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# Traditional Versus New Oral Anticoagulants in Clinical Practice of Oral Surgery.

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**ABSTRACT**

The oral surgeons are frequently asked to manage patients who are receiving oral anticoagulants. The aim 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 before oral surgery interventions to prevent hemorrhage. 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 extensive hand search were performed on English-language publications beginning in 1960 till now. 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. It is too early to make comments on how to choose among the different new anticoagulants, not only because no head-to-head comparative study has been yet performed, but also because the currently available data are insufficient to make a meaningful choice possible.

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

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## INTRODUCTION

Arterial and venous thrombo embolism is still the most frequent cause of morbidity and mortality in high- and middle-income countries, as well as in emerging economies. 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 [1].

The dentist today is seeing increased numbers ofpatients with chronic medical illnesses. Among thesepatients are those that are being treated with anticoagulantdrugs or antiplatelet agents to prevent venous orarterial thrombosis. A major concern in the managementof dental patients taking antithrombotic agents isthe potential for excessive bleeding after invasivedental procedures [2].The pathologic basis of arterial thrombosis involvesatherosclerotic vascular disease associated withplatelet thrombi. Thrombin is a major mediator in thistype of thrombosis. Drug therapyof arterial thrombiinvolves agents with antithrombin and antiplateletactivity. Venous thrombi usually occur in the presenceof a normal vessel wall, with stasis or hypercoagulabilitybeing the major predisposing factors. Drugs thatprevent thrombin formation or lyse fibrin clots are themajor agents used in the treatment of 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 1960 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) [3]. Oral anticoagulants are the group of drugs used to treatmany cardiovascular diseases. The vitamin K antagonists, among whichare warfarin and acenocoumarol, have low therapeuticindex as its pharmacological management is difficultand need continuous monitoring, also have multipleinteractions with other drugs and food. Many of thepatients being treated with warfarin have an inadequateanticoagulation [4]. 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. Thus, this issue is still controversial [5-7].

The anticoagulant effect in turn depends on the half-life of the inhibited factors. In this sense, the half-lives of factors VII, IX, X and II are 6, 24, 40 and 60 hours, respectively. Blood coagulation factor VII is the first to be affected, prolonging prothrombin time (PT). Factors IX, X and II are posterior affected: factor IX prolongs activated partial thromboplastin time (aPTT), while factors X and II prolong both PT and aPTT. These are well tolerated drugs, with rapid absorption via the oral route. The peak plasma concentrations are reached one hour after administration, though the reduction in coagulation factors takes place 48-72 hours after dosing. The half-life of warfarin is 48-72 hours, versus 8-10 hours in the case of acenocoumarol. Thus, the effects of warfarin are longer lasting in terms of both the induction and disappearance of therapeutic action [3, 8-10].

However, patients who interrupt oral anticoagulants therapy are at risk of developing a thromboembolism with or without bridging therapy. On the other hand, oral anticoagulants therapy can be continued without interruption for procedures such as dentoalveolar surgeries that rarely cause significant or life-threatening bleeding. Stopping oral anticoagulants is problematic because of its slow unpredictable reversal [2, 11-14].

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**Interruption of Oral Anticoagulant Therapy, Risk of Thrombotic Episode and Limitations of Traditional Anticoagulants**

The risk for thromboembolism depends on several factors, including the clinical indications for anticoagulation. Anticoagulation is required in the management of patients with prosthetic heart valves, chronic atrial fibrillation, hypercoagulable states (ie, protein C deficiency, protein S deficiency, factor V Leiden mutation, antithrombin III deficiency, antiphospholipid-antibody syndrome), venous or arterial thromboembolism, and cerebrovascular disease with strokes. However, patients who require anticoagulation do not have equal risk of developing thromboembolism [9,14,15].

The goal of managing anticoagulated patients who need surgery is to prevent major or life-threatening bleeding while protecting against thromboembolism. Some procedures such as intra-abdominal, intrathoracic, major cancer surgery, removal of head and neck tumors, and extra oral open reduction of facial fractures are associated with considerable bleeding [9, 16,17].

Some patients are particularly sensitive to OACs, and the activity of these drugs moreover can be affected by a range of factors including individual patient response, diet, or the simultaneous administration of other commonly used drugs such as antibiotics, analgesics, or even herbal remedies. As a result, regular monitoring is required, and such control must be more frequent when changes occur in any of the aforementioned aspects. OAC action is monitored on the basis of the effect of such drugs on prothrombin time (PT), i.e., the time required for the clotting of citrate-treated plasma, after adding calcium and thromboplastin. Thromboplastin is extracted from different tissues with different levels of sensitivity - a fact that complicates the comparison of PT test results. The PT results are usually reported as the ratio patient time / control time. The simple ratio is extremely variable, depending on the sensitivity of the reagent used - thus making it impossible to establish universally applicable therapeutic margins [18].

For this reason, in 1978 the World Health Organization (WHO) recommended PT standardization, and in 1983 it introduced the INR (international normalized ratio), which is calculated by raising the simple ratio tothe international sensitivity index (ISI) of the thromboplastin used [19]. Thus, INR = (patient time / control time) ISI.

This is the formula used to standardize PT, allowing comparison regardless of the thromboplastin used by the different laboratories, and ensuring increased reliability in monitoring OAC treatment. At the same time, the different international societies established recommendations regarding the therapeutic anticoagulation levels to be maintained according to the existing patient pathology - the corresponding INR value ranging from 2 to 3.5. Because of that there is a strong correlation between INR and bleeding risk - the latter increasing when INR >4 (Table 1).

**Table 1: Therapeutic anticoagulation levels**

| Clinical pathology INR | INR |
|---|---|
| - Prophylaxis – venous thromboembolism (high risk surgery) | 2.0-3.0 |
| - Prophylaxis – venous thromboembolism (hip surgery) | 2.0-3.0 |
| - Treatment of deep venous thrombosis or pulmonary embolism | 2.0-3.0 |
| - Prevention of systemic embolism in patients with atrial fibrillation, heart valve disease, bio prostheses, or acute myocardial infarction | 2.0-3.0 |
| - Valve prostheses, recurrent systemic embolism, recurrent myocardial Infarction | 2.5-3.5 |

INR = International Normalized Ratio

The recommendations vary according to the bleeding risk of the surgical intervention and the indication of anticoagulation therapy (i.e., the thromboembolic risk of the patient). Thus, for example, treatment to prevent venous thromboembolism is not the same as treatment for dealing with an acute thrombotic episode.

Although consensus is lacking, the expert groups [18] do establish a series of recommendations:

- For patients at low risk of bleeding after the operation, anticoagulation can be maintained at the lower limit of the therapeutic range (INR = 2.0).
- For patients at high bleeding risk, anticoagulation should be maintained at sub therapeutic levels (INR = 1.5).

Accordingly, acenocoumarol should be suspended 3-4 days before surgery (4-5 days in the case of warfarin). On day -3, low molecular weight heparin (LMWH) should be provided at therapeutic, medium or prophylactic doses, depending on whether the thrombotic risk of the patient is high, moderate or low, respectively. This is to be maintained until 12 hours before surgery, followed 12 hours after surgery be reintroduction of the original treatment, provided there is no bleeding.

In spite of the excellent clinical results obtained with traditional anticoagulants, there is much space for improvement in clinical practice in terms of their clinical applicability, safety, and efficacy. The comparative advantages and disadvantages of traditional anticoagulants, and the corresponding clinical consequences, are summarized in Table 2.

**Table 2: Comparative advantages and disadvantages of traditional anticoagulant and corresponding clinical consequences**

| Comparative advantage or disadvantage | Consequence |
|---|---|
| **LMWH versus UH:** | |
| Better bioavailability | Subcutaneous administration |
| Less binding to endothelium | Longer half-life, which permits once-daily administration |
| Less binding to plasma proteins | More predictable anticoagulant response, which obviates need for monitoring |
| Less binding to platelet factor 4 | Lower risk of thrombocytopenia |
| Less binding to bone cells | Lower risk of osteoporosis |
| Protamine sulphate less effective as antidote | Less rapid reversal in case of overdose and/or bleeding complications |
| **Fondaparinux versus LMWH :** | |
| Improved safety lower risk of thrombocytopenia and osteoporosis | No risk of biological contamination; |
| Defined target | Single target (factor Xa) versus multiple targets |
| Less potent inhibition of factor Xa than heparin | Risk of catheter thrombosis in acute coronary syndromes, unless supplemental heparin is administered |
| **Vitamin K antagonists versus LMWH and fondaparinux:** | |
| Oral administration | Easier outpatient treatment |
| Interaction with food, drugs and genetic polymorphisms | Need of regular laboratory control for dose adjustment |
| Longer plasma half-life | Less rapid reversal in case of overdose and/or bleeding complication |

**New oral anticoagulants versus traditional**

New oral anticoagulants, with distinctly different mechanisms ofaction, are poised to replace the vitamin K antagonist (VKAs) and have the potential todramatically change the way we manage patients at risk for venousand arterial thromboembolic disease.

In contrast to the 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, manyof the new agents rely on targeting a particular coagulation factorand directly inhibiting it (Table 3)[20].The new oral anticoagulants include dabigatran etexilate, which inhibits thrombin, and rivaroxaban, apixaban, and edoxaban, which inhibit factor Xa.

Although the Non-vitamin K antagonist oral anticoagulants (NOACs) are relatively novel and new at present, they will not remain so forever [21]. Consequently, several alternative names have been proposed for these drugs, as follows [22]:

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- Target-Specific Oral anticoagulants (TSOCs),
- Direct Oral AntiCoagulants (DOACs),
- Oral Direct Inhibitors (ODIs),
- Non-monitored Oral AntiCoagulants (NOACs),
- Non-warfarin Oral AntiCoagulants (NOACs),
- Non- vitamin K antagonist Oral AntiCoagulants (NOACs), etc.

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 [23,24].

**Table 3: Pharmacologic Features and Guide for New Anticoagulants**

| **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 |
| **Guide to the discontinuation of Pradaxa® before procedures or surgeries** | | | |
| **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 |

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 [25-27].

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 [25].

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

**Interruption and Limitations of Oral Anticoagulants**

The risk for thromboembolism depends on several factors, including the clinical indications for anticoagulation: prosthetic heart valves, chronic atrial fibrillation, hypercoagulable states venous or arterial thromboembolism, and cerebrovascular disease with strokes. However, patients who require anticoagulation do not have equal risk of developing thromboembolism [9, 14, 15].

Some procedures such as intra-abdominal, intrathoracic, major cancer surgery, removal of head and neck tumors, and extra oral open reduction of facial fractures are associated with considerable bleeding [9, 16, 17].

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**Dental Procedures and Bridging Therapy**

Depending on the existing thromboembolic risk, the American Heart Association 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 [28-30].

Assael [23] 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. A common approach to managing patients with a low risk of thromboembolism needing surgery is to interrupt oral anticoagulants therapy for several days before and after surgery. Patients with a high risk of thromboembolism commonly stop OA and bridge anticoagulation with unfractionated heparin (UHF) or low-molecular-weight heparin (LMWH) [8].

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 [31,32,33].

A review by Wahl [32] found little to no risk of significantbleeding following dental surgical procedures inpatients with a PT of 1.5 to 2 times normal. Wahl [32] 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 [34-37].

**Oral Surgery Procedures and management of bleeding**

Management of oral surgery procedures on patients treated with 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 and atibiotic profilaxis.Procedures including single and multiple dental extractions, full mouth extractions, and alveolectomies are associated with very few bleeding episodes in patients who continue oral anticoagulants.

In Sindet–Pedersen's original article [35] anti-coagulant-treated patients undergoing oral surgery were prescribed a 4.8% aqueous solution of tranexamic acid for seven days post-surgery to prevent re-bleeding secondary to fibrinolysis of the wound clot. The results of the most scientific studies confirm that anticoagulation treatment with warfarin need not be withdrawn prior to dental extractions, provided that the patients do not have a preoperative INR value greater than 4.0, and local measures including antifibrinolytic therapy is instituted [26, 38-40].

Wahl [32] published a review of perioperative management of patients receiving oral anticoagulants in 1998. He summarized the outcome of 2,014 dental surgical procedures in patients who continued oral anticoagulation. Serious bleeding occurred in only 12 of the procedures, and 5 of the 12 bleeds were associated with INRs above therapeutic levels. Wahl [32] also examined reports including 493 patients who discontinued warfarin; 5 of these patients developed serious thromboembolic complication, resulting in 4 deaths.

Martinowitz et al. [41] followed 40 patients having 63 teeth removed without altering the oral anticoagulation. Local hemostasis was obtained using a biological adhesive after placing thrombin soaked gauze into the socket for 3 minutes. Recently, some authors [17, 32-34] have recommended that most anticoagulated patients are capable of withstanding routine, limited, oral surgery procedures without additional medical intervention such as an antifibrinolytic mouthwash provided a good surgical technique is employed. A 4.8% tranexamic acid mouthwash is effective in controlling local hemostasis in anticoagulated patients undergoing dental extractions.

In 2003, Carter et al. [38, 39] conducted a randomized study in patients under oral anticoagulation and subjected to extractions without modifying the OAC regimen, and applying two types of hemostatic agents (4.8% tranexamic acid and autologous fibrin adhesive). The authors concluded that both approaches are effective and safe in controlling post-extraction bleeding.

Autologous fibrin adhesive applied to the socket walls in turn was recommended when the patient has difficulties performing rinses correctly [38]. Posterior studies reported the same efficacy in controlling hemostasis by applying rinses for only two days. Tranexamic acid has no marketing license in some countries, and fibrin adhesives are not recommended by all authors, due to the risk of disease transmission - though such systems are subjected to viral inactivation processes - and their high cost.

Post-extraction bleeding is generally controlled by local measures such as socket curettage, suturing, and local compression, thanks to easy access to the bleeding zone [42,43].

When such measures prove insufficient, and the anticoagulation effect must be suppressed, this can be done by administering vitamin K. In this sense, intravenous administration elicits faster effects than the oral route – the recommended dose being 5-10mg. The use of concentrates of prothrombin complex or fresh frozen plasma is reserved for cases of important bleeding.

## 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. 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. It is too early to make comments on how to choose among the different new anticoagulants, because the currently available data are insufficient to make a meaningful choice possible.

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