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Grado en ODONTOLOGÍA

Trabajo Fin de Grado

Systematic review on the effects of the discontinuation of the anticoagulant therapy and the postoperative bleeding, in patients under new oral anticoagulants after dental extraction.

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Index

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List of the signs and acronyms:

DOACs- Direct Oral Anticoagulants

INR- International Normalized Ratio

NOACs- The non-vitamin K antagonist oral anticoagulants

OAT- Oral Anticoagulant Therapy

PT- Prothrombin time

PTT- Partial thromboplastin time

VKAs- Vitamin K Antagonists

Keywords:

I. New oral anticoagulants

II. Novel oral anticoagulants

III. Non-vitamin K oral anticoagulants

IV. NVKA oral anticoagulants

V. NOACs

VI. DOACs

VII. Direct oral anticoagulants

VIII. Dental extraction

IX. Tooth extraction

X. Exodontia

XI. Simple extraction

XII. Dentoalveolar surgery

XIII. Oral surgery

XIV. Dabigatran

XV. Rivaroxaban

XVI. Apixaban

XVII. Edoxaban

XVIII. Postoperative complications

XIX. Postoperative bleeding

XX. Bleeding risk

Abstract

Background: The present systematic review compares the effects of the discontinuation of the anticoagulant therapy and the postoperative bleeding, in patients under new oral anticoagulants after dental extraction. The purpose of this study is to determine the postoperative complications of the DOACs after a simple dental extraction in comparison to the VKAs and with patients not under anticoagulants. The other aim of this study is to determine the postoperative complications of the DOACs in the case of an alteration of the anticoagulant regimen before a dental extraction.

Materials and methods: The electronic search was conducted on two databases (Medline complete and Scopus) including studies from 2011 until December 2021. The research included patients under DOACs undergoing simple dental extraction. The inclusion criteria included randomized controlled trials, cohort studies, case series, retrospective cohort, prospective cohort and studies on human individuals. The research excluded other types of anticoagulants and patients undergoing other invasive dental treatments. The risk of bias was assessed according to the CASPE guide.

Results: A total of seven studies were selected, complying to all the inclusion criteria. Nine hundred thirty-one patients were treated. The bleeding rate had a different scale in the seven studies. The studies used different hemostatic measures after the dental extraction. In the majority of the studies the bleeding rate was ranging from none, minor, moderate. All the studies included a postoperative follow up from the day of the surgery. The bleeding is immediate and minor after a dental extraction for patients under DOACs, VKAs and with no-OAT. And altering the DOACs regimen did not alter the bleeding.

Discussion: The most frequent postoperative complication encountered in this review is immediate and delayed bleeding. However, given the novelty of the DOACs, there is not enough evidence on the complications of anticoagulants related to the dental extractions and most studies about DOACs and VKAs

include patients taking antiplatelet in addition to the anticoagulants covered in this review. Moreover, the hemostatic measures are different in the studies, which can influence the bleeding rate. All the included studies about the discontinuation of the DOAC therapy show the same results and many studies are still in progress on this topic.

Conclusion: The most frequent postoperative complication for patients under DOACs and patients under VKAs after a simple dental extraction is minor bleeding: immediate or delayed. Patients under new oral anticoagulant treatment and patients not under anticoagulant have the same postoperative bleeding risk after a dental extraction. DOACs are a safe drug and do not require the discontinuation/alteration of the therapy for a simple dental extraction. Further studies are required to determine if surgical procedures in dentistry require an alteration of the DOAC regimen.

1. Introduction

1.1. Coagulation

The oral anticoagulant therapy is an increasingly common treatment in the population. Especially in the Western World, where thrombotic disorders are one of the leading causes of death. (1) In the dental field, it is essential to monitor the patients taking anticoagulants, in order to achieve the adequate protocol as treatment. Furthermore, to understand how to treat patients requiring this special care, we need to know how the normal process of coagulation functions.

In Greek, haeme means blood and stasis the arrest. The first stage of hemostasis, also called primary hemostasis, is the result of complex interactions between platelets, vessel walls and adhesive proteins leading to the formation of initial ‘platelet plug’. This will lead to a series of steps: platelet adhesion, platelet secretion and platelet aggregation. (2)

The second stage of hemostasis is coagulation; which is a vital protective mechanism in our body. As soon as there is an injury or damage to the wall of a vessel, the coagulation factors are activated to form a network of fibrin on the lesions and seal them. (3) It involves many substances circulating in the blood also called coagulation factors. These are proteins produced mainly by the liver, and are designed by a Roman numeral from I to XIII. On contact with platelets, the coagulation factors interact in cascade leading to the production of thrombin (Figure 1) - or activated factor II-. Its main role is to transform soluble fibrinogen into insoluble fibrin to form a clot. (4)

From the activation of the factor X (Figure 1), the beginning of the so-called common pathway of coagulation starts, leading to the formation of a clot. (5) The third and last stage of hemostasis is fibrinolysis which results in the re-permeabilization of the blood vessel.

To prevent the clot from spreading inappropriately, there are natural anticoagulants, called inhibitors, which are also produced by the liver:

antithrombin, protein C, protein S, etc. However, in some diseases, the coagulation is altered, leading to hematopoietic diseases, such as thromboembolism. To treat and prevent these abnormalities and inhibit the coagulation system more selectively, anticoagulants will be prescribed. (6) They can be administered orally or intravenously.

The most well-known intravenous anticoagulant is heparin. It inhibits thrombosis by bonding with antithrombin III. (7)

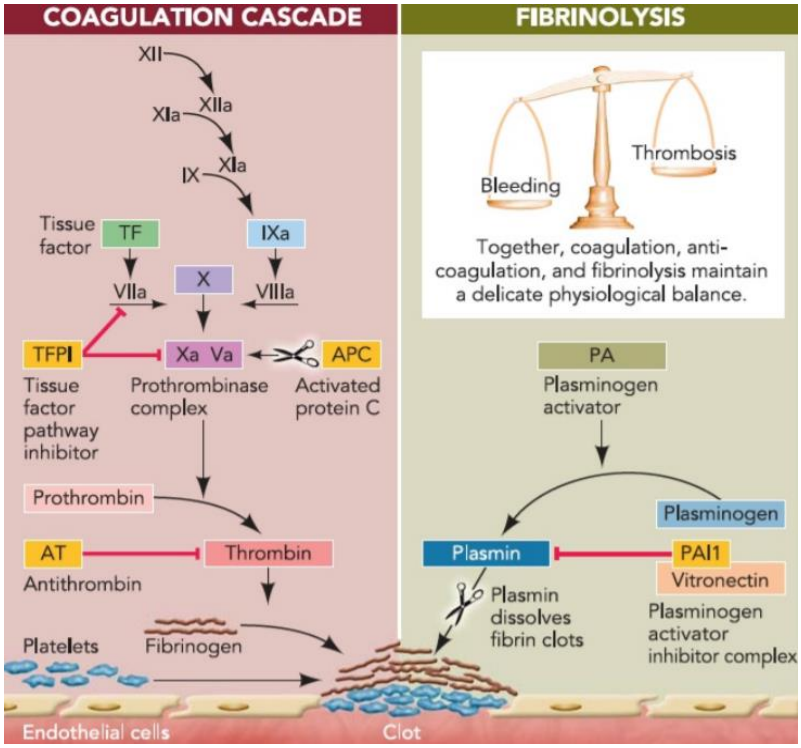

Figure 1. Scheme of the coagulation-anticoagulation system (8)[1]

1.2. The oral anticoagulants

Also called blood thinners, the anticoagulants will prevent the blood clots from impeding blood flowing freely to the heart and the brain by making it more "liquid".

There two different types of blood thinners:

[1] Sun H. The interaction between pathogens and the host coagulation system. Physiology (Bethesda). 2006 Aug;21:281-8. doi: 10.1152/physiol.00059.2005.

- **Anticoagulants:** delay the body's process of making clots.
- **Antiplatelets:** (i.e. aspirin and clopidogrel) prevent blood cells called platelets from clumping together to form a clot. They are mainly prescribed for patients who had a heart attack or stroke. (9)

There are two types of oral anticoagulants: VKAs and NOACs: Oral antivitamin K anticoagulants are used in atrial fibrillation (valvular or non-valvular) and direct-acting oral anticoagulants (DOA) are used in non-valvular atrial fibrillation.

- Vitamin K antagonists (VKAs): VKAs (fluindione, warfarin, and acenocoumarol) inhibit the regeneration of vitamin K, a cofactor in the c-carboxylation of coagulation factors II, VII, IX, and X as well as the inhibitors protein C, protein S, and protein Z. These proteins lose their function in hemostasis with decreasing number of carboxyl groups due to their inability to bind to a phospholipid surface, and to localize the coagulation process. (6)

- The non-vitamin K antagonist oral anticoagulants (NOACs): These agents include four different drugs: Dabigatran, which inhibits thrombin, whereas rivaroxaban, apixaban, and edoxaban inhibit factor Xa. The NOACs are as effective as warfarin, but are more convenient to administer since they can be given in fixed doses without routine coagulation monitoring. They are also safer since they are associated with less intracranial bleeding. (10)

1.2.1. Indications

Indications of VKAs and NOACs
- Treatment of venous thromboembolism (VTE) and deep venous thrombosis (DVT) to prevent recurrent disease and in patients who have been treated with a parenteral anticoagulant for 5-10

days
- Arterial thrombosis in patients with mechanical heart valves
- Atrial fibrillation without stroke (only VKAs)
- Stroke and systemic embolism in patients with non-valvular atrial fibrillation
- Post-discharge prophylaxis for VTE or pulmonary embolism (PE) after major orthopedic surgery such as hip or knee replacement surgery
- Major cardiovascular events (cardiovascular death, myocardial infarction and stroke) in patients with chronic coronary artery disease or peripheral artery disease
- 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

Figure 2. Indication of oral anticoagulants (11,12,13)

Patients under the conditions presented in Figure 2 will require oral anticoagulants.

1.2.2. VKAs anticoagulant monitoring

The patients under a NVKAs anticoagulant therapy do not require to be monitored every week (INR: International Normalized Ratio) as the patients under the VKAs therapy. However, they will have to be under daily medication. (14) During invasive dental treatments, some blood analytic measures should be monitored:

Baseline laboratory measurements ahead of VKAs anticoagulants therapy should include an INR to monitor anticoagulant response in addition to a complete blood count with platelets.

The laboratory measurements will include a platelet count, PTT (Partial Thromboplastin Time), PT (Prothrombin Time) and TT (Thrombin Time) in addition to the INR. Moreover, to be able to perform invasive treatments in dentistry, these values should also be measured before, during or/and a treatment:

- Platelet count: the normal values range between 150.000 and 450.000/mm^3 and the limit to perform an invasive dental treatment (dental extraction, implant) on a patient is around 50.000 mm^3.
- INR: The normal values of INR are around 0.9-1.1. For anticoagulated patients, target INR levels will differ and will depend on the indication for which the drug is prescribed and can range from 2.0 to 3.5. (15)

  The patients with mechanical aortic valves have an INR ranging between 2.0 and 3.0, whereas patients with mechanical mitral valve or mechanical valves in both the aortic and mitral position have an INR ranging between 2.5 and 3.5 (16)

  In case of undergoing an invasive dental treatment, the patients will have to present their INR records while attending for a dental treatment, from the day of the procedure. If the patient's INR is equal or above 4, the dentist will have to inform the patient and his general medical practitioner and delay the treatment until the INR reaches a value lower than 4. In case of an emergency, the patient can be referred to the hospital.

  However, if the value is ranging between 2.0 and 3.5, the patient can be treated following the general hemostatic instructions. (15)

1.2.3. Adverse effects

1.2.3.1. Vitamin K antagonists

- Drug-drug interactions: Since the VKAs are highly bound to plasma proteins, many medications might compete for protein-binding sites and potentiate the anticoagulant action of VKAs. An increased PT-INR will be noticed later on, in most of the cases. The medications generating this interaction are the following: Barbiturates, Carbamazepine, Chlordiazepoxide, Propofol, Ethanol, Azathioprine, Mesalazine, Sulfasalazine, Chelating agents, Cyclosporine, Etretinate, Anti-flu vaccine, Menthol, Mercaptopurine, Methimazole, Multivitamin supplies and Raloxifene. (14)

Moreover, some antifungal drugs (fluconazole, miconazole) and antibiotics (azithromycin, ciprofloxacin) alter the pharmacokinetics and increase the PT-INR values. Increasing the PT-INR values will lead to the risk of hemorrhage when combined with VKAs and alter the gut flora, resulting in a diminution of the gut absorption of Vitamin K. It can also alter the elimination of the drug.

- Food and herbal medicines interactions: The VKAs have an interaction with the following aliment: chamomile, soybean/soy milk, mango, ginseng, cranberry, green/leafy vegetables. (14).

- Bleeding: It is known to be the most common adverse effect of the anticoagulants. It can range from minor bleeding to life-threatening major bleeding. However, the benefits of the treatment outweigh the risk in most of the cases. (17).

1.2.3.2. Non-vitamin K antagonists

The use of these anticoagulants is well tolerated and their adverse effects are relatively lower than the conventional ones at each level. Several studies revealed a drug-drug interaction in addition to bleeding as adverse effects,

although there is not enough information yet about their interaction with food and herbal medicine.

- Drug-Drug interactions:

    - Dabigatran presents a pharmacological interaction with the following drugs: Amiodarone, Carbamazepine, Cyclosporine, Dronedarone, Ketoconazole, Phenytoin, Rifampicin, St. John's wort, Verapamil, Quinidine, Quinine and Proton pump inhibitors.

    - Rivaroxaban presents a pharmacological interaction with the following drugs: Amiodarone, Azithromycin, Chloramphenicol, Clarithromycin, Cyclosporine, Diltiazem, Dronedarone, Erythromycin, Itraconazole, Ketoconazole, Naproxen, Quinidine, Quinine, Ritonavir, Verapamil, Carbamazepine, Hypericum perforatum, Phenytoin, Rifampicin, Phenobarbital, Phenytoin, Rifampicin and systemic antifungals (14)

- Bleeding: Apixaban, edoxaban and dabigatran were associated with less total bleeding and death than patients under VKAs, but not rivaroxaban (18). Patients taking NOACs show a renal function decline resulting in an increased bleeding.

1.3. New oral anticoagulants

This new treatment presents an alternative safer and as effective as VKAs in anticoagulation. To describe these drugs various terms are used, such as novel oral anticoagulants, new oral anticoagulants, direct oral anticoagulants (DOACs) or non-vitamin k oral anticoagulants (NOACs). They brought many advantages in comparison to the VKAs: no known food effect, fixed dosing, rapid onset of action, fewer drug interactions, short offset period, no requirement for routine monitoring. (19)

The NOACs inhibit directly specific proteins within the coagulation cascade, whereas the VKAs inhibit the synthesis of vitamin K dependent clotting factors instead. (20)

1.3.1. Dabigatran, direct inhibition of thrombin

The mechanism of action of Dabigatran is the direct inhibition of thrombin to hinder the conversion of fibrinogen to fibrin, preventing a clot formation. This drug has a quick onset of action (between 0.5 to 2 hours) and the plasma half-life is about 12 hours. The use of Dabigatran should be avoided if the patient has a creatinine clearance <30 ml/min, since its excretion is 80% by the kidneys. However, Dabigatran is the only dialyzable DOAC. Its dosage is 150 mg, twice a day and its reversal agent is Idarucizumab. (21)

- Indications:
  - Stroke prevention in NVAF (Nonvalvular Atrial Fibrillation)
  - Treatment of deep vein thrombosis and pulmonary embolism
  - Prevention of recurrent deep vein thrombosis and pulmonary embolism
  - Prevention of thromboembolism after total hip replacement. (22)

1.3.2. Direct Inhibitors of Factor Xa

The mechanism of action of these drugs (Rivaroxaban, Apixaban, Edoxaban) is binding the active site of factor Xa to inactivate this factor and impede the progression of the coagulation cascade, thrombin activation and the clot formation. These drugs have a short half-life and rapid onset of action, making it easier to interrupt and initiate the anticoagulant treatment after surgery. These drugs should be avoided if the creatinine clearance is lower than 15ml/min. Moreover, they have the same specific reversal agent: Andexanet alfa. (21)

1.3.2.1. Rivaroxaban,

The plasma half-life of Rivaroxaban is around 9-13 hours and the renal excretion is around 66%. It is a single-dose daily medication of 15 mg. (21)

- Indications:
  - Stroke prevention in NVAF
  - Treatment of deep vein thrombosis and pulmonary embolism
  - Prevention of recurrent deep vein thrombosis and pulmonary embolism
  - Prevention of thromboembolism after total knee replacement and after total hip replacement
  - Prevention of thromboembolism in hospitalized acutely ill medical patients
  - Prevention of major cardiovascular events in patients with chronic CAD/peripheral artery disease (22).

1.3.2.2. Apixaban

Apixaban has a plasma half-life between 10 and 14 hours. It has a lower renal excretion compared to the other DOACs, which is around 25%. This drug is prescribed 5 mg twice a day.

- Indications:
  - Stroke prevention in NVAF
  - Prevention of thromboembolism after total knee replacement and after total hip replacement
  - Treatment of deep vein thrombosis and pulmonary embolism
  - Prevention of recurrent deep vein thrombosis and pulmonary embolism. (22)

1.3.2.3. Edoxaban.

This daily medication has an effective half-life of 10-14 hours and a renal excretion of 35%. The dosage of Edoxaban is 60mg once a day. It is indicated for stroke prevention in NVAF and treatment of deep vein thrombosis and pulmonary embolism. (22)

1.4. Dental extraction

A dental extraction is the removal of a tooth from its alveolar socket. This procedure is performed by dentists if the tooth is broken, damaged by decay or because of a periodontal disease. (23)

1.4.1. Simple dental extraction

A simple dental extraction is the removal of a tooth that is fully erupted. For this treatment, the patient is anesthetized, to numb the area and reduce the pain. The dentist uses elevators and dental forceps as instruments in order to elevate the tooth and grasp the crown of the tooth. No flap opening or suture is required in a simple dental extraction, also called non-surgical dental extraction. (24)

1.5. Justification, hypothesis and objectives

Justification:

The anticoagulant treatment started 80 years ago with unfractionated heparin. Later on, different anticoagulants were discovered and prescribed until 2010, where the first new oral anticoagulant was developed: Dabigatran. Followed by Rivaroxaban (2011), Apixaban (2012), Edoxaban (2014), Betrixaban (2017). (25)

These drugs are prescribed daily by doctors and more and more over the years, due to the aging of the population. Nevertheless, until today, many health professionals are not aware of the management of the patients under new oral anticoagulants since it is a new drug on the market that differs a lot from the conventional ones (i.e. VKAs or Heparin) in its use and its dosage.

Many studies explain that it is a new drug for dentists and that more studies are required in order to study the complications and the management of patients under new oral anticoagulants in order to be prepared before the invasive procedures.

A few guidelines are available on many databases; However, many doubts are still present towards these new drugs.

One of the daily treatments at a dentist is the simple dental extraction. It is also an invasive procedure, although presenting minimal risks as long as it is performed in an aseptic area, respecting the hemostatic procedures. However, in case of a patient under anticoagulants, this procedure can present many risks and perioperative complications that the dentist should be aware of.

For all the aforementioned, a review of the literature evaluating the possible discontinuation of the anticoagulant therapy and the postoperative bleeding of patients under new oral anticoagulants after a simple dental extraction was justified in order to analyze the issues derived.

Hypothesis

- The working hypothesis of this study is that there is a reduction of the postoperative bleeding time in DOACs in comparison to the VKAs anticoagulants.

- The bleeding is minimal the days following the procedure.

- There is no need to discontinue/alter the anticoagulation therapy the day of the procedure.

Objectives

- **Primary objective:**

    - Determine the postoperative complications of the DOACs after a simple dental extraction in comparison to the VKAs.

- **Secondary objectives:**

    - Determine the postoperative complications of the DOACs after a simple dental extraction in comparison to patients not under any anticoagulant regimen.

    - Determine the effect of the discontinuation/alteration of the anticoagulant therapy on the postoperative bleeding.

2. Materials and methods

The present systematic review was carried out according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) (26).

2.1. Identification of the PICO question

The database Medline via MedLine complete and Scopus were used to search for indexed articles on patients taking NOACs while undergoing a simple dental extraction, published until December 2021, to answer the following question: **Among anticoagulant patients undergoing simple dental extraction (P), do direct oral anticoagulants (I) demonstrate a reduction of the intra- and postoperative complications (O) in comparison to VKAs anticoagulants (C)?**

This study question was established according to an adaptation of the PICO structured question. This approach is suitable for conducting systematic qualitative reviews in health interventions. The format of the question was established as follows:

P (Population): Anticoagulant patients undergoing simple dental extraction

I (Intervention): Direct oral anticoagulants (DOACs)

C (Comparison): Vitamin K antagonists (VKAs) as anticoagulants or patients without control group

O (Results): Intra- and post- operative complications

O1: Reduction of the post-operative bleeding time

O2: No alteration of the treatment the day of the procedure

O3: Minimal complications the days following the procedure

2.2. Information sources and data search

An automated search was carried out in the two aforementioned databases (Medline complete and Scopus) with the following keywords: ‘new oral anticoagulants’ , ‘novel oral anticoagulants’ , ‘non-vitamin K oral anticoagulants’ , ‘NVKA oral anticoagulants’ , ‘NOACs’ , ‘DOACs’ , ‘Direct oral anticoagulants’ , ‘dental extraction’ , ‘tooth extraction’, ‘exodontia’, ‘simple extraction’, ‘dentoalveolar surgery’ , ‘oral surgery’ , ‘Dabigatran’ , ‘Rivaroxaban’ , ‘Apixaban’ , ‘Edoxaban’ , ‘post-operative complications’, ‘post-operative bleeding’ , ‘bleeding risk’

Table 1: Keywords inspired by the PICO elements

PICO Elements	Keywords	MeSH Words
P (Population)	“simple dental extraction” “Dental extraction” “exodontia” “dentoalveolar surgery”	“Tooth extraction” “surgery,oral”
I (Intervention)	”direct oral anticoagulants” “oral anticoagulants” “ new oral anticoagulants” “novel oral anticoagulants” “non-vitamin K oral anticoagulants” “NVKA oral anticoagulants” “NOACs” “DOACs”	”anticoagulants”
C (Comparison)	”vitamin K antagonists anticoagulants” “conventional anticoagulants” “VKAs anticoagulants”	”anticoagulants” ”
O (Outcome)	”intraoperative complications” “postoperative complications” “complications” “bleeding” risk”	“bleeding time” “risk factors”

The keywords were combined with the Boolean AND and OR operators, as well as the controlled terms (such as the “MeSh” words) in an attempt to obtain the best and broadest search results.

The search on Medline Complete and Scopus was as follow on December 2021: ((simple dental extraction) OR (Dental extraction) OR (exodontia) OR (dentoalveolar surgery) OR (Tooth extraction) OR (surgery,oral)) AND ((direct oral anticoagulants) OR (oral anticoagulants) OR (new oral anticoagulants) OR (novel oral anticoagulants) OR (non-vitamin K oral anticoagulants) OR (NVKA oral anticoagulants) OR (NOACs) OR (DOACs) OR (anticoagulants)) AND ((vitamin K antagonists anticoagulants) OR (conventional anticoagulants) OR (VKAs anticoagulants) OR (anticoagulants)) AND ((intraoperative complications) OR (postoperative complications) OR (complications) OR (bleeding) OR (bleeding time) OR (risk factors))

The search was completed with a review of the references provided in each of the studies in order to identify any additional studies. Finally, a cross-search of potentially interesting articles was carried out for the introduction.

2.3. Inclusion and exclusion criteria

Before starting the study, a series of inclusion and exclusion criteria were established. The inclusion criteria were:

- Type of patient: Patients taking dabigatran, rivaroxaban, apixaban or edoxaban undergoing dental extraction.

- Type of treatment: Simple dental extraction.

- Type of study: Randomized controlled trials; cohort studies; case series; retrospective cohort; prospective cohort; studies on human individuals; publications in English or Spanish; studies about more than 5 patients; published until December 2021.

- Type of Results Variables: Studies that will provide data related to assessing bleeding risk after a simple dental extraction in patients undertaking NOACs with or without altering the anticoagulation therapy. And they were collected as secondary variables: the complications of the NOACs after the dental extraction; the comparison of bleeding risk and the complications of the NOACs with the VKAs.

The exclusion criteria were: Studies about patients taking intravenous anticoagulants; patients undergoing other dental treatments; studies published before 2011.

Database	Search	Filters	Date
MedLine Complete	((simple dental extraction) OR (Dental extraction) OR (exodontia) OR (dentoalveolar surgery) OR (Tooth extraction) OR (surgery,oral)) AND ((direct oral anticoagulants) OR (oral anticoagulants) OR (new oral anticoagulants) OR (novel oral anticoagulants) OR (non-vitamin K oral anticoagulants) OR (NVKA oral anticoagulants) OR (NOACs) OR (DOACs) OR (anticoagulants)) AND ((vitamin K antagonists anticoagulants) OR (conventional anticoagulants) OR (VKAs anticoagulants) OR (anticoagulants)) AND ((intraoperative complications) OR (postoperative complications)	- Language: Spanish or English - Studies between January 2011 and December 2021 - Humans - Dentistry & Oral Sciences Source	December 27th 2021

	OR (complications) OR (bleeding) OR (bleeding time) OR (risk factors))		
Scopus	((simple dental extraction) OR (Dental extraction) OR (exodontia) OR (dentoalveolar surgery) OR (Tooth extraction) OR (surgery,oral)) AND ((direct oral anticoagulants) OR (oral anticoagulants) OR (new oral anticoagulants) OR (novel oral anticoagulants) OR (non-vitamin K oral anticoagulants) OR (NVKA oral anticoagulants) OR (NOACs) OR (DOACs) OR (anticoagulants)) AND ((vitamin K antagonists anticoagulants) OR (conventional anticoagulants) OR (VKAs anticoagulants) OR (anticoagulants)) AND ((intraoperative complications) OR (postoperative complications) OR (complications) OR (bleeding) OR (bleeding time) OR (risk factors))	- Language: Spanish or English - Studies between January 2011 and December 2021 - Humans - Publication stage: final - Dentistry - Article	December 31st 2021

2.4. Study Selection Process

The selection of the studies was carried out by two reviewers (AH, ML). A selection process was carried out in four stages.

The first stage reviewed the titles in order to eliminate irrelevant publications, followed by the removal of the duplicated articles. Then, the abstracts were reviewed and filtered according to the type of study, type of invasive treatment, type of extraction, type of anticoagulants, type of

antithrombotic drugs, and result variables. The last stage consisted of a complete reading of each article and extracting the data according to a predetermined data extraction form to confirm the eligibility of the studies.

In case of any disagreement, it was resolved by mutual consensus of both the reviewers.

2.5. Data extraction

The following information was extracted from the studies: Title, authors detail, year of publication, country of origin, study design (i.e. case series, prospective cohort), age and gender of the patients, type of DOAC, other oral anticoagulants (VKAs), study size, number of teeth extracted, teeth extraction method, hemostatic measures, bleeding rate, interruption of DOAC or not, follow-up time post extraction.

These data were independently extracted. The data of the selected studies were summarized in a tabular. (Table 6)

2.6. Quality assessment

Using the CASPE Guide

The quality of the included studies was assessed by two reviewers (AH, ML) in order to assess the methodological quality and risk of bias of all included articles.

The methodological quality of the studies was performed according to the CASPE guideline (27). Studies were considered to be at “low risk of bias” if they meet all the criteria. If there was a possible bias in at least one criteria, they were considered to have an “uncertain risk of bias”. And the studies with a “high risk of bias” were those where one or more criteria were not met or with doubts in more than one criteria.

The degree of agreement regarding the evaluation of the quality of the studies was obtained with the Cohen kappa test, following the Landis and Koch scale (28).

3. Results

3.1. Study Selection: Flow chart

A total of 1034 articles were obtained from the initial search process: Medline Complete (n=332) and Scopus (n=732). No extra article was found through hand searching.

Among the 1034 articles, 90 were excluded because they were duplications and 930 were excluded since they were not identified as potentially eligible articles through the screened by titles and abstracts and the inclusion criteria. Another screening was carried out according to the type of study and 7 articles were excluded. As a result, 7 articles met all the inclusion criteria and were included in the present systematic review (Figure 3). The information related to the excluded articles and the reasons for their exclusion is presented in Table 3.

The k-value for agreement between the interexaminer on the study inclusion was 1.0 (titles and abstracts) and 1.0 (study type), indicating "complete" agreement, respectively, based on the criteria from Landis and Koch (28).

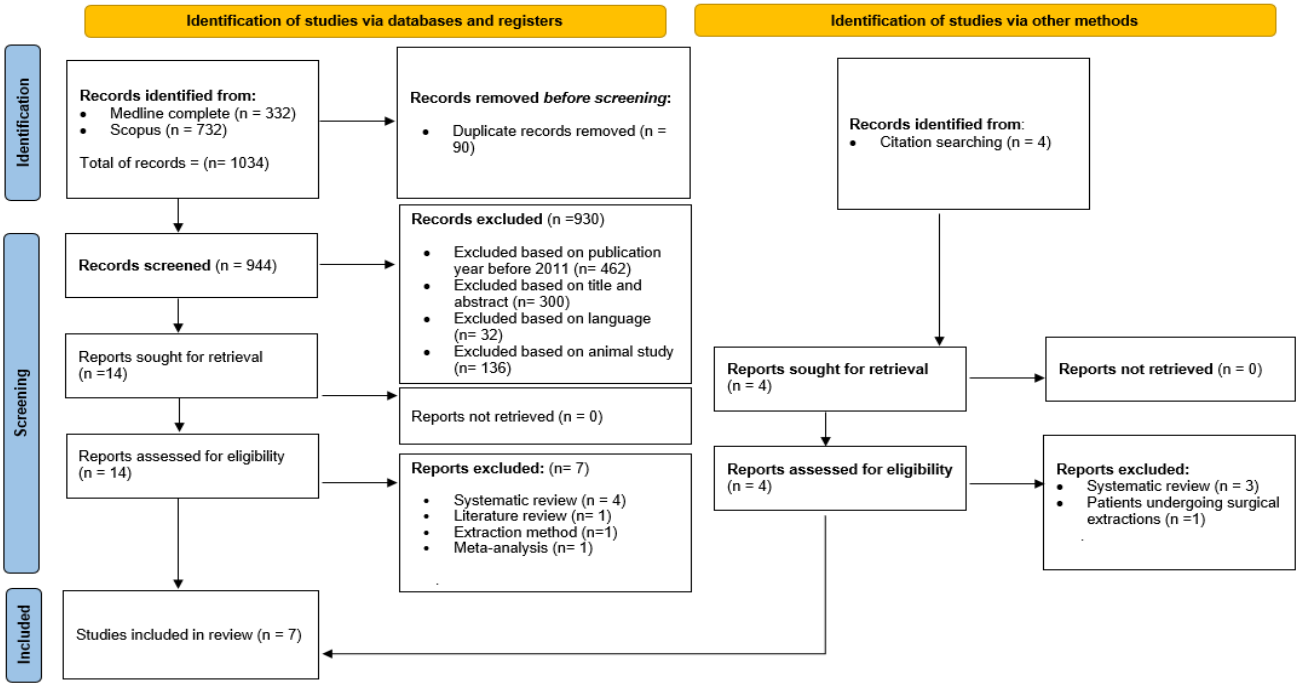

Figure 3. Flowchart of study search and article selection process during the systematic review.

Author	**Journal**	**Reasons for exclusion**
Manfredini M. et al	Journal of clinical medicine	Systematic review
Madeley E. et al	Evidence-Based Dentistry	Systematic review
Nathwani S. et al	British Dental Journal	Literature review
Hua W. et al	Frontiers in Pharmacology	Systematic review
Müller M. et al	Clinical Oral Investigations	Extraction method: surgical extraction methods only
Yang S. et al	BMC Oral Health	Meta-analysis
Kämmerer P.W. et al	Clinical Oral Investigations	Systematic review

Table 3: Articles excluded and their reason for exclusion from this systematic review after the second screening

3.2. Assessment of quality and risk of bias of the included studies

	Miclotte et al, 2016
Are the study results valid?	
Did the study address a clearly focused issue?	Yes
Did the authors use an appropriate method to answer their question?	Yes
Were the cases recruited in an acceptable manner?	Can't tell
Were the controls selected in an acceptable way?	Yes
Was the exposure accurately measured to minimize bias?	Yes
(a) Aside from the experimental intervention, were the groups treated equally?	Can't tell
(b) Have the authors taken account of the potential confounding factors in the design and/or in their analysis?	Yes
What are the results?	
How large was the treatment effect?	There was no difference in the procedural bleeding score or in early bleeding events. Delayed bleeding occurred more frequently in anticoagulated compared to non-anticoagulated patients
How precise was the estimate of the treatment effect?	$p < 0.05$
Do you believe the results?	Yes
Will the results help locally?	
Can the results be applied to the local population?	Yes
Do the results of this study fit with other available evidence?	Can't tell

Table 4: Assessment of quality and risk of bias of a case-control study according to the CASPE guideline

	A Lababidi et al, 2018	Rocha et al, 2020	Mauprivez et al, 2016	Yagyuu et al, 2017	Berton et al, 2018
Are the results of the study valid?					
Did the study address a clearly focused issue?	Yes	Yes	Yes	Yes	Yes
Was the cohort recruited in an acceptable way?	Yes	Yes	Yes	Yes	Yes
Was the exposure accurately measured to minimise bias?	Yes	Yes	Yes	Yes	Yes
Was the outcome accurately measured to minimise bias?	Yes	Yes	Yes	Yes	Yes
(a) Have the authors identified all important confounding factors?	Yes	Yes	Yes	Yes	Yes
(b) Have they taken account of the confounding factors in the design and/or analysis?	Yes	Yes	Yes	Cannot tell	Yes
(a) Was the follow up of subjects complete enough?	Yes	Yes	Yes	No	Yes
(b) Was the follow up of subjects long enough?	Yes	Yes	Yes	Cannot tell	Yes
What are the results?					
What are the results of this study?	No bleeding events were recorded in the DOAC cessation group. Comparison of the incidence of bleeding events between the non-cessation DOAC group and the warfarin group showed no statistically significant difference	No bleeding events were observed in procedures carried out in individuals of the DOAC group. The dental bleeding scores obtained for the DOAC and VKA groups were similar.	The difference in the number of bleeding events between the two groups was not statistically significant. For the DOAC group, 91.67% bleeding events were mild and 8.33 % were moderate	DOAC extractions did not significantly increase the risk of postextraction bleeding, compared to VKA. The incidences of postextraction bleeding per tooth for the DOAC, VKA and no anticoagulant extractions were 10.4%, 12.0% and 0.9%, respectively	No statistically significant difference resulted in post-operative bleeding events between the groups. 53 subjects of the DOAC group (81.6%) and 45 (69.3%) of the VKA group did not report any post-operative bleeding
How precise are the results?	$p = 0.56$	Cannot tell	95%	95%	$p < 0.05$
Do you believe the results?	Yes	Yes	Yes	Yes	Yes
Will the results help locally?					
Can the results be applied to the local population?	Yes	Yes	Yes	Yes	Yes
Do the results of this study fit with other available evidence?	Yes	Yes	Yes	Yes	Yes
Will this change your clinical decision?	No	No	No	No	No

Table 5: Assessment of quality and risk of bias of a cohort studies according to the CASPE guideline

For the reviewed studies, an uncertain risk of bias was considered in all 6 studies (Tables 4 and 5). For the one case series study, it was considered to have a high risk of bias due to the very nature of the type of study.

The k value (Cohen kappa test) on the agreement between the reviewers of the methodological quality was 0.80 according to the Landis & Koch scale.

3.3. Analysis of the main characteristics of the reviewed studies

Of the 7 articles included in this review, there was 1 case series (29), 1 prospective observational study (30), 1 prospective case-control study (31), 3 cohort studies (32,34,35) and 1 prospective comparative study (33).

A total of 931 patients were treated, with an average age of 70 years and a majority of them were male.

A total of 1795 teeth were extracted: 375 extractions on patients taking DOACs, 305 extractions under VKAs and 1115 extractions on non-OAT patients.

In two studies apixaban, dabigatran and rivaroxaban were compared, while in three studies apixaban, dabigatran and rivaroxaban were compared in addition to VKAs as warfarin or fluindione. There was one study comparing apixaban, dabigatran, edoxaban and rivaroxaban with VKAs and one study comparing VKAs and DOACs in general.

Non-OATs patients were compared with patients under DOACs in one study and with patients under DOACs and patients under VKAs in another study

In two studies the patients underwent surgical and simple dental extractions but the overall percentage of surgical extractions was inferior to 15%.

Table 6 describes the general sample characteristics of the included studies and table 6bis describes more specific characteristics of the included studies.

In all the included studies elevators and forceps were used for the extraction while performing an atraumatic extraction without cutting the surrounding bone nor cutting the gum, followed by the complete curettage of the inflamed granulation tissue. After this, hemostatic measures were taken.

There were two studies (31, 35) in which the hemostatic measures were suturing after the compression with gauze. In two studies (29, 30) absorbable hemostatic sponges such as oxidized cellulose, gelatin sponge was used in addition to suturing in all the patients, whilst in three studies (32, 33,34) the use of absorbable hemostats was only performed if there as a lack of adequate bleeding control. In one study (34), the hemostatic measures differed according to the patient: application of hemostatic agent and suturing of the socket and/or the use of an antifibrinolytic mouthwash at home postoperatively, no additional hemostatic measures at all or only the application of hemostatic agent and suturing of the socket.

The sutures were performed after the extractions with non-absorbable material as 4-0 silk, 4.0 polyglactin 910 sutures, Vicryl® 3-0, 3.0 nylon. These sutures were performed for every case except in two studies (32, 34) in which the suturing was not performed in every case.

The oral anticoagulant therapy with DOACs was discontinued before the extraction in two studies (31, 34). The dose of NOAC was skipped on the morning of the procedure in the first study (31) and was restarted according to the normal regimen of the treatment, at least 4 h after the dental extraction following the achievement of an adequate hemostasis. In the other study (34), the perioperative cessation of the NOAC therapy was ranging from 1 to 14 days.

The bleeding rate had a different scale in the seven studies. In the majority of the studies the bleeding rate was ranging from none, minor, moderate to severe as detailed in table 6bis. The bleeding rate was not described in one study (32), however it was mentioned that all the post extraction bleeding could have been stopped with local hemostatic treatment, which represents a minor bleeding rate. Moreover, in the Berton et al study (33), the code 0 represents no bleeding, 1 and 2 represent a minor bleeding since it

can be stopped by a simple compression and the codes 3 and 4 represent a major bleeding. In the present review, minor bleeding represents the post extraction bleeding that can be stopped with local hemostatic measure. Moderate bleeding corresponds to every bleeding event requiring an unscheduled medical appointment, although non-major. And major bleeding represents postoperative bleeding events in patients requiring hospitalization after the dental extraction.

The seven studies included a postoperative follow up from the day of the surgery. In five studies (29,31,32,33,35) the follow up started 30 min after the extraction and the second one was one week after, whereas an additional follow up was also performed 3 days after the extraction in one study (30). In one study (34), the follow-up was fulfilled on phone call 2 days after the extraction and 2 weeks postoperatively.

Authors	Year	Country	Study Design	Age (mean)		Gender (men:women)			Type of OAT	Study size	Number of teeth extracted
Morimoto et al (29)	2015	Japan	Case series	43-86		17:02			Rivaroxaban, Apixaban, Dabigatran	19 patients	21 simple dental extraction
Mauprivez et al (30)	2016	France	Prospective observational study	DOACs group: 70.26 ±2.07	VKAs group: 70.60 ±2.80	DOACs group: 14:17	VKAs group: 11:9		Apixaban, Dabigatran, Rivaroxaban, VKAs (warfarin, fluindione)	51 patients	DOAC group: 73 VKA group: 53
Miclotte et al (31)	2016	Belgium	Prospective case-control study	Non-OAT patients: 72	DOACs patients: 76	Non-OAT patients: 13:13	DOACs patients: 15:11		Apixaban, Dabigatran, Rivaroxaban	52 patients	DOAC group: 68
Yagyuu et al (32)	2017	Japan	Retrospective cohort study	DOACs patients: 72.3±7.1	VKAs patients: 73.7±15.6	DOACs group: 38:34	VKAs group: 63:37		Apixaban, Rivaroxaban, Dabigatran, Edoxaban, VKAs	541 patients	DOACs group: 72 VKAs group: 100 No OAT group: 1024
Berton et al (33)	2018	Italy	Prospective comparative study	DOACs patients: 76 ± 9.2	VKAs patients: 76 ± 7.7	DOACs patients: 34:31	VKAs patients: 31:34		DOACs and VKAs patients	130 patients	65 in each group
A Lababidi et al (34)	2018	Australia	Retrospective controlled cohort study	DOACs patients: 72 ±2.00	VKAs patients: 71 ± 1.49	DOACs patients: 20:23	VKAs patients: 26:24		Apixaban, Dabigatran, Rivaroxaban, Warfarin	93 patients	DOAC group:46 simple exodoncia Warfarin group:52 simple exodoncia
Rocha et al (35)	2020	Brazil	Prospective cohort	DOACs patients: 35-70	VKAs patients: 34-72	Non-OAT patients: 12:3	DOACs patients: 12:3	VKAs patients: 12:3	Warfarin, Rivaroxaban, Dabigatran, Apixaban	45 patients	DOAC group:30 Non OAT group: 24-33 VKA group:25-35

DOAC: Direct Oral Anticoagulants, **VKA:** Vitamin K Antagonist, **OAT:** Oral Anticoagulant Therapy

Table 6: General sample characteristics of the included studies

Table 6bis: General sample characteristics of the included studies

Authors	Extraction method	Hemostatic measures	Suture	Bleeding rate	Interruption of DOACs	Follow-up
Morimoto et al	Elevators and forceps, and inflamed granulation tissue completely curetted	Oxidized cellulose or atelocollagen sponge	Sutures using 4-0 silk	None, mild , severe	No	30min after the extraction and 1 week after
Mauprivez et al	Elevators and/or forceps, and inflamed granulation tissue completely curetted	Application of an absorbable gelatin sponge	The wound was closed with 4.0 polyglactin 910 sutures	Mild, moderate, severe	No	The day of the surgery, 3 days after, 7 days after
Miclotte et al	Loosing the gingiva with a syndesmotome followed by forceps extraction	Suture with adequate hemostasis	Suture with Vicryl® 3-0	Scale from 1 to 5 1 = bleeding 5 = continued bleeding despite standard measures	Yes	The day of the extraction, after 7 days
Yagyuu et al	Exodoncia without removing the surrounding bone or cutting the gum.	Compression with gauze, injection of local anaesthetics with vasoconstrictor and/or use of absorbable haemostats	Not in every case	/	No	30min and 7 days after the extraction
Berton et al	Use of elevators and forceps, socket debridement with manual curettes	Compression with a roll of gauze and in case of lack of adequate bleeding control, absorbable oxidized cellulose sponges or gauze compression soaked with tranexamic acid 500 mg/ml	Non-absorbable suture	Bleeding classification according to Iwabuchi: from 0 to 4	No	30min after the extraction and 1 week after
A Lababidi et al	Up to 4 teeth extractions	Haemostatic agent and suturing of the socket, antifibrinolytic mouthwash for use at home, no additional haemostatic measures at all, suturing, packing and suturing alone, without any additional operative haemostatic measures	Not in every case	Minor, major	Yes	2-day follow-up/phone call and 2-week postoperative appointment/ phone call
Rocha et al	Atraumatic extraction with elevators and forceps	Wound closure with sutures and a piece of sterile gauze bitten by the participant	3.0 nylon sutures	The values varied from 2 to 14, for which lower scores indicated less intraoperative bleeding.	No	The day of the surgery and 7 days after

3.4. Synthesis results

3.4.1. The postoperative complications of the DOACs after a simple dental extraction in comparison to the VKAs.

Among the selected articles, five studies (30, 32, 33, 34, 35) were comparing the complications of the DOACs and VKAs after a dental extraction.

The present studies have shown that the most common postoperative complication after a simple dental extraction was immediate postoperative bleeding. Being mostly minor in both groups, there was no significant difference in the immediate postoperative bleeding rate for the DOAC and VKA group after tooth extraction as detailed in table 7.

Table 7: Comparison of the immediate postoperative bleeding rate after dental extraction according to the oral anticoagulant.

	Immediate postoperative bleeding rate according to the oral anticoagulant	
Studies	**DOACs**	**VKAs**
Mauprivez et al (30)	Minor	Minor
Yagyuu et al (32)	Minor	Minor
Berton et al (33)	Minor	Minor
A Lababidi et al (34)	Minor	Minor
Rocha et al (35)	None	None

Furthermore, another complication encountered was delayed bleeding (table 8) in the majority of the studies. In the present review, delayed bleeding corresponds to every bleeding event occurring at least 1-2h after the dental

extraction up to the end of the follow-up period. Overall, delayed bleeding was more encountered in patients under VKAs.

Table 8: Comparison of the number of patients with delayed postoperative bleeding after simple dental extraction in patients under VKAs and DOACs

	Number of patients with delayed bleeding according to the oral anticoagulant	
Studies	**DOACs**	**VKAs**
Mauprivez y al (30)	7 (31)	5 (20)
Berton et al (33)	5 (65)	8 (65)
A Lababidi et al (34)	2 (43)	5 (50)
Rocha et al (35)	0 (15)	1 (15)

In order to control the bleeding, additional hemostatic measures were required in three of the present studies. In the study of A Lababidi et al (34), the majority of the procedures within the DOAC group required additional hemostatic measures following the dental extraction as: haemostatic agent and suturing of the socket; antifibrinolytic mouthwash for use at home; no additional haemostatic measures; suturing or packing and suturing alone. Whereas in the study of Rocha et al (35) only the procedures within the VKA group needed extra hemostatic measures after the dental extraction. In the case of the Berton al study (33) both groups required extra hemostatic measures of post-extraction.

In addition, other complications have been observed in the articles as well as those cited above. Two postoperative infections and one cutaneous ecchymosis were noticed on DOAC patients in the study of Berton et al (33) and swelling/erythema during wound healing in both groups in the study of Rocha et al (35).

3.4.2. The postoperative complications of the DOACs after a simple dental extraction in comparison to patients not under oral anticoagulant therapy.

Among the selected articles, three studies (29, 31 35) are studying the complications of the patients under DOAC therapy. One article presents the possible complications after tooth extraction for patients under DOAC and the two other studies are comparing the postoperative complications of patients under DOAC therapy and patients not under oral anticoagulant therapy following a simple dental extraction procedure.

In the study of Morimoto et al (29) the postoperative complication was a postoperative minor bleeding rate. However, it is not mentioned if the bleeding rate was considered immediate or delayed.

Table 9: Comparison of the immediate postoperative bleeding rate after dental extraction

	Immediate postoperative bleeding rate for DOAC and control group	
Studies	**DOACs**	**Non-OAT**
Miclotte et al (31)	Minor/moderate	Minor
Rocha et al (35)	None	None

From the comparison on table 9 we can underline the difference of the postoperative bleeding observed in the different studies. In the studies of Morimoto et al (29) and Miclotte et al (31), all the patients experienced bleeding after the extraction in contrast to the study of Rocha el al (35) where no bleeding happened post-extraction.

Furthermore, delayed bleeding (table 10) was only noticed in one study.

Table 10: Comparison of the number of patients with delayed postoperative bleeding after simple dental extraction in patients under DOACs and control group

	Delayed postoperative bleeding rate for DOAC and control group	
Studies	**DOACs**	**Non-OAT**
Miclotte et al (31)	7 (26)	0 (26)
Rocha et al (35)	0 (15)	0 (15)

Moreover, postoperative additional hemostatic measures were only carried out in one study (35), where it was required for one procedure in the non-anticoagulated group whilst no additional hemostatic measure was needed in individuals of the DOAC group following the extraction.

3.4.3. The effect of the alteration of the anticoagulant therapy on the postoperative bleeding

In the selected articles, two studies (31, 34) included patients with cessation of the morning dose of DOAC the day of the dental extraction.

Table 11: Postoperative bleeding rate of patients with cessation of DOAC the morning of the procedure

Studies	Bleeding rate
Miclotte et al (31)	Minor/moderate
A Lababidi et al (34)	None

In the study of A Lababidi et al (34), no bleeding events were observed for these patients (table 11), however most of the procedures included additional hemostatic measures following the extraction.

Furthermore, in the study of Miclotte et al (31) high bleeding scores were encountered during the procedure for the majority of the patients participating in the study; and the postoperative bleeding -although predominantly minor- was observed immediately after the exodontia but also up to 6 days after the extraction in some cases.

4. Discussion

The present systematic review provides information based on the postoperative complications of novel oral anticoagulants after a simple dental extraction. As well as the complications of discontinuation of the anticoagulant therapy for this type of anticoagulant after a simple dental extraction.

Among the postoperative complications of the new oral anticoagulants and the vitamin K antagonists after a simple dental extraction, bleeding is the most frequent complication encountered in the studies (30, 32, 33, 34, 35). We can encounter two types of bleeding: Immediate post-operative bleeding and non-immediate/delayed bleeding.

The most frequent type of bleeding is the immediate postoperative bleeding. It is encountered in all the studies. In this review, the bleeding is mild in the two groups of oral anticoagulants. Therefore, both medications present similar immediate complications.

In the case of the delayed bleeding post extraction it is not present in all the studies of this review. It is only present in a minority of patients in the studies of Mauprivez et al (30), Berton et al (33), Lababidi et al (34), and Rocha et al (35). There is not a big difference in the number of patients with delayed bleeding after the simple exodontia between the two groups of oral anticoagulants.

Similarly, several studies reported patients undertaking the same therapy whilst undergoing dental extraction and the same complications are mentioned. Therefore, in the study of Brennan et al (36), the bleeding post extraction between the DOACs and warfarin group are comparable, being minor in both groups. Moreover, the study of Wenbing Hua et al (37) has reported that the outcomes for bleeding are also mild in both groups. However, the bleeding was less

excessive for patients taking DOACs in comparison with the group of VKAs patients and the bleeding risk was also lower.

The results of the present review show that all the studies used the same extraction method. However, one of the limitations is that the hemostatic measures are different in the studies, which can influence the bleeding rate. Thereby, the study of Berton et al (33) employed additional hemostatic measures, whereas the study of Lababidi et al (34) either extra hemostatic measures were employed or no additional hemostatic measures at all.

Most studies represent similar results. However, given the novelty of the DOACs, there are not enough published studies about the complications of anticoagulants related to the dental extractions and most studies about DOACs and VKAs include patients taking antiplatelets in addition to the anticoagulants covered in this review. And, among the limitations of the present study, the number of eligible patients in the studies is limited since surgical extractions were excluded. Also, the review was not randomized, which can lead to residual confounding.

After a simple dental extraction, all the patients experience bleeding as a complication, whether under DOACs or not under any oral anticoagulant (including antiplatelets). In the present review, the studies of Morimoto et al (29) and Miclotte et al (31) have reported similar complications: minor bleeding immediately after the dental extraction for the patients under DOACS and the patients not under anticoagulants. In contrast to the study of Rocha et al (35) where no postoperative bleeding was experienced except for 1 patient. Also, no delayed bleeding is encountered in this comparison group.

The study of Bensi et al (39) has reported different results with delayed bleeding. In this study, many patients under DOACs experienced bleeding up to 7 days after the dental procedure.

Moreover, in the present review, no additional hemostatic measures were required following the dental extraction in the studies (29, 31, 35) comparing the patients under DOACs and the patients not under any oral anticoagulants.

One of the limitations of the obtained result is the lack of studies about the complications of DOACs in dentistry for every invasive treatment separately. In the case of this review, there is weak evidence of the postoperative bleeding management and complications after a simple dental extraction. Another limitation of our results is the complications according to the comorbidities. In the study of Cocero et al (38), the bleeding was compared in patients under DOACs and not under anticoagulants, with and without comorbidities in both groups, in order to identify the risks of bleeding after the extraction in the case of patients under DOACs.

In the present review, there is a lack of studies since most of the published articles comparing the patients under DOACs with patients not under anticoagulants include patients under combined anticoagulant therapy (DOAC and VKA or DOAC and antiplatelets) as in the study of Müller et al (40), leading to a lack of evidence on this topic and biased results.

Moreover, further studies should include comparison of the complications of every DOAC (Apixaban, Dabigatran, Edoxaban, Rivaroxaban) especially with the low evidence about Edoxaban in the present review since it is only encountered in one study (32). It should also include comparison of the complications according to the indication of the DOACs therapy.

The results of the present review also showed that the alteration of the DOACs therapy for the dental extraction, does not impact the bleeding rate in comparison to the continued therapy according to the studies of Miclotte et al (31) and Lababidi et al (34). However, the discontinuation of the new oral

anticoagulants therapy leads to higher bleeding scores during the procedure (31) requiring additional hemostatic measures after the dental extraction (34).

Another complication of the alteration of the DOACs therapy is the delayed bleeding mentioned in several studies, requiring additional hemostatic measures.

Among the limitations of this review, only two studies (31, 34) compare the complications of the DOACS discontinuation. And in both studies, only a small number of patients are treated (40 patients in total).

According to the study of Nathwani and Wanis (41), local hemostatic measures allow to manage appropriately patients under DOACs after a dental extraction and the discontinuation of this anticoagulant treatment for the dental extraction should be decided by the prescribing physician. Also, this treatment alteration might lead to a higher risk of thromboembolic event.

The present review has the same weakness as the study of Caliskan et al (42). In fact, as in the studies included for the review (31, 34), both reviews do not consider the short half-life of the DOACs and the time period between intake and tooth extraction.

Despite the limitations of the number of studies including the discontinuation of DOACs for a simple dental extraction, further studies should include comparison of the discontinuation of DOACs and VKAs before undergoing dental extraction, in order to have more information about the postoperative complications of both oral anticoagulants for the dental clinicians. Further studies should also include more invasive oral surgical procedures since different outcomes can be obtained.

Furthermore, being a recent treatment, the lack of studies and evidence prevents us from being able to say whether the discontinuation of DOAC therapy before an invasive dental procedure (in the present review, simple dental extraction) will help reduce the postoperative complications.

However, all the published studies concerning the discontinuation of the DOAC therapy show the same results and many studies are still in progress on this subject.

5. Conclusion

- The most frequent postoperative complication for patients under DOACs and patients under VKAs after a simple dental extraction is bleeding. In both groups, the bleeding is mostly minor and can be immediate or delayed. To manage this complication, the dental clinician will have to perform additional hemostatic measures.

- Patients under new oral anticoagulant treatment have the same postoperative bleeding risk after a dental extraction as patients not under anticoagulant. In both groups, minor bleeding is experienced immediately after the extraction. However, delayed bleeding does not occur in patients who are not under anticoagulants.

- DOACs are a safe drug and do not require the discontinuation/alteration of the regimen for a simple dental extraction. Further studies are required to determine if surgical procedures in dentistry may require an alteration of the DOAC regimen.

Conflict of interest

The authors declare that they have no conflicts of interest in this study.

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Annex 1: PRISMA Checklist 2020 (26)

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Front page
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	6
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	15
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	17
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	20-21
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	19-20
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	19-20
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	22-23
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	23
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	23
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	18
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	23-24
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	18
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	23
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	N/R
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	23
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	N/R
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	N/R
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	N/R
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	23
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	N/R

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	25-26
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	26
Study characteristics	17	Cite each included study and present its characteristics.	32-33
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	27-29
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	29-31
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	34, 36, 38
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	35-38
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	N/R
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	N/R
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	29
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	N/R
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	40, 42, 43
	23b	Discuss any limitations of the evidence included in the review.	41, 42
	23c	Discuss any limitations of the review processes used.	40, 41, 42
	23d	Discuss implications of the results for practice, policy, and future research.	41, 42
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	N/R
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	N/R
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	N/R
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	N/R
Competing interests	26	Declare any competing interests of review authors.	N/R
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	N/R

Annex 2: Article paper format following the publication standards of the Journal of Clinical and Experimental Dentistry

Systematic review on the effects of the discontinuation of the anticoagulant therapy and the postoperative bleeding, in patients under new oral anticoagulants after dental extraction.

New oral anticoagulants and simple dental extraction

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Abstract

Background: The present systematic review compares the effects of the discontinuation of the anticoagulant therapy and the postoperative bleeding, in patients under new oral anticoagulants after dental extraction. The purpose of this study is to determine the postoperative complications of the DOACs after a simple dental extraction in comparison to the VKAs and with patients not under anticoagulants. This study aims to determine the postoperative complications of the DOACs in the case of an alteration of the anticoagulant regimen before a dental extraction.

Materials and methods: The electronic search was conducted on two databases (MedLine complete and Scopus). The research included patients under DOACs undergoing simple dental extraction. The inclusion criteria included randomized controlled trials, cohort studies, case series, retrospective cohort, prospective cohort and studies on human individuals.

Results: 7 studies were selected, complying to all the inclusion criteria. 931 patients were treated. The bleeding rate was ranging from none, minor, moderate. All the studies included a postoperative follow up from the day of the surgery. The bleeding is immediate and minor after a dental extraction for patients under DOACs, VKAs and with no-OAT.

Conclusion: The most frequent postoperative complication for patients under DOACs and patients under VKAs after a simple dental extraction is minor bleeding: immediate or delayed. DOACs are a safe drug and do not require the discontinuation/alteration of the

therapy for a simple dental extraction. Further studies are required to determine if surgical procedures in dentistry require an alteration of the DOAC regimen.

Keywords: "*New oral anticoagulants", "NAOCs", "DOACs", "VKAs", "Exodontia", "Simple extraction", "Dabigatran", "Rivaroxaban", "Apixaban", "Edoxaban", "Postoperative bleeding*

Introduction

The oral anticoagulant therapy (OAT) is an increasingly common treatment in the population. In the dental field, it is essential to monitor the patients taking anticoagulants, in order to achieve the adequate protocol as treatment. To prevent the clot from spreading inappropriately, there are natural anticoagulants, called inhibitors, which are also produced by the liver: antithrombin, protein C, protein S, etc. However, in some diseases, the coagulation is altered, leading to hematopoietic diseases, such as thromboembolism. To treat and prevent these abnormalities and inhibit the coagulation system more selectively, anticoagulants will be prescribed. (1) They can be administered orally or intravenously.

There are two types of oral anticoagulants: VKAs (Vitamin K Antagonists) and NOACs (Novel Oral Anticoagulants): Oral antivitamin K anticoagulants are used in atrial fibrillation (valvular or non-valvular) and direct-acting oral anticoagulants (DOA) are used in non-valvular atrial fibrillation (1). The patients under a NOACs have to be under daily medication. (2) The first new oral anticoagulant was developed in 2010: Dabigatran. Followed by Rivaroxaban (2011), Apixaban (2012), Edoxaban (2014). (3) These drugs are prescribed more and more over the years, due to the aging of the population. Nevertheless, until today, many health professionals are not aware of the management of the patients under new oral anticoagulants since it is a new drug on the market that differs a lot from the conventional ones (i.e. VKAs or Heparin) in its use and its dosage. It is a new drug for dentists and more studies are required in order to study the complications and the management of patients under new oral anticoagulants in order to be prepared before the invasive procedures. A few guidelines are available on many databases; however, many doubts are still present towards these new drugs. One of the daily treatments at a dentist is the simple dental extraction. It is also an invasive procedure, although presenting minimal risks as long as it is performed

in an aseptic area, respecting the hemostatic procedures. However, in case of a patient under anticoagulants, this procedure can present many risks and perioperative complications that the dentist should be aware of. For all the aforementioned, the aim of the present review is to evaluate the possible discontinuation/alteration of the anticoagulant therapy and the postoperative bleeding of patients under new oral anticoagulants after a simple dental extraction was performed in order to analyze the issues derived.

Materials and methods

- Protocol and focused question: The present systematic review was carried out according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) (4). The following focus question was employed according to the population, intervention, comparison, and outcome study design: Among anticoagulant patients undergoing simple dental extraction, do direct oral anticoagulants demonstrate a reduction of the intra- and postoperative complications in comparison to VKAs anticoagulants?

-Selection criteria: Before starting the study, a series of inclusion and exclusion criteria were established. Patients taking dabigatran, rivaroxaban, apixaban or edoxaban undergoing a simple dental extraction were included. The types of studies included randomized controlled trials; cohort studies; case series; retrospective cohort; prospective cohort; studies on human individuals; publications in English or Spanish; studies about more than 5 patients; published until December 2021. The variable included studies that will provide data related to assessing bleeding risk after a simple dental extraction in patients undertaking NOACs with or without altering the anticoagulation therapy. And studies comparing the bleeding risk and the complications of the NOACs with the VKAs. Studies about patients taking intravenous anticoagulants, patients undergoing other dental treatment, and studies published before 2011 were excluded.

-Search strategy: An electronic search was carried out by the authors in two databases: Medline complete and Scopus including articles until December 2021. The following keywords were combined with the Boolean AND and OR

operators, as well as the controlled terms (such as the “MeSh” words) in an attempt to obtain the best and broadest search: “((simple dental extraction) OR (Dental extraction) OR (exodontia) OR (dentoalveolar surgery) OR (Tooth extraction) OR (surgery,oral)) AND ((direct oral anticoagulants) OR (oral anticoagulants) OR (new oral anticoagulants) OR (novel oral anticoagulants) OR (non-vitamin K oral anticoagulants) OR (NVKA oral anticoagulants) OR (NOACs) OR (DOACs) OR (anticoagulants)) AND ((vitamin K antagonists anticoagulants) OR (conventional anticoagulants) OR (VKAs anticoagulants) OR (anticoagulants)) AND ((intraoperative complications) OR (postoperative complications) OR (complications) OR (bleeding) OR (bleeding time) OR (risk factors))” The search was completed with a review of the references provided in each of the studies in order to identify any additional studies. Finally, a cross-search of potentially interesting articles was carried out for the introduction.

-Screening methods and data abstraction: The selection of the studies was carried out by two reviewers (AH, ML). A selection process was carried out. The titles were reviewed in order to eliminate irrelevant publications, followed by the removal of the duplicated articles. The abstracts were reviewed and filtered according to the type of study, type of invasive treatment, type of extraction, type of anticoagulants, and result variables. The last stage consisted of a complete reading of each article and extracting the data according to a predetermined data extraction form to confirm the eligibility of the studies. In case of any disagreement, it was resolved by mutual consensus of both the reviewers. The following information was extracted from the studies: Authors detail, year of publication, country, study design, age and gender of the patients, type of DOAC, other oral anticoagulants (VKAs), study size, number of teeth extracted, teeth extraction method, hemostatic measures, bleeding rate, interruption of DOAC or not, follow-up time post extraction. These data were independently extracted.

- Risk of bias in individual studies: The quality of the included studies was assessed by two reviewers (AH, ML) in order to assess the methodological quality and risk of bias of all included articles. The methodological quality of the studies

was performed according to the CASPE guideline (5). Studies were considered to be at “low risk of bias” if they meet all the criteria. If there was a possible bias in at least one criteria, they were considered to have an “uncertain risk of bias”. And the studies with a “high risk of bias” were those where one or more criteria were not met or with doubts in more than one criteria. The degree of agreement regarding the evaluation of the quality of the studies was obtained with the Cohen kappa test, following the Landis and Koch scale (6).

- Case definitions: A simple dental extraction is the removal of a tooth that is fully erupted. For this treatment, the patient is anesthetized, to numb the area and reduce the pain. The dentist uses elevators and dental forceps as instruments in order to elevate the tooth and grasp the crown of the tooth. No flap opening or suture is required in a simple dental extraction, also called non-surgical dental extraction. (7)

Results

-Study selection: A total of 1034 articles were obtained from the initial search process: Medline Complete (n=332) and Scopus (n=732). Among the 1034 articles, 90 were excluded because they were duplications and 930 were excluded since they were not identified as potentially eligible articles through the screened by titles and abstracts and the inclusion criteria. Another screening was carried out according to the type of study and 7 articles were excluded. As a result, 7 articles met all the inclusion criteria and were included in the present systematic review (Figure 1). The k-value for agreement between the interexaminer on the study inclusion was 1.0 (titles and abstracts) and 1.0 (study type), indicating "complete" agreement, respectively, based on the criteria from Landis and Koch (6).

- Characteristics of included studies (table 1): Of the 7 articles included in this review, there was 1 case series (8), 1 prospective observational study (9), 1 prospective case-control study (10), 3 cohort studies (11,13,14) and 1 prospective comparative study (12). A total of 931 patients were treated, with an average age of 70 years and a majority of them were male. A total of 1795 teeth were

extracted: 375 on patients taking DOACs, 305 under VKAs and 1115 on non-OAT patients. There was one study comparing apixaban, dabigatran, edoxaban and rivaroxaban with VKAs and one study comparing VKAs and DOACs in general. Non-OATs patients were compared with patients under DOACs in one study and with patients under DOACs and patients under VKAs in another study. In two studies the patients underwent surgical and simple dental extractions but the overall percentage of surgical extractions was inferior to 15%. In all the included studies elevators and forceps were used for the extraction while performing an atraumatic extraction without cutting the surrounding bone nor cutting the gum, followed by the complete curettage of the inflamed granulation tissue. After this, hemostatic measures were taken. There were two studies (10,14) in which the hemostatic measures were suturing after the compression with gauze. In two studies (8,9) absorbable hemostatic sponges such as oxidized cellulose, gelatin sponge was used in addition to suturing in all the patients, whilst in three studies (11, 12, 13) the use of absorbable hemostats was only performed if there as a lack of adequate bleeding control. The sutures were performed after the extractions with non-absorbable material as 4-0 silk, 4.0 polyglactin 910 sutures, Vicryl® 3-0, 3.0 nylon. These sutures were performed for every case except in two studies (11,13) in which the suturing was not performed in every case. The oral anticoagulant therapy with DOACs was discontinued before the extraction in two studies (10,13). The dose of NOAC was skipped on the morning of the procedure in the first study (10) and was restarted according to the normal regimen of the treatment, at least 4 h after the dental extraction following the achievement of an adequate hemostasis. In the other study (13), the perioperative cessation of the NOAC therapy was ranging from 1 to 14 days. In the majority of the studies the bleeding rate was ranging from none, minor, moderate to severe. The bleeding rate was not described in one study (11), however it was mentioned that all the post extraction bleeding could have been stopped with local hemostatic treatment, which represents a minor bleeding rate. The 7 studies included a postoperative follow up from the day of the surgery from 30min after the extraction

up to 2 weeks after.

- Risk of bias across studies: For the reviewed studies, an uncertain risk of bias was considered in all 7 studies. For the one case series study, it was considered to have a high risk of bias due to the very nature of the type of study. The k value (Cohen kappa test) on the agreement between the reviewers of the methodological quality was 0.80 according to the Landis & Koch scale (6).

- Synthesis of the results: Among the selected articles, five studies (8,10,11,12, 13) were comparing the complications of the DOACs and VKAs after a dental extraction. The present studies have shown that the most common postoperative complication after a simple dental extraction was immediate postoperative bleeding. Being mostly minor in both groups, there was no significant difference in the immediate postoperative bleeding rate for the DOAC and VKA group after tooth extraction as detailed in table 2.

Furthermore, another complication encountered was delayed bleeding (table 3) in the majority of the studies. Overall, delayed bleeding was more encountered in patients under VKAs. In order to control the bleeding, additional hemostatic measures were required in three of the present studies. In the study of Rocha et al (14) only the procedures within the VKA group needed extra hemostatic measures after the dental extraction. In the case of the Berton al study (12) both groups required extra hemostatic measures of post extraction.

Among the selected articles, three studies (8,10,14) are studying the complications of the patients under DOAC therapy. One article presents the possible complications after tooth extraction for patients under DOAC and the two other studies are comparing the postoperative complications of patients under DOAC therapy and patients not under oral anticoagulant therapy following a simple dental extraction procedure.

In the study of Morimoto et al (8) the postoperative complication was a postoperative minor bleeding rate. However, it is not mentioned if the bleeding rate was considered immediate or delayed. In the studies of Morimoto et al (8) and Miclotte et al (10), all the patients experienced bleeding after the extraction in

contrast to the study of Rocha el al (14) where no bleeding happened post-extraction. Furthermore, delayed bleeding was only noticed in the study of Miclotte et al (10). Moreover, postoperative additional hemostatic measures were only carried out in one study (14), where it was required for one procedure in the non-anticoagulated group whilst no additional hemostatic measure was needed in individuals of the DOAC group following the extraction.

In the selected articles, two studies (10, 13) included patients with cessation of the morning dose of DOAC the day of the dental extraction.

In the study of A Lababidi et al (13), no bleeding events were observed for these patients, however most of the procedures included additional hemostatic measures following the extraction. Furthermore, in the study of Miclotte et al (10) high bleeding scores were encountered during the procedure for the majority of the patients participating in the study; and the postoperative bleeding -although predominantly minor- was observed immediately after the exodontia but also up to 6 days after the extraction in some cases.

Discussion:

The present systematic review provides information based on the postoperative complications of novel oral anticoagulants after a simple dental extraction. As well as the complications of discontinuation of the anticoagulant therapy for this type of anticoagulant after a simple dental extraction.

Among the postoperative complications of the new oral anticoagulants and the vitamin K antagonists after a simple dental extraction, bleeding is the most frequent complication encountered in the studies (8,10,11,12,13). We can encounter two types of bleeding: Immediate and non-immediate/delayed post-operative bleeding. Being encountered in all the studies, the most frequent type of bleeding is the immediate postoperative bleeding. In this review, the bleeding is mild in the two groups of oral anticoagulants. Therefore, both medications present similar immediate complications. In the case of the delayed bleeding post extraction it is not present in all the studies of this review. It is only present in a minority of patients in the studies of Mauprivez et al (9), Berton et al (12), Lababidi et al (13),

and Rocha et al (14). There is not a big difference in the number of patients with delayed bleeding after the simple exodontia between the two groups of oral anticoagulants. The study of Wenbing Hua et al (16) has reported that the outcomes for bleeding was less excessive for patients taking DOACs in comparison with the group of VKAs patients and the bleeding risk was also lower. One of the limitations of the present review is that the hemostatic measures are different in the studies, which can influence the bleeding rate. Thereby, the study of Berton et al (12) employed additional hemostatic measures, whereas the study of Lababidi et al (13) either extra hemostatic measures were employed or no additional hemostatic measures at all. However, given the novelty of the DOACs, there are not enough published studies about the complications of anticoagulants related to the dental extractions. And, among the limitations of the present study, the number of eligible patients in the studies is limited since surgical extractions were excluded.

Also, the review was not randomized, which can lead to residual confounding.

After a simple dental extraction, all the patients experience bleeding as a complication, whether under DOACs or not under any oral anticoagulant (including antiplatelets). In the present review, the studies of Morimoto et al (8) and Miclotte et al (10) have reported similar complications: minor bleeding immediately after the dental extraction for the patients under DOACS and the patients not under anticoagulants. In contrast to the study of Rocha et al (14) where no postoperative bleeding was experienced except for 1 patient. Another limitation of our results is the complications according to the comorbidities. In the study of Cocero et al (18), the bleeding was compared in patients under DOACs and not under anticoagulants, with and without comorbidities in both groups, in order to identify the risks of bleeding after the extraction in the case of patients under DOACs. In the present review, there is a lack of studies since most of the published articles comparing the patients under DOACs with patients not under anticoagulants include patients under combined anticoagulant therapy (DOAC and VKA or DOAC and antiplatelets) as in the study of Müller et al (19), leading to

a lack of evidence on this topic and biased results. Moreover, further studies should include comparison of the complications of every DOAC (Apixaban, Dabigatran, Edoxaban, Rivaroxaban) especially with the low evidence about Edoxaban in the present review since it is only encountered in one study (11). It should also include comparison of the complications according to the indication of the DOACs therapy. The results of the present review also showed that the alteration of the DOACs therapy for the dental extraction, does not impact the bleeding rate in comparison to the continued therapy according to the studies of Miclotte et al (10) and Lababidi et al (13). However, the discontinuation of the new oral anticoagulants therapy leads to higher bleeding scores during the procedure (10) requiring additional hemostatic measures after the dental extraction (14). Another complication of the alteration of the DOACs therapy is the delayed bleeding mentioned in several studies, requiring additional hemostatic measures. Among the limitations of this review, only two studies (10,13) compare the complications of the DOACs discontinuation. And in both studies, only a small number of patients are treated (40 patients in total). According to the study of Nathwani and Wanis (20), local hemostatic measures allow to manage appropriately patients under DOACs after a dental extraction and the discontinuation of this anticoagulant treatment for the dental extraction should be decided by the prescribing physician. The present review has the same weakness as the study of Caliskan et al (21). In fact, as in the studies included for the review (10,13), both reviews do not consider the short half-life of the DOACs and the time period between intake and tooth extraction. Despite the limitations of the number of studies including the discontinuation of DOACs for a simple dental extraction, further studies should include comparison of the discontinuation of DOACs and VKAs before undergoing dental extraction, in order to have more information about the postoperative complications of both oral anticoagulants for the dental clinicians. Furthermore, the lack of studies and evidence prevents us from being able to say whether the discontinuation of DOAC therapy before an invasive dental procedure (in the present review, simple dental extraction) will help reduce

the postoperative complications. However, all the published studies concerning the discontinuation of the DOAC therapy show the same results and many studies are still in progress on this subject.

In conclusion, the most frequent postoperative complication for patients under DOACs and patients under VKAs after a simple dental extraction is minor bleeding: immediate or delayed. Patients under new oral anticoagulant treatment and patients not under anticoagulant have the same postoperative bleeding risk after a dental extraction. DOACs are a safe drug and do not require the discontinuation/alteration of the therapy for a simple dental extraction. Further studies are required to determine if surgical extraction and other dental surgical procedures may require an alteration of the DOAC regimen.

Conflict of interest

The authors declare that they have no conflicts of interest in this study.

Role of the funding source

No external funding, apart from the support of the author's institution, was available for this study.

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Annex 1:

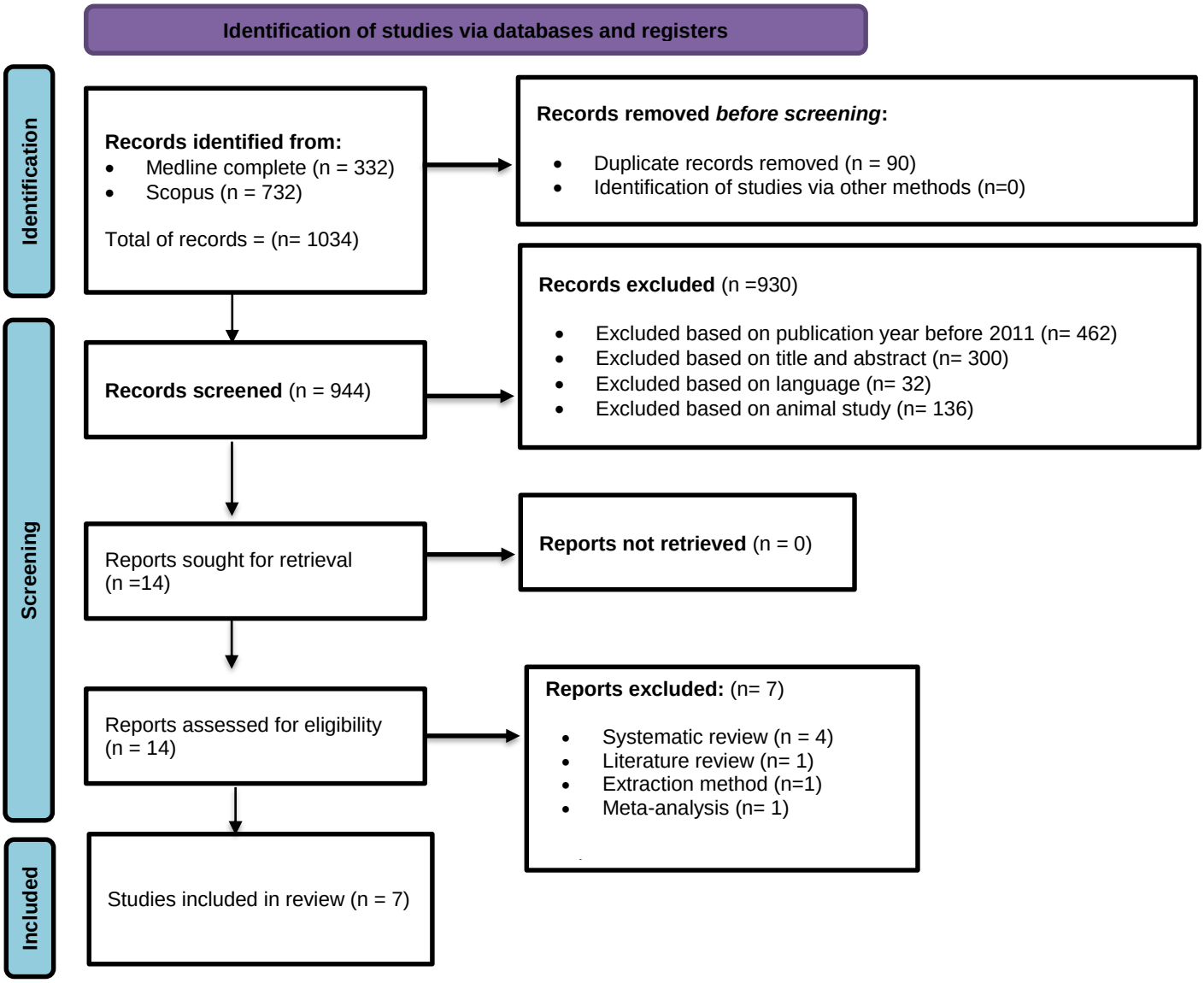

Figure 1. Flow diagram of study search and article selection process during the systematic review according to the PRISMA guideline (Ref PRISMA).

Annex 2;

Table 1: General sample characteristics of the included studies

Authors	Year	Country	Study Design	Age (mean)		Gender (men:women)		Type of OAT	Study size	Number of teeth extracted
Morimoto et al (8)	2015	Japan	Case series	43-86		17:02		Rivaroxaban, Apixaban, Dabigatran	19 patients	21 simple dental extraction
Mauprivez et al (9)	2016	France	Prospective observational study	DOACs group: 70.26 ±2.07	VKAs group: 70.60 ±2.80	DOACs group: 14:17	VKAs group: 11:9	Apixaban, Dabigatran, Rivaroxaban, VKAs (warfarin, fluindione)	51 patients	DOAC group: 73 VKA group: 53
Miclotte et al (10)	2016	Belgium	Prospective case-control study	Non-OAT patients: 72	DOACs patients: 76	Non-OAT patients: 13:13	DOACs patients: 15:11	Apixaban, Dabigatran, Rivaroxaban	52 patients	DOAC group: 68
Yagyuu et al (11)	2017	Japan	Retrospective cohort study	DOACs patients: 72.3±7.1	VKAs patients: 73.7±15.6	DOACs group: 38:34	VKAs group: 63:37	Apixaban, Rivaroxaban, Dabigatran, Edoxaban, VKAs	541 patients	DOACs group: 72 VKAs group: 100 No OAT group: 1024
Berton et al (12)	2018	Italy	Prospective comparative study	DOACs patients: 76 ± 9.2	VKAs patients: 76 ± 7.7	DOACs patients: 34:31	VKAs patients**:** 31:34	DOACs and VKAs patients	130 patients	65 in each group
A Lababidi et al (13)	2018	Australia	Retrospective controlled cohort study	DOACs patients: 72 ±2.00	VKAs patients: 71 ± 1.49	DOACs patients: 20:23	VKAs patients: 26:24	Apixaban, Dabigatran, Rivaroxaban, Warfarin	93 patients	DOAC group:46 simple exodontias Warfarin group:52 simple exodontia
Rocha et al(14)	2020	Brazil	Prospective cohort	DOACs patients: 35-70	VKAs patients: 34-72	Non-OAT patients: 12:3	DOACs patients: 12:3 / VKAs patients: 12:3	Warfarin, Rivaroxaban, Dabigatran, Apixaban	45 patients	DOAC group:30 Non OAT group: 24-33 VKA group:25-35

DOAC: Direct Oral Anticoagulants, VKA: Vitamin K Antagonist, OAT: Oral Anticoagulant Therapy

Table 1 bis: General sample characteristics of the included studies

Authors	Extraction method	Hemostatic measures	Suture	Bleeding rate	Interruption of DOACs	Follow-up
Morimoto et al (8)	Elevators and/or forceps, and curettes	Oxidized cellulose or atelocollagen sponge	Sutures using 4-0 silk	None, mild, sever	No	30min and 1 week after the extraction
Mauprivez et al (9)	Elevators and/or forceps, and curettes	Absorbable gelatin sponge	The wound was closed with 4.0 polyglactin 910 sutures	Mild, moderate, severe	No	The day of the surgery, 3 days after, 1-week after
Miclotte et al (10)	Syndesmotomy followed by forceps extraction	Suture with adequate hemostasis	Suture with Vicryl® 3-0	From 1 to 5 1 = bleeding 5 = continued bleeding despite standard measures	**Yes**	The day of the extraction and after 1 week
Yagyuu et al (11)	Elevators and/or forceps, and curettes	Compression with gauze, injection of local anaesthetics with vasoconstrictor and/or use of absorbable haemostats	Not in every case	HAS-BLED, ATRIA, ORBIT	**No**	30min and 1 week after the extraction
Berton et al (12)	Use of elevators and forceps and curettes	Compression with a roll of gauze, absorbable oxidized cellulose sponges or gauze compression soaked with tranexamic acid 500 mg/ml	Non-absorbable suture	Bleeding classification according to Iwabuchi: from 0 to 4	**No**	30min and 1 week after the extraction
A Lababidi et al (13)	Up to 4 teeth extractions	Hemostatic agent and suturing of the socket, antifibrinolytic mouthwash for use at home, no additional hemostatic measures at all, suturing, packing and suturing alone, without any additional operative hemostatic measures	Not in every case	Minor, major	**Yes**	2-day follow-up/phone call and 2-week postoperative appointment/ phone call
Rocha et al (14)	Atraumatic extraction with elevators and forceps	Sutures and a piece of sterile gauze bitten by the participant	3.0 nylon sutures	From 2 to 14, for which lower scores indicated less intraoperative bleeding.	**No**	30min and 1 week after the extraction

Annex 3:

Table 2: Comparison of the immediate postoperative bleeding rate after dental extraction according to the oral anticoagulant.

	Immediate postoperative bleeding rate according to the oral anticoagulant	
Studies	**DOACs**	**VKAs**
Mauprivez et al (9)	Minor	Minor
Yagyuu et al (11)	Minor	Minor
Berton et al (12)	Minor	Minor
A Lababidi et al (13)	Minor	Minor
Rocha et al (14)	None	None

Annex 4:

Table 3: Comparison of the number of patients with delayed postoperative bleeding after simple dental extraction in patients under VKAs and DOACs

	Number of patients with delayed bleeding according to the oral anticoagulant	
Studies	**DOACs**	**VKAs**
Mauprivez y al (9)	7 (31)	5 (20)
Berton et al (12)	5 (65)	8 (65)
A Lababidi et al (13)	2 (43)	5 (50)
Rocha et al (14)	0 (15)	1 (15)