# NEW ORAL ANTICOAGULANTS – THE NEWEST UPDATE IN DENTAL SURGERY

**Dimova Cena*, Kovacevska Ivona*, Angelovska Bistra****
*"Goce Delcev" University – 2000 Stip, R. Macedonia, Faculty of medical sciences,*
**- General Dentistry, **- Pharmacy, email: cena.dimova@ugd.edu.mk*

## ABSTRACT

Aim of this study is to review the evidence of different therapy approach, to highlight the areas of major concern, and to suggest specific oral surgery treatment for patients on new oral anticoagulants.

A Medline and an extensive hand search were performed on English-language publications beginning in 1971 till now. The pertinent literature and clinical protocols of hospital dentistry departments have been extensively reviewed, presented and discussed.

Several evolving clinical practices in the last years have been detected: anticoagulants are generally not discontinued; oral surgery is performed despite laboratory values showing significant bleeding tendency; new effective local hemostatic modalities are used to prevent bleeding; Patients at risk are referred to hospital-based clinics.

The management of oral surgery procedures on patients treated with new anticoagulants should be influenced by several factors: laboratory values, extent and urgency of the intervention, treating physician's recommendation, available facilities, dentist expertise, and patient's oral, medical, and general condition.

***Key words:*** *oral surgery, oral anticoagulants, low-molecular heparin, bleeding.*

## Introduction

Thrombosis is the formation, from the components of blood, of an abnormal mass within the vascular system. It involves the interaction of vascular, cellular, and humoral factors within a flowing stream of blood. Thrombosis and the complicating emboli that can result are among the most important causes of sickness and death in developed countries. Thrombosis is of greater overall clinical importance in terms of morbidity and mortality than all of the hemorrhagic disorders combined. Excessive activation of coagulation or inhibition of anticoagulant mechanisms may result in hypercoagulability and thrombosis. Injury to the vessel wall, alterations in blood flow, and changes in the composition of blood are major factors leading to thrombosis [7].

The dentist today is seeing increased numbers of patients with chronic medical illnesses. Among these patients are those that are being treated with anticoagulant drugs or antiplatelet agents to prevent venous or arterial thrombosis. A major concern in the management of dental patients taking antithrombotic agents is the potential for excessive bleeding after invasive dental procedures [5]. The pathologic basis for arterial thrombosis involves atherosclerotic vascular disease associated with platelet thrombi. Thrombin is a major mediator in this type of thrombosis. Drug therapy for arterial thrombi involves agents with antithrombin and antiplatelet activity. Venous thrombi usually occur in the presence of a normal vessel wall, with stasis or hypercoagulability being the major predisposing factors. Drugs that prevent thrombin formation or lyse fibrin clots are the major agents used to treat venous thrombi.

Aim of this study is to review the evidence of different therapy approach, to highlight the areas of major concern, and to suggest specific oral surgery treatment for patients on new oral anticoagulants.

A Medline and an extensive hand search were performed on English-language publications beginning in 1971 till now. The pertinent literature and clinical protocols of hospital dentistry departments have been extensively reviewed, presented and discussed.

**Oral anticoagulants – withdraw or continuing**

The term oral anticoagulant (OAC) refers to oral vitamin K antagonists, including mainly sodium warfarin (the most widely used agent in Anglo-Saxon countries) and acenocoumarol (widely used in some countries of Europe) [11].

Oral anticoagulants are a group of drugs used to treat many cardiovascular diseases, such as in the prophylaxis of systemic embolism (whose risk is increased in patients with atrial fibrillation or have undergone orthopaedic surgery). The vitamin K antagonists, among which are warfarin and acenocoumarol, have low therapeutic index as its pharmacological management is difficult and need continuous monitoring, also have multiple interactions with other drugs and food. Many of the patients being treated with warfarin have an inadequate anticoagulation [2].

The oral and maxillofacial surgeons are frequently asked to manage patients who are receiving oral anticoagulants. The goal of treatment is to minimize the risk of hemorrhage while continuing to protect the patient against thromboembolism formation. The ordinary treatment includes the interruption of anticoagulant therapy for oral surgery interventions to prevent hemorrhage. However, this practice may logically increase the risk of a potentially life-threatening thromboembolism. Thus, this issue is still controversial [5].

Assael [3] said that the hemostasis care of the oral anticoagulated patients is a shared responsibility and oral and maxillofacial surgeons, and the hematology/coagulation team huddle to determine the steps.

**New oral anticoagulants**

New oral anticoagulants, with distinctly different mechanisms of action, are poised to replace the VKAs and have the potential to dramatically change the way we manage patients at risk for venous and arterial thromboembolic disease. In contrast to the vitamin K antagonist (VKAs), which target an enzyme in the vitamin K pathway that leads to the reduction of the functional levels of factors II, VII, IX, and X, many of the new agents rely on targeting a particular coagulation factor and directly inhibiting it.

Figure 1 identifies a number of new agents and their target factor. This discussion will focus on three such agents that are most advanced in development and likely to be the first to reach market in the United States.

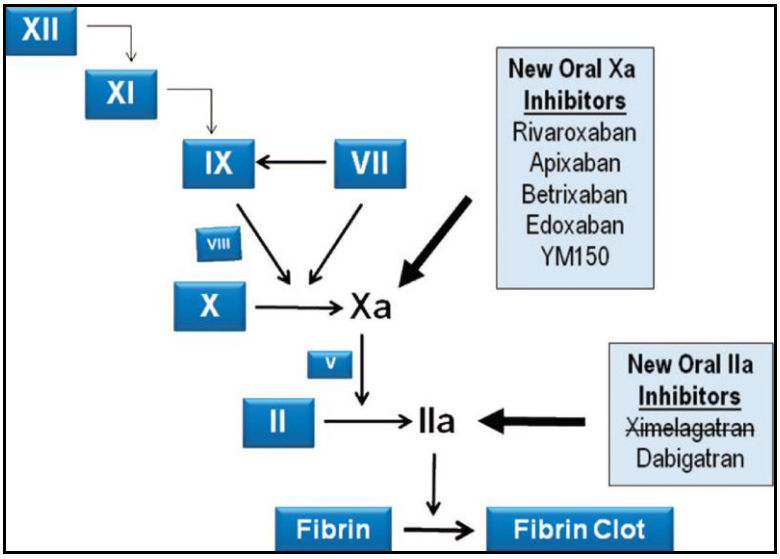


**Figure 1.** New oral anticoagulants under development that target factor IIa and factor Xa. (Adapted from reference 1)

Several evolving clinical practices in the last years have been detected: anticoagulants are generally not discontinued; oral surgery is performed despite laboratory values showing significant bleeding tendency; new effective local hemostatic modalities are used to prevent bleeding; Patients at risk are referred to hospital-based clinics [1].

The patient on Pradaxa® (Dabigatran) may need interruption of therapy for dental work, a medical procedure such as colonoscopy, or minor or major surgical procedure. As to when exactly to take the last dose of Pradaxa® before the procedure depends on (a) what type of procedure is planned and how much bleeding to expect with it, and (b) whether the patient is at high or low risk for thrombosis if he/she is off anticoagulants for some period of time [4].

***Table 1. Pharmacologic Features of Dabigatran Etexilate, Rivaroxaban, and Apixaban***

| | Dabigatran Etexilate | Apixaban | Rivaroxaban |
|---|---|---|---|
| Target | Thrombin | Factor Xa | Factor Xa |
| Prodrug | Yes | No | No |
| Dosing | Fixed, once daily | Fixed, twice daily | Fixed, once daily |
| Bioavailability (%) | 6 | 50 | 80 |
| Monitoring | No | No | No |
| Half-life (h) | 12-14* | 12.7 | 7-11 |
| Renal clearance (%) | 80 | 25 | 65 |
| Interactions | P-gp inhibitors** | Potent CYP3A4 inhibitors† | Combined P-gp inhibitors + CYP3A4 inhibitors† |

*In healthy volunteers, 14-17 hours in patients undergoing major orthopaedic surgery.
**P-glycoprotein (P-gp) inhibitors include verapamil, clarithromycin, and quinidine.
Quinidine is contraindicated in patients receiving dabigatran.
†Cytochrome P450 (CYP) 3A4 inhibitors include ketoconazole, macrolide antibiotics, and protease inhibitors.

Dabigatran eteksilate **(**Pradaxa) with ATS cod B01AE07 (classification - antithrombotic) Boehringer Ingelheim (caps. 75mg и 110 mg) is registered in Macedonia, Serbia and Bulgaria. Rivaroxaban is not registered in the region.

***Table2. Guide to the discontinuation of Pradaxa® before procedures or surgeries*** (adapted from reference 2)

| **Renal Function** (CrCL mL/min) | **Half-life (hours), mean (range)** | **Timing of Discontinuation Prior to Procedure (Minimum)** | |
|---|---|---|---|
| | | **Standard Risk of Bleeding** | **High Risk of Bleeding*** |
| > 80 | 13 (11 – 22) | 24 hours | 2 – 4 days |
| 50 – 80 | 15 (12 – 34) | 24 hours | 2 – 4 days |
| 30 – 50 | 18 (13 – 23) | > 48 hours | > 4 days |
| < 30 | 27 (22 – 35) | 48 – 120 hours | > 5 days |

* Examples: heart surgery, neurosurgery (brain, spinal cord, nerves), abdominal or surgery involving major organs; or procedures requiring guaranteed no bleeding (i.e., spinal anesthesia), or when additional risk factors for bleeding are present (low blood platelets, bleeding disorder, previous major bleeding, etc.).

**Dental Procedures and Bridging Therapy**

Depending on the existing thromboembolic risk, the American Heart Association / American College of Cardiology Foundation Guide to Warfarin Therapy recommends different heparin management regimens for the patients with moderate, high and low thromboembolic risk. In

general, heparins are not reintroduced before 12 hours post-surgery and dosing is postponed for longer periods in the case of evidence of bleeding [9].

Most patients treated with standard heparin are hospitalized and will be placed on warfarin once discharged. Dental emergencies in these hospitalized patients should be treated as conservatively as possible, avoiding invasive procedures. Consultation with the patient's physician is recommended. In contrast, patients undergoing hemodialysis are administered heparin in an outpatient setting. Since the half-life of heparin is only 1 to 2 hours,1 these patients can safely receive invasive dental treatment.the day after dialysis.

Alternatively, the attending physician may give permission for hemodialysis to be performed without heparin when major surgical procedures are required on the day of dialysis.

Many dental procedures can be done on full dose anticoagulation. Detailed recommendations as to which dental procedures can be done on full dose anticoagulation (teeth cleaning, root canal, one or two teeth extractions) and for which the anticoagulant level needs to be reduced have been published. A similar approach can likely be taken in patients on Pradaxa®. However, it is also easy to tell the patient not to take his/her evening dose of Pradaxa® on the day before the procedure and not to take the morning dose on the day of the dental procedure; and then to restart the evening of the day of the procedure. However, individualized recommendations need to be given [8, 10].

A review by Wahl [12] found little to no risk of significant bleeding following dental surgical procedures in patients with a PT of 1.5 to 2 times normal. Wahl [12] also reported evidence that there was little risk of bleeding complications even if the PT is up to 2.5 times normal, and a greater risk of adverse outcome is associated with stopping anticoagulation.

Life threatening or major bleeding in patients who need high-risk surgery is avoided by stopping oral anticoagulants with or without bridging therapy. The Food and Drug Administration has not approved bridging therapy with LMWH in patients with prosthetic heart valves, and UFH is frequently recommended for bridging therapy in these high-risk patients who develop arterial thromboembolism.

Bridging with UFH or LMWH is done to shorten the interval of sub therapeutic anticoagulation while waiting for the reversal of oral anticoagulation. For patients with a low risk of thromboembolism, bridging is not recommended because the efficacy of bridging with UFH and LMWH does not outweigh the risk of postoperative bleeding [6]. During the past 20 years, the approval of anticoagulants such as low-molecular-weight heparins (LMWHs), indirect factor Xa inhibitors and direct thrombin inhibitors has signaled a growing interest in antithrombotic compounds that have relatively discrete targets within the coagulation pathway.

Patients with a low risk of thromboembolism can stop the oral anticoagulant and restart it after the surgery. Stopping oral anticoagulant and bridging is not recommended for procedures for which major bleeding is not likely to develop.

**Conclusion**

The currently available anticoagulant agents all target thrombin or FXa, either indirectly or directly. Thrombin is a logical target because of its multiple roles in coagulation.

The management of oral surgery procedures on patients treated with new anticoagulants should be influenced by several factors: laboratory values, extent and urgency of the intervention, treating physician's recommendation, available facilities, dentist expertise, and patient's oral, medical, and general condition.

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