Oral Surgery in Patients Taking Direct Oral Anticoagulants (DOACs): A Practical Review of the Literature

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Abstract: Recently, four new oral anticoagulant – dabigatran etexilate (direct thrombin inhibitor) and rivaroxaban, apixaban and edoxaban (Xa factor direct inhibitor) – have been approved for the prevention of venous thrombosis and cardiovascular events. As the number of patients taking these drugs is increasing, it is important that the dentist is familiar with these new oral anticoagulants, their indications, methods of action and in particular the management of the patients undergoing oral surgery.

This literature review is conducted to highlight the medical uses of these new oral anticoagulants and their pharmacologic properties, the clinical condition of the patient that may influence the choice to discontinue the DOAC and peri-operative management of the patient. Collaboration with the attending physician is crucial.

Keywords: DOACs, Coagulation, Surgery, Peri-operative planning.

INTRODUCTION

In the last fifty years warfarin, a vitamin K antagonist, has been considered the oral anticoagulant of choice. However, some problems arise from the narrow therapeutic index of this drug, such as the necessity to frequently monitor the coagulation status of the patients and the resulting dose adjustment, as well as multiple food and drugs interactions. The need for agents with less monitoring requirements, fewer food and drug interactions, and a lower risk of major bleeding led to the development of direct oral anticoagulants (DOACs) [1].

These new molecules are capable of acting selectively and specifically on the individual components of the coagulation cascade providing a more predictable coagulating effect.

DOACs have enormous advantages: they guarantee a more predictable response, they do not require a constant monitoring of the patient, they are administered at fixed doses, facilitating adherence to therapy, they show minimal drugs and food interactions and they have a wide therapeutic margin.

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However, new oral anticoagulants also have some disadvantages: the main one is that there is no antidote for overdose or bleeding, in addition to the double daily administration of certain DOACs, and the higher cost [2].

The purpose of this literature review is to summarize the parameters that affect the peri-operative management of the patient being treated with DOACs.

METHODS

A comprehensive literature search covering the period August 2005– June 2019 was conducted using International Pharmaceutical Abstracts, PubMed, and Ovid MEDLINE to locate review articles, guidelines and clinical trials that were appropriate and relevant for this review. The following terms were used in the literature search: Pradaxa, Xarelto, Eliquis, Savaysa, dabigatran, rivaroxaban, apixaban, edoxaban, atrial fibrillation (also AFib), VTE, venous thromboembolism, factor Xa inhibitors, direct thrombin inibitor, DOAC, NAO.

What are DOACs?

The acronym DOAC stands for Direct Oral Anticoagulant and includes a group of medications composed of direct thrombin inhibitors (DTI) and inhibitors of factor Xa (FXaIs).

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Dabigatran etexilate is the prodrug of dabigatran (originally known as BIBR 953), that specifically and reversibly inhibits both free and clot-bound thrombin [3-5]. Because of its high polarity, dabigatran is not orally available; therefore, the prodrug of dabigatran, dabigatran etexilate, was developed to facilitate gastrointestinal absorption [5]. After oral administration, dabigatran etexilate is rapidly hydrolyzed by nonspecific, ubiquitous esterases to the active form, dabigatran [6].

Rivaroxaban, apixaban and edoxaban are orally administered, selective, reversible, direct inhibitors of factor Xa [1, 6].

How do DOACs Work?

Dabigatran etexilate (Pradaxa®) is the prodrug of dabigatran (originally known as BIBR 953), a potent, non-peptidic small molecule that specifically and reversibly inhibits both free and clot-bound thrombin by binding to the active site of the thrombin molecule so that it cannot catalyze fibrinogen into fibrin [7, 8].

Rivaroxaban (Xarelto®), apixaban (Eliquis®) and edoxaban (Savaysa®) bind directly to the factor Xa that is a protease that converts prothrombin (factor II) to thrombin, used to convert fibrinogen to fibrin and resulting in clot formation. As a result, when compared to DTI, FxaIs act on the previous phase of the coagulation cascade, so that no thrombin is present [8].

The selection of a factor Xa inhibitor is important, as the agent serves as a medium between the intrinsic and extrinsic coagulation pathways. Factor Xa inhibitors demonstrate a dual mechanism of action by inhibiting free factor Xa and the factor Xa produced by prothrombinase, leading to an overall reduction of thrombin [1].

Rivaroxaban and Apixaban reversibly inhibit factor Xa bound within the prothrombinase complex as well as the free enzyme, while Edoxaban inactivates only the clot-bound factor Xa [1, 6].

What are DOACs used for?

DOACs are used for prevention and treatment of cardiovascular events, embolism and deep venous thrombosis. Specific indications are listed below in Table **1** [1, 8-13]. Knowledge regarding DOACs indications might be useful when taking patients medical history, in order to identify medical conditions not reported by the patients.

Edoxaban is safe and effective in patients with creatinine clearance of < 95 ml/min and for this reason, relative to warfarin therapy, edoxaban use requires increased monitoring of renal function, weight and interactions with P-glycoprotein inducers and inhibitors [1].

Table 1: Indications for DOACs

		Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Prevention	stroke and systemic embolism in patients with NVAF	Yes	Yes	Yes	Yes
	recurrence of DVT and PE in patients who have been previously treated	Yes		Yes	
	DVT and PE in patients who have undergone hip/knee replacement surgery	Yes	Yes	Yes	
	recurrence DVT and/or PE in patients at continued risk for recurrent DVT and/or PE after completion of initial treatment lasting at least 6 months		Yes		
	major cardiovascular events (CV death, MI and stroke) in patients with chronic CAD or PAD		Yes (in combination with aspirin)		
Treatment	DVT and PE in patients who have been treated with a parenteral anticoagulant for 5-10 days	Yes	Yes	Yes	

CAD: coronary artery disease; CV: cardiovascular; DVT: deep venous thrombosis; MI: myocardial infarction; NVAF: nonvalvular atrial fibrillation; PAD: peripheral artery disease; PE: pulmonary embolism.

Half-Life, Daily Administration and Posology

In order to safely perform oral surgery procedures the knowledge of DOACS half-life and dosage is crucially important. In cases where the bleeding risk associated with the operation is not high, in order to decrease the post-operative bleeding it is necessary to carry out the operation at the latest from the last drug intake.

Pharmacological properties of the DOACs are listed below in Table **2** [5, 6, 8, 14, 15].

The mean plasma terminal half-life of dabigatran is comprised between 12 and 14 h, independently of dose. As a result, therapeutic concentrations are maintained for 24-hour periods [7].

In the management of VTE, after parenteral anticoagulation, edoxaban 60 mg once daily can be administered. Patients with body weight of ≤60 kg or who are on concomitant therapy with a P-gp inhibitor or a CLcr of <15 mL/ min is safe to reduce the dosage to 30 mg [1].

Which tests are used for measuring anticoagulation?

Although DOACs influence on the most common coagulation tests (aPTT, PT, INR) vary markedly, they are less relevant due to the high variable response linked both to instrumental conditions and to physiological conditions.

Therefore they are considered less useful for evaluating the patient's coagulation. On the contrary, more precise laboratory tests, such as thrombin clotting time (TT) ecarin clotting time (ECT), dilute prothrombin time, FXa inhibition assay are not commonly performed. Therefore, in case of procedures with low risk of bleeding, the coagulation status in patients using DOAC can be indirectly estimated knowing the drug pharmacological parameters and the patient's health conditions.

TT and ECT were the most sensitive clotting assays in patients taking dabigatran, followed by aPTT and the PT (expressed as the international normalized ratio [INR]) [5, 7]. While measurement of aPTT may provide a qualitative indication of dabigatran anticoagulant activity, like other DTIs, [16] it is not suitable for the precise quantification of anticoagulant effect especially at high plasma concentrations of dabigatran [17]. Dabigatran has little effect on the PT at clinically relevant plasma concentrations [1]. Both the ECT and the TT, which are particularly sensitive to the effects of DTI, display a linear dose-response with therapeutic concentrations of dabigatran.

Table 2: Summary of the Pharmacokinetic Profile of NAO After Oral Administration

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Prodrug	Yes	No	No	No
Target	Thrombin	Factor Xa	Factor Xa	Factor Xa
Absolute bioavailability	3-7%	80%-100%	>50%	61.8%
Time to maximum plasma concentration	1.5-4 h	2.5-4 h	2 h	1-3 h
Half-life, healthy young and elderly volunteers	12-18 hours	5-13 h	9-14 h	8-10 hours
Daily administration	1 or 2	1 QD	2	60 mg QD
Biliary excretion	~20%			62%
Renal clearance	80-85%	66%	25%	35-50%
Plasma protein binding	35%	90%	87%	40-59%
Test	ECT, TT, INR*, aPTT*	PT*, aPTT*, FXa inhibition assay	FXa inhibition assay, dilute prothrombin time, INR*, aPTT*	aPTT*, PT*, INR*, anti-factor Xa activity

* these are considered second line diagnostic test because they are not directly proportional to the degree of anti-coagulation.

Rivaroxaban prolongs PT and aPTT, with the PT being more sensitive than the aPTT depending on the reagents used for testing. However, the effect of the drug on these tests is short-lived, with prolongation only seen at peak drug levels. Factor Xa inhibition is the best test to monitor drug concentrations in plasma [6, 15].

Apixaban prolongs the INR and the aPTT in a concentration-dependent fashion. However, its effect on these tests is minimal at therapeutic concentrations. It can be monitored using a factor Xa inhibition assay or a dilute prothrombin time [6].

Edoxaban has dose-dependent effects on aPTT, PT and INR values and anti-factor Xa activity. INR returns to baseline levels within 12 hours; prolonged increases in aPTT and PT values occur, but those values return to baseline levels within 24 hours after edoxaban dosing. Anti–factor Xa activity also increases in a dose-dependent manner with edoxaban use. Bleeding time is independent of dosing, formulation, or diet factors [1].

Drug Interactions

DOACs may have stimulating or inhibitory effect on P- Glycoprotein and CYP3A4 (Table **3**) [1, 6, 8, 17, 18]. As a result, medications metabolized by these enzymes may affect the coagulation status of the patient. Strong P-Glycoprotein inducers which can be used in dentistry include rifampin, dexamethasone. Strong P-gp inhibitor include ketoconazole; moderate P-gp inhibitor include clarithromycin, itraconazole. Strong inhibitors of both CYP3A4 and P-gp include Clarithromycin, Erythromycin and systemic azole-antimycotics, such as ketoconazole, itraconazole, voriconazole, and posaconazole. Clinical effect of clarithromycin and erythromycin is not considered to be clinically relevant [19, 20].

Because non–COX-selective NSAIDs (and salicylates) inhibit platelet aggregation and may cause gastrointestinal bleeding and peptic ulceration and/or perforation, it may be prudent to increase monitoring of the patient for signs and symptoms of bleeding if these drugs are used concomitantly, especially in the context of oral surgery procedures. Moreover, clinical trials have shown increased bleeding with concomitant use of DOACs and NSAIDs, as well as rivaroxaban and opioid [21, 22].

Elimination pathway

All of the DOACs are cleared by the kidneys to a different degree (Table **2**). Renal function alterations can cause drug accumulation and consequently affect coagulation. Renal excretion of unchanged dabigatran is the predominant elimination pathway, with about 80% of an intravenous dose excreted unchanged in the urine. The remainder is conjugated with glucuronic acid to form acylglucuronides, which are predominantly excreted via the bile with only very small amounts of conjugates found in urine. These conjugates are pharmacologically active [1]. Approximately 66% of the rivaroxaban dose is excreted via the kidneys, and the remainder is excreted in the feces [6].

Approximately one-third of apixaban and edoxaban are excreted by the kidneys, whereas the remainder appears in the feces [1, 6].

Renal Function

When planning dental procedures in patients treated with DOACs, the evaluation of renal function is very important. A good renal function demonstrates an acceptable anti-coagulation state. On the other hand it allows to achieve the coagulation recovery by discontinuing the medication if hemorrhagic events occur. In Table **4** the dabigatran half-life trend is shown as a function of creatinine clearance [8]. In the case of patients with impaired renal function, the opinion of the attending physician should always be sought.

Hepatic Impairment

The pharmacokinetic profile of dabigatran is not substantially affected by moderate hepatic impairment (Child-Pugh B) [14].

Table 3: Potential Interactions of Oral Anticoagulants with Drugs used or Prescribed in Dentistry

Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Proton pump inhibitors; P-Glycoprotein inducers and inhibitors; NSAIDs and salicylates	Potent CYP3A4 and P-Glycoprotein inhibitors; NSAIDs and salicylates;	Potent CYP3A4 and P-Glycoprotein inhibitors	P- Glycoprotein inhibitors

Table 4: Dabigatran Half-Life as a Function of Creatinine Clearance

Renal Function (CrCl, mL/min)	Dabigatran Half-Life (h)
>80	13 h
>50 to ≤80	15 h
>30 to ≤50	18 h
≤30	27 h

Rivaroxaban is metabolized in the liver via CYP 3A4, CYP 2J2, and CYP-independent mechanisms. The drug is contraindicated in patients with severe liver disease because metabolic inactivation may be impaired [6].

Elderly Patients

In patients over the age of 65 a decreased kidney function is assumed, therefore they are considered at risk. Therefore, the creatinine clearance evaluation in elderly patients is recommended in order to exclude reduce excretory capacity.

In healthy volunteers, dabigatran exposure is 40% to 60% higher in older than in younger participants, reflecting age-related reduction in creatinine clearance (CLCR) [2, 17].

During a clinical trial, no major bleedings were shown in patients over the age of 65, who underwent dental extraction up to 3 teeth and with good renal function [2].

Continuing or Discontinuing the Treatment?

Discontinuation or continuation of DOACs treatment depends on many factors, such as cardiovascular or venous events as a result of discontinuation, renal function and bleeding risk associated with surgery.

In patients undergoing low-bleeding risk procedures (up to a maximum of 3 dental extractions or 2 or 3 dental implants in the anterior region), with a proper renal function, it seems safe enough not to discontinue the DOACs treatment if the adequate hemostatic agents are used.

In patients treated with the new oral anticoagulants, who require interventions at low risk of bleeding (*e.g*. extraction up to 3 dental elements), where a good local hemostasis can be reached, experts suggest not to interrupt therapy with DOACs.

However, a recent study has found that even when three contiguous teeth are extracted, bleeding may occur when these are multirooted teeth [23].

In the case of complex oral surgery (extraction >4 dental elements) suspension of the DOACs has to take into consideration.

However, it remains essential to communicate with the medical specialist in order to ensure safe and appropriate dental treatment [2].

It does not appear that it would be necessary to discontinue the use of dabigatran or rivaroxaban before dental treatment likely, including most uncomplicated tooth extractions, in most patients, especially if adjunctive local hemostatic measures (*e.g*., absorbable gelatin or oxidized cellulose sponges, sutures, local pressure [with sterile gauze pads moistened with water, normal saline solution, or 5% tranexamic acid solution], etc.) are used appropriately when indicated.

However, in situations where oral/maxillofacial surgical procedures may require the temporary discontinuation of dabigatran or rivaroxaban owing to concerns for possible complications resulting from excessive bleeding and/or impaired hemostasis, dabigatran or rivaroxaban should be discontinued at least 24 hours before elective surgery, or longer, depending on the risk of bleeding based on the type and complexity of the surgical procedure, the presence and degree of any renal impairment, and the presence of other risks for impaired hemostasis [8].

Gomez-Moreno *et al*. did not observe an increased bleeding risk in dabigatran-treated patients who underwent up to two dental implants placement in the posterior region and three dental implants in the anterior region. In their clinical trial, patients (age < 75 years) showed no renal function alterations and the flap design was without the releasing incision. According to their study protocol the procedure was carried out 12 hours after the last administration of dabigatran and the following dosage was postponed by 8 hours after the surgery. The next day the medication was taken regularly. Following surgery, local hemostatic measures were taken consisting of non-absorbable sutures and compression with sterile gauzes soaked in 5% tranexamic acid [24].

Gomez-Moreno *et al*. did not observe an increased bleeding risk in patients treated with rivaroxaban without modification of the anticoagulant therapy who

underwent up to two dental implants placement in the posterior region and three dental implants in the anterior region. In their clinical trial patients (age < 75 years) showed no renal function alterations and the flap design was without the releasing incision. However, the time window between the last administration of the medication and the surgery is not specified in this study [25].

According to a clinical trial on 12 patients subjected to tooth extractions treated with DOACs, no post-surgery bleedings were observed. In this study the medication was not discontinued, the patients did not suffer from renal failure and the surgery was carried out at the latest instant from the last administration of the medication. In addition, hemostatic agents were used and the medication was reintroduced the day after the surgery [2].

According to the study carried out by Hanken *et al*., continued mono or dual anticoagulation therapy with rivaroxaban (and aspirin), increases postoperative bleeding risk for oral surgical procedures, although the bleeding complications are manageable. Although anticoagulation therapy in general increases the postoperative bleeding risk, according to their results, and considering that discontinuation of anticoagulation therapy may result fatal (thromboembolic events), continuing anticoagulation therapy, including with rivaroxaban, during oral surgical procedures may be recommended; furthermore, it is advisable to monitor the patient closely for up to 1 week with a 24-h hotline available as well as a preoperative consultation with the primary physician or the cardiologist.

Moreover, the discontinuation of anticoagulation therapy with substitution of low-molecular-weight or unfractionated heparin as a bridging regimen also increases the incidence of myocardial infarction, stroke and systemic embolism, hospitalization, and/or death within 30 days. Furthermore, heparin bridging increases the bleeding incidence to 5 % [10].

In the case of complex oral surgery (extraction >4 dental elements) suspension of the DOACS has to take into consideration: the risk of bleeding, renal function, the anticoagulant used (Table **5**).

Reintroduction of the Discontinued Medication

If discontinued, administration of DOACs should not be restarted after oral/maxillofacial surgical procedures until the risk of postoperative bleeding is minimal (*i.e*., after a stable fibrin clot is formed). Because the onset of the anticoagulant effect of these drugs is rapid (compared with warfarin).

A postoperative discontinuation from a minimum of 8 to a maximum of 48 hours has been adopted depending on the type of surgery [8]. According to a clinical study on patients undergoing dental implants placement, dabigatran was administered 8 hours after the surgery after being discontinued 24 hours before the surgery [24]. In a clinical study on 12 patients undergoing up to 3 dental extractions, the medication was reintroduced the day after the surgery [1].

Peri-Operative Diet

Although food consumption during the postoperative period may delay the plasma concentration peak of the

Table 5: Interruption of DOAC Therapy before Surgery

	Dabigatran		Rivaroxaban		Apixaban	
Renal function (ClCr ml/min)	Low risk	High risk	Low risk	High risk	Low risk	High risk
≥80	24 h	48 h	24 h	48 h	24 h	48 h
50-79	36 h	72 h	24 h	48 h	24 h	48 h
30-49	48 h	72 h	24 h	48 h	24 h	48 h
15-29	Not indicated	Not indicated	36 h	48 h	36 h	48 h
<15						
Adapted from [2]						

medication, it does not seem to have clinical relevance. On the contrary, the fluid intake reduction could lead to drug accumulation.

Food prolongs the time to peak plasma dabigatran levels by approximately 2 hours without influencing the maximum concentration or the plasmatic concentration over time AUC [5].

Food intake had a negligible impact on edoxaban pharmacokinetics and pharmacodynamics. Edoxaban's daily dosing schedule and the flexibility of taking the drug with or without food offer greater ease of compliance, which might allow patients to use this medication without the restrictions associated with other DOACs [2]. During postoperative period the patient may influence the dabigatran elimination pathway by changing the fluids intake [7].

Surgical Planning

Although a correct surgical planning is necessary in all patients, [26] who assumes DOACs needs an even more scrupulous planning.

In patients treated with DOACs the bleeding may start up to the 6th day after surgery. In addition, bleeding episodes are much more frequent in patients treated with DOAC if compared to healthy patients [10].

In order to achieve a proper post-operative hemostasis, in accordance with the drug administration schedule, the surgery should be carried out early in the morning. In addition, in order to guarantee an adequate patient support in the recovery period, the surgery should be carried out at the beginning of the week.

In a recent study, dental extraction were performed at least 4 hours after the last DOAC intake.

Out of a total of 100 treated patients, were observed 3 minor bleedings, managed by the patient by applying a dressing saturated with TA on the post-alveolar socket for 20 minutes, and 1 moderate bleeding, treated with necrotic clot removal and placement of a new suture. All the bleeding appeared in multi-rooted extraction [23].

In case of intervention at low risk of bleeding (*e.g.* extraction up to 3 dental elements) experts EHRA (European Heart Rhythm Association) suggest not to interrupt therapy with new oral anticoagulants, using, for the operation, the minimum time step of the drug:

- 12 h after the last dose of dabigatran,

- 12 h after the last dose of apixaban,

- 24 h after the last dose of rivaroxaban [2].

In case of extraction of contiguous multi-rooted teeth or extraction of more than 3 teeth, dentists can split surgery in more than one session [23].

Since it is possible to postpone these surgical procedures in most cases, it is advisable to seek the advice of the attending physician since it is not always possible to obtain a complete medical history from the patient.

Improvement of Coagulation

Postoperative bleeding complications after oral surgery occurs significantly more often in patients under continued rivaroxaban therapy (11.5 %) than in the control cases without anticoagulation/antiplatelet medication (0.7 %) [10].

In order to promote adequate hemostasis, the following precautions have been implemented in the previous studies: accurate suturing technique, irrigation of the alveoli by antifibrinolitic agents such us tranexamic acid together with gelatin sponges, collagen and resorbable oxycellulose applied into the extraction socket to achieve local hemostasis, acrylic splint for wound protection, local compression, application of fibrin glue and secondary sutures, accurate alveolar bone cleaning to remove bleeding granulation tissue, post-operative wound compression with gauze soaked in tranexamic acid, ice bag and mouth rinses with a 10 ml of 5% tranexamic acid aqueous solution for 2 minutes, repeated 4 times daily for 7 days [10].

Supportive strategies to control severe bleeding include delayed administration of the next dose of dabigatran or discontinuation, maintenance of adequate diuresis, mechanical compression, surgical hemostasis, and transfusion of blood products (packed red cells or fresh frozen plasma). The half-life of dabigatran is only 12 to 14 hours so, given adequate renal function, within 12 hours of a dose of dabigatran etexilate (150 mg) at steady state, plasma concentrations are approximately 60 ng/mL (corresponding to an aPTT about 1.5 times baseline) [17, 27]. In addition, because of the low plasma protein binding, dabigatran is dialysable.

CONCLUSIONS

The planning of a surgical intervention in a patient taking DOACs requires knowledge of the pharmacological aspects of the drug and the collection of a scrupulous medical history. These drugs carry a significant burden of adverse and serious effects, and the oral surgeon's role is to offer patients adequate and safe treatment, promoting health and improvements in their quality of life. In interventions at low bleeding risk, if the patient's state of health allows it, it is considered correct to maintain the patient's anticoagulative status. In higher risk cases it may be necessary to replace oral anticoagulant therapy with parenteral therapy. Collaboration with the attending physician is crucial in order to avoid iatrogenic complication.

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