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REVIEW ARTICLE

New Oral Anti Coagulants – A guide for Plastic Surgeons

***Vipul Gargya[1], Omar Allam[1], Lance De Ross[1]**

[1]Brandon Plastic Surgery, Division of Plastic Surgery, Brandon, FL, USA

*vipulgargya@gmail.com

ABSTRACT

With the advent of new oral anticoagulants (NOACs), it is a challenge for a plastic surgeon to stay updated with the myriad of new medications, and their associated mechanisms of action, laboratory monitoring, adverse events and potential reversal agents. The limitations of warfarin therapy include varying pharmacokinetic profiles, multitude of food and drug interactions, hypersensitivity, resistance, therapy failure and frequent laboratory monitoring)[1]. Hence there are an increasing number of patients who are presenting to their plastic surgeon on alterative antithrombotic agents. The aim of this paper is to educate Plastic Surgeons regarding NOAC's, and their management in the operative setting.

Introduction

With the advent of new oral anticoagulants (NOACs), it is a challenge for a plastic surgeon to stay updated with the myriad of new medications, and their associated mechanisms of action, laboratory monitoring, adverse events and potential reversal agents. The limitations of warfarin therapy include varying pharmacokinetic profiles, multitude of food and drug interactions, hypersensitivity, resistance, therapy failure and frequent laboratory monitoring)[1]. Hence there are an increasing number of patients who are presenting to their plastic surgeon on alterative antithrombotic agents. In some instances, the newer oral anticoagulants are being pushed to be used in lieu of traditional oral anticoagulants like warfarin[2].

Use of oral anticoagulants is thought by some surgeons to increase the risk of perioperative bleeding and other complications such as impaired wound healing, infection and return to operating room in this patient population. Many surgeons prefer discontinuing anticoagulation therapy, particularly when the procedure involves highly vascularized areas, such as the face and nose, where bleeding may affect functional or esthetic results[3]. The purpose of this review is to examine the mechanism of these drugs, and give recommendations on operative management of these drugs for the plastic surgeon.

Mechanisms of anticoagulation

Hemostasis is obtained via the coagulation cascade, which is a regulated series of reactions involving endothelium, platelets and coagulation factors. Ultimately this results in formation of thrombus containing platelets and fibrin. Like multiple biochemical pathways in mammals, both positive and negative feedback maintains regulation of coagulation[4].

NOACs act on three main areas of the coagulation cascade (Figure 1) to obtain their anticoagulation effects. 1) Tissue factor pathway inhibitor (TFPI) and activated protein C (APC) inactivate Factor VIIa, 2) Activated protein C inhibits the activity of prothrombinase complex by inactivating Factor Va, and 3) antithrombin (AT) inhibits activity of Factor Xa and thrombin (Levy et al, 2010).

The ideal anticoagulant drug will inhibit factors that promote clotting such as Factor Xa and activate factors that promote fibrinolysis such as AT.

Direct Thrombin Inhibitors

Thrombin converts soluble fibrinogen to fibrin and activates Factors V, VII, and XI, which results in further thrombin formation and potentiates platelets. Thrombin also stabilizes the clot by increasing cross linking between fibrin molecules, via its action on Factor XIII[5].

Hence a drug targeting thrombin results in inhibition of fibrin generation, and also destabilizes clot formation. An example of an oral direct thrombin inhibitor is dabigatran (PradaxaÔ). A schematic for the action site for direct thrombin inhibitors is seen in Figure 1.

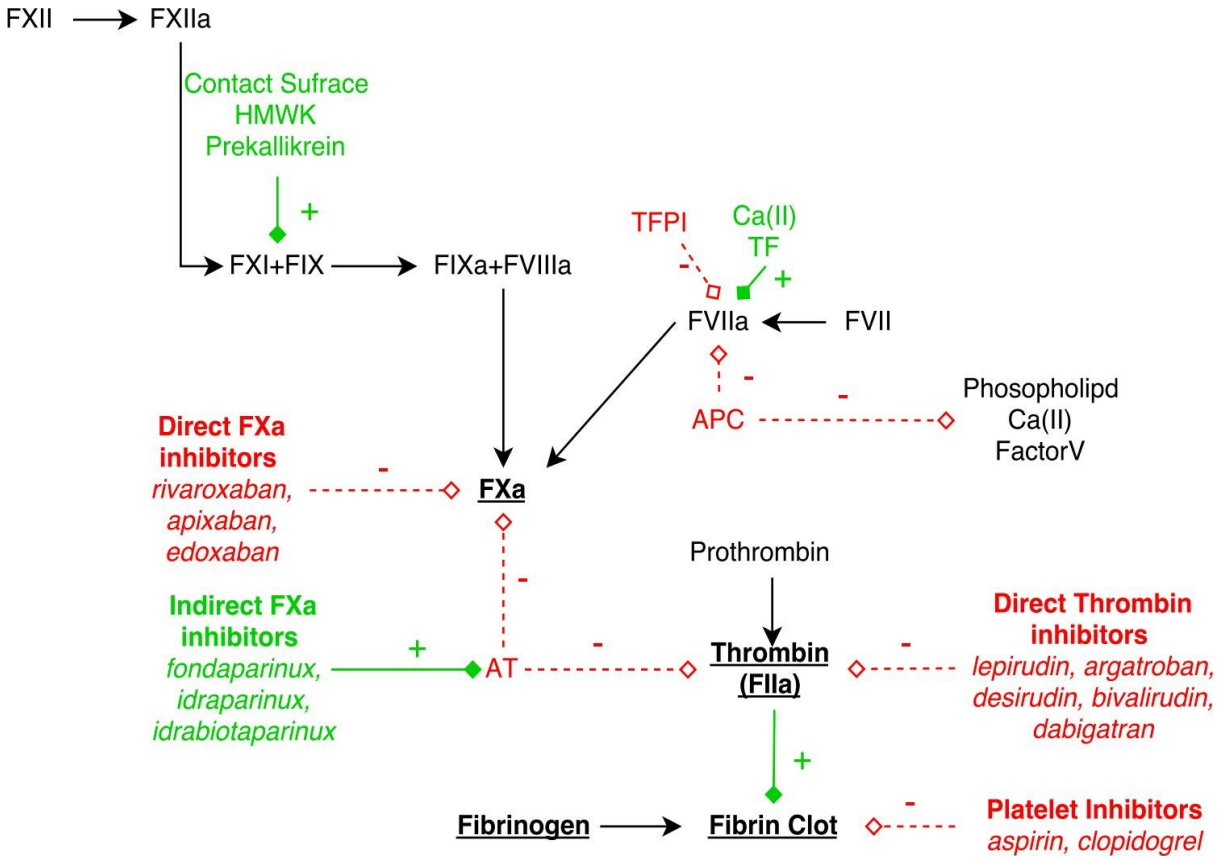

Figure 1. Pharmacologic targets for the inhibition of fibrin production including antiplatelet agents, thrombin and factor Xa inhibitors. APC, Activated protein C; AT, antithrombin; Ca+, calcium; HMWK, high-molecular-weight kininogen; TF, tissue factor; TFPI, tissue factor pathway inhibiton

Lepirudin, argatroban, desirudin and bivalirudin are all parenteral direct thrombin inhibitors. Dabigatran is approved for use by the FDA in treatment of non-valvular Atrial Fibrillation, DVT/ PE treatment and prophylaxis. It has a half life of 12–16 hours; hence for creatinine clearance greater than or equal to 80 mL/min it is advised to take the final oral dose three days prior to major surgery with relatively high bleeding risk, and it is advised to take the final oral dose two days prior to minor surgery with relatively low bleeding risk. No bridging is required if the patient is taking dabigatran. Patients with a creatinine clearance greater than or equal to 80 mL/min the drug may be restarted 48-72 hours post operatively for major surgery with relatively high bleeding risk, and may be restarted 24 hours after minor surgery with relatively low bleeding risk. Of note, the drug has renal excretion, hence it should be used with caution in patients with renal impairment. For a creatinine clearance of less than 30 mL/min, dabigatran is not recommended for use. It is also contraindicated for use in severe hepatic failure, defined as an AST/ALT ratio of

greater than three times the upper normal limit[6]. Since dabigatran has a consistent dose – response relationship, it does not require regular laboratory monitoring like warfarin does.

Factor Xa Inhibitors

Factor Xa inhibitors can be indirect or direct inhibitors, as seen in Figure 1. The oral anticoagulants in this class are direct Factor Xa inhibitors, hence we will focus on them from here in. Rivaroxaban (XareltoÔ) and apixiban (EliquisÔ) are oral direct Factor Xa inhibitors that bind to free Factor Xa. The free Factor Xa can be found as part of the prothombinase complex or Factor Xa that is part of an active clot[7] These drugs exhibit rapid onset of action and stable pharmacokinetics, mitigating the need for heparin bridging (Douketis, 2010).

Rivaroxaban is approved for use by the FDA in treatment of non-valvular Atrial Fibrillation and DVT/PE prophylaxis.

Due to the short half-life of rivaroxaban (5–9 hours), the manufacturer suggests it may be taken up to the day prior to surgery unless the patient has renal impairment. However, research by Massicotte et al recommends lengthier abstinence from the drug as has been outlined below. It is advised for patients with a creatinine clearance greater than or equal to 30 mL/min to take the final oral dose three days prior to major surgery with relatively high bleeding risk, and it is advised to take the final oral dose two days prior to minor surgery with relatively low bleeding risk. No bridging is required if the patient is taking Rivaroxaban. The drug may be restarted 48-72 hours post operatively for patients with a creatinine clearance greater than or equal to 30 mL/min for major surgery with relatively high bleeding risk, and may be restarted 24 hours after minor surgery with relatively low bleeding risk[8] Of note, the drug has renal excretion, hence it should be used with caution in patients with renal impairment. For a creatinine clearance of less than 30 mL/min, rivaroxaban is not recommended for use. Its use is contraindicated in severe hepatic failure, defined as an AST/ALT ratio of greater than three times the upper normal limit[9].

Apixiban is approved for use by the FDA in treatment of non-valvular Atrial Fibrillation, DVT/ PE treatment and prophylaxis. Apixiban has a half-life of 12-17 hours; hence it is advised for patients with a creatinine clearance greater than or equal to 50 mL/min to take the final oral dose three days prior to major surgery with relatively high bleeding risk, and it is advised to take the final oral dose two days prior to minor surgery with relatively low bleeding risk. No bridging is required if the patient is taking apixiban. The drug may be restarted 48-72 hours post operatively for patients with a creatinine clearance greater than or equal to 50 mL/min for major surgery with relatively high bleeding risk, and may be restarted 24 hours after minor surgery with relatively low bleeding risk. With its low renal elimination, apixiban can be used up to a creatinine clearance of 15 mL/min, lower than the 30 mL/min limit for rivaroxaban and dabigatran. It is contraindicated for use in severe hepatic failure, defined as an AST/ALT ratio of greater than three times the upper

normal limit[1]. Due to stable pharmacokinetics and dose – response relationships, rivaroxaban and apixiban do not require regular laboratory monitoring like warfarin does.

Anticoagulant and creatinine clearance	Preoperative Management in High bleeding risk: Major surgery	Preoperative Management in Low bleeding risk: Minor surgery	Need for bridging*	Drug clearance	Monitoring need
Dabigatran > 80mL/min	Last Dose 3 days before surgery (Half life 12 - 16 hours)	Last Dose 2 days before surgery	No	Esterase metabolism / Renal ExcreCon (80% Renal)	No
Rivaroxaban >30 mL/min	Last Dose 3 days before surgery (Half life 5 - 9 hours)	Last Dose 2 days before surgery	No	HepaCc (CYP) metabolism / Renal excreCon (66% Renal, 33% Feces)	No
Apixiban >50 mL/min	Last Dose 3 days before surgery (Half life 12 - 17 hours)	Last Dose 2 days before surgery	No	HepaCc (CYP) metabolism / Renal excreCon (25% Renal, 56% Feces)	No

Table 1: Preoperative and Perioperative management of NOACs

**As NOACs have a rapid onset and offset of action, in general bridging anticoagulation during the perioperative period with low molecular weight heparin (LMWH) is not needed. If the patient is to undergo a lengthy NPO period post operatively and is at moderate to high risk for a thromboembolic event, LMWH therapy should be considered in conjunction with a consult to a specialized service such as Hematology or Internal Medicine[10].*

Anticoagulant and creatinine	Onset of action (Tmax)	Post operative management in High bleeding risk: Major surgery	Post operative management in Low bleeding risk: Minor surgery
Dabigatran >80 mL/min	2 – 3 hours	Resume 48 – 72 hours aRer surgery	Resume 24 hours aRer surgery
Rivaroxaban >30mL/min	3 hours	Resume 48 – 72 hours aRer surgery	Resume 24 hours aRer surgery
Apixiban >50mL/min	3 hours	Resume 48 – 72 hours aRer surgery	Resume 24 hours aRer surgery

Table 2: Post operative management of NOACs

Anticoagulant and creatinine clearance	Preoperative Management in High bleeding risk: Major surgery	Preoperative Management in Low bleeding risk: Minor surgery	Post operative management in High bleeding risk: Major surgery	Post operative management in Low bleeding risk: Minor surgery
Dabigatran 50 to <80 mL/min	Last Dose 3 days before surgery	Last Dose 2 days before surgery	Resume 48 – 72 hours aRer surgery	Resume 24 hours aRer surgery
30 to <50 mL/ min	Last Dose 4-5 days before surgery	Last Dose 3 days before surgery	Resume 48 – 72 hours aRer surgery	Resume 24 hours aRer surgery
<30 mL/min	Last Dose 6 days before surgery	Last Dose 4 days before surgery	AlternaCve anCcoagulaCon should be used	AlternaCve anCcoagulaCon should be used
Rivaroxaban <30 mL/min	Last Dose 4 days before surgery	Last Dose 3 days before surgery	AlternaCve anCcoagulaCon should be used	AlternaCve anCcoagulaCon should be used
Apixiban 30-50 mL/min	Last Dose 4 days before surgery	Last Dose 3 days before surgery	Resume 48 – 72 hours aRer surgery	Resume 24 hours aRer surgery

Table 3: Management of NOACs in patients with sub optimal creatinine clearance

Bleeding rates and risks with new oral anticoagulants

Novel oral anticoagulants have consistently been found to be associated with lower incidence of major/fatal bleeding compared to traditional anticoagulants. In fact, the safety, efficacy and predictability of NOACs are the main driving forces behind the rapid expansion of their use therapeutically. The lower incidence of bleeding seen with new oral anticoagulants has been attributed partially to their very short half-life; their effects fade quickly, usually 12-24 hours after the last dose (Kumar et al, 2016). Taking this into consideration, it has been hypothesized that most surgery can be performed safely 12-24 hours after the last dose, though more caution needs to be taken in unpredictable or emergency surgery situations[11].

A thorough assessment of pre-operative risk is crucial with patients on both traditional anticoagulants and NOACs. For NOACs, this assessment includes knowledge of the type and duration of surgery being performed, renal function and thromboembolic risk factors [11] NOACs, most specifically dabigatran, are renally cleared, leading to a need for knowledge of renal function. In patients with renal dysfunction, the 12-24 hour cessation of NOACs may not be adequate prior to surgery; however, most NOACs are generally contraindicated in these patients[12].

When comparing individual NOACs to more traditional anticoagulants, specifically warfarin, studies showed reduced rates of fatal/major hemorrhage with the use of rivaroxaban (ROCKET AF trial), apixaban (ARISTOTLE trial) and dabigatran (RELY trial) in a clinical setting. Levels of dabigatran (thrombin inhibitor) can be measured using the activated partial thromboplastin time (aPTT), where a time more than double the normal upper limit can be associated with a higher bleeding risk. For rivaroxaban and apixaban (Factor Xa inhibitor), both PT and aPTT can be affected, though only PT can be used as a meaningful evaluation of Xa inhibitor effect. Specific assays also exist as a method to measure both types of NOACs and to assess bleeding risk[12].

New oral anticoagulants vs traditional anticoagulation

Various studies have been conducted to look at the use of NOACs (dabigatran, rivaroxaban, and apixiban) compared to traditional anticoagulants in a clinical setting. Differences of particular interest include time of onset, half-life, drug interactions, and incidence of major/fatal bleeding.

In comparison to warfarin, NOACs have been found to have a more rapid onset, predictable anticoagulant effect, shorter half-life, and fewer drug and dietary interactions. In combination, these differences allow NOACs to be given at fixed doses without the consistent coagulation monitoring that is needed for patients on vitamin K antagonist, warfarin [13] Similar results were seen when NOACS were compared to heparin, an activator of anti- thrombin cofactor III[12].

A point of concern for clinicians is the dependence of NOACs, specifically dabigatran, on renal clearance. About 80% of dabigatram is renally cleared leading to an increase in exposure to the drug in patients with renal dysfunction. Other NOACs also undergo renal clearance, though to a lesser extent than dabigatram[13]. Another point of concern for clinicians and surgeons is the lack of a reversal agents for NOACs.

Reversal Agents for new oral anticoagulants

The absence of specific reversal agents has been an area of concern for surgeons. Three antidotes specific for the reversal of NOACs are currently in different stages of development: idarucizumab, andexanet alfa, and ciraparantag. Idaricizumab is an antibody fragment that binds dabigatram, thus neutralizing its anticoagulant effect. It is indicated in patients on dabigatram that require emergency surgery or that are experiencing uncontrollable bleeding. Ciraparantag is a molecule that binds to dabigatran and direct Xa inhibitors (as well as heparin, low molecular weight heparin and fondaparinux) to possibly reduce/reverse their effects. Animal studies have found it to reduce bleeding, but whether it completely reverses the mentioned anticoagulants has yet to be proved. Lastly, andexanet alfa is a mutant Factor Xa that acts as a Factor Xa decoy. It has a strong affinity for Factor Xa inhibitors as well as antithrombin III-inhibitor complex.

Anexanet can reverse dabigatran and new Factor Xa inhibitors. They can also reverse the

effects of molecular-weight heparin and fondaparinux. Current information about these reversal agents have been gathered from phase I and II trials, and have yet to be confirmed in more clinically- meaningful phase III trials[14].

In emergency/trauma surgery situations, current management of patients on NOACs involve the use of blood products and other antidotes. Other antidotes include administration of procoagulant drugs (like antifibrinolytic agents), hemodialysis in patients with renal impairment (specifically for dabigatram) and administration of haemostatic agents like prothrombin complex concentrate (PCC). Blood products include the use of fresh frozen plasma (FFP), which is not routinely recommended unless there is severe hemorrhage[14].

Reversal Agent	Target NOAC	Mechanism
Idaraucizuma b	Dabigatran	An antibody fragment that binds free and thrombin bound dabigatran neutralizing its function within minutes (Pollack et al., 2015). Currently in phase 3 trails.
Andexanet alfa	Factor Xa inhibitors (Rivaroxaban, Apixiban, and Edoxaban)	A Factor Xa decoy that rapidly sequesters Factors Xa inhibitors (Sarich et al., 2015). Currently in phase 2 trails.
PER977	Non-Specific	Reverses the effects of NOAC through hydrogen bonding (Sarich et al., 2015). Currently in phase 1-2 clinical trails

Table 4. NOAC Reversal Agents in Development

An algorithm for suggested management of patients with major bleeding receiving NOACs is outlined in Figure 2.

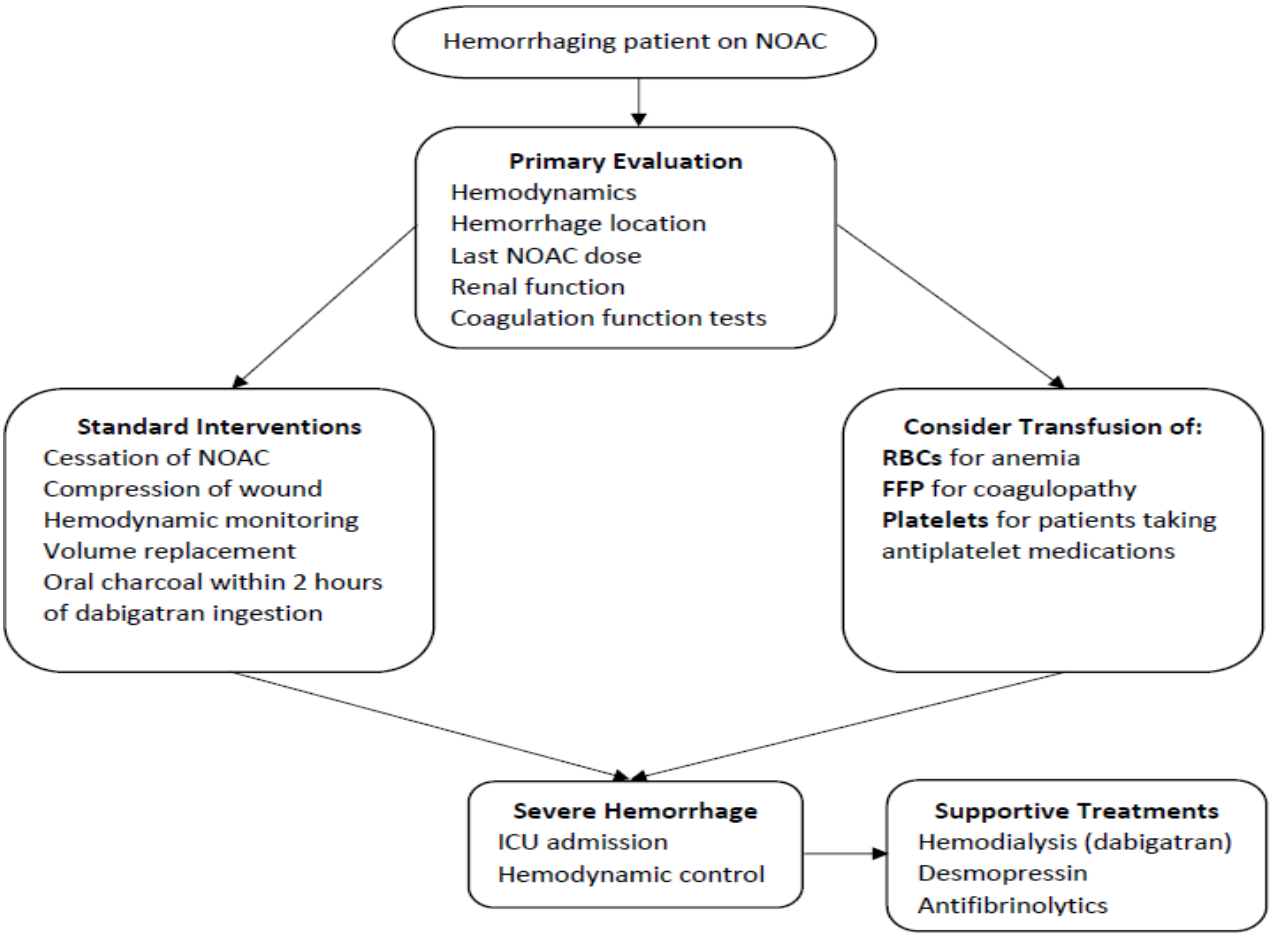

Figure 2: Management of patients with major bleeding receiving NOAC

**Preferred agent for rivaroxaban/apixiban ** Preferred agent for dabigatran. DIC-disseminated intravascular coagulation, FFP-fresh frozen plasma, PCC-prothrombin complex concentrate, RBC-red blood cell* [15].

Conclusion

NOACs are now frequently used in the clinical setting. It is imperative that plastic surgeons have a working understanding of these drugs and their management in the operative setting. Knowledge about NOACs will result in less anxiety for the plastic surgeon when faced with patients on NOACs and potentially less complications for the patient; if their plastic surgeon is truly knowledgeable and cognizant regarding regulation of NOACs in the operative setting.

Based on the information delineated in this paper, we recommend that for procedures that require extensive undermining that NOAC's are held 3 days before surgery and re started 3 days after surgery. Examples of such procedures will include Rhytidectomy, Abdominoplasty, Breast Reduction, liposuction with lipoaspirate >200cc, brachioplasty and

any fasciocutaneous or muscular flap. For surgeries that require less extensive undermining, NOAC's can be held 2 days before surgery and re started 2 days after surgery. Examples of such procedures include small facial cutaneous lesion excisions, liposuction with lipoaspirate <200cc, Mastopexy with <100g tissue removal and scar revisions with limited undermining.

Corresponding author
Vipul Gargya
Brandon Plastic Surgery
Division of Plastic Surgery
Brandon, FL, USA

E-mail: vipulgargya@gmail.com

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