Review article

DENTAL CONSIDERATIONS IN PATIENTS TAKING NEW ANTIPLATELET AND ANTICOAGULANT DRUGS

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ABSTRACT

Atherosclerosis and the resulting cardiovascular and cerebrovascular diseases (myocardial infarction, coronary artery disease and stroke) are the leading cause of mortality and morbidity in the developed countries. Worldwide, over 10 million deaths per annum are caused by arterial thrombosis (ischaemic stroke, heart disease, peripheral gangrene).

Leading in the treatment and prevention of thrombotic complications are the anticoagulant and antiplatelet drugs which are taken by millions of patients worldwide.

A review of the literature shows that clinical trials involving dental extractions in patients taking antithrombotic drugs have been conducted for more than 50 years and are still ongoing.

Recently, new antiplatelet and anticoagulant drugs: direct thrombin inhibitors, factor Xa inhibitors and a new class of oral thienopyridines (inhibitors of Glycoprotein IIb/IIIa and P2Y12 receptors) have been introduced on the market and are becoming increasingly common. The implications of these drugs during dental treatment are not yet known, and there is not enough information available within the literature on safe use during dental surgery. The **purpose** of the present review is to discuss the pharmacological properties of the new antiplatelet and anticoagulant drugs, their usage in the perioperative setting, and some guidance for dental practitioners performing invasive dental procedures.

Keywords: haemostasis alteration, blood coagulation disorders, new antiplatelet drugs, dental management antiplatelet, oral surgery, NOA, thrombosis.

INTRODUCTION

With prolonged life expectancy, the number of elderly patients requiring dental treatment increases. These patients often are with chronic diseases, treated with multiple medications. The leading cause of mortality and disability in the world are cardiovascular and cerebrovascular diseases. The cardiovascular diseases annually cause nearly one-third of the planet's mortality, 47 percent of mortality in Europe and over 60 percent in Bulgaria. Leading in the treatment of these diseases and the prevention of their complications are the antithrombotic medications, which application grows at an annual rate above 10% [1].

Arterial and venous thrombosis has an important impact on worldwide morbidity and mortality. Worldwide over 10 million deaths per annum are caused by arterial thrombi, resulting in ischaemic stroke, heart disease or peripheral gangrene.

Platelets are the key pro-thrombotic element in the *arterial thrombosis*, forming aggregates interconnected by fibrin, thus antiplatelet drugs are leading in the treatment of arterial thrombosis. Half a million deaths related to *venous thromboembolism* occur in the European Union per year [2]. Venous thrombi consist mainly of fibrin with few cells in between. Anticoagulants are the drugs of choice to prevent or treat these conditions [2].

Three main classes of antiplatelet agents are licensed for the treatment of atherothrombosis: **acetylsalicylic acid** (aspirin), **P2Y12 inhibitors** (ticlopidine, clopidogrel, prasugrel, cangrelor, ticagrelor), and **GpIIb/IIIa receptor antagonists** (abciximab, eptifibatide, and tirofiban). While the latter have intravenous administration in ACS in combination with other antithrombotic agents (their effect being unpredictable when administered orally), the former two classes are widely used chronically [3].

NEW ÀNTIPLATELET ÀGENTS

The clinical efficacy of aspirin, ticlopidine, and clopidogrel is only partial because they inhibit TXA2-mediated or ADP-mediated platelet aggregation, leaving the activity of other platelet agonists such as thrombin largely unaffected. Another drawback is the high inter-individual variability in platelet inhibition by clopidogrel, which is attributed to differences in the extent of clopidogrel prodrug metabolism. Clinical, cellular and genetic factors have been associated with clopidogrel resistance. This variability is clinically important since many studies have demonstrated that patients exhibiting high on-treatment platelet reactivity (clopidogrel resistance or hyporesponsiveness) are not adequately protected from major adverse cardiac events. It is estimated that approximately one-third

of clopidogrel-treated patients exhibit a diminished ex vivo platelet response to clopidogrel [4].

Ticlopidine, clopidogrel, prasugrel, and ticagrelor are approved P2Y12 antagonists, whereas cangrelor is still in clinical development. **Ticlopidine** is not frequently prescribed, owing to its unfavourable safety profile; whereas **clopidogrel** is the most widely used P2Y12 inhibitor. **Prasugrel** and **ticagrelor** are novel P2Y12 receptor inhibitors. Prasugrel acts as an irreversible oral inhibitor of the P2Y12 receptor. Ticagrelor, a cyclopentyl-triazolo-pyrimidine, is the first orally available reversible antagonist of the P2Y12 receptor (Table 1) [5].

Class	Mechanism of action	Drug	Time to reach a peak plasma concentration	Metabolism to active metabolite	Route of elimination	Elimination half-life	Time required to restore platelet function
Salicylates (COX inhibitors)	Inhibition of cyclooxygenase	Acetylsalicylic acid, Aloxipyrine, Carba-salate calcium, Indufene, Triflusal Abciximab	30-40 minutes	No	Liver by deacetylation to salicylic acid	Irreplaceable inhibition of platelets	30% on the 48 h
Glycoprotein IIb / IIIa antagonists	Reversibly binding to the platelet receptor glycoprotein (GP) IIb/IIIa	(ReoPro)monoclonal antibody 7E3 (c7E3 Fab) **i.v.**	10-30 min	No	Degradation by proteolysis in the kidney	10-30 min	48 h
		Eptifibatide (Integrilin**i.v.**		No	renal excretion (98%).	2,5 h	4 h
		Tirofiban (Aggrastat) **i.v.**		No	Urine (65%); feces (25%)	2 h	4-8 h
	Platelets glycoprotein (GP) IIb/IIIa antagonist	Roxifiban p.o.		Yes			
	Platelets glycoprotein (GP) IIb/IIIa antagonist	Orbofiban p.o.				18h	
Thienopyridines	P2Y12 reversible receptor inhibition	Clopidogrel p.o.	2-4 hours (300 mg.)	Yes	Liver through a 2-step process involving CYP3A5 / 2CD19 to an active metabolite	6–8 hours	5-7 days (40% on 3 days)
	P2Y12 reversible receptor inhibition	Ticlopidine p.o.	2 hours	Yes	Liver CYP2CD19 to an active metabolite	12 hours	12 hours (single dose) 4-5 days (multiple intake)
	P2Y12 reversible receptor inhibition	Prasugrel p.o.	1-2 hours (60 mg.)	Metabolite (R-138727)	Liver CYP2CD19 to an active metabolite	2-15 h	2 weeks
Sulphonylurea	P2Y12 reversible receptor inhibition	Elinogrel p.o. i.v.	20 min	No	Liver and kidney	No	8 hours after single dose of 10 mg: longer at high dose (-1 day)
ADP-analogue	P2Y12 irreversible receptor inhibition	Cangrelor i.v.	3-9 min	No	Liver (58%) and kidney(35%)	minutes	1-2 h
Cyclopentyl-triazolopyrimidine	P2Y12 irreversible receptor inhibition	Ticagrelor p.o.	1,5-3 hours	No	Liver to an active metabolite	6–12 hours	5 days
Phosphodiesterase inhibitor	Inhibition of phosphodiesterase	Dipyridamole p.o.	75 min	No	Liver glucoro-nidation to an active metabolite	10 hours	2 days (?)
Phosphodiesterase III inhibitor	selective inhibitor of phosphodiesterase type III	Cilostazol p.o. twice-daily	-	No	Liver CYP3A4/ 2CD19 . To active metabolite	11–13 hours	2 days (?)

TP-receptor antagonist	PAR-1 Inhibition selective thromboxane prostanoid (TP) antagonist	Terutroban (S18886) p.o.	30 min-2 hours	No	?	6-10 hours	?
PAR-1 receptor inhibitor derived from the natural product himbacine	PAR-1 Inhibition	SCH 205831 p.o.	Orally	No	?	No	?
PAR-1 selective receptor inhibitors	PAR-1 Inhibition	Vorapaxar (CSH-530348) p.o.	Hours after the loading dose	No	Liver, biliary excretion	No	126–269 hours
	PAR-1 Inhibition	SCH 602539 p.o.		No			
	PAR-1 Inhibition	Atopaxar (E5555) p.o.		No			
vWF antagonists (humanized monoclonal antibody to Vwf)	Inhibition of high-shearstress-induced platelet aggregation in a concentration dependent manner	AJW200 IgG4 humanized monoclonal antibody to human vWF derived from Sp2/0 mouse myeloma cells.	24 hours			12 hours	
	Binds with high afьinity to the activated vWF A1-domain and inhibits vWF dependent platelet aggregation through preventing Gp-Ib receptor to interact with Willebrand factor	ARC1779 second-generation, nuclease resistant aptamer, which has been conjugated to a 20-kDA polyethylene glyco	1-2 hours			2 hours	8–12 hours

Prasugrel (Efient®)

Prasugrel is a third generation thienopyridine, which acts as a selective and irreversible inhibitor of the P2Y12 receptor. Prasugrelexhibits a more rapid antiplatelet effect *ex vivo* compared with clopidogrel owing to its faster metabolic activation.

Pharmacokinetics/pharmacodynamics.Prasugrel is an oral prodrug that requires conversion into an active metabolite (R-138727) by the hepatic cytochrome P450 (CYP) system. Prasugrel is transformed through hydrolyzation of esterases into the thiolactone, R-95913 and then further metabolized via oxidation of intestinal and hepatic CYP450 into active metabolite R-138727 [6]. The active metabolite of prasugrel appears rapidly in the blood after ingestion, showing a significant effect after 15 min with a median time to reach a 20% inhibition of platelet aggregation 30 min after administration [7]. Inhibition of platelet aggregation reaches a steady-state after 2–4 days [6]. Prasugrel's metabolites are eliminated with a median half-life ranging from 3 to 9 h. Two-thirds of metabolites are excreted in the urine, one-third in feces [7].

Ticagrelor(Brilique™, AZD6140)

Ticagrelor is an adenosine triphosphate analogue, which belongs to new chemical class cyclopentyl-triazolo-pyrimidines. It is the first reversibly binding oral ADP receptor P2Y12 antagonist, which is highly selective for the receptor.

Pharmacokinetics/pharmacodynamics. Ticagrelor'sactive form does not need the metabolic activation required with thienopyridines. Ticagrelor targets the P2Y12 receptor via a mechanism that is non-competitive with ADP, suggesting the existence of a binding site on P2Y12 independent to that of ADP. Thus, ticagrelor may act through an allosteric mechanism preventing G-protein-mediated signal transduction following ADP binding to P2Y12 [8].

Ticagrelor is administered twice a dayorally. It is rapidly absorbed in the small intestine, and its plasma half-life occurs between 1.5 and 3 hours after administration with a steady-state concentration after 2 to 3 days. Ticagrelor is eliminated through the gastrointestinal tract, with less than 1% through the urine, suggesting that renal dose adjustment is not necessary.

Ticagrelor is metabolized in the liver primarily through CYP3A4/5 isoenzymes. Some of the ticagrelor metabolites exhibit antiplatelet activity. One of them, AR-C 124910XX, is present at approximately one-third of the

plasma concentration of ticagrelor and has a half-life of 8–12 hours. Following cessation, the antiplatelet effects of ticagrelor decline rapidly over 72 h and normal platelet reactivity is achieved after approximately 5 days [4].

Concomitant use of CYP3A4 inhibitors such as ketoconazole, diltiazem, ritonavir, and clarithromycin or inducers (rifampicin, phenytoin, carbamazepine, and dexamethasone) can prolong the plasma half-life of ticagrelor, so it should be avoided [9].

Cangrelor

Cangrelor is a reversible, short-acting, potent, competitive P2Y12 inhibitor that has the advantage of being an active drug not requiring metabolic conversion, although it is not orally available.

Pharmacokinetics/pharmacodynamics. With a plasma half-life of 3–9 min, cangrelor after intravenous administration achieves a high level of platelet inhibition within 5 min and reaches steady state concentration within 15–30 min. of administration. Cangrelor is not a prodrug, it is administered in an active form, and it is metabolized in the plasma by dephosphorylation to its nucleoside, which is inactive. In contrast to clopidogrel and prasugrel, cangrelor is rapidly reversible [10]. The combination of the very short half-life and reversible binding underlie the rapid recovery of platelet function in 1–2 hours following the termination of intravenous infusion of cangrelor. The onset of action of clopidogrel and prasugrel is delayed when co-administered with cangrelor, demonstrating that cangrelor favourably binds to the P2Y12 receptor and prevents the inhibition of prasugrel's or clopidogrel's metabolite [4].

Integrin áIIbâ3 (GPIIb / IIIa) receptor antagonists

Expression of the functionally active integrin áIIbâ3 (GPIIb/IIIa)on the platelet surface is the final stage of platelet aggregation, making it the subject of development for new antiplatelet drugs [10]. In the mid-70s, Nurden and Caen in France, and Phillips in the U.S.A. found deficiencies of two different platelet membrane glycoproteins in several tribes with Glanzmann thrombasthenia. They have been defined as glycoproteins GPIIb and GPIIIa, existing as a Ca-dependent complex (GPIIb/IIIa) on the surface of the platelets.

Following recognition that the expression of functionally active integrin aIIbb3 (GPIIb/IIIa)on the platelet surface is the final common pathway of platelet aggregation, this glycoprotein became the target of novel antiplatelet drugs [11].

Correlation of all these findings suggested that blockade of GPIIb/IIIa receptors could be a particularly desirable therapeutic strategy because, firstly, the monoclonal antibodies to GPIIb/IIIa are more potent inhibitors of platelet function than aspirin; secondly, GPIIb/IIIa is platelet-specific; thirdly, inhibition of GPIIb/IIIa still leaves platelet adhesion largely intact, contributing to haemostasis without causing thrombotic damage; and fourthly, the haemorrhagic diathesis produced by the in-herited deficiency of GPIIb/IIIa receptors in Glanzmann thrombasthenia only rarely produces spontaneous brain haemorrhage, the most feared complication of anticoagulant and antiplatelet therapy.

The success of blockade of GPII / IIIa platelet receptors with intravenous agents (**abciximab, eptifibatide, tirofiban**) leads to the development of several oral GPIIb/IIIaantagonists [10]. Unfortunately, the oral inhibitors are not clinically effective due to their low bioavailability that leads to a large peak-trough difference and to drug-induced conformational changes in GPIIb / IIIa and possible pharmacogenomics effects in response to the drugs, in particular, the PlA polymorphism in GPIIb / IIIa. The other novel platelet inhibitors are currently in advanced clinical testing [12].

Routine monitoring

Platelet function testing was initially designed for identification of platelets function disorders. Later, in detecting the role of platelets in the development of athero-thrombosis, these tests become useful for monitoring of the antiplatelet drug therapy [13].

Numerous platelet function tests are available (e.g. turbidometric light transmittance, Verify Now, Thrombelastogram, Multiplate, Platelet Function Analyser-100). Currently laboratory control of the antiplatelet therapy is not widely applied in the clinical practice due to the lack of a standardized drug resistance definition found in some patients and to the lack of a generally accepted test for platelet function testing. In addition, there is controversy in the interpretation of the laboratory results of resistance, as is not clear whether they directly turn into an inadequate biological response with a direct clinical application [14].

Drug-drug interactions

Membrane transporter proteins such as P gpcan have important effects on the pharmacokinetics of the drugs. Verapamil, diltiazem, quinidine, dronedarone, carvedilol, captopril and amiodarone are inhibitors of P-gp, which also plays an important role in the intestinal efflux of clopidogrel and ticagrelor. Moreover, in vitro studies have indicated that ticagrelor and its active metabolite, AR C124910XX, are inhibitors of the P gp transporter. The activity of carboxylesterases, which play an important role in the biotransformation of many drugs, can be inhibited or induced by drugs such as dexamethasone, phenobarbital, and polycyclic aromatic hydrocarbons [4].

Dental considerations

Most practical recommendations consider dental procedures as minor interventions associated with a low risk of bleeding and self-limited blood loss that can be managed with local haemostatic agents. According to the Scottish Dental Clinical Effectiveness Programme guidance, dental interventions based on the associated bleeding risks can be divided as: (Table 2.) [15].

Table 2. Bleeding risks and dental procedures recommended by the Scottish Dental Clinical Effectiveness Programme [15].

Dental procedures that are unlikely to cause bleeding	Dental procedures that are likely to cause bleeding	
	Low bleeding risk procedures	High bleeding risk procedures
Local anaesthesia by infiltration, intraligamentary or mental nerve block; Local anaesthesia by inferior dental block or other regional nerve blocks;	Simple extractions (1–3, with restricted wound size);	Complex extractions, adjacent extractions that will cause a large wound, or more than three extractions at once;
Basic periodontal examination (BPE);	Incision and drainage of intraoral swellings;	Flap raising procedures; Elective surgical extractions; Periodontal surgery; Periradicular surgery; Crown lengthening; Dental implant surgery;
Supragingival removal of plaque, calculus, and stain;	Detailed six-point full periodontal examination;	
Direct or indirect restorations with supragingival margins;	Root surface instrumentation (RSI);	
Endodontics (orthograde);	Direct or indirect restorations with subgingival margins.	
Impressions and other prosthetic procedures;		Gingival recontouring;
Fitting and adjustment oforthodontic appliances.		Biopsies.

Few studies showed that risk of haemorrhage in patients taking direct thrombin inhibitors is similar to those taking warfarin with INR 2 - 3 [16]. For patients requiring simple dental extraction or minor oral surgery as localized periodontal surgery, apical osteotomy, incisional biopsies or excision of a localized mucosal lesion, it can be assumed that the risk is similar to that of patients taking vitamin k antagonists and with an INR < 3.

Surgical procedures should be performed as late as possible after the last intake of dabigatran and local haemostatic measures as suturing, gelatine sponge or cellulose mesh, tranexamic acid mouth rinse mast be considered for control of postoperative bleeding [15, 17].

Patients who are treated with antiplatelet medications may have additional medical conditions: liver impairment or alcoholism; kidney failure; thrombocytopenia, haemophilia, or other hematologic disorders; treatment with cytotoxic medication that can increase the risk of prolonged bleeding after dental treatment. In these situations, dental practitioners are advised to consult the patient's physician to determine whether care can safely be delivered in a primary care office [17]. Any suggested modification to the medication regimen prior to dental surgery should be done in consultation with and on the advice of the patient's physician [18, 19].

Pain control in the postoperative period

In the postoperative period for pain control Paracetamol is the most suitable choice for patients taking dabigatran. Concomitant treatment of new antiplatelets with NSAIDs may increase the risk of bleeding [19].

NEW ORAL ANTICOAGULANTS

For more than 80 yr, vitamin K antagonists have been the most frequently prescribed oral anticoagulants. Although highly effective agents they do have numerous limitations: an unpredictable pharmacological profile in different patients, based on genetic factors; multiple foods and drug interactions, and therefore require frequent laboratory monitoring and dose adjustment. They have a slow onset and offset of action and a hypercoagulable state as a result of warfarin-mediated protein C and S deficiency that develops in some patients [20]. Therefore, they have a narrow therapeutic window, the risk of stroke and systemic embolism increases with lower levels of anticoagulation (INR <2.0) and bleeding risk is higher when the INR is above 3.0. VKAs have a long half-life and a slow onset of action requiring binding therapy, and after cessation, the drug is eliminated from the plasma slowly for 3-5 days [21]. All this leads to the search for new molecules and the discovery of the direct anticoagulants (Table 3): factor Xa inhibitors and direct thrombin inhibitors. Unlike vitamin K antagonists, they do not require frequent monitoring, are administered orally and act on specific and single purposes of the coagulation cascade. They have a wide therapeutic margin, low drug- to- drug interactions and no significant food interactions [22, 23]. Their limitations are the lack of effective antidote, high cost and limitations in patients with kidney disease. Prior to surgery, discontinuation of their intake depends on creatinine clearance for 12-120 hours [24].

Table 3. Anticoagulant drugs

Class	Mechanism of action	Drug	Time to reach peak plasma concentration	Route of administration	Route of elimination	Elimination half-life	Drug detection tests
Coumarin derivatives	Indirect action	Acenocoumarol	60-120 min	Per os	Liver	8-11 hours	INR
	Indirect action	Warfarin sodium	1-1,30 hours	Per os	Liver	36-42 hours	INR
	1,3-Indanediones	Chlorindione					
	1,3-Indanediones	Diphenindione					
	1,3-Indanediones	Phenindione				5 – 10 hours	
	Others	Thioclomarol					
Factor Xa inhibitors	second-generation low molecular weight heparin	Bemiparin		s.c.		5.3 hours	Heparin Anti-Xa
	Heparin group/ glycosamino-glycans/	Certoparin		s.c.			
		Dalteparin		s.c., i.v.	Renal	3-5 hours s.c 2,1-2,3 h i.v.	
		Enoxaparin		s.c., i.v.	Liver into low molecular weight species by either or both desulfation and depolymerization	4.5 hours	
		Nadroparin (Fraxiparine)	3-5 hours	SC (except for haemodialysis)	Renal	3,5 hours (SC dose)	
		Parnaparin	2-4 hours	s.c.	Renal		
		Reviparin			Renal		
	90% for Anti-Xa activity, 67% for Anti-IIa activit	Tinzaparin			Minor metabolisation in liver by desulfation and/or depolymerization; excretion via kidneys in almost unchanged form	200 min. for Anti-Xa activity, 257. min for Anti-IIa activity	
		Fondaparinux			Renally excreted unchanged	17-21 hours	
		Idraparinux			Renal		
		Danaparoid sodium			Renal		
		Dermatan sulfate			Renal		
		Sulodexide			Renal		
Factor Xa inhibitors	Direct Reversible Xa Inhibitor	Apixaban (Elequis®)	3-4 hours	Per os twise daily	25 % renal, 55 % intestinal, remnant hepatic	9-12 hours	PT, anti Xa testing
Factor Xa inhibitors	Direct Xa Inhibitors	Betrixaban	3-4 hours	Per os onse daily	Liver	20 hours	
Factor Xa inhibitors	Direct Xa Inhibitors	Edoxaban	1-2 hours	Renal elimi-nation 50%, not recommen-ded if e GFR <30 mL/min	Metabolized in the biliary-fecal system in about 65% and is mainly excreted by the kidneys	6-11 hours	PT, anti Xa testing
Factor Xa inhibitors	Direct Xa Inhibitors	Otamyxaban					
Factor Xa inhibitors	Direct Xa Inhibitors	Rivaroxaban (Xarelto®)	2,5-4 hours	Per os onse or twise daily	66 % renal, 28 % in feces	5–10 h; 12–13 h in patients > 75 years	PT, anti Xa testing
Factor Xa inhibitors	Bivalent	Hirudine i.v.	i.v.		Kidneys	i.v. 40 min s.c. 150–240 min	

Factor Xa inhibitors	Bivalent	Bivalirudin i.v.	i.v.		Combination of renal mechanisms and proteolytic cleavage	~25 minutes in patients with normal renal function	
Direct thrombin (F II) inhibitors	Monovalent	Argatroban	1 hour		Renal	45 min	
Direct thrombin (F II) inhibitors	Monovalent	Dabigatran (Pradaxa®)	2-4 hours		80 % renal, 20 % hepatic Not recommended if eGFR <60 mL/min; contraindicated if eGFR<30 mL/min; renal elimination 80%	12–14 h; 14–17 h in elderly; 15–18 h in moderate renal impairment; up to 28 h in advanced renal impairment	aPTT, TT, ecarincloting time
Direct thrombin (F II) inhibitors	Monovalent	Melagatran i.v.		No	Renal (80%)	1.5–2 hours in young, healthy people, up to 4–5 hours in 70-year-old patients	aPTT, PT, TT, OCT assay
Direct thrombin (F II) inhibitors	Monovalent	Ximelagatran p.o.	1,5-2,5 h	Melagatran	Renal (80%)	3-5 hours	aPTT, PT, TT, OCT assay

New oral anticoagulants

In 2004, Ximelagatran was licensed by the European Medical Agency, thus becoming the first oral thrombin inhibitor on the market. As a result of potential hepatotoxicity, it was withdrawn soon after [25]. Since 2008, further new oral anticoagulants have been introduced. These include the direct thrombin inhibitor, dabigatran, and the direct factor X inhibitors, such as rivaroxaban, apixaban, and edoxaban. Other new oral anticoagulants (NOACs) are currently being tested in clinical trials.

Dabigatran (Pradaxa®)

Dabigatran etexilate (Pradaxa®, Boehringer Ingelheim, Spain) is the first orally administered direct thrombin inhibitor. It was the first approved NOA in 2008 by the EU and in 2010 by the Food and Drug Administration (FDA).

Pharmacokinetics/pharmacodynamics. Dabigatran is taken **twice daily**. It is a specific, reversible direct thrombin inhibitor that, after oral administration, is rapidly absorbed and converted to its active form, through esterase catalysed hydrolysis in the plasma. Mechanism of action of dabigatran is to bind with the active site on free and clot-bound thrombin (factor IIa), so it cannot transform fibrinogen into fibrin. It has a rapid onset of action with a peak plasma concentration at 0.5–4 h. Twenty percent of the absorbed drug undergoes hepatic metabolism, while 80% is excreted unchanged via the renal system, and the dosage must be reduced in patients with renal impairment (Creatinine Clearance (CrCl) < 50 ml/min). The half-life elimination is determined by renal function and in healthy patients is 12-14 h, 14-17 h in elderly, up to 18 hours in patients with CrCL between 30 and 50 ml/min and up to 28 h in advanced renal impairment (creatinine clearance <15–30 ml/min). Creatinine levels should also be considered even the medication is discontinued before a surgical procedure [26].

Apixaban(Elequis®)

Apixaban is the most recently introduced direct anticoagulant. Apixaban (Eliquis) is taken **twice a day**. It is a reversible orally administered FXainhibitor with the same therapeutic indications of dabigatran and rivaroxaban.

Pharmacokinetics/pharmacodynamics. After oral administration, the peak plasma concentration is reached in 1–3 h with a bioavailability of approximately 60 %. The half-life of the drug is about 12 h, and it is excreted almost totally in bile. As rivaroxaban, no specific reversal agent exists for apixaban. In case of emergency situations, recombinant factor VIIa, recombinant factor Xa or activated thrombin complexes can be used. However, few data are available for a correct management of apixaban in case of haemorrhage, and further studies are needed in this respect [27].

Rivaroxaban(Xarelto®)

Rivaroxaban is an oral selective, reversible direct FXa inhibitor that binds with the part of factor XaIthat catalyses the activation of prothrombin (factor II).

Pharmacokinetics/pharmacodynamics. Rivaroxaban is most commonly taken **once a day**, either in the morning or at night. It can inhibit free factor Xa but also clot bound factor Xa, and factor Xa bound to the prothrombinase complex. The drug reaches the peak plasma concentration in 2.5–4 h after oral administration. The half-life is 5.7– 9.2 h (up to 12–13 h in patients older than 75 years) Elimination is 66 % renal and 28 % in feces [28].

Edoxaban

Edoxaban is a direct, highly selective and competitive inhibitor of factor Xa. It is indicated for the prevention of stroke/systemic embolism in atrial fibrillation (AF) and for the treatment of venous thromboembolism (VTE).

Pharmacokinetics/pharmacodynamics. It has a bioavailability of 62%. Co-administration of strong P-glycoprotein inhibitors (e.g. ketoconazole, amiodarone,

verapamil, or quinidine) causes an increased effect of edoxaban, necessitating a dose reduction of 50%. Dose adjustment should be made in patients with moderate renal impairment [29].

Routine monitoring
Routine monitoring of the anticoagulant effect of NOA is not required. In the emergency situation, the thrombin clotting time (TT) and the ecarin clotting time (ECT) are the most sensitive tests for measuring the anti-coagulation rate. Activated partial thromboplastin time (aPTT) is less sensitive, but also can be used in case of emergency. [24, 26, 30, 31].FXaIs, including **rivaroxaban**, slightly prolong prothrombin time (PT) and aPTT. No routine monitoring of rivaroxaban is generally required; however, in case of an emergency,anti-factor Xa is reported as the most accurate measurement of anticoagulation[28].

In October 2015, the U.S. Food and Drug Administration approved **antidote** of dabigatran Idarucizumab, a monoclonal antibody (Praxbind®, BoehringerIngelheim Pharmaceuticals, Inc., Germany) for the treatment of patients on dabigatran etexilate when reversal of the antico-agulant effect is needed for emergency surgery/urgent procedures, or in life-threatening or uncontrolled bleeding. For minutes Idarucizumab completely reverses the anticoagulant activity of dabigatran in 88 to 98 % of patients [32].

Drug-drug interactions
Dabigatran has few clinically significant drug and food interactions. Concomitant intake of Ketoconazole, amiodarone and verapamil may increase the anticoagulant effect of dabigatran, whilst rifampicin may decrease its effect. The risk of bleeding may alsobe increased by concomitant use of other anticoagulants, antiplatelets, non-cox-selective NSAIDs and salicylates. Paracetamol and opioid analgesics are appropriate alternatives for pain management [33].

Drug-drug interactions affecting the pharmacokinetics of *rivaroxaban* Co-administration of *apixaban*and rivaroxaban with the strong CYP3A4 (e.g. phenytoin, carbamazepine, phenobarbital, rifampicin) leads to over 50% decrease of plasma concentration of the drugs. P-gp inhibitors, such as Ketoconazole and ritonavir, may increase dramatically plasma concentrations of apixaban [33, 34].

Concomitant treatment with *edoxaban*is contraindicated in subjects receiving ritonavir, cyclosporine, erythromycin, azithromycin, clarithromycin, ketoconazole, itraconazole because these drugs increase its steady-state plasma concentrations [29].

Dental considerations
The major concern in the treatment of patients taking DOACs is the risk of haemorrhage in dental surgical procedures. Depending on the type of dental procedure and the medical condition of the patient, the risk of bleeding should be considered with the risk of thrombo-embolic complications.

Several treatment approaches can be considered: continue DOACs, time dental treatment as late as possible after the last DOACs dose, discontinue DOACs for 24hrs, or discontinue DOACs for 48hrs [35].

Patients taking NOAC who requires a dental procedure with low bleeding risk, treatment should be made without interrupting of the anticoagulant medication.

Patients, who are taking NOAC and requires a dental procedure with higher bleeding risk, should omit (apixaban, dabigatran) or delay (rivaroxaban) their morning dose on the day of their dental treatment. If the patient takes rivaroxaban once daily in the evening, there is no need for modification of the intake, as long as at least 4 hours are past after the dental treatment [15].

In addition:
Treatment preferably should be planned early in the day to allow monitoring and management of bleeding complications. Surgical trauma should be minimized over separate visits, and more complex cases should be referred to a more experienced dentist or an oral surgeon. Local haemostatic measures as gelatine sponge and wound suturing should be used to achieve haemostasis.

Advise the patient on the next drug intake: For rivaroxaban (taken once a day), the delayed morning dose may be taken 4 hours after haemostasis has been achieved. The next dose should be taken as usual the following morning. If the patient normally takes their rivaroxaban in the evening, they can take this at the usual time as no earlier than 4 hours after haemostasis has been achieved.

For apixaban or dabigatran (taken twice a day), having missed the morning dose, the patient should take their evening dose at the usual time as long as no earlier than 4 hours after haemostasis has been achieved.

Advise the patient to contact the practice for advice if bleeding occurs prior to, or after, restarting their NOAC.

The patient should avoid missing subsequent doses of their NOAC unless absolutely required in an emergency situation to control bleeding [15].

Unlike warfarin, where the dose can be adjusted according to the INR, the new drugs are prescribed at fixed doses. Depending on the pharmacokinetics of the drug, patients with impaired liver (alcohol dependence, chronic viral or autoimmune hepatitis, primary biliary cirrhosis) or renal function (Table 4), with a myelodysplastic disorder, haematological malignancy or other bleeding disorders (Willebrand's disease, haemophilia, idiopathic thrombocytopenic purpura) and patients on chemotherapy may have a higher risk of bleeding following an invasive dental procedure. These patients should be referred to an oral and maxillofacial surgeon, especially when the required extractions are complex, extensive or have a high risk of postoperative bleeding [36]. The French Working Group on Perioperative Hemostasis and the French Study Group on Thrombosis and Hemostasis suggests extended interruption of treatment prior to interventions with a high risk of bleeding. [30] (Table 4).

Table 4. Recommendations on the interval between last dose of direct or non-vitamin-K-dependent oral anticoagulant and intervention/procedure depending on bleeding risk and renal function* [30]

Renal function (CrCl mL/min)	Apixaban/edoxaban/rivaroxaban		Dabigatran	
	Low Bleeding risk	High bleeding risk	Low bleeding risk	High Bleeding risk
≥ 80	≥ 24 h	≥ 48 h	≥ 24 h	≥ 48 (–72*) h
50 - 79	≥ 24 h	≥ 48 (–72*) h	≥ 36 h	≥ 72 (–96*) h
30 - 49	≥ 24 h	≥ 48 (≥ 72–96*) h	≥ 48 h	≥ 96 h
15 - 29	≥ 36 h	≥ 48 (≥ 96*) h	No indication for DOACs!	
<15	No indication for DOACs!			

Pain control in the postoperative period

Concomitant treatment of NOA with NSAIDs may increase the risk of bleeding.

Paracetamol or opioid medications are safer alternatives for pain control. [18] Dabigatran acts as a substrate of P- glycoprotein 1 (P-gp 1), a significant protein of the cell membrane that pumps many foreign substances out of cells. The concomitant assumption of strong P-gp 1 inducers like dexamethasone, rifampicin or carbamazepine, has been reported to significantly decrease the plasma concentration and peak serum concentration of dabigatran. Hence, these drugs are not recommended in patients taking DTIs. The administration of Pgp 1 inhibitors like ketoconazole (and possibly itraconazole, erythromycin, clarithromycin) should be avoided [34].

DISCUSSION

Millions of people worldwide are taking haemostasis altering medications, and the need of teeth extraction requires a special approach. Routine practice in the past was the discontinuation of the therapy prior to dental extraction. Nowadays, discontinuation of oral antiplatelet and anticoagulant drugs is not recommended because the risk of severe thromboembolic complications outweighs the risk of bleeding. With the introduction of the new P2Y12 inhibitors (prasugrel, ticagrelor, cangrelor) and the direct oral anticoagulants (dabigatran, rivaroxaban, and apixaban) the dental practitioners are facing an obscure risk of bleeding during oral surgical procedures. In the existing literature, there are not yet a sufficient number of studies defining a clear protocol for dental management in concomitant use of these drugs.

In a review by Muñoz-Corcuera et al. the authors suggest that each case should be treated individually, taking into consideration the risk of embolism, bleeding and renal function [26]. Depending on the risk of bleeding, Curto et al. classified dental treatments in two groups: procedures with low and procedures with medium/high risks of bleeding [37]. Low-risk procedures include simple tooth extractions, oral surgery lasting less than 45 minutes and muco-gingival surgical procedures. The extraction of more than three teeth at once and oral surgery lasting more than 45 minutes were considered medium/high risk procedures. In this group, the instructions to stop DOACs should be consulted with the specialist physician. The authors suggest that for low risk procedures discontinuation of dabigatran is not necessary, and apixaban can be administered at a usual dose on the day, after the procedure [37].

CONCLUSION

Currently, available evidence suggests that most dental interventions can be safely performed without the interruption of the antithrombotic therapy. However, further studies are needed to establish evidence-based guidelines for the periprocedural antithrombotic management of patients receiving direct oral anticoagulants or novel antiplatelet agents.

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