Updates on the non-vitamin K oral anti-coagulants (NOACs)

Review Article

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ABSTRACT

Background: Non-vitamin K oral anti-coagulants (NOACs), are direct oral anticoagulants (DOACs), two classes of DOACs are available; reversible thrombin inhibitor (Dabigatran) and the active factor (Xa) inhibitors (Rivaroxaban, apixaban, betrixaban and edoxaban).

Main body: NOACs offer rapid onset of action, fast time to effect, few food and drugs interactions and no need for international normalized ratio (INR) monitoring, with improved patient compliance over warfarin. Local hemostatic measures and withholding the next dose achieve hemostasis in patients presenting with minor bleeding, waiting for drug clearance. Administration of reversal agents is considered in patients with major bleeding, or those requiring rapid reversal for emergency surgery. The Food and Drug Administration (FDA) has approved two reversal agents; idarucizumab for dabigatran and andexanet alfa for apixaban and rivaroxaban. Several agents are in different phases of clinical trials; with ciraparantag showing promising results. The high cost and limited availability remain a concern in their use.

Conclusion: NOACs offer better patient compliance, with reversal agents need for patients presenting with major bleeding.

Key Words: Andexanet alfa, direct oral anticoagulants, idarucizumab and non-vitamin K oral anti-coagulants.

Received: 20 February 2024**, Accepted:** 07 June 2024

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ISSN: 2090-925X, 2024, Vol.16, No. 2

INTRODUCTION

Vitamin K antagonists (VKA) and heparin derivatives were the available anticoagulants. Warfarin was the only available oral agent until the introduction of NOACs in 2010. Dabigatran was the first NOAC introduced. VKAs have multiple targets in the coagulation pathway; whereas, the NOACs are characterized by specificity, as they have single target in the coagulation pathway, thus, prevent systemic thromboembolism with 50 % reduction of intracranial hemorrhage (Spahn *et al,* 2019). Agents under trials target single molecules, which limit non-specific effects and reveal which target is most appropriate for each indication. Thus, thrombin and factor (Xa) became the targets of NOACs (Patel *et al,* 2018). Two reversal agents were approved by the FDA, the American College of Cardiology (ACC), the American Heart Association (AHA) and the Heart Rhythm Society (HRS) (ACC/AHA/HRS); idarucizumab for dabigatran and and exanet alfa for apixaban and rivaroxaban (Mujer *et al,* 2020).

MAIN TEXT

Prior to the initiation of NOACs, proper assessment for age, weight; BMI more than 40 kg/m^2 or weight more than 120 kg carry the risk of under dosing (Martin *et al*, 2016), comorbidities, previous major bleeding and drug intake; especially P-glycoprotein and cytochrome (CYP) 3A4 drugs. Laboratory investigations; hemoglobin level, liver and kidney function tests and the coagulation profile are done (Chang *et al,* 2017).

Indications of NOACs:

1. Non-valvular atrial fibrillation (NVAF); for prevention of ischemic stroke and systemic embolization, in patients with one or more risk factors; 75 years old, hypertension, diabetes mellitus, left ventricular ejection fraction of 30 %, previous cerebral stroke, transient ischemic attack or systemic embolism (Joppa *et al,* 2018).

2. Prevention of venous thromboembolism (VTE) after major knee or hip surgery (Chan *et al,* 2020).

3. Rivaroxaban is approved for prevention of cardiovascular events after acute coronary syndrome or Peripheral arterial disease (Plosker, 2014).

Pharmacokinetics of NOACs:

1. Dabigatran etexilate (Pradaxa®); the prodrug with etexilate is less basic to facilitate its absorption,

DOI: 10.21608/ASJA.2024.263987.1059

which depends on intestinal permeability glycoprotein (P-gp) transport. The plasma esterase rapidly hydrolyzes it to active dabigatran (Fawzy and Lip, 2019). Food intake decreases its absorption without affecting its bioavailability (3 - 7 %). Peak plasma concentration is reached 1.5 - 3 hours after intake. Its half-life is 14 - 17 hours. It has moderate volume of distribution (VD) 50 - 70 L and low plasma protein (pp) binding (35 %), with 20 % metabolized by conjugation. It needs dose adjustment with renal impairment and is contraindicated in severe renal impairment (CrCl < 30 ml/min); as 80 % 0f the drug is renally excreted unchanged (Kumar *et al,* 2019). It is contraindicated in patients with Child–Pugh score of C and used cautiously in patients with Child–Pugh score of B. Dabigatran and its active metabolites (acyl glucuronides) are competitive, direct, free and clot bound thrombin (factor IIa) inhibitors. It reversibly inhibits the active site of thrombin, thus preventing thrombin induced platelet aggregation, activation of factors V, VIII and XI and thrombin mediated conversion of fibrinogen to fibrin, thus thrombus formation (Chen *et al,* 2020).

2. Rivaroxaban (Xarelto®); is rapidly absorbed depending on intestinal P-gp transporters. It reaches peak plasma concentration in 2 - 4 h (Kreutz, 2014). Food intake increases its bioavailability by increasing the drug solubility and dissolution. It has moderate VD of 50 L and is highly pp bound (> 90 %). Its half-life is 5.7 - 9.2 hours, reaching 11-13 h in elderly patients due to decreased renal function. It is metabolized in the liver (65 %) by CYP 450; enzymes 3A4 and 2J2, with hepatobiliary elimination, so its use is avoided in moderate to severe liver disease. It needs dose adjustments with renal impairment and is contraindicated in severe renal impairment (CrCl < 30 ml/min); as one third of the drug is renally excreted unchanged (Stampfuss *et al,* 2013).

3. Apixaban (Eliquis®); its absorption depends on intestinal P-gp transporters. Food doesn't affect its bioavailability (50 %), with high pp binding (87 %) (Fawzy and Lip 2019). It has the least VD of 23 L. Its half-life is 13.5 (9.9) hours. It is metabolized by CYP3A4/3A5 and sulfotransferase 1A1 with 75 % hepatobiliary and 25 % renal elimination. It is used cautiously with mild to moderate hepatic impairment and is contraindicated in severe hepatic disease. It needs dose adjustments with renal impairment and is contraindicated in severe renal impairment (CrCl < 30 ml/min) (Kumar *et al,* 2019).

4. Edoxaban (Savaysa®); its absorption depends on intestinal P-gp transporters. Food doesn't affect its bioavailability (62 %), with 55 % of the drug bound to pp. It has large VD of 107 L. The drug is metabolized by cytosol carboxyl esterase 1 enzyme, liver microsomes, CYP3A4 enzymes and glucuronidation reactions (Gelosa *et al,* 2018). 50 % of the drug undergoes renal elimination unchanged and 50 % undergoes biliary secretion. No dose adjustment with renal impairment and is contraindicated in severe hepatic impairment (Parasrampuria and Truitt 2016).

5. Agents targeting FXI and FXII are under development (Fredenburgh and Weitz 2021). They include small oral molecules. The small molecule inhibitors of FXI, are directed at the active exosites. Orally available FXIa inhibitors include JNJ70033093 (BMS-986177), BAY 2433334 and ONO-5450598 (Sachetto and Mackman 2019).

Pharmacodynamics of NOACs:

1. P-gp competitors; are contraindicated with DOACs, verapamil, amiodarone, anti-mycotics, macrolides antibiotics and antiretroviral protease inhibitors, increase DOACs plasma concentrations with an increased risk of bleeding. P-gp inducers; rifampicin reduce DOAC concentrations to subclinical dose (Bernier *et al,* 2019).

2. CYP450 inhibitors or inducers; clarithromycin, ketoconazole, phenytoin and rifampicin have no drug interactions with dabigatran (Roberti *et al,* 2021).

3. CYP3A4 inhibitors or inducers; clarithromycin, ketoconazole, phenytoin and rifampicin aren't recommended with rivaroxaban, apixaban and edoxaban (Steffel *et al,* 2018).

4. Histamine (H2) receptor antagonists, proton pump inhibitors; reduce dabigatran absorption by 12 and 30 % respectively, with no dose adjustment needed (Heidbuchel *et al,* 2013).

5. Dexamethasone and valproic acid; are contraindicated with all DOACs (Steffel *et al,* 2018).

6. Antiplatelet drugs or selective serotonin reuptake inhibitors; increase the risk of major bleeding on co-administration (Zhang *et al,* 2020).

Contraindications of NOACs (Bernier et al, 2019):

Hypersensitivity to the drug or its components, active major bleeding, history of bleeding in the last 3 months,

patients with anti-phospholipid syndrome (APS) and history of thrombosis, patients triple positive for lupus anticoagulant, anticardiolipin and anti–beta2 glycoprotein I antibodies, DOACs lead to higher rates of recurrent thrombotic events compared with VKA.

a. Dabigatran; prosthetic heart valve as the European REALIGN study was stopped due to increased risk of strokes, myocardial infarction, transient ischemic attacks and thromboembolism than warfarin, increased bleeding after valve surgery than in patients on warfarin.

b. Rivaroxaban; history of bronchiectasis, pulmonary cavitation or pulmonary hemorrhage, cancer, active gastroduodenal ulcer in the last 3 months, transcatheter aortic valve replacement (TAVR); increased risk of bleeding, prosthetic heart valves; safety and efficacy aren't studied.

c. Edoxaban; prosthetic heart valves, moderate to severe mitral stenosis.

d. Apixaban; prosthetic heart valves.

Laboratory tests for NOACs:

1. The PT and INR: Lack sensitivity and specificity to monitor the NOACs, it is sensitive to rivaroxaban than other FXa inhibitors (Favaloro and Lippi 2015).

2. The aPTT: Normal aPTT excludes dabigatran supra therapeutic level (Conway *et al,* 2017).

3. Liquid chromatography or tandem mass spectrometry: The most accurate to measure the drug concentrations; however, it isn't widely available. NOAC ≤ 30 ng/ml has minimal risk of bleeding (Godier *et al,* 2017).

4. Anti-factor Xa chromogenic assays: Measure the anti-factor Xa activity (IU/ml) (Steffel *et al,* 2018).

5. Thrombin time (TT), dilute thrombin time (dTT) and ecarin-based assays: Have high degree of linearity with dabigatran, quantify and monitor its activity. A normal thrombin time excludes dabigatran presence and supra therapeutic anti-FXa levels (Conway *et al,* 2017).

6. The viscoelastic hemostatic assays; rotational thromboelastometry and thromboelastography: Determine the need for a specific reversal agent in patients who received 4 factor prothrombin concentrate complex (4F-PCC) (Pavoni *et al,* 2022).

Indications of reversal agents:

Life threatening bleeding, NOAC related intracerebral hemorrhage (NOAC-ICH) or rapid reversal for emergent surgery (Gerner *et al,* 2019).

A. Non-specific reversal agents:

1. Activated PCC (aPCC), Factor Eight Inhibitor Activity Bypassing Agent (FEIBA®); used for dabigatran (Khoo *et al*, 2013).

2. Inactivated 4F-PCC (Kcentra®); It is four clotting factors (II, VII, IX and X), it is used for factor Xa inhibitor associated bleeding (Mujer *et al*, 2020).

3. Tranexamic acid as a hemostatic agent (Thomas and Makris, 2018).

4. Desmopressin in an attempt to normalize hemostasis (Spahn *et al*, 2019).

5. Recombinant factor VIIa; may be used for apixaban after evaluation in clinical trials.

6. Coagulation factors II, IX or X concentrates need to be evaluated in clinical studies.

7. Protamine sulfate and vitamin K; have no effect.

8. Fresh frozen plasma (FFP); shows no improvement in bleeding outcomes (Yip and Deng, 2017).

9. Activated charcoal; prevents NOACs absorption with acute over ingestion, if administered within 1-2 hours of intake, however it increases the risk of aspiration, in patients with disturbed conscious level (Raval *et al*, 2017).

10. Hemodialysis can be done for dabigatran due to its weak plasma proteins affinity and predominant renal excretion (Kashiura *et al*, 2016).

B. Specific reversal agents:

1. Idarucizumab (Praxbind), is a humanized antibody fragment with 45 minutes half-life, it has structural similarities with thrombin and mimics its binding to dabigatran, it is renally excreted (Hu *et al*, 2016), 5 g (2.5 g/50 mL vial) are intravenously administered, it gives immediate and complete reversal. In the RE-VERSE AD study, the primary endpoint of reversal within 4 hours measured by diluted thrombin time (dTT) and ecarin clotting time (ECT), was observed in 100 % of patients. Onset of complete reversal was

immediate and was maintained for 24 hours in most patients. The FDA approved idarucizumab in 2015 (Pollack *et al*, 2017).

2. Andexanet alfa, is a modified human factor Xa trap protein that sequesters factor Xa inhibitors, its half-life is 1 hour. High dose of 800 mg IV bolus at a rate of 30 mg/min followed by 8 mg/min continuous infusion for 120 minutes. A low dose of 400 mg IV bolus at a rate of 30 mg/min followed by 4 mg/min continuous infusion for 120 minutes. Andexanet Alfa (AA) received FDA approval in 2018 for rivaroxaban and apixaban (Mujer *et al*, 2020).

C. Agents in development:

1. Ciraparantag (aripazine or PER 977); is a synthetic molecule designed to be a universal antidote; for unfractionated heparin, low molecular weight heparin, dabigatran and oral direct factor Xa inhibitor (Galliazzo *et al*, 2018). It binds to its target by charge interactions and hydrogen bonding. It received a fast track designation by the FDA. It binds to contact pathway activators such as celite, kaolin and in vitro anticoagulants such as citrate, EDTA and heparin. Thus, interferes with assays that use these reagents. A point of care whole blood clotting time is developing to overcome these limitations in the presence of ciraparantag (Samuelson and Cuker, 2017).

2. Zymogen-like FXa; is a catalytically inactive form of factor Xa, it binds to the NOAC to counteract its effects on endogenous factor X. It is effective in patients before the onset of bleeding by removing the inhibitor through molecular engagement (Thalji *et al*, 2016).

3. Engineered factor Xa variants; modification of the active site of factor Xa disrupts apixaban binding to the active site of factor Xa (Verhoef *et al*, 2017).

Perioperative interruption and resumption of NOACs:

The aim is to minimize the peri-operative risk of venous thromboembolism and bleeding. The perioperative management reported by the PAUSE (Perioperative Anticoagulant Use for Surgery Evaluation) study with no need for heparin bridging or coagulation function testing, for patients on DOAC for NVAF and undergoing elective surgery, was that for low and moderate risk of bleeding surgery, the DOAC is omitted one day before the operation and resumed one day after the operation, when hemostasis is assured, with two days total interruption period. For high risk of bleeding surgery, the DOAC is omitted two days before and resumed two days after the operation, when hemostasis is assured, with four days total interruption period. For patients with impaired kidney function (CrCl 30 - 50 mL/min); dabigatran is omitted two days before a low to moderate risk of bleeding surgery and four days before a high risk of bleeding surgery, whereas, direct factor Xa inhibitors do not require adjustments for kidney function. With this approach, the residual DOAC levels were in a low range < 50 ng/mL in most patients (Shaw *et al*, 2020).

For emergency surgery, if possible to be postponed for 24 - 48 hours after the last NOACs dose and in geriatric patients (> 75/80 years), low body weight (< 60 kg) patients and patients with renal impairment (CrCl < 50 ml/min), surgery needs to be postponed for more than 48 hours. If surgery cannot be postponed, the NOAC plasma level is measured; Level < 30 ng/ml is considered safe for high risk of bleeding surgery, level > 200 ng/ml is associated with a major risk of bleeding, level 30 - 200 ng/ml, each case is assessed depending on the risk of bleeding (Graf and Korte, 2016).

Neuraxial anesthesia and deep nerve blocks with NOACs:

The incidence of vertebral canal hematoma is increased, especially with spinal stenosis or scoliosis. In 2012, Douketis and his colleagues recommended postponing elective procedures if a thrombotic event (VTE, myocardial infarction, transient ischaemic attack, stroke) or major hemorrhage (decrease in hemoglobin of 2 g/dl, transfusion of 2 units of packed red blood cells, internal organ bleeding) occurred in the last 3 months or the patient is pregnant or 6 weeks post-partum (Neal *et al*, 2015).

For oral thrombin inhibitors (Dabigatran): The American Society of Regional Anesthesia (ASRA) recommends its pre-operative interruption according to the CrCl; 120 hour for CrCl 30 - 49 ml/min, 96 hours for CrCl 50-79 ml/min, 72 hours for CrCl > 80 ml/min and is avoided for CrCl 30 ml/min. Dabigatran isn't administered with neuraxial catheters inserted and catheters are removed 6 hours before dabigatran administration (Ashken and West, 2021).

For oral Xa factor inhibitors (rivaroxaban, edoxaban and apixaban). The ASRA recommends pre-operative interruption by 72 hours or to measure anti-factor Xa level if neuraxial anesthesia is intended earlier, however, the safe residual level isn't detected. They aren't administered with neuraxial catheters inserted and catheters are removed 6 hours before their administration (Ashken and West, 2021).

Non-deep plexus and peripheral nerves block:

The ASRA recommends performing the block with considering the vascularity and compressibility of the anatomical site and the potential complications of bleeding at this site (Ashken and West, 2021).

CONCLUSION

NOACs have different FDA approved indications. Safe peri-operative use with neuraxial anesthesia is dependent on their pharmacokinetics, with no need for LMWH bridging. NOACs can be resumed 24 - 48 hours after surgery.

ABBREVIATIONS

- **AA:** Andexanet Alfa.
- **ACC:** American College of Cardiology.
- **AHA:** American Heart Association.
- **aPCC:** Activated PCC.
- **APS:** anti-phospholipid syndrome.
- **ASRA:** American Society of Regional Anesthesia .
- **CYP:** cytochrome P.
- **DOACs:** Direct Oral Anticoagulants.
- **dTT:** dilute thrombin time.
- **ECT:** ecarin clotting time.
- **FDA:** Food and Drug Administration.
- **FEIBA:** Factor Eight Inhibitor Activity Bypassing Agent.
- **FFP:** Fresh frozen plasma.
- **4F-PCC:** 4 factor prothrombin concentrate complex.
- **H2:** Histamine.
- **HRS:** Heart Rhythm Society.
- **NOACs:** Non-vitamin K oral anti-coagulants.
- **NOAC-ICH:** NOAC related intracerebral hemorrhage.
- **PAUSE:** Perioperative Anticoagulant Use for Surgery Evaluation.
- **P-gp:** permeability glycoprotein.
- **pp:** plasma protein.
- **TAVR:** Transcatheter aortic valve replacement.
- **TT:** Thrombin time.
- **VD:** volume of distribution.
- **VKA:** Vitamin K antagonists.

CONFLICTS OF INTEREST

There are no conflicts of interest.

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