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https://doi.org/10.31925/farmacia.2020.2.3 **REVIEW**

OVERVIEW OF NON-VITAMIN K ORAL ANTICOAGULANTS

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Abstract

Clotting is a highly complex process and its excessive activation can lead to major risk events. Therefore, anticoagulant treatment is one of the mainstays of pharmacology. Vitamin K antagonists were the only oral anticoagulants available for more than half a century. In the early 2000s new possibilities emerged in this field. The direct and selective mechanism by which they inhibit clotting factors along with their rapid onset of action, the diminished intra-and interindividual variability, the short half-life, the fact that routine therapeutic drug monitoring is not necessary, their strong antithrombotic effect were the main supporting arguments put forth for the use of the direct anticoagulants. Taking into account their innovative aspect, health practitioners were reluctant to prescribe these new drugs and invoked their main shortcomings, both medical (e.g.: lack of an antidote, higher bleeding risk when impaired renal function, certain prescribing restrictions etc.) and financial ones. Why should a non-vitamin K oral anticoagulant (NOAC) be used instead of a vitamin K antagonist? Which would be the best option among the NOACs? These are the most important questions that need answers, which can be obtained by studying the pharmacologic profile of these drugs.

Rezumat

Coagularea sanguină este un proces complex, iar activarea excesivă a acestuia poate duce la situații clinice cu riscuri majore. Tratamentul anticoagulant reprezintă așadar un capitol important al farmacologiei. Pentru mai bine de o jumătate de secol, antivitaminele K au fost singurele anticoagulante orale disponibile. Abia începând cu anul 2000 și-au făcut apariția publicații care anunțau debutul unor noi agenți farmacologici din clasa anticoagulantelor orale. Mecanismul lor direct și selectiv de inhibare a factorilor coagulării și debutul rapid al acțiunii farmacologice, variabilitatea intra- și interindividuală mai redusă a efectului, timpul de înjumătățire mai scurt, lipsa necesității de a monitoriza frecvent intensitatea efectului farmacodinamic, acțiunea antitrombotică eficientă au constituit principalele argumente care le-au impus. Așa cum se întâmplă însă cu tot ceea ce este inovativ, profesioniștii din domeniul medical au fost reticenți față de aceste noi medicamente, dezvăluindu-le rapid principalele neajunsuri, de la aspecte medicale (lipsa unui antidot, riscul hemoragic mai ridicat în cazul unei disfuncții renale, unele restricții de utilizare) până la aspecte pecuniare. De ce am utiliza un anticoagulant nou în detrimentul anticoagulantului tradițional? Dintre noile anticoagulante, ce opțiune ar fi de preferat? Acestea reprezintă cele mai importante dintre multele întrebări la care se poate obține un răspuns prin studierea profilului farmacologic al acestor medicamente.

Keywords: novel anticoagulants, mechanism of action, renal function

Introduction

In order to be introduced into the therapeutic arsenal of certain diseases, any drug must have a satisfactory efficacy and safety profile. Efficacy refers to the presence of an appropriate pharmacological activity in relation to a specific medical indication, and the safety profile refers to the absence of potentially harmful side-effects caused by the treatment [1]. For anticoagulant drugs, the efficacy profile refers to the prophylaxis of thromboembolic events associated with certain clinical conditions such as atrial fibrillation, postoperative status, neoplasia, thrombophilia, etc., and the safety profile takes into consideration first of all bleeding, i.e. onset, location and severity. Both profiles depend on the pharmacodynamic and pharmacokinetic characteristics of a particular chemical compound [2].

The non-vitamin K oral anticoagulants (NOAC's, previously referred as "new oral anticoagulants") represent a remarkable recent advance in anticoagulant therapy, which compensates the main disadvantages of antivitamin K drugs: the narrow therapeutic window, therefore the need for close monitoring of the therapy, and frequent and important interactions with concomitant nutrition and medication. Five large randomized clinical trials: RE-LY (2009), ROCKET AF (2011), ARISTOTLE (2011), AVERROES (2011) and ENGAGE AF TIMI 48 (2013), introduced dabigatran, rivaroxaban, apixaban and edoxaban to the oral anticoagulation treatment used for over 70 years, comparing the benefits and risks of each of

these drugs to the benefits and risks of warfarin, the main representative of antivitamin K [3]. In June 2017, betrixaban, the newest direct oral anticoagulant, was approved. As a result of the favourable results demonstrating the non-inferiority of this class of drugs in terms of thromboembolic events, gastro-intestinal and cerebral haemorrhage, as well as global mortality, NOAC's have begun to be used more and more, but the experience of their use is still limited, which requires their further study.

The subject of this review is related to the way and the extent to which certain factors that depend on either the organism (age, gender, body weight, coagulation status at the molecular level, hepatic function and renal function, etc.) or the medication (mechanism of action, dose range, bioavailability, half-life, renal clearance, drug interactions) modify the action and expected effect of NOAC's. The choice of this topic is justified by the fact that, although there are many papers that consider the pharmacological factors that can influence the NOAC's effect in the body, there are no analyses that integrate these factors and display a hierarchy depending on their importance.

This paper brings in a synthesis, but also an analysis of recent literature and a critical evaluation of it, highlighting both the progresses and the discoveries made, as well as the gaps and the new research perspectives in the field. Both, original articles as well as recent review articles or meta-analyses from European and American publications have been cited, addressing the factors that can influence the NOAC's effect in the human body.

NOAC's mechanism of action

The effectiveness of vitamin K antagonists as anti-coagulant therapy is proven. Their mechanism of action consists in blocking the vitamin K-dependent carboxylation of factors II, VII, IX, X through competition with vitamin K, which makes the synthesized factors inoperative. It is noteworthy that they intervene at several levels of the coagulation process. Anti-vitamin K (AVK) treatment problems are not related to their mechanism of action, but to the absolute necessity of a TTR (time in therapeutic range) of at least 60%, which can be extremely difficult (requires periodic control, attention to drug and food interactions). Unlike AVK, NOAC, although in a direct manner (the onset of action is concomitant with Tmax), act on a single link of the coagulation process (Figure 1).

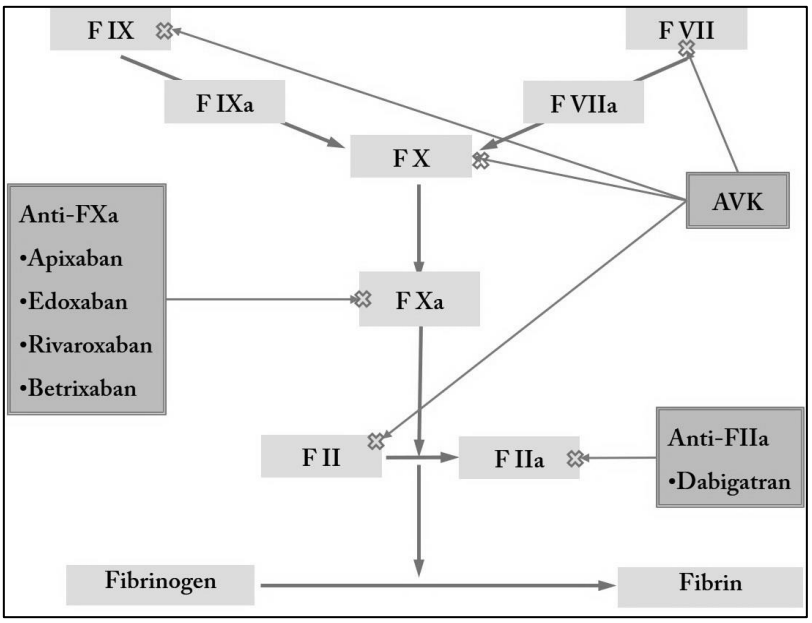

Figure 1.
Main oral anticoagulants sites of action

Depending on the level at which they intervene in the coagulation cascade, the direct anticoagulants are divided into two classes: *-gatrans* (factor IIa-thrombin inhibition) and *-xabans* (factor Xa inhibition). There were divergent views on the mechanism that could generate a stronger antithrombotic effect. Factor Xa occupies a central position in the coagulation process, being 1000 times more thrombogenic than factor IIa, which could make it a much more effective target in the anticoagulant treatment [4]. However, thrombin has a thrombogenic effect mediated by several processes: fibrinogen catabolism to fibrin, activation of factor XIII, followed by the activation of α2-antiplasmin, activation of factor V and VIII, stimulation of its own synthesis, acts as a platelet agonist [5].

Although the mechanism of action is currently not a solid criterion used to decide on whether opting for an anticoagulant or for another, there is some evidence suggesting that the effectiveness of the *-xabans* would be superior to the *-gatrans*. A recent US study aimed at identifying the need for a transoesophageal echocardiography assessment prior to the ablation of atrial fibrillation after 4 weeks of NOAC treatment revealed the highest rate of spontaneous echo contrast/thrombi in the left atrium for dabigatran (5.4% compared to 4.8% for rivaroxaban and 0% for apixaban; the differences between rivaroxaban and apixaban may be attributed to the interval of administration or pharmacokinetic properties) [6]. Other recent studies also pointed out that the risk of stroke/systemic embolism would be greater on dabigatran than on rivaroxaban or apixaban [7]; a study evaluating the periprocedural rate of thromboembolic complications had results favouring warfarin and apixaban (0% *vs*. dabigatran 2.1%) [8]. In the ARISTOTLE study, out of 86 included patients, only one was found with spontaneous echo contrast after preprocedural treatment with apixaban [9].

The efficacy of dabigatran in the prevention or treatment of thromboembolic events is demonstrated in many large-scale studies to be similar to AVK [10, 11], and is indisputable. However, what remains to be determined is whether the effectiveness of factor Xa inhibition is indeed so great as to condition the choice of *-xaban* at the expense of a *-gatran*. Of course, there are many other important criteria to consider when choosing a NOAC, especially patient preference and renal function status. Since current literature focuses on indirect comparisons between NOAC, more studies are needed to include NOAC representatives at the same time, so that their effectiveness profile can be directly compared.

The importance of correct NOAC dosing and treatment adherence

Given the lack of monitoring of NOAC's action, it is very important that the pre-established and approved doses by the American and European professional societies are respected. Otherwise, overdosing or under-dosing may lead to haemorrhages, thromboembolic events, increased rates of hospitalization and general mortality. The dose of a drug is a pharmacological parameter with a major influence on the pharmaco-dynamic effect, and the dose-effect curve for NOAC's indicates a linear relationship: increasing the dose is associated with increasing the intensity of the effect to a certain level beyond which any dose induces the same intensity of effect. The first and most rigorous analysis on this topic indicated that, in general, the recommended doses and the way to adjust them according to particular situations (glomerular filtration rate, age and body weight) are respected in 87% of cases; besides that, it was overdosed in 3.4% and under-dosed in 9.4% of cases [12]. The category of patients receiving a higher dose showed a higher mortality rate of any cause, while those who received a lower dose had a higher rate of cardiovascular hospitalizations [12, 13]. What is not clear is the mechanism: was haemorrhage the cause of death in overdose situations? Was a thromboembolic event the cause for hospitalizations in under-dosing situations? The main reasons for incorrect dosing are age-related, concomitant administration of aspirin, results of CHA2DS2-Vasc (a score used for predicting stroke risk, which includes heart failure, hypertension, age, diabetes, previous stroke or thromboembolism, vascular disease and female sex), HAS-BLED (a score assessing bleeding risk, based on the presence of hypertension, abnormal renal and liver function, history of stroke or major bleeding, labile INR, age, alcohol abuse, use of other drugs predisposing to bleeding) scores, but also of incorrect renal function evaluation, subject discussed below in this paper [12].

It is very important to follow the guidelines when establishing the dosage; irrespective of the ischemic risk, the recommended doses should not be increased; in patients with higher haemorrhagic risk, it is recommended to change the NOAC by choosing one with a proven superior safety profile (e.g. replacing rivaroxaban with apixaban) [14, 15].

Equally important to the dosing compliance is long-term adherence. Adherence is very important for keeping the desired effect consistent, given the shorter half-life of the NOAC (about 12 hours); however, adherence to NOAC is superior to adherence to antivitamin K, which was estimated to be around 50% one year after initiation [16]. It also appears that adherence is better as the interval of administration is longer (adhesion to rivaroxaban is superior to adhesion to apixaban or dabigatran) [17]. There are few published studies on this topic, explained mostly by the difficulty of measuring this parameter [18].

Metabolism and elimination of NOAC: renal function, hepatic function

The functional status of these two organs must be known prior to initiation of any pharmacological therapy, since at least partial metabolism of any drug, sometimes activation and partial excretion is being processed by the liver, and the kidney is responsible for the clearance of most pharmacological agents.

On the one hand, the liver is the organ through which most coagulation factors (I, II, V, VII, IX, X) are synthesized, and subsequently any acute or chronic illness will influence the plasma level of these factors. On the other hand, as mentioned in Table I, liver enzyme complexes play an important role in inactivating NOAC's through various biochemical processes, especially rivaroxaban and apixaban and less dabigatran and edoxaban, which have minimal hepatic metabolism.

In the context of decreasing serum levels of coagulation factors and increasing the NOAC active plasma fraction, the anticoagulant activity is much more intense, resulting in a higher risk of major bleeding.

The severity of liver dysfunction represents the main parameter that determines the risk of bleeding, and is assessed through the Child-Pugh score, based on the levels of albumin, bilirubin and INR, on the presence of ascites and encephalopathy, or simpler but also more superficial by determining the values of liver transaminases. The area under the curve (AUC) of the plasma concentration (total amount of drug absorbed by the body) is a pharmacokinetic parameter that reflects the degree of exposure of the body to a particular drug and tends to have higher values in the case of liver failure. In a moderate liver dysfunction, Child-Pugh class B, AUC is 2.27% and 1.09% higher for rivaroxaban and apixaban respectively, and 5.6% and 4.8% lower for dabigatran and edoxaban respectively [19], which would indicate a higher risk of bleeding when using rivaroxaban and apixaban for the above-mentioned reasons. Studies that emerged shortly after the approval and implementation of NOAC's advocated a more prudent attitude towards their use in hepatic cirrhosis: these two representatives were contraindicated in Child-Pugh class C liver cirrhosis and when the transaminase levels were twice above the normal. For dabigatran and edoxaban, caution is advised, but they are not contraindicated [19].

New studies and clinical experience have changed this paradigm: from excessive caution to encouraging the use of NOAC even in severe hepatic dysfunction (Child-Pugh class C, hepatic cytolysis syndrome), with dose adjustments based on the clinical judgment of the doctor. A 2017 study, judging by the safety and efficacy profiles, compared 3 groups of cirrhotic patients with clear indication for anticoagulant therapy (atrial fibrillation) that received either a NOAC, warfarin or no anticoagulant at all; the results were clearly favourable for NOAC: no thromboembolic event and a 2.3% non-major bleeding rate, whereas those receiving warfarin had a 2.4% thromboembolic event rate and 11.8% haemorrhagic events, and 5% of those who did not receive any anticoagulant had at least one thromboembolic complication and 6% haemorrhagic events. In addition, those who received NOAC had the longest survival rate without bleeding. A drawback of this study would be the fact that the patients enrolled in Child-Pugh class A/B had a higher representation than patients enrolled in Child-Pugh class C, which influenced the statistical significance [20]. It is now considered that the status of the liver function does not influence the indication for anticoagulant therapy or dose adjustments, unlike the renal function [21].

Thromboembolic risk is 2.5 times higher in mild or moderate renal dysfunction and 5 times higher in severe renal dysfunction, and the haemorrhagic risk is at least double compared to the general population [22], thus anticoagulant therapy may be frequently needed in chronic kidney disease, a condition that also involves higher bleeding risk. The preference for direct anticoagulants would be motivated by a TTR (time in therapeutic range) < 60% for antivitamin K [23] and the fact that antivitamin K would increase the risk of calciphylaxis (vascular calcifications), as they inhibit the synthesis and activity of matrix Gla protein [24]. Table I lists the direct anticoagulants that can be used, as well as their dose adjustments based on eGFR (estimated glomerular filtration rate). The GFR estimation method also needs to be taken into consideration. Most trials used the Cockcroft-Gault method to calculate creatinine clearance, and based on this, dose adjustments were made, but it has been proven that this method overestimates eGFR and predisposes to overdosing phenomena and consecutive hemorrhages. The Modification of Diet in Renal Disease (MDRD) and Chronic Kidney Disease Epidemiology Collaboration (CKDepi) formulas were then developed, which are much more used due to superior accuracy [25]. Considering that renal function significantly influences pharmacokinetic parameters: half-life, the area under the curve, the distribution volume, it is very important to have a correct and standardized assessment [26, 27]. Long-term administration of anticoagulants, whether antivitamin K or novel oral anticoagulants, invariably associates with a decline in the renal function, linked either to the mechanism of action of anticoagulants (requires a longer period of time to activate) or to the so called "anticoagulant-induced nephropathy" (rapid decline in renal function). Thus, a vicious circle is formed: kidney function conditions the indication and dosage for NOAC, and administration of anticoagulants has a negative effect on the glomerular filtration rate. The current guidelines (American Heart Association, American College of Cardiology, Heart Rhythm Society, European Heart Rhythm Association) recommend the use of antivitamin K when eGFR < 30 mL/min/1.73 m^2 and for dialyzed patients, as novel oral anticoagulants are harder to remove through dialysis due to the relatively high protein binding rate and because of the high volume distribution, more than 0.7 L/kg [28].

Table I

Pharmacological profile of direct anticoagulants [1, 2]

Pharmacological parameter	DABIGATRAN	RIVAROXABAN	APIXABAN	EDOXABAN
Mechanism of action	Direct, reversible, selective thrombin (factor IIa) inhibitor	Direct, reversible, selective factor Xa inhibitor		
Criteria for pharmacodynamic assessment	The dilute thrombin time, ECT, aPTT	Minor, variable, non-standardized changes of INR, aPTT, Quick test, factor Xa activity		
		HepTest (heparin test)	The Rotachrom chromogenic test	The Rotachrom chromogenic test
Dose	75 mg/110 mg/150 mg	15 mg 20 mg	2.5 mg 5 mg	30 mg 60 mg
Need for dose adjustment	Clinical indication CrCl < 50 mL/min Age ≥ 75 years Weight < 50 kg Drug interactions	Clinical indication	Clinical indication CrCl < 30 mL/min Weight < 60 kg Age ≥ 80 years	Clinical indication
Administration interval	Every 12 hours	Every 24 hours	Every 12 hours	Every 24 hours
Bioavailability	3 - 7% (75% in the absence of the capsule shell)	66% without food 100% with food	50%	62%
The influence of food on bioavailability	No influence	Increased bioavailability by 40%. It is administered with food.	No influence	Increased bioavailability by 6 - 22%
Hepatic metabolism	Minimal Glucuronyl-conjugation, independent of cytochrome P450 enzymes	CYP3A4, CYP2J2 Mechanisms: oxidation of the morpholinone moiety, hydrolysis of amide bonds	CYP3A4, CYP3A5 Mechanisms: O-demethylation, hydroxylation	Minimal (< 4%) CYP3A4
Cmax	70.8 ng/mL, depending on the used dose	125 μg/L	67 - 251 ng/mL, depending on the used dose	
Tmax	2 hours	2 - 4 hours	3 - 4 hours	1 - 2 hours
Half-life	12 - 17 hours	5 - 9 hours (young patients) 11 - 13 hours (> 65 years old)	12 hours	9 - 11 hours
Plasma protein binding rate	34 - 35%	92 - 95%	87%	
Distribution volume	60 - 70 L	50 L	20 L	
Ability to cross biological barriers	Crosses the placenta, is excreted in breast milk.	Crosses the placenta, has teratogenic effect. It is excreted in breast milk.	It is excreted in breast milk.	Crosses the placenta, possible teratogenic effect. It is excreted in breast milk.
Clearance **Kidney** **Intestinal, biliary**	 80% 20%	 35% 65%	 27% 73%	 50% 50%
Total plasma clearance	71 - 144 L/hour	6 L/hour	3.3 L/hour	21.8 L/hour
Drug interactions	Drugs that interfere with haemostasis: antiplatelets, heparin, antivitamin K Nonsteroidal and steroidal anti-inflammatory drugs Powerful CYP3A4 and P-gp inhibitors: azole antimycotics (ketoconazole, itraconazole, voriconazole, posaconazole), HIV protease inhibitors Moderate/weak CYP3A4 and P-gp inhibitors: verapamil, diltiazem, naproxen, amiodarone, dronedarone, erythromycin, clarithromycin, quinidine Powerful CYP3A4 and P-gp inducers: rifampicin, carbamazepine, phenytoin, phenobarbital			
The need to monitor the therapy	It is not necessary. Eventually, with an indicative role in overdose situations and haemorrhage.			
Antidote	The only NOAC that benefits from an antidote is dabigatran: idarucizumab [3].			
Approved indications	Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation with one or more risk factors. Treatment of DVT and PE, and prevention of recurrent DVT and PE in adults. VTE prevention following hip/knee replacement surgery.			

aPTT: activated partial thromboplastin time; DVT: deep vein thrombosis; ECT: ecarin clotting time; INR: international normalized ratio; PE: pulmonary embolism; VTE: venous thromboembolism.

However, the use of new anticoagulants, even in the situation described above, is on the rise (mostly in the case of apixaban, which has the lowest renal elimination rate). New studies show that NOAC's do not induce significant renal function degradation, explained mostly by the mechanism of action: inhibiting Xa and IIa factors reduces vascular inflammation and oxidative stress. There were no differences between the NOAC representatives regarding the decrease in creatinine clearance over time [29]. Anticoagulant-induced nephropathy is a clinical entity that occurs following a massive glomerular haemorrhage, representing a diagnosis of exclusion (the diagnosis of certainty requires renal biopsy). It manifests through acute kidney

injury, has a poor prognosis and rarely associates with full recovery of the renal function. Currently, it cannot be said that NOAC is associated less frequently or more frequently than warfarin with this condition [30].

Drug interactions

NOAC's interact primarily with the cytochrome CYP3A4 and P-glycoprotein inhibitors or inducers listed in Table I. Their association, although not recommended [1, 2], has not shown a substantial change in their plasma activity. An example of this is the association of apixaban to dronedarone, which did not show a higher risk of bleeding compared to the use of apixaban without dronedarone [31]. The combination of NOAC with antivitamin K or injectable heparins is totally contraindicated, and association with antiplatelets, especially prasugrel and ticagrelor, increases the risk of bleeding at least three times [32, 33].

Age

Generally, older age is associated with poor metabolism and elimination, thus with an increase in half-life and an increase in peak plasma concentrations. Over the age of 75, administration of NOAC leads to a higher risk of bleeding, whereas between 18-64 years of age, the risk of stroke prevails over the risk of haemorrhage [34]. The indications for dose adjustment by age are presented in Table I.

Body weight

It is known that the individual variation of the pharmacodynamic effect depends, among many other factors, on the body weight of the individual, which affects the volume of distribution and the plasma concentration. Caution is advised when using NOAC in individuals weighing < 50 kg or > 150 kg. Otherwise, no correlation between weight and a certain efficacy or safety profile has been demonstrated [35].

Conclusions

Non-vitamin K oral anticoagulants represent a drug class with an efficacy profile that allows them to be used on a wide range of patients. It can be concluded that the antithrombotic efficacy is somewhat similar, regardless of the mechanism of action, but largely depends on the correct dosing and compliance with the administration interval. AUC, Cmax, half-life are pharmacokinetic parameters of major importance in achieving the expected effect of the NOAC, and have a variability mainly related to the renal function and less to the hepatic function. Other factors to consider include: age, weight, drug interactions, co-morbidities, coagulation status. The safety profile has two major disadvantages: there is no standardized test to determine their activity level and there is no antidote (except for dabigatran, which has the antidote idarubizumab).

Conflict of interest

The authors declare no conflict of interest.

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