SECIB

ORAL SURGERY IN PATIENTS WITH COAGULATION DISORDERS

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1. PRESENTATION OF THE SECIB

The SECIB (Spanish Society of Oral Surgery) is a non-profit scientific association with its own legal personality and full capacity to act at a national level, bringing together professionals in Dentistry, Stomatology and Medicine who have a clinical or scientific interest in Oral Surgery. In this environment, the approach and implementation of this Clinical Practice Guideline (CPG) must be framed, which seeks to jointly evaluate the available evidence on the management of patients with coagulation disorders, to organise and present it appropriately to both professionals and patients. Likewise, it serves to generate recommendations based on scientific evidence that can be disseminated through relevant social and scientific media, to allow them to be applied by oral surgeons in Spain and worldwide in their clinical practice, thereby benefiting the patient.

2. AUTHORSHIP

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3. INTRODUCTION OF THE WORK GROUP

The Association has commissioned a group of experts to develop a CPG on the management of patients with coagulation disorders in dental surgical procedures, such as fitting of implants or dental extractions. This Guideline has been proposed addressing different cases to cover the greatest number of scenarios possible that oral health professionals face with this type of patient. The group that has prepared this CPG is made up of clinical and university experts in the area of health sciences, based on the available scientific evidence.

4. METHODOLOGY

The CPG is an important source of evidence and must therefore be based on an extensive literature review, as well as an exhaustive critical assessment of the articles evaluated. For its preparation, a work group made up of ten professionals was established, selected for their profiles as specific experts in the field. Additionally, there was collaboration from two external reviewers who participated as independent professionals. Finally, the guideline was evaluated and validated by the Spanish Society of Oral Medicine (SEMO), the Spanish Society for Odonto-Stomatology for Patients with Special Needs (SEOENE) and the Spanish Society for Healthcare Quality (SECA). The preparation of the Guideline was carried out in three consecutive phases, some of which were undertaken in parallel at certain times:

- **Phase 1:** Definition of the scope of the guideline and literature search, from June 2019 to January 2020. Milestones included: Definition of clinical doubts, preliminary literature search: first approach to the literature search to redefine the objectives and scope of the CPG; introduction of the Mendeley bibliographic manager; reading and analysis of evidence.

- **Phase 2:** Generation of documentation by the group of experts, from October 2019 to September 2020. Milestones included: Redefinition of the scope of the guidelines and literature searches necessary; second literature search; reading and analysis of evidence; preparation of PICO questions; formulation of recommendations.

- **Phase 3:** Preparation and standardisation of documents, from July 2020 to January 2021. Milestones included: Compilation of prepared documentation; resolution of literature doubts and other media; initial standardisation of documents; preparation of the v.00 initial draft of the working document.

About the working methodology

The document has followed a rigorous methodological process based on the indications of the document “Preparation of Clinical Practice Guide-

lines in the National Health System. Methodological manual" **(1)** and the recommendations available in the Health Guide **(1)**. Likewise, the scientific literature available up to December 2021 has been reviewed.
After cataloguing each piece of evidence found corresponding to a PICO question, we allocate them a grade of recommendation, classified with letters A, B, C or D, with the following meanings:

A) based on at least one meta-analysis, one systematic review, one 1++ clinical trial, or a volume of scientific evidence made up of studies classified as 1+ and with great consistency between them.

B) volume of scientific evidence made up of studies classified as 2++, directly applicable to the target population of the guideline and showing great consistency between them; or from scientific evidence extrapolated from scientific studies classified as 1++ or 1+.

C) volume of scientific evidence made up of studies classified as 2+, directly applicable to the target population of the guideline and showing great consistency between them; or from scientific evidence extrapolated from scientific studies classified as 2++.

D) scientific evidence of level 3 or 4, or scientific evidence extrapolated from studies classified as 2+.

About the literature search

The first approach to the literature through the MEDLINE/PubMed database contributed to realistically defining the scope and objectives of the guideline. The second phase of the search began once the initial approach had been evaluated, observing that it was necessary to redefine both the search criteria and the scope of the guidelines themselves. From there, the criteria for defining the questions in PICO format were defined and continued being completed until December 2021. The search strategies were reviewed following the document by Sampson et al. "An evidence-based practice guideline for the peer review of electronic search strategies", published in 2009 in the Journal of Clinical Epidemiology **(2)**.

About the methodological support model: the role of the external consulting team
The methodological support team was made up of a technical expert in methodology and evidence-based healthcare and a librarian specialised in the field of Health. Additionally, an external methodological support model was used (3, 4), and for reasons of efficiency and profitability, external advice was incorporated in the preparation and development of projects **(5, 6).**

5. JUSTIFICATION OF THE CPG

The current CPGs in patients with coagulation disorders are based on studies carried out in different geographical areas of the world, whose idiosyncrasy requires a critical vision to allow global extrapolation of results to our daily practice. For example, the majority of the literature available on the haemorrhagic risk of anticoagulated patients who require dental extraction and are treated with a coumarin drug revolves around warfarin, although in Spain the coumarin drug used most is acenocoumarol. Another example is the determination of the ideal INR value for treating patients. Some clinical guidelines for the management of anticoagulated patients, such as the Scottish Dental Clinical Effectiveness Programme (SDCEP) recommend not modifying the anticoagulant treatment regimen in patients with an INR of less than 4, it being recommended that this INR be determined in the 24 hours prior to dental treatment or valid for up to 72 hours if its value is usually stable over time. However, almost half of anticoagulated patients have difficulty achieving adequate INR control (Spanish Federation of Anticoagulated Associations). In other Spanish guidelines, such as that published the Spanish Society of Cardiology and the Spanish Society of Epidemiology and Public Health, this value is reduced to an INR of 3, recommending not treating the patient without consulting the doctor and adjusting the anticoagulant dose in case of presenting a higher INR. Professionals who must decide the guidelines for the management of these patients, above all with regard to continuation of the anticoagulant/antiplatelet treatment when they are going to undergo a surgical procedure, have doubts because the protocols have undergone variations over a relatively short period of time.

6. CLINICAL ISSUES ANALYSED

1. In patients anticoagulated with a coumarin drug (acenocoumarol or warfarin) who require dental extraction, is there an increased risk haemorrhagic risk in comparison with non-anticoagulated patients? What if they also take antiplatelet medication?

The number of patients treated with anticoagulant therapy has increased worldwide in recent years, as its use is recommended for prevention of primary and secondary thrombotic events **(1)**. Specifically, coumarin derivatives, such as Warfarin (Aldocumar®) and acenocoumarol (Sintrom®), are two of the 100 medications most prescribed in developed countries to reduce the risk of thromboembolism, especially in patients with prosthetic heart valves **(2)**. The action mechanism of both medications is based on interfering with the metabolism of vitamin K with the resulting reduction of the plasmatic concentration of coagulation factors, although there are pharmacokinetic and pharmacodynamic differences between them. The most interesting at a clinical level is the half-life of both, as that of acenocoumarol is between 5 and 9 hours, while that of warfarin is longer, between 29 and 45 hours **(3)**. The majority of the literature available on the haemorrhagic risk of anticoagulated patients who require dental extraction and are treated with a coumarin drug revolves around Warfarin; however, in Spain the coumarin drug used most is acenocoumarol **(4)**. Dental extraction is a common procedure, and in the case of anticoagulated patients, dentists often consult the need to alter the medication schedule due to the perceived risk of potential uncontrolled bleeding after dental treatment **(5)**. Some clinical guidelines for the management of anticoagulated patients, such as the guideline of the Scottish Dental Clinical Effectiveness Programme recommend not modifying the anticoagulant treatment in patients with an INR (International Normalized Ratio) of less than 4, it being recommended that this INR be determined in the 24 hours prior to dental treatment or valid for up to 72 hours if its value is usually stable over time. However, almost half of anticoagulated patients have difficulty achieving adequate INR control (Spanish Federation of Anticoagulated Associations) and changes may be significant in hours. In other Spanish guidelines, such as that published by the Spanish Society of Cardiology and the Spanish Society of Epidemiology and Public Health (https://secardiologia.es/images/institucional/SESPO-Protocolo.pdf, 2019) , this value is reduced to an INR of 3, recommending not treating the patient without consulting the doctor and adjusting the dose in case of presenting a higher INR. Furthermore, patients who present thrombotic episodes when already receiving antiplatelet therapy are additionally treated with anticoagulant medication. This makes it difficult to evaluate the risk of bleeding in these patients and increases uncertainty for dental personnel and for the patient themselves.
In general, the classic guideline of suspension of the anticoagulant treatment by bridging therapy with low molecular weight herapin prior to a dental extraction has been ruled out due to the increased risk of thromboembolic processes and sometimes of greater risk of bleeding after the procedure **(6)**. The majority of studies carried out in the West report that over 99% of anticoagulated patients have not had significant postoperative bleeding and have not required more than local control measures, with on cases of relevant morbidity or fatality. However, 22 embolic complications have been described (from a total cohort of 2775 patients anticoagulated with warfarin) including 6 fatal, when the anticoagulant dose was reduced or discontinued **(7)**. Nevertheless, the numerous differences detected between guidelines make a rigorous analysis of the evidence necessary.

Evaluation and synthesis of the evidence

A total of 8 articles (5 prospective studies and 3 retrospective studies) have been selected to answer the PICO question: *Patient*, anticoagulated with dicoumarins; *Intervention*, dental extraction; *Comparison*, with antiplatelet patients or patients who are not anticoagulated or antiplatelet; *Outcome*, modification of the relative haemorrhagic risk (PICO Study Table 1). For the evaluation of scientific evidence, the articles were reviewed using the GRADE system.
Recent meta-analyses suggest that the risk of bleeding in anticoagulated patients after dental extractions is higher compared with non-anticoagulated patients, although this difference does not appear to be statistically significant (RR:2.003, 95% CI: 0.987–4.063, p= 0.054) **(8)** In general terms, the

studies included in our work share these prevalence results, reflecting 0 - 1.2% of non-anticoagulated patients bleeding after dental extractions, compared with 2.77 - 54.6% of anticoagulated patients (Table 1). Yamada et al. (2019) compared the bleeding rate between anticoagulated and non-anticoagulated patients and considered other associated risk factors such as number of extractions, type of tooth and degree of soft tissue inflammation in the extraction area. Preoperative administration of antibiotics (OR=2.533, p< 0.05), INR levels greater than 2.11 (compared with anticoagulated patients with a lower INR) (OR= 3.798, p<0.01) and intraoperative difficulties for controlling bleeding (OR= 6.230, p< 0.05) **(9)** were the most significant risk factors. The results of the ROC (Receiver operating characteristics) analysis on the limit of the INR value for identifying patients at risk were similar to those obtained by Febbo et al. (2016), who observed a similar risk of bleeding in patients with INR less than 2.2 and in healthy controls **(10)**. The study of patients with dual therapy, anticoagulant and antiplatelet, was carried out in a total of 3 articles **(9, 11, 12)**. The multivariate analysis of the study by Iwabuchi et al. (2014) concluded that the incidence of post-extraction bleeding in patients receiving antiplatelet therapy is lower than that of patients anticoagulated only with warfarin (OR= 0.1, p= 0.049) **(13)**, and in the study by Yagyuu et al. this difference does not appear to be significant **(14)**. In general terms, the studies are heterogeneous in aspects analysed such as the inclusion criteria for patients treated with warfarin, the evaluation of postoperative bleeding, the management guideline with anticoagulant treatment, the number of extractions carried out, and follow-up time.

The inclusion criteria for patients who are treated with warfarin differ in the limit of the INR value, as some do not specify whether the INR value is an excluding factor **(9)**, some exclude patients with an INR greater than 3 **(11, 15)** and others greater than 4 **(16–18)**. Other studies include patients who replace warfarin with a heparin bridging therapy **(16)** and others who do not discontinue treatment with warfarin **(19)**. Another difference is the definition of the main variable, as in some studies the patient is defined as the main risk measurement variable (7,20) while in others this is the dental extraction itself **(14)**.

To evaluate the risk of post-extraction bleeding, there is no validated and universally accepted method for measuring oral bleeding, therefore it is difficult to establish comparisons. However, there are different scales used by researchers such as the HAS-BLED, applied by the team of Kataoka et al., whose conclusion was that this scale was insufficient for predicting post-extraction bleeding and that patients with warfarin and antiplatelet drugs had a risk 3 times greater of suffering postoperative bleeding compared with healthy controls **(21)**. In the studies that we have included, some works, such as that by Yamada et al. (2020) classified the degree of bleeding of patients (grade 1-3) in accordance with the categorisation proposed in the work by Hasegawa et al. (2017) **(22)**. Other authors, such as Caliskan et al. (2017) and Karsh et al., measured the amount of bleeding by weighing the milligrams of blood embedded in the gauze used to stop the haemorrhage **(18, 19)**. Another difference that we have observed is that some authors included only patients who underwent the extraction of a single tooth **(12)** and others who had more than one extraction **(15, 17).** The follow-up time also varies a lot between some studies and others, some not specifying the follow-up time, some having a 7-day follow-up period **(15, 19)** and others up to 10 days **(17)**. The only article that we found that specified a vitamin K antagonist other than warfarin was that of Bajkin et al. (2015) **(15)**.

Conclusions and recommendations for future research

Dental extraction in patients anticoagulated with dicoumarins appears predictable if factors such as INR ranges are controlled, if a single tooth is extracted and local haemostatic measures are applied to control the haemorrhage. The risk of postoperative bleeding of these patients appears similar to the risk of healthy individuals when the INR value does not exceed 2.2. In other conditions such as INR greater than 3 or several extractions, there is little evidence available to answer this question, therefore in these cases it is recommended to contact the patient's doctor to decide a treatment plan (**Grade C recommendation**). Without doubt, in this review, we have lacked more studies on acenocoumarol, as the majority included patients treated with warfarin or did not specify the vitamin K antagonist drug administered **(12)** such as warfarin. Design: This study was

a retrospective cohort analysis. Incidence rates and propensity score-matched regression models were used to compare the risks of bleeding after tooth extractions involving DOACs and VKAs. Setting: The study took place in a single university hospital in Japan. Participants: Between April 2013 and April 2015, 543 patients underwent a total of 1196 simple tooth extractions. Primary outcome measure The primary outcome measure was the occurrence of postextraction bleeding, which was defined as bleeding that could not be stopped by biting down on gauze and required medical treatment between 30 min and 7 days after the extraction. Results: A total of 1196 tooth extractions (634 procedures. Studies designed to assess the risk of bleeding must very clearly define aspects such as: the follow-up time of the patient, which we recommend to be at least 7 days; the main risk variable, which we recommend be dental extraction, as the medical condition of the patient may vary at different times; the INR range which will be established to include anticoagulated patients; the target population (as the CYP2C9 isoenzyme polymorphism prevalent in the Asian population is more important for warfarin clearance, requiring INR levels to be lower than in the Caucasian population) **(23)**randomized, multicenter trial. METHODS: The study population consisted of patients with NVAF (<80 years old; factors associated with the surgical process such as the number of teeth extracted, the degree of surgical difficulty or the degree of inflammation of the soft tissues; as well as recording whether or not the patient has been previously treated with antibiotics or concomitant treatment with antiplatelet drugs.

2. In patients anticoagulated with herapin who require dental extraction, is there an increased haemorrhagic risk in comparison with non-anticoagulated patients? What if they also take antiplatelet medication?

Herapins are substances with antithrombotic and anticoagulant activity through the inhibition of Factor Xa and factor IIa respectively, the effect against the latter being the least potent. They are therefore expected to entail a lower risk of haemorrhage than vitamin K antagonists (VKA) but with the same antithrombotic activity (1). Herapins are inactivated by digestive enzymes, therefore they are very poorly absorbed orally, and the subcutaneous or parenteral route is chosen for their administration. Depending on whether the herapin used is unfractionated (UFH), low molecular weight (LMWH) or ultra-low molecular weight (ULMWH), its half-life can be between 8 and 24 hours **(2)**. The most common adverse effects are haemorrhage and thrombocytopenia, the latter being late onset (onset between 1 and 2 weeks after having started the treatment) and without association with dose, age or administration route, but instead as an individual response of the patient. The joint administration of herapin with other agents that influence haemostasis, such as antiplatelets, anticoagulants or NSAIDs (non-steroidal anti-inflammatories), can enhance its effect **(3)**. The most common indications for herapins are for situations which require a rapid action and short duration, such as the treatment of deep vein thrombosis and for its prevention after certain surgeries **(4)**. In every day dental practice, the best time for extraction of the heparinised patient is "the day after" the last dose administered; that is, distancing the intervention so that there is greater drug clearance. Patients treated with herapin are mostly patients anticoagulated with VKA drugs who have replaced, by medical indication, their usual treatment with subcutaneous herapin 2 or 3 days before dental treatment **(5)**. A reflection of this is the scarce literature that we have found in this search including patients treated with herapin for reasons other than bridging oral anticoagulants **(6–9)**. Currently, 3 factors must be considered in these patients: the risk of thrombosis according to the underlying condition, the risk of bleeding due to the type of intervention and renal clearance.

Evaluation and synthesis of the evidence

A total of 4 articles (3 prospective studies and 1 retrospective study) have been selected to answer the PICO question: *Patient*, anticoagulated with herapin; *Intervention*, dental extraction; *Comparison*, with antiplatelet patients or patients who are not anticoagulated or antiplatelet; *Outcome*, modification of the relative haemorrhagic risk (PICO Study Table 2). All studies evaluated the risk of bleeding in anticoagulated patients who replaced warfarin with low molecular weight herapin, using at least one comparison group with patients who were not antiplatelet or anticoagulated . The team of Yu-Lu et al. (2018) and of Schmitt et al. (2020) also included a group of individuals treated with antiplatelet agents (although they were not anticoagulated). In

the study by Buchbender et al. (2021) the risk of bleeding was higher in patients who discontinued warfarin and changed to LMWH compared with their usual anticoagulant treatment, within the recommended INR range, this difference being statistically significant ($p< 0.001$). These results coincide with the study by Erden et al. (2016), which has not been included in this review due to lacking a control group, where the 36 patients with prosthetic valves who required multiple dental extractions changed from treatment with warfarin to LMWH, concluding that continuing with warfarin produced less total bleeding compared with discontinuing and using bridging therapy with LMWH **(10)**.

Theoretically, the advantage of using low molecular weight herapin as a bridge is that it has a predictable anticoagulation effect with a significantly shorter half-life than that expected of vitamin K antagonists. Nevertheless, the current trend and what anticoagulation guidelines recommend is not interrupting the anticoagulant treatment, evaluating the INR (less than 3) for dental extraction and using local haemostatic measures **(11)**. The heterogeneity of the studies demonstrates the need to establish criteria which facilitate the design of controlled trials for the evaluation of bleeding. There is a notable difference in the bleeding index in the study by Buchbender et al. (2021) in which the risk of postoperative bleeding in the control group was 12.9%, compared with the 0 - 0.7% of the other studies. Another limitation that must be highlighted is the sample size, as the study by Schmidt et al. (2020) only included 2 patients treated with herapin. An important aspect of this study is that 4 patients treated with warfarin who did not undergo LMWH bridging therapy had to be hospitalised.

Conclusions and recommendations for future research

The evidence on dental extractions in patients treated with herapin seems to reflect an increased risk of bleeding in comparison with the guideline to continue anticoagulant treatment with vitamin K antagonists. Nevertheless, it seems that local haemostatic measures should be sufficient to contain the post-extraction haemorrhage in any case (**Grade D recommendation**). Since, according to guidelines from other surgical specialities, the risk of bleeding in our speciality is considered low or very low, this expert opinion should be taken into account until an acceptable level of evidence is obtained.

3. In patients anticoagulated with DOACs (Direct Oral Anticoagulants) who require dental extraction, is there an increased haemorrhagic risk in comparison with non-anticoagulated patients? What if they also take antiplatelet medication?

For clinicians, the use of anticoagulants for any systemic condition entails maintaining a good balance between the efficacy of the drug for reducing the risk of thromboembolism without increasing the risk of haemorrhage **(1)**. Atrial fibrillation is the most common chronic cardiac arrhythmia in our population, whose presence increases the risk of suffering stroke and systemic embolism by 5 **(2)**. In recent years, Direct Oral Anticoagulants (DOACs) have been overtaking vitamin K antagonists (VKA) such as acenocoumarol and warfarin in the prevention of thromboembolic events and their complications. Patients treated with acenocoumarol or warfarin have a narrow therapeutic range and require periodic monitoring of prothrombin time, usually expressed as INR. Traditionally, patients with any contraindication for being treated with VKA were treated with antiplatelet agents. The literature on the prevalence of anticoagulated patients in Spain with DOAC or VKA calculates that they reach a proportion of 13/1000 inhabitants **(3)**.

DOACs can be direct inhibitors of thrombin, such as **dabigatran** etexilate (Pradaxa®), or direct inhibitors of activated factor X such as **rivaroxaban** (Xarelto®), **apixaban** (Eliquis®) and **edoxaban** (Lixiana®). The main advantages of DOACs are a faster onset of action, a longer therapeutic window, a shorter half-life (between 9 and 17 hours depending on the drug), and less drug and food interaction. The most feared complication with VKAs is intracranial bleeding. DOACs have shown a lower number of episodes of this complication but maintaining their efficacy for prevention and treatment of thrombosis **(4)**. In general, the use of these DOACs is especially limited in patients with severe renal and hepatic insufficiency, and in these patients their dose must be adjusted individually **(5)**. In addition to the common advantages of DOACS described above, there are individual advantages such as with the use of dabigatran, as idarucizumab, a monoclonal antibody, reverses its effect **(6)**. Dabigatran etexilate

is metabolised in dabigatran, its active metabolite, and directly inhibits thrombin. Coagulation tests observe prolonged activated partial thromboplastin time and a minimal effect on prothrombin time. The plasmatic peak is obtained after 2 hours, and the half-life with a single dose is 8 hours but can reach 12-17 hours after multiple doses. The most used concentrations are 110 - 220mg per day, depending on the medical conditions of the patient. Rivaroxaban selectively binds to factor Xa and reversibly inhibits it. Food does not interfere in its absorption, the plasmatic peak is reached after 3 hours, and the half-life varies between young and elderly adults (between 5 and 13 hours). In general, direct inhibitors of factor Xa prolong prothrombin time and reduce partial thromboplastin time. The recommended concentration is 15 - 20mg depending on the systemic conditions of the patient. Apixaban has similar pharmacological characteristics to rivaroxaban, but with lower bioavailability (50% instead of 80%). The recommended concentration is 2.5 - 5mg/day **(5)**. In reality, most dentists usually consult with the specialist doctor, this trend occurring less as experience is gained **(7)**. The majority are aware of the effect that vitamin K antagonists and antiplatelets have on patients and considerations for oral surgeries, but DOACs are less well known **(8)**. In the meta-analysis by Shi et al. (2017), they concluded that, in general, the risk of postoperative bleeding in anticoagulated patients was higher (RR: 2.7) compared with healthy individuals. This meta-analysis included studies with anticoagulated patients with VKA and DOACs, specifying that the relative risk of bleeding in the latter was 1.6 compared with 3 in the former; this difference was statistically significant **(9)**. Authors such as Brennan et al. (2020) observed similar bleeding rates in patients treated with DOACs and with warfarin with an INR of 2 - 4 **(10)**. However, we cannot ignore the results of studies on how medication affects the quality of life of patients, as this is affected by constant controls and follow-up of patients treated with VKA **(11)**. Postoperative bleeding complications after a dental extract range from minor bleeding events to haemorrhages which may be life-threatening for the patient. However, current clinical guidelines advocate for maintaining anticoagulant therapy, both with DOACs and VKAs (within the considerations specified for the latter in previous PICO questions) **(12)**, although they also highlight that due to the lack of evidence in this matter, clinicians must apply their own clinical experience to determine the appropriate measures for controlling this condition **(13)**. This last observation reinforces the need for more clinical studies which help to determine the bleeding rate in patients treated with DOACs.

Evaluation and synthesis of the evidence

A total of 5 articles (1 prospective study and 4 retrospective studies) have been selected to answer the PICO question: *Patient*, anticoagulated with DOAC; *Intervention*, dental extraction; *Comparison*, with antiplatelet patients or patients who are not anticoagulated or antiplatelet; *Outcome*, modification of the relative haemorrhagic risk (PICO Study Table 3). All studies detected a higher post-extraction bleeding rate in patients anticoagulated with DOACs than in healthy controls **(14–18)**. Nevertheless, the majority are retrospective studies, and in prospective designs treatment with DOAC is suspended for at least the morning of the procedure in a non-random manner, the dose being resumed a minimum of 4 hours after surgery and in the absence of bleeding. The inclusion of patients with dual treatment, anticoagulant and antiplatelet, was specified in the study by Hanken et al. (2016), although with a very low representation, with only 2 of 337 patients, and in that of Yagyuu et al. (2017) with 4 patients out of a total of 543 **(14, 15)**. None of the articles were able to compare the risk of bleeding of the patients with dual therapy compared with monotherapy, as the representation within the sample size was not sufficient; however, recent meta-analyses appear to show that the concomitant use of treatment with DOACs and antiplatelet drugs does not seem to have a significant effect in terms of postoperative bleeding, although a greater tendency towards bleeding is observed **(19)**. This meta-analysis also found no significant differences between the risk of postoperative bleeding in patients treated with different DOACs or with vitamin K antagonists **(19)**. However, these authors highlighted that it is an issue that has not been resolved given the low level of existing evidence. In general, the degree of variability in the designs of the studies selected to answer this PICO question is enormous, therefore they are not representative. In the study by Miller et al. (2018) **(17)**, 11,320 patients were included, of which only 12 took DOACs (0.11%). Furthermore, the DOAC guideline varied a lot between some patients and others, as 9 out of the 12 discontin-

ued the treatment up to 5 days before surgery. The representation of the types of DOACs included in the studies is also heterogeneous. In the study by Müller et al. (2019) **(18)** patients treated with rivaroxaban and apixaban were included, in that of Miller et al. (2018) **(17)** all were represented (although only one patient treated with edoxaban was included), in the study by Miclotte et al. (2018) **(16)** no patients treated with edoxaban were included, in the study by Yagyuu et al. (2017) only patients treated with edoxaban and dabigatran were included, and in that of Hanken et al. (2016) **(14)** only patients treated with rivaroxaban were included. In the introduction we state the pharmacodynamic and pharmacokinetic differences existing between the DOACs included in these studies, therefore it is necessary to carry out clinical studies that include a cohort of patients with a larger sample size, where there is representation of patients treated with the different DOACs which is significant for being able to extrapolate the results to daily clinical practice. The recommendations of the Practice Guideline for Non-Vitamin K Antagonist Oral Anticoagulants recommend that the dose not be modified before surgical procedures, or in any case, that the morning dose be suppressed **(20)**. However, the level of evidence is low, it is based on pharmacological information, and it does not classify oral surgery treatments.

Conclusions and recommendations

The evidence on the risk of postoperative bleeding after dental extractions in patients treated with DOACs, based on the literature published to date, appears to demonstrate an increased risk of bleeding compared with healthy individuals (**Grade D recommendation**). However, the evidence for these results is limited and heterogeneous. In most of the articles included there are not adequate sample sizes. Most of the studies are retrospective and apply different protocols in these patients, from the continuation of the treatment to the discontinuation of the dose on the day of surgery and up to 5 days before the extraction. This necessitates controlled clinical trials with a representative sample size of all types of DOACs and with healthy controls.

4. In patients anticoagulated with a coumarin drug (acenocoumarol or warfarin) who require fitting of dental implants, is there an increased haemorrhagic risk in comparison with non-anticoagulated patients? What if they also take antiplatelet medication?

Acenocoumarol and warfarin are the main anticoagulant inhibitors of vitamin K which are used in the population, mainly to prevent thromboemolism in cardiac patients **(1, 2)**. Oral surgery treatments in anticoagulated patients have often been carried out following various protocols, such as bridging therapy to replace the anticoagulant with herapin, suspending or reducing the dose of the anticoagulant during the days before and after surgery, or maintaining the anticoagulant using subsequent haemostasis measures **(3)**. Thus, to prevent postoperative haemorrhage, different haemostatic methods are usually used, consisting of suturing the wound, placement of gauze or using antifibrinolytic drugs such as tranexamic acid **(4, 5, 6)**. Numerous studies have shown that undergoing minor surgery such as extraction or fitting of dental implants does not require suspension of the anticoagulant, provided that the INR has a value between 2 and 3 **(7,8)**. However, due to methodological inconsistencies in many of these studies, the safety of these surgical procedures in anticoagulated patients is still debated today **(9)**. Despite numerous reviews having evaluated the association between anticoagulation and the occurrence of haemorrhages, the majority of them only provide data on haemorrhagic risk in extractions **(10, 11)**. If we focus on studies evaluating implant therapy, Shi et al. (2017) **(8)** reported a relative risk of haemorrhages of 2.136 (p= 0.118), while Miziara et al. (2021) **(12)**, in turn, found a relative risk of 2.19 (p= 0.09), therefore concluding that there were no significant differences between anticoagulated and non-anticoagulated patients with regard to the risk of occurrence of haemorrhages. The literature review carried out on this issue has revealed the lack of clear evidence on this matter **(13, 14)**. The absence of randomised clinical trials, and the fact that the majority of studies published combine results from different surgical interventions and different anticoagulant treatment options, make it considerably difficult to draw conclusions which allow the question at hand to be answered with adequate evidence.

Evaluation and synthesis of the evidence

A total of 4 articles (all prospective studies) have been selected to answer the PICO question: Patient, anticoagulated with dicoumarins; Intervention, fitting of dental implants; Comparison, with antiplatelet patients or patients who are not anticoagulated or antiplatelet; Outcome, modification of the relative haemorrhagic risk (PICO Study Table 4). Based on the analysis of the abstracts and full texts of the articles found, as well as the 4 prospective trials **(3, 9, 15, 16)** 2 systematic reviews were included **(8, 17)**. For the evaluation of scientific evidence, the articles were reviewed using the GRADE system. None of the prospective studies were randomised, all 4 having a low level of evidence. The systematic reviews included primary studies with a low level of evidence, therefore the level of evidence of these reviews is also low. In the trial carried out by Bacci et al. (2021) **(15)** implants were fitted in patients treated with warfarin and in patients without anticoagulant treatment. These authors found a relative risk of postoperative haemorrhage of 1.45 in the anticoagulated patients, without statistical significance compared with the control group.

Broekema et al. (2014) **(9)** evaluated the occurrence of haemorrhages, comparing between patients without anticoagulant treatment, patients treated with vitamin K antagonists (without specifying which one) and antiplatelet patients (without specifying which antiplatelet agent), who underwent different types of surgeries. No haemorrhage occurred in patients who received implants; therefore, no differences were found between groups. The study by Clemm et al. (2016) **(3)** compared the occurrence of haemorrhages between patients without anticoagulant treatment and patients with some type of treatment, subdivided into those treated with vitamin K antagonists, antiplatelet agents, bridging therapy with herapin or direct anticoagulants, who received implants. These authors reported a higher frequency of postoperative haemorrhages in the anticoagulated group with vitamin K antagonists compared with those not anticoagulated (p= 0.038), while they did not find significant differences in antiplatelet agents or in treatments with direct anticoagulants, although these results were not only related with patients who received single or multiple implants, but also included patients who underwent bone regeneration or sinus lifting techniques, which are a priori more invasive procedures. Sannino et al. (2020) **(16)** evaluated the occurrence of haemorrhages in fitting of implants through the “all-on-four” technique and immediate loading in patients treated with warfarin, with direct anticoagulants or without anticoagulant treatment. In this case, a significant increase in haemorrhages was found in patients treated with warfarin compared with the other groups (p= 0.002). However, the authors themselves acknowledge that although in this study more invasive surgical procedures were carried out than the implant insertion itself, given that the extractions and bone regularisation procedures had already been carried out, the haemorrhages occurring were easily controlled through local haemostasis techniques **(16)**. The systematic review by Shi et al. (2017) **(8)** included 5 articles related to implants, 3 of which we have previously mentioned **(3, 9, 15)**, the other 2 dealing with direct anticoagulants. These authors estimated a relative risk of postoperative haemorrhage of 2.136 (p= 0.118) in anticoagulated patients compared with non-anticoagulated patients, but this value was calculated including trials on direct anticoagulants, therefore it is not fully applicable to the question at hand. The review carried out by Miziara et al. (2021) **(17)** included the same articles as the previous review, reporting an odds ratio of 2.19 (p= 0.09), concluding that there were no significant differences between groups with regard to the occurrence of haemorrhages. However, this review also has the problem of the previous review, which is that this value was calculated including articles on direct anticoagulants, therefore it cannot be considered conclusive in our case.

Therefore, the evidence shows that although in some cases the risk of haemorrhage is slightly higher in patients treated with vitamin K antagonist anticoagulants, it also shows that the interruption of anticoagulant therapy generates a high risk of suffering thromboembolic events, with greater morbidity than resulting from the possible haemorrhage suffered when continuing the anticoagulant therapy **(19, 20)**. All the trials reviewed to answer this question have significant methodological inconsistencies, such as the use of small sample sizes, the absence of comparison between patients continuing their anticoagulant treatment and those who discontinue it, the inclusion of different types of surgeries in the statistical calculations and the generation of hypotheses not supported by the re-

sults obtained **(3, 18)**. Having analysed the scientific literature available on this issue, we can conclude that there is no evidence that the continuation of the anticoagulant treatment in patients undergoing fitting of implants significantly increases the risk of haemorrhage. In the event that it occurs, the local haemostatic measures usually used are normally sufficient to stop it. Additionally, as the increased thromboembolic risk derived from suspension of the anticoagulant generates a considerably greater morbidity than the potential haemorrhage, the interruption of the anticoagulant therapy is not justified in patients who will receive implants. With regard to antiplatelet treatment, there are no studies that evaluate whether the joint treatment of oral anticoagulants and antiplatelet agents, compared with the use of only anticoagulants, alters the risk of haemorrhages in patients undergoing implant surgery.

Conclusions and recommendations for future research

The continuation of oral anticoagulant treatment in patients undergoing simple surgeries in fitting of dental implants does not entail a significant increase in the risk of haemorrhages compared with stopping or reducing the treatment, therefore its suspension is not justified (**Grade D recommendation**). Future lines of research should study the possible effect of oral anticoagulants on the risk of haemorrhages through randomised clinical trials with an adequate sample size and a more or less uniform design with regard to single or multiple implants without complementary surgery, evaluating the effect of this type of medication on patients undergoing fitting of implants to allow valid conclusions to be drawn. These trials should be carried out with patients undergoing only implant surgery, as if patients undergo different surgical techniques, these results are not conclusive for any of them. Additionally, it should also be evaluated whether the joint use of oral anticoagulants and antiplatelet medication modifies the haemorrhagic risk, to thereby be able to create protocols that guide clinical practice. In the same way, patients who continue anticoagulant treatment and those who suspend it should be compared, in order to be able to obtain results with sufficient scientific evidence which contribute to guiding clinical practice.

5. In patients anticoagulated with herapin who require fitting of dental implants, is there an increased haemorrhagic risk in comparison with non-anticoagulated patients? What if they also take antiplatelet medication?

Herapin exerts its anticoagulant effect by acting on various factors involved in coagulation, mainly thrombin and factor X **(1-8)**.

Evaluation and synthesis of the evidence

One prospective article was selected to answer the PICO question: *Patient*, anticoagulated with herapin; *Intervention*, fitting of dental implants; *Comparison*, with antiplatelet patients or patients who are not anticoagulated or antiplatelet; *Outcome*, modification of the relative haemorrhagic risk (PICO Study Table 5). For the evaluation of scientific evidence, the articles were reviewed using the GRADE system. Based on the analysis of the abstracts and the full text of the articles found, a single article was included on the occurrence of haemorrhages in patients treated with herapin who received implants **(9)** Vitamin-K inhibitors, Vitamin-K inhibitor withdrawal bridged with heparin (LMWH. This study is prospective and non-randomised; therefore, its level of evidence is low. Clemm et al. (2019) **(9)** Vitamin-K inhibitors, Vitamin-K inhibitor withdrawal bridged with heparin (LMWH evaluated the risk of intraoperative and postoperative haemorrhages in patients who received implants, including five subgroups of patients treated with single or multiple implants, therefore the effect to be studied is limited. Within this study, one of the groups evaluated consisted of patients taking oral anticoagulants whose oral anticoagulant was replaced before the surgical intervention with a low molecular weight herapin. These authors reported a higher frequency of postoperative haemorrhages in these patients compared with non-anticoagulated patients (p= 0.069). However, when comparing this group with patients taking vitamin K antagonists, no differences were found related with the occurrence of haemorrhages (p= 0.498). Therefore, in both patients who continued their oral anticoagulant treatment and in those who replaced it with herapin, the risk of haemorrhages is greater than in non-anticoagulated patients, therefore the use of this type of "herapin bridging therapy" does not provide benefits with regard to continuing with the oral treatment. However, the

results of this study must be taken with caution, as it presents various inconsistencies in its methodology. Firstly, there is a large difference between the sample size of both groups (447 patients in the control group and 117 in the study group), and the necessary sample size was also not calculated prior to starting the study. Furthermore, one of the conclusions of the authors was that the replacement of the oral anticoagulant with low molecular weight herapin was associated with a higher haemorrhagic and thromboembolic risk, a hypothesis that is not supported by the results obtained **(10)**. The scientific literature available on this specific issue is very limited, as there are numerous trials and reviews where herapin treatment is evaluated, but the vast majority of these studies deal with extractions and not implants. Given this lack of studies, we can obtain an idea of the question at hand by analysing the trials that have evaluated the use of herapin in cases of extractions, taking into account that the fitting of an implant is generally a procedure less susceptible to generating haemorrhages than an extraction. Bajkin et al. (2009) **(5)** concluded that there was no need to use bridging therapies with low molecular weight herapin in anticoagulated patients undergoing minor dentoalveolar surgeries, such as extractions or fitting of implants. In turn, the systematic review carried out by Chahine et al. (2019) **(11)** concluded that bridging therapy with herapin was associated with an increased incidence of haemorrhages, and therefore recommended to maintain the oral anticoagulant treatment, always using local haemostatic measures. After analysing the scientific literature available on this issue, we can conclude that there is no evidence that herapin treatment in patients receiving implants entails a significant increase in the risk of haemorrhages. With regard to the antiplatelet treatment, there are no studies that analyse whether the joint treatment of herapin and antiplatelet agents modifies the risk of haemorrhage compared with patients treated only with herapin.

Conclusions and recommendations for future research

Treatment with herapin in patients undergoing simple surgeries for fitting of implants does not entail a significant increase in the risk of haemorrhages, therefore its continuation is recommended during this type of surgery (**Grade D recommendation**). The replacement of the oral anticoagulant with herapin in patients undergoing simple surgeries for fitting implants does not provide benefits related with the risk of haemorrhages, therefore this action is not justified (**Grade D recommendation**). Future lines of research should study the possible effect of herapin on the risk of oral anticoagulant haemorrhages through randomised clinical trials evaluating the effect of this type of medication on patients undergoing fitting of implants to allow valid conclusions to be drawn. These trials should include a large sample of patients, allowing comparison between continuation of the treatment with herapin and the suspension of this type of therapy, as well as a control group, to be able to analyse whether these situations modify the risk of haemorrhages. Additionally, studies should also evaluate whether the joint use of herapin and antiplatelet medication modifies the risk of haemorrhages, to thereby be able to create protocols that guide clinical practice.

6. In patients anticoagulated with a direct oral anticoagulant (DOAC) who require fitting of dental implants, is there an increased haemorrhagic risk in comparison with non-anticoagulated patients? What if they also take antiplatelet medication?

Evaluation and synthesis of the evidence

Three articles were selected to answer the PICO question: *Patient*, treated with direct oral anticoagulants; *Intervention*, fitting of dental implants; *Comparison*, with antiplatelet patients or patients who are not anticoagulated or antiplatelet; *Outcome*, modification of the relative haemorrhagic risk (PICO Study Table 6). For the evaluation of scientific evidence, the articles were reviewed using the GRADE system. All the studies included were prospective and with a cohort design. However, in all cases they have very small samples, with a few dozen patients treated with DOACs and a larger control group without medication.

The first 2 articles are by the same research group and have the same methodology. The difference is in the active substance: in one it is rivaroxaban **(1)** and in the other, dabigatran **(2)**. The first article compared 18 patients who took rivaroxaban, with a control group of 39 patients who did not take this medication **(1)**. The second compared 29 patients undergoing treatment with dabigatran with 42 pa-

tients who did not take it **(2)**. In both cases, gauze soaked in an antifibrinolytic (tranexamic acid) was used after the intervention and then 3 times a day for 4 days. In both publications, postoperative bleeding was recorded using a 4-category scale **(3)**. In the case of rivaroxaban, the treatment regimen was not modified. There were no differences in postoperative bleeding between the anticoagulated group and the control group. The only haemorrhagic incidents were moderate postoperative bleeding between 5% and 6% of cases, without statistically significant differences between the rivaroxaban group and the control group **(1)**. In the case of dabigatran, implants were fitted 12 hours after the last dose, and it was not resumed until 8 hours later. There were also no differences in postoperative bleeding between the anticoagulated and control group patients. There was only 7% to 5% postoperative bleeding, which was classified as minor. The difference between the groups was not statistically significant **(2)**. In the 2 previous studies, the patients were recruited from different centres and there is little information on how the calibration was carried out. Furthermore, taking into account that the difficulty is often found in recruiting patients for the treatment group, few controls were included. A proportion of 3 to 4 controls for each patient in treatment would have increased the robustness of the research. Additionally, in both studies there was a selection bias, as the patients of the control group required bone regeneration techniques in some cases, while those in the anticoagulated group did not. This may have increased bleeding in the control group, as treatments with a higher potential risk of bleeding were carried out in this group. This bias would act by reducing the differences between the groups and may therefore underestimate the effect of rivaroxaban and dabigatran on the postoperative haemorrhage. A prospective cohort study aimed to determine the risk of intraoperative and postoperative bleeding in patients receiving anticoagulant treatment undergoing osseointegrated implant surgery and bone augmentation procedures **(4)**. Patients receiving antithrombotic drugs (coumarin anticoagulants, herapin, direct oral anticoagulants and antiplatelet agents) were compared with a control group. The 16 patients who were taking direct oral anticoagulants were being treated with apixaban, dabigatran or rivaroxaban, and the pharmacological treatment was not suspended or modified. They were compared with a control group (447 patients) who did not take anticoagulant or antiplatelet medication. Intraoperative and postoperative bleeding was classified as minor (minimal bleeding from the wound, controllable by compression), moderate (presence of blood clots in the surgical field and need for additional haemostatic measures) or severe (arterial bleeding, need for haemostatic measures and review of the wound). A higher risk of severe intraoperative bleeding was observed in patients treated with direct oral anticoagulants (28.6%) compared with controls (2.9%). However, postoperative bleeding was practically nil in both groups. The conclusion was that in implant and bone regeneration procedures, treatment with direct oral anticoagulants may slightly increase intraoperative bleeding and does not appear to have any relevant effect on postoperative bleeding. However, the sample of patients being treated with these drugs was small and heterogeneous. Additionally, the methodology of this cohort study could have caused a bias in the assessment of bleeding, due to the lack of blinding of the observer, who could therefore know the patient's medication. This could have exaggerated the difference between patients treated with direct oral anticoagulants and controls. No other relevant information is available on the treatment of implants in patients treated with direct oral anticoagulants. Other published studies correspond to a case series, do not include a control group, include treatments which are not implants, or are non-systematic reviews. The recommendations of the Practical Guideline for Non-Vitamin K Antagonist Anticoagulants propose that the dose should not be modified before oral surgery, or in any case, the morning dose should be suppressed **(5)**. However, the level of evidence is nil, it is based on pharmacological information, and it does not classify the oral surgery treatments. No information is available on the effect that the addition of antiplatelet agents to direct oral anticoagulants may have in patients undergoing implant treatments.

Conclusions and recommendations for future research

Patients being treated with direct oral anticoagulants can be safely treated with osseointegrated implants. Intraoperative bleeding may be slightly greater, although postoperative bleeding appears to be similar to that of patients not taking anticoagulants (**Grade D recommendation**). There is no clinical information to determine the effect that the additional administration of an antiplatelet agent may have in these patients (no recommendation). Further studies should be carried out which include larger samples, as the current studies only have a few dozen cases, as well as having designs which are more specific and not so heterogeneous. It would also be necessary to increase the methodological quality of the studies, as there are numerous biases that limit the strength of the recommendations. Randomised, blinded and statistically robust clinical trials with an acceptable sample size would be desirable.

7. In patients with hereditary coagulopathies who require dental extraction, is there an increased haemorrhagic risk in comparison with healthy individuals? What about patients who require dental implants?

There are multiple hereditary haemostasis disorders which can have an impact on the oral cavity. However, the most common coagulopathies are Von Willebrand disease and haemophilia A and B. It is estimated that the prevalence of Von Willebrand disease is slightly below 1%, although the symptomatic disease is 10 times less frequent **(1)**. Cases of haemophilia are much rarer, and it has been estimated that they affect 17 in 100,000 men (haemophilia A) and around 4 in 100,000 men (haemophilia B) **(2)**. Approximately one third of haemophilia cases are considered severe **(2)**. These diseases can have different levels of severity, but especially in the case of haemophilia and severe forms of Von Willebrand disease, they reduce life expectancy. In patients with hereditary coagulopathies, especially the most severe, it is necessary to apply a strategy to prevent tooth loss, and in the case of extractions being unavoidable, to consult the corresponding haematology unit. To carry out minor surgery, preoperative preparation is usually carried out in these patients and haemostasis measures are adopted. In the most minor cases, the treatment can be carried out on an outpatient basis, but in other cases the treatments should be carried out in a single session, in a hospital setting, using an appropriate anaesthetic support technique for the underlying pathology. Patients with hereditary coagulopathies may require oral surgery interventions. The most common are dental extractions. However, in recent years, the replacement of missing teeth with dental implants has also been offered for this group of patients. Although there is more information on the risk of bleeding associated with dental extractions, due to being a more common treatment, it should be considered whether the fitting of implants is a safe procedure in these patients. Generally, the fitting of dental implants entails a lower risk of bleeding than dental extractions, due to the dental implant mechanically plugging the bone tissue. However, bone regeneration techniques are not recommended, due to the risk of causing haematomas. With the ageing of the population, it is foreseeable that demand for dental implants will increase in the future in patients with hereditary coagulopathies.

Evaluation and synthesis of the evidence

No studies were found to answer the PICO question: *Patient*, with hereditary coagulopathy; *Intervention*, dental extraction; *Comparison*, with patients without hereditary coagulopathy; *Outcome*, modification of the relative haemorrhagic risk. The risk of bleeding in patients with hereditary coagulopathies depends on the severity of the disorder; that is, mainly on the reduction of the coagulation factor **(5)**. No studies were found with a control group that evaluated the risk of bleeding from implant fitting surgery in patients with hereditary coagulopathies. Only clinical cases and a case series were found, summarised below. In patients with haemophilia, a dental extraction is considered a minor surgical procedure, in contrast to multiple extractions, which have been considered a major surgical procedure (**Grade D recommendation**) **(3)**. In haemophilia patients with inhibitors, due to the increased risk of bleeding, it has been suggested to consider any oral surgery treatment as major surgery (**Grade D recommendation**) **(3)**. In patients with haemophilia, it has been decided to maintain prophylactic treatment, usually in severe cases, but not to administer additional factor before surgery. In a study with 50 patients with haemophilia A and B and Von Willebrand disease without prior pharmacological treatment (except for the usual prophylaxis), 8% of cases of postoperative bleeding were recorded (4 cases, 3 of them haemophilia A and 1 haemophilia B). Cases of bleeding were successfully treated using postoperative factor VIII and IX **(4)**. This strategy (not using factor preoperative-

ly) allows oral surgery treatments to be carried out without the need for hospitalisation, on an outpatient basis. Oral surgery should be scheduled on the same day as the prophylactic factor treatment, to minimise the risk of bleeding and additional visits **(5)**. Another more widespread strategy is to administer factor preoperatively until reaching more than 50% of the normal values (**Grade 2C recommendation**) **(5)**. In haemophilia patients with inhibitors, treatment with activated prothrombin complexes (aPCC) 50–75 IU/kg every 12 hours, with a total of 2–3 doses, is recommended, starting just before the intervention, or with recombinant factor VII (rFVIIa) 90–120 µg/kg/2 hours, with a total of 3–4 doses, starting minutes before the intervention (**Grade D recommendation**) **(3)**. A previous study by Franchini et al. (2005) dealt with 7 patients with type 1 Von Willebrand disease who were administered desmopressin 0.3mg/kg 1 hour before the intervention, achieving 30-50% of the normal factor values. Postoperative bleeding occurred in only one patient (14%). Therefore, in patients with type 1 Von Willebrand disease, it appears safe to fit dental implants after a treatment with desmopressin **(6)**. An additional clinical case showed that this treatment resulted in no appreciable postoperative bleeding **(7)**. In more severe forms of the disease, or in case of a contraindication to desmopressin, platelet transfusion may be necessary **(8)**. There are some publications of isolated cases of implant treatments in patients with haemophilia A, following treatment with factor VIII. The patients received treatment with factor VIII before fitting 2 dental implants in each case and after 6-12 hours **(9,10,13)**. No haemorrhagic complications were observed. A 4-month prospective observational study has recently been published, in which infusions of the corresponding factor were used before and after the fitting of the implants, in addition to oral antifibrinolytics and local haemostatic measures; of the 15 surgeries carried out to fit 21 implants, haemorrhages were only detected in 3 of them, the implant success parameters not having been altered when evaluated after 4 months **(14)**. In addition to the aforementioned clinical cases, 3 consensus documents and 1 clinical practice guideline were identified, although they are not specific for implants, but instead for oral surgery, which mainly includes dental extractions. One consensus document insists on the need for a preventive strategy, in order to avoid dental extractions and the need to replace missing teeth **(11)**. The consensus documents highlight that in patients with haemophilia and other hereditary/congenital haemorrhagic disorders, it should be evaluated whether the treatment must be carried out only with local anaesthesia or whether sedation or general anaesthesia is appropriate. **(11)**. It is recommended to avoid trunk blocks of the upper maxillary and lower dental nerve, due to the risk of generating a haematoma. The block with the Gow-Gates technique has been proposed as an alternative to the trunk block of the lower dental nerve, due to the lower risk of causing a haematoma compromising the airway**(12)**. However, it is recommended to preferably use infiltrative techniques **(11,12)**. In any case, it has been indicated that the risk of bleeding as a result of a nerve block is minimised with the use of current needles in dentistry **(12)**. It is recommended not to use non-steroidal anti-inflammatory drugs due to the risk of bleeding, and it is suggested to use other analgesics or long-duration anaesthetics **(12)**. One of the consensus documents does not offer recommendations on dental implant treatment **(11)**. To plan these procedures, diagnosis through three-dimensional images (computed tomography) is strongly recommended, in order to avoid the risk of inadvertently perforating cortices (especially the lingual cortex), which can cause severe bleeding in patients with coagulopathies **(12)**. There is a clinical practice guideline which offers some recommendations in the treatment of implants in patients with congenital/hereditary coagulopathies **(5)**. In any case, it is acknowledged that there is not sufficient evidence with regard to the safety of the treatment of these patients with dental implants. Therefore, individualised treatment and consultation with the corresponding haematology unit are recommended **(5)**. In any case, before surgical procedures, it is recommended to increase the deficient factor up to 50%, or to administer vasopressin, and to use an antifibrinolytic locally (for example, 5% tranexamic acid), along with other local measures (use of collagen, cellulose, fibrin or cyanoacrylate sponges, among others) **(5, 11, 12)**. In fact, patients who receive prophylactic factor appear to have a lower risk of bleeding in oral surgery **(12)**. Bone augmentation techniques are considered contraindicated in these patients **(12)**.

Conclusions and recommendations for future research

There is not sufficient information on the increased risk of intraoperative or postoperative bleeding in patients with hereditary coagulopathies compared with healthy individuals, in dental extraction or implant treatments. Dental extractions must be carried out after evaluating the percentage of the deficient factor (over or under 5%). In the most serious cases, it is necessary to guarantee a minimum factor before dental extraction. Cases of haemophilia with inhibitors must be considered serious and may require further patient preparation.

Therefore, there is not sufficient data to contraindicate dental implant treatment in patients with hereditary/congenital coagulopathies, such as haemophilia or Von Willebrand disease. Nevertheless, it appears feasible to fit dental implants, as the risk of bleeding appears lower than that of dental extractions (**Grade D recommendation**). Therefore, trunk anaesthetic techniques should be avoided, undertaking a three-dimensional diagnosis with computed tomography and applying bleeding prevention measures before, during and after the intervention (**Grade D recommendation**). In any case, an individual evaluation of the case should be carried out with the haematology unit or haemophilia centre. Studies should be carried out with a higher grade of evidence, because to date only case series, isolated clinical cases, expert documents and one clinical practice guideline are available. The latter are based on the first studies, and there are therefore no studies with grade 2 evidence. Specific studies should be carried out, selecting larger samples from each coagulopathy, especially the most frequent ones, such as haemophilia A or Von Willebrand disease, in order to develop specific protocols or guidelines for each one. These studies should include larger samples, as the current ones only have a few dozen cases. It would also be necessary to increase the methodological quality by designing suitable and homogeneous studies which can offer grade 2 evidence at the minimum.

8. In patients anticoagulated with a coumarin drug (acenocoumarol or warfarin) who require dental extraction, what reduction of haemorrhagic risk is produced by LOCAL HAEMOSTATIC MEASURES in comparison with non-anticoagulated patients? What if they also take antiplatelet medication?

Local haemostatic measures can be carried out through sutures, compression with gauze (soaked in medications or not), sponges (gelatine, fibrin, collagen, etc.), tissue adhesives, as well as filling materials and waxes **(1-10)**. Within these measures, compression with gauze soaked in tranexamic acid is usually the most used. Tranexamic acid is an antifibrinolytic that reversibly inhibits plasminogen, preventing the plasmin from being degraded to fibrin **(6, 7)**. Some authors recommend the use of tranexamic through irrigation, while others recommend applying it using soaked gauze to thereby reduce the risk of clot dissolution **(7)**. In any case, when comparing between different haemostatic measures, there is no evidence that any is superior to the others, therefore no haemostatic measure is better than another **(6)**. In the literature published on this issue, it is clear that there is a low incidence of postoperative haemorrhages occurring in anticoagulated patients undergoing extractions, demonstrating that it is not necessary to suspend the treatment, but that it is enough to use local haemostatic measures, which constitute a key element in these patients. **(6, 7, 10)**.

Evaluation and synthesis of the evidence

None of the articles analysed were selected to answer the PICO question, as none included the comparison group of non-anticoagulated patients or patients who were neither antiplatelet or anticoagulated: Patient, anticoagulated with coumarins; Intervention, dental extraction with application of local haemostasis measures; Comparison, with antiplatelet patients or patients who are not anticoagulated or antiplatelet; Outcome, modification of the relative haemorrhagic risk. For the evaluation of scientific evidence, the articles were reviewed using the GRADE system. Finally, 3 articles **(11–13)** and 7 systematic reviews were selected **(6, 10, 15–19)**. In the trial carried out by Bajkin et al. (2014) **(11)**, 90 patients anticoagulated with warfarin or acenocoumarol and INR≤ 3 were divided into 3 groups, in order to compare the haemostatic capacity of sutures, gelatine sponges and compression with dry gauze. After undertaking the extractions, 1 episode of postoperative haemorrhage was recorded in the sutured patients, 2 in patients in whom the gelatine sponge was used, and another 2 in patients who had compression applied with gauze. No significant differences were

found between groups (p= 0.811) and all haemorrhages were easily controlled with local haemostatic measures. These results demonstrate that minor oral surgery procedures - such as simple extractions - can be carried out safely without altering the dose of anticoagulant and without the need to use other haemostatic measures beyond compression with gauze that is usually performed, while suturing is usually sufficient in patients where adequate primary haemostasis is not achieved. Scarano et al. (2014) **(12)** evaluated the incidence of postoperative haemorrhage in 30 patients treated with warfarin and INR between 2 and 3 who underwent 42 extractions. When comparing the haemostatic efficiency of the suture and intra-alveolar calcium sulphate, a significantly lower frequency of haemorrhages was found in the first postoperative day in patients who used calcium sulphate (p< 0.001). Soares et al. (2015) **(13)** carried out 84 extractions in 38 patients treated with warfarin. These authors divided the patients into 3 groups: in the first group they used gauze soaked in tranexamic acid as a haemostatic measure; in the second a fibrin sponge; and in the third a dry gauze. Additionally, all patients were sutured. Upon evaluating the occurrence of postoperative haemorrhages, they found that the incidence of haemorrhage was not associated with the haemostatic method used (p= 0.769), while it was positively correlated with the patient's age (p= 0.005). These authors therefore associated the risk of postoperative haemorrhage with the age of the patient, regardless of the previous INR and the haemostatic measure used. It should be mentioned that in the studies by Bajkin et al. (2014) **(11)** and Scarano et al. (2014) **(12)**, only patients with an INR< 3 were included. Currently there are patients whose INR target rises to 3.5 according to the main oral anticoagulation guidelines **(19)**, therefore future studies should consider the inclusion of patients with INR values up to 3.5 - 4, as in the prevention of certain cardiac pathologies patients must maintain these INR values. In the guideline on anticoagulated patients undergoing oral surgery published by Perry et al. (2007) **(20)**, it is indicated that in patients undergoing oral surgery procedures, maintaining the anticoagulant therapy is valid for INR values ≤ 4, recommending the use of local haemostatic measures such as oxidised cellulose, collagen sponges, sutures or tranexamic acid. In the systematic review by Ockerman et al. (2019) **(6)**, the efficacy of various haemostatic methods was compared in anticoagulated patients, such as pressure with gauze, gauze soaked in tranexamic acid, different types of sponges and glues, calcium sulphate, haemostatics based on plant extracts, as well as irrigation through epsilon aminocaproic acid or tranexamic acid. After analysing all these local haemostasis methods, they concluded that tranexamic acid significantly reduces postoperative bleeding compared with a placebo, although there is no clear evidence of its superiority over other haemostatic methods. Costa et al. 2013 **(14)**, in turn, evaluated the frequency of haemorrhagic complications in anticoagulated patients through the analysis of 24 primary studies. In a total of 3891 patients undergoing extractions under anticoagulant treatment, 171 postoperative haemorrhages occurred, which is a considerably low percentage. In most cases, tranexamic acid was used as a haemostatic measure on its own or with other measures such as sponges or sutures, reaching the conclusion that extractions in anticoagulated patients can be carried out without the need to suspend the anticoagulant therapy, provided that appropriate local haemostatic measures are used. Kämmerer et al. (2015) **(10)** evaluated 16 clinical trials where different local haemostatic measures were used, such as gelatine, collagen or fibrin sponges, sutures, histoacrylic glue, cellulose, antifibrinolytics, or a combination of several of these. No significant differences were found with regard to the appearance of postoperative haemorrhages compared with continuing, modifying or suspending the anticoagulant treatment, therefore they recommended not to modify the anticoagulant therapy and to use local haemostatic measures, as the potential haemorrhagic complications can be managed easily by applying these measures. Queiroz et al. (2016) **(15)**, in another systematic review, evaluated 18 studies where a total of 4116 extractions were carried out in 1821 patients under anticoagulant treatment. Among the haemostatic measures evaluated, the most frequent were tranexamic acid, cellulose or gelatine sponges and sutures. Postoperative haemorrhages occurred in 6.58% of patients who used tranexamic acid, 7.92% who used cellulose sponges and 9.95% who used gelatine sponges and sutures. These authors concluded that the local haemostatic measures, especially tranexamic acid and the different types of sponges, are effective in the prevention and control of postoperative bleeding, therefore not recommending suspension of the anticoagulant treatment provided that these haemostatic measures are carried out. Moreno-Drada et al. (2021) **(16)** carried out a systematic review with meta-analysis which included 14 studies in which the occurrence of haemorrhagic events was analysed in relation with the use of different haemostatic measures. Of these measures, cyanoacrylate, tranexamic acid and calcium sulphate were effective compared with a placebo. These authors reported a beneficial effect of tranexamic acid in the reduction of haemorrhagic events compared with a placebo (RR= -3.72), with moderate evidence according to GRADE, while in the case of cyanoacrylate and calcium sulphate the evidence was classified as very low. Therefore, in anticoagulated patients undergoing oral surgery, the use of haemostatic measures and in particular tranexamic acid contributes to reducing the incidence of haemorrhagic events, therefore their use is essential in this type of patient. The Cochrane Library has published several systematic reviews on this subject. In the review of interventions for treating postoperative haemorrhages carried out by Kumbargere et al. (2018) **(17)** no quality clinical trials were found for inclusion, therefore they concluded that it was necessary to carry out high-quality randomised trials that provide evidence on the interventions available for treating and preventing postoperative bleeding after an extraction. Furthermore, in the review by Engelen et al. (2018) **(18)** on the use of antifibrinolytics in the prevention of postoperative haemorrhages in anticoagulated patients undergoing oral surgery, they concluded that there appears to be a beneficial effect in the local application of tranexamic acid, although the small number of quality clinical trials published on this issue does not allow us to determine the specific efficacy of the antifibrinolytic agents in this type of patient. To answer this question, studies whose results are expressed in terms of haemostasis time and not frequency of haemorrhages have been excluded. However, given that the haemostasis time is related with the occurrence of subsequent bleeding, we believe it is necessary to mention them. In all of them, a reduction of the time necessary for achieving haemostasis through the use of different local haemostatics was confirmed, whether with haemostatic dressings such as HemCon® **(21)** or Axiostat® **(22)**, with gelatine sponges and LED light **(23)** or with tranexamic acid **(24)**. With regard to patients with antiplatelet treatment, the search carried out did not identify any quality study on this issue. However, the main reviews that have evaluated patients with antiplatelet therapy undergoing oral surgery agree that it is not necessary to suspend or modify the antiplatelet guideline provided that the necessary haemostatic measures are used **(6, 25, 26)**. Having analysed the scientific literature available on this issue, we can conclude that the application of local haemostatic measures to prevent postoperative haemorrhages after undertaking an extraction is essential in patients receiving anticoagulant treatment. These haemostatic measures can vary between sutures, sponges of different compositions (collagen, fibrin, gelatine, etc.), tissue adhesives, filling materials such as calcium sulphate or cellulose, compression with gauze soaked in antifibrinolytic agents (epsilon aminocaproic acid, tranexamic acid), etc. Although most of the studies do not find advantages in any of these measures over the others, there does seem to be more evidence on the beneficial effects of tranexamic acid; this antifibrinolytic, especially used in the form of soaked gauze, produces adequate haemostasis which considerably reduces the appearance of postoperative haemorrhages.

Conclusions and recommendations for future research

In anticoagulated patients undergoing simple extractions it is not recommended to suspend anticoagulant treatment, recommending the use of local haemostatic measures **(Grade C recommendation)**. No advantages of any local haemostatic measure over the others have been shown, therefore it is recommended to use those that have more evidence, such as sutures, collagen or cellulose sponges, as well as compression with gauze soaked in tranexamic acid **(Grade C recommendation)**. The occurrence of postoperative haemorrhages increases with the age of the patient, therefore in elderly patients undergoing simple extractions, the use of local haemostatic measures is especially recommended **(Grade C recommendation)**. Future lines of research should study the effect of different local haemostasis measures through randomised clinical trials evaluating the effect of these measures on anticoagulated patients undergoing extractions to allow valid conclusions to be drawn. These trials should be carried out on large samples

of patients where anticoagulation is not suspended and whose INR is in the therapeutic range recommended in the main guidelines and protocols. With regard to the above, patients with an INR of between 2 and 4 should be included, as it is common to find patients with INR levels above 3, and to thereby be able to evaluate whether these haemostatic measures continue to be effective with such INR values. Additionally, the effectiveness of these haemostatic measures should be studied in patients who combine anticoagulant and anti-platelet treatment, to thereby be able to create protocols to guide clinical practice in this type of patient.

9. In patients anticoagulated with herapin who require dental extraction, what reduction of haemorrhagic risk is produced by LOCAL HAEMOSTATIC MEASURES in comparison with non-anticoagulated patients? What if they also take antiplatelet medication?

Evaluation and synthesis of the evidence

None of the articles analysed could be selected to answer the PICO question, as none responded to the statement of the question: Patient, anticoagulated with herapin; Intervention, dental extraction with application of local haemostasis measures; Comparison, with antiplatelet patients or patients who are not anticoagulated or antiplatelet; Outcome, modification of the relative haemorrhagic risk. For the evaluation of scientific evidence, the articles were reviewed using the GRADE system.

As no study has been included to be able to answer this question, we believe it is necessary to approach this issue through related studies. Numerous works have made it clear that anticoagulant treatment does not entail an increased risk of significant haemorrhages in patients undergoing oral surgery **(10–13)**, while there is a consensus on the importance of the use of local haemostatic measures in this type of patient **(7–9)**. When analysing postoperative bleeding in patients treated with low molecular weight herapin undergoing oral surgery, it was observed that the occurrence of postoperative haemorrhages in this type of patient was very infrequent, and that in case of occurring it could be managed through local haemostatic measures such as compression with gauze or using haemostatic sponges **(14)**. In the trial by Bajkin et al. **(3)**, not included in this question due to being from before 2010, they evaluated the risk of haemorrhages in patients with oral anticoagulation, compared with patients receiving herapin treatment. Despite using haemostatic sponges for patients with oral anticoagulation and not using any haemostatic measure in patients receiving herapin treatment, the percentage of postoperative haemorrhages was lower in the latter group. In the literature review carried out on this question, no quality trials were found which evaluated local haemostatic measures in patients receiving joint treatment of herapin and antiplatelet medication undergoing oral surgery. As no randomised clinical studies have been found that could be included to answer this question, there is a clear lack of evidence on this issue. There is an evident need for well-designed clinical studies on this matter. Therefore, given the lack of evidence, and until quality studies on which clinical practice can be based are published, the dentist must base their clinical decisions on the recommendations of experts and in conjunction with the published literature related with this issue to deal with this type of situation.

Conclusions and recommendations for future research

In patients anticoagulated with herapin and undergoing extractions, it is recommended to carry out an exhaustive anamnesis to ascertain the time this treatment takes and to have precise knowledge of the half-life of the herapin used. The surgical procedure should be carried out at the time of maximum decrease of plasma concentrations of the drug, to then continue the anticoagulant treatment in the conventional regime, simultaneously applying local haemostatic measures such as compression with dry gauze or preferably soaked in tranexamic acid, suturing of the wound or the use of different types of sponges or haemostatic dressings **(Grade D recommendation)**.

Due to the lack of current evidence, future lines of research should focus on being able to answer this PICO question through well-designed clinical trials evaluating the effectiveness of the different local haemostatic measures in patients receiving herapin treatment undergoing extractions with randomised trials, blinded and with statistical power in terms of adequate sample size.

10. In patients anticoagulated with DOACs who require dental extraction, what reduction of haemorrhagic risk is produced by LOCAL HAEMOSTATIC MEASURES in comparison with non-anticoagulated patients? What if they also take antiplatelet medication?

Evaluation and synthesis of the evidence

None of the articles analysed were selected to answer the PICO question, as none of those identified responded to the statement of the question: Patient, anticoagulated with DOACs; Intervention, dental extraction with application of local haemostasis measures; Comparison, with antiplatelet patients or patients who are not anticoagulated or antiplatelet; Outcome, modification of the relative haemorrhagic risk. For the evaluation of scientific evidence, the articles were reviewed using the GRADE system. However, we believe it necessary to mention several studies that do not directly answer the question at hand, but which may shed light on this issue. Upon analysing the occurrence of haemorrhages in patients treated with warfarin or with DOACs, Brennan et al. (2020) **(9)** found comparable bleeding between both groups, as well as between the different types of DOACs. These authors used the same local haemostatic measures in all patients, consisting of a cellulose dressing, suturing of the wound, and compression with dry gauze, therefore they sustain that extractions are safe in patients treated with DOACs if the necessary haemostatic measures are used. Another similar study also found no differences between the different DOACs compared with the occurrence of haemorrhages, concluding that the treatment with direct oral anticoagulants can be maintained in patients undergoing extractions, it being sufficient to use local haemostatic measures **(10)**. In the trial by Rocha et al. (2020) **(11)** they also found no differences in the occurrence of postoperative haemorrhages in patients treated with DOACs compared with patients without anticoagulant treatment, using suturing and compression with dry gauze as a local haemostatic measure in all patients. Pippi et al. (2021) **(12)**, in turn, carried out extractions in anticoagulated patients using local haemostatic measures of gelatine sponges, suturing and compression with gauze, concluding that prior suspension of the anticoagulant treatment was not necessary, regardless of the type of anticoagulant used. These authors, however, suggested that the antibiotic treatment prior to the extraction was associated with a higher risk of postoperative haemorrhage, regardless of the type of anticoagulant used, therefore in anticoagulated patients, the antibiotic therapy should be reserved only for cases where it is essential. Other authors, using different haemostatic measures such as compression with dry gauze or soaked in tranexamic acid, sponges of different compositions, electrocoagulation or sutures, also found no significant differences in the appearance of haemorrhages between anticoagulated and non-anticoagulated patients, recommending continuation of treatment during the extraction and the subsequent use of haemostatic measures **(1)**. Inokoshi et al. (2021) **(13)**, when performing removals in anticoagulated patients using haemostatic measures of sutures, as well as others such as cellulose dressings, found a significantly higher frequency of haemorrhages in patients anticoagulated with rivaroxaban. The percentage, which reached 32%, was significantly higher than that reported in other similar studies, therefore the authors related it with the characteristics of the patients in the sample, who were over 65 years of age and polymedicated. It is important to place even greater emphasis on the appropriate local haemostatic measures in elderly anticoagulated patients and users of other drugs, because the risk of haemorrhage increases considerably. Ockerman et al. (2021) **(14)** evaluated the effectiveness of mouthwashes with tranexamic acid in patients treated with a DOAC undergoing extractions, concluding that tranexamic acid does not reduce the proportion of perioperative bleeding except in the case of multiple extractions.

Conclusions and recommendations for future research

Due to the lack of quality scientific evidence in the literature on this issue, it is proposed to recommend the opinion of experts. In patients anticoagulated with a direct anticoagulant drug and undergoing extractions, it is recommended to have precise knowledge of the half-life of the drug used, so that the dental extraction can be carried out at the time of maximum decrease of the plasmatic concentrations of the specific anticoagulant, delaying its ingestion after the extraction by at least 4 hours, simultaneously applying local haemostatic mea-

sures such as sutures, different sponges or haemostatic dressings, or compression with dry gauze or preferably soaked in tranexamic acid **(Grade D recommendation)**. Taking into account the current limited evidence and its methodology, future lines of research should focus on being able to answer this PICO question through well-designed clinical trials, with an adequate sample size, evaluating the effectiveness of the different local haemostatic measures in patients treated with DOACs undergoing extractions, compared with healthy individuals.

11. In patients anticoagulated with a coumarin drug (acenocoumarol or warfarin) who require dental extraction, what reduction of haemorrhagic risk is produced by the PHARMACOLOGICAL TREATMENT in comparison with non-anticoagulated patients? What if they also take antiplatelet medication?

Evaluation and synthesis of the evidence

None of the articles analysed could be selected to answer the PICO question, as none of those identified conformed to the statement of the question: Patient, anticoagulated with coumarin drug; Intervention, dental extraction with application of pharmacological treatment; Comparison, with antiplatelet patients or patients who are not anticoagulated or antiplatelet; Outcome, modification of the relative haemorrhagic risk. For the evaluation of scientific evidence, the articles were reviewed using the GRADE system. However, we believe it is necessary to mention that several reviewed studies can guide us in making clinical practice recommendations on this issue. Almost all articles identified to answer this question evaluated the different haemostatic measures that can be carried out in anticoagulated patients to prevent and treat haemorrhages generated by a dental extraction, all of them analysing local and non-systemic haemostasis measures. In the review of the Cochrane Library carried out by Engelen et al. (2018) **(9)** on antifibrinolytic therapy for preventing haemorrhages in anticoagulated patients undergoing minor oral surgery, no trials were found which analysed the use of tranexamic acid systematically, either orally or intravenously, it instead being applied locally in all the studies identified, coinciding with other reviewed articles **(5, 10–12)**. The risk level of systemic use is very high, while its local or topical use has been demonstrated in clinical practice, although well-designed trials would be necessary to corroborate its efficacy and provide an acceptable level of evidence. Several of these studies refer to tranexamic acid used topically or locally reducing the risk of postoperative haemorrhage without having systemic effects, as its absorption is minimal when applied in this way **(5, 10)**.

Tranexamic acid is a synthetic antifibrinolytic which, administered in small doses, is a competitive inhibitor of the conversion of plasminogen to plasmin, while in high doses it non-competitively blocks plasmin, inhibiting the dissolving and degradation effect that it exerts on the blood clot. The systemic effects of tranexamic acid when administered externally or parenterally are significant. Although there is no clinical evidence that tranexamic acid increases the likelihood of thromboembolic events, there are reports of cases where it has been associated with thrombotic events. Its use has also been associated with the appearance of convulsions **(13)**. Of all the literature reviewed to answer this question, only the study by Morimoto et al. (2010) **(14)** used a pharmacological treatment to reduce the haemorrhagic risk in patients with oral anticoagulation. However, this study has not been included in the PICO question at hand due to its low level of evidence and the individual characteristics of the patients included. These authors described 2 clinical cases of patients receiving antiplatelet treatment with acetylsalicylic acid and anticoagulant with warfarin, in whom a prothrombin complex concentrate was administered to promptly decrease the INR figures, reducing the risk of perioperative haemorrhages. These patients had cardiopathies which required them to have a ventricular assist system installed, therefore they had to maintain very high INR values of around 4-5. In these patients, a prothrombin concentrate was administered 30 minutes prior to the extraction, achieving a reduction of INR from 5 to around 1.5 in the following 15 minutes, allowing the extraction to be carried out without any haemorrhage occurring. Subsequently, the patients continued the anticoagulant and antiplatelet treatment according to the usual regimen, recovering therapeutic INR levels in the 48 hours following the extraction. It must be taken into account that these clinical situations are very uncommon in daily practice and that they must be carried out in a hospital setting. These authors report that with INR values of up to 5, it is sufficient to administer 500U of prothrombin concentrate to reduce these levels to values close to 1.5. In this way, in patients with mechanical cardiac support devices, requiring anticoagulation with very high INR values, it is possible to carry out the extraction first using a prothrombin complex concentrate, reducing the risk of haemorrhage associated with the extraction, and without the need to suspend the anticoagulant treatment, which would considerably increase the possibility of a thromboembolic event occurring. Therefore, it is possible to observe the limited scientific literature available on the use of medications as haemostatic measures in patients undergoing extractions; these drugs are generally used in patients with coagulopathies such as haemophilia or Von Willebrand disease, while in patients receiving oral anticoagulant treatment it is sufficient to apply local haemostatic measures, reserving these pharmacological agents for special situations, which should be carried out in a hospital setting.

Conclusions and recommendations for future research

Due to the lack of quality scientific evidence in the literature on this issue, it is proposed to recommend the opinion of experts. In patients anticoagulated with a coumarin drug who require extractions, it is recommended to continue the oral anticoagulant treatment, concomitantly applying local haemostatic measures consisting of sutures, compression with dry gauze or preferably soaked in tranexamic acid, sponges or haemostatic dressings, without the need to use other systemic drugs to reduce the haemorrhagic risk **(Grade D recommendation)**. Future lines of research should focus on being able to answer this PICO question through well-designed clinical trials, evaluating the effectiveness of different pharmacological treatments aimed at promoting haemostasis in patients anticoagulated with coumarin drugs undergoing extractions.

12. In patients anticoagulated with herapin who require dental extraction, what reduction of haemorrhagic risk is produced by the PHARMACOLOGICAL TREATMENT in comparison with non-anticoagulated patients? What if they also take antiplatelet medication?

Evaluation and synthesis of the evidence

No article satisfied the criteria for answering the PICO question: *Patient*, anticoagulated with heparin; *Intervention*, dental extraction with application of pharmacological treatment; *Comparison*, with antiplatelet patients or patients who are not anticoagulated or antiplatelet; *Outcome*, modification of the relative haemorrhagic risk. All included studies referred to the application of local measures, but none to systemic measures. In general, we also did not find clinical trials that specifically studied the haemorrhagic risk in a sample of patients treated with herapin **(10)**. Instead, these patients are usually treated as a subgroup among anticoagulated patients and generally with a low percentage of representation, therefore the level of evidence is nil **(11–15)**. Among the haemostatic treatments after the dental extraction are gauze soaked in tranexamic acid, sponges, glue, calcium sulphate, epsilon aminocaproic acid and tranexamic acid **(16)**. The limited scientific literature available on the use of systemic drugs as haemostatic measures in patients undergoing extractions and treated with herapin reinforces the idea that these drugs must be reserved for patients with congenital coagulopathies such as haemophilia or Von Willebrand disease, while in patients receiving anticoagulant treatment it is sufficient to apply local haemostatic measures, leaving these pharmacological methods for special situations, which should be carried out in a hospital setting.

Systemic haemostatic measures can work through the inhibition of fibrinolysis or by promoting coagulation and include administration of plasma, platelet concentrates, coagulation factor replacement therapy, desmopressin, vasopressin, tranexamic acid or epsilon aminocaproic acid **(1-8)**. Most clinical practice guidelines recommend the use of local measures aimed at promoting haemostasis, as the systemic route through different drugs is less widespread and less well known by dentists **(8, 9)**.

Conclusions and recommendations for future research

In patients anticoagulated with a herapin and undergoing extractions, in the absence of studies providing evidence, recommendations are made such as the use of local haemostatic measures consisting of sutures, compression with dry gauze or prefera-

bly soaked in tranexamic acid, sponges or haemostatic dressings, without the need to use pharmacological treatment to reduce the haemorrhagic risk **(Grade D recommendation)**. Future lines of research should focus on being able to answer this PICO question through well-designed clinical trials, evaluating the effectiveness of different pharmacological treatments aimed at promoting haemostasis in patients treated with herapin undergoing extractions.

13. In patients anticoagulated with DOACs who require dental extraction, what reduction of haemorrhagic risk is produced by the PHARMACOLOGICAL TREATMENT in comparison with non-anticoagulated patients? What if they also take antiplatelet medication?

Evaluation and synthesis of the evidence

No article was selected to answer the PICO question: *Patient*, anticoagulated with DOACs; *Intervention*, dental extraction with application of pharmacological treatment; *Comparison*, with antiplatelet patients or patients who are not anticoagulated or antiplatelet; *Outcome*, modification of the relative haemorrhagic risk. The articles analysed deal with patients treated with anticoagulants, in whom known local haemostatic measures were applied (sutures, haemostatic sponges, tranexamic acid, etc.) **(8, 14–20)**. Although the initial literature generally recommended suspending dabigatran, rivaroxaban and apixaban 24 hours before the surgical intervention **(21)**, or not discontinuing the drug at all, many recent works suggest that for more invasive dental procedures, it would be enough to delay administration of the drug **(21)**. The limited scientific literature available on the use of systemic drugs as haemostatic measures in patients undergoing extractions and treated with DOACs reinforces the idea that these drugs must be reserved for patients with congenital coagulopathies such as haemophilia or Von Willebrand disease, while in patients receiving anticoagulant treatment it is sufficient to use local haemostatic measures, leaving these pharmacological methods for special situations, which should be carried out in a hospital setting.

Conclusions and recommendations for future research

In patients anticoagulated with a DOACs and undergoing extractions, it is recommended to use local haemostatic measures consisting of sutures, compression with dry gauze or preferably soaked in tranexamic acid, sponges or haemostatic dressings, without the need to resort to systemic pharmacological treatment to reduce the haemorrhagic risk **(Grade D recommendation)**. Future lines of research should focus on being able to answer this PICO question through well-designed clinical trials, evaluating the effectiveness of different pharmacological treatments aimed at promoting haemostasis in patients treated with DOACs undergoing extractions.

14. In patients with hereditary coagulopathies who require dental extraction, what reduction of haemorrhagic risk is produced by LOCAL HAEMOSTATIC MEASURES in comparison with healthy individuals? What about patients who require dental implants?

Evaluation and synthesis of the evidence

No article has been included to analyse the evidence on this issue due to the lack of control groups with healthy individuals, therefore this PICO question cannot be answered based on the available literature: *Patient*, with hereditary coagulopathies; *Intervention*, dental extraction or implant; *Comparison*, with healthy individuals without hereditary or acquired coagulopathies; *Outcome*, modification of the relative haemorrhagic risk. In oral surgical practice, various local haemostatic agents have been used to help develop a clot through platelet adhesion, platelet activation and coagulation. Haemostatic agents vary in efficacy, cost and ease of use. Among the simple procedures for controlling the haemorrhage are gelatine sponges, cellulose-oxidase, compression with gauze soaked in tranexamic acid and collagen dressings, among others. To reduce the risk of haemorrhages in hereditary coagulopathies, several systemic pharmacological measures which may be useful have been described **(8–10)**. In addition to the aforementioned congenital diseases, there are less frequent deficiencies such as factor V, whose management in the dental clinic appears to benefit

from local haemostatic measures such as the sue of haemostatic sponges, sutures and tranexamic acid mouthwashes **(7)**. The group of Kazancioglu et al. (2013) used only local measures, specifically a commercialised medicinal plant extract (*Ankaferd Blood Stopper; ABS*), in patients with haemophilia A undergoing dental extractions. The results showed a shorter postoperative bleeding time in patients who had ABS applied compared with patients whose coagulation had been controlled with gauze. The study included patients with mild and moderate haemophilia A and did not describe any postoperative complications **(11)**. Some authors state that in mild congenital haemopathies, oral surgeries could be carried out with standard local haemostatic measures and strict home follow-up, although the evidence is limited **(4, 12, 13)**.

Conclusions and recommendations for future research

When giving a recommendation on this issue, there is no article in which the PICO question posed has been fully studied; therefore, the level of recommendation in this section is based on the opinion of the experts signing the guideline. With regard to the local haemostasis measures, we have not found literature where they are used as the sole resource for haemorrhagic control, as they are usually applied after an obligatory consultation with the haematologist and combined with pharmacological measures. There are hardly any studies in this group of patients who receive dental implants, therefore the available evidence is insufficient. **(Grade D recommendation)** Among the most important considerations are the preparation of a treatment plan after a detailed clinical history and consultation with the haematologist, and treatment being carried out first thing in the morning and at the start of the week. Future lines of research should focus on being able to answer this PICO question through well-designed clinical trials, evaluating the effectiveness of the different local haemostasis measures aimed at promoting haemostasis in patients with congenital coagulopathies undergoing extractions.

15. In patients with hereditary coagulopathies who require dental extraction, what reduction of haemorrhagic risk is produced by PHARMACOLOGICAL TREATMENT in comparison with healthy individuals? What about patients who require dental implants?

Evaluation and synthesis of the evidence

None of the articles analysed could be selected to answer the PICO question, as none satisfied the statement of the question: *Patient*, with hereditary coagulopathy; *Intervention*, dental extraction with application of pharmacological treatment; *Comparison*, with antiplatelet patients or patients who are not anticoagulated or antiplatelet; *Outcome*, modification of the relative haemorrhagic risk. For the evaluation of scientific evidence, the articles were reviewed using the GRADE system. All the articles found in the literature search were ruled out due to not fulfilling the inclusion criteria, the most common reason being the lack of a control group. The available evidence is based on clinical trials, case series and systematic reviews **(6–8, 10–18)**. In the review by Galen et al. (2019) the efficacy of tranexamic acid and epsilon aminocaproic acid were shown for preventing post-extraction bleeding in patients with haemophilia and Von Willebrand disease, but these results were not compared with healthy individuals, and the articles included in this review did not consider the fitting of implants. Other systematic reviews that studied dental care in patients with congenital haemopathies, such as by Watterson et al. (2017) and Coppola et al. (2015) agreed that more studies on the issue were necessary (especially randomised clinical trials), as the available evidence was of low quality for supporting the efficacy of antifibrinolytic therapy in oral surgical procedures in this group of patients **(13, 14)**. None of the studies published on this subject incorporated control groups made up of healthy individuals, therefore this PICO question cannot be answered based on the current literature. Although there are interesting clinical trials, all compare different interventions between groups of patients with coagulopathies.

Conclusions and recommendations for future research

When giving a recommendation on this issue, we have not found any article that has fully studied the PICO question posed. There is no conclusive evidence, and through the literature available this

question cannot be answered. The level of recommendation of this section is based on the opinion of the experts signing the guideline. Based on previous clinical recommendations and our clinical experience, the pharmacological treatment must always be carried out through consultation with the haematologist, and in case of doubt, surgery should be carried out in a hospital setting. **(Grade D Recommendation)**. More research is necessary to improve the base of evidence in the treatment of people with haemophilia or Von Willebrand disease, as well as other less common congenital coagulation disorders.

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