



## NOACS: AN EMERGING CLASS OF ORAL ANTICOAGULANTS-A REVIEW ARTICLE

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### ABSTRACT

NOACs commonly known as novel oral anticoagulants, which are non-vitamin K antagonist. Which are relatively newer in the market. It has displaced vitamin K antagonists, notably warfarin, for many indications. These agents are dabigatran, rivaroxaban, apixaban, and edoxaban. The drugs are licensed to prevent stroke and also systemic embolism in patients on treatment for atrial fibrillation and prevent venous thromboembolism. Rivaroxaban and apixaban are approved for prophylaxis of thrombus following surgical hip or knee arthroplasty. The recent surveys reveal that use of NOACs has steeply increased due to its safety profile and convenience to use. Also, the studies have shown that NOACs have lesser bleeding complications and associated mortality in contrast to traditional anticoagulants.

**KEYWORDS:** NOAC, VKA, Anticoagulant.

### INTRODUCTION

Oral anticoagulants are drugs that are extensively used for the prevention and therapy of thromboembolism.<sup>[1]</sup> Initially vitamin K antagonist were the only feasible oral anticoagulant. There is a substantial downside with the use of vitamin K antagonist(VKAs) such as increased risk of bleeding, narrow therapeutic index, individualized dosing based on INR, and many more.<sup>[2,3]</sup> NOACs resolved these issues to a remarkable extent. It is at least as effective as traditional anticoagulant and is convenient to administer as it is given as fixed doses without routine coagulation monitoring.<sup>[1]</sup> It has a predictable and consistent PK-PD profile.<sup>[4]</sup> NOACs include four drugs of which dabigatran was the first to be approved in 2010. It is a direct thrombin inhibitor. Rivaroxaban (2011), apixaban (2014) and edoxaban (2015) fall under direct factor Xa inhibitor.<sup>[5]</sup>

NOACs act by two different mechanism. Based on this it is grouped as direct thrombin inhibitor and direct factor Xa inhibitor. The former category inhibits coagulation by directly binding to thrombin and prevents the formation of fibrin by restricting thrombin from breaking fibrinogen. The latter group inhibit factor Xa which is trypsin like serine protease that plays a critical role in the

blood coagulation cascade.<sup>[9]</sup> It has a principle position in linking the intrinsic and extrinsic pathways. These agents bind directly to factor Xa and prevent them from cleaving prothrombin to thrombin.<sup>[10]</sup>

Due to the predictable characteristics of NOACs, routine monitoring to assess the coagulation is not necessary. However testing may be useful in specific situations such as patients who are bleeding, over dosed or require invasive procedure.<sup>[11]</sup> The available test can be divided based on the process of measurement. They are clot-based assay, chromogenic assay, and liquid chromatography-mass spectrometry.

Table 1: Clinical profile of NOAC.

Anticoagulant	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
<b>Mechanism of action</b>	Direct thrombin inhibitor	Direct factor Xa inhibitor	Direct factor Xa inhibitor	Direct factor Xa inhibitor
<b>Prodrug</b>	Yes	No	No	No
<b>Absorption</b>	Rapid	Rapid	3-4hr	Rapid
<b>Bioavailability</b>	6%	66% w/o food up to 100% with food	50%	62%
<b>Half life</b>	12-17hr	5-9hr(young) 11-13hr(elderly)	12hr	9-11hr
<b>Vd</b>	50-70L	50L	21L	107L
<b>Time to reach max.plasma concentration</b>	0.5-2hr	2-4hr	1-4hr	1-2hr
<b>Protein binding</b>	35%	92-95%	87%	55%
<b>Liver metabolism</b>	No	Yes	Yes	Minimal
<b>Renal excretion</b>	80%	35%	25%	50%
<b>GI tolerability</b>	Dyspepsia	No problem	No problem	No problem
<b>Absorption with food</b>	No effect	39% and above	No effect	6-22%
<b>Effect of diet</b>	Delays absorption; time to reach peak level extend to 4hr	Peak level attain at 3hr on fasting and 4hr with food. Factor Xa inhibition higher with food	No effect on exposure	No effect on exposure
<b>Effect of age(bioavailability)</b>	1.7-2 times high in elders	Greater in elderly with half life 11-13hr with no difference in concentration	Exposure is 32% greater in patients above 65year of age	Exposure is 32% greater in patients over 65year of age
<b>Effect of bodyweight</b>	None	<50kg have 24% increased exposure & >120kg have 24% reduced exposure	<50kg have 20-30% increased exposure & >120kg have 20-30% reduced exposure	<50kg have 20-30% increased exposure & >120kg have 20-30% reduced exposure
<b>Doses, dosing and dosage form</b>	75,110,150mg Two times a day Capsule	2.5,10,15,20mg One time a day Tablet	2.5,5mg Two times a day Tablet	15,30,60mg One time a day Tablet
<b>ADR</b>	>10% GI symptoms(dyspepsia) 1-10% gastritis,esophagitis <1% allergic oedema, thrombocytopenia	>10% hematologic & oncologic hemorrhage 1-10% pruritus, abdominal pain,<1% angioedema,cholestasis	>10% hematologic & oncologic hemorrhage 1-10% haematuria, epistaxis, <1% hyper sensitivity reaction, haematoma.	>10% hematologic & oncologic hemorrhage 1-10% skin rash,anaemia <1% intra cranial haemorrhage,interstitial pulmonary disease
<b>Contraindication</b>	Serious hyper sensitivity reaction	Serious hyper sensitivity reaction	Serious hyper sensitivity reaction	Serious hyper sensitivity reaction

Table 2: NOACs – Indications and doses.

Drug	Non valvular atrial fibrillation(to prevent stroke and systemic embolism)	Venous thromboembolism prophylaxis	DVT and PE	Others
Dabigatran	150 mg twice daily	110mg 1-4hr after completion of surgery and establishment of haemostasis or the initial dose of 220mg after haemostasis is achieved and continued for 10-14 days	150mg twice daily	
Rivaroxaban	20mg once daily with the evening meal	10mg once daily for 31-39 days	15mg twice daily with food for 21 days followed by	CAD:2.5mg twice daily with low dose aspirin; heparin induced thrombocytopenia:15mg daily

			20mg once daily with food	with food for 21 days followed by 20mg once daily
Apixaban	5mg twice daily	2.5mg twice daily beginning 12-24hr post operatively	10mg twice daily for 7 days followed by 5mg twice daily	Heparin induced thrombocytopenia: 10mg twice daily for 7 days followed by 5mg twice daily
Edoxaban	60mg once daily		Patient weight >60kg, 60mg once daily & ≤60kg, 30mg once daily	

### Perioperative management of NOACs

The faster onset and offset of action of NOAC have made the perioperative fairly easy. NOACs should be pre operatively paused for operation with a high chance of bleeding risk. The factors which determine the time duration of pause are the renal function of the patient and perioperative bleeding possibility. In case the patient has administered with medication that increase the half life of NOACs, the pre operative pause should be prolonged up to 12hr.<sup>[12,13]</sup> Bridging with heparin is not mandatory for NOACs. The drug therapy can be resumed only when the risk of perioperative bleeding has become lowered and GI passage is back to normal. NOAC is re-established within 6-8hr and the farthest being 24hr post operation for procedure having low bleeding risk.<sup>[12,14]</sup> For operation with high risk of bleeding, NOACs are restarted within 48-72hr post operatively.<sup>[12]</sup>

If there occurs an emergency for surgery with high perioperative bleeding risk, the administration of antidote is considered. The level of drug in plasma should be assessed before the administration of an antidote.<sup>[15,16]</sup> It

is done to assess the level of coagulation. Idarucizumab is the recognized antidote to dabigatran. It is administered before emergency surgical procedure having a high possibility for bleeding and also the plasma level of the drug is above 30ng/ml. In major bleeding conditions, idarucizumab might be given at plasma level above 50ng/ml. Idarucizumab shows a high affinity for binding to dabigatran and its metabolites. It eliminates the complex renally. Idarucizumab is administered intravenously at 2.5mg dose initially and then a maintenance dose within 15min.<sup>[15,17]</sup> For factor Xa inhibitor, andexanet alpha is the approved antidote in major bleeding event. Andexanet alpha acts by binding with the agents and eliminates it. In bleeding conditions, an IV bolus and continuous IV infusion of the drug is administered for 120min. The low dose regimen is 400mg bolus + 4mg/min infusion, and the high dose regimen 800mg bolus + 8mg/min infusion. What regimen to be chosen is determined by the dose of anticoagulant and time period after the last intake. Aripazine or PER 977 is universal antidote for NOACs, on which clinical trial are going on<sup>[18]</sup> (Table 3).

**Table 3: Pre and post operative care for patients on NOACs.**

Drugs	Dabigatran	Rivaroxaban	Edoxaban	Apixaban
<b>Renal function (based on creatinine clearance)</b>	Normal function or mild impairment with creatinine clearance >50ml/min Moderate impairment with CrCl between 30-50ml/min	Normal, mild or moderate impairment with CrCl >30ml/min	Normal, mild or moderate impairment with CrCl >30ml/min	Normal, mild or moderate impairment with CrCl >30ml/min
<b>Pre operative care (Minor surgical procedure)</b>	Withhold therapy for 2 days prior to surgery (i.e., omit 2 doses) Withhold therapy for 3 days prior to surgery (i.e., omit 4 doses)	Withhold therapy for 2 days prior to surgery (i.e., omit 1 dose)	Withhold therapy for 2 days prior to surgery (i.e., omit 1 dose)	Withhold therapy for 2 days prior to surgery (i.e., omit 1 doses)
<b>Post operative care</b>	Resume 24hr following surgery	Resume 24hr following surgery	Resume 24hr following surgery	Resume 24hr following surgery
<b>Pre operative care (Major surgical procedure)</b>	Withhold therapy for 3 days prior to surgery (i.e., omit 4 doses) Withhold therapy for 4-5 days prior to surgery (i.e., omit 6-8 doses)	Withhold therapy for 3 days prior to surgery (i.e., omit 2 doses)	Withhold therapy for 3 days prior to surgery (i.e., omit 4 doses)	Withhold therapy for 3 days prior to surgery (i.e., omit 4 doses)
<b>Post operative care</b>	Resume 48hr following surgery Resume 48hr following surgery	Resume 48hr following surgery	Resume 48hr following surgery	Resume 48hr following surgery

### Advantages

NOACs become popular in the market due to the advantages over traditional anticoagulants. It has erased the need of heparin bridging as it has sudden onset as well as offset action, which eliminates the chances of bleeding if the patient require surgical treatment. Along with these benefits any patients with acute thrombosis does not require any initial treatment with a parenteral anticoagulant.<sup>[19]</sup> It reduces the need for a routine coagulation monitoring also it convenience for the patients as NOACs have fixed daily oral doses. The actions of the NOACs are not affected by the intake of foods. Hence the patient does not need to avoid certain foods or put any dietary restrictions.<sup>[20]</sup>

Due to the wide therapeutic window, the chance of bleeding complications are reduced. NOACs have specific coagulation enzyme targets; therefore, off target adverse effect are almost nil. It also shows greater efficacy in patients having atrial fibrillation. And they are less prone to have intracranial hemorrhage (ICH) with an exception for dabigatran (150mg of the drug causes equal rate of ICH as warfarin).<sup>[21]</sup> Studies show that NOACs have minimal interactions with other drugs. It permits the concomitant administration of other drugs with NOACs. It is unlike VKAs which exhibit a wide range of drug interaction.<sup>[9]</sup>

### Disadvantage

The acquisition costs are higher for NOACs compared to VKAs; hence it limits the usage. This makes the healthcare system prefer warfarin over NOACs though INR is poorly controlled with it.<sup>[1]</sup> NOACs lack the need for routine investigation of the drug in plasma or modification of dose except for emergency situation where the drug exposure assessment is required. This arena demands a large number of studies, because most of the tests are not reliable and provide accurate tests. There is only limited evidence available to assess the coagulation testing ability.<sup>[2]</sup> Primarily, specific tests are still not routinely available in many centres. Even if available, the expertise is not available round the clock. Thus it is difficult to assess the level of coagulation in emergency situations. Also there are no international calibration standard for the assays.<sup>[33]</sup>

The dose adjustment are done according to the patient characteristics outlined in the monograph of each agents since there is very little evidence in suggestion to improve safety levels of the drug in relation to clinical characteristics like age, renal function and concomitant medication.<sup>[1]</sup> Dose adjustment for patients at extremes of body weight is still debated upon as data on these clinical trials are insufficient at present.<sup>[1]</sup> There are limited studies with regard to the usage of NOACs in pregnant women and breast feeding mothers along with patients having hepatic disease. whether it is safe on long term use or not has not yet been confirmed.<sup>[7]</sup>

### CONCLUSION

The forthcoming years tend to show a tremendous increase in the use of NOACs. This can be understood from the rate of usage of NOACs in recent years. This is the result of better patient compliance, safety profile and easier management of these drugs compared to traditional anticoagulants. Globally, the medical practitioners eagerly use NOACs over VKAs but are uncertain to use due to limited evidence.<sup>[2]</sup> However it will have greater progress in the near future as many studies are being conducted that will make it more accessible to the patients in terms of dosing regimen and efficacy. The cost will gradually reduce to an affordable price.<sup>[2]</sup> Innovative protocols will be designed to minimize the possibility of haemorrhage.<sup>[22]</sup> Advanced studies will be carried out to determine dosing pattern for special populations such as pregnant and lactating women, geriatrics, paediatrics and patients with renal hepatic dysfunction.<sup>[7]</sup> Many studies are being conducted to authorize the safety in long term use of drugs.<sup>[7]</sup> International standards for specific assays for NOACs are to be established to alleviate the variation in the results of laboratory values.<sup>[11]</sup>

### Abbreviations

NOACs: Novel oral anticoagulants; VKA: Vitamin K antagonist; GI: Gastro intestinal; CrCl: Creatinine clearance.

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