Bleeding and thromboembolic risk in patients under anticoagulant therapy receiving oral surgery: a systematic review

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Abstract

Background and aims. There is an increasing number of patients with cardiovascular diseases who require anticoagulant treatment to address the underlying disease. Types of anticoagulants include vitamin K antagonists, such as warfarin and coumarin derivatives, and also newer oral anticoagulants, including rivaroxaban, apixaban, edoxaban, and dabigatran. The use of these anticoagulants may impact the condition of patients undergoing oral surgery. If the treatment is discontinued, the patient may be at risk of thrombosis. On the other hand, if the treatment is continued, the patient may experience a postoperative bleeding episode, placing them at risk of both thrombosis and bleeding.

Method. The present article systematically reviews two different therapeutic regimens and their influence on hemorrhagic and thromboembolic events. The review included research from three databases and four specialized journals. The regimens examined were continuous versus discontinuous anticoagulant treatment and continuous versus interruption and switch to bridging therapy.

Results. The most common surgical procedure examined in the review was tooth extraction, with a few studies also including soft tissue procedures. A total of seven eligible articles were identified, with five using the first treatment regimen of continuous versus discontinuous anticoagulant. These studies reported several cases of bleeding under continuous anticoagulant treatment during surgery. Two articles used the second treatment regimen of continuous versus interruption and switch to bridging therapy.

Conclusions. The results of both treatment categories (continuous versus discontinuous anticoagulant and continuous versus interruption and switch to bridging therapy) showed no significant differences in terms of bleeding events. However, the use of scores that assess the risk of thrombosis and bleeding can assist surgeons in anticipating the degree of postoperative complications and making informed treatment decisions.

Keywords: anticoagulant therapy, thromboembolic risk, oral surgery

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Background and aims

Atrial fibrillation is the most common type of arrhythmia. Risk factors for developing atrial fibrillation include hypertension, diabetes, heart disease, age, and sex of the patient. There has been an increasing trend of atrial fibrillation among patients [1]. Those diagnosed with atrial fibrillation often receive therapy with anticoagulant medication to prevent and treat episodes of thromboembolism. Anticoagulant preparations are also prescribed to individuals with mechanical heart valves. It is expected that the number of people requiring this type of treatment will increase in the future [2].

Anticoagulant drugs are used to prevent and treat thromboembolism and are classified into three main categories: vitamin K antagonists (VKAs) such as warfarin and coumarin derivatives, heparin derivatives including low molecular weight heparin (LMWH) and unfractionated heparin (UFH), and novel oral anticoagulants or direct oral anticoagulants (NOACs or DOACs) including apixaban - *Eliquis*©, dabigatran - *Pradaxa*©, edoxaban - *Lixiana*© and rivaroxaban - *Xarelto*©. VKAs work by inhibiting the formation of vitamin K-dependent factors (factors II, VII, IX, X, and proteins C and S) in the coagulation cascade, while DOACs act on either factor Xa or thrombin (IIa) to prevent coagulation. Among the new oral anticoagulants, rivaroxaban, apixaban and edoxaban inhibit factor Xa and dabigatran inhibits factor IIa [3]. DOACs are divided according to the factor on which they act from the coagulation cascade - factor Xa inhibitors and direct thrombin (IIa) inhibitors [2]. DOACs are commonly used to reduce the risk of stroke in non-valvular atrial fibrillation, and to treat deep vein thrombosis and pulmonary embolism. In patients with cardiovascular diseases who require oral surgery, the standard protocol is to discontinue anticoagulant medication for a few days before the procedure [4].

For warfarin, this may require a discontinuation period of up to 5 days to achieve hemostasis [3]. During this interruption, the patient is at risk of thrombosis, and when anticoagulant treatment is resumed, there is a risk of postoperative bleeding. It is important for doctors to carefully balance these risks and decide when to stop and resume anticoagulant treatment, as well as whether bridging therapy is necessary, to anticipate the degree of bleeding and minimize complications [2].

The purpose of this systematic review was to investigate the bleeding and thromboembolic risk in patients receiving oral surgical procedures under two different anticoagulant therapy regimens: continuous versus discontinuous anticoagulant therapy, and continuous versus interruption and switching to bridging therapy. The review also aimed to identify the different methods of hemostasis used, the type and technique of anesthesia, and the anesthetic agents used in these patients. The review was divided into two parts to address these objectives.

Methods

This study adhered to the PRISMA 2020 Checklist for systematic reviews and meta-analysis [5] and included research from three databases and four international journals published between January 2000 and March 2021: PubMed, ScienceDirect, Cochrane Library, Ovid databases, Journal of Oral and Maxillofacial Surgery, British Journal of Oral and Maxillofacial Surgery, The Journal of Craniofacial Surgery. The keywords and filters used for the search process in each database or journal are listed in table I.

Table I. The keywords and filters applied for searching.

Keywords and filters applied for each database and journal
PubMed: anticoagulant AND dental AND surgery Filters: Clinical trials, Randomized controlled trials Publication date: 2000-2021
ScienceDirect: anticoagulant AND dental AND surgery Filters: Research articles Publication date: 2000-2021
Cochrane Library: anticoagulant AND dental AND surgery Search: All Text Filters: Trials Publication date: 2000-2021
Journal of Oral and Maxillofacial Surgery (JOMS): anticoagulant AND dental AND surgery Filters: Research articles Publication date: 2000-2021
British Journal of Oral and Maxillofacial Surgery (BJOMS): anticoagulant AND dental AND surgery Filters: Research articles Publication date: 2000-2021
The Journal of Craniofacial Surgery (JCraniofacialSurgery): anticoagulant AND dental AND surgery Filters: Articles Publication date: 2000-2021
Ovid (lwwreprints.ovidds.com): anticoagulant AND dental AND surgery Filters: Randomized controlled trials Publication date: 2000-2021

To ensure that no potential research papers were omitted, separate searches were conducted using different keywords for each database and journal, as shown in table II. The publication date filter was kept the same for each database and journal. After obtaining the total number of scientific papers, the Mendeley Desktop version 1.19.8 [6] was used to remove duplicates. The selected articles were thoroughly reviewed and the inclusion criteria were applied (Table III).

The papers considered eligible were included in the systematic review. Articles that did not meet the inclusion criteria were removed from the study (Table IV).

Table II. Separate research keywords used for databases and journals.

Database / Journal	Second research and keywords applied
PubMed **ScienceDirect** **Cochrane Library** **Journal of Oral and Maxillofacial Surgery (JOMS)** **British Journal of Oral and Maxillofacial Surgery (BJOMS)** **The Journal of Craniofacial Surgery (JCraniofacialSurgery)** **Ovid (lwwreprints.ovidds.com)**	* (vitamin K antagonist) AND (dental) AND (surgery) * (vitamin K antagonist) AND ((dental) OR (tooth) OR (teeth)) AND ((surgery) OR (surgical)) * (anticoagulant) AND (dental) AND (surgery) AND ((bleeding) OR (thromb)) * ((vitamin K antagonist) OR (new oral anticoagulant) OR (NOAC) OR (NOACs) OR (oral anticoagulant) OR (OAC) OR (OACs) OR (direct oral anticoagulant) OR (DOAC) OR (DOACs)) AND (dental) AND (surgery) * ((rivaroxaban) OR (Xarelto)) AND (dental) AND (surgery) * ((apixaban) OR (Eliquis)) AND (dental) AND (surgery) * ((dabigatran) OR (Pradaxa)) AND (dental) AND (surgery) * ((warfarin) OR (Coumadin) OR (acenocoumarin) OR (Acenocoumarol)) AND (dental) AND (surgery) * (direct factor Xa inhibitors) AND (dental) AND (surgery) * ((heparin) OR (low molecular weight heparin) OR (LMWH) OR (unfractionated heparin) OR (UFH)) AND (dental) AND (surgery) * ((enoxaparin) OR (dalteparin) OR (nadroparin)) AND (dental) AND (surgery) ** For each database and journal publication date: 2000-2021

Table III. Inclusion criteria applied for each scientific paper.

Inclusion criteria
1. Adult patients (above 18 years old)
2. Controlled Clinical Trial (CCT) or Randomized Controlled Trial (RCT)
3. Prospective and/or Experimental-Control design: continuous anticoagulant therapy *versus* stopped or reduced anticoagulant therapy **or** continuous anticoagulant *versus* stopped or reduced anticoagulant and bridging therapy with low molecular weight heparin or unfractionated heparin
4. Patients under anticoagulant therapy for cardiovascular diseases or other pathologies: vitamin K antagonists, oral anticoagulants (OACs), direct oral anticoagulants (DOACs), novel oral anticoagulants (NOACs), Heparin or Low-molecular weight heparin (LMWH)
5. Patients requiring dental, dentoalveolar, or oral surgical procedures
6. Results presented quantitatively
7. Articles with an IMRAD structure (introduction, material and method, results, discussion) written in English

Table IV. Exclusion criteria for article selection.

Exclusion criteria
1. Patients under 18 years old and pregnant women
2. Different study types and designs (case report, cohort studies, series of case reports, guidelines, review, meta-analysis, letters to the editor, books)
3. Articles comparing patients under anticoagulant therapy with only healthy or never-medicated patients
4. Patients on antiplatelet drugs or dual therapy (anticoagulant and antiplatelet medication) or different medication
5. Patients requiring other surgical procedures (other than dental, dentoalveolar, or oral)
6. Patients receiving additional interventions, other than the main surgical procedure that could affect the investigated outcome
7. Article written in another language than English

For each article, a quality score was calculated using the Jadad Quality Score [7]. This score was determined by assigning points (0 or 1) for each question (with a maximum possible score of 5). Scores between 0-2 were considered low quality, while scores between 3-5 were considered high quality. To assess the risk of bias, graphical models of assessment were created using the robvis tool available online [8]. Using the template provided by the application, each bias field was completed for each article. Two graphical representations were then generated: the first showed the bias domains for each article, and the second showed the bias domains of all the articles assessed together.

Results

Identifying the eligible articles

A total of 1488 articles were identified in the search process. No additional scientific articles were found through additional searches in all databases and journals. After removing 194 duplicates, 1294 papers were moved on to the title and abstract screening process. Of these, 1090 papers were eliminated using the Mendeley Desktop version [6]. The remaining 204 articles were fully reviewed, and 197 were eliminated due to insufficient information regarding the target population and surgical procedures. A total of 7 articles were included in the present systematic review. The selection process is shown in Figure 1 according to the PRISMA graphical model [5].

Extraction of data of interest

Five trials compared groups receiving continuous versus discontinuous anticoagulant therapy (Al-Mubarak et al. 2007 [9], Campbell et al. 2000 [10], Cannon and Dharmar 2003 [11], Evans et al. 2002 [12], Sacco et al. 2007 [13]), while two trials compared continuous versus interrupted anticoagulant therapy with heparin bridging (Bajkin et al. 2009 [14], Karslı et al. 2011 [15]). Both treatment regimens included additional groups. A total of 813 patients were included in the clinical trials, with 559 receiving continuous versus discontinuous anticoagulant therapy and 254 receiving heparin bridging treatment. The relevant data are listed in table V.

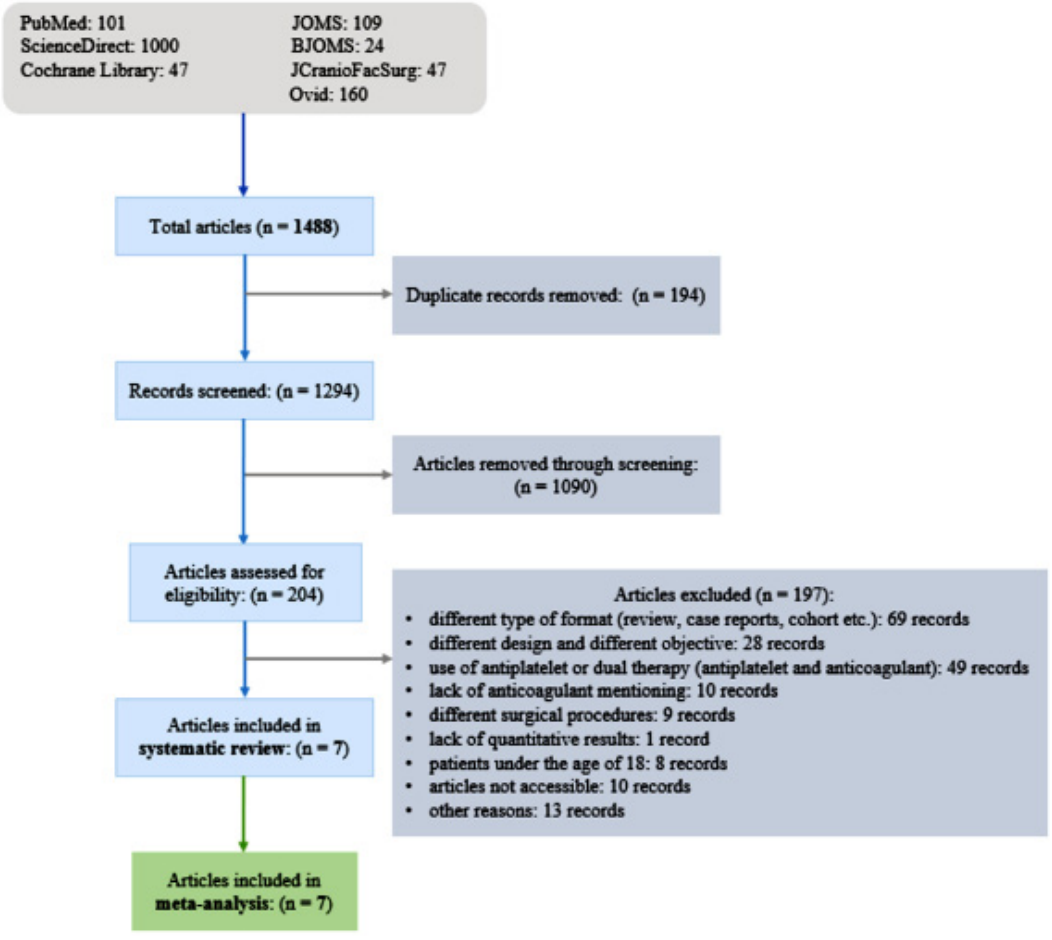

Figure 1. The flow diagram of researched papers, according to PRISMA statement [5].

Table V. Variables of interest in eligible studies.

First author/authors Year of publication Database/Journal	Al-Mubarak et al., 2007 [9], British Dental Journal
Study type Study design	Prospective study Group 1 (warfarin discontinued, no suture) Group 2 (warfarin continued, no suture) Group 3 (warfarin discontinued, with suture) Group 4 (warfarin continued, with suture)
†Patients ‡Age	214 Group 1 (n = 48; 22 M, 26 F), 52.3 ± 14.3 years Group 2 (n = 58; 27 M. 31 F). 51.7 ± 14.7 years Group 3 (n = 56; 25 M. 31 F). 48.7 ± 13.1 years Group 4 (n = 52; 24 M. 28 F). 53.1 ± 13.7 years
Exclusion criteria	Chronic liver or renal disease Patients on drugs that could affect liver function or hemostasis (other than warfarin)
Pathology for anticoagulant treatment and additional comorbidities	Not specified
Anticoagulant	Warfarin, daily maintenance dose 2-10 mg for more than one year
Time of discontinuation of oral anticoagulant	Groups 1 and 3: warfarin was discontinued two days before the surgical intervention Warfarin was resumed 12 hours after the procedure
Bridging	None
Oral surgical procedure	Dental extractions with forceps and elevators
⸸Preoperatory INR	Preoperative baseline INR Group 1: INR 1.8 ± 0.4 Group 2: INR 2.4 ± 0.5 Group 3: INR 1.9 ± 0.4 Group 4: INR 2.7 ± 0.4
⸸ Postoperatory INR	Days 1, 3 and postoperative: Group 1: INR 1.6 ± 0.4 (day 1); 2.1 ± 0.7 (day 3); 2.3 ± 0.6 (day 7) Group 2: INR 2.4 ± 0.5 (day 1); 2.5 ± 0.7 (day 3); 2.5 ± 0.6 (day 7) Group 3: INR 1.8 ± 0.3 (day 1); 1.9 ± 0.7 (day 3); 2.3 ± 0.7 (day 7) Group 4: INR 2.7 ± 0.6 (day 1); 2.6 ± 0.5 (day 3); 2.7 ± 0.6 (day 7)
INR and bleeding/thromboembolism relationship	All patients were divided based on the INR value and bleeding incidence (day 1 visit) into 3 groups: INR 1 - 2 (13.6 %), INR > 2 - 3 (19.8 %), INR > 3 (54.21 %) There was a link between elevated INR levels and increased bleeding frequency Bleeding was more common in patients with INR > 3.0 compared to those with INR < 3.0
Postoperative bleeding (first 24 to 48 hours after the procedure)	Group 1 and Group 3: 15 cases Group 2 and Group 4: 27 cases
First author/authors Year of publication Database/Journal	**Campbell et al., 2000 [10], J Oral Maxillofac Surg.**
Study type Study design	Clinical Controlled Trial Experimental group (continuous anticoagulant regimen) Control group (interrupted anticoagulant regimen) Additional group (never on anticoagulant therapy)
†Patients ‡Age	35 Experimental group (n = 12) Control group (n = 13) Additional group (n = 10)
Exclusion criteria	Not specified
Pathology for anticoagulant treatment and additional comorbidities	Not specified
Anticoagulant	Coumadin
Time of discontinuation of oral anticoagulant	Control group: 72 to 96 hours before surgery
Bridging	None
Oral surgical procedure	Dental extractions, Alveoloplasty, Limited intraoral soft tissue surgery (biopsy, frenectomy)
⸸Preoperative INR	Experimental group: INR 2.0 (1.2 - 2.9) Control group: INR 2.0 (1.1 - 3.0) Additional group: not determined 10 patients on Coumadin (5 experimental, 5 control) were sub-therapeutically anticoagulated (INR < 2.0) Of these, 5 patients (3 experimental, 2 control) had INR 1.5 or greater
⸸ Post-operative INR	Not specified
INR and bleeding/thromboembolism relationship	Experimental group:1.4 ml blood loss per unit (0.1 to 4.5 ml range) Control group: 2.2 ml blood loss per unit (0.2 to 6.3 ml range) Additional group: 1.4 ml blood loss per unit (0.6 to 2.1 ml range) More surgery was performed in the experimental group, however total blood loss and blood loss per unit were no greater than in the control group or the additional group
Postoperative bleeding (first 24 to 48 hours after the procedure)	Three cases mentioned, "a lot" of bleeding (1 experimental, 2 controls) after leaving the clinic No patient had postoperative bleeding serious enough to require therapeutic intervention

Table V. Variables of interest in eligible studies (continuation).

First author/authors Year of publication Database/Journal	Cannon and Dharmar, 2003 [11], Australian Dental Journal
Study type Study design	Clinical Controlled Trial Study group (continuous anticoagulant) Control group (interrupted anticoagulant)
†Patients ‡Age	70 Control group: first 35 patients; 23 M, 12 F; 64.2 (36-78) years Study group: next 35 patients; 17 M, 18 F; 62.4 (38-80) years
Exclusion criteria	INR outside the range of 2-4 Liver disease Medication affecting the liver function
Pathology for anticoagulant treatment and additional comorbidities	Deep vein thrombosis Transient cerebral ischemic attacks Myocardial infarction Arrhythmias (AF and SVT) Valvular disorders Prosthetic valve replacement Coronary artery by-pass graft Stroke (CVA) Pulmonary embolism Vascular thromboembolism
Anticoagulant	Warfarin, average dose of 3.9 mg (1.5 to 7.5 mg)
Time of discontinuation of oral anticoagulant	Control group: anticoagulant stopped for two days before the surgery If INR was not below 2, surgery was postponed for one or two days Warfarin treatment was resumed the same day for the control group
Bridging	None
Oral surgical procedure	Dental extractions using forceps and elevators, Surgical procedures requiring a mucoperiosteal flap and bone removal (using a bur), Surgical removal, Biopsies, Closure of oro-antral fistula *Antibiotic prophylaxis for both groups if needed
⭳Preoperatory INR	Initial assessment for all patients: INR 3.4 (2.1 - 4) Perioperative INR Control group: INR brought down to 1.6 (1.4 - 1.9)
⭳ Post operatory INR	Not specified
INR and bleeding/thromboembolism relationship	No thromboembolic events reported in the control group, although the INR levels dropped after anticoagulant cessation
Postoperative bleeding (first 24 to 48 hours after the procedure)	No case of immediate postoperative bleeding during the first 30 minutes Control group: 3 cases of intermittent oozing the for first 24 hours Study group: 2 cases of intermittent oozing the for first 24 hours
First author/authors Year of publication Database/Journal	**Evans et al., 2002 [12], BJOMS**
Study type Study design	Randomized Controlled Trial Control group (interrupted anticoagulant) Anticoagulant group (continuous anticoagulant)
†Patients ‡Age	Initially, 117 recruited 109 completed the trial Control group (anticoagulant withdrawal), n=52; 37 M; 66 (30-93) years Anticoagulant group (anticoagulant continued), n=57; 36 M; 67 (36-92) years
Exclusion criteria	Impossibility to give informed consent No access to a telephone Liver disease or coagulopathies Impossibility to attend the follow-up consultations INR > 4 on surgery day
Pathology for anticoagulant treatment and additional comorbidities	Not specified
Anticoagulant	Warfarin
Time of discontinuation of oral anticoagulant	Control group: warfarin stopped two days before surgery If INR was > 2, surgery was rescheduled for the next day Warfarin intake was resumed on the same day
Bridging	None
Oral surgical procedure	Dental extractions using forceps and elevators, with minimum mucoperiosteal flap rise and minimum bone removal *Antibiotic prophylaxis for both groups, if needed
⭳Preoperatory INR	Control group (anticoagulant withdrawal): INR 1.6 (1.2-2.3) Anticoagulant group (anticoagulant continued): INR 2.5 (1.2-4.7)
⭳ Post-operatory INR	Not specified
INR and bleeding/thromboembolism relationship	Higher bleeding rate in the anticoagulant group than in the control group (26% compared to 14%)
Postoperative bleeding (first 24 to 48 hours after the procedure)	Anticoagulant group: 15 cases Control group: 7 cases

Table V. Variables of interest in eligible studies (continuation).

First author/authors Year of publication Database/Journal	Sacco et al., 2007 [13], J Thromb Haemost
Study type Study design	Prospective Randomized open-label study Group A (reduced oral anticoagulant) Group B (continuous oral anticoagulant)
†Patients ‡Age	131 Group A: n=66; 37 M, 29 F; 64 (29-87 years) Group B: n=65; 29 M, 36 F; 61 (29-86 years)
Exclusion criteria	Low platelet count (less than 100 x 109/L) Liver disease Renal disease Limited physical and psychological ability that prevented protocol completion
Pathology for anticoagulant treatment and additional comorbidities	Artificial cardiac valve Heart valvopathy Atrial fibrillation Peripheral arteriopathy Myocardial infarction Pulmonary embolism Deep vein thrombosis Hypertension Liver disease Diabetes Renal insufficiency
Anticoagulant	Acenocoumarol or Warfarin
Time of discontinuation of oral anticoagulant	Group A: anticoagulant reduced until INR was 1.5 - 2.0 Anticoagulant was resumed 48 hours later
Bridging	None
Oral surgical procedure	Simple and multiple dental extractions with mucoperiosteal flap rise (using forceps and elevators), bone removal (using a bur), and granular tissue removal Removal of cystic formations with corticotomy Insertion of endo-osseous implants with small mucoperiosteal flap *Antibiotic prophylaxis (amoxicillin 2 g orally 1 hour before surgery and 1 g 6 hours afterward; for penicillin allergy, erythromycin 2 g before and 1 g 6 hours after surgery)
⸸Preoperative INR	Before surgery day: Group A: INR 2.74 ± 0.72 Group B: INR 2.80 ± 0.50 On the day of the surgery: Group A: INR 1.77 (± 0.26) Group B: INR 2.89 (± 0.42)
⸸ Post-operative INR	INR between 1.5 – 2.0 (target of 1.8)
INR and bleeding/thromboembolism relationship	No thromboembolic case was reported
Postoperative bleeding (first 24 to 48 hours after the procedure)	Group A: 10 cases (15.1%) Group B: 6 cases (9.2%)
First author/authors Year of publication Database/Journal	**Bajkin et al., 2009 [14], J Oral Maxillofac Surg**
Study type Study design	Randomized Prospective trial Group A (continuous oral anticoagulant therapy) Group B (discontinued oral anticoagulant, bridging with low-molecular-weight heparin)
†Patients ‡Age	214 Group A (n = 109; 66 M, 43 F); 62.1 ± 11.4; (31-79) years Group B (n = 105; 57 M, 48 F); 59.6 ± 11; (22-77) years, with INR ≤ 4.0 on the intervention day
Exclusion criteria	Liver or renal disease Pregnant women Patients on medication that affect liver function or hemostasis Previous thromboembolic complications on OAT, with serious hemorrhage during dental extractions even before starting OAT History of heparin-induced thrombocytopenia
Pathology for anticoagulant treatment and additional comorbidities	Prosthetic valve replacement Cardiac arrhythmia (atrial fibrillation) Atrial fibrillation and valvular disease Venous thromboembolic disease Ischemic heart disease Cerebrovascular accident Dilated cardiomyopathy Hereditary thrombophilia

Table V. Variables of interest in eligible studies (continuation).

First author/authors Year of publication Database/Journal	Bajkin et al., 2009 [14], J Oral Maxillofac Surg
Anticoagulant	Group A: 103 Acenocoumarol; 6 Warfarin Group B: 92 Acenocoumarol; 12 Warfarin; 1 Phenprocoumon
Time of discontinuation of oral anticoagulant	Group B: discontinued OAT 3 to 4 days before the intervention, for an INR < 1.5 on surgery day and bridging therapy with LMWH If the INR was higher than 1.5, patients were kept on OAT for another day
Bridging	LMWH: nadroparin-calcium 0.3 to 0.6 ml (2,850 to 5,700 IU anti-Xa) subcutaneously once or twice a day Bridging started the day after OAT cessation Bridging was discontinued at least 12 hours before the procedure (morning dosage omitted for the twice regime). Oral anticoagulant therapy restarted in the evening of the intervention day
Oral surgical procedure	Simple extraction of one or more teeth, without mucoperiosteal flap rise *Antibiotic prophylaxis (one dose) for patients with cardiac valve disease
⸸Preoperative INR	3-4 days before the surgery: Group B: INR 2.49 ± 0.6 (1.75 - 4.1) On procedure day: Group A: INR 2.45 ± 0.54 (1.68 – 4.0) Group B: INR 1.26 ± 0.11 (1.06 – 1.47)
⸸ Post-operative INR	Not specified
INR and bleeding/thromboembolism relationship	Patients on continuous anticoagulant therapy had more frequent bleeding cases than those on LMWH therapy, with no statistical significance No statistical connection between the INR range and bleeding cases in patients with continuous anticoagulant treatment
Postoperative bleeding (first 24 to 48 hours after the procedure)	Group A: 8 cases (7.34%) Group B: 5 cases (4,76%)
First author/authors Year of publication Database/Journal	**Karslı et al., 2011 [15], JOMS**
Study type Study design	Clinical Prospective Controlled study Group 1 (continuous warfarin) Group 2 (anticoagulant bridged with low-molecular-weight heparin) Group 3 (anticoagulant bridged with unfractionated heparin) Group 4 or Control group (healthy individuals)
†Patients ‡Age	40 21 M, 19 F; 43.5 (26-72) years Group 1 (n = 13) Group 2 (n = 12) Group 3 (n = 11) Group 4 (n = 13)
Exclusion criteria	Extractions with flap rise
Pathology for anticoagulant treatment and additional comorbidities	Part of patients with Artificial heart valve
Anticoagulant	Warfarin
Time of discontinuation of oral anticoagulant	Groups 2 and 3: warfarin was stopped three days before the surgical intervention and patients were kept under hospitalization during discontinuation If INR was > 4.0, surgery was rescheduled until the value was < 4.0
Bridging	Group 2: Low-molecular weight heparin Group 3: Unfractionated heparin Heparin was administered once the INR was < 2.0 The surgical procedures were performed 24 hours after the last dosage of low-molecular-weight heparin was administered subcutaneously and 6 hours after the last dose of unfractionated heparin was administered intravenously Heparin administration continued after hemostasis was achieved Heparin was stopped 48 hours after the procedure, and patients were advised to resume the warfarin therapy
Oral surgical procedure	Dental extractions using luxators and forceps *Antibiotic prophylaxis for groups 1 and 3
⸸Preoperative INR	Group 1: INR 2.6 ± 0.7 Group 2: INR 1.6 ± 0.4 Group 3: INR 1.6 ± 0.4
⸸ Post-operative INR	Not specified
INR and bleeding/thromboembolism relationship	There was a significant difference and a positive correlation regarding the amount of bleeding and the INR level between the groups Group 1 had an increased amount of bleeding compared with group 4, without statistical significance
Postoperative bleeding (first 24 to 48 hours after the procedure)	Group 1: 6 cases Group 2: 3 cases Group 3: 3 cases Group 4: 3 cases

†Patients M (males), F (females); Age (mean ± SD) or mean (range)
‡ Mean ±SD or Mean (SD) or Mean (range); ⸸ Mean ±SD or Mean (SD) or Mean (range)
Abbreviations: *LMWH (low-molecular-weight heparin); UFH (unfractionated heparin); OAT (oral anticoagulant therapy); OAC (oral anticoagulant)*

Table VI. Methods for performing hemostasis implemented in trials.

First author/authors Year of publication	Hemostasis methods
Al-Mubarak et al., 2007 [9]	Initially finger pressure with sterile gauze for 6-10 minutes (exchanged gauze when needed) Groups 3 and 4: non-resorbable suture material (*UNISILK* 4/0, round-body non-capillary braided silk black)
Campbell et al., 2000 [10]	Surgical sponges used for blotting the surgical field
Cannon and Dharmar, 2003 [11]	For both groups, pressure gauze method for 20 minutes Control group: all sockets packed with *Surgicel*© and sutured with 3/0 plain catgut Study group: no local hemostatic agent was used Sutures and local hemostatic agents were used if bone or soft tissue was removed
Evans et al., 2002 [12]	Every extraction site packed with oxycellulose dressing (*Surgicel*©) and sutured with 3/0 polyglactin 910 (*Vicryl*©) Gauze swab biting for 10 minutes Tranexamic mouth rinse was not permitted
Sacco et al., 2007 [13]	Suture application for both groups Group A: no other hemostatic measures Group B: gelatin and oxidized cellulose sponges (during surgery); tranexamic acid as local applications on the surgical wound and as mouthwash every 6 hours for 2 days
Bajkin et al., 2009 [14]	Group A: resorbable collagen sponges Group B: no additional method applied Both groups kept a local pressure and firm bite on sterile gauze for 30 minutes For superficial hemorrhage, a superficial gauze for 10 minutes In case of inefficiency, a new hemostatic agent (resorbable collagen sponge) into the wound, and suture For uncontrolled prolonged hemorrhage (group A), vitamin K or fresh-frozen plasma (indicated by the hematologist)
Karslı et al., 2011 [15]	Gauze swabs at the end of the procedure for 20 minutes Afterward, oxycellulose dressing (*Surgicel*©), suture with 3.0 silk, and gauze swab bite for 1 hour Patients were given additional gauze swabs at discharge

Hemostasis methods

The most commonly used method for achieving hemostasis was post-extraction suture, followed by compressive tamponade. Tranexamic acid, vitamin K, and frozen plasma were also mentioned as auxiliary materials. The methods used for hemostasis are shown in table VI.

Anesthetic agent and technique

The most frequently used anesthetic agents were lidocaine (Al-Mubarak et al. 2007 [9], Evans et al. 2002 [12]) and mepivacaine (Bajkin et al. 2009 [14], Sacco et al. 2007 [13]). Only one trial used prilocaine (Karslı et al. 2011 [15]). Six articles mentioned local anesthesia techniques, such as local infiltrations, intraligamentary or nerve blocks (Al-Mubarak et al. 2007 [9], Bajkin et al. 2009 [14], Cannon and Dharmar 2003 [11], Evans et al. 2002 [12], Karslı et al. 2011 [15], Sacco et al. 2007 [13]). Three papers mentioned the use of adrenaline (Evans et al. 2002 [12], Karslı et al. 2011 [15], Sacco et al. 2007 [13]).

Surveillance of post-interventional bleeding

The clinical trials had a variable follow-up period for immediate bleeding, ranging from 20 minutes to two hours. Two articles did not specify the monitoring period (Campbell et al. 2000 [10], Karslı et al. 2011 [15]). Only one study chose to monitor patients during pre-operative hospitalization (Karslı et al. 2011 [15]). The most common follow-up consultations were one week after the end of surgery.

Quality assessment using Jadad Scale

Based on the quality score, three trials had a minimum score of 0 and one trial had a maximum score of 3. A low score was assigned to six trials. The quality assessment and assigned scores are listed in table VII.

Table VII. Quality scoring, according to Jadad Scale [7].

Article	Quality Appraisal Score
Al-Mubarak et al., 2007 [9]	1 (low)
Campbell et al., 2000 [10]	0 (low)
Cannon and Dharmar, 2003 [11]	0 (low)
Evans et al., 2002 [12]	3 (high)
Sacco et al., 2007 [13]	2 (low)
Bajkin et al., 2009 [14]	1 (low)
Karslı et al., 2011 [15]	0 (low)

Risk of bias analysis

The most affected area was the patient randomization process. There were different methods for presenting and quantifying the results in terms of bleeding cases. Errors were observed in terms of reporting the results. The least affected area was the deviation from the intended objective. Two trials had a higher degree of bias, while five studies had a lower risk for possible bias (Figure 2). The higher risk of bias was related to the randomization process (Figure 3).

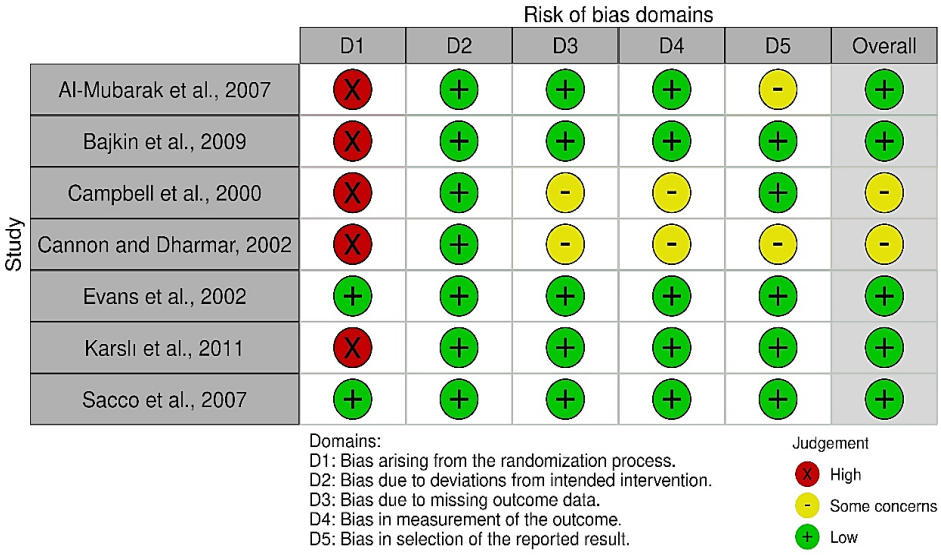

Figure 2. Risk of bias domains for each eligible article, according to robvis [8].

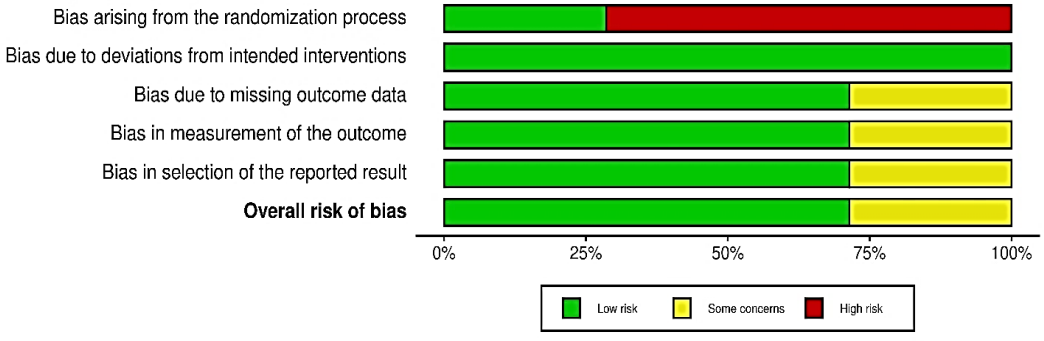

Figure 3. The overall risk of bias, according to robvis [8].

Discussion

The objectives of this study were successfully achieved. Seven meta-analyses and nine systematic reviews were found in the databases and journals that examined the risk of bleeding in patients on anticoagulant therapy undergoing oral surgery. Based on the included articles, this study found that trials preferred the continuation of anticoagulants during surgery, which was consistent with the findings of other studies [16,17].

The included patients underwent various interventions, with tooth extraction being the most common. Four trials included soft tissue maneuvers. Some articles stated that certain oral surgical interventions, such as simple dental extractions and biopsies of soft tissue, generally have a low risk of bleeding [18,19].

However, procedures such as raising a mucoperiosteal flap, multiple or serial teeth extractions, dental implant insertion, and maxillofacial surgical procedures have been evaluated as having a high risk of bleeding [20,21].

The risks of thrombosis and bleeding should be evaluated in the preoperative stage according to the underlying pathology and the complexity of the surgery. According to the 2010 European Society of Cardiology (ESC) guidelines, the risk of thromboembolism and stroke caused by atrial fibrillation can be assessed using the CHA2DS2-VASc score. This score includes conditions such as congestive heart failure, stroke, thromboembolism, and transient ischemic attack, as well as risk factors for cardiovascular disease (such as diabetes, advanced age,

and being female) [22].

Patients with a high thromboembolic risk may benefit from long-term anticoagulant treatment. In those at low risk, the anticoagulant may be given at a lower dose for 1-2 weeks before surgery [3]. Regarding the risk of bleeding, it is possible to stratify patients into low, intermediate, or high categories with the help of the ACCP (American College of Chest Physicians) guide [23].

The risk of bleeding in patients on uninterrupted treatment should be assessed using the HAS-BLED score, which may indicate the need to adjust factors that affect bleeding. Discontinuation of anticoagulants should not be based solely on a high bleeding score [24].

To ensure that bleeding is kept under control during surgery and to prevent excess bleeding, the level of anticoagulant medication should be sufficient at the time it is stopped. The INR, or international normalized ratio, of patients taking warfarin, can be used to determine when to discontinue the medication, as mentioned in reference [3]. When warfarin or phenprocoumon are resumed after a period of discontinuation, the anticoagulant effects of these medications may be delayed, leaving patients at risk for blood clotting. In such cases, bridging therapy may be recommended, as stated in reference [2].

Bridging therapy may not be necessary for low-risk patients due to their low risk of thrombosis, but patient-related factors and the type of surgery should be taken into account for those at intermediate risk. High-risk patients should receive heparin to prevent thrombosis. Warfarin may be discontinued 5 days before surgery, as mentioned in reference [2], and bridging therapy may be considered for patients with a high risk of stroke and thrombosis, according to reference [25]. Low molecular weight heparins (LMWHs) are well-suited for use as bridging agents due to their appropriate dosing according to protocols, predictable effects depending on the dose, subcutaneous administration, and short half-life, as noted in reference [3]. Unfractionated heparin given intravenously should be stopped 4-6 hours before surgery, according to reference [2], and the last dose of LMWH should be given 24 hours before the procedure, as stated in reference [26]. For patients at high risk of bleeding, heparin may be given for 48-72 hours postoperatively, while for those at low risk of bleeding, LMWH may be resumed either in the evening of the procedure or 24 hours postoperatively.

There is a connection between the summary of post-procedural anticoagulant treatment and the risk of post-interventional bleeding, according to reference [3]. Patients taking NOACs, or non-vitamin K antagonist oral anticoagulants, who take a single daily dose can resume the medication on the same day with a missed dose or the next day with no missed doses. Those taking DOACs, or direct oral anticoagulants, in two doses per day, can resume the medication on the same day with one missed dose or the next day with two missed doses, as mentioned in reference [25]. In some cases, DOACs and heparin can be resumed at their full dose within 6-12 hours of surgery. Warfarin, which takes 5-10 days to reach its anticoagulant effect, can be resumed when the patient can swallow, according to reference [3], and under good hemostasis, it can be resumed 12-24 hours after surgery, as stated in reference [2].

There are various options available to achieve hemostasis, such as supraalveolar compressive tamponade, oxidized cellulose, foam gel, cyanoacrylate glue, tranexamic acid products, fibrin adhesives, chlorhexidine adhesive gel, calcium alginate, resorbable gelatin sponges, or collagen sponges, as listed in reference [27]. It is important to note that each of these agents promotes hemostasis differently. In terms of anesthesia, one study found that using epinephrine in minimal doses does not cause complications in patients with various cardiovascular conditions, as noted in reference [28].

This study has several limitations, such as a limited number of randomized clinical trials included, low-quality scores, uncertainty, and heterogeneity in trial methodologies, such as the randomization process, measurement methods, reporting of bleeding cases, and the use of various hemostatic agents. It also included only articles written in English.

The number of patients with atrial fibrillation is expected to increase due to contributing risk factors, as mentioned in reference [29]. The 2020 ESC guidelines have changed the way atrial fibrillation is described in terms of treatment and prognosis, using the 4S-AF model, which takes into account the risk of stroke, the severity of symptoms, the burden of atrial fibrillation, and the severity of the substrate, as noted in reference [24]. Given these characteristics, the risk of thrombosis and bleeding should be evaluated before subjecting the patient to surgical procedures.

The risk of thrombosis and bleeding should be carefully evaluated before subjecting patients to surgical procedures, taking into account their characteristics. Communication between the oral surgeon and the cardiologist can aid in deciding whether to continue or discontinue anticoagulant treatment. Further research is needed to better understand the risks faced by patients and to enhance the quality and safety of surgical procedures.

Conclusions

Both categories of therapy (continuous versus discontinuous anticoagulant, and continuous versus interruption and switch to bridging therapy) have shown no differences in the incidence of bleeding. Using scores that assess the risk of thrombosis and bleeding can help the surgeon anticipate the likelihood of postoperative complications.

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