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REVIEW ARTICLE

Risk of bleeding with dental implant surgery in patients on anticoagulant or antiplatelet drugs: a systematic review and meta-analysis

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ABSTRACT

Introduction: A large number of patients under oral anticoagulant (OAC) or antiplatelet (AP) therapy require dental implantation. We systematically reviewed evidence on the risk of bleeding after implant placement with continued OAC or AP therapy.

Methods: PubMed, Embase and CENTRAL were searched for studies comparing bleeding outcomes after implant placement between OAC/AP therapy *vs.* controls or OAC *vs.* AP therapy.

Results: Seven studies were included. Pooled analysis showed no significant difference in the risk of bleeding with continued OAC therapy *vs.* control (RR 1.81 95% confidence interval [CI] 0.70, 4.63 $I^2 = 14\%$ $p = .22$). Subgroup analysis depending on the type of OAC showed there was a non-significant tendency of increased risk of bleeding with Vitamin K antagonists (VKAs) (RR 3.42 95% CI 1.00, 11.67 $I^2 = 23\%$ $p = .05$) but not with direct oral anticoagulants (DOACs) (RR 1.67 95% CI 0.49, 5.70 $I^2 = 0\%$ $p = .41$). Limited data suggest an increased risk of bleeding with OAC as compared to AP (RR 0.08 95% CI 0.01, 0.76 $I^2 = 0\%$ $p = .03$).

Conclusions: Continuation of OAC therapy in patients undergoing implant surgery does not increase the risk of bleeding provided local haemostatic measures are used. The indirect comparison suggests bleeding tendency may be higher with VKAs as compared to DOAC.

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Introduction

Dental implant is now one of the most common modalities for prosthetic tooth replacement across the globe. Trends suggest that the overall use of implants is gradually increasing and up to 23% of patients may have implants in 2026 [1]. Interestingly, the largest increase in the use of dental implants over the last two decades has been noted in the age-group of 65–74 years [1]. Management of patients in this age group also entails dealing with several comorbidities treated by a variety of different medications. Due to the high prevalence of cardiovascular and cerebrovascular diseases, long-term prescription of antiplatelets (APs) and oral anticoagulants (OAC) is common in older adults for prophylaxis against thromboembolic events [2,3]. These drugs are commonly used in patients after myocardial infarction, percutaneous coronary interventions, placement of prosthetic heart valves, atrial fibrillation, pulmonary embolism, stroke and joint replacement surgeries [4].

Since dental implantation is a minor oral surgical procedure, hesitation exists amongst clinicians for using this modality in patients under OAC or AP therapy due to the risk of intraoperative or postoperative bleeding [5]. Owing to this uncertainty, patients may be recommended other less invasive prosthetic modalities like fixed partial dentures or cast partial dentures or consultation is sought with the physician for interruption of the drug. Indeed, one has to balance the risk of bleeding *vs.* the risk of thromboembolic events due to the stoppage of the drug [6].

Much research has been conducted on the bleeding risk with dental surgery in patients under OAC or AP therapy. However, most of it has been focussed on dental extraction as it is the most common minor oral surgical procedure [7,8]. Shi et al. [7] in a recent meta-analysis of 12 studies have indicated that the risk of bleeding is greater in anticoagulated patients undergoing minor oral surgery as compared to healthy controls. The majority of studies in their review were on dental extraction with just four studies focussing on dental implants. In another study, Bajkin et al. [9] have reviewed the literature on bleeding tendencies after implant placement in anticoagulated patients but no meta-analysis was conducted in their review. Despite the widespread use of OAC and AP drugs as well as dental implantation procedures in the general population, it is still not clear how these medications influence the risk of bleeding following surgical placement of a dental implant. There is a need for evidence on the risk of bleeding with AP, OAC, different types of OAC (Vitamin K antagonists [VKAs] and direct oral anticoagulants [DOACs]), and between AP *vs.* OAC to guide clinical practice. Thus, this study aimed to conduct a systematic literature search and pool evidence on the risk of bleeding in patients under AP and OAC therapy undergoing dental implant surgery.

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Material and methods

We framed the following research questions for the review: 1) Is there a difference in the risk of bleeding after implant placement between patients under OAC or AP therapy *vs.* controls? 2) Is there a difference in the risk of bleeding after implant placement between patients under OAC *vs.* AP therapy?

Eligibility criteria

We included studies fulfilling the following criteria:

1) Study population consisting of patients under OAC or AP therapy receiving dental implants. 2) Patients were to continue the OAC or AP drug during the surgical procedure. 3) Studies comparing bleeding outcomes between OAC, AP or control groups. There was no limitation based on the study type or language of publication.

Exclusion criteria were: 1) Studies assessing bleeding risk after stoppage of OAC or AP therapy. 2) Studies on any dental procedures other than the placement of dental implants or studies not reporting separate data for dental implant procedures. 3) Studies with sample size of <10 patients. 3) Studies not reporting data on post-operative bleeding. 4) Case reports, case series and review articles.

Literature search

We took the help of a medical librarian to systematically search PubMed, Embase and CENTRAL upto 1 February 2021. The keywords for the database search were: 'Anticoagulant', 'Antiplatelet', 'Antithrombotic', 'Warfarin', 'Direct oral anticoagulants', 'Novel oral anticoagulants', 'Bleeding', 'dental surgery', 'bleeding' and 'dental implants' (Supplementary Table 1). Once the initial search was completed, the two reviewers involved in the search process examined the titles and abstract of the studies to look for relevant articles. Once these were identified, they underwent further full-text evaluation against the eligibility criteria of the review. Studies fulfilling the same were included in the review. If there were disagreements, the reviewers resolved it *via* discussion. Manual scoping of the reference list of included studies was also conducted in the end to look for additional references. We also followed the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement for the review [10].

Data extraction and risk of bias assessment

A data extraction sheet was prepared at the beginning of the review and its final version was endorsed by all the reviewers. Data on author name, publication year, study type, location, study drugs, sample size, age and gender of the sample, number of implants, intraoperative haemostasis technique and outcomes were extracted. This was done by two reviewers independently. If there were disagreements, the reviewers resolved it *via* discussion. The outcome of interest was to compare the bleeding risk between OAC *vs.* control, AP *vs.* control, and OAC *vs.* AP.

As included studies were observational in nature, the Newcastle–Ottawa scale was selected for quality assessment [11]. Points were given to each study for selection of study population, comparability and outcomes. The scale has a maximum score of nine. Quality assessment was also done by two study investigators independent of each other.

Statistical analysis

The statistical analysis was conducted using 'Review Manager' (RevMan version 5.3; Nordic Cochrane Centre [Cochrane Collaboration], Copenhagen, Denmark; 2014). Quantitative analysis of data was conducted if there were three studies reporting similar outcomes with the same groups. We calculated risk ratios (RRs) with the 95% confidence intervals (CIs) for comparing the risk of bleeding between different groups. Sub-group analysis was conducted for the type of OAC drug (VKAs and DOACs). The random-effects model was used for the analysis. The I^2 statistic was used to evaluate heterogeneity between studies. Since <10 articles were available in each meta-analysis, we did not use funnel plots to examine for publication bias.

Results

Study details

The systematic search identified 626 unique articles (Figure 1). Of these, 609 studies were not considered due to non-relevance. Seventeen studies were eligible for full-text analysis and 10 were excluded with reasons. The remaining seven studies were included in the review [12–18]. The majority were prospective studies while two were retrospective studies (Table 1). Except for one study, all studies compared the risk of bleeding between OAC or AP and a group of control patients not under any OAC/AP therapy. There was a wide variation in the sample size of the included studies. The majority of studies did not report the number of implants placed per group. Local haemostatic measures were used to control intraoperative bleeding. Most studies used suturing and pressure pack of tranexamic acid. The Newcastle–Ottawa scale score of the included studies ranged from 6 to 8.

Meta-analysis

Six studies compared the risk of bleeding between patients under OAC therapy and controls. Meta-analysis indicated no statistically significant difference in the risk of bleeding between the two groups (RR 1.81 95% CI 0.70, 4.63 $I^2 = 14\%$ $p = .22$) (Figure 2). We further conducted a sub-group analysis based on the type of OAC drug. With data from four studies comparing VKAs and control, our pooled analysis indicated a non-significant tendency of increased risk of bleeding with VKAs (RR 3.42 95% CI 1.00, 11.67 $I^2 = 23\%$ $p = .05$) (Figure 3). Six studies compared bleeding outcomes between DOACs and control. However, in three of these studies [13,16,18], the number of patients on DOACs was very small (2–8 patients). Hence, these studies were not included in the meta-analysis.

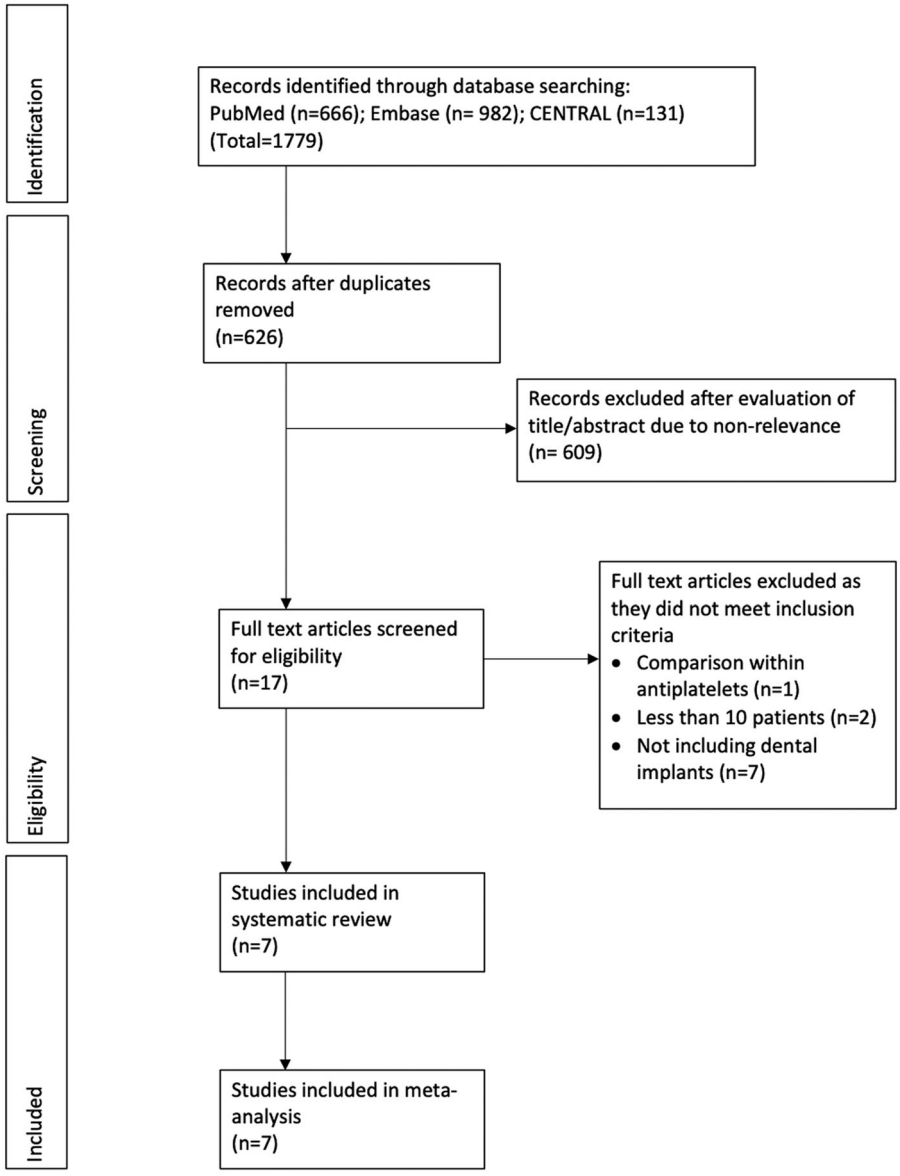

Figure 1. Study flow-chart.

Pooled analysis of the remaining three studies indicated no difference in the risk of bleeding between DOACs and control (RR 1.67 95% CI 0.49, 5.70 $I^2 = 0\%$ $p = .41$) (Figure 4).

As only two studies compared outcomes of AP *vs*. control, a meta-analysis was not conducted. Manor et al. [18] reported no case of bleeding in 40 patients under AP therapy but seven cases in controls. Similarly, Clemm et al. [13] also reported no case of bleeding with AP (40 patients) but 2 episodes of bleeding in controls (271 patients). In the last analysis, three studies comparing OAC and AP were pooled. Data suggests increased risk of bleeding with OAC as compared to AP (RR 0.08 95% CI 0.01, 0.76 $I^2 = 0\%$ $p = .03$) (Figure 5).

Discussion

The dilemma of whether to stop OAC/AP drugs, reduce the dosage, or continue these medications during dental implant surgery continues to exist. No standardized guidelines exist for managing dental surgical patients under OAC or AP therapy [7] and much of the evidence has been derived from expert opinions and narrative reviews [9,19]. Several authors have reported their experience of treating oral surgical patients without interruption of OAC or AP therapy [20–22] and a pooled analysis of such data would not only increase the power of the analysis but also present the most reliable evidence in the literature to direct clinical practice. In this context, our study presents important evidence for implantologists by deciphering the role of these drugs on bleeding risks after the placement of dental implants.

For the first analysis comparing OAC *vs*. healthy controls, our results indicated that continuation of OAC is not associated with an increased risk of bleeding in anticoagulated patients. The only prior meta-analysis evaluating bleeding risk following implant surgery between 121 patients on OAC and 461 healthy controls has also reported similar outcomes (RR 2.14 95% CI 0.83, 5.53) [7]. In comparison, our review with an added sample of two more studies with 131 patients in the OAC group and 161 patients in the control group

Table 1. Details of included studies.

Study	Location	Study type	Study groups	INR for VKA patients	Sample size	Mean age (years)	Male Gender (%)	Number of implants	Bleeding episodes	Intra-operative haemostasis technique	NOS score
Manor et al. [18]	Israel	Retrospective	Warfarin	<3	9	NR	NR	NR	0	Suturing, Gelfoam and pressure pack of tranexamic acid	8
			DOAC		2				0		
			Aspirin		39				0		
			Clopidogrel		1				0		
			Combinations		21				4		
			Control		121				7		
Sannino et al. [17]	Italy	Prospective	Warfarin	<3.5	40	NR	NR	160	11	Bone wax, Gelfoam, suturing, pressure pack of tranexamic acid	8
			Rivaroxaban		40			160	3		
			Control		40			160	1		
Rubino et al. [16]	USA	Retrospective	Warfarin	NR	10	NR	NR	14	1	NR	6
			DOAC		2			2	0		
			Aspirin		122			154	0		
			Clopidogrel		8			8	0		
			Combinations		34			40	1		
Gomez-Moreno et al. [15]	Spain	Prospective	Dabigatran	–	29	66.7 ± 9.15	65.5	NR	2	Suturing, pressure pack of tranexamic acid	8
			Control		42	NR	NR		2		
Gomez-Moreno et al. [12]	Spain	Prospective	Rivaroxaban	–	18	64.4 ± 7.8	66.7	NR	1	Suturing, pressure pack of tranexamic acid	8
			Control		39	NR	NR		2		
Clemm et al. [13]	Germany	Prospective	VKA	2.62 ± 0.52	16	NR	NR	NR	1	Suturing, electrocautery	7
			DOAC		8				0		
			Antiplatelets		40				0		
			Control		271				2		
Bacci et al. [14]	Italy	Prospective	Warfarin	<3	50	56.2 ± 8.9	75	NR	2	Suturing, pressure pack of tranexamic acid	8
			Control		109	NR	NR		3		

NR: not reported; NOS: Newcastle–Ottawa Scale; VKA: vitamin K inhibitors.

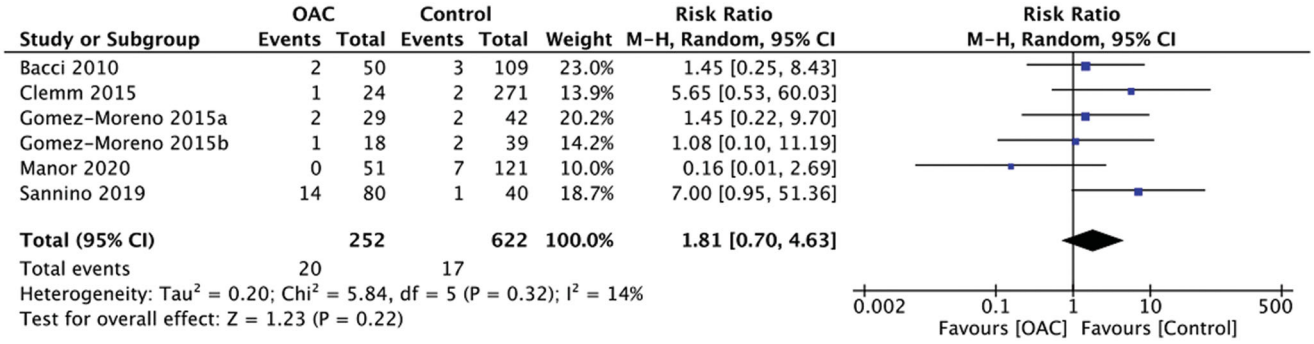

Figure 2. Meta-analysis of bleeding outcomes between patients on OAC *vs.* controls.

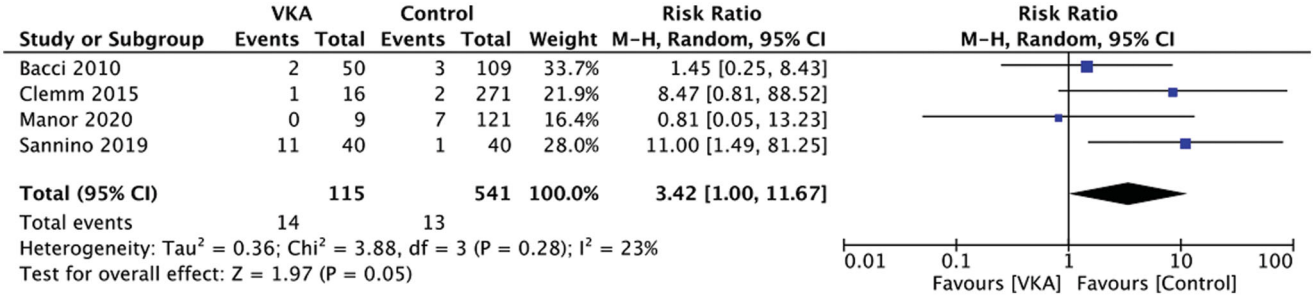

Figure 3. Meta-analysis of bleeding outcomes between patients on VKAs *vs.* controls.

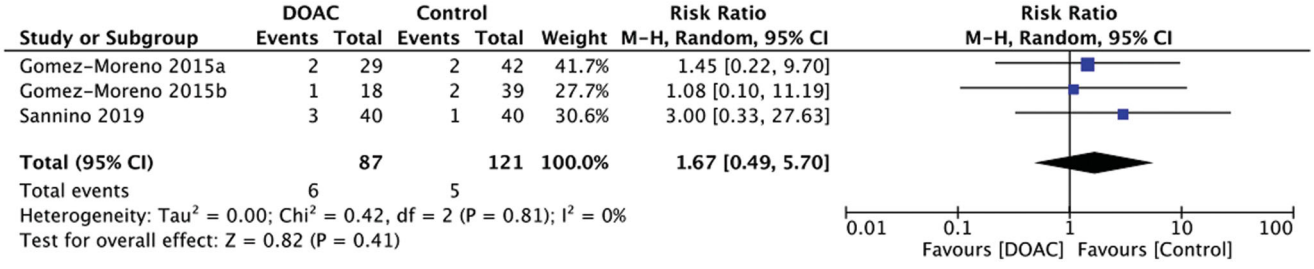

Figure 4. Meta-analysis of bleeding outcomes between patients on DOACs *vs.* controls.

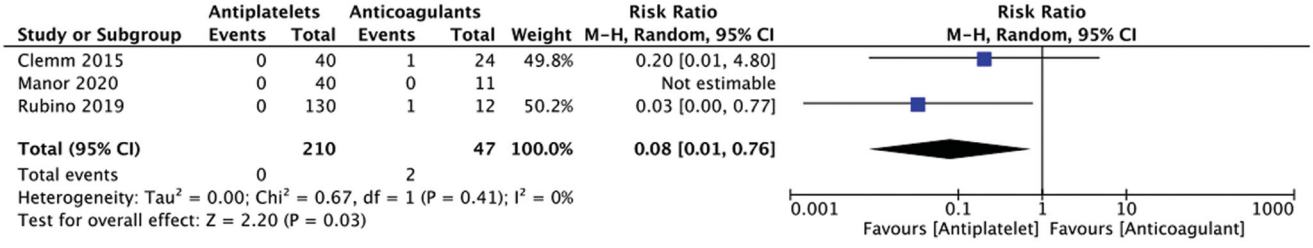

Figure 5. Meta-analysis of bleeding outcomes between patients on AP *vs.* OAC.

presents critical updated evidence. In a recent study, Galletti et al. [23] have reported no episodes of major bleeding after dental implant placement in a sample of 12 patients with a 24-h interruption of OAC therapy. The lack of any bleeding episodes can well be explained by the interrupted anticoagulant effect but the conversely increased risk of thromboembolism is also an important consideration. Studies on patients undergoing major surgeries have demonstrated an increased risk of thromboembolic events related to OAC withdrawal and it is directly related to the duration of drug interruption [24]. Since drug discontinuation for oral surgical procedures is performed only for a short duration and the majority of studies involve a limited number of patients the risk of thromboembolism with drug interruption for dental procedures has not been quantified to date. However, studies have shown that dental treatment may be safely performed in patients under OAC and the duration of drug interruption has no influence on the risk of bleeding [20,21]. Andrade et al. [8] in a review of randomized controlled trials have also shown no difference in bleeding tendencies with continuation or interruption of OAC drugs for dental extractions. The degree of invasiveness of the procedure is an

important factor influencing the risk of bleeding with OAC drugs [5]. Most authors consider the surgical trauma of dental extraction to be equivalent to that of implant placement [9,19]. Indeed, the results of our analysis are in agreement with studies on dental extraction. Shi et al. [7] have shown no increased risk of bleeding in anticoagulated patients undergoing dental extractions as compared to healthy controls (RR 2.00 95% CI 0.99, 4.06). Important to note is that the non-increased risk of bleeding in anticoagulated patients is seen only when adequate local haemostatic measures are used intraoperatively. Studies included in our review as well as those on dental extractions have reported the use of suturing and haemostatic agents like gelfoam and pressure packs of tranexamic acid to control bleeding during the procedure [7–9]. Furthermore, none of the postoperative bleeding episodes in the anticoagulated group required reversal of OAC or hospital admission with all patients managed by local haemostatic techniques.

Amongst OAC drugs, VKAs (warfarin, acenocoumarol and phenprocoumon) have been the most widely used agents for several decades [25]. However, in recent times, DOACs like apixaban, dabigatran and rivaroxaban which are direct thrombin and factor Xa inhibitors have been introduced into clinical practice [26,27]. DOACs have several advantages over VKAs as they have a faster onset of action, more predictable anticoagulant response, wider therapeutic index and restricted drug interactions. Moreover, VKAs require regular therapeutic monitoring by International normalization ratio (INR) measurements while no such monitoring of anticoagulant action is needed for DOACs [26,27]. To present separate evidence on these two classes of OAC, a subgroup analysis was performed. While our results indicated no difference in the risk of bleeding with DOACs as compared to healthy controls, there was a non-significant but increased tendency of bleeding with VKAs after implant surgery. Studies recommend that minor oral surgical procedures may be safely performed with INR < 3.5 and the majority of studies in the review included patients within this INR range [16]. A limitation of our review is that we were unable to directly compare VKAs and DOACs in a meta-analysis owing to the limited availability of data. The tendency of increased bleeding with warfarin and not with DOACs may be attributed to the pharmacokinetic properties of these drugs. DOACs have a short half-life and peak drug concentration is reached at 1–4 h [28]. Since the drug concentration is significantly reduced after 6–12 h of the last dose, procedures performed after such a time-gap are associated with a reduced risk of bleeding [29]. However, studies on dental extraction have reported a similar risk of bleeding between VKAs and DOACs [29,30], and future studies with larger sample sizes are required to directly compare bleeding tendencies with the two classes of drugs after implant surgery.

AP drugs like aspirin, clopidogrel, ticlopidine and prasugrel act on the first stage of haemostasis and inhibit platelet aggregation [31]. Due to the different mechanisms of actions of these AP drugs, combinations like low-dose-aspirin plus clopidogrel are often used for prophylaxis against thromboembolic events [32]. Due to limited data on implant patients, our review was unable to compare bleeding outcomes with continued AP therapy. However, data from dental extraction studies indicate that the risk of bleeding is not increased with uninterrupted single or dual AP therapy provided local haemostatic measures are used [32,33]. Tabrizi et al. [34] in a cross-over study have demonstrated that there is no difference in the risk of bleeding with continued or interrupted AP therapy in patients undergoing dental implant surgery. Limited data in our review suggest that bleeding risk may be higher with OAC as compared to AP. Similar results have been demonstrated by Martinez-Moreno et al. [35] for patients undergoing dental extractions.

The limitations of our review need to be mentioned. Only a small number of studies were available for analysis and with small sample size. Not all studies compared OAC, AP and controls which further reduced the power of our meta-analysis. Second, the quality of local haemostatic measures may have varied across studies and this could have influenced results. Third, we were unable to perform a direct comparison between VKAs and DOACs. Nevertheless, our review presents critical updated evidence on the risk of bleeding with OAC for dental implant surgeries. Unlike previous studies [7,9], a separate meta-analysis was conducted for VKAs *vs*. controls, DOACs *vs.* controls and OAC *vs.* AP. We hope the results of our study would allow implantologists to make informed decisions and promote further research on this subject.

Conclusions

Continuation of OAC therapy in patients undergoing implant surgery does not increase the risk of bleeding provided local haemostatic measures are used. Indirect comparison suggests bleeding tendency may be higher with VKAs as compared to DOAC. Limited data suggest the risk of bleeding may be higher in patients on OAC as compared to AP therapy. Further studies with a larger sample size are needed to strengthen the evidence.

Author contributions

LZ Conceptualized and Designed the study; LZ did Literature search and Data collection; LH Analysed the data; LZ and LH Wrote the article; LZ and LH Reviewed and Edited the manuscript. All authors read and approved the final manuscript.

Disclosure statement

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Data availability statement

The data that support the findings of this study are available from the corresponding author, [LH], upon reasonable request.

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