Impact of direct oral anticoagulants on bleeding tendency and postoperative complications in oral surgery: a systematic review of controlled studies

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Objective. The recommendations for the management of direct oral anticoagulants (DOACs) in oral surgery are inconsistent. The present review evaluated whether DOACs increase the risk of bleeding during oral surgery and postoperative complications.

Study Design. The patients undergoing oral surgery and receiving a DOAC were compared with the patients receiving a DOAC different from the exposure, a vitamin K antagonist (VKA), or no anticoagulant. Three electronic databases were searched for eligible clinical trials and systematic reviews. The risk of bias was assessed, data were extracted, a meta-analysis was done, and the Grading of Recommendations, Assessment, Development and Evaluations certainty-of-evidence ratings were determined.

Results. Three clinical trials comparing patients receiving DOAC medication with patients on a VKA were eligible. A meta-analysis of bleeding 7 days postoperatively detected no significant differences between patients continuing DOAC or VKA medication during and after surgery. All of the point estimates favored uninterrupted DOAC over VKA therapy. Tranexamic acid was topically administered to some patients.

Conclusions. Based on an interpreted trend among 3 studies with mixed patient populations, the risk of bleeding during the first 7 postoperative days may be lower for patients on uninterrupted DOAC than VKA therapy (⊕⊕◻◻), but the effect size of the risk is unclear. 80 of 274 included patients experienced postoperative bleeding. (Oral Surg Oral Med Oral Pathol Oral Radiol 2023;135:333−346)

Direct oral anticoagulants (DOACs) are recommended for multiple indications, including the prevention of thromboembolism among patients with nonvalvular atrial fibrillation and prevention and treatment of deep vein thrombosis.[1] Given these indications, thrombosis during discontinuation of DOACs is a possible risk.[1] Multiple DOACs are available on the market, including rivaroxaban, apixaban, and edoxaban (direct factor Xa inhibitors) and dabigatran (a direct thrombin inhibitor). Some countries have also approved the factor Xa inhibitor betrixaban for various indications.[2]

Vitamin K antagonists (VKAs), including warfarin and acenocoumarol act by inhibiting the production of clotting factors II, VII, IX, and X and of regulatory factors protein C, S, and Z. For many years, VKAs have been the most common anticoagulants, and the recommendation to continue VKA treatment during oral surgery is well established.[3,4] The recommendations for how to treat patients receiving a DOAC before and during oral surgery, however, have been inconsistent, which may lead to varying decisions for similar cases, and possibly, an unnecessary discontinuation of DOAC with a higher attendant risk of thromboembolism.[2,5] The principal drawback of any prophylactic or therapeutic treatment of thromboembolism is always bleeding. Although such problems are known to be less with DOACs compared with VKAs, the prevalence and severity are largely uncharted, including for oral surgery.[6]

The present systematic review evaluated whether continuing a prescribed DOAC therapy during and after oral surgery increases the risk of bleeding and other complications. The focused question was "Are there any differences in bleeding during surgery, impact on surgery, duration of surgery, or postoperative complications among oral surgery patients who receive a DOAC compared with a DOAC different than the exposure, another blood thinner such as a VKA or a platelet inhibitor, or no anticoagulant?"

Statement of Clinical Relevance

The risk of postoperative bleeding after oral surgery may be lower for patients on a direct oral anticoagulant than a vitamin K antagonist, but the certainty of evidence is low. The evidence has indicated a very low risk of extensive postoperative bleeding for both groups.

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MATERIALS AND METHODS

The study protocol for the present review was registered at https://www.crd.york.ac.uk/prospero (registration code CRD42020167352). The present systematic review and meta-analysis followed the Preferred Reporting Items for Systematic reviews and Meta-Analyses 2020 statement[7] and the guidelines of the Institute of Medicine.[8]

Eligibility criteria

Table 1 presents the eligibility criteria and the Population, Exposure, Comparator and Outcomes for the present review.

Search methods

Table 2 and Figure 1 present details of the searches made in 3 electronic databases: PubMed, the Cochrane Library, and the Web of Science Core Collection. The searches covered the publications through 24 June 2021. The reference lists of the included articles were hand searched for potentially relevant trials. Additionally, the International Network of Agencies for Health Technology Assessment, Google.com, Scholar.Google.com, PubMed.gov, Epistemonekos.org, and the Health Technology Assessment (HTA) databases in Denmark, Sweden, Norway, and the United Kingdom were searched for HTA reports through September 1, 2021. The authors designed and carried out the searches in collaboration with information specialists at Malmö University and the HTA Syd.

Publication selection

Two of the authors (K.J. and A.NA.) independently reviewed the titles and abstracts of the retrieved publications to initially exclude irrelevant studies according to the inclusion and exclusion criteria (Table 1). In the second step, each publication was read in full text by at least 2 of the 5 authors in our team. Table 3 presents the excluded studies and reasons for exclusion in this step. Disagreements during the process were resolved by discussion between the authors; in cases of uncertainty, the publication remained included for evaluation in the next step.

Risk of bias assessment of individual studies

At least 2 of the 5 authors independently assessed the risk of bias in the included studies. The risk of bias in nonrandomized studies of interventions tool[9] was used to assess original clinical trials as having low, moderate, serious, or critical risk of bias. If one of the risk of bias in nonrandomized studies of interventions-I domains was assessed as critical risk, we excluded the study without further review (Table 4). The risk of bias in systematic reviews tool[10] was used for assessing the methodological risk of bias of a systematic review as low, moderate, or high risk (Table 5).

Table 1. Study design for the present systematic review on DOAC management among oral surgery patients (n = 599 publications initially found); 3 original clinical trials met the eligibility criteria

Criteria	*Description*
Focused clinical question	Are there any differences in bleeding during surgery, impact on surgery, duration of surgery, or postoperative complications among oral surgery patients who receive a DOAC compared with a DOAC different from the exposure, a VKA, or no anticoagulant?"
Population	Patients undergoing oral and/or maxillofacial surgery
Exposure	Medication with any DOAC, with or without discontinuation of DOAC treatment in conjunction with surgery
Controls	Administration of a different DOAC than the exposure
	Administration of other blood thinners than the exposure
	Interruption of DOAC administration for surgery during a different period than the intervention
	No blood thinners administered
Outcome	The frequency and severity of any postoperative bleeding occurring after oral and maxillofacial surgery (primary)
	Other postoperative complications
	Bleeding volume during surgery;
	Surgical difficulty
	Time of surgery
	Other relevant measurements of bleeding
Inclusion criteria	Controlled clinical trials with a follow-up
	Systematic reviews on DOAC management that report which databases were searched and the keywords used
Exclusion criteria	Case reports
	Case series
	Studies not reporting patient-level data
	Studies in languages other than English, Swedish, Norwegian, Danish, and German

DOAC, direct oral anticoagulant; *VKA*, vitamin K antagonist.

Data extraction

One author (K.J.) extracted the data and another (A.NA.) checked that the information had been extracted correctly. Age, sex, socio-economic status, number of included patients, follow-up time, type of drugs administered in the intervention and control groups, and results relevant for the present systematic review were extracted from original clinical trials. The purpose, main outcomes, the authors' judgment of the level of certainty, and any potential gaps of knowledge were extracted from systematic reviews. Only the information

Table 2. Search strategies

Database	*Search terms*	*References found*
PubMed (United States National Library of Medicine)*	#1: dental OR dentistry [MeSH] OR "maxillofacial surgery" OR "oral surgery" OR tooth extraction OR dentistry #2: doac OR noac OR novel oral anticoagulant OR direct oral anticoagulant OR non-vitamin K oral anticoagulant OR rivaroxaban OR dabigatran OR apixaban OR edoxaban OR "Dabigatran" [MeSH] OR "Rivaroxaban" [MeSH] OR Direct Acting Oral Anticoagulant OR Factor Xa Inhibitor OR "Factor Xa Inhibitors" [MeSH] OR Pradaxa OR Pradax OR Prazaxa OR Xarelto OR Eliquis OR Savaysa OR Lixiana OR Roteas Searched: #1 AND #2	465
Cochrane Library (John Wiley & Sons, Inc.)†	#1: dental OR "maxillofacial surgery" OR "oral surgery" OR tooth extraction OR dentistry OR dentistry [MeSH] #2: doac OR noac OR novel oral anticoagulant OR direct oral anticoagulant OR non-vitamin K oral anticoagulant OR rivaroxaban* OR dabigatran* OR apixaban* OR edoxaban* OR Dabigatran [MeSH] OR Rivaroxaban [MeSH] OR direct acting oral anticoagulant OR factor xa inhibitor OR factor xa Inhibitors [MeSH] OR pradaxa OR pradax OR prazaxa OR xarelto OR eliquis OR savaysa OR lixiana OR roteas Searched: #1 AND #2	20
Web of Science Core Collection (Clarivate)‡	#1: dental* OR "maxillofacial surg*" OR "oral surg*" OR "tooth extract*" OR "teeth extract*" OR dentistry #2: doac OR doacs OR noac OR noacs OR novel oral anticoagulant OR novel oral anticoagulants OR direct oral anticoagulant OR direct oral anticoagulants OR non-vitamin K oral anticoagulant OR non-vitamin K oral anticoagulants OR rivaroxaban* OR dabigatran* OR apixaban* OR edoxaban* OR direct acting oral anticoagulant OR direct acting oral anticoagulants OR factor Xa inhibitor* OR pradaxa OR pradax OR prazaxa OR xarelto OR eliquis OR savaysa OR lixiana OR roteas Searched: #1 AND #2	114

MeSH, Medical Subject Headings, used to index articles in the National Library of Medicine.
*All subordinated MeSH terms included.
†MeSH terms searched as "explode all trees", all other terms searched as ti, ab, kw.
‡All terms searched as "Topic" in the "Basic Search" mode.

of interest for the present systematic review was extracted. The authors of individual studies were not contacted to clarify missing or unclear information.

Statistical analysis

A meta-analysis was performed in Stata 15 SE (Statacorp LLC) using the metan command to determine the difference between patients receiving a DOAC and patients receiving a VKA in postoperative bleeding of any kind during the first week after oral surgery.[11] To include the effect measures from all of the studies with a low or moderate risk of bias in the analysis, the measures were calculated to log odds ratios with standard errors and included in a DerSimonian and Laird random-effects model.[12]

Certainty of evidence

The Grading of Recommendations, Assessment, Development and Evaluations (GRADE) approach[13] was used to determine the certainty of evidence in original clinical trials as high, moderate, low, or very low.

RESULTS

Literature search and study selection

We identified 511 unique articles after removing 91 duplicates; 55 of the articles were read in full text. Table 3 presents the 32 studies that were excluded after full-text eligibility assessment and the reasons for exclusion. The remaining 21 original clinical trials and 2 systematic reviews were eligible for risk of bias assessment. No relevant HTA reports were identified. Figure 1 presents a flow chart of the selection process.

Quality assessment of clinical trials and data extraction

Fourteen clinical trials[14-27] were excluded due to a critical risk of bias for the domain "confounding bias"; another 4 studies[5,28-30] were excluded due to an overall serious risk of bias. No clinical trials with an overall low risk of bias were identified, but 3 original clinical trials[31-33] were estimated to have a moderate risk of bias and were included (Table 4). The 3 included studies were from 3 different continents and were

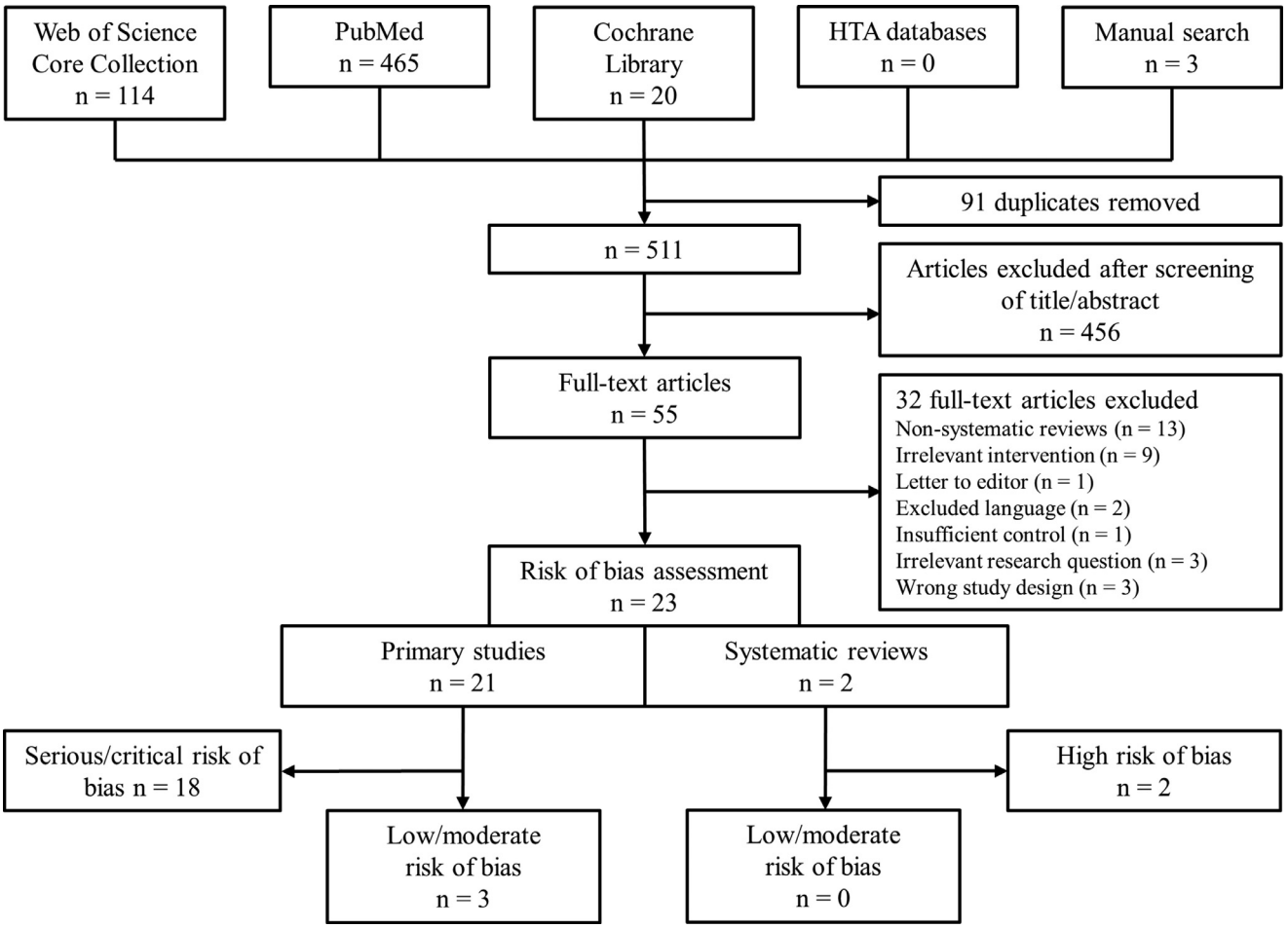

Fig. 1. Flow chart of publication selection for the present systematic review on direct oral anticoagulant management from 602 searched publications. *HTA*, health technology assessment.

prospective, controlled single-center cohort studies with a follow-up of 7 days; they were recently published between 2018 and 2020, comprised a total of 274 patients, and compared the patients who continued taking a DOAC with the patients who continued taking a VKA during and after oral surgery (Table 6). In all 3 included original clinical trials, tranexamic acid was applied topically as part of the postoperative hemostatic protocols. Andrade et al.[31] used crushed pills of tranexamic acid, whereas Berton et al.[32] applied compression with gauze soaked in tranexamic acid solution for a few patients (6%), and only if hemostasis was not achieved after suturing and 30 minutes of compression. Brennan et al.[33] instructed patients to bite on a gauze soaked in 5% tranexamic acid solution if hemostasis was not achieved after biting on a gauze for 60 min (Table 6). The only common outcome measure reported in all 3 studies was bleeding during the first 7 postoperative days. Andrade et al.[31] reported bleeding in 0/12 (0%) patients on a DOAC and 8/25 (32%) patients on a VKA. Berton et al.[32] reported postoperative bleeding in 12/65 (18%) patients receiving a DOAC and 20/65 (31%) patients receiving a VKA. Brennan et al.[33] reported postoperative bleeding for 31/86 (36%) of patients receiving a DOAC and 9/21 (43%) of patients receiving a VKA. The meta-analysis of this outcome measure found no significant difference between the groups (odds ratio [OR] 0.56; 95% CI, 0.27-1.17). Because all of the point estimates favored DOAC over VKA (Figure 2), the GRADE certainty of evidence in Table 7 for the outcome measure bleeding during the first 7 postoperative days was based on the trend observed in the data that all of the point estimates from single studies favored DOAC. The aggregated point estimates and CIs determined in the meta-analysis did not affect grading.

One patient experienced postoperative bleeding requiring revision of the surgical wound. The patient was taking a VKA (warfarin) and had gotten tooth #26 (FDI world dental federation notation) extracted without the elevation of a mucoperiosteal flap or ostectomy.[32] None of the 274 patients included in the meta-

Table 3. Excluded publications (n = 32) after full-text evaluation (n = 55) and reasons for exclusion

Non-systematic review

Bajkin B, Mirkovic S, Vučinić P, Vučković B, Marjanović M. Dental management of patients taking antiplatelet, oral anticoagulant and novel anticoagulant medications. *Vojnosanit Pregl.* 2019;76:635-640.

Curto A, Albaladejo A. Implications of apixaban for dental treatments. *J Clin Exp Dent.* 2016;8:e611-e614.

Curto A, Albaladejo A, Alvarado A. Dental management of patients taking novel oral anticoagulants (NOAs): dabigatran. *J Clin Exp Dent.* 2017;9:e289-e293.

Curto A, Curto D, Sanchez J. Managing patients taking edoxaban in dentistry. *J Clin Exp Dent.* 2017;9:e308-e311.

Elad S, Marshall J, Meyerowitz C, Connolly G. Novel anticoagulants: general overview and practical considerations for dental practitioners. *Oral Dis.* 2016;22:23-32.

Fortier K, Shroff D, Reebye UN. Review: an overview and analysis of novel oral anticoagulants and their dental implications. *Gerodontology.* 2018;35:78-86.

Munoz-Corcuera M, Ramirez-Martinez-Acitores L, Lopez-Pintor RM, Casanas-Gil E, Hernandez-Vallejo G. Dabigatran: a new oral anticoagulant. Guidelines to follow in oral surgery procedures. A systematic review of the literature. *Med Oral Patol Oral Cir Bucal.* 2016;21:e679-e688.

Nathwani S, Wanis C. Novel oral anticoagulants and exodontia: the evidence. *Br Dent J.* 2017;222:623-628.

Serrano-Sanchez V, Ripolles-de Ramon J, Collado-Yurrita L, et al. New horizons in anticoagulation: direct oral anticoagulants and their implications in oral surgery. *Med Oral Patol Oral Cir Bucal.* 2017;22:e601-e608.

Shi Q, Xu J, Zhang T, Zhang B, Liu H. Post-operative bleeding risk in dental surgery for patients on oral anticoagulant therapy: a meta-analysis of observational studies. *Front Pharmacol.* 2017;8:58.

Stelea CG, Dîmbu E, Andrian S, Ciurcanu OE, Stelea AL, Bologa C. Assessing the bleeding risk in patients using direct oral anticoagulants submitted to dental surgery procedures: a systematic review *Rom J Oral Rehabil.* 2018;10:103-108.

Val M, Berrone M, Marino R, Gandolfo S, Pentenero M. New oral anticoagulants: pharmacological properties and their management in dentistry. *Dent Cadmos.* 2016;84:482-492.

van Diermen DE, van der Waal I, Hoogstraten J. Management recommendations for invasive dental treatment in patients using oral antithrombotic medication, including novel oral anticoagulants. *Oral Surg Oral Med Oral Pathol Oral Radiol.* 2013;116:709-716.

Irrelevant intervention

Cabbar F, Cabbar AT, Cosansu K, Cekirdekci EI. Effects of direct oral anticoagulants on quality of life during periprocedural management for dental extractions. *J Oral Maxillofac Surg.* 2019;77:904-911.

Calcia TBB, Oballe HJR, de Oliveira Silva AM, Friedrich SA, Muniz F. Is alteration in single drug anticoagulant/antiplatelet regimen necessary in patients who need minor oral surgery? A systematic review with meta-analysis. *Clin Oral Investig.* 2021;25:3369-3381.

Cocero N, Basso M, Grosso S, Carossa S. Direct oral anticoagulants and medical comorbidities in patients needing dental extractions: management of the risk of bleeding. *J Oral Maxillofac Surg.* 2019;77:463-470.

de Andrade NK, Motta RHL, Bergamaschi CC, et al. Bleeding risk in patients using oral anticoagulants undergoing surgical procedures in dentistry: a systematic review and meta-analysis. *Front Pharmacol.* 2019;10:866.

Healey JS, Eikelboom J, Douketis J, et al. Periprocedural bleeding and thromboembolic events with dabigatran compared with warfarin: results from the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) randomized trial. *Circulation.* 2012;126:343-348.

Lanau N, Mareque J, Giner L, Zabalza M. Direct oral anticoagulants and its implications in dentistry. A review of literature. *J Clin Exp Dent.* 2017;9:e1346-e1354.

Lusk KA, Snoga JL, Benitez RM, Sarbacker GB. Management of direct-acting oral anticoagulants surrounding dental procedures with low-to-moderate risk of bleeding. *J Pharm Pract.* 2018;31:202-207.

Mingarro-de-Leon A, Chaveli-Lopez B. Alternative to oral dicoumarin anticoagulants: considerations in dental care. *J Clin Exp Dent.* 2013;5:e273-278.

Rubino RT, Dawson DR, 3rd, Kryscio RJ, Al-Sabbagh M, Miller CS. Postoperative bleeding associated with antiplatelet and anticoagulant drugs: a retrospective study. *Oral Surg Oral Med Oral Pathol Oral Radiol.* 2019;128:243-249.

Letter to editor

Joob B, Wiwanitkit V. Direct oral anticoagulants, vitamin K antagonists, and simple single tooth extraction. *Clin Oral Investig.* 2019;23:1495.

Excluded language

Lukacs D, Staczer N, Vajta L, Olasz L, Joob-Fancsaly A, Szalma J. Dental and oral surgical treatment of medication-induced bleeding patients: audit of the national guideline in Hungary. *Orv Hetil.* 2016;157:1722-1728.

Mata A, Mendonça C, Caramês J, et al. Management of hypocoagulated patients in dental medicine − clinical guidance. *Rev Port Estomatol Med Dent Cir Maxilofac.* 2018;59:131-139.

Insufficient control

Patel JP, Woolcombe SA, Patel RK, et al. Managing direct oral anticoagulants in patients undergoing dentoalveolar surgery. *Br Dent J.* 2017;222:245-249.

Irrelevant research question or methodological setup

Manfredi M, Dave B, Percudani D, et al. World workshop on oral medicine VII: direct anticoagulant agents management for invasive oral procedures: a systematic review and meta-analysis. *Oral Dis.* 2019;25(suppl 1):157-173.

Muller M, Schlittler F, Schaller B, Nagler M, Exadaktylos AK, Sauter TC. Characteristics, treatment and outcome of bleeding after tooth extraction in patients on DOAC and phenprocoumon compared to non-anticoagulated patients—a retrospective study of emergency department consultations. *Clin Oral Investig.* 2019;23:2273-2278.

Sahar-Helft S, Chackartchi T, Polak D, Findler M. Dental treatment in the era of new anti-thrombotic agents. *Int Dent J.* 2018;68:131-137.

Wrong study design

(*continued*)

Dawoud BES, Kent S, Tabbenor O, George P, Dhanda J. Dental implants and risk of bleeding in patients on oral anticoagulants: a systematic review and meta-analysis. *Int J Implant Dent.* 2021;7:82.
Morimoto Y, Yokoe C, Imai Y, Sugihara M, Futatsuki T. Tooth extraction in patients taking nonvitamin K antagonist oral anticoagulants. *J Dent Sci.* 2016;11:59-64.
Yagyuu T, Kawakami M, Ueyama Y, et al. Risks of postextraction bleeding after receiving direct oral anticoagulants or warfarin: a retrospective cohort study. *BMJ Open.* 2017;7:e015952.

analysis experienced overt hemorrhage leading to a hemoglobin drop ≥3 g/dL, fatality, a need for a blood transfusion, or other bleeding type 3 to 5 according to the Bleeding Academic Research Consortium definition for bleeding.[34] Other outcome measures of interest reported in the original clinical trials were bleeding after various time points and hemorrhage classified by the type of intervention that was required to stop the bleeding (Table 7).

Quality assessment of systematic reviews

The 2 systematic reviews were assessed as having a high risk of bias and were excluded.[35,36]

Evidence gaps

No or insufficient information was found for the following outcome measures: other postoperative complications, bleeding volume during surgery, surgical difficulty, and time of surgery. The discussion section presents information about these outcome measures.

Summary of findings

Table 7 presents a summary of the effects of postoperative bleeding reported in patients undergoing 1 or more dental or surgical extractions while continuing their DOAC or VKA therapy during and after surgery. The certainty of evidence for the outcome measures in Table 7 was judged to be low or very low.

DISCUSSION

The present systematic review investigated the differences regarding postoperative complications, bleeding during surgery, impact on surgery, and duration of surgery in patients receiving a DOAC compared with patients receiving a different DOAC, another blood thinner such as a VKA or a platelet inhibitor, or no anticoagulant. Our study protocol specified the limits of the present review to include oral and maxillofacial surgery, but we found no information on maxillofacial surgery and thus reported only the information on oral surgery. All of the included original clinical trials compared patients receiving a DOAC with patients receiving a VKA. No clinical trial comparing patients receiving a DOAC with patients receiving a platelet inhibitor was found.

Fourteen clinical trials[14-27] were excluded because the domain "confounding bias" was estimated to have a critical risk of bias. Underlying causes for exclusion were lack of information about confounding factors such as sex, age, surgical extent, and diseases that might have affected bleeding tendency. Further, many of the excluded studies did not adjust statistically for confounding factors, and information about how patients were included was not reported adequately.

The present systematic review had several limitations. There was lack of evidence of solid quality because the information on some outcome measures were missing and the evidence for the remaining outcome measures was graded as low or very low (Tables 1 and 7).

None of the 274 patients included in the meta-analysis experienced overt hemorrhage requiring transfusion or leading to fatality, but because the sample size was considered too small for correctly evaluating this outcome measure, the certainty of evidence was judged as very low. Zero to 36% of the patients receiving a DOAC, and 31% to 43% of the patients receiving a VKA during and after surgery experienced bleeding during the first 7 postoperative days. Only 0 to 6% of the patients receiving a DOAC and 2% to 10% of the patients receiving a VKA returned to the office, either because of bleeding requiring pharmacologic intervention, bleeding that required surgery with additional sutures and/or diathermocoagulation, or because of nonmajor bleeding that required medical but not surgical intervention. Overall, the risk of postoperative bleeding was noticeable in both groups, but the bleedings were manageable. In an outpatient setting, however, the treatment may be less controlled, which may entail an increased risk of extensive postoperative bleeding compared with the patients treated in clinical studies.

Tranexamic acid was not the focus for the present systematic review, but the topical use of tranexamic acid as a hemostatic agent in oral surgery procedures is common for patients receiving anticoagulants. The side effects related to topical administration of tranexamic solution in the mouth is rare.[37] Tranexamic acid was used as a topical hemostatic agent in the included original clinical trials, but it is unclear how many (and

Table 4. Methodological assessment of the remaining clinical trials after full text assessment (n=21) with the risk of bias in non-randomized studies of interventions (ROBINS-I) tool.[9] Three studies were estimated to have a moderate risk of overall bias and included in the meta-analysis; 14 studies[14-27] were excluded without further review because the risk of confounding bias was considered critical.

	ROBINS-I assessment								
Clinical trial	**Overall bias**	Confounding bias	Selection bias	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Reporting bias	Conflicts of interest
Andrade (2018)[31]	🟡	🟡	🔴	🟢	🟡	🟢	🟡	🔴	🟢
Berton (2019)[32]	🟡	🟡	🔴	🟢	🟡	🟡	🟡	🟡	🟢
Brennan (2020)[33]	🟡	🟡	🔴	🟢	🟡	🔴	🟡	🟡	🟢
Caliskan (2017)[28]	🔴	🔴	🔴	🟢	🟢	🟢	🟡	🔴	🟢
Mauprivez (2016)[5]	🔴	🔴	🔴	🟢	🔴	🟢	🟡	🔴	🔴
Miclotte (2017)[29]	🔴	🔴	🔴	🟢	🔴	🟢	🟡	🔴	🟢
Yoshikawa (2019)[30]	🔴	🟡	🔴	🟢	🟡	🟡	🔴	🔴	🟢

Risk of bias: 🟢 = low
🟡 = moderate
🔴 = serious

Table 5. Methodological assessment with the risk of bias in systematic reviews (ROBIS) tool[10]

	ROBIS assessment					
Systematic review	**Overall bias**	Eligibility criteria for included studies	Identification and selection of studies	Data collection and study appraisal	Synthesis and findings	Conflicts of interest
Bensi (2018)[35]	🔴	🟢	🔴	🟡	🔴	🟢
Chahine (2019)[36]	🔴	🔴	🔴	🔴	🔴	🔴
Risk of bias:	🟢 = low	🟡 = moderate	🔴 = high			

which) patients were treated with tranexamic acid. It is possible that in between-group differences have been reduced because, mainly, the patients experiencing early postoperative bleeding received tranexamic acid. It is also possible that the occurrence of any postoperative bleeding for both patients receiving DOAC and VKA has been slightly reduced by the usage of tranexamic acid.

One outcome measure of interest in the present systematic review was the bleeding volume during surgery. Brennan et al.[33] assessed bleeding immediately after surgery by measuring gauze weight difference before and after biting on gauze for at least half an hour and until total hemostasis of the surgical field occurred. We excluded these measurements from the present systematic review, however, because we considered the estimated risk of bias to be serious due to large baseline variations. The gauze is usually moistened with saline before being placed orally; during biting, varying amounts of saline may evaporate or be pressed out of the gauze, and saliva may be sucked into the gauze. Thus, it is difficult to accurately determine how much of the before-and-after weight difference of the gauze is caused by bleeding from the surgical site.

Another outcome measure for this systematic review was duration of the surgery. Berton et al.[32] reported that the duration of the surgery was comparable between the patients receiving a DOAC or a VKA; Andrade et al.[31] did not report duration of surgery; and Brennan et al.[33] reported that the risk of postoperative bleeding for patients on a DOAC increased with the length of the surgery. Another factor likely influencing the time required for surgery is the extent of the surgery. Surgical extractions of multi-rooted teeth will probably require more time than extraction of a single-rooted tooth. An inexperienced surgeon may also need more time than a surgeon with more experience for the same procedure. Surgical difficulty, which also was an outcome measure of interest for this systematic review, can be hard to determine and measure because it is highly subjective and influenced by the experience of the surgeon. None of the included studies reported surgical difficulty. Berton et al.[32] was the only eligible publication that reported the outcome measure "other postoperative complications." Seven days postoperatively, 2 patients had infections and 1 patient, cutaneous ecchymosis; all 3 were receiving a DOAC.

Figure 2 presents a forest plot of bleeding during the first 7 postoperative days. We found no significant between-group differences, but because all of the studies favored DOACs over VKAs, risks were judged to be lower among patients receiving a DOAC. The GRADE certainty of evidence for this and all of the other outcome measures reported in the included

Table 6. Study characteristics of the 3 clinical prospective, controlled, single-center cohort trials with a follow-up of 7 days included in the present systematic review on DOAC management.

Author (Year) Country	*Study groups, Participants n (%)*		*Age (years)*	*Gender m/ f (n)*	*History*	*INR/renal function*	*Surgery*	*Local haemostatic*
Andrade (2018)[31] Brazil	Intervention 12 (32)	Dabigatran 12 (32)	71 (65.5-80) (median, IQR)	7/5	All patients were cared for at a cardiology centre and diagnosed with atrial fibrillation. 4 patients had diabetes mellitus type 2. Blood pressure: 130 (102.5–137.5)/ 80 (62.5–80) mm Hg (median, IQR). No antiplatelet therapy.	Not reported	3 patients underwent traumatic dental extraction. Number of extracted teeth/ patient were 1 (1–1.75) (median, IQR)	For both intervention and control groups: adequate sutures, cellulose sponge, and crushed pills of tranexamic acid
	Control 25 (68)	Warfarin 25 (68)	67 (54.5-75.5) (median, IQR)	13/12	All patients were cared for at a cardiology centre and were diagnosed with atrial fibrillation. 10 patients had diabetes mellitus type 2. Blood pressure: 120 (110-140) / 80 (70-85) mm Hg (median, IQR). No antiplatelet therapy.	INR 2-3	5 patients underwent traumatic dental extraction. Number of extracted teeth/ patient were 1 (1-1.5) (median, IQR)	
Berton (2019)[32] Italy	Intervention 65 (50)	Dabigatran 11 (8) Rivaroxaban 28 (22) Apixaban 22 (17) Edoxaban 4 (3)	76 ± 9.2 (mean ±SD)	34/31	Homogeneity between Intervention and Control groups for age, gender, and indication for anticoagulant-treatment. The most common indication for DOAC therapy was atrial fibrillation (62%). CHA2DS2–VASc and HAS-BLED were comparable between the intervention and control groups. No antiplatelet therapy.	INR 2-3	One simple dental extraction. If multiple teeth had the same priority, the most mesial tooth was extracted for both intervention and control groups. Time of surgery was 6 ± 4.7 min (mean ±SD)	For both intervention and control groups: sutures, compression with a gauze roll. Periodical ice pack application (5 min on—5 min off) for at least 2 h. If haemostasis was not achieved after 30 min, oxidized cellulose or compression with gauze soaked in tranexamic acid solution was applied.
	Control 65 (50)	Warfarin 61 (47) Acenocoumarol 4 (3)	76 ± 7.7 (mean ±SD)	31/34 54/32	The most common indication for VKA therapy was atrial fibrillation (71%). No antiplatelet therapy.	INR 2-3	Time of surgery was 5 ± 4.1 min (mean ±SD)	

(*continued on next page*)

Table 6. Continued

Author (Year) Country	*Study groups, Participants n (%)*		*Age (years)*	*Gender m/f (n)*	*History*	*INR/renal function*	*Surgery*	*Local haemostatic*
Brennan (2020)[33] Australia	Intervention 86 (80)	Dabigatran 15 (14) Rivaroxaban 30 (28) Apixaban 41 (38)	73 (67–78) median (IQR)		The most common indication for DOAC therapy was atrial fibrillation (80%). Systolic blood pressure 133 (121–146) mm Hg (median, IQR). Exclusion criteria: Platelet count < 50 x10^9/L, severe active oral infection, C-G CrCl < 25 mL/min (Apixaban), C-G CrCl < 30 mL/min (Dabigatran, Rivaroxaban). 9 patients (8%) had concurrent single antiplatelet therapy.	C-G CrCl 76 (54–102) mL/min, (median, IQR)	< 4 contiguous teeth were extracted. 1 (1–2) tooth (median, IQR) was extracted. 15 (17%) patients underwent surgical extraction. Time of surgery was 17 (11–27) min (median, IQR).	For both intervention and control: oxidized cellulose (Surgicel) was placed in the extraction socket before suturing. If haemostasis was not achieved after biting on a gauze for 60 min, patients were instructed to bite on a gauze soaked in 5% tranexamic acid solution.
	Control 21 (20)	Warfarin 21 (20)	71 (62–79) median (IQR)	18/3	The most common indication for VKA therapy was atrial fibrillation (62%). Systolic blood pressure 123 (118–148) mm Hg (median, IQR). Patients with platelet count <50 x109/L or severe active oral infection excluded. No antiplatelet therapy.	INR 2–4. 1 patient had INR > 3 and minor postoperative bleeding, the remaining patients had INR 2–3. C-G CrCl 78 (47–121) mL/min, (median, IQR).	< 4 contiguous teeth were extracted. 2 (1–3) teeth (median, IQR) were extracted. 2 (10%) patients underwent surgical extraction. Time of surgery was 22 (11–37) min (median, IQR).	

C-G CrCl, Cockcroft-Gault creatinine clearance; *CHA2DS2-VASc*, clinical prediction rules for estimating the risk of stroke in people with non-rheumatic atrial fibrillation; *HAS-BLED*, a medical tool for calculating the 1-year risk of major bleeding in patients on blood thinning drugs for atrial fibrillation; *INR*, international normalized ratio; *VKA*, vitamin K antagonist.

publications were judged to be low or very low, indicating that the estimated effect is very uncertain.

Table 7 summarizes the findings of the present review. Although there is a risk of misinterpretation due to the vague nature of the results, we choose to present our findings in a way that is easily accessible for clinicians. The results of the meta-analysis are presented as odds ratios (ORs) because 1 of the included studies[33] used adjusted multiple logistic regression analyses and presented the results as ORs. An OR may also be more clinically relevant than other ratios. The reason for not presenting any funnel plots was that only 3 original clinical trials were included, which could make a funnel plot deceptive.

It is noteworthy that in situations of extensive bleeding today, there are antidotes for all DOACs, but the antidotes are expensive and the antidote for factor Xa inhibitors has an attendant risk of a rebound effect.[38] The risk of gastrointestinal bleeding is known to be higher for most DOACs compared to VKAs.[39] However, it is unclear whether any DOAC is prone to give rise to more bleeding than another DOAC in an oral surgical setting. Direct comparative data are lacking but needed.

CONCLUSIONS

Eighty of the 274 patients included in the present systematic review experienced bleeding during the first 7 postoperative days. The certainty of the scientific evidence to assess the risk of bleeding complication associated with oral surgery in patients receiving a DOAC is low (⊕⊕◯◯). The risk of postoperative bleeding after oral surgery, however, may be lower for the patients receiving a DOAC throughout the pre- and postoperative periods, including during surgery, compared with the patients who receive a VKA within the therapeutic range. This conclusion will apply to the surgical procedures that employed tranexamic acid as a topical hemostatic agent to some extent, and was based on an interpreted trend rather than a significant between-group difference (OR 0.56; 95% CI, 0.27-1.17). The effect size of the risk, however, is unclear, that is, the number needed to harm was not possible to calculate.

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PRESENTATION

The abstract was submitted to the Scandinavian Association of Oral and Maxillofacial Surgeons (SFOMK) 2022 and was accepted as an oral presentation.

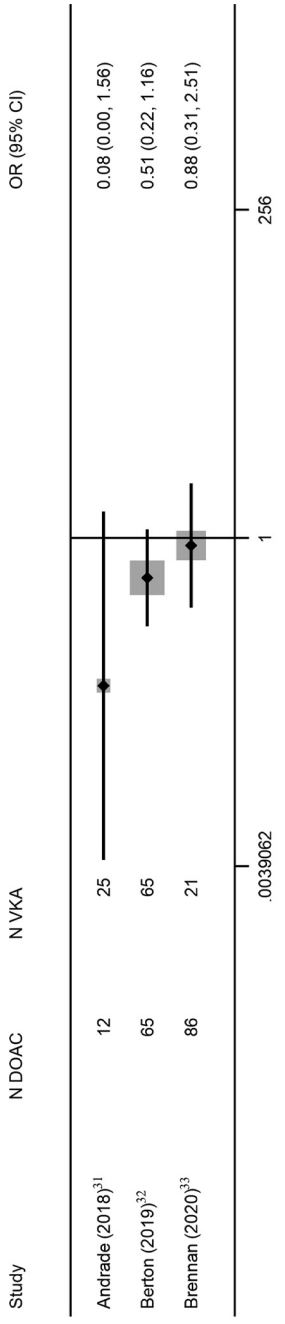

Fig. 2. Forest plot of bleeding during the first 7 post-operative days. *DOAC*, direct oral anticoagulant; *VKA*, vitamin K antagonist.

Table 7. Summary of findings of the effects of postoperative bleeding reported in patients undergoing 1 or more dental or surgical extractions while continuing their DOAC or VKA therapy during and after surgery

Outcome, publications	*No. of participants (studies)*	*Results (patients experiencing bleeding/total number of patients)*	*Certainty of evidence (GRADE)*	*Reason for downgrading*
Any bleeding during the first 7 postoperative days Andrade et al.[31] Berton et al.[32] Brennan et al.[33]	274 (3) 37 (1) 130 (1) 107 (1)	Lower risk for DOAC compared with VKA DOAC: 0/12 (0%), VKA: 8/25 (32%) DOAC: 12/65 (18%), VKA: 20/65 (31%) DOAC: 31/86 (36%), VKA: 9/21 (43%)	Low ⊕⊕◻◻	Risk of bias—1†,‡,§ Imprecision—1¶,**
Extensive postoperative bleeding leading to hemoglobin drop ≥3 g/dL, fatality, need for transfusion, or other bleeding type 3-5* Andrade et al.[31] Berton et al.[32] Brennan et al.[33]	274 (3)	Low risk both for DOAC and VKA because no patient experienced overt hemorrhage	Very low ⊕◻◻◻	Risk of bias—1†,‡,§ Imprecision—2**,††
Bleeding 24 h after extraction Andrade et al.[31]	37 (1)	Lower risk for DOAC (0/12) 0%, compared with VKA (8/25) 32%	Very low ⊕◻◻◻	Risk of bias—1†,‡,§ Imprecision—2‖,¶,**
Bleeding 48 h after extraction Andrade et al.[31]	37 (1)	Lower risk for DOAC (0/12) 0%, compared with VKA (5/25) 20%	Very low ⊕◻◻◻	Risk of bias—1†,‡,§ Imprecision—2‖,¶,**
Bleeding day 3-7 postoperatively Andrade et al.[31]	37 (1)	Lower risk for DOAC (0/12) 0%, compared with VKA (5/25) 20%	Very low ⊕◻◻◻	Risk of bias—1†,‡,§ Imprecision—2‖,¶,**
Bleeding once or twice in the first postoperative week stopped by simple compression Berton et al.[32]	130 (1)	Lower risk for DOAC (7/65) 11%, compared with VKA (12/65) 19%	Very low ⊕◻◻◻	Risk of bias—1†,‡,§ Imprecision—2‖,¶,**
Bleeding more than twice a week stopped by simple compression Berton et al.[32]	130 (1)	Lower risk for DOAC (4/65) 6%, compared with VKA (6/65) 9%	Very low ⊕◻◻◻	Risk of bias—1†,‡,§ Imprecision—2‖,¶,**
Bleeding requiring pharmacologic intervention (tranexamic acid) Berton et al.[32]	130 (1)	Equal risk for DOAC (1/65) 2%, compared with VKA (1/65) 2%	Very low ⊕◻◻◻	Risk of bias—1†,‡,§ Imprecision—2‖,¶,**
Bleeding that required surgery with additional sutures and/or diathermocoagulation Berton et al.[32]	130 (1)	Lower risk for DOAC (0/65) 0%, compared with VKA (1/65) 2%	Very low ⊕◻◻◻	Risk of bias—1†,‡,§ Imprecision—2‖,¶,**
Nonmajor bleeding that required medical but not surgical intervention Brennan et al.[33]	107 (1)	Lower risk for DOAC (5/86) 6%, compared with VKA (2/21) 10%	Very low ⊕◻◻◻	Risk of bias—1†,‡ Imprecision—2‖,¶,**

DOAC, direct oral anticoagulant; *VKA*, vitmain K antognist; *GRADE*, Grading of Recommendations, Assessment, Development and Evaluations approach.

⊕⊕⊕⊕ = Certainty of evidence according to the Grading of Recommendations, Assessment, Development and Evaluations approach.[13]

*According to the Bleeding Academic Research Consortium definition for bleeding.

†Study execution: confounding bias, measurement bias, reporting bias and bias due to deviations from intended interventions.

‡Selection of participants.

§Statistics.

‖One study.

¶Few events.

**Few participants.

††Zero events.

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