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ORIGINAL ARTICLE

Should we fear direct oral anticoagulants more than vitamin K antagonists in simple single tooth extraction? A prospective comparative study

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Abstract

Objectives The aim of this prospective comparative clinical study was to evaluate the effect of oral anticoagulants on peri- and post-operative bleeding during simple single tooth extractions, comparing patients in treatment with vitamin K antagonists (VKAs) and patients assuming direct oral anticoagulants (DOACs).

Materials and methods Patients under oral anticoagulant therapy needing dental extraction were eligible for entering the study; patients were enrolled following inclusion and exclusion criteria and divided into VKAs and DOAC group according to the anticoagulation therapy. Included patients underwent a simple single dental extraction with elevators and forceps with a maximum surgical time of 15 minutes, without anticoagulation therapy discontinuation. All participants were assessed pre-operatively, during surgery, 30 min minutes and 7 days after surgery. Biological complications were registered and post-extraction bleeding was clinically defined according to Iwabuchi classification. Parametric and non-parametric tests were used to evaluate the variables between the groups.

Results Sixty-five patients per group were enrolled and 130 teeth were extracted. The two groups were comparable for pre-, peri-, and post-operative variables. Only 1 patient of DOAC group and 2 patients for VKA group needed medical evaluation for post-extractive bleeding. No statistically significant difference resulted in post-operative bleeding events between the groups ($p = 0.425$).

Conclusions DOAC and VKA patients showed the same incidence of bleeding complications after simple single tooth extraction. Bleeding events were not statistically significant and not clinically relevant.

Clinical relevance Patients assuming DOACs can be treated similarly to patients in VKAs therapy with INR index between 2 and 3. Non-ceasing of DOAC therapy seems to be appropriate for simple single dental extractions.

Keywords Direct oral anticoagulants · DOAC · Novel oral anticoagulants · NOAC · Simple single tooth extraction · Bleeding risk

Introduction

Oral anticoagulant therapy (OAT) is extensively used to prevent, treat, or reduce the risk of thromboembolism in atrial fibrillation, treatment of venous thromboembolism, cerebrovascular accidents, ischemic heart disease, myocardial infarction, bypass surgery, and prosthetic heart valve placement [1]. Since 1950, vitamin K antagonists (VKA), such as warfarin and acenocoumarol, have been the oral anticoagulants of choice [2]. Recently, direct oral anticoagulants (DOACs) have been introduced, improving, and simplifying the management of patients in anticoagulation therapy [3]. DOACs are recognized as the "ideal anticoagulants" for their specific target on coagulation cascade, fixed dose, immediate onset of action, predictable pharmacokinetic and dose response, no routine monitoring and limited interactions with food, and other drugs [4].

Rivaroxaban, apixaban, and edoxaban are direct factor Xa inhibitors (as "X" in their names suggests), while dabigatran

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is a direct thrombin inhibitor. Dabigatran and apixaban require daily double administration, while rivaroxaban and edoxaban only one. All DOACs have short half-life (7–14 hs) and rapidly reach peak plasma concentration (2–3 hs). Currently, a reversible agent (idarucizumab) is available for dabigatran [5], while andexanet alfa (antidote for direct factor Xa inhibitors) has been only recently approved by FDA [6]. The lack for a specific and rapid monitoring exam [7], as international normalized ratio (INR) for VKA, requires particular attention from physicians and dentists, especially when dealing with surgical procedures. In fact, while the management of patients on VKA who require dental extractions/oral surgery is well documented in literature [8, 9], there is lack of evidence and consensus about the protocol to apply in patients assuming DOACs. A recent literature review about DOACs and their implications in dentistry [10, 11] suggests that these drugs are relatively safe in terms of general and peri-operative bleeding. It is of paramount importance to individualize the approach, evaluating the difficulty of the procedure, the risk of bleeding, the risk of embolism, and the renal function of each specific patient. The bridging with heparin, often applied in patients on VKAs, is not recommended in any case in patients on DOACs; only the suspension or the delay of a single dose can be considered. Costantinides et al. [12] suggested non-ceasing protocol for low bleeding risk in dentoalveolar surgery; conversely, if the risk of surgical bleeding is considered high (multiple extractions, surgery lasting more than 45 min, head and neck cancer) or if a patient has kidney impairment, the drug has to be suspended 24 h before surgery and restarted at least after 24 hs post-operatively. Two recently published studies [13, 14] considered ceasing and non-ceasing protocols for dentoalveolar surgical procedures, reporting no difference in bleeding events between the two approaches.

The aim of the present prospective clinical study is therefore to evaluate the effect of oral anticoagulants on peri- and post-operative bleeding during simple single tooth extractions, comparing DOAC and VKA patients.

Material and methods

This study was designed in accordance with the principles expressed by the Helsinki Declaration (1964) and its later amendments, to Good Clinical Practice (GCP) guidelines, and it was approved by the Institutional Ethical Committee (CEUR) with univocal code 2016-OS022-ASUITS. The present study was registered in a public register of clinical trials (Clinicaltrials.gov), with reference number NCT03124030. The present study was reported according to the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) guidelines (http://www.strobe-statement.org) [15].

Patients under oral anticoagulant therapy, needing dental extractions and referred to the University Hospital of Trieste (Italy), have been recruited. Patients were enrolled according to inclusion and exclusion criteria, therefore divided into VKA and DOAC group according to their oral anticoagulant therapy. Inclusion and exclusion criteria for both groups are listed in Table 1. An informed consent was obtained from all individual participants included in the study.

During the pre-operative assessment, demographic data and medical history were collected. The pre-operative variables considered in this study are listed in Table 2. Specific scoring systems to assess the bleeding risk (HAS-BLED and CHA_2DS_2VASC) were calculated for each patient in collaboration with an expert cardiologist (ADL). A comprehensive intra-oral examination was performed, including the evaluation of oral hygiene level, and the indications for tooth extraction. Periapical and/or panoramic radiographs were acquired when necessary. If the patient needed more than one extraction, only one tooth was included in the study, following criteria of priority (severity of pathology or symptoms). Only the selected tooth was extracted and evaluated in the first appointment. If more than one tooth showed the same priority, the more mesial was selected. Patients underwent professional oral hygiene 1 week prior to the extraction procedure. Arterial pressure and pre-surgical INR were collected the day of the surgery in both groups, in order to detect eventual prothrombin time alterations depending from other than the pharmacological therapy. Antibiotic prophylaxis was prescribed when indicated (amoxicillin 2 g 1 h before surgery or clarithromycin 500 mg in case of allergy) and patients were asked to rinse for 1 min with chlorhexidine 0.2% mouthwash immediately before the procedure.

Simple extraction was defined as an extraction using forceps and/or elevator, not requiring the elevation of a mucoperiosteal flap and/or ostectomy [13].

The surgical procedure was performed by the same oral surgeon (FB) and standardized as follows:

- Local anesthesia with vasoconstrictor (if not contraindicated)
- Luxation and extraction with elevators and forceps
- Socket debridement with manual curettes
- Sterile sodium chloride 0.9% irrigation of the socket
- Non-absorbable suture [16]
- Compression with a roll of gauze for hemostasis
- Ice pack discontinuous application (5 min on—5 min off) for at least 2 h

Intra-operative variables were recorded as listed in Table 3. If the duration of the procedure exceeded 15 min (starting from periotomy until the complete tooth extraction), or needed the elevation of a mucoperiosteal flap and/or ostectomy, the patient dropped out from the study. After suturing, oral cavity

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Table 1 Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Male and female patients ≥ 20 years	Smoke > 10 cigarettes per day
Healthy patients (≤ ASA 3)	Assumption of any antiplatelet medication and heparin medication or washout period after antiplatelet or heparin medication of at least 1 month
At least 2 months of DOAC therapy with: dabigatran (PRADAXA) or rivaroxaban (XARELTO) or apixaban (ELIQUIS) or edoxaban (LIXIANA)	Assumption of OAT medications (warfarin, acenocoumarol) for patients in DOAC therapy
At least 3 months of OAT therapy with warfarin (COUMADIN) or acenocoumarol (SINTROM) for VKA group	Assumption of any DOACs, dabigatran (PRADAXA) or rivaroxaban (XARELTO) or apixaban (ELIQUIS) or edoxaban (LIXIANA), for patients in OAT therapy
Indication for extraction of a single tooth	Uncontrolled hypertension
No other contraindications for tooth extraction	Chronic hepatitis and/or reduction of hepatic function
Accepted platelet count within 30 days prior to the procedure must be > 50,000/dl.	Coagulopathy (in excess or defect)
INR measured the day of the procedure should be between 2.0 and 3.0	Head and neck radiotherapy (previous 10 years)

was dried with aspirators and cheeks spread out; a cotton roll was gently compressed over the wound for 20 s. Quantitative assessment of the cotton roll imbibition before and after gauze compression was carried out with analytical balance (AND HR-120, A&D Instruments LTD, Oxfordshire, UK). The patient remained under observation for 30 min, thereafter the achievement of the hemostasis was evaluated by the same operator (FB). In case of lack of adequate bleeding control, absorbable oxidized cellulose sponges (Gelita-Spon¸ Gelita Medical GmbH, Eberbach, Germany) or gauze compression soaked with tranexamic acid 500 mg/ml (Acido Tranexamico, Bioindustria L.I.M., Novi Ligure, Italy) were applied. Once the hemostasis was achieved, the patient was discharged with thorough post-surgical recommendations. Patients were prescribed to assume paracetamol 1 g in case of pain and chlorhexidine 0.2% three times a day rinsing was prescribed starting after the first post-operative day. In case of unstoppable bleeding, the patient was taught to refer to the dental emergency department. A simple form was delivered for the annotation of the number of bleeding events and their management (gauze compression or medical assistance), painkiller consumption, and post-operative VAS scale. On the seventh day, patients were assessed for biological complications (bruising, hematoma, swelling, site infection, nerve injury) and sutures were removed from the surgical site. Post-extraction bleeding, when occurring, was recorded and clinically defined according to the classification of Iwabuchi et al. [17] (Table 4). The bleeding record of score 2 or higher was considered clinically significant and classified as post-operative hemorrhagic complication for this study. Onset, course, severity of complications, and the procedures provided by the patient himself or by the clinicians to solve them were also collected.

Predictor and outcome variables

This prospective study tested the null hypothesis of no differences in post-operative bleeding after single tooth extraction between patients assuming vitamin K antagonists and direct

Table 2 Preclinical assessment

Personal data	Gender, age
General evaluation	Medical history
Pharmacological therapy	The concomitant use of antiplatelet agents, or drugs that have known interactions with anticoagulant therapy, ACE inhibitors and pump inhibitors
Smoking habits	y/n, how much
Anticoagulant therapy	Type, duration, prescription
Previous post-surgical bleeding	Referred by the patient
Coagulation disorders	Depending on liver, platelets, vessels, other interfering drugs
Blood sample	PT-INR, platelet count, Cr, hepatic function, Ht, Hb
Tooth extraction indication	Endodontic, periodontal, etc.

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Table 3 Intraoperative variables

Pre-operative fast PT-INR record	For VKA therapy the value must be between 2.0 and 3.0 For DOAC therapy should be physiological
Site of extraction	According to ADA system
Gingival inflammation of the extraction site	None to mild, moderate to severe
Starting time of intervention	From the periotomy
Finishing time of intervention	When the tooth is completely extracted
Granulation tissue in the socket	None to scarce, moderate to abundant
Cotton roll imbibition assay	Before/after weight comparison

oral anticoagulants against the alternative hypothesis of a difference.

The primary predictor variable was the pharmacological therapy (oral anticoagulants). Other variables, possibly correlated with the predictor and outcome variables, were also included as follows: (i) patient-related variables, including age, gender, and smoking status (ii) local variables, including residual granulation tissue and gingival inflammation (Tables 2, 3, and 6).

Primary outcome measure

- Post-operative bleeding after single tooth extraction

Secondary outcome measures

- Any complications or adverse events: ecchymosis, nerve injury, alveolitis
- Cotton roll imbibition assay: measure of immediately post-operative hemostasis

Statistical analysis

A sample size of at least 64 patients per group was requested to detect an effect size of 0.6 (referred as indicative of medium effect) between the groups with an alpha level set at 0.05 and a power of 80% [18].

Parametric methods for continuous variables were chosen after having tested the normality of the data using Shapiro–Wilk test and the equality of variance among the datasets using Levene test. The differences between groups in age and gender distribution were tested using *t* test and Fisher's exact test for independent samples, respectively. The difference between VKA and DOAC groups regarding other drugs assumption and smoking habits, were tested using chi-squared test. HAS-BLED and CHA_2DS_2VASC [19, 20] scores have been compared using Mann–Whitney test.

t test for independent samples was used to analyze the difference between groups in complete blood count values before oral surgery and Kruskal–Wallis test was used to analyze the influence of the granulation tissue and gingival inflammation on the amount of bleeding.

The primary outcome has been assessed with Mann–Whitney test while secondary outcomes (biological complications and cotton roll imbibition assay) have been tested using *t* test for independent samples and Chi-squared test, respectively.

A value of $p < 0.05$ was chosen as the level of statistical significance. Data were processed using SPSS software version 15.0 (SPSS® Inc., Chicago, Illinois, USA).

Results

One hundred fifty patients under oral anticoagulation therapy needing tooth extraction were enrolled in this study between August 2016 and March 2018. Sixty-five patients for the DOAC group and 85 for the VKA group were enrolled but 20 VKA patients dropped out due to altered INR value,

Table 4 Bleeding classification according to Iwabuchi

Code	Clinical evidence
0	No bleeding
1	Bleeding stopped by simple compression (once or twice a week)
2	Bleeding stopped by simple compression (more than twice in the week)
3	Bleeding requiring pharmacological intervention (tranexamic acid)
4	Bleeding that requires medical intervention (surgery with additional sutures and/or diathermocoagulation)

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measured the day of extraction. Finally, 65 DOAC patients and 65 VKA patients were included in the final analysis.

Pre-operative variables

The two groups resulted homogeneous for age (mean 76 ± 9.2 for DOAC and 76 ± 7.7 for VKA $p = 0.126$), gender ($p = 0.660$), and for the pathology for which they assumed OAT ($p = 0.158$).

No differences were found about the distribution of other medications assumed between the groups (ACE inhibitors, pump inhibitors) or about smoking habits. In the DOAC group, 11 patients (17%) took dabigatran, 28 (43.1%) rivaroxaban, 22 (33.8%) apixaban, and 4 (6.1%) edoxaban, while in the VKA group, 61 (93.9%) took warfarin and the remaining 4 (6.1%) acenocoumarol. The most frequent indication both for DOACs and VKA was atrial fibrillation, with 40 (61.5%) and 46 (70.8%) respectively distributed in the groups. In addition, the values of CHA_2DS_2-VASC and HAS-BLED resulted evenly distributed between the two groups ($p = 0.629$). The considered hematic parameters (sampled within 30 days before intervention) were found in the normal range in all patients [number of platelets, hepatic enzymes (ALT U/L, AST U/L and γ-GT), serum creatinine, hematocrit, and hemoglobin]. Detailed descriptive data are listed in Table 5.

Intra-operative variables

Single and multi-rooted extracted teeth were equally distributed in the groups [35 (53.8%) and 30 (46.2%) for DOAC, 33 (50.8%), and 32 (49.2%) for VKA, respectively]. The most frequent indication for tooth extraction was endodontic/conservative [26 (40%) and 29 (44.6%) patients for DOAC and VKA groups, respectively], with no significantly different distribution ($p = 0.470$) along with the other indications (i.e., periodontal issues and combination of the above). Surgical time needed for complete tooth extraction varied from 1 to 15 min with a mean of 6 ± 4.7 min for DOAC group and 5 ± 4.1 min for VKA group. The grade of gingival inflammation and the presence of intra-alveolar granulation tissue in the surgical site were similar between the groups ($p = 0.528$ and $p = 0.087$). Detailed distribution is summarized in Table 6.

Immediately post-operative assessment

Most of the patients achieved complete hemostasis immediately, with an average cotton roll imbibition rate of 0.055 g ± 0.044 for DOAC group and 0.063 g ± 0.040 for VKA. The lack of hemostasis within 30 min after surgery was supplied with the use of hemostatic sponges and tranexamic acid or the combined use of these products nearly for the same number of patients in both groups ($p = 0.448$). In DOAC group, 10 (15.4%) patients were managed with the application of oxidized cellulose sponges, one patient (1.5%) with tranexamic acid and 2 (3.1%) patients with the combination of both hemostatic agents. For VKA group, oxidized cellulose sponges were used in 14 patients (21.6%), in one patient (1.5%), additional sutures were performed and in one patient (1.5%) tranexamic acid was applied on soaked gauze.

Late post-operative assessment

At sutures removal, biological complications were encountered in three out of 130 procedures (all three were recorded in DOAC group—two post-extractive infections and one cutaneous ecchymosis). With regard to the main outcome of this study, no statistically significant difference resulted in post-operative bleeding events between the groups ($p = 0.425$). In particular, 7 patients (10.8%) in the DOAC group experienced a single post-operative bleeding event managed with a gauze compression within 1 week after surgery, 4 patients (6.1%) more than two bleeding episodes needing compression maneuvers, and one patient (1.5%) needed pharmacological procedure (tranexamic acid soaked gauze), provided when presenting at the dental first aid. In the VKA group, 13 patients (20%) reported a single bleeding episode, 6 (9.2%) more than two, one patient (1.5%) needed pharmacological procedure, and one patient (1.5%) required the revision of the surgical wound (Table 7). Table 8 listed local and systemic characteristics of patients who presented clinically significant bleeding events (according to Iwabuchi [17]) in the first post-operative week. Moreover, none of the patients reported symptoms regarding poor pain control or additional analgesic intake except for paracetamol tablet administered post-operatively. Non-parametric statistical analysis was unable to show a correlation between bleeding events and inflammation ($p = 0.41$), while the presence of granulation tissue seemed to influence bleeding ($p = 0.05$). The frequency of bleeding events was surprisingly higher in class 0 and 1 (absence or scarce granulation tissue); however, it has to be considered that the numerosity of 0 and 1 classes was higher compared with class 2 and 3. Consequently, the clinical significance of the outcome "bleeding" has to be still investigated in regard to the presence and the amount of granulation tissue.

Discussion

Patients enrolled in this study showed a low incidence of bleeding events following simple single dental extraction. In detail, 53 subjects of the DOAC group (81.6%) and 45 (69.3%) of the VKA group did not report any post-operative bleeding. Clinically significant bleeding, according to Iwabuchi and coworkers [17], occurred in 7.6% and 12.2% of DOAC and VKA patients, respectively, and only 1.5%

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Table 5 Descriptive detailed data

	DOAC group ($n = 65$)	VKA group ($n = 65$)	P value
Age (years)			0.126
Mean ± sd	76 ± 9.2	76 ± 7.7	
Gender			0.660
Male *n* (%)	34 (52.3%)	31 (47.7%)	
Female *n* (%)	31 (47.7%)	34 (52.3%)	
OAT			
Dabigatran *n* (%)	11 (17%)	0 (0%)	
Rivaroxaban *n* (%)	28 (43.1%)	0 (0%)	
Apixaban *n* (%)	22 (33.8%)	0 (0%)	
Edoxaban *n* (%)	4 (6.1%)	0 (0%)	
Warfarin *n* (%)	0 (0%)	61 (93.9%)	
Acenocoumarol *n* (%)	0 (0%)	4 (6.1%)	
Indication for OAT			0.158
Atrial fibrillation *n* (%)	40 (61.5%)	46 (70.8%)	
VTE *n* (%)	4 (6.1%)	6 (9.2%)	
Stroke *n* (%)	8 (12.3%)	1 (1.5%)	
Pulmonary embolism *n* (%)	3 (4.6%)	2 (3.1%)	
Combination *n* (%)	10 (15.4%)	10 (15.4%)	
Smoking habits (less than 10 cigarettes)			0.205
Yes *n* (%)	6 (9.2%)	11(17%)	
No *n* (%)	59 (90.8%)	54 (83%)	
CHA_2DS_2-VASC (from 0 to 9)			0.629
Score 0 *n* (%)	1 (1.5%)	0 (0%)	
Score ≥ 1 *n* (%)	11 (17%)	11 (17%)	
Score ≥ 2 *n* (%)	53 (81.5%)	54 (83%)	
HAS-BLED (from 0 to 9)			0.081
Score < 3 *n* (%)	62 (95.4%)	54 (83%)	
Score ≥ 3 *n* (%)	3 (4.6%)	11 (17%)	

(DOAC) and 3% (VKA) needed for medical evaluation and intervention. However, these differences did not result statistically significant ($p = 0.425$). The balanced distribution of demographic data, OAT indications, and local variables between the two groups of the study made the results of bleeding outcome assessment more accessible.

This is, to the authors' knowledge, the first prospective study with a strict research protocol aimed to highlight difference in bleeding events among DOAC and VKA patients after dental extractions. Restrictive inclusion criteria have been designed to eliminate as much variables as possible. For this reason, only simple dental extractions (one tooth per patient), defined as closed surgical procedure of tooth removal performed within 15 min, were included in order to limit local confounders and detect the real impact of the medication on the bleeding outcome. Previous studies [21–24] reported that local trauma can bring to an increased patient morbidity, delayed wound healing, and increased post-operative pain, along with bleeding complications and infections. The results of the present study showed no statistically difference in post-operative bleeding events between the groups, with 7.6% and 12.2% of clinically relevant bleeding complications for DOAC and VKA, respectively. In both groups, the routine drug assumption was not modified: this result is in accordance with previous studies conducted with non-ceasing protocols [13, 14]. Conversely, Miclotte et al. [25] instructed their patient to skip the dose of DOACs on the morning of the surgery; Patel et al. [26] prepared a specific scheme for their patients to continue or to change the DOACs administration according to the patient past medical history, the indication for anticoagulation, the renal function, and the bleeding risk of the procedure. Regardless of the DOAC protocol adopted, a recent meta-analysis reported a threefold increased risk of bleeding events in patients taking direct oral anticoagulants when compared with otherwise healthy people [10].

Since the introduction of DOACs, improving scientific evidence showed that these medications have an impact on surgical procedure similar to VKA. However, well-designed

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Table 6 Local variables

	DOAC group ($n = 65$)	VKA group ($n = 65$)
Tooth		
Single-rooted *n* (%)	35 (53.8%)	32 (49.2%)
Multi-rooted *n* (%)	30 (46.2%)	33 (50.8%)
Extraction indication		
Periodontal disease *n* (%)	13 (20%)	16 (24.6%)
Caries/Endodontic *n* (%)	26 (40%)	29 (44.6%)
Pure endodontic *n* (%)	0 (0%)	0 (0%)
Combination *n* (%)	26 (40%)	20 (30.8%)
Gingival inflammation		
Absent *n* (%)	18 (27.7%)	14 (21.6%)
Mild *n* (%)	26 (40%)	32 (49.2%)
Moderate *n* (%)	16 (24.6%)	17 (26.1%)
Severe *n* (%)	5 (7.7%)	2 (3.1%)
Intra-alveolar granulation tissue		
Absent *n* (%)	22 (33.8%)	13 (20%)
Mild *n* (%)	17 (26.1%)	27 (41.6%)
Moderate *n* (%)	11 (17%)	16 (24.6%)
Severe *n* (%)	15 (23.1%)	9 (13.8%)
Surgical time		
< 10 min *n* (%)	49 (75.4%)	55 (84.6%)
≥ 10 min *n* (%)	16 (24.6%)	10 (15.4%)

studies are still necessary to help scientific community to formulate final conclusions. While the guidelines of the American College of Chest Physician and of the British Society of Haematology do not recommend the suspension of anticoagulation therapy for patients in VKA who will undergo simple dental surgical procedures (INR < 3), such recommendations cannot be automatically extended to daily practice for DOACs ~~yet~~. Indeed, scientific literature evidence is solid in highlighting the risk of thromboembolism (TE) after suspension of VKA [27–29]; conversely, only a few reports deal with TE risk after ceasing DOACs. Vene and coworkers [30] recently reported a 20-fold increased risk of short-term thromboembolic events after discontinuing dabigatran and rivaroxaban. Moreover, the authors found a distinct clustering of TE in the first weeks after DOACs discontinuation with a median occurring on day 14 (range 1–37 days) after ceasing. This evidence confirms how critical might be a shortened suspension interval even for the newly anticoagulant therapy and therefore the correct indications for ceasing as well. On the other hand, it has to be taken into account that a thromboembolic event after suspension of the anticoagulation effect for 12–24 h is extremely uncommon; however, management of patients with polypharmacy issues and possible legal issues should also be carefully considered before deciding drug suspension. Costantinides and coworkers [12], after collecting many guidelines in a discussion paper, suggested the non-cease protocol for DOAC patients undergoing simple dentoalveolar surgery, taking into account renal function. Lababidi and coworkers [14] recently reported no significant difference in bleeding events between DOAC and VKA patients undergoing dentoalveolar surgery, despite the underlined confounders. Similarly, Mauprivez et al. [13] did not report any difference in post-operative bleeding with an odds ratio between the groups of 0.77 (95% confidence interval 0.19–3.19; $p = 0.723$). Unfortunately, even in this case, protocol biases such as patient effect, sample numerosity, and surgical standardization were not sufficiently controlled. Many protocols have been suggested for drug suspension, according to renal function, for elective surgical procedure that must be taken into consideration for more extended oral surgery procedure, such as bone block harvesting, regenerative procedures, and extraction of impacted teeth.

Even in case of drug suspension, DOACs plasmatic half-lives bring interesting advantages to the patient and the surgeon. Differently from VKA, DOACs provide a short effect

Table 7 Intra-operative details of hemostatic agents and bleeding events

	DOAC group ($n = 65$)	VKA group ($n = 65$)
Intra-operative hemostatic agents		
None *n* (%)	52 (80%)	49 (75.4%)
Oxidized cellulose *n* (%)	10 (15.4%)	14 (21.6%)
Additional sutures *n* (%)	0 (0%)	1 (1.5%)
Tranexamic acid *n* (%)	1 (1.5%)	1 (1.5%)
Combination *n* (%)	2 (3.1%)	0 (0%)
Post-operative bleeding events		
No bleeding *n* (%)	53 (81.6%)	45 (69.3%)
Single compression *n* (%)	7 (10.8%)	12 (18.5%)
More than two compressions *n* (%)	4 (6.1%)	6 (9.2%)
Need for pharmacological intervention *n* (%)	1 (1.5%)	1 (1.5%)
Need for surgical reoperation *n* (%)	0 (0%)	1 (1.5%)

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Table 8 Patients who suffered clinical relevant post-operative bleeding

ID	Gender	Age	Drug	Time of assumption	Time of intervention	HAS-BLED	Platelet count × 10 ^ 3/μl	Ct. mg/dl	INR	Mean PA	Extracted tooth	Gingival inflammation	Intra-alveolar granulation tissue	Duration of the procedure (min)	Local hemostat	Bleeding events
1	F	86	Rivaroxaban	8:00	11:30	2	171	1.0	1.4	96.67	27	Moderate	Abundant	6	None	Medication
5	M	85	Rivaroxaban	8:00	12:15	2	209	0.9	1.1	86.67	45	Mild	Scarce	7	None	More than two compressions
29	F	72	Dabigatran	8:00 20:00	8:45	2	205	0.9	1.0	96.67	26	Moderate	Abundant	1	Combination	More than two compressions
30	M	72	Rivaroxaban	14:00	8:30	2	180	1.4	1.2	96.67	27	Moderate	Moderate	1	None	More than two compressions
55	F	85	Apixaban	8:00 20:00	11:00	1	223	0.7	1.1	100.00	11	Mild	Absent	14	Oxidized cellulose	More than two compressions
69	F	82	Warfarin	17:00	11:30	3	192	1.2	2.1	70.00	34	Absent	Absent	1	None	More than two compressions
76	F	66	Warfarin	17:30	13:30	2	244	0.9	2.0	95.33	36	Moderate	Scarce	2	None	More than two compressions
78	F	76	Warfarin	17:00	10:00	1	182	1.5	2.7	83.33	48	Moderate	Scarce	8	None	Medication
79	F	81	Warfarin	17.00	11.30	1	204	0.7	2.7	91.67	26	Mild	Scarce	7	None	More than two compressions
89	F	74	Warfarin	19:00	12:00	1	197	1.2	1.5	93.33	26	Moderate	Abundant	9	Oxidized cellulose	Surgical int.
100	M	80	Warfarin	18:00	9:00	1	106	1.3	1.6	93.33	35	Mild	Abundant	1	None	More than two compressions
102	M	66	Acenocoumarol	18:00	11:00	2	202	0.9	2.1	116.67	17	Mild	Moderate	8	Tranexamic acid	More than two compressions
105	F	93	Warfarin	15:00	12:00	2	186	0.9	2.5	93.33	47	Absent	Scarce	4	None	More than two compressions

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with a rapid return to physiological hemostasis, according to each drug half-life (dabigatran, 12–17 h; rivaroxaban, 5–13 h; apixaban, 12–18 h). This could lead to a shorter thus safer ceasing period. Furthermore, bridging DOAC therapy with low-molecular-weight heparin is not indicated (differently from VKA) because the half-life of both molecules is very similar.

In the present study, patients were asked not to alter the drug assumption scheme, both for VKA (as literature suggests) and DOACs. Twenty VKA patients dropped out for out-of-range INR, and 13 of them showed uncontrollable fluctuation of INR value also after appointment re-scheduling. The remaining patients showed an INR > 5 and were referred to the first aid for vitamin K administration. These dropouts indicate how VKA patients may be delicate to be managed in outpatient setting and how direct INR measurement is fundamental before surgical intervention.

Safe management of intra-operative bleeding was carried out with local hemostatic agents (e.g., local compression, topic ice, etc.) and the "cotton roll imbibition assay," a quantitative method to measure intra-operative bleeding, showed no statistical difference between groups ($p = 0.321$). The lack of hemostasis in 30 min after surgery was supplied with the use of hemostatic agents and tranexamic acid or the combined use of these products nearly for the same number of patients of both groups. While the majority of the whole sample (> 75%) achieved the hemostasis at the end of the procedure, 20% of DOAC group and 24.6% of VKA patients needed the application of hemostatic agents. In the present study, the totality of OAT patients reached immediate post-operative hemostasis with the correct use of the commonly used hemostatic techniques. Furthermore, the slight weight increase of the cotton roll after compression suggests a clinically irrelevant quantity of bleeding.

Moreover, likely due to the limited incidence of the complications occurred, no association could be found between bleeding events and local and systemic factors. Considering the five cases of clinically significant bleeding occurred in DOAC group, three out of five patients assumed rivaroxaban, which could be possibly associated with increased risk of bleeding, as previously reported [10]. Further associations among the variables cannot be drown, probably for the reduced number of adverse events among the patients.

The previous increasing scientific evidence along with the results of the present study suggests not to cease DOAC therapy for low-risk oral surgery procedures. This important clinical implication will help clinicians to easily handle patients assuming direct oral anticoagulants, without exposing them to potentially harmful thromboembolic risk.

Moreover, even in more serious scenarios, mostly expected into hospital settings, clinicians may adopt direct antagonists: idarucizumab represents the currently approved inhibitor of dabigatran and recently (May 2018) andexanet alpha has been approved by FDA as reverse agent of apixaban and rivaroxaban. DOACs ideal characteristics of pharmacodynamics and pharmacokinetics, including specific target on coagulation cascade, fixed dose, rapid onset, predictable effect, and limited interactions with food and drugs [31], make these drugs easy to handle even for non-specialist healthcare providers. Conversely, for VKAs patients, INR measurement is always required, and surgical procedures must be canceled for altered INR values as the multiple interactions of these drugs can lead to adverse bleeding events.

The debate is still open regarding the cost-benefit analysis between discontinuing DOAC therapy with increasing risk of thromboembolic events and continuing these medications with an increasing risk of bleeding after more complex interventions. Further studies are needed to better understand the clinical effects of DOACs in advanced oral surgery procedures.

The strict protocol of this study, designed to control potential confounders, represents at the same time a limitation, as only a selected group of patients was included. For this reason, inadequate renal function, comorbidities, multiple tooth extractions, and bad oral hygiene could negatively influence the outcomes and modify the limited impact on bleeding complications we encountered in our sample. Moreover, the inclusion of different medications in DOAC group together with different time of drug assumption may represent another confounder. Therefore, a greater number of patients with different systemic and local characteristics should be evaluated in prospective studies, to help scientific community to better understand the behavior of these drugs for in- and out-patient oral surgical procedures.

Conclusions

The results of the present study suggested the non-discontinuation of DOACs for simple single dental extractions, similarly to VKA medications. The small amount of bleeding complications encountered in our sample could encourage to adopt this approach in everyday practice. Conversely, further studies should be focused on the bleeding risk in more advanced surgical procedures with standardized ceasing protocols, according to the augmented bleeding risk.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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