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NOACs: an emerging class of oral anticoagulants-a review article

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Abstract

Background: NOACs, commonly known as novel oral anticoagulants, are the non-vitamin K antagonist oral anticoagulants 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.

Main body: The drugs are licenced 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. The upcoming years are known to be NOACs' age due to the significant findings in this area.

Conclusion: Therefore, a basic understanding on these drugs is highly recommended to provide a better service to the patients. This article aims to provide quick and brief information on the novel class of drugs. It equips an overview of NOAC and deals with the following areas: (i) pharmacology, (ii) laboratory methods, (iii) peri-operative management, (iv) advantages, (v) challenges, and (vi) future.

Keywords: NOAC, VKA, Anticoagulants

Background

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

Main text

Pharmacological aspects of NOACs

Unlike VKAs, NOACs have more predictable PK-PD properties [4]. Due to this appreciable characteristic, NOACs are used at fixed doses without periodic monitoring of coagulation parameters [6]. A relevant relationship allying clinical characteristics and plasma drug levels and/or pharmacodynamics responses with safety and efficacy has been established by pharmacokinetics-pharmacodynamics analyses of vital trials with NOACs. Absolving these analyses, dosing instructions and contraindications are placed on the basis of clinical characteristics in relation to plasma drug levels and/or

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pharmacodynamics responses, reduction of stroke, and bleeding chances are provided by pharmaceutical manufacturers and regulatory authority to make effective use of the risk and benefit profile of NOACs in the current world. By knowing the effect of these factors on blood levels, it is certain that for almost all patients, the drug exposure falls within a limit without monitoring coagulation (Tables 1 and 2) [8].

Mechanism of action

NOACs act by two different mechanisms. 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 inhibits factor Xa which is trypsin-like serine protease that plays a critical role in the blood coagulation cascade [9]. It has a principal position in linking the intrinsic and extrinsic pathways to the final common coagulation pathway. These agents bind directly to factor Xa and prevent them from cleaving prothrombin to thrombin [10].

Laboratory tests

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, are overdosed, or require invasive procedures [11]. The available tests can be divided based on the process of measurement.

Clot-based assays

Assays based on clot formation are widely available. These tests work by measuring the time period for the plasma-containing NOAC to be monitored to form coagulum after adding calcium and activator. It includes prothrombin time (PT), dilute prothrombin time, activated partial thromboplastin time (aPTT), hep test, ecarin clotting time (ECT), and hemoclot as well as prothrombinase-induced clotting time (PiCT). However, these are not specific to NOACs [12].

PT is used to assess the coagulation with rivaroxaban. It determines the time taken as the plasma sample produces clot after adding calcium along with thromboplastin. The final results are generated as seconds. The limitations for the test are high inter-laboratory variability; patients with hepatic impairment or sepsis may show protracted PT results, as well as transient PT values may be obtained due to the short half-life of the drug. Also, PT reagents are insensitive at a low concentration of the drug producing false results. Dilute PT assays also show the same limitations. Neoplastine plus is the suggested agent to estimate the effect of the drug [13–15].

aPTT test is used to monitor coagulation of rivaroxaban and apixaban. It estimates comprehensive functioning of the intrinsic coagulation pathway. It is executed by adding contact activator and cephalins to a plasma sample that has been citrated. The preincubation period is provided before the addition of calcium, and then the measurement of clotting time is performed [12]. However, it is less sensitive than PT. It can be used as a screening test [16].

HepTest is an anti-factor Xa analysis based on clot formation. Calcium chloride and thromboplastin are added to plasma sample after incubation with bovine factor Xa. This test is used to estimate the coagulation with rivaroxaban [14]. ECT is another test to determine the clotting of thrombin using venom obtained from snake to form prothrombin intermediate. Even though it has been found to be useful for monitoring dabigatran activity, it lacks sensitivity and does not have an available system for standardization and validation [17]. Whereas hemoclot is a test used to determine dabigatran that is found to have high sensitivity and good reproducibility [13, 16], PiCT is a reliable method for assessing rivaroxaban and dabigatran in blood samples. Like all the tests, it lacks sensitivity at low concentrations [12].

Chromogenic assays

Chromogenic assays are quantitative tests that determine the variation in absorbance using chromophore labelled substrate. The coagulation factor to be determined cleaves the labelled substrate of a particular clotting factor, which is a process blocked by the anticoagulant. These assays are more certain than clot-based assays. It is a very useful technique to measure the coagulation of rivaroxaban and provide accurate results [12].

Recently, STA Rotachrom, Technochrom® anti-Xa, and Biophen DiXaI® have received European sanction for trade purposes. STA Rotachrom is anti-factor Xa chromogenic test which helps in assessing the activity of both rivaroxaban and apixaban. It is more precise and a definite substitute to the prothrombin test for estimating rivaroxaban [18, 19].

Liquid chromatography-mass spectrometry(LC-MS/MS)

Liquid chromatography-coupled tandem mass spectroscopy is the novel type of measurement of anticoagulants and is helpful in clinical situations where the bleeding cause is yet to be determined. It is the most reliable laboratory assay to investigate the plasma level of the drugs. It is highly specific and provides reliable and accurate results. The simultaneous determination of dabigatran, rivaroxaban, and apixaban can be done within 3 min. The main limitation of the assay is that it is only available in specialized laboratories. Thus, it can be used as an arbitration method for serious conditions [20].

Table 1 Clinical profile of NOACs [7]

Anticoagulant	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Mechanism of action	Direct thrombin inhibitor	Direct factor Xa inhibitor	Direct factor Xa inhibitor	Direct factor Xa inhibitor
Prodrug	Yes	No	No	No
Absorption	Rapid	Rapid	3-4 h	Rapid
Bioavailability	6%	66% w/o food Up to 100% with food	50%	62%
Half-life	12–17 h	5-9 h(young) 11-13 h(elderly)	12 h	9-11 h
Vd	50–70 L	50 L	21 L	107 L
Time to reach max. plasma conc.	0.5–2 h	2-4 h	1-4 h	1-2 h
Protein binding	35%	92-95%	87%	55%
Liver metabolism	No	Yes	Yes	Minimal
Renal excretion	80%	35%	25%	50%
Gastro-intestinal tolerability	Dyspepsia	No Problem	No Problem	No Problem
Absorption with food	No effect	39% & above	No effect	6-22% more
Effect of diet	Delays absorption; time to reach peak level extends to 4 h	Peak levels attain at 3 h on fasting and 4 h with food. Factor Xa inhibition higher with food	No effect on exposure	No effect on exposure
Effect of age	Bioavailability is 1.7–2 times high in elders	Bioavailability is greater in elderly with half-life 11-13 h with no difference in concentration	Exposure is 32% greater in patients above 65 years of age	Exposure is 32% greater in patients over 65 years of age
Effect of body weight	None	Weight < 50 kg have 24% increased exposure & weight > 120 kg have 24% reduced exposure	Weight < 50 kg have 20-30% increased exposure & weight > 120 kg have 20-30% reduced exposure	Weight < 50 kg have 20-30% increased exposure & weight > 120 kg have 20-30% reduced exposure
Effect of renal impairment	Severely impaired; 6 times higher exposure with half-life 28 h	Similar increase in exposure with moderate or severe renal impairment	No effect on peak concentration. Increase in exposure of 16, 29, and 44% for creatinine clearance of 51–80, 30–50, and 15–29% ml/min, respectively.	No effect on peak concentration. Increase in exposure of 16, 29, and 44% for creatinine clearance of 51–80, 30–50, and 15–29% ml/min, respectively.
Effect of hepatic impairment	None with Child-Pugh classification B	Significantly increased on exposure with Child-Pugh classification B	No change in exposure with Child-Pugh classification A or B	No change in exposure with Child-Pugh classification A or B
Doses	75 mg, 110 mg, 150 mg	2.5 mg, 10 mg, 15 mg, 20 mg	2.5 mg, 5 mg	15 mg, 30 mg, 60 mg
Dosing	Two times a day	One time a day	Two times a day	One time a day
Dosage form	Capsule	Tablet	Tablet	Tablet
ADR	> 10% gastro-intestinal symptoms (like dyspepsia); 1–10% gastritis, esophagitis; < 1% allergic oedema, thrombocytopenia	>1 0% haematologic and oncologic haemorrhage; 1–10% pruritus, abdominal pain; < 1% angioedema, cholestasis	> 10% haematologic and oncologic haemorrhage; 1–10% haematuria, epistaxis; < 1% hyper-sensitivity reaction, haematoma	> 10% haematologic and oncologic haemorrhage; 1–10% skin rash, anaemia; < 1% intra cranial haemorrhage, interstitial pulmonary disease
Contra indications	Serious hyper-sensitivity reactions	Serious hyper-sensitivity reactions	Serious hyper-sensitivity reactions	Serious hyper-sensitivity reactions

Table 2 NOACs—indications and doses [7]

Drug	Non-valvular atrial fibrillation (to prevent stroke and systemic embolism)	Venous thromboembolism prophylaxis	DVT and PE	Others
Dabigatran	150 mg twice daily	110 mg 1 to 4 h after completion of surgery and establishment of haemostasis, or the initial dose of 220 mg after haemostasis is achieved and continued for 10–14 days	150 mg twice daily	
Rivaroxaban	20 mg once daily with the evening meal	10 mg once daily for 31–39 days	15 mg twice daily with food for 21 days followed by 20 mg once daily with food	CAD: 2.5 mg twice daily with low-dose aspirin; heparin-induced thrombocytopenia: 15 mg daily with food for 21 days followed by 20 mg once daily
Apixaban	5 mg twice daily	2.5 mg twice daily beginning 12–24 h post-operatively	10 mg twice daily for 7 days followed by 5 mg twice daily	Heparin-induced thrombocytopenia:10 mg twice daily for 7 days followed by 5 mg twice daily
Edoxaban	60 mg once daily		Patient weight > 60 kg, 60 mg once daily, and ≤ 60 kg,30 mg once daily	

Peri-operative management of NOAC

The faster onset and offset of action of NOACs have made the peri-operative management 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 peri-operative bleeding possibility. In case the patient has administered with medications that increase the half-life of NOACs, the pre-operative pause should be prolonged up to 12 h [21, 22]. Bridging with heparin is not mandatory for NOACs. The drug therapy can be resumed only when the risk of peri-operative bleeding has become lowered and gastro-intestinal passage is back to normal. NOAC is re-established within 6–8 h and the farthest being 24 h post-operation for procedures having low bleeding risk [21–23]. For operations with a high risk of bleeding, NOACs are restarted within 48–72 h post-operatively [21].

If there occurs an emergency for surgery with high peri-operative bleeding risk, the administration of antidote is considered. The level of drug in plasma should be assessed before the administration of an antidote [24, 25]. It is done to assess the level of coagulation. Idarucizumab is the recognized antidote to dabigatran. It is administered before emergency surgical procedures having a high possibility for bleeding and also the plasma level of the drug is above 30 ng/ml. In major bleeding conditions, idarucizumab might be given at plasma level above 50 ng/ml. Idarucizumab shows a high affinity for binding to dabigatran and its metabolites. It eliminates the complex renally. Idarucizumab is administered intravenously at 2.5-mg dose initially and then a maintenance dose within 15 min [24–26]. For factor Xa inhibitors, andexanet alpha is the approved antidote in major bleeding events. Andexanet alpha acts by binding with the agents and eliminates it. In bleeding conditions, an IV bolus and a continuous intravenous infusion of the drug is administered for 120 min. The low-dose regimen is 400 mg bolus + 4 mg/min infusion, and the high-dose regimen is 800 mg bolus + 8 mg/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 the universal antidote for NOACs, on which clinical trials are going on [27] (Table 3).

Advantages

NOACs become popular in the market due to advantages over traditional anticoagulants. Some of the many advantages are dealt here. Firstly, it has erased the need for heparin bridging as it has sudden onset as well as offset action, which eliminates the chances of bleeding if the patient requires surgical treatments. Along with these benefits, the rapid onset and offset actions mean any patient with acute thrombosis does not require any initial treatment with a parenteral anticoagulant [29].

Its popularity accounts not only for its predictable anticoagulant effects which in turn reduce the need for a routine coagulation monitoring but also its convenience for the patients as NOACs have fixed daily oral doses. This is possible since they have predictable PK properties and absolute bioavailability, regardless of the demographic variables [30].

Most importantly, the actions of NOACs are not affected by the intake of foods. Hence, the patient does not need to avoid certain foods or put any dietary restrictions [31]. Also, due to the wide therapeutic window, the chances of bleeding complications are exponentially reduced. NOACs have specific coagulation enzyme targets; therefore, off-target adverse effects are almost nil. It also shows greater efficacy in patients

Table 3 Pre- and post-operative care for patients on NOACs [28]

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

having atrial fibrillation. And they are less prone to have intracranial haemorrhage (ICH) with an exception for dabigatran (150 mg of the drug causes equal rate of ICH as warfarin) [32].

Lastly, the 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 interactions [9].

Challenges

Even though NOACs brought about several advantages over VKAs, there still exist some challenges that need to be overcome. Even though current guidelines favour the use of NOACs, there are several domains that need contemplation and studies to guarantee the safe and effective use of the drug. It lacks empirical evidence on its proper use which makes clinicians less interested to switch over to NOACs [2]. Some of the main demerits are addressed below.

The drug 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 [1].

Unlike warfarin, NOACs lack the need for routine investigation of the drug in plasma or modification of dose except for emergency situations 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 [2]. 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 standards for the assays. Thus, there are chances for considerable variations between laboratories [33].

There is no system to optimize non-compliance of NOACs like VKAs. This is due to the shorter half-life of the drugs. Thus patients require follow-up to ensure their medication compliance. The endurance with NOACs is unsatisfactory and efforts are in progress to enhance compliance [1, 2].

Switching from NOAC to warfarin is a bit complex. Warfarin shows gradual outset of action (5–10 days). Thus, NOACs should be administered along with warfarin till the INR is in the desired value. Once sole therapy is in place, the INR should be re-evaluated 24 h after the last dose of NOACs. This is done to guarantee adequate anticoagulation. Close monitoring of INR is suggested for the first month until stable INR values are achieved [34].

For CKD patients, a yearly examination of renal function is advised especially for dabigatran (80% elimination renally). The current ESC guidelines state that the use of NOACs is undesirable in CKD patients having CrCl < 30 ml/min. Administration of NOACs is not suggested in patients with AF and undergoing haemodialysis [35, 36].

The dose adjustments are done according to the patient characteristics outlined in the monograph of each agent 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 medications [1].

Dose adjustment for patients at extremes of body weight is still debated upon as data on these clinical trials are insufficient at present [1].

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 [7].

Future trends of NOACs (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 the limited evidence [2]. 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 [2]. Innovative protocols will be designed to minimize the possibility of haemorrhage [37]. Advanced studies will be carried out to determine dosing patterns for special populations such as pregnant and lactating women, geriatrics and paediatrics, and patients with renal and hepatic dysfunction [7]. Many studies are being conducted to authorize the safety in long-term use of drugs [7]. International standards for specific assays for NOACs are to be established to alleviate the variation in the results of laboratory values [11].

Abbreviations

NOACs: Novel oral anticoagulants; VKA: Vitamin K antagonist; CrCl: Creatinine clearance

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Authors' contributions

Ms. CP has played a critical role in collection and analysation of data regarding the topic. Her immense contribution to writing the manuscript is irreplaceable. She is the main author and has shown immense interests for the work. She has approved the submitted version. Ms. MB was a contributor in data collection and aided in writing the manuscript. Dr. AR has made critical suggestions to the conception and substantively revised the work. Dr. KK was the supporting pillar for writing manuscript and drafted the work. All authors have read and approved the manuscript.

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