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# Novel Oral Anticoagulants: Comparative Pharmacology and Dental Implications

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## Abstract

Novel oral anticoagulants (NOACs), direct thrombin inhibitor (dabigatran) and factor Xa inhibitors (rivaroxaban, apixaban and edoxaban) are available in market as an alternative to warfarin. They are widely being prescribed by medical practitioners as these drugs overcome some of the major drawbacks with the existing medications. Absence of any specific management guidelines and lack of antidote are major concern for dental treatment of patients on NOACs. This review details the pharmacological profile of vitamin K anticoagulants and emerging NOACs. In order to assist dental professionals in decision making, case studies showing management of patients on NOACs undergoing dental treatment are also summarized. Since available data are not sufficient to establish an evidence-based dental management, the dentist must use caution and attention when treating patients taking dabigatran, rivaroxaban, apixaban and edoxaban.

**Keywords**

Anticoagulant; Dabigatran; Rivaroxaban; Apixaban; Edoxaban; Dental; Pharmacology

**Abbreviations:** NOACs: Novel Oral Anticoagulants; TF: Tissue Factor; FVII: Factor VII; VKA: VIT K Anticoagulants; VTE: Venous Thromboembolism; NVAF: Non Valvular Atrial Fibrillation

## Introduction

The increase in life expectancy, and the prevalence of chronic diseases, including heart disorders and cerebrovascular events, has resulted in a growing number of patients on anticoagulant therapy coming for dental surgeries. Anticoagulant therapy is typically the goal for treatment and prevention of thromboembolic diseases [1]. Interest in the development of new anticoagulation medications is growing because of the limitations of parentally administered heparin, the various drug interactions and monitoring concerns associated with vitamin K antagonists such as warfarin [2]. During the last few years, a series of novel targeted anticoagulants have been developed and approved for treatment of various conditions. These include oral direct factor Xa inhibitors (Rivaroxaban, Apixaban and Edoxaban) and direct thrombin inhibitor (Dabigatran).

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Before proceeding for surgery, dentists have to assess the thromboembolic risk related to the disease, and bleeding risks related to surgery. The treatments for when there is a risk of bleeding include the use of injectable anesthetics, tooth extractions, placing osseointegrated implants, periodontal surgery and periodontal curettage, minor oral surgery and root canal therapy. The knowledge of the correct protocol outpatient management is a prerequisite for starting treatment. To date, however, the management of these patients for minor oral surgery (such as for osseointegrated implants) is still a complex issue. A strong debate exists between the risk of uncontrolled bleeding in case of continuation of therapy or the possibility of thromboembolic complications in the case of discontinuation of the medication [3].

This article reviews novel oral anticoagulants and the implications referred to the dental care of patients administered these drugs.

## History of Anticoagulants

Historically, the first line of defense against blood clots, including pulmonary embolism, deep vein thrombosis, peripheral artery embolism, stroke due to atrial fibrillation, myocardial infarction, is an anticoagulant being used for many years. Traditional therapies including heparin and vitamin K antagonists (VKA) ruled the market though both therapies had significant drawbacks. More recently, oral anticoagulants with specific targets are being approved by regulatory agencies and prescribed by medical practitioners. These include direct thrombin inhibitors (Dabigatran) and direct factor Xa inhibitors (Rivaroxaban and Apixaban) [4].

### Coagulation cascade

The coagulation cascade is a biochemical interaction of 13 coagulation factors that take place on different cell surfaces in 3 phases: initiation, amplification and propagation, as shown in Figure 1 [5]. The process is initiated by the contact of tissue factor (TF), present in membrane of cells around blood vessels like smooth muscle cells and fibroblasts, with bloodstream. TF quickly activates Factor VII (FVII) forming FVIIa/TF complex responsible for activating FIX and FX. FXa along with FVa forms a prothrombinase complex on surface of cells expressing TF. This complex transforms small amounts of prothrombin to thrombin to induce platelet activation. The amplification phase occurs on negatively charged platelets where thrombin formed earlier activates FV, FVIII and FXI. The activation of platelets lead to change in membrane permeability allowing entry of calcium ions and release of chemotactic substances to attract clotting factors to the surface to begin the propagation phase. Propagation phase is characterized by migration of large number of platelets to the site of injury and the production of tenase and prothrombinase complex on the surface of activated platelets. As a result, prothrombin is converted into thrombin, resulting in the cleavage of fibrinogen to fibrin monomer. This then polymerizes to consolidate the platelet plug [5,6].

### Anticoagulants

In a healthy individual, a fine balance is maintained between procoagulant and anticoagulant factors, so that coagulation only begins in order to heal injuries. While normal blood clots are a natural

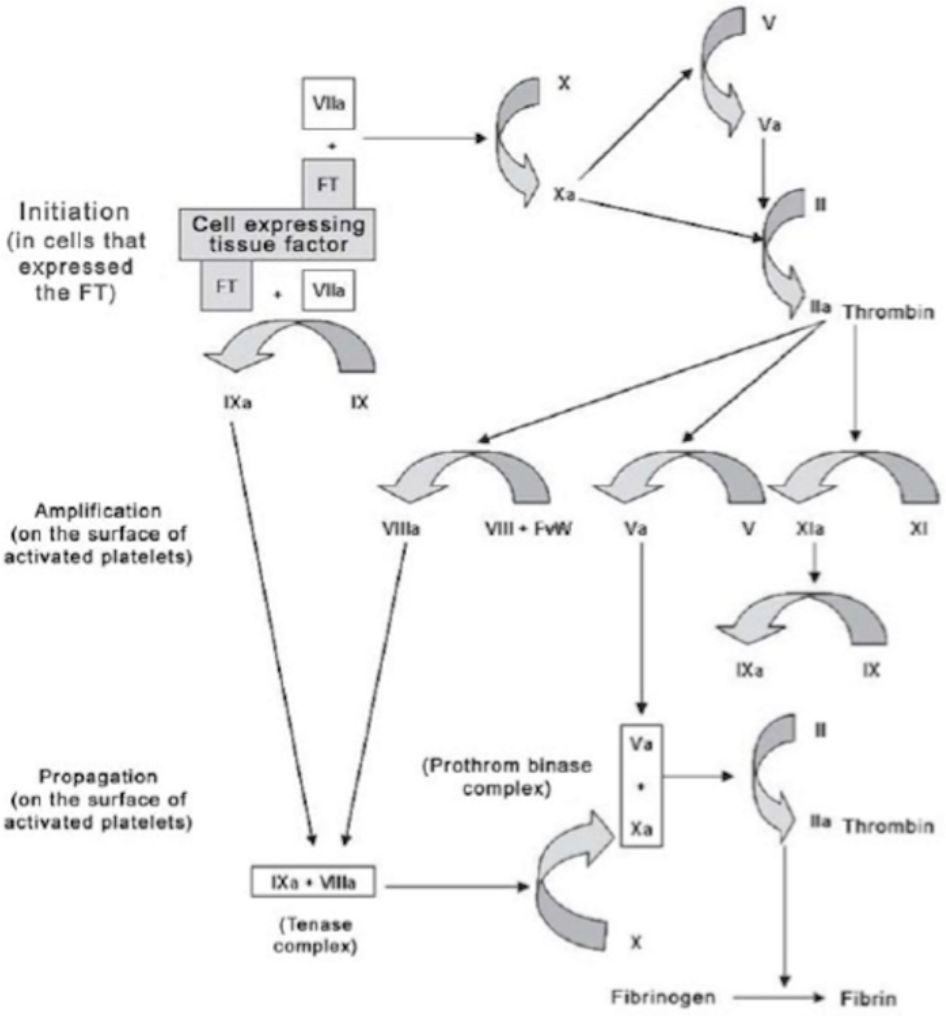


**Figure 1**: Coagulation cascade.

part of healing, abnormal arterial and venous blood clots (thrombosis) are a significant cause of death and disability. Prophylaxis using anticoagulants is management of thrombosis in the high risk patients.

## VIT K anticoagulants

The VKAs in clinical use are structurally derived from 4-hydroxycoumarin. They non-competitively inhibit the vitamin K epoxide reductase complex subunit 1 essential in the recycling of vitamin K in the liver. As vitamin K serves as a co-factor in the activation of clotting factors II, VII, IX and X, the inhibition of its recycling results in strong anticoagulation activity. Vitamin K also serves as a co-factor for the anticoagulant proteins C, S and Z, which also affects the regulation of the procoagulant–anticoagulant system [7]. Two drugs are currently available on the market as Coumadin (warfarin sodium, Bristol-Myers Squibb Srl, Rome, Italy) and Sintrom (acenocumarolo, Novartis Farma, Origgio and Varese, Italy). Warfarin has 2 functions: anticoagulant activity and antithrombotic effect. Therapeutic doses of warfarin reduce the production of functional vitamin K dependent clotting factors by ~30-50%. A concomitant reduction in carboxylation of secreted clotting factors yields a 10-40% decrease in the biologic activity of the clotting factors. As a result, the coagulation system becomes functionally deficient [8]. Both medications show good oral absorption, a high tendency to union to plasmatic proteins, hepatic and renal metabolism and a half-life between 10 and 24 hours [6].

## Novel oral anticoagulants

The new oral anticoagulants (NOACs) represent novel direct-acting medications that are selective for one specific coagulation factor, either thrombin or activated factor Xa. Several NOACs, such as dabigatran, rivaroxaban, apixaban, and edoxaban, have been used in many countries. The main characteristics of VKAs and NOACs are listed in Table 1.

**Dabigatran**: Dabigatran was the first approved NOAC; approved in 2008 by the EU and by the FDA in 2010. It is a direct thrombin (FIIa) inhibitor that prevents the conversion of fibrinogen to fibrin and thereby prevents clot formation. Dabigatran is indicated to reduce the risk of stroke and systemic embolism in patients with non valvular atrial fibrillation (NVAF) [9]. Dabigatran is poorly absorbed by the gastro-intestinal tract, and it is therefore given as the prodrug

**Table 1**: Pharmacokinetics of NOACs.

| NOACs | Target | Brand Name | Bioavailability | Metabolism | Elimination | Half life |
|---|---|---|---|---|---|---|
| Dabigatran | Direct thrombin inhibitor | Pradaxa | 3-7% | Plasmatic and hepatic esterases | Renal (80%) | 12-17 hrs |
| Rivaroxaban | FXa inhibitor | Xarelto | 60-80% | CYP Enzymes | Urine (66%)<br>Feces (28%) | 5-9 hrs |
| Apixaban | FXa inhibitor | Eliquis | 50% | CYP Enzymes | Urine (27%)<br>Feces (Biliary/ intestinal) | 12 hrs |
| Edoxaban | FXa inhibitor | Savaysa | 60% | CYP Enzymes | Renal (50%)<br>Biliary/intestinal excretion | 8-10 hrs |

**Table 2**: Management protocol in patients taking dabigatran.

| Creatinine clearance (ml/min) | Time of discontinuation after last dose of dabigatran before surgery | |
|---|---|---|
| | Standard bleeding risk | High bleeding risk* |
| >80 | 24 hrs | 2-4 days |
| >50 to ≤ 80 | 24 hrs | 2-4 days |
| >30 to ≤ 50 | At least 2 days | 4 days |
| ≤ 30# | 2-5 days | >5 days |

*Determining factors for high bleeding risk: Type of surgery requiring complete hemostasis (cardiac, neuro, abdominal, spinal anesthesia), advancing age, co-morbidities (e.g. major cardiac, respiratory or liver disease) and concomitant use of antiplatelet therapy
#Dabigatran is contraindicated in such patients

dabigatran etexilate which is transformed to dabigatran (active) through hydrolysis by plasmatic and hepatic esterases. It binds to the active site of thrombin univalently, thereby inactivating both bound fibrin and unbound (i.e. free) thrombin, thus inactivating thrombus expansion. By inhibiting thrombin, dabigatran prevents a cascade of events: conversion of fibrinogen into fibrin, positive feedback amplification of coagulation activation, cross-linking of fibrin monomers, platelet activation and inhibition of fibrinolysis [7]. The trade name of dabigatran etexilate is Pradaxa (Boehringer Ingelheim, Ingelheim, Germany). Dabigatran etexilate is usually administered twice daily with a bioavailability following an oral administration of 3-7%, and it has a fairly rapid onset of action, with maximum plasma concentration occurring 2-4 hours after intake and its terminal half-life is 12-17 hours [9]. 20% of the absorbed drug undergoes hepatic metabolism, but the pharmacokinetic profile of dabigatran was not altered in patients with moderate hepatic impairment. 80% of the drug is excreted unchanged via the renal system, and the dosage must be reduced for patients with renal insufficiency (creatinine clearance [CrCl] <50 mL/min) [2]. Dabigatran shows a very low potential for drug–drug interactions and the absorption is not affected by food. A few drug-drug interac¬tions that have been demonstrated with dabigatran include quinidine, ketoconazole, amiodarone, and verapamil which can increase the dabigatran plasma concentrations. Co-administration of other anticoagulants or non-steroidal anti-inflammatory drugs will also increase dabigatran level. Rifampicin and some proton pump inhibitors such as omeprazole will decrease dabigatran levels [10]. Adverse events associated with the use of dabigatran include dyspepsia, dizziness, dyspnea, peripheral edema, back pain, arthralgia, diarrhea and nasopharyngitis. Conventional tests such as prothrombin time (PT) or activated partial thromboplastin time (aPTT) are not ideal for assaying the effects of dabigatran, whereas diluted thrombin time (dTT), ecarin clotting time (ECT), and aPTT measured by Hemoclot thrombin inhibitor assay (Hyphen BioMed, Neuville-sur-Oise, France) are sensitive tests for assessing its activity [11]. Significant regulatory bodies, FDA and EU recently granted approval of Praxbind (idarucizumab) as a reversal agent for patients treated with Pradaxa in case of emergency surgery/urgent procedures or in life-threatening or uncontrolled bleeding [12,13].

**Rivaroxaban**: Rivaroxaban is an oxazolidinone derivative that exerts a direct inhibitory effect upon factor Xa, thereby blocking the transformation of prothrombin into throm¬bin, and thus ultimately inhibiting blood clot formation. It is indicated to reduce the risk of stroke and systemic embolism in patients with non valvular atrial fibrillation who present one or more risk factors (congestive heart failure, hy¬pertension, age ≥ 75 years, diabetes mellitus, previous stroke or transient ischemic attack episodes), treatment and reduction of recurrence risk of deep vein thrombosis and pulmonary embolism. It is indicated in the prophylaxis of venous throm¬boembolism in adults subjected to elective hip or knee replacement surgery [1,14]. The trade name of rivaroxaban is Xarelto (Bayer HealthCare, Leverkusen, Germany). It is a non-basic compound that is rapidly absorbable and has a high bioavailability (60%–80%) after oral administration. Pharmacokinetics of rivaroxaban is dose dependent, with maximum concentration occurring 2.5-4 hours after oral administration. Rivaroxaban is metabolized via cytochrome p450 enzymes and approximately one-third of the absorbed dose is excreted unchanged in the urine, with the remaining two-thirds excreted as inactive metabolites in both the urine and feces. The terminal elimination half-life of rivaroxaban is 5-9 hours in healthy subjects aged 20 to 45 years and 11-13 hours in the elderly [7,14,15]. Inhibitors and inducers of these cytochrome p450 enzymes or transporters (e.g., P-gp) may result in changes in rivaroxaban levels. Compared to healthy subjects with normal creatinine clearance and liver function, rivaroxaban levels increase in subjects with renal impairment and moderate hepatic impairment (Child-Pugh B) [14]. Rivaroxaban prolongs the PT/INR and the aPTT, and therefore these tests are not good measures of the level of anticoagulation. Instead, antifactor Xa levels can be used to measure the anticoagulant effect, without having to routinely monitor level of anticoagulation [16]. Like other direct action oral anticoagulants, rivaroxaban has no specific approved antidote. Recently, FDA granted orphan drug designation to andexanet alfa for reversing the anticoagulant effect of direct or indirect FXa inhibitors in patients experiencing a serious, uncontrolled bleeding event or who require urgent or emergency surgery [17,18].

**Apixaban**: Apixaban, a NOAC sold under the trade name Eliquis, is an anticoagulant which was approved by the FDA in 2012 for the treatment of pulmonary embolism and secondary prophylaxis of deep vein thrombosis. It is also used as a safe and attractive alternative to warfarin to prevent strokes in patients with atrial fibrillation. Apixaban, similar to rivaroxaban, works by selectively inhibiting

both free, and clot-bound FXa in a reversible manner, and by inhibiting prothrombinase activity. Apixaban has a bioavailability of 50% for doses up to 10mg. On administration, it is rapidly absorbed in stomach, distal small intestine and ascending colon reaching its peak plasma concentration between 3-4 hours. It is unaffected by the presence of food and is metabolized by cytochrome p450 enzymes, and is a substrate of efflux transporters. Like all other NOACs, it has a short half-life of 12 hours, if administered orally, and 5 hours, if administered by IV however, unlike other NOACs, it has the smallest renal clearance (27%). Combined administration with potent P-glycoprotein and CYP3A4 inhibitors is contradicted [1,15,19]. As a result of FXa inhibition, apixaban prolongs clotting tests such as PT, INR, and aPTT. No routine coagulation test seems to be suitable to measure apixaban levels. Antidote to reverse the effect of Apixaban, Andexanet alfa, is under trials [17,18].

**Edoxaban**: Edoxaban (LixianaTM, SavaysaTM), an oral direct inhibitor of factor Xa, was recently approved in the United States for prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation and for treatment of venous thromboembolism (VTE), though it is approved for prevention of VTE following total knee and hip arthroplasty earlier in Japan. Edoxaban has an oral bioavailability of approximately 60 % exhibiting a linear pharmacokinetics with a terminal half-life of 8-10 h. Peak plasma concentration is achieved 1-2 h after ingestion [20]. Renal clearance accounts for approximately 50% of the total clearance of edoxaban, so its dose must be adjusted in case of renal failure. Metabolism of edoxaban also depends on the CYP34A system and it is also a substrate for the efflux transporter P-glycoprotein (P-gp) and thus drug levels can be affected by concomitant medication use affecting this system (eg, ketoconazole, clarithromycin) [15,21]. The use of edoxaban in patients with moderate or severe hepatic impairment (Child-Pugh B and C) is not recommended although no dose reduction is required in patients with mild hepatic impairment (Child-Pugh A). As a result of FXa inhibition, edoxaban prolongs clotting time tests such as PT and aPTT and thus are not useful in monitoring the anticoagulant effect of edoxaban [21].

### Pros and Cons of NOACS

While VKAs (particularly, warfarin) were a major development in anticoagulation, trends appear to be changing fast in past few years. NOACs have been positioned as next generation, equally effective, easier to use, safer anticoagulant treatment options for patients with thromboembolic condition and atrial fibrillation. The main difference between the two groups of drugs is their mechanism of action. In effect, while the classical drugs block d-carboxylation of the vitamin K-dependent coagulation factors (II, VII, IX, X), the new anticoagulants inhibit the coagulation factors directly, thereby ensuring a safer and more predictable response. NOACs have a more rapid onset of action than VKAs (~1.5-3 hrs) after oral administration; along with rapid offset of action which is important if patients require surgery. Rapid onset and offset properties of NOACs reduce the need for "bridging" patients at high risk of thrombosis with a parenteral anticoagulant (heparin) which is required in case of VKAs due to their slow action. VKAs also present numerous food and drug interactions, making it necessary to adopt measures of caution referred to diet and especially to changes in concomitant medication. VKAs have a narrow therapeutic margin which implies an unpredictable anticoagulant effect, with the need for regular coagulation controls and dose adjustments in order to keep the international normalized ratio (INR) within normal limits. Advantages of NOACs include minimal drug–drug and food interactions and predictable relevant PK and PD parameters, no routine monitoring required, regardless of body weight, age, sex, race, and demographic variations along with wide therapeutic windows, thereby administering fixed dose to patients.

Despite the abovementioned advantages, the clinical experience gained with the new oral anticoagulants is still limited, and there are also potential inconveniences such as the lack of a direct antidote or of studies conducted in specific patient populations, e.g., obese individuals, pregnant women, pediatric or low-weight patients, etc. Additionally, NOACs have not yet been applied in patients with mechanical mitral valve issues (with increased rates of thromboembolic and bleeding complications), patients with malignant disease, and those with antiphospholipid syndrome, which is associated with a greater risk of thrombophilic states. NOACs must be administered cautiously in patients or elderly with hepatic or renal insufficiency with continuous monitoring. Additional disadvantages of NOACs, when compared to VKAs, are its cost and the importance of patient compliance. Moreover, short half-lives of NOACs can be considered both an advantage and a disadvantage under various circumstances. For example, the advantage of the short half-life of an NOAC may be relevant for emergency surgery and in cases of bleeding due to accumulation of the drug in the blood, whereas the short half-life is a disadvantage if the patient is non-compliant, which could put the patient at risk for thrombosis [1,7,15].

## Clinical Comparison of vka and NOACS

### In medical field

A recent observational nationwide cohort study evaluating the effectiveness and safety of the NOACs compared to warfarin in anticoagulant naïve patients with non valvular atrial fibrillation [NVAF] was conducted by Larsen et al. Among the study population of 61678 patients, 57% received warfarin, 21% dabigatran 150 mg, 12% rivaroxaban 20 mg and 12% apixaban 5 mg. No significant difference was found between NOACs and warfarin for ischemic stroke, while the risks of death or any bleeding were significantly lower for apixaban and dabigatran compared with warfarin [22]. In a meta-analysis of 10 RCTs in patients with AF, bleeding risk with NOACs versus VKA/aspirin was not statistically different (OR 0.89, 95% CI 0.74-1.06), though there was considerable heterogeneity among these studies [23]. Meta-analysis of 3 RCTs conducted in 2013 also revealed similar findings stating that the NOACs seem no more effective than warfarin for prevention of non-hemorrhagic stroke and systemic embolic events in the overall NVAF population, but are generally associated with a lower risk of intracranial bleeding than warfarin [24].

Hulle et al. conducted a meta-analysis to determine the efficacy and safety of NOACs as compared with those of VKAs in patients with acute VTE. On analyzing 5 studies, they found that NOACs have comparable efficacy to that of VKAs and are associated with a significantly lower risk of bleeding complications. RRs for recurrent VTE, fatal PE and overall mortality for NOACs vs. VKAs were 0.88, 1.02 and 0.97 respectively [25]. Similar findings were reported by Cohen et al in a review comparing the results of Phase III trials of NOACs in VTE [26].

Harel et al reported the efficacy and safety of the NOACs versus VKA for AF and VTE in patients with CKD. Among 8 RCTs selected, no significant difference in the primary efficacy outcomes of stroke

and systemic thromboembolism and recurrent thromboembolism or thromboembolism-related death with NOACs versus VKAs was observed. The risk of major bleeding (primary safety outcome) was also similar between the groups [27].

### In dental field

As discussed above, there were several studies that showed that NOACs were as effective as the oral VKA in preventing thrombotic events with fewer major or fatal bleeding complications, though evidences for management of patients taking NOACs in oral surgery are not clear. In a secondary analysis of the RE-LY study (dabigatran in atrial fibrillation), 10% of the patients who needed an invasive procedure needed dental intervention; there were no significant differences in the bleeding rates between the Dabigatran and the warfarin group, however, the intervention was performed after cessation of Dabigatran for at least 24 h [28].

### Management of oral health of patients on NOACS

With ever increasing popularity of NOACs due to the benefits including predictable pharmacokinetics, rapid onset, minimal food and drug interactions, easy administration, no regular monitoring required, and short half-life, it is not surprising that the number of such patients being addressed by dental practitioners is increasing at a fast rate. Sparsity of defined management guidelines for such patients and paucity of clinical data in this field, force the dental professionals to rely on pharmacological data for these drugs.

There are minimal reports in the literature of clinical exposure to these medications in dentistry.

Breik et al. presented a case series of five patients taking dabigatran and speculated that continuation of dabigatran is safe for scaling, restorative treatment, endodontics, and single tooth extractions, provided additional local haemostatic measures are used. For multiple dental extractions, there should be dialogue with the patient's physician in regards to dabigatran cessation evaluating the risk of embolism and need of hemostasis. Authors further suggested that drug must be resumed 24-48h postoperatively though drug manufacturer recommend resuming drug as soon as hemostasis is achieved [29].

Romond et al. presented a case report of a patient with normal renal function taking dabigatran for atrial fibrillation who underwent eight extractions, alveoplasty, and tuberosity reduction. Dabigatran was withheld the night before surgery and resumed the day after. Resorbable gelatine sponges and sutures were placed, following curettage of the tooth sockets. No postoperative bleeding was observed, although an immediate denture may have assisted in maintaining postoperative hemostasis [30].

Gomez-Moreno et al. evaluated the incidence of bleeding complications after dental implant placement in 71 patients in treatment by dabigatran. They found no statistically significant difference in the number of bleeding complications between dabigatran patients and systemically healthy control subjects. Dental implant surgery in patients taking dabigatran can be performed safely 12 h after the last dose of dabigatran, applying local hemostatic measures and resuming the prescribed medication regime 8 h after surgery [31].

Communication with the primary care physician is fundamental to the dental treatment planning of patients on NOACs. A detailed history of underlying diseases, medical background, medication list and allergies should be obtained prior to initiating any dental treatment [32]. Bleeding risk associated with the treatment, renal function and local hemostatic measures available are a few essentials to be considered [33]. Simple extractions of <3 teeth and surgery lasting less than 45 minutes can be included in minor bleeding risk interventions. Suspension of the NOACs does not seem necessary in these cases. Hemostasis is to be facilitated, with local measures designed to help healing and minimize the risk of post-extraction bleeding. Major bleeding risks include multiple extractions (>3 teeth), surgeries lasting more than 45 minutes, and head and neck cancer surgery. Therefore, depending on the type of operation, the existence of renal failure, and the risk of hemostatic alterations, the medication should be suspended for a number of days before the operation is carried out [1]. Van Ryn summarizes the management protocol (Table 2) in patients taking dabigatran and undergoing elective surgery or invasive procedures taking creatinine clearance and bleeding risk into consideration. Administration of NOACs should not be restarted after oral/maxillofacial surgical procedures until the risk of post-operative bleeding is minimal (i.e. after a stable fibrin clot is formed), usually within 24-48 hours following surgery, because onset of the anticoagulant effect of these drugs is rapid [34].

## Conclusion

Market size of NOACs is ever increasing with their ease of use and more favorable pharmacodynamics profile. Research pertaining to dental treatment in patients on NOACs is very limited making it imperative for dental professionals to have a complete knowledge about these drugs, their indications and mechanism of action which can aid in decision making. Lack of specific antidote (except dabigatran) in event of postoperative bleeding along with dearth of clinical studies makes it difficult to outline a standardized protocol for patient management. To conclude, risk assessment of bleeding and thromboembolic complications should be done with patient's physician as patient's health and safety remains the priority concern during treatment.

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