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Review Paper

Novel oral anticoagulants (NOACs): Overview

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ABSTRACT

Non-vitamin K antagonist oral anticoagulants (NOACs) are replacing warfarin in a variety of situations. Dabigatran, which inhibits thrombin, and rivaroxaban, apixaban, and edoxaban, which inhibit factor Xa, are among these medications.In the United States, all four medications are authorised for stroke prevention in atrial fibrillation and for the treatment of venous thromboembolism, with rivaroxaban and apixaban being approved for thromboprophylaxis following elective hip or knee arthroplasty. NOACs are at least as effective as warfarin, but they are not only easier to administer since they may be given in set dosages without frequent coagulation monitoring, but they are also safer because they have been linked to reduced intracranial haemorrhage As part of a theme series on NOACs, this article compares the pharmacological profiles of the NOACs to that of warfarin, identifies the NOAC doses for each approved indication, provides an overview of the completed phase III trials with the NOACs, briefly discusses the ongoing studies with the NOACs for new indications, and reviews the emerging real-world data with the NOACs.

Introduction

Thromboembolism is very important clinically owing to its usual fatal complications. It is considered, either venous or arterial, the third commonest cardiovascular morbidity after coronary artery disease and stroke. [(1)] It is very important to treat those thrombotic events medically and so the appearance of anticoagulant drugs is considered a medical revolution. Their form of preparation is either oral or parenteral. Throughout the previous 6 decades, vitamin K antagonists (VKAs), were the sole used oral anticoagulant agents [(2)] however, recently discovered new agents with anticoagulation actions have emerged, known as novel oral anticoagulants. Compared to VKAs, this new generation of anticoagulants had more expectable effects, and efficiency in both prophylactic and therapeutic issues of venous thromboembolism (VTE) and especially in prevention of ischemic strokes and other systemic embolization in non-valvular atrial fibrillation (NVAF) patients. [(3)] The VKA dose is individualized for every patient, in comparison to the fixed doses of NOACs, except patients with hepatic or renal impairment. NOACs are direct inhibitors activated thrombin (IIa) and factor Xa. Although, NOAC have more advantages over VKAs, they are not ideal because they own some drawbacks inferior to VKAs. The aim of this work is reviewing previous literatures belonging to nature, mechanisms, advantages and disadvantages of these new drugs. [(4)]

Vitamin K anticoagulants (VKAs)

In 1941, Karl Paul Link was the first to discover oral anticoagulant agents, which was dicumarol. VKAs are derivatives of 4-hydroxycoumarin, which inhibit vitamin K epoxide and H2 reductase enzymes [(5)] which reduce vitamin KH2 levels, and limit its effect on γ-carboxylation of the vitamin K-dependent coagulation factors II, VII, IX, and X which are synthetized by the liver. VKAs also reduce the actions of proteins S and C inhibiting their procoagulant effects dependent on vitamin K, so one should use low-molecular-weight heparins (LMWHs) as a bridging regimen until the action of VKAs is well established. [(3)] Warfarin is firstly preferred in most regions, mainly in Canada and United States. [(6)] VKAs use is indicated in various situations, such as pulmonary embolism, deep vein thrombosis, recurrent ischemic strokes in NVAF patients, also in acute coronary syndrome, vacuities and patients with implanted prosthetic or tissue heart valves. Moreover, they also are used as a preventive strategy in post-orthopedic surgeries. [(7)]

New oral anticoagulant drugs (NOACs)

They are new direct-acting drugs acting selectively on one specific coagulation factor, either activated thrombin or factor Xa. Recently, these medications have emerged for use in thromboembolic prophylaxis in knee or hip surgeries in the Europe and other

areas. [8] For example, rivaroxaban, apixaban and dabigatran, have been approved in many regions. The mechanism of action of the two groups of drugs are illustrated in Figure(1).

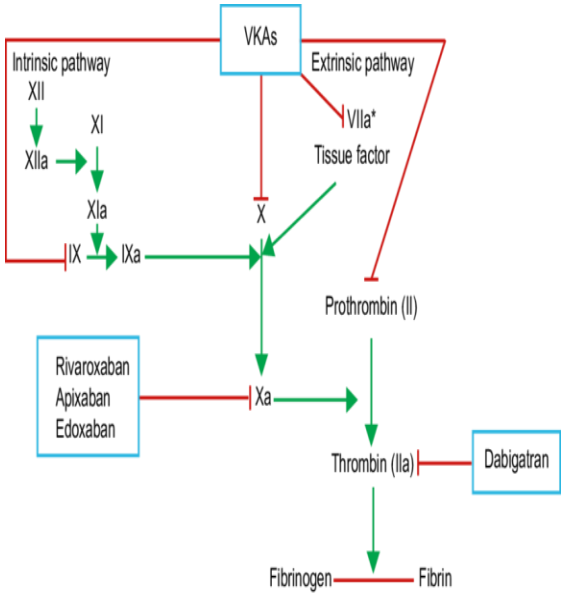

Fig 1: F VIIa, activated factor VII; VKAs, vitamin K antagonists: Xa, activated factor x *(Ymer H Mekaj et al.; 2015).*

Dabigatran

According to RE-LY trial (the randomized evaluation of long-term anticoagulant therapy) of warfarin, the first drug as NOAC was approved in 2008, dabigatran, in comparison to warfarin. [9] A new oral thrombin inhibitor, which reduces risks of systemic embolization and ischemic strokes in NVAF and thus inhibits thrombus formation by limiting conversion of fibrinogen into fibrin. Biochemically, dabigatran is a Hirudin counterpart, a small artificial molecule with a monovalent bond with only one thrombin site. It is produced from dabigatran etexilate which quickly turns into dabigatran after oral and liver metabolism. It is given with or without food and quickly absorbed, but has low oral bioavailability of about (6 -7%). [10] The relationship between dabigatran plasma concentration and peak plasma concentration (Cmax) and doses unrelated to age or sex, 1-2 hours after oral dosing. Its plasma half-life is about 10-13 hours, regardless of the prescribed dose. It is absorbed and bio-transformed in intestinal cells, liver cells and hepatic veins. It does not influence hepatic cytochrome P450 and, so, it is unlikely to interact with other drugs. In contrast to VKA, dabigatran has an expectable dose response relationship and so we do not need any monitoring. [11] The main way to eliminate dabigatran in the human body is kidneys (80%). As shown by RE-LY trial in prevention of systemic embolization and ischemic strokes, dabigatran is equal or superior to warfarin in NVAF. In this trial, 110 mg of dabigatran, was similar to warfarin in rates of ischemic strokes and systemic embolization and had a significantly lower bleeding rate. In addition, a dose of 150 mg had a lower rate than warfarin of systemic embolization and ischemic strokes, but with a similar significant bleeding. [12]

Rivaroxaban

Rivaroxaban was approved in the Europe by the year 2008 based on (ROCKET AF) trial, rivaroxaban versus warfarin results in the treatment of non-valvular AF. As a derivative of oxazolidinone, [13] Rivaroxaban selectively inhibits factor Xa. which has a pivotal role in the coagulation pathways either intrinsic or extrinsic ones and so limits thrombin generation which can be achieved directly or indirectly by use of NOACs or parenteral anticoagulants such as fondaparinux, unfractionated heparin and LMWHs. It has rapid absorption after oral intake with high bioavailability (60% to 80%) and this is dose-related, with C-max about 2 to 4 hours. About one third of the drug is excreted in urine and stool in unchanged form. [15].

Hepatic metabolism occurs mainly via CYP3A4 isozyme. Eriksson and Turpie et al., recommended use of rivaroxaban with or within 2 hours of meals. The ideal doses of rivaroxaban have an average half-life ranging from 4 to 7 hours [16]. Serum concentration of rivaroxaban for 24 hours is 10 ng / mL and its anti-factor Xa activity is about 0.17 IU / mL. [17] So, the administration of a single dose of rivaroxaban can provide the required daily activity of anticoagulant action. Twice-daily dosing of 2.5 mg rivaroxaban is only reserved for acute coronary syndrome combined with antiplatelet in patients with glomerular filtration rate (eGFR) >15 mL / min. and having raised cardiac enzymes. [18] Mega et al. stated also that this dose of rivaroxaban reduces fatal cardiovascular events (2.7% vs 4.1% with p value = 0.002) without any added benefits for survival for twice daily dose of 5 mg rivaroxaban. [19]. Although the literature lacks information on use of rivaroxaban in the elderly patients, rivaroxaban 5 mg doses may be used safely at age 75 to prevent thromboembolism.

With respect to the pharmacokinetics and pharmacodynamics (PD), rivaroxaban, has no difference in sex or race. Nevertheless, they are influenced by renal and hepatic impairment, depending on the degree; so, mild liver disease (Child-Pugh class A) does not affect pharmacokinetics and pharmacodynamics of the drug. [19]

Apixaban

It is a direct inhibitor of factor Xa [20] having anticoagulant properties similar to rivaroxaban, this prevents activation of prothrombin into thrombin and thus prevents formation of fibrin from fibrinogen. It was approved by the 2011 based on the results of ARISTOTLE trial (Apixaban for the reduction of stroke and other thromboembolism in AF). It has also rapid absorption and bioavailability of about 66% and is not affected by food intake. It has a half-life ranging from 8 to 15 hours similar to other NOACs, however, Its renal clearance is very low approaching 25% and metabolized hepatically via CYP isoenzymes (CYP3A4). Previous studies stated that apixaban was preferable to warfarin in prophylaxis against systemic embolization and ischemic strokes in AF, In addition, incidence of hemorrhagic strokes was less for apixaban than warfarin and low mortality rate as well. [21]

Indications for NOACs use

These include prevention of systemic embolization especially in NVAF. [13] mostly for treatment and prevention of recurrent pulmonary embolism. Rivaroxaban was firstly approved in Europe for these purposes in acute coronary syndrome; but not for clinical practice similar to apixaban and dabigatran. After knee or hip replacement surgeries, they were beneficial to LMWH (enoxaparin) in prevention of DVT. [23] Also, edoxaban is used prophylactically in lower-limb orthopedic surgeries to prevent DVT and also systemic embolization.

Contraindications to use NOACs

Clinically significant bleeding, coagulopathic liver diseases and other risk factors for bleeding, other anticoagulants, antiplatelets and nonsteroidal anti-inflammatory drugs (NSAIDs) all contraindicate the use of NOACs. [4] Furthermore, allergy to NOACs is a contraindication. [24] NOACs should be cautiously used regarding age, weight, and renal functions, such that Dabigatran should not be used in severe renal failure (eGFR < 30 mL / min), rivaroxaban and apixaban are not used with eGFR< 15 mL / min. Edoxaban is contraindicated with eGFR > 0.95 ml / min (increase cerebral infarction), but should be given once daily dosing of 30 mg with a eGFR > 15 to 50 mL / min. Elderly over the age of 80 and those weighing more than 60 kg should receive aa twice daily dose of 2.5 mg apixaban. [25,26]

Benefits of NOACs

NOACs have many advantages over VKAs in prevention and treatment of AF, ischemic strokes, PE, and other thrombophilia-related diseases. In comparison to VKAs, they prevent different thromboembolic factors and disorders, absence of interactions with foods, little interactions with other drugs, expectable PD and PK, rapid action, short half-life and unneeded laboratory surveillance. [27]

Drug–drug interactions

Few or no drug-drug interactions for NOACs allow simultaneous use of other drugs with NOACs. Some mechanisms of these interactions are the re-secretion of a P-gp transporter after gut absorption. which may be involved in renal clearance. [28] Two-thirds of rivaroxaban is metabolized by the CYP system, particularly CYP3A4. Drugs as verapamil, dronedarone and amiodarone which are used frequently in AF are substrates of P-gp . Therefore, concomitant use of CYP3A4 inhibitors or inducers with NOACs is not recommended due to altered plasma concentrations. Most apixaban is eliminated by the liver as an unchanged drug, of which only a small part is metabolized by CYP3A4. However, it should be used cautiously with inducers of CYP3A4 and P-gp. [4] Dabigatran contains little drug-drug interactions of clinical importance, but it is a substrate of P-gp. So, drugs like amiodarone, ketoconazole and verapamil can increase the anticoagulant effects of NOACs, and should be avoided. Also, phenytoin increases the metabolism of rivaroxaban and, therefore, decrease its anticoagulant effects. [4]

Interactions of NOACs with food

Unlike VKAs, which are influenced by consumption of foods, mostly those containing vitamin K, NOACs do not interact with foods. So, patients on NOACs should not avoid any foods as they do not encounter any difficulty to balance the anticoagulant therapy. In some circumstances, patients have a disturbed metabolism of vitamin K, such as insufficient intake of vitamin K, causes of malabsorption and indigestion, as well as disturbed gut micro flora following antibiotics or GIT infections. [25]

Expectable PD and PK

NOACs have the advantage of expectable PK over VKAs. As regard, rivaroxaban has expectable pharmacokinetics, and this is proportional to its dosing due to very high oral bioavailability which increases its anticoagulant effect with the plasma concentration. [24] Other classes of NOACs have expectable PK, but with different properties and in different ways. These parameters are consistent regardless of age, sex and weight. So, it is possible to use fixed doses without the need for anticoagulant monitoring. [29]

Rapid action of NOACs:

The most important benefit of NOACs is rapidity of action (approximately 1.5 to 3 hours) and this is very important in cases requiring urgent surgical intervention. In addition, this eliminates the needed bridging with parenteral anticoagulant therapy in patients with acute thrombotic event. [30]

Laboratory surveillance: Another significant property is that there is no monitoring needed, irrespective of age, sex, weight and other demographics. Other benefits of NOACs over VKA include a broad therapeutic range, a lower risk of cerebral hemorrhage, increased effectiveness in AF patients. [37]

Drawbacks of NOACs

NOACs use is limited in certain conditions such as pregnancy, infants and children. [3] In addition to non-approval in mitral prosthesis as it increases bleeding and thromboembolism as well, also malignancy and antiphospholipid syndrome with increased risk of thrombophilia. [25]

NOACs and Renal impairment

A major benefit of NOACs over VKAs is the unneeded regular monitoring, but, this is not helpful in cases of impaired hepatic or renal function. [31] About 80% of dabigatran, 25% apixaban and 33% rivaroxaban are eliminated through the kidneys as active substances. So renal functions should be evaluated before administration of NOACs drugs. Actually, we should use Cockroft-Gault equation to calculate eGFR taking into account the weight of the patient. So, NOACs are used cautiously in chronic renal failure, particularly in elderly who have a moderate eGFR (30-50 mL / min) or decreased (10-30 mL / min) one. And as we said before, dabigatran should not be used in severe renal impairment, as 80% is excreted by the kidneys, while rivaroxaban and apixaban can be used cautiously with dose adjustment. [32]

NOACs and Liver disease

Apixaban and rivaroxaban should not be used in liver diseases associated with coagulopathy and significant clinical risk. But, they can be used cautiously in patients with mild to moderate hepatic diseases, with dose adjustment. In cases of severe hepatic impairment (Child-Pugh Class C) and Class B or C Child-Pugh cirrhotic patients, rivaroxaban is contraindicated, while in the case of mild or moderate liver disease, apixaban can be given with caution, and dose adjustment is needed. [33]

Additional disadvantages of NOACs

High cost and poor compliance which increases thromboembolic risk are other disadvantages of these drugs. [3] Also short half-life should be evaluated as risk benefit ratio. The absence of antidote is another disadvantage in cases of overdose bleeding. [33,34]

Conclusion

Oral anticoagulation with VKA have some problems with large individual variability of its effects, major food and interactions, and the needed frequent monitoring; so, new anticoagulant drugs called NOACs (novel oral anticoagulants), have emerged since the last 7 years. Their benefits over VKA are their high effectiveness in stroke prevention in NVAF and lone AF patients, lower bleeding risks, easy administration, little food and drug interactions, expectable PD and PK, fast action and lag, short half-life and unneeded frequent monitoring. However, NOACs own some disadvantages, such as high cost, poor compliance, the lack of antidotes and limited experience. Moreover, little or no use in severe hepatic and renal impairment (no specific surveillance test), prosthetic cardiac valves, individuals under 18 years and elderly. Many studies are needed to verify the use of NOACs in the prevention and treatment of thromboembolism.

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