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A REVIEW ON NOVEL ORAL ANTICOAGULANTS

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ABSTRACT

Plan: *This article reveals the significance of novel oral anticoagulants in place of conventional vitamin K antagonists. Vitamin K antagonists were commonly used since 1941 but it has lot of inconveniences.*

Preface: *Anticoagulants are drugs used to reduce the coagulability of blood. Mainly used for the prevention of disorders characterized by abnormal blood clots and emboli. Warfarin, a vitamin K antagonist was the only choice for chronic oral anticoagulation for more than half a century. It requires periodic monitoring of INR, its efficacy and safety depends upon time in the therapeutic range.*

Outcome: *Recently novel oral anticoagulants (NOAC's) have been introduced, offering similar effectiveness, safety and convenience of vitamin K antagonist not requiring lab monitoring. This review describes the currently approved NOAC's.*

1. INTRODUCTION

Thrombosis is the most common underlying pathology of the three major cardiovascular diseases: ischemic heart disease, ischemic stroke and venousthrombo-embolism. The global burden of diseases, injuries, and risk factors (GBD) study of WHO 2010 documented that ischemic heart disease and stroke collectively caused one in four deaths worldwide[1]. Atrial fibrillation is the most common arrhythmia in elderly and it is responsible for significant morbidity and mortality from cardio embolic complications like stroke [2].Warfarin has traditionally been used for stroke prevention for more than fifty years. It has a lot of limitations like major bleeding risk, frequent monitoring of INR values, drug-drug, drug-food interactions etc. Three new oral anticoagulants Dabigatran, Rivaroxaban and Apixaban have been approved by US FDA after completing their phase III clinical trials[3].

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2.1. Dabigatran etexilate

Dabigatran was the first NOAC approved in many countries worldwide (In 2008 by European Union and by FDA in October 2010) for the prevention of stroke and blood clots from AF based on the results of RE-LY trial (Randomized Evaluation of Long Term Anticoagulant Therapy, warfarin compared with dabigatran)[5]. This oral direct reversible thrombin inhibitor connects to thrombin with high specificity and affinity, inactivating both fibrin bound as well as unbound thrombin. Dabigatran etexilate is a prodrug that is rapidly converted to dabigatran, which reversibly blocks the active site of thrombin[6]. The normal dose range is 150mg BID and 75mg BID for patients with CrCl 15-30mg/ml. This drug has oral bioavailability of approximately 6%, peak onset of action is in 2 hours. Plasma $t_{1/2}$ is 12-14 hours. Thereis no drug- food interaction. Drug interactions are seen if concomitantly used along with P glycoprotein inducers, and also with drugs that affect bleeding risk[7,13]. The most common adverse effect associated with dabigatran is dyspepsia. A specific antidote is not available. Dabigatran is approved for stroke prevention in AF. In March 2008, European Union approved the use of dabigaran for DVT prevention post elective total hip or knee replacement surgery[8, 9].

2.2. Rivaroxaban

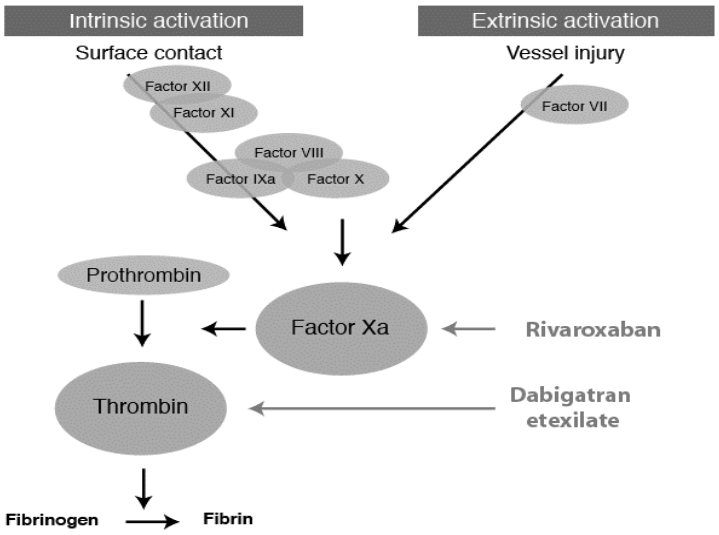
Rivaroxaban is the second new oral anticoagulant approved in September 2008 by European Medicines Agency (EMA) and by the FDA based on the results of the ROCKET AF (Rivaroxaban Versus Warfarin in Non valvular Atrial Fibrillaion) trial. It is a direct factor x_a inhibitor, which connects reversibly to the active site of factor x_a, with high specificity, and acts independently of endogenous antithrombin. So, it suppresses the production of new molecules and plasma thrombin has no significant effect on the activity of existing thrombin. It has 80% oral bioavailability; a peak onset of action is in 3 hours and a plasma $t_{1/2}$ of 7-11 hours. One by third of drug is excreted unchanged in urine.[7]Approved normal dose is 20mg QID.Patients with CrCl 15-50mg/ml, should take 15mg QID. Rivaroxaban should be taken along with the evening meal as its bioavailability decreases if not taken with food. Drug interactions are seen with P glycoprotein and strong CYP3A4 inhibitors. The most common side effect of rivaroxaban is anaemia and bleeding[10].

2.3. Apixaban

Apixaban is the third new oral anticoagulant approved by the FDA and by EMA in May 2011, based on the ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation).It is another oral reversible direct factor X_a antagonist. It has rapid absorption of upto 15 hours half-life and the food does not affect its bioavailability. Thirty five percent of the drug is excreted by the kidneys.[7]Normal dose is 5mg BID. Dosage adjustments have to be made with age, body weight, renal function etc[11].There is no drug food interaction. Drug interactions are seen with P-glycoprotein inhibitors and the drugs that affect haemostasis. The most frequent adverse reactions are epistaxis, hematuria and bleeding in the gut and eye[12].

2.4. Other Agents

Edoxaban and Betrixaban, other factor X_a inhibitors are in evaluation but not yet recommended by the FDA. Edoxaban was non inferior to warfarin regarding prevention of systemic embolism or stroke and had a significant reduction of bleeding and death from cardiovascular causes. Betrixaban is a new direct factor X_a inhibitor and was studied in phase II studies in atrial fibrillation[14].



Mechanism of action of NOAC (Photo courtesy: pharmacology-notes-free.blogspot.com)

Table 1: Overview of design of the pivotal phase III trials of new oral anticoagulants compared with warfarin in non valvular Atrial Fibrillation

Clinical trial	*Rely*	*Rocket af*	*Aristotle*	*Engage af*
Sample size	18,113	14,264	18,201	21,107
New treatment & Dose	Dabigatran 110mg BID &150 mg BID	Rivaoxaban 20mg	Apixaban 5mg	Edoxaban 30mg QID&60m QID
Dosage adjustment	No	At randomization	At randomization	During trial
Design	Non inferiority PROBE	Non inferiority Double blind	Non inferiority Double blind	Non inferiority Double blind
Patients	$CHADS_2$>=1	$CHADS_2$>=2	$CHADS_2$>=1	$CHADS_2$>=2
Primary outcome	Stroke or systemic embolism	Stroke or systemic embolism	Stroke or systemic embolism	Stroke or systemic embolism
Safety outcome	Major bleeding	Major bleeding	Major bleeding	Major bleeding

Table 2: Comparison of warfarin with NOAC

	Warfarin	*Apixaban*	*Dabigatran*	*Rivaroxaban*
Daily doses	1	2	2	1
Dosage	1mg,3mg,5mg,10mg	5mg	110mg,150mg	20mg
Mechanism of action	Vitamin K antagonist	Direct X_a inhibitor	Free and blood clot bound thrombin inhibitor	Direct X_a inhibitor
Monitoring	INR	No	NO	NO
Bioavailability	100%	50%	6-7.2%	80%
Peak plasma concentration	2-3 days	3-4 hours	1.5 hours	3 hours
Half life	2 -5 days	10-14 hours	14-17 hours	4-9 hours
Indications FDA	Venous thrombosis and PE, thromboembolic complications associated to atrial fibrillation and heart valve replacement	Prevention of thromboembolic events in patients subjected to elective knee replacement surgery	Prevention of cerebrovascular events and systemic embolism in non valvular atrial fibrillation	Prevention ofVTE,hip and knee replacement surgery,preventon of cerebrovascular events and systemic embolism in non valvular atrial fibrillation
interactions	Salicylates,NSAIDS,tetracycline,ciprofloxacin,miconazole and metronidazole	CYP3A4 inhibitors,CYP3A4/p-glycoprotein inhibitors/inducers	Rifampicin,amiodarone,p-glycoprotein inhibitors/inducers	CYP3A4 inhibitors,CYP3A4/p-glycoprotein inhibitors/inducers
metabolism	Hepatic	Hepatic 55%, renal 25%	Renal80% Hepatic 20%	Renal
Current status	Over 50 years in market	Marketed in Januvary 2013	Marketted over 70 countries since 2010	
Recommended drug detection tests	INR	Pt,Anti X_a testing calibrated for apixaban	aPTT,thrombin time, diluted thrombin time	PT,Anti X_a testing calibrated for rivaroxaban

2.5. Current Indian scenario

Dabigatran, apixaban and rivaroxaban has been approved in India for marketing in 2014 for additional indications also. Dabigatran etexilate mesilate hard gelatin capsule 75/110/150mg (Pradaxa) has been used in the treatment & prevention of acute DVT & PE. Apixaban tablet 2.5mg/5mg (Eliquis) – In prevention of stroke and systemic embolism in adult patients with NVAF, including those with one or more risk factors such as prior stroke or TIA, age>=75, HT,DM,symptomatic HF[15] (NYHA class>=II) .Compared to warfarin, apixaban also results in less bleeding including intracranial haemorrhage. Rivaroxaban tablet 15/20mg (Xarelto) – In treatment and prevention of DVT and PE, for prevention of stroke and systemic embolism in patients with NVAF[16].

3. CONCLUSION

NOAC's are clinically equivalent to warfarin. Practical advantages of NOAC over warfarin are lack of dietary interaction, convenience in usage, frequent laboratory monitoring is not required, few drug-drug interactions, in patients whom warfarin is ineffective etc. Limitations of NOAC are high cost, no specific lab monitoring tests, no antidote, serious bleeding in renal failure etc.

Available data from various clinical trials confirm that the NOAC appear to offer a realistic alternative to the traditional management strategy of parenteral anticoagulant followed by VKA.

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