Pomeranian J Life Sci 2021;67(4):17-24 doi: 10.21164/pomjlifesci.785

Patient taking direct oral anticoagulants (DOACs) has to undergo oral surgery – considerations for practitioners

Marcin Pasternak[1, A] ✉, Justyna Kaczkowska[2, B]

[1] Jagiellonian University Medical College, Department of Pharmacology, Division of Clinical Pharmacology, Grzegórzecka 16, 31-531 Cracow, Poland
[2] Jagiellonian University Medical College, Department of Oral Surgery, Montelupich 4, 31-155 Cracow, Poland

[A] ORCID: 0000-0003-1082-0590; [B] ORCID: 0000-0002-5648-0387

✉ marcin.pasternak@uj.edu.pl

ABSTRACT
Haemostasis is an excellently orchestrated process; however, thrombosis or excessive bleeding can result in a breakdown of this subtly regulated mechanism. Anticoagulants prevent the formation of thrombi by blocking the coagulation cascade. Surgical interventions in anticoagulated patients carry a risk of periprocedural bleeding. Over the last decade, new agents – direct oral anticoagulants (DOACs) – were introduced into clinical practice to overcome the drawbacks of classic agents used for the prevention of thrombotic events. The most remarkable difference in comparison with traditional anticoagulants is the elimination of the need for monitoring. The article covers periprocedural management in DOAC-treated patients undergoing oral surgery procedures. Direct oral anticoagulants are characterized, paying attention to pharmacokinetic properties important for oral surgeons. Bleeding risk related to oral and dental implant surgery procedures are presented, followed by considerations crucial for the evaluation of patient-related bleeding factors. Aspects of surgical planning are discussed. Adequate measures and aids helpful in oral surgery interventions together with post-operative care are also summarized.
Keywords: factor X inhibitors; direct thrombin inhibitor; oral surgery; bleeding.

INTRODUCTION

Haemostasis refers to the subtly regulated dynamic process of maintaining fluidity of the blood, vessel injury repair and blood loss limitation together with the prevention of vascular occlusion and inadequate perfusion of vital organs [1].

This constantly evolving process occurs as a result of the interaction of the compounds of Virchow's triad, i.e.: endothelial cells, blood composition and vascular flow [2]. Excessive bleeding or thrombosis represents a breakdown of haemostatic mechanisms [1]. While antiplatelet agents inhibit platelet aggregation, anticoagulants prevent thrombosis through blocking the coagulation cascade after platelet aggregation [2, 3].

The routine use of oral anticoagulants is related to the haemostatic imbalance between clotting and blood anticoagulation, and significant variations in this relationship may increase the risk of haemorrhage or thromboembolism [4]. Various diseases and medical conditions require oral anticoagulant therapy. Indications include stroke prevention in relation to non-valvular atrial fibrillation, thromboprophylaxis following mechanical heart valve replacement, stent placement or orthopaedic surgery, prevention and treatment of deep vein thrombosis as well as pulmonary embolism and the prevention of arterial thrombosis in patients who have experienced an acute coronary syndrome [5, 6]. Therefore, encountering patients receiving these agents in routine dental practice is highly likely.

Although most oral surgery procedures are considered to carry a low risk of bleeding, patients on anticoagulant therapy are at an increased risk of bleeding complications during and after dental surgery [7]. Vitamin K antagonists (VKAs) are considered the treatment of choice for preventing thrombotic events but cause several issues, including the frequent need to adjust the dosage and monitor patients' coagulation status, as well as multiple drug–drug and dietary interactions [8]. Although warfarin – a model drug of VKAs and the most frequently used agent of this group – has been a popular oral anticoagulant drug for over 60 years, it has limitations such as dietary and drug interactions, narrow therapeutic range, and the need for monitoring. One of the major drawbacks of its alternative – heparin – is the need for parenteral administration [9]. The armamentarium of anticoagulant therapy has evolved considerably over the last decade with the introduction of several new agents [5].

CHARACTERISTICS OF DIRECT ORAL ANTICOAGULANTS

New anticoagulants that have been introduced in recent years exhibit improved safety and superior therapeutic value in comparison with their predecessors – VKAs [9]. These agents are used with increased frequency in clinical practice, gradually replacing the existing antithrombotic agents, administered parenterally (heparin) or orally (VKAs) [10]. In many initial studies, they were described as either 'new' or 'novel' oral anticoagulants (NOACs); however, the use of these terms has some limitations. The term 'No AC' is used in medicine to denote that the patient is not taking an anticoagulant, which could lead to confusion. In addition,

naming the drugs new or novel is time-limited. Therefore, the terms 'direct oral anticoagulant' (DOAC) and 'target-specific oral anticoagulant' (TSOAC) have begun to appear in the literature, and both seem to be more appropriate. The former name has been adopted by the International Society on Thrombosis and Haemostasis Scientific and Standardisation Committee [9]. Sometimes DOACs are referred to as 'non-VKA oral anticoagulants' [3].

Direct oral anticoagulant consist of 2 sub-groups: factor Xa inhibitors (FXaI) – often denominated as the 'xabans'– and direct thrombin inhibitors (DTIs), both of which target one specific factor in the coagulation cascade [11]. Inhibitors of factor Xa block thrombin generation, whereas dabigatran – a DTI – blocks the activity of thrombin (factor IIa) – the enzyme that catalyses the conversion of fibrinogen to fibrin [12]. The mechanism of action of DOACs on coagulation process is shown in Figure 1.

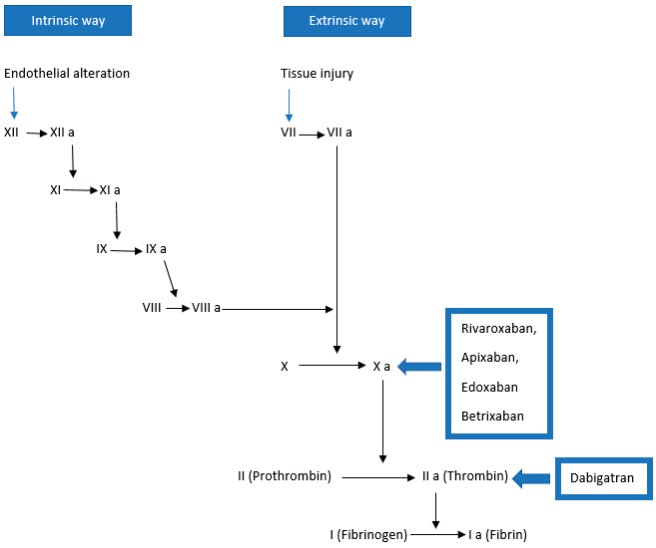

FIGURE 1. A model of blood coagulation with mechanism of action of direct oral anticoagulants

These agents are increasingly being prescribed and their use has significant implications for the management of patients requiring anticoagulant therapy. The most remarkable difference in comparison with traditional anticoagulants is the elimination of the need for monitoring, even if a patient will undergo surgery. Secondly, these agents are administered orally at a fixed daily dose, making patient compliance more straightforward [9].

The group of FXaIs consists of rivaroxaban, apixaban and endoxaban. These drugs inhibit factor Xa in the final common pathway of clotting, having a major impact on antithrombotic pharmacotherapy [1]. Betrixaban, currently approved only in the United States, is the newest drug of this family and as such exhibits similar mechanisms of action [13]. Factor Xa inhibitors are administered as fixed doses, do not require monitoring, and are characterized by a rapid onset of action and a shorter half-life in comparison to warfarin [1]. Fondaparinux, a synthetic pentasaccharide derivate chemically related to low-molecular-weight heparins is another agent that inhibits the same factor, but because it is administered parenterally, it will not be discussed further in this paper [3].

Rivaroxaban is a derivate of oxazolidone, and it inhibits free factor Xa by binding reversibly with a prothrombinase complex. Taken with food, it has high oral bioavailability and it is extensively protein-bound [14, 15]. The drug is a substrate for the cytochrome P450 system and the P-glycoprotein transporter. Co-administration of agents inhibiting both CYP450 and P-glycoprotein (e.g., antimycotic ketoconazole, macrolide antibiotics clarithromycin and erythromycin) result in increased rivaroxaban effect [16].

Apixaban, administered twice daily, is approved for the prevention of stroke in nonvalvular atrial fibrillation. Similarly to other agents of this group, it is excreted in part by the kidneys and liver and therefore its use is not recommended for patients with significant renal or hepatic impairment [1]. Food does not have a clinically meaningful impact on bioavailability, and apixaban has limited clinically relevant interactions with most commonly-prescribed medications [17]. The drug is a substrate of the cytochrome P450 system and P-glycoprotein, similar to rivaroxaban; therefore, drugs inhibiting both CYP450 and P-glycoprotein coupled with an impairment of renal or hepatic function result in an increased drug effect [15].

Edoxaban is approved in Europe for stroke prevention in patients with atrial fibrillation, and also for the treatment and prevention of venous thromboembolism (VTE). Edoxaban is a highly selective, once-daily, direct, reversible inhibitor of factor Xa. A reduced dose is required in patients with moderate or severe renal impairment (creatinine clearance 15–50 mL/min), low body weight (≤60 kg), or concomitant use of strong P-glycoprotein inhibitors including cyclosporine, dronedarone, macrolide antibiotics (erythromycin, clarithromycin), azithromycin or ketoconazole [18]. It is rapidly absorbed, has relatively high bioavailability, and exhibits highly selective, competitive, concentration-dependent inhibition of factor Xa [19, 20]. Edoxaban rapidly induces anticoagulation activity and has a wider therapeutic window than the VKA – warfarin [18].

Betrixaban is approved only in the United States and indicated for thromboprophylaxis of VTE in hospitalized medical patients. The drug is a new DOAC with a different pharmacokinetic profile than other agents previously described. It has the longest half-life in the DOAC class, exhibits the lowest renal clearance, and is mainly excreted unchanged in the bile [21]. Unlike other xabans and dabigatran, the United States label of betrixaban supports the use of the drug at a reduced dose in patients with severe renal impairment. Betrixaban is administered once daily and the suggested treatment duration is 35–42 days [22].

Andexanet alfa is a modified and recombined factor Xa and serves as the antidote for its inhibitors in emergency cases of life-threatening bleeding [3]. A promising anticoagulant reversal agent that could serve as an antidote both for xaban drugs and dabigatran is ciraparantag [23].

Dabigatran etexilate is a prodrug for dabigatran administered twice daily. Dabigatran and its metabolites are DTIs. After ingestion, dabigatran etexilate is rapidly absorbed via the gastrointestinal tract, and then quickly converted to dabigatran. The drug is a substance for the P-glycoprotein efflux pump; however, P-glycoprotein inhibitors or inducers do not have a clinically significant effect on its clearance. The anticoagulant effect of dabigatran can

be reduced by rifampicin, dexamethasone and carbamazepine. Concomitant use of ketoconazole, amiodarone, quinidine and clopidogrel increases the effect of dabigatran. Other anticoagulants, antiplatelet agents, non-steroid anti-inflammatory drugs (NSAIDs), salicylates and certain herbs (e.g., alfalfa and anise) do not induce an interaction, but they can increase the risk of bleeding, and therefore, should be avoided. Drugs that can be used to control pain in patients taking dabigatran are opioids or acetaminophen [24]. Dabigatran is eliminated predominantly by the kidneys, therefore dosage reduction is recommended in patients with renal impairment [25].

The anticoagulation effect of dabigatran can be reversed by the use of a monoclonal antibody fragment: idarucizumab as well as ciraparantag [3, 23]. Although dabigatran will prolong the partial thromboplastin time, activated partial thromboplastin time and thrombin time, some differences in routine coagulation tests vary in degree of severity to the aforementioned agents as well as other DOACs and should be used only as indicators of additional screening in emergency clinical interventions.

The recommended ways of assessing the activity of DTIs are dilute thrombin clotting time and ecarin clotting time. The effect of rivaroxaban and apixaban can be determined by anti-Xa activity assay calibrated with a rivaroxaban and apixaban standard [10].

The main pharmacokinetic features of DOACs important in oral surgery management are listed in Table 1.

PERIPROCEDURAL BLEEDING RISK EVALUATION IN ORAL SURGERY

A bleeding complication is excessive or prolonged bleeding or bleeding that is not controlled by initial haemostasis [2]. This adverse event is one of the main concerns in everyday dental practice [20]. Although patients on anticoagulant therapy for the prevention of cardiovascular accidents present an increased risk of bleeding following surgery, significant bleeding after oral surgical procedures in these patients is relatively rare and oral surgery itself is considered as carrying low risk for bleeding due to the possibility of direct haemostasis [2, 15].

The extent of the surgical wound is related to the risk of post-procedural bleeding [15].

The American Association of Oral and Maxillofacial Surgeons stratified the most frequently performed surgical procedures into 4 levels according to the risk of bleeding. First – in which bleeding risk is not clinically important; 2nd – with low procedural bleeding risk; 3rd – in which bleeding risk is moderate; and 4th – carrying a high procedural bleeding risk [26].

In the 1st category, i.e., procedures where the bleeding risk is not clinically relevant, local infiltrative anaesthesia was included, followed by intraligamentary and mental block [2, 26]. Interventions associated with a low risk of periprocedural bleeding include local anaesthesia by inferior alveolar nerve block, due to the proximity of the inferior alveolar artery at the injection site. Simple dental extractions or extraction of up to 3 erupted teeth with restricted wound size and incision are considered as having a low perioperative bleeding risk [6]. It has been stressed recently that the extraction of multi-rooted teeth carries a greater bleeding risk in comparison with single-rooted teeth extraction. Therefore, it may be appropriate to consider extraction of 1 multi-rooted tooth as presenting low risk for periprocedural bleeding like extraction of up to 3 single-rooted teeth during a single appointment [15]. Incision and drainage of intra-oral swellings and extraction of loose teeth are also considered as low bleeding risk procedures, together with oral surgery laser procedures [27].

TABLE 1. Main pharmacokinetic features of direct oral anticoagulants

Drug	Rivaroxaban	Apixaban	Edoxaban	Betrixaban*	Dabigatran
Mechanism of action	factor X activated inhibitor	factor X activated inhibitor	factor X activated inhibitor	factor X activated inhibitor	direct thrombin inhibitor
Bioavailability after oral administration	66% without food, >80% with food	50%	62%	34%	3–7%
Dosage	once daily	twice daily	once daily	once daily	twice daily
The drug half-life	5–9 h (elderly 11–13 h)	12 h	10–14 h	19–27 h	12–17 h
T max	2–4 h	3–4 h	1–2 h	3–4 h	2–3 h
Hepatic metabolism (CYP3A4 –involved)	yes	yes	minimal (<4% elimination)	no	no
Plasma protein binding	90%	90%	50%	60%	35%
Renal clearance	33%	25%	50%	11%	80%
Excretion	hepatic 75%, renal 25%	hepatic 66%, renal 33%	hepatic 50%, renal 50%	hepatic (mainly bile), renal <5%	renal 80%, bile 20%
Antidote	Andexanet alpha, Ciraparantag	Andexanet alpha, Ciraparantag	Andexanet alpha, Ciraparantag	Andexanet alpha, Ciraparantag	Idarucizumab, Ciraparantag

CYP3A4 – Cytochrome P450 3A4
* Betrixaban is only approved in the United States for VTE thromboprophylaxis in acute medical patients.

Moderate bleeding risk occurs in cases of surgical and more complex dental extractions, or in the case of extraction of more than 2 multi-rooted or over 3 single-rooted teeth. Surgical extractions of impacted teeth with flap raising and bone removal, as well as alveolar ridge bone grafting, biopsy or excisions of oral soft tissue lesions, endodontic surgery, hemisection, removal of hyperplastic mucosal tissue with a scalpel, gingivoplasty in preprosthetic treatment, and odontogenic cyst removal are procedures considered as presenting a moderate risk of bleeding [26, 27].

Periodontal plastic surgery procedures, including gum augmentation with autogenous soft tissue transplants from the palatal mucosa, excision of bone or large soft tissue pathology and maxillo-facial surgery interventions including orthognathic procedures, facial trauma repair using open techniques, corrective jaw or facial surgery radical reconstructive procedures, treatment of bone fractures with plate and screw osteosynthesis entail a high risk of bleeding [6, 26, 27]. Oral surgery procedures with related bleeding risk are summarized in Table 2.

TABLE 2. Oral surgery procedures with related bleeding risk

Bleeding risk level	Procedure
Not clinically relevant	local anaesthesia by infiltration, intraligamentary block, mental block
Low	inferior alveolar nerve block, simple dental extractions: of up to 3 erupted single-rooted teeth, extraction of 1 multi-rooted tooth or extraction of loose teeth, oral surgery laser procedures (e.g., removal of epulis fissuratum, evaporation of the lesion with a laser – when there are no indications for histopathological examination), incision and drainage of intraoral swellings
Moderate	dental (surgical) extractions, complex extractions of more than 3 single-rooted teeth, extraction of 2 and more multi-rooted teeth, complex surgical extractions, extractions of impacted teeth, interventions including flap raising and bone removal, alveolar ridge bone grafting biopsy or excision oral soft tissue lesion apicoectomy, hemisection, preprosthetic surgery, removal of an odontogenic cyst, removal of a small tumour
High	periodontal plastic surgery procedures, maxilla-facial surgery interventions: facial trauma repair by open techniques, corrective jaw or facial surgery, bone excision or large soft tissue pathology, orthognathic procedures, radical reconstructive procedures, treatment of bone fractures with plate and screw osteosynthesis

In dental implant surgery, positioning 1–3 implants in the anterior region as well as up to 2 implants in the posterior region are considered to have a low bleeding risk, especially when the procedure is performed using the flapless method [15, 28]. Segmental implantations and sinus lifts conducted with the closed method are associated with moderate bleeding risk. Simultaneous implantation between 6–10 implants in a toothless jaw with the formation of a large flap and a bilateral sinus lift using the lateral window method entail a high risk of bleeding [29]. Dental implant surgery procedures with related bleeding risk are summarized in Table 3.

TABLE 3. Dental implant surgery procedures with related bleeding risk

Bleeding risk level	Procedure
Low	single implantation, positioning up to 3 implants in the anterior region, positioning up to 2 implants in the posterior region, implantation using the flapless method
Moderate	segmental implantations, closed sinus lift technique
High	simultaneous implantation between 6–10 implants in a toothless jaw with the formation of a large flap, bilateral sinus lift with the lateral window approach

Individual characteristics of each patient are an important consideration for periprocedural risk evaluation [2]. A useful tool in the evaluation of patient-related bleeding factors is the HAS-BLED score. Although it is used for major bleeding risk assessment in patients with atrial fibrillation on VKA therapy, the HAS-BLED score offers a predictive and clinically relevant performance of bleeding risk in DOAC-treated patients with this condition [30]. HAS-BLED is an acronym for conditions assessed during evaluation: H – for hypertension – defined as systolic blood pressure >160 mmHg; A – for abnormal renal function as a presence of chronic dialysis, renal transplantation, or serum concentrations of creatinine ≥200 μmol/L, abnormal liver functions like chronic hepatic disease (e.g., cirrhosis) or biochemical signs of essential hepatic malfunctions, such as – bilirubin >2x upper limit of normal (ULN), aspartate aminotransferase or alanine aminotransferase >3x ULN; S – for stroke: history of stroke; B – stands for other predispositions to major bleeding; L – for labile International Normalized Ratio (INR assessed in VKA-treated patients), time in therapeutic range <60%; E – for elderly (>65 years); D – for drugs: concomitant use of antiplatelet agents or nonsteroidal anti-inflammatory drugs, alcohol or drug abuse history (≥8 drinks/week). Each condition is counted as 1 point. A score equal or higher than 3 indicates an increased risk of bleeding [31].

Other conditions that increase the risk of bleeding in DOAC-treated patients, and therefore should be taken into consideration, are qualitative or quantitative abnormalities of platelet function [26]. Apart from NSAIDs and antiplatelet agents, selective serotonin reuptake inhibitors (SSRIs), cytotoxic drugs and agents associated with bone marrow suppression present an aforementioned adverse effect [6]. History of bleeding events and occurrence of bleeding events with similar procedure are of importance in patient-related bleeding risk evaluation [26]. HAS-BLED score and considerations important in the evaluation of patient-related bleeding risk factors are summarized in Table 4.

TABLE 4. HAS-BLED score and considerations important in the evaluation of patient-related bleeding risk factors

HAS-BLED parameters[1]	hypertension	0–1
	abnormal renal function, abnormal liver function	0–2 (each counts for 1)
	history of stroke	0–1
	history of major bleeding events or predispositions to major bleeding (e.g., anaemia, diathesis)	0–1
	labile INR[2]	0–1
	elderly	0–1
	concomitant use of antiplatelet agent or nonsteroidal anti-inflammatory drug, history of alcohol or drug abuse	0–1
Additional conditions important for bleeding risk evaluation	qualitative or quantitative platelet abnormalities, SSRIs, cytotoxic drugs and agents associated with bone marrow suppression, bleeding event within 3 months prior to the procedure, bleeding history due to similar procedures	

INR – International Normalized Ratio; SSRIs – selective serotonin reuptake inhibitors
[1] Presence of each condition is counted as 1. A score equal to 3 or higher indicates an increased bleeding risk.
[2] INR is evaluated in patients on VKA therapy, DOACs have no impact on INR, therefore it is not evaluated in these patients.

PERIPROCEDURAL MANAGEMENT OF PATIENTS ON DIRECT ORAL ANTICOAGULANT THERAPY IN ORAL SURGERY

The periprocedural management of a patient on DOAC therapy scheduled for oral surgery is based on the drug half-life and patient's renal function [8]. As it is presented in Table 5, alterations in kidney function do not change significantly mean half-lives of the 4 DOACs currently available in the EU. Renal impairment does not appear to affect the pharmacodynamics of xabans and dabigatran but has a different effect on the pharmacokinetics of these drugs. However, it should be noted that renal failure itself is a condition associated with an increased risk of bleeding and thromboembolic events [32]

The evaluation of renal function in DOAC-treated patients before undertaking oral surgery procedures is of paramount importance [33]. Sufficient kidney function demonstrates an acceptable anticoagulation state while it allows for achieving coagulation recovery by the temporary discontinuation of the drug administration in the case of haemorrhagic event [15]. Although DOACs are contraindicated in patients with significant renal impairment, they are considered as a reasonable choice for anticoagulant therapy in atrial fibrillation with coexistent mild or moderate renal failure [34]. Therefore, oral surgeons should not rule out a decrease in kidney function in patients subjected to DOAC therapy [15]. Renal function is also known to deteriorate with age, which contributes to reduced excretory capacity in elderly patients on DOAC therapy [35].

Accurate surgical planning is always necessary and in the case of undertaking oral surgery procedures in DOAC-treated patients, planning should be even more scrupulous [15]. Drugs administered to the patient must be analysed, and the cause for the administration of these agents as well as individualized risk of bleeding related to the procedure and patient's general condition need to be identified [20]. Based on the evaluation of the patient's age, renal and hepatic function, half-life of the drug, and the time point for the last dose, the anticoagulant effect of an agent at a given time can be estimated and weighted against the risk of bleeding during invasive procedures [36]. The 3 main possible options regarding anticoagulant therapy in patients presenting for surgery are as follows:

- continuation of medication with the same dose,
- diminishing the dose,
- temporary interruption of anticoagulant pharmacotherapy – always in consultation with the attending physician [33].

Parenteral bridging, i.e., the discontinuation of anticoagulation therapy and temporary substitution with low molecular weight heparin, in contrast to VKA-therapy, is of no use in case

TABLE 5. The impact of the renal function on mean half-lives of direct oral anticoagulants

Renal function CrCl (mL/min)	Rivaroxaban	Apixaban	Edoxaban	Dabigatran
>80	5–9 h (elderly 11–13 h)	9–12 h	10–14 h	12–17 h
50–80	8.7 h	14.6 h	8.6 h	17 h
30–50	9 h	17.6 h	9.4 h	19 h
15–30	9.5 h	17.3 h	16.9 h	28 h – the drug administration in such patients is contraidicated
≥15	no data – the drug is not used in these patients	no data – the drug is not used in these patients	no data – the drug is not used in these patients	no data – the drug is not used in these patients

CrCl – creatinine clearance

TABLE 6. Temporary interruption of direct oral anticoagulant therapy related to the bleeding risk of procedure and patient renal function

Renal function CrCl (mL/min)	Rivaroxaban, apixaban, edoxaban		Dabigatran	
	low-risk procedure	high-risk procedure	low-risk procedure	high-risk procedure
≥80	24 h	48 h	24 h	48 h
50–79	24 h	48 h	36 h	72 h
30–49	24 h	48 h	48 h	96 h
15–29	36 h	48 h	the drug is not indicated	
<15	drugs are not indicated		the drug is not indicated	

CrCl – creatinine clearance

of DOACs. Furthermore, this strategy not only exhibits no benefits in thromboembolism prevention but even increases the risk of bleeding [37].

Due to the increased risk of perioperative haemorrhage, surgical procedures in patients receiving anticoagulant therapy remain a challenge. The continued use of anticoagulants increases the risk of bleeding but their withdrawal, on the other hand, increases the risk of thromboembolic complications [38]. The recommended duration of the temporary interruption for each DOAC relates to drug metabolism, risk of bleeding during surgery, and patient-related factors that increase the risk of bleeding. In patients with a higher risk of bleeding, if possible, it is prudent to postpone elective procedures to correct factors that increase the risk of bleeding [26]. When a higher risk is identified due to the intervention itself, the clinician can consider a phased approach consisting of low-risk procedures over separate appointments [2].

Direct oral anticoagulant therapy should be implemented in patients with normal renal function subjected to oral surgery procedures carrying a low risk of perioperative bleeding [8]. However, intervention should not be performed at the peak plasma concentration of the drug [37]. In general, with regard to rivaroxaban and edoxaban administered once daily, these procedures can be conducted 12–24 h after the last dose and the pharmacotherapy should be restarted 6 h later or even earlier if haemostasis is achieved [34]. In the cases of dabigatran and apixaban administered twice a day, the proposed strategy implies skipping 1 dose [26, 37]. In patients requiring oral surgery interventions carrying moderate and high periprocedural bleeding risk, DOAC should be discontinued for at least 2–3 drug half-lives, but always in consultation with the attending physician. If ceased pre-operatively therapy can be re-commenced after stable clot formation – usually after 24–48 h [39].

In patients with altered renal function, the time of DOAC suspension should be longer, since this condition is related to an increase in maximum plasma concentration and a longer half-life of the DOAC [40]. The duration of proposed temporary interruption of DOAC therapy for oral surgery interventions carrying low and high bleeding risk in patients with different renal function is shown in Table 6.

Despite prominent vascularization of the oral cavity, surgical interventions in this anatomical region are considered as carrying a relatively low risk of periprocedural bleeding due to the possibility of direct haemostasis. Performing a procedure in a minimally invasive way is fundamental, together with employing adjunctive haemostatic measures [40]. Bleeding risk can be decreased by careful and accurate suturing. Tranexamic acid (TXA) is a helpful agent that can be used for surgical wound irrigation immediately after the procedure, and as a mouthwash in the following week [15]. In case of the latter, it has to be stressed to patients that rinsing should be gentle and passive [11]. The use of fibrin glue can also be taken into consideration [15]. In anticoagulated patients undergoing dental extractions, including a gelatine or cellulose sponge application into the extraction socket may be an advisable measure [41]. Platelet-rich fibrin (PRF) was proven to favour clot formation and stability after extractions in patients treated with xabans [38]. Local pressure is a simple and helpful measure, and can be assisted by the use of a gauze soaked in TXA following wound protection with an acrylic splint [15]. It is also reasonable to provide written information for a patient as well as contact details in case of any adverse event. Fluid intake reduction can lead to drug accumulation and a consequent increase of anticoagulation resulting in post-operative bleeding. Therefore, maintaining correct hydration after surgery is of importance [15]. The 1st follow-up appointment should be scheduled 24 h after the procedure [24]. Clinical trials have proven increased bleeding with concomitant use of DOACs and some anti-inflammatory drugs namely NSAIDs and salicylates; the administration of opioids in rivaroxaban-treated patients is reported as posing a risk of similar adverse effects [42]. In postprocedural pain management, paracetamol (acetaminophen) is the drug of choice for DOAC-treated patients [37]. The oral surgeon can consider other postoperative pain management strategies, e.g., the administration of a long-acting anaesthetic like bupivacaine or ropivacaine at the surgical site following surgery [43]. Adequate measures improving haemostasis after oral surgery interventions in DOAC-treated patients together with advisable precautions useful in postoperative care are summarized in Table 7.

TABLE 7. Measures improving haemostasis after oral surgery interventions in direct oral anticoagulant-treated patients, precautions useful in postoperative care

Measures improving haemostasis
• performing the procedure in the least traumatic way possible, • in case of extraction: alveoli irrigation with TXA, gelatine sponge, oxycellulose or PRF application into the extraction socket, • accurate suturing technique, • fibrin glue use, • acrylic splint for wound protection, • local pressure, • post-procedural wound compression with gauze soaked with TXA for 30–60 min, • provide written information for a patient, • provide contact information for a patient in case of any adverse effect
Postoperative recommendations
• 5% TXA aqueous solution for passive mouth rinses 4 times daily for 2 days (up to 7 days after interventions carrying higher bleeding risk), • active rinsing is contraindicated, • cold food is recommended, • patient should maintain fluid intake, • first follow-up appointment is scheduled for 24 h after the procedure
Pain management
• avoid NSAIDs and salicylates in DOAC-treated patients, • use of opioids is not recommended in patients on rivaroxaban therapy, • paracetamol with opioids can be used in patients taking apixaban, edoxaban and dabigatran, • paracetamol alone can be used in rivaroxaban-treated patients

TXA – tranexamic acid; PRF – platelet-rich fibrin; NSAIDs – non-steroid anti-inflammatory drugs; DOAC – direct oral anticoagulant

SUMMARY

Direct oral anticoagulants present a valuable and safe option in anticoagulant therapy. Due to their increasing use, encountering DOAC-treated patients in dental practices is almost certain. Therefore, understanding the properties of these drugs is essential for dental professionals, in particular those carrying out invasive procedures in the dentoalveolar region. For the vast majority of oral surgery out-patient interventions, DOAC therapy can be maintained. All invasive procedures should be performed on the lowest drug plasma concentration possible, and local haemostatic measures have to be employed routinely. Careful evaluation of the bleeding risk related to the patient's general condition is of paramount importance, together with scrupulous surgery planning. In complex patients with clinical characteristics predisposing to bleeding – especially a decrease in renal function – and with procedures carrying a higher risk of perioperative bleeding, a temporary interruption of DOAC therapy may be required, always in consultation with the attending physician. An individualized approach is essential and allows to perform oral surgery interventions in a safe and effective manner.

REFERENCES

1. Zehnder JL. Drugs Used in Disorders of Coagulation. In: Katzung BG, editor. Basic & Clinical Pharmacology. 13th ed. New York: McGraw Hill Education; 2015. p. 584-601.
2. Lee JK. Dental management of patients on anti-thrombotic agents. J Korean Assoc Oral Maxillofac Surg 2018;44(4):143-50.
3. Jawień J. Leki wpływające na układ krwiotwórczy i układ krzepnięcia. In: Olszanecki R, Wołkow P, Jawień J, Korbut R, editors. Farmakologia. 2nd ed. Warszawa: PZWL Wydawnictwo Lekarskie; 2019. p. 454-77.
4. de Andrade NK, Motta RHL, Bergamaschi CC, Oliveira LB, Guimarães CC, Araújo JO, et al. Bleeding risk in patients using oral anticoagulants undergoing surgical procedures in dentistry: a systematic review and meta-analysis. Front Pharmacol 2019;10:866.
5. Khan N. Safe, effective and appropriate prescribing of anticoagulant therapies. Br J Cardiac Nurs 2019;14(4):1-11.
6. Lanau N, Mareque J, Giner L, Zabalza M. Direct oral anticoagulants and its implications in dentistry. A review of literature. J Clin Exp Dent 2017;9(11):e1346-54.
7. de Campos N, Furlaneto F, Buischi YDP. Bleeding in Dental Surgery. IntechOpen 2019. https://www.intechopen.com/online-first/69934 [22.03.2021].
8. Sivolella S, De Biagi M, Brunello G, Berengo M, Pengo V. Managing dentoalveolar surgical procedures in patients taking new oral anticoagulants. Odontology 2015;103(3):258-63.
9. Johnston S. An evidence summary of the management of patients taking direct oral anticoagulants (DOACs) undergoing dental surgery. Int J Oral Maxillofac Surg 2016;45(5):618-30.
10. Raszeja-Specht A, Michno A. Doustne antykoagulanty o działaniu bezpośrednim – nowe wyzwanie dla diagnostyki laboratoryjnej. Diagn Lab 2015;51(3):221-8.
11. Mauprivez C, Khonsari RH, Razouk O, Goudot P, Lesclous P, Descroix V. Management of dental extraction in patients undergoing anticoagulant oral direct treatment: a pilot study. Oral Surg Oral Med Oral Pathol Oral Radiol 2016;122(5):e146-55.
12. Gross PL, Weitz JI. New anticoagulants for treatment of venous thromboembolism. Arterioscler Thromb Vascul Biol 2008;28(3):380-6.
13. El Hussein MT, Cuncannon A. DARE to prescribe: Strategy to guide direct oral anticoagulant therapy. J Nurse Pract 2020;16(7):509-13.
14. Gómez-Moreno G, Aguilar-Salvatierra A, Fernández-Cejas E, Delgado-Ruiz RA, Markovic A, Calvo-Guirado JL. Dental implant surgery in patients in treatment with the anticoagulant oral rivaroxaban. Clin Oral Implants Res 2016;27(6):730-3.
15. Lupi SM, Rodriguez Y Baena A. Patients taking direct oral anticoagulants (DOAC) undergoing oral surgery: a review of the literature and a proposal of a peri-operative management protocol. Healthcare (Basel) 2020;8(3):281.
16. Willmann S, Coboeken K, Kapsa S, Thelen K, Mundhenke M, Fischer K, et al. Applications of physiologically based pharmacokinetic modeling of rivaroxaban – renal and hepatic impairment and drug–drug interaction potential. J Clin Pharmacol 2021;61(5):656-65.
17. Byon W, Garonzik S, Boyd RA, Frost CE. Apixaban: a clinical pharmacokinetic and pharmacodynamic review. Clin Pharmacok 2019;58(10):1265-79.

18. De Caterina R, Kelly P, Monteiro P, Deharo JC, de Asmundis C, López-de-Sá E, et al. Design and rationale of the Edoxaban Treatment in routine clinical practice for patients with Atrial Fibrillation in Europe (ETNA-AF-Europe) study. J Cardiovasc Med 2019;20(2):97-104.
19. Lip GY, Agnelli G. Edoxaban: a focused review of its clinical pharmacology. Eur Heart J 2014;35(28):1844-55.
20. Martínez-Moreno E, Martínez-López F, Rodríguez-Lozano FJ, Oñate-Sánchez RE. Bleeding complications in anticoagulated and/or antiplatelet-treated patients at the dental office: a retrospective study. Int J Environ Res Public Health 2021;18(4):1609.
21. Huisman MV, Klok FA. Pharmacological properties of betrixaban. Eur Heart J Suppl 2018;20(Suppl E):E12-5.
22. Patadiya N, Dumpala R. A high profile review on new oral clotting factor Xa inhibitor: betrixaban. Eur J Pharm Med Res 2021;8(1):239-47.
23. Ansell J, Laulicht BE, Bakhru SH, Burnett A, Jiang X, Chen L, et al. Ciraparantag, an anticoagulant reversal drug: mechanism of action, pharmacokinetics, and reversal of anticoagulants. Blood 2021;137(1):115-25. doi: 10.1182/blood.2020007116.
24. Muñoz-Corcuera M, Ramírez-Martínez-Acitores L, López-Pintor RM, Casañas-Gil E, Hernández-Vallejo G. Dabigatran: A new oral anticoagulant. Guidelines to follow in oral surgery procedures. A systematic review of the literature. Med Oral Patol Oral Cir Bucal 2016;21(6):e679-88.
25. Skripka A, Sychev D, Bochkov P, Shevchenko R, Krupenin P, Kogay V, et al. Factors affecting trough plasma dabigatran concentrations in patients with atrial fibrillation and chronic kidney disease. High Blood Press Cardiovasc Prev 2020;27(2):151-6.
26. Doherty JU, Gluckman TJ, Hucker WJ, Januzzi JL, Ortel TL, Saxonhouse SJ, et al. 2017 ACC expert consensus decision pathway for periprocedural management of anticoagulation in patients with nonvalvular atrial fibrillation: a report of the American College of Cardiology Clinical Expert Consensus Document Task Force. J Am Coll Cardiol 2017;69(7):871-98.
27. Pruszczyk P, Ciurzyński M, Opolski G, Stępińska J, Wożakowska-Kapłon B, Kalarus Z, et al. Wspólne stanowisko kardiologiczno-stomatologiczne dotyczące postępowania u pacjentów leczonych przeciwzakrzepowo poddawanych zabiegom stomatologicznym. Kardiol Pol 2016;74(1):87-98. doi: 10.5603/KP.2016.0014.
28. Gómez-Moreno G, Fernández-Cejas E, Aguilar-Salvatierra A, de Carlos F, Delgado-Ruiz RA, Calvo-Guirado JL. Dental implant surgery in patients in treatment by dabigatran. Clin Oral Implants Res 2018;29(6):644-8.
29. Olek M, Blukacz M, Dawiec G. Wskazania i przeciwwskazania do stosowania leczenia odtwórczego z zastosowaniem implantów stomatologicznych. Twój Prz Stomatol 2020;3:62-8.
30. Dincq AS, Lessire S, Douxfils J, Dogné JM, Gourdin M, Mullier F. Management of non-vitamin K antagonist oral anticoagulants in the perioperative setting. Biomed Res Int 2014;2014:385014.
31. Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJ, Lip GY. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. Chest 2010;138(5):1093-100.
32. Padrini R. Clinical pharmacokinetics and pharmacodynamics of direct oral anticoagulants in patients with renal failure. Eur J Drug Metab Pharmacokinet 2019;44(1):1-12.
33. Chahine J, Khoudary MN, Nasr S. Anticoagulation use prior to common dental procedures: a systematic review. Cardiol Res Pract 2019;2019:9308631.
34. Steffel J, Verhamme P, Potpara TS, Albaladejo P, Antz M, Desteghe L, et al. The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. Eur Heart J 2018;39(16):1330-93.
35. Vílchez JA, Gallego P, Lip GY. Safety of new oral anticoagulant drugs: a perspective. Ther Adv Drug Saf 2014;5(1):8-20.
36. Fenger-Eriksen C, Münster AM, Grove EL. New oral anticoagulants: clinical indications, monitoring and treatment of acute bleeding complications. Acta Anaesthesiol Scand 2014;58(6):651-9.
37. Ciulla MM, Vivona P. Novel oral anticoagulants: a practical guide for dentists. Italian J Dental Med 2018;3(1):7-11.
38. de Almeida Barros Mourão CF, Miron RJ, de Mello Machado RC, Ghanaati S, Alves GG, Calasans-Maia MD. Usefulness of platelet-rich fibrin as a hemostatic agent after dental extractions in patients receiving anticoagulant therapy with factor Xa inhibitors: a case series. Oral Maxillofac Surg 2019;23(3):381-6.
39. O'Connell JE, Stassen LF. New oral anticoagulants and their implications for dental patients. J Ir Dent Assoc 2014;60(3):137-43.
40. Caliskan M, Tükel HC, Benlidayi E, Deniz A. Is it necessary to alter anticoagulation therapy for tooth extraction in patients taking direct oral anticoagulants? Med Oral Patol Oral Cir Bucal 2017;22(6):e767-73.
41. Lakdawala YA, Masood S, Jawed S, Younus H. Common methods to arrest haemorrhage after tooth extraction in Dental out patient department. Pak J Surg 2020;36(3):260-3.
42. Foerster KI, Hermann S, Mikus G, Haefeli WE. Drug–drug interactions with direct oral anticoagulants. Clin Pharmacokinet 2020;59(8):967-80.
43. Pasternak M, Woroń J. Postępowanie w bólu poekstrakcyjnym. Ból 2020;21(1):47-52. doi: 10.5604/01.3001.0014.3422.