigatran: mode of action, pharmacokinetics and pharmacodynamics, and safety and efficacy in phase 1 subjects. The American journal of medicine, 2016 Nov 1; 129(11): S64-72.
11. Mueck W, Stampfuss J, Kubitza D, Becka M. Clinical pharmacokinetic and pharmacodynamic profile of rivaroxaban. Clinical pharmacokinetics, 2014 Jan 1; 53(1): 1-6.
12. Li J, Halaszynski T. Neuraxial and peripheral nerve blocks in patients taking anticoagulant or thromboprophylactic drugs: challenges and solutions. Local and regional anesthesia, 2015; 8: 21.
13. Kreutz R. Pharmacodynamic and pharmacokinetic basics of rivaroxaban. Fundamental & clinical pharmacology, 2012 Feb; 26(1): 27-32.
14. Kaw D, Malhotra D. Hematology: issues in the dialysis patient: platelet dysfunction and end-stage renal disease. InSeminars in dialysis, 2006 Jul (Vol. 19, No. 4, pp. 317-322). Malden, USA: Blackwell Publishing Inc.
15. Pinto DJ, Orwat MJ, Koch S, Rossi KA, Alexander RS, Smallwood A, Wong PC, Rendina AR, Luettgen JM, Knabb RM, He K. Discovery of 1-(4-methoxyphenyl)-7-oxo-6-(4-(2-oxopiperidin-1-yl) phenyl)-4, 5, 6, 7-tetrahydro-1 H-pyrazolo [3, 4-c] pyridine-3-carboxamide (Apixaban), a highly potent, selective, efficacious, and orally bioavailable inhibitor of blood coagulation factor Xa. Journal of medicinal chemistry, 2007 Nov 1; 50(22): 5339-56.
16. Gant TG, Shahbaz MM, inventors; Auspex Pharmaceuticals Inc, assignee. Pyrazole carboxamide inhibitors of factor xa. United States patent application US 12/558,906. 2010 May 27.
17. DeHaas KA. The direct oral anticoagulants apixaban, rivaroxaban, and edoxaban. American Society for Clinical Laboratory Science, 2017 Jan 1; 30(1): 2-6.
18. Huisman MV, Klok FA. Pharmacological properties of betrixaban. European Heart Journal Supplements, 2018 May 1; 20(suppl): E12-5.
19. Garland SG, DeRemer CE, Smith SM, Gums JG. Betrixaban: a new oral factor Xa inhibitor for extended venous thromboembolism prophylaxis in high-risk hospitalized patients. Annals of Pharmacotherapy, 2018 Jun; 52(6): 554-61.
20. Cuker A, Burnett A, Triller D, Crowther M, Ansell J, Van Cott EM, Wirth D, Kaatz S. Reversal of direct oral anticoagulants: Guidance from the Anticoagulation Forum. American journal of hematology, 2019 Jun; 94(6): 697-709.
21. Madurska MJ, Sachse KA, Jansen JO, Rasmussen TE, Morrison JJ. Fibrinolysis in trauma: a review. European Journal of Trauma and Emergency Surgery, 2018 Feb 1; 44(1): 35-44.