



# Management of Patients Using Oral Anticoagulant Agent in Dental Practice

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## ABSTRACT

An increasing number of patients in our country use oral anticoagulants for the prophylaxis and treatment of thromboembolic events. The cornerstone of these groups of agents is warfarin, a vitamin K antagonist, which has been the single alternative used by oral route for several years. However, due to warfarin's late onset and long lasting action and the intense interactions with food and drugs, newer oral anticoagulants have emerged in the market in recent years. Dabigatran, rivaroxaban and apixaban are the novel agents used in our country.

Those drugs should be regulated in the perioperative period when patients receiving oral anticoagulants are referred for dental interventions. The interruption of agents may result in lethal consequences of thromboembolic events, while continuing raises the risk of bleeding. This review outlines the various properties of the oral anticoagulants and the most recent recommendations and guidelines regarding the management of dental patients taking these medications.

**Keywords:** Warfarin, dental approach, novel, bleeding risk, thromboembolism, dabigatran, rivaroxaban, apixaban

## Introduction

Oral anticoagulant agents are used for the treatment of arterial and venous thromboembolism (VTE) or prophylaxis. Patients using these agents frequently refer to clinics for dental interventions. Withdrawing oral anticoagulants during the perioperative period increases the risk of thromboembolism and maintenance of them is associated with the risk of bleeding. Dentists should consider the risk of thromboembolism and bleeding under the guidance of a cardiologist and choose the most appropriate option among discontinuation, continuation or bridging.

Heart valve prosthesis, atrial fibrillation (AF) and VTE/pulmonary embolism history are the most important risk factors for thromboembolism. Thrombophilia tendency and some systemic diseases also increase the risk of thromboembolism (Table 1).

The risk of bleeding (no risk of bleeding, low or high risk of bleeding) is also affected by factors such as hypertension, liver

and kidney failure, old age, predisposition to bleeding, and other drugs and alcohol use that increase bleeding

## Warfarin and Bridging

The prototype of oral anticoagulant agents is warfarin, which is an antagonist of vitamin K-dependent factors (FII, FVII, FIX, FX). The therapeutic effect of warfarin is monitored by prothrombin time and international normalized ratio (INR) (therapeutic level INR: 2.5-3.5±0.5). However, the effectiveness of the agent should be checked frequently, due to its interactions with food, differences of the patients in response to the drug and narrow therapeutic range of the drug (1,2).

Discontinuation of warfarin during the perioperative period is not preferred in terms of risk of thromboembolism. Warfarin is continued or replaced by another anticoagulant agent. "Bridging" means replacing an agent with another drug that has similar effects. Since warfarin has a long half-life, it is necessary

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**Received:** 10.10.2017  
**Accepted:** 03.11.2018

**Cite this article as:** Doganay Ö, Yücesoy T, Alkan A. Management of Patients Using Oral Anticoagulant Agent in Dental Practice. Bezmialem Science 2019;7(3):240-4.

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to interrupt taking warfarin 5 days prior to the preoperative period to reduce bleeding. Patients are exposed to the risk of thromboembolism in a large window as a result of slow reach to the therapeutic level when the drug is started again during the postoperative period. It is thought that discontinuation of warfarin for a while and bridging with another short- and fast-acting agent (heparin derivatives) is both protective and reduces the risk of bleeding. It is aimed to eliminate the effect of heparin in the morning of surgery by skipping the morning dose and to maintain thromboembolism prophylaxis after homeostasis is achieved in postoperative period by re-starting heparin. Bridging is recommended in patients with high thromboembolism risk who will undergo interventions with major bleeding risk. In patients with moderate risk of thrombosis, patient-based decisions are made by taking into account the risk of bleeding (3).

Warfarin is most commonly bridged by low molecular weight heparin (LMWH). Since this method is generally preferred in patients at high risk of thromboembolism, it is recommended that heparin be administered in a therapeutic dose (Enoxaparin 2x1mg/kg, therapeutic dose: 2x80 mg for a patient weighing 80 kg, Clexane 2x0.8 mL). In the bridging protocol, warfarin is stopped 5 days before the surgery and LMWH is initiated 3 days before the surgery. INR follow-up is required to maintain a value of 1.4 or lower before the surgery. Patients should continue with LMWH for 5-7 days after the onset of warfarin in the postoperative period, which is necessary to achieve therapeutic INR level. After the decision is made that there is no risk of bleeding, 48-72 hours after major surgeries, and 24 hours after minor surgeries, LMWH is initiated. Warfarin is also initiated with the dose used in preoperative period, with LMWH and when INR reaches therapeutic level (2-3), LMWH is stopped (3).

Recent studies show that bridging with LMWH does not affect the frequency of thromboembolism but increases bleeding dramatically (3-5). When all studies are evaluated together, the rate of perioperative bleeding is 13/1 with bridging and 5/1 without bridging (6). Although it is known that thromboembolic events may be more vital than bleeding, such a high risk of bleeding is also a major drawback.

Beyer-Westendorf et al. (7) reported that major surgery and bridging with LMWH were the factors that increased the risk of bleeding in perioperative period in the Dresden study on new generation oral anticoagulants (drugs were continued, stopped or bridged with LMWH). Douketis et al. (8) stopped warfarin in patients with AF with low risk of thromboembolism and treated one group with placebo and treated other group with 100 IU/kg dalteparin bridging treatment. The incidence of thromboembolism was found to be 0.3% and 0.4% in the groups, while the incidence of major and minor bleeding was significantly higher in the bridging group with dalteparin (8). The most common reason for the increase in bleeding with bridging was early onset of LMWH in postoperative period and not skipping the evening dose of LMWH which was given in therapeutic doses (2x1), in preoperative period (3).

### New Generation Oral Anticoagulant Agents

In recent years, new-generation oral anticoagulant agents (NOACs), which are fast acting, have short half-life, have less drug and food interaction, have more predictable effects and do not need to be followed by laboratory tests, have been introduced. These are dabigatran, a direct thrombin inhibitor (Pradaxa, Boehringer Ingelheim, İstanbul, Turkey); rivaroxaban, a factor Xa inhibitor (Xarelto, Bayer, İstanbul, Turkey); and apixaban, a factor Xa inhibitor (Eliquis, Bristol Myers Squibb, İstanbul, Turkey). Features of NOACs are summarized in Table 2 (9-12).

**Dabigatran (Pradaxa):** It is a thrombin inhibitor and is often used in a dose of 2x150 mg. Thrombin time (TT) and ecarin clotting time (ECT) are tests that measure the efficacy of dabigatran, and minimal prolongation is observed in activated partial thromboplastin time (aPTT). In the case of renal failure, its effect is prolonged and dose adjustment is required, since it is excreted from the kidney.

**Rivaroxaban (Xarelto):** It is a factor Xa inhibitor and is often used in a dose of 1x15-20 mg. Its efficacy is measured with anti-factor Xa level.

**Table 1.** Classification of thromboembolism risk

Risk	Mechanical valve	Atrial fibrillation	Venous thromboembolism
<b>High</b>	Mitral valve prosthesis Caged ball, tilting-disk aortic valve prosthesis CVA/TIA <6 months	CHADS <sub>2</sub> score 5-6 CVA/TIA <3 months Rheumatic valvular disease	VTE <3 months Severe thrombophilia (+)
<b>Moderate</b>	Aortic valve bioprosthesis and other risk factors (*)	CHADS <sub>2</sub> score 3-4	VTE 3-12 months Recurrent VTE Active cancer Mild thrombophilia
<b>Low</b>	Aortic valve bioprosthesis	CHADS <sub>2</sub> score 1-2 No history of CVA/TIA	VTE >12 months without other risk factors

CVA: Cerebrovascular accident, TIA: Transient ischemic attack, CHADS<sub>2</sub> score: A scoring scale to determine thromboembolism risk in atrial fibrillation. (C: Congestive heart failure, H: Hypertension, A: Age>75 years, D: Diabetes mellitus, S:Stroke-2 points), (\*) Other risk factors: Congestive heart failure, hypertension, age>75 years, diabetes mellitus, AF, history of CVA/TIA, (+) Severe thrombophilia: Protein C and Protein S deficiency, antithrombin, anti-phospholipid antibodies, (&) Hafif trombofili: Heterozigot faktör V Leiden, protrombin gen mutasyonu, VTE: Venous thromboembolism

**Apixaban (Eliquis):** It is a factor Xa inhibitor and is often used in a dose of 2x5 mg. Its efficacy is measured with anti-factor Xa level.

The most important disadvantage of NOACs is the problem faced in reversing their effects. While the effect of warfarin can be eliminated with proper doses of vitamin K and fresh frozen plasma infusion, idarucizumab which is the antidote of dabigatran, a NOAC, is not available in our country. Prothrombin complex concentrate is recommended for bleeding due to these agents (10).

**Dental Management in Patients Using Oral Anticoagulants**

Dentists should determine the treatment approach by evaluating the risk of bleeding in dental interventions in patients using oral anticoagulants perioperatively. The risk of bleeding in dental procedures is classified in different ways in different sources (1,2,13,14). Table 3 shows the classification of bleeding risk according to the guidelines of the Scottish Dental Clinical Effectiveness Programme (SDCEP) (1).

When the literature is examined, there are highly reliable studies searching the use of warfarin in dental interventions, but there are no evidence-based data for NOAC use. However, most

studies support the idea of continuing anticoagulant treatment in patients undergoing outpatient dental surgery, including tooth extraction (15,16)

Dental interventions are usually evaluated in the group of operations with minor bleeding risk and in patients with INR level below 4, it is recommended to continue warfarin (1,2,11,15-20). In patients with stable INR levels, the INR level obtained in the last 72 hours may be acceptable, but in patients with labil INR levels, the INR level obtained in the last 24 hours should be evaluated. If the patient’s INR level is 4 or higher, the patient should be consulted to his/her physician and dental treatments should be postponed until the INR level falls below 4. For emergency treatment, the patient should be directed to an upper level dental treatment center.

Broekema et al. reported that dental procedures can be performed in patients using warfarin with INR level of 3.5 or lower (checked in the last 24 hours) without discontinuing treatment (20). These operations include simultaneous extraction of no more than 3 teeth, surgical removal of buried teeth, periodontal treatment, apical resection, abscess drainage or dentoalveolar surgery performed by placing up to 3 implants. It is recommended that the operations be performed atraumatically, that the

**Table 2.** Features of new generation oral anticoagulant agents

	Dabigatran	Rivaroxaban	Apixaban
Implementation	PO, 2x1	PO, 1x1	PO, 2x1
Peak affect	1-3 h	2-4 h	1-3 h
Half-life	12-14 h	5-13 h	8-15 h
Elimination	80% renal, 20% feces	65% renal, 35% hepatic	25% renal, 70% hepatic
PT	+/-	+/-	+/-
aPTT	+/-	+/-	+/-
TT	+++	-	-
Anti-Xa level	-	+++	+++
Antagonization	Idarucizumab	4 PCCs (Cofact)	4 PCCs (Cofact)

PT: Prothrombin time, aPTT: Activated partial thromboplastin time, TT: Thrombin time, PCC: Prothrombin complex concntrate

**Table 3.** Risk of postoperative bleeding in dental interventions

Dental interventions that are not expected to cause bleeding	Dental interventions that may cause bleeding	
	Bleeding complication with low risk	Bleeding complication with high risk
Local anesthesia (infiltration, intraligamentar, mental nerve block, inferior dental block or other regional nerve block)	Simple extractions (1-3 teeth) Incision and intraoral drainage Root surface straightening and subgingival curettage Direct or indirect restorations in the subgingival margin	Complicated extractions (large wound surface or extraction of more than 3 teeth)
Basic periodontal examination		Interventions with flap removal:
Removal of supragingival plaque, stone and discoloration		-Elective surgical teeth extraction
Direct or indirect restorations in supragingival margin		-Periodontal surgery
Endodontic interventions		-Preprosthetic surgery
Prosthetic interventions		-Periradicular surgery
Ortodontic interventions		-Surgical crown lengthening
		-Dental implant surgery
		-Gingival contouring
		biopsy

suction socket is sutured close to the mouth, that the patient is discharged after the bleeding is stopped and information is given and that the mouth is rinsed with 5% tranexamic acid during the postoperative 5 days (20).

Recommendations on the use of new generation oral anticoagulants are based on clinical experience, pharmacodynamics, and expert opinions. According to the SDCEP (1), in patients taking NOACs with low risk of bleeding, dental treatment should be performed without discontinuation of the drug. Many national guidelines and reviews including expert opinions recommend that many attempts at dentistry should be made without discontinuing NOACs (2,9-11,17-19,21-23). In this group of patients using NOACs, it is emphasized that there is no place to bridge with LMWH during the perioperative period (18,19,24).

New-generation oral anticoagulant drugs are generally preferred in patients with lower risk of thrombosis (such as non-valvular AF), so they can be discontinued when there is a need for more major surgery. Dabigatran and apixaban are stopped 12 hours before, whereas rivaroxaban is stopped 24 hours before a dental intervention with high risk of bleeding by skipping the dose on the morning of the intervention. Rivaroxaban should be started four hours after the bleeding is under control and dabigatran and apixaban could be initiated by giving the evening dose (25).

## Conclusion

In conclusion, it is observed that there is no need to bridge with LMWH routinely in perioperative period in patients who are currently using oral anticoagulants and who will undergo dental intervention. In line with this data, we believe that a large number of dental interventions can be performed using local hemostatic precautions without stopping oral anticoagulants and warfarin.

## Authorship Contributions

Concept: A.A., Ö.D., Design: Ö.D., T.Y., Literature Search: T.Y., Writing: Ö.D.

**Peer-review:** Externally peer-reviewed.

**Conflict of Interest:** No conflict of interest was declared by the authors.

**Financial Disclosure:** The authors declared that this study received no financial support.

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