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Bibliographic review

New oral anticoagulants: implications in odontology

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ABSTRACT

The number of patients with cardiovascular problems who come in for dental consultation has increased in the recent years. The most prevalent cardiovascular pathologies are: hypertension, ischemic heart disease and arrhythmias, with atrial fibrillation (AF) being the most common. One of the fundamental pillars of care for patients with AF is prevention of thromboembolic stroke because of its severity and the potential for prevention with the use of anticoagulant drugs.

Vitamin-K antagonists have been the most widely used anticoagulants over the past 50 years. However, the advent of new oral anticoagulants (NOACs), supported by clinical trials in more than 50,000 patients, has led to a revolution in cardiovascular therapy that is changing the recommendations of international clinical practice guidelines for the treatment of AF. As a result, anticoagulant treatment with NOACs is a therapeutic challenge for dentists and we should be familiar with its treatment protocol, since despite being safer drugs, they can complicate an hemorrhagic event, for there is no antidote (except in the case of Dabigatran).

The purpose of this review is to provide an update on the new oral anticoagulants and their implications on dental treatment.

Dabigatran, Rivaroxaban and Apixaban are reviewed, along with their pharmacological properties, indications and contraindications, as well as the protocol to be followed in the event of an intervention that results in bleeding in the oral cavity

KEYWORDS

New oral anticoagulants; Thrombotic risk; Hemorrhagic risk; Oral surgery; Dabigatran; Rivaroxaban; Apixaban.

ABBREVIATIONS

OAC: oral anticoagulant; NOAC: new oral anticoagulant; VKA: vitamin K antagonist; LMWH: low molecular weight heparin; HBP: high blood pressure; INR: international normalized ratio; AF: atrial fibrillation; VTE: venous thromboembolism; TIA: transient ischemic attack; PE: pulmonary embolism; AMI: acute myocardial infarction; CHF: congestive heart failure; DVT: deep vein thrombosis; P-gp: P-glycoprotein; PT: prothrombin time; aPTT: activated partial thromboplastin time; DTT: diluted thrombin time; TT: thrombin time; ECT: ecarin clotting time; FFP: fresh frozen plasma; PCC: prothrombin complex concentrate.

INTRODUCTION

The number of patients with cardiovascular problems who come in for dental consultation has increased in recent years. Because they have a good quality of life, they are candidates for any type of dental treatment including surgery. The majority of these patients have suffered from angina, infarctions or strokes, or they have chronic diseases such as high blood pressure (HBP) or atrial fibrillation (AF) and they take antihypertensive, anti-platelet or anticoagulant (OAC) medications on a daily basis.

Acenocoumarol (Sintrom®) is a drug that belongs to the vitamin K antagonists (AVK) group and has been used for more than 50 years to prevent brain embolism in patients with atrial fibrillation. However, it has a delayed onset of action and a narrow therapeutic range given that low dosages do not prevent thrombosis and large dosages may lead to hemorrhage. Therefore, strict monthly monitoring is required to adjust the dosage. In addition, there are many interactions: dietary (green vegetables...), pharmacological (antibiotic, anti-fungal) and even viral diseases (cold, flu...). More than 700,000 people take Sintrom® in Spain and the majority are over 70 years of age. This results in high costs for the healthcare system, not because of acenocoumarol itself, which is cheap, but because of the necessary monthly monitoring.

New oral anticoagulants (NOACs) have been developed in the recent years and they are progressively replacing Sintrom® because they do not have variations, have few interactions and do not require laboratory monitoring. Their efficacy is backed by clinical trials carried out with the collaboration of more than 50,000 individuals. As new clinical trials are published, the indications for these new drugs increase, given that they are as effective as acenocoumarol for the prevention of thrombosis but they are safer when considering the risk of bleeding, which is the primary problem with anticoagulant drugs. The incidence of hemorrhage, especially intracranial hemorrhage, is indicative of the drug's safety, which is lower in NOACs.[1]

ATRIAL FIBRILLATION (AF)

Atrial fibrillation is the most common arrhythmia. More than a million individuals (1-2%) have AF in Spain with an estimated prevalence of 8% of the Spanish population over 60 years of age. An important consequence of AF is that it results in a fivefold increase in the risk of stroke, meaning 1 out of every 5 strokes is due to this arrhythmia.[1] In addition, stroke caused by AF is thromboembolic and more severe than an ischemic stroke. It can have fatal consequences in both sexes, from minor to severe disability or even death. In addition, half of strokes are usually recurrent, meaning that a previous stroke predisposes to a subsequent event. In other words, it is a risk factor. To address this, many Spanish hospitals have what is called a "stroke code", which consists of activating an emergency specialized treatment protocol within the first minutes in order to prevent the fatal consequences derived from a stroke.

However, the risk of stroke is no longer unpredictable. Currently, there are tools to predict the risk of stroke in patients with AF.[1] Since 2001, the CHADS2 risk stratification criteria (Table 1) has served to

Table 1. Stratification of stroke risk ($CHADS_2$ scale)

$CHADS_2$	Criteria	Points
C (Congestive heart failure)	Recent history of CHF	1
H (Hypertension)	HBP	1
A (Age)	Age > 75 years	1
D (Diabetes)	History of diabetes mellitus	1
S_2 (Stroke)	History of stroke/TIA (double points)	2
Maximum score		6

0: Low Risk No treatment or treatment with anti-platelet agents
1. Medium risk. Treatment with anti-platelet agents or oral anticoagulants
≥2: High risk. Treatment with oral anticoagulants

grossly classify the entire population. The risk factors on this scoring scale are the following: congestive heart failure (CHF), High Blood Pressure (HBP), age over 75 years, diabetes mellitus, and history of stroke or transient ischemic attach (TIA). On this scale, 0 is low risk, 1 is moderate risk and more than 1 is high risk. Low risk may or may not be treated with anti-platelet medications, moderate risk requires anti-platelet or anticoagulant treatment and high risk always requires oral anticoagulant treatment.[1] The CHADS2 criteria have been recently modified in order to discriminate between low and moderate risk populations (CHADS2 0 or 1). New criteria were presented in 2010 named CHA2DS2-VASc (Table 2) which added three additional factors: female sex, age 65 to 74 years and vascular events [Acute Myocardial Infarction (AMI) or peripheral arterial disease] each scoring 1 point. Age over 74 is 2 points with a maximum score of 9. On this scale, 0 is low risk, 1 is intermediate risk and ≥ 2 is high risk. Anticoagulant treatment is used when the risk is ≥ 1.[1]

Table 2. Stratification of stroke risk (CHA_2DS_2-VAS_c scale)

CHA_2DS_2-VASc	Criteria	Points
C (Congestive heart failure)	CHF	1
H (Hypertension)	Hypertension	1
A_2 (Age)	Age ≥ 75 years	2
D (Diabetes)	Diabetes mellitus	1
S_2 (Stroke)	History of stroke/TIA (double points)	2
V (Vascular disease)	Vascular disease (AMI or peripheral)	1
A (Age)	Age 41-60 years	1
Sc (Sex category)	Female sex	1
Maximum score		9

0: Low Risk No treatment or treatment with anti-platelet agents
1. Medium risk. Treatment with anti-platelet agents or oral anticoagulants
≥2: High risk. Treatment with oral anticoagulants

Another important criteria to keep in mind is the risk of bleeding in patients with AF who are on anticoagulants, which is measured using the HAS-BLED scale (Table 3). Risk factors for bleeding include uncontrolled HBP, altered renal and/or liver function, history of stroke, history of bleeding, labile INR, age greater than or equal to 65 years and use of medications or alcohol. On this scale, 0 is considered low risk, 1-2 is medium risk and ≥ 3 is high risk. A score ≥ 3 indicates a high risk of bleeding, meaning the patient must be closely monitored under any treatment (antithrombotic or anticoagulant).[1]

NOACs

The new oral anticoagulants have become substitutes for vitamin K antagonists because they have a greater therapeutic index, have few interactions and do not require monthly monitoring for dosage adjustment, as they are administered at fixed dosages. The mechanism of action for NOACs is different than that of acenocoumarol (Sintrom®) or warfarin (Aldocumar®), which are anti-vitamin K drugs (AVK) that inhibit the synthesis of coagulation factors II, VII, IX and X in the liver. NOACs are direct thrombin inhibitors (Dabigatran) or factor Xa inhibitors (Rivaroxaban and Apixaban).[2-4] Several clinical trials have demonstrated their efficacy.

The Re-LY study[5], a randomized multicentric study carried out with 18,000 participants with non-valvular AF, compared dabigatran (110 mg q12 h and 150 mg q12h) versus warfarin (dosage adjusted for an INR between 2 and 3) for 2 years. The occurrence of thromboembolic stroke was recorded as the efficacy endpoint variable and the occurrence of severe hemorrhage was the safety endpoint variable. The study concluded that dabigatran 150 mg was associated with a lower rate of stroke than warfarin. Severe hemorrhages were significantly lower with dabigatran 110 mg. However, the percentage of treatment abandonment was greater with dabigatran due to dyspepsia.

Table 3. Bleeding risk stratification table HAS-BLED scale

Risk factor	Description	Score
H ("Hypertension")	Uncontrolled hypertension (systolic blood pressure ≥ 160 mmHg)	1
A ("Abnormal kidney and/or liver function")	Renal or hepatic insufficiency	1 per pathology (1 or 2)
S ("Stroke")	Previous history of stroke	1
B ("Bleeding")	History of bleeding, anemia or predisposition towards bleeding	1
L ("Labile INR")	Unstable/high INR (less than 60% of the therapeutic range)	1
E ("Elderly")	Age ≥ 65 years	1
D ("Drugs and/or alcohol")	Medications that affect hemostasis (e.g.: Acetylsalicylic Acid (ASA), clopidogrel) and/or intake of ≥ 8 alcoholic drinks per week	1 for each (1 or 2)
Maximum score		9

0: Low risk
1-2: Medium risk
3: High risk.
A score ≥ 3 indicates a high risk of bleeding, meaning the patient must be closely monitored with any treatment (anti-platelet or anticoagulant)

The ROCKET AF study[6], carried out with more than 14,000 patients with non-valvular AF, studied rivaroxaban (20 mg daily) versus warfarin. The study concluded that rivaroxaban was not inferior to warfarin in the prevention of stroke or embolism, and the risk of bleeding was not different.

The ARISTOTLE study[7], carried out with the collaboration of more than 18,000 patients with non-valvular AF, compared apixaban (5 mg q12h) versus warfarin (at a dosage to keep INR between 2 and 3). The results revealed that apixaban was superior to warfarin in the prevention of thromboembolic stroke, caused less bleeding and annual mortality was lower.

Based on these evidences, NOACs are gradually replacing Sintrom®.

According to the Spanish Agency for Medications and Health Products, the current indications for NOACs are:

- Primary prevention of Venous Thromboembolic Events (VTE) in adult patients undergoing total hip or knee replacement surgery.
- Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation, with one or more risk factors.
- Treatment of deep vein thrombosis and pulmonary embolism (except dabigatran).

In general, the contraindications for NOACs[1] are:

- Patients with prosthetic heart valves (in whom the use of AVKs is better).
- Patients with AF who also have a stent (treated with acenocoumarol and double anti-platelet therapy with acetylsalicylic acid-Adiro® and clopidogrel-Plavix®).
- Patients with severe renal insufficiency (with a creatinine clearance <15 ml/min).
- Patients with severe liver disease (associated with coagulopathies).
- Pregnancy and lactation.
- Patients with high bleeding-risk diseases (gastrointestinal ulcers, aneurysms, neoplasms, etc.).

Dabigatran (Pradaxa®) is a direct thrombin inhibitor (factor IIa). It is ingested as a prodrug (dabigatran etexilate), which is transformed by plasma and liver esterases into dabigatran. It is a competitive and reversible thrombin inhibitor that blocks the conversion of fibrinogen to fibrin, thereby inhibiting clot formation. It has been shown to inhibit free thrombin, thrombin bound to fibrin and thrombin-induced platelet aggregation.[3] It is absorbed orally, though its bioavailability is around 5-6%. Its onset of action takes 1-1.5 hours and its half-life is 12-18 hours (Table 4).[4] Eighty percent is excreted unchanged in urine, so patients with very severe renal insufficiency, with a creatinine clearance less than 15 ml/min, it should not be used.[8] It is not metabolized in the liver nor is it a cytochrome P450 substrate. it is a P glycoprotein (P-gp) substrate, so P-gp inhibitors such as amiodarone may increase its effect. Only 30% binds to plasma proteins, so in the event of overdose or hemorrhage, hemodialysis may help remove it as it has a 70% free fraction.[3,9].

Prothrombin time (PT) and INR are not valid for evaluating the risk of hemorrhage. Activated partial thromboplastin time (aPTT) provides a qualitative but not a quantitative measure, although it may be useful to determine excess anticoagulant activity. An aPTT greater than 80 seconds is associated with an increased risk of bleeding. An aPTT less than 30 seconds indicates an absence of anticoagulant activity. Du et al.[10] carried out a study to compare the efficacy of different methods for measuring plasma concentrations of dabigatran and concluded that the most specific tests are the Hemoclot and ecarin time (ET) tests. Hemoclot is a variant of the diluted thrombin time (dTT) that is specifically calibrated for dabigatran. This test identifies patients with higher risk of hemorrhage in a more precise, sensitive and specific way. If the time is greater than 60 seconds, it is associated with an increased risk of bleeding. It is not routinely performed, but rather only in case of severe bleeding or emergency surgery. Ecarin time (ET) transforms prothrombin into meizothrombin, a labile thrombin precursor. Both compounds are inhibited by dabigatran, resulting in prolonged coagulation time. There is a linear correlation between prolonged ET and dabigatran concentrations. It is not influenced by heparin, which is probably the most accurate test, but it is costly and not available in many laboratories.[10]

In July 2015, an antidote for dabigatran named Idarucizumab was developed.[11] It is the only NOAC with an antidote. The rest are being tested in phase II clinical trials.[11]

We should also be aware of drug interactions. P-gp inhibitors (amiodarone, verapamil, quinidine, ketoconazole, dronedarone, clarithromycin) increase plasma dabigatran concentration, P-gp inducers (rifampicin, carbamazepine or phenytoin) lower it. Other drugs that affect P-gp (ritonavir, protease inhibitors) and other anticoagulants or anti-platelet agents (acenocoumarol, heparin, ASA, clopidogrel) also interfere.[5,12]

The most common side effect of dabigatran is dyspepsia.

Rivaroxaban (Xarelto®) is a direct and reversible factor Xa inhibitor that interrupts the intrinsic and extrinsic coagulation pathways. Its onset of action ranges between 30 and 180 minutes and its half-life is 7 to 9 hours (11 in the elderly).[3] Ninety-five percent binds to protein so hemodialysis does not contribute to its elimination (Table 4). Fifty percent of the drug is metabolized in the liver via cytochrome P450 and the remainder is eliminated unchanged by urine, so in patients with severe renal insufficiency, and a creatinine clearance less than 15 ml/min, should not be used. It has been available in Spain since 2012.

The usual dosage is 20 mg daily in a single dose, taken with food to avoid dyspepsia, 10 mg daily in the prevention of venous thromboembolism in knee and hip replacement surgery.[14]

INR is not useful for measuring the anticoagulant activity of rivaroxaban. However, prothrombin time (PT) and activated partial thromboplastin time (aPTT) can be used. Specific calibration curves are re-

Table 4. Characteristics of NOAC$_S$

	Dabigatran	Rivaroxaban	Apixaban
Brand name	Pradaxa®	Xarelto®	Eliquis®
Peak plasma concentration (hours)	1-1.5	2-4	3-4
Time to reach maximum concentration (hours)	2	3	3
Plasma half life (hours)	12-18	7- 9 (11 in the elderly)	8-15
Protein binding	30-35%	90-95%	87-90%
Excretion	Renal (80%)	Renal (66%)	Renal (25-30%)
Bioavailability	6%	80%	60%
Elimination by dialysis	Yes	No	No
CYP metabolism	No	30% CYP3A4, CYP2J2	15%CYP3A4
GP-P transport	Yes	Yes	Yes
Inhibited coagulation factors	IIa (inhibits free thrombin, thrombin bound to fibrin and thrombin-induced platelet aggregation)	Xa	Xa
Dosage	110 mg/ 12h or 150 mg/ 12h	20 mg/ daily	2.5 mg/ 12h
Indications	· Prevention of VTE in adult patients undergoing hip or knee replacement surgery. · Prevention of stroke and systemic embolism in adult patients with non-valvular AF	· Prevention of VTE in adult patients undergoing hip or knee replacement surgery. · Prevention of stroke and systemic embolism in adult patients with non-valvular AF · Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) and prevention of recurrences.	· Prevention of VTE in adult patients undergoing hip or knee replacement surgery. · Prevention of stroke and systemic embolism in adult patients with non-valvular AF · Treatment of deep vein thrombosis and pulmonary embolism and prevention of recurrences.
Drug interactions	· Contraindicated Dronedarone, ketoconazole, itraconazole, cyclosporine, tacrolimus. · Caution with: rifampicin, phenytoin, carbamazepine and St. John's Wort.	· Contraindicated: azole antifungals, HIV protease inhibitors. · Caution with: rifampicin, phenobarbital, phenytoin, carbamazepine and St. John's Wort.	· Contraindicated: azole antifungals, HIV protease inhibitors. · Caution with: rifampicin, phenobarbital, phenytoin, carbamazepine and St. John's Wort.

quired. ET and thrombin time (TT) are not useful because thrombin is not affected. A new test called the Heptest, which measures anti-Xa activity, is available. It is an adequate but costly method. Chromogenic methods for measuring anti-Xa activity may be useful in emergency surgery situations.[15]

Its drug interactions are: drugs that interact with cytochrome P450 (azole antifungals such as Ketoconazole and HIV protease inhibitors such as Ritonavir). Rivaroxaban also interacts with other anticoagulants and anti-platelet agents. Cytochrome P450 and P-gp inhibitors (azole antifungals, protease inhibitors) increase its blood concentration and cytochrome P450 inducers (Rifampin) reduce its concentration.[6]

The most common side effect of this drug is nausea and, in rare cases, arthralgia, edema, rash, pruritus, dizziness, generalized malaise or asthenia, all of which are mild. Episodes of bleeding of the mucosae and anemia are the most common adverse reactions. Episodes of bleeding correspond mostly to epistaxis, bleeding of the gums, gastrointestinal bleeding and genitourinary bleeding.[16]

Apixaban (Eliquis®) is a direct and reversible factor Xa inhibitor. Oral bioavailability is 66%, its effect takes between 30 and 120 minutes and its half life is 8 to 15 hours. It binds extensively to plasma proteins so it is not dialyzable. Thirty percent is metabolized in the liver via cytochrome P450 and 70% is eliminated via the fecal route with the remaining 30% eliminated renally[17], but it is also contraindicated in patients with severe renal insufficiency (Table 4).

The normal dosage is 2.5 mg q12h but it may be increased in some cases such as treatment for deep vein thrombosis and PE, in which the initial dosage is 20 mg daily for the first 7 days and then reduced to 10 mg.[7,14]

Its main drug interaction is with other medications that affect hemostasis such as anticoagulants, antiplatelet agents and NSAIDs. However, it also interacts with cytochrome P450 and P-gp inhibitors (azole antifungals and protease inhibitors), which increase plasma concentration of apixaban. Cytochrome P450 and P-gp inducers (phenytoin, carbamazepine, phenobarbital) reduce plasma concentrations.[17]

IMPLICATIONS ON DENTAL TREATMENT. TREATMENT PROTOCOLS

There has been a lot of controversy in recent years regarding patients who were taking acenocoumarol who need dental treatment that involves bleeding. Initially, Sintrom was discontinued and substituted by Low Weight Molecular Heparin (LWMH), keeping INR between 2-3 and performing surgery using only local hemostasis measures.

With the arrival of NOACs, dentists need to know how to avoid bleeding in these patients without provoking a thromboembolic accident. The management of patients who take NOACs requires the dentist to make decisions, so professionals must be familiar with the indications and contraindications of these anticoagulants in order to avoid bleeding (that is usually not significant) and the onset of a thromboembolic accident caused by discontinuing anticoagulant treatment (which has greater repercussions on the patient's quality of life).[18]

As there is no standardized method to evaluate the risk of bleeding in these patients nor an antagonist in the event of hemorrhage, except in the case of dabigatran, management of these patients can be a challenge for the dentist.

In cases of high thromboembolic risk, the dental treatment should be planned in consensus with the patient's cardiologist. Before carrying out any treatment in the dental clinic, a thorough medical history including underlying diseases, personal and family history, medications and allergies, etc. should be taken.

Three aspects should be considered when planning treatment in these patients[18]:

- Type of dental treatment and estimation of the amount of possible bleeding involved. In a healthy

patient, the risk of bleeding is only related to the complexity of treatment.

- Medical history (risk of bleeding versus risk of thromboembolism)
- Availability of local and systemic hemostatic measures[19]

In general, hospital physicians consider surgical interventions in the oral cavity to be of low risk. Examples of procedures that involve bleeding include extractions, radicular filing and polishing, biopsy sampling (especially in inflamed or vascular areas), periodontal graft, implant placement techniques or regenerative techniques. One should also take into account factors such as the number of teeth affected, the number of implants placed, soft tissue trauma, the level of invasion, severity of local inflammation, etc. All of these factors should be part of a general evaluation of the risk of hemorrhage.[20]

When the dental procedure carries a low risk of hemorrhage, the NOAC regimen does not have to be modified. Simple dental surgical acts are extractions of up to 3 teeth, radicular filing and polishing and surgery for placement of 3 or fewer implants. Complex surgical acts are those that involve more than 3 extractions or placement of more than 3 implants, bone and connective tissue grafts, nasal sinus and fossae elevations, as well as other bone regeneration techniques (split crest, bone distraction, Khoury, etc.). Prior to surgery, elimination of inflammation and irritation of oral cavity tissues is recommended in order to avoid a greater tendency towards bleeding (radicular filing and polishing, oral hygiene techniques, recommend antiseptic mouthwash on days prior to surgery, etc.). [21,22]

Evaluation of the medical history should focus on factors that increase the risk of hemorrhage (renal insufficiency, liver damage or use of drugs that increase bleeding such as anti-platelet agents and corticosteroids) or increase the risk of thromboembolism. Both factors can be measured using the HAS-BLED and CHA2DS2-VAS_c scales, respectively. If the patient has a high risk of suffering thromboembolism, anticoagulant therapy cannot be interrupted. In such cases, it may be necessary to postpone the procedure and reschedule it or carry out treatment without discontinuing the NOAC[21] (Table 5).

Table 5. Treatment protocol in oral surgery based on the risk of Thromboembolism (CHA_2-DS_2-VAS_c) and bleeding (HAS-BLED)

Hemorrhagic risk (HAS-BLED)

Thromboembolism risk (CHA_2-DS_2-VAS_c)	HIGH (≥3)		MEDIUM (1-2)		LOW (0)	
	Complex surgery	Simple surgery	Complex surgery	Simple surgery	Complex surgery	Simple surgery
HIGH (≥2)	Postpone surgery	Postpone surgery	Perform the surgery as late as possible after the last dose	Maintain NOAC	Maintain NOAC	Maintain NOAC
MEDIUM (1)	Discontinue 1 dose of NOAC	Discontinue 1 dose of NOAC	Discontinue 1 dose of NOAC	Postpone the daily dose or perform the surgery as late as possible after the last dose	Postpone the daily dose or perform the surgery as late as possible after the last dose	Maintain NOAC
LOW (0)	Discontinue 24-48h	Discontinue 24-48h	Discontinue 24-48h	Discontinue 1 dose of NOAC	Discontinue 1 dose of NOAC	Maintain NOAC

In summary, there are three options when confronting a patient who is taking NOACs who will undergo dental treatment[21] (Figure):

1- Treat the patient while continuing anticoagulant therapy.

2- Postpone the daily dose until the procedure is done or skip one dose (especially in those who require two daily doses). Another valid approach would be to perform the dental treatment as late as possible after the last NOAC dose.

3- Temporarily discontinue the NOAC, the day of surgery or the day before (24-48h).

The last two options reduce blood NOAC levels although not completely, so there still is a risk of bleeding. Despite the fact that discontinuing NOACs for a longer period (generally three days prior to the day of surgery) is recommended for hospital surgical procedures, it is believed that the majority of dental treatments can be carried out safely with a minimal interruption in NOAC treatment. In general, the tendency should be to change the regimen and dosage as little as possible and, in the opinion of many authors, this second option is the one that best meets this objective. However, decisions should be made on an individual basis according to each patient's characteristics.[21]

Special considerations in these patients should include the availability of local hemostatic measures (tranexamic acid, hemostatic sponges, oxidized cellulose, antifibrinolytic rinses, etc.) so that they can be applied when necessary. Chitosan (Hem-Con®) has also become available in recent years. It is a polysaccharide that produces local red blood cell aggregation without intervening in coagulation and is very useful for stopping hemorrhages in emergency situations. In addition, attempts should be made to make the procedures as atraumatic as possible. Good primary closure should be performed and we must keep the patient under observation for 45-60' postoperatively until adequate hemostasis is achieved. If the anticoagulant has been discontinued, you must ensure that no delayed bleeding occurs when restarting anticoagulant therapy. This usually occurs the first day after surgery.[17]

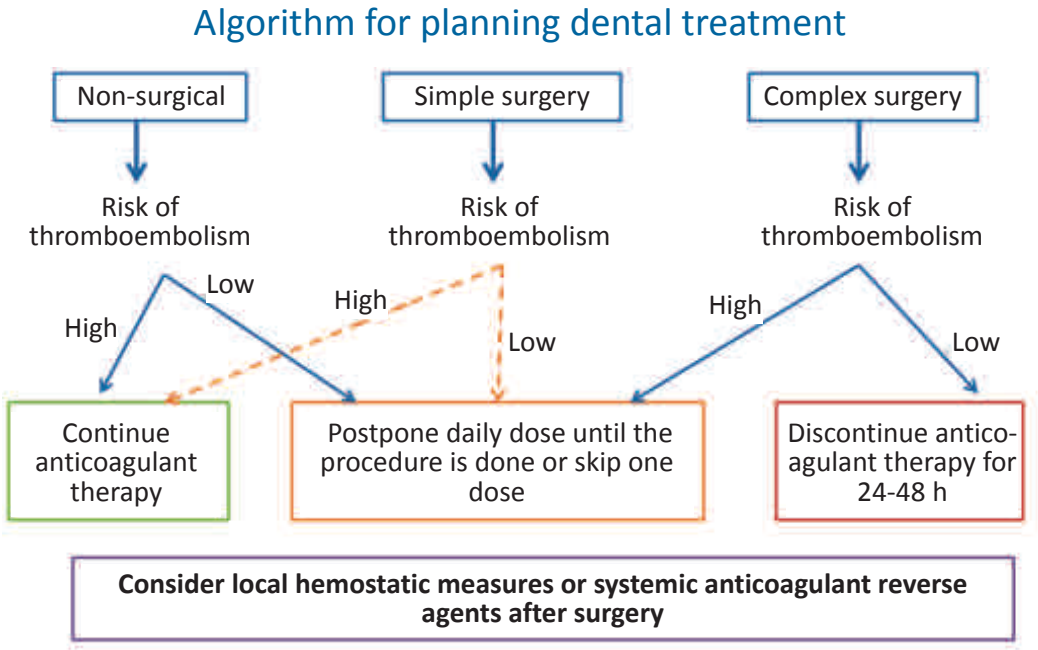

Figure. Algorithm for planning dental treatment. Modified from Elad et al, 2016[21]

The patient will be instructed to perform tranexamic acid rinses for 2 to 7 days and scheduled for a follow-up visit on the days after surgery in order to ensure adequate monitoring. Postoperative indications are of great importance in these patients, and clear written information is recommended.[20]

Before performing any procedure, we must consider systemic measures for the treatment of uncontrolled hemorrhage; these measures depend on the type of NOAC. In the case of dabigatran, a protocol for emergency hemodialysis should be followed since this is the treatment of choice in cases of plasma overdose, in order to reduce the drug's blood concentration . It may also be necessary if the patient has renal dysfunction. Transfusions of concentrated coagulation factors can be done in the hospital for other NOACs.[21]

More clinical studies are needed to establish clear directives on the dental treatment of patients who take NOACs, as well as a specific test to stratify these patients based on their risk of bleeding.

REVERTING THE ANTICOAGULANT EFFECT

The new oral anticoagulants are not exempt from hemorrhagic complications and because there is no specific antidote, there may be problems in managing hemorrhages.

An antidote for dabigatran, idarucizumab (Praxbind®), was introduced in Europe in 2015. This is the first agent for reverting a non-vitamin K antagonist anticoagulant to obtain approval in the European Union, which makes dabigatran the first and only NOAC to have a reverting agent.[11]

NOACs have a short half-life, so in the majority of cases of hemorrhage caused by these drugs, the response is to simply discontinue therapy, keep the patient under observation and provide support treatment when necessary. The use of systemic reversing agents will only be necessary in more severe situations that may represent a risk to the patient's life.[23]

An example of a systemic reversing agent is activated charcoal, which absorbs drugs and toxins on its surface as it passes through the gastrointestinal tract, thereby avoiding or reducing their absorption systemically. When the last NOAC dose has been recently administered, within 2 hours, oral administration of activated charcoal can decrease its absorption.

It has been shown that administration of fresh frozen plasma (FFP) can reduce hemorrhage volume in patients who take high-dose dabigatran, but it is less effective in patients who take low dosages. Recombinant factor VIIa has also been shown to effectively revert the anticoagulant effect of dabigatran. We have already mentioned that hemodialysis has been shown to be an effective measure in cases of plasma overdose of dabigatran due to its low level of plasma protein binding. It has also been postulated that blood infusion of activated charcoal may be a useful method for eliminating dabigatran, although this requires further study.[24]

Conversely, hemodialysis does not work for eliminating rivaroxaban and apixaban due to the high level of plasma protein binding.

Regarding rivaroxaban, current recommendations are controversial given that they are based on animal models and few clinical experiences. These studies indicate that administration of recombinant factor VIIa has a moderate effect on stopping bleeding caused by rivaroxaban.[25] Prothrombin complex concentrate (PCC) was studied in a clinical trial with 12 healthy volunteers in which it was capable of immediately and completely reverting the anticoagulant effect of rivaroxaban. However, more studies are needed to measure its effect.[24] The use of perioperative tranexamic acid has been shown to significantly reduce postoperative blood loss in patients treated with rivaroxaban. Neither vitamin K, protamine or plasma transfusion modifies the anticoagulant effect of rivaroxaban.

No specific antidote is known for apixaban. However, phase II trials are underway testing two synthetic molecules, Andexanet alpha and Aripazine, and the preliminary results are promising[11,25].

CONCLUSIONS

1. NOACs should not be discontinued in patients who are at high thromboembolic risk.
2. When the dental procedure carries a low risk of hemorrhage, the NOAC regimen does not need to be modified.
3. Before performing a dental procedure that involves a risk of bleeding, consensus must be reached with the cardiologist on the best possible regimen for each patient based on the thromboembolic risk and the risk of bleeding. The options are:

- Do not discontinue the drug.
- Postpone the daily dose until after the procedure.
- Discontinue the drug 24-48 hours prior to surgery and restore it the next day.

The authors state they have no conflicts of interest.

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