# DIFFERENCES BETWEEN WARFARIN AND NEW ORAL ANTICOAGULANTS IN DENTAL CLINICAL PRACTICE

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**SUMMARY**

The oral anticoagulant therapy is used for the cure and the prevention of thromboembolic diseases. In the last fifty years the warfarin has been considered the oral anticoagulant of choice. However, its use is limited by a narrow therapeutic index and by a complex pharmacodynamics, which requires regular adjustments and monitoring of the dose. Recently, three new oral anticoagulant – dabigatran etexilato (direct thrombin inhibitor), rivaroxaban and apixaban (Xa factor direct inhibitor) – have been approved for use in Europe. Increasing the number of patients taking these drugs, it is important that the dentist knows these new oral anticoagulants, their indications and methods of action, in particular for the management of patients, who require invasive treatments. With regard to the management of the patient threated with the new oral anticoagulants (NAO), there have been new significant changes in the procedure compared to the one followed by patients treated with warfarin. This led to the development of new guidelines that the dentist has to follow in order to ensure a safe and appropriate dental treatment and reduce any postoperative complications. The aim of this work is to evaluate the effectiveness of the new oral anticoagulants compared to warfarin, especially in terms of risks of bleeding events and intra and postoperative complications, in patients requiring multiple dental extractions.

**Key words:** new oral anticoagulants, oral surgery.

## Introduction

The oral anticoagulant therapy finds its application in various pathological conditions and for different indications: pulmonary embolism, atrial fibrillation, venous thrombosis cardiac and rheumatic valve, myocardial infarction, transient ischemic attacks and strokes. For over fifty years the vitamin K antagonists, such as warfarin have been considered the treatment of choice for the prevention and the treatment of the thromboembolic diseases. This drug, however, having a narrow therapeutic index, poses different problems, such as the necessity to frequently change the dose, continuously monitor the coagulation status of the patients, as well as multiple drugs and foods interactions. Patients who use it, are, therefore, forced to frequent laboratory controls, to dietary restrictions and to risks when they are subjected to other drug treatments. Recently three new oral anticoagulants have been approved in North America and Europe: dabigatran etexilato (direct thrombin inhibitor), rivaroxaban e apixaban (direct Xa factor inhibitor). In Europe, they are used for the primary and short-term prevention of venous thromboembolic events in adult patients who have undergone elective surgery of the hip or the knee; for the prevention of stroke and of systemic embolism in adult patients with non-valvular atrial fibrillation with one or more additional risk factors.

These new molecules are capable of acting selectively and specifically on the individual components of the coagulative cascade, in

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particular the dabigran directly inhibits thrombin, while apixaban and rivaroxaban directly inhibit the Xa factor, thereby providing a more predictable coagulating effect. The new oral anticoagulant drugs, due to their short biological half-life and to their rapid anticoagulant effect have several advantages compared to the AVK: they are characterized by the predictability of response, they do not require a constant monitoring of the coagulation, they are administered at fixed doses-facilitating adherence to therapy, they show minimal drugs interactions, they are characterized by the absence of food interactions and a wide therapeutic margin.

However, together with the enormous benefits described above, the new oral anticoagulant limits should also be emphasized: the double daily dosing of certain medicines, the high costs and the fact that there is no antidote for overdose or bleeding.

Since the use of the new anticoagulants will increase over time, it is important for the dentist to understand the mechanisms of actions, the reversal strategies and the management guidelines for patients taking oral anticoagulants.

This led to new guidelines that the dentist together with the specialist – who follows the patients' hemodynamic activity – should follow in order to ensure a safe appropriate dental treatment and reduce, in this way, any postoperative complications.

The present work has the objective to evaluate the effectiveness of the new oral anticoagulants compared to warfarin, especially in terms of the risks of bleeding events and intra and postoperative complications in patients requiring multiple dental extractions.

## Materials and methods

For this study 50 patients treated with oral anticoagulants at the Department of Special Oral Pathology of the "Policlinico Tor Vergata", requiring multiple dental extractions were selected. They were divided into two groups.

Group A consisted of 12 patients treated with the new oral anticoagulants (7 males and 5 females) with an average age of 69.41years (DS 3.98 years), while the Group B consisted of 38 patients treated with Warfarin replaced by LWMH (22 males and 16 females), with an average age of 72.31 (DS=5.32 years). The study inclusion criteria were: taking direct and indirect anticoagulants, hearth disease (atrial fibrillation) or vascular disease (pulmonary embolism and deep vein thrombosis); over 65 years of age; multiple dental extractions.

Patients were excluded from the study because of one of the following conditions: liver disease, severe renal failure, disorders of haemostasis and coagulation, patients having valvular prosthesis, history of prolonged bleeding events, teeth with mobility grade 3 and impacted teeth.

In the patients of Group B the INR and the PT has been measured 7 days before and the morning of surgery. All the patients, at the first inspection, had a INR >3; being the bleeding risk high and the thromboembolic moderate, in agreement with the medical specialist, it has been decided to interrupt the therapy with warfarin and replace it with the bridging therapy, in the perioperative, i.e. with more manageable anticoagulant drugs, such as low molecular weight heparins (LMWH).

Therefore, during this period, the thromboembolic prophylaxis was obtained with the LMWH, administered subcutaneously once or twice a day depending on the patient body weight and with due consideration for the risk of developing thromboembolic complications.

The patients started the bridging therapy the day after having interrupted the TAO. The above mentioned therapy with LMWH was discontinued 12 hours before the surgery.

The morning of the surgery the patients had INR < 1.5.

About 12 hours after the surgery, the heparin was administered and the following day the patients were able to take the TAO. After having achieved the therapeutic range of INR, the heparin therapy was discontinued. Patients of group A were made not to interrupt the therapy, but since the multiple extractions, up to three dental extractions, are





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among the low risk interventions, the time phase of minimum action of the drug was exploited, i.e. 12-24 hours after the last assumption, if the drug is dual (dabigran and apixaban) or a single (rivaroxaban) daily administration. The anticoagulant was re-introduced the day after the surgery. Both groups followed the operators procedures currently established.

Before the extraction the patients were made to rinse 60 seconds with 10 ml of (based chlorhexidine 0,2% pure product), in order to reduce the bacterial charge of the treated site and, therefore, promote healing of the surgical wound; for the treated patients, the penicillins (amoxicillin + clavulanic acid) have been the primary choice of antibiotic prophylaxis, because of their minimal interactions with the oral anticoagulants.

These procedures were performed under local anaestethic containing a vasoconstrictor, articaine with epinephrine 1:200.000, with a technique using infiltration, an atraumatic surgical technique was used and, after the surgery, an accurate alveolar bone cleaning was performed, removing any easy bleeding granulation tissue, often responsible for postoperative bleeding; then the irrigation of the alveoli by anfibrinolitic agents such us tranaxemic acid was performed together with the application of emostatic materials, such as a based haemostatic gelatine sponge (SPONGOSTAN™). As a result, the wound was sutured with a non absorbable 3-0 floss and at the end was compressed using gauze soaked in tranexamic acid for about 15 minutes.

In the post-operative the patients were recommended to apply an ice bag for 3-4 hours and they were suggested to follow a liquid and cold diet for three days after the surgery and a soft and lukewarm diet for the following 7 days. In any case, patients were asked to avoid substances causing hyperaemia (alcohol, tobacco, hot foods).

Patients were also recommended to make mouth rinses with a 10 ml of 5% tranexamic acid aqueous solution for 2 minutes, repeated 4 times daily for 7 days. On the second postoperative day, however, patients had to make mouth rinse with a 0.12% chlorhexidine digluconate solution 3 times a day. Patients followed the prescribed antibiotic therapy and they were allowed to take analgesics, such as paracetamol, at normal doses.

Patients were observed for 60 minutes until the cessation of bleeding linked to the procedure.

The postoperative bleeding has been evaluated and recorded by a monitoring follow-up: immediately after the extraction, after 24 hours, after 72 hours and after 7 days. On the seventh day the sutures were removed and the status of healing was checked.

## Results

The results associated with the management of oral surgery have showed a good reliability with respect to intra and post-operative complications, especially in patients of Group A.

27% cases of Group B showed an increased intraoperative bleeding; that fact has resulted in a reduction of the visibility of the operative field and greater difficulty in operating procedures, event not occurred in Group A.

In Group B postoperative complications were:

- in 3 patients (7.89%) formation of extra-alveolar clots (Figure 1) and bleeding >24 hours, which required a reoperation by the clinician;
- in 4 patients (10:52%) bleeding <24 hours, controlled by a suitable pressure on the wound with a gauze pad moistened with tranexamic acid, which did not require reoperation by the clinician;
- in 3 patients (7.89%) uncontrollable bleeding after 24 hours, which required reoperation by the clinician;
- in 2 patients (5,26%) haematomas on their face; however, they did not show any bleeding after 24 hours.

In 15.78% of cases of Group B, widespread bleeding episodes required reoperation by the clinician, which consisted of changing the systemic therapy with heparins and applying additional sutures at the surgical site. In cases of extra - alveolar clots the clot responsible for the bleeding has been removed; the site has been buffered with gauze soaked in hydrogen peroxide and, finally, addi-



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tional sutures to reduce the bleeding risk have been applied.
In the Group A a good haemostasis management has been obtained, without bleeding complications intra and post-operative: only in two patients (16.66%) a delayed healing has been seen. After the extractions, in fact, no cases of severe bleeding needing a hospital management have been detected, local hemostatic measures were enough.
Furthermore, no thromboembolic complications have been detected within the subsequent 30 days after surgery.

## Discussion

The management of anticoagulated patients, who have to undergo dental oral surgery, is very delicate and can lead to serious consequences if appropriate protocols for the control of hemostasis and thromboembolic risk are not applied.
In patients taking warfarin who require oral surgery, the standard is to monitor the anticoagulant activity through PT (Prothrombin Time), and INR (International Normalized Ratio).
As said by Abdullah WA et al., the INR is not the only factor that estimates the risk of bleeding; other factors related to the patient or the procedure may affect it.
Currently, most of the guidelines indicate that the optimum value of INR for dental surgeries is 2.5, because it minimizes the risk of bleeding or of thromboembolic events.
In patients with an INR >3.5 that must undergo complex surgeries (i.e. multiple extractions) it is necessary, to rely on the experts advice of those who follow the patient's hemodynamic capacity (to change the medication), in order to properly assess the thromboembolic risk and the bleeding risk.
In the opinion of several experts, such patients should suspend warfarin 5 days before any surgical intervention and replace it temporarily with the bridging therapy using low molecular weight heparin.
In cases where the bridging therapy is required, a correct dosage of the therapy with LMWH is fundamental to obtain adequate anticoagulation therapy.
Treatment guidelines recommend treatment with full-dose LMWH for patients at high thromboembolic risk; in patients with an intermediate thromboembolic risk, however, prophylactic doses of LMWH are used.
LMWH provide an adequate prophylaxis in patients who stopped anticoagulation after oral surgery procedures.
The primary therapeutic objective of the bridging therapy is to reduce to the lowest level the risk of thromboembolism during the period in which the TAO, routine conduct, is not recommended or contraindicated. An equally important objective of the bridging therapy is to minimize the risk of perioperative bleeding.
While the management of patients on warfarin who require invasive dental procedures is well documented in literature, the limited randomized clinical studies for patients treated with NAO conducted till now, do not allow to establish a specific management protocol. However, the results based on the evidence related to the classical anticoagulants and existing reviews on new drugs allow us to establish some guidelines.
In patients treated with the new oral anticoagulants, who require interventions at low risk of bleeding (e.g. extraction up to 3 dental elements), where a good local haemostasis can be reached, experts EHRA (European Heart Rhythm Association) suggest not to interrupt therapy with NAO, using, for the operation, the minimum time step of the medicine (12 h after the last dose of dabigatran and apixaban, 24 h after the last dose of rivaroxaban). Instead, in the case of complex oral surgery (extraction >4 dental elements) suspension of the NAO has to take into consideration: the risk of bleeding, renal function, the anticoagulant used (Table 1).
Even in the absence of controlled studies, it is likely that, given the reduced half-life of these drugs, discontinuation of therapy can be practiced 24 hours before surgery, ensuring perfect haemostasis; re-initiation on the same day of the intervention would result in exposure to thromboem-



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**Table 1** - Interruption of NAO therapy before surgery

| | Dabigatran | | Rivaroxaban | | Apixaban | |
|---|---|---|---|---|---|---|
| Renal function | Low risk | High risk | Low risk | High risk | Low risk | High risk |
| ClCr 80ml/min | 24h | 48h | 24h | 48h | 24h | 48h |
| ClCr 50-80ml/min | 36 | 72 | 24h | 48h | 24h | 48h |
| ClCr 30-49ml/min | 48 | 96 | 24h | 48h | 24h | 48h |
| ClCr 15-30ml/min | Not indicated | Not indicated | 36h | 48h | 36 | 48h |
| ClCr <15ml/min | | | | | | |
| | | | no official data are available | | | |

bolic risk reduced to 24-48 hours compared to 6-7 days of traditional TAO.
It is therefore necessary to agree with the specialist who follows the hemodynamic activity of the patient about the type of dental surgery to be performed, so that, if appropriate, he can decide to affect anticoagulant therapy.
The NAO, thanks both to their short half-life and their rapid anticoagulant effect, theoretically show numerous advantages compared to the AVK: it can be supposed that a brief suspension on intervention occasion will be sufficient, without carrying out the "bridging therapy".
The data supporting this behaviour are still very limited, both regards the supporting evidence and clinical experience. Most of current guidelines are derived from expert opinion and the pharmacological properties of the new oral anticoagulants, it is essential, therefore, that each local situation closely cooperates with prescribers centers and that a careful monitoring of clinical effects is implemented.
In performed multiple extractions, the protracted bleeding was more common in sites with a greater degree of local inflammation. However, in most cases, the intra- and postoperative bleeding has been controlled through the use of local haemostatic. Proceeding to a review of the literature, we found that more commonly used medical devices are: mouthwash and administration of tranexamic acid, the fibriniche pastes, gelatin sponges, collagen and resorbable oxycellulose.
It should be noted that even the most common maneuvers for obtaining effective haemostasis (tamponade with sterile gauze and sutures) are fundamental in these patients. Only 15% of treated patients, Group B, required reoperation by the clinician; in any case it has always been a manageable bleeding, in the clinic itself, using local hemostatic. No severe bleedings that required hospitalization, were found.

## Conclusion

In conclusion, from the study we conducted, we could assess that the risk of intra- and postoperative bleeding after multiple dental extractions in patients treated with the new oral anticoagulants, was low.
Since the use of these new anticoagulants is likely to increase over time, it is important for the dentist to know the management guidelines for patients taking these medicine.
Most dentists, fearing the possible complications intra and post-operative, prefer to delegate to hospitals anticoagulated patients. In our view the NAO are safe and effective medications, which allow an easier patient management also in the dental practice, without there being a need for treatment in dental clinic. However, it remains essential to communicate with the medical specialist in order to ensure safe and appropriate dental treat-



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ment.
The limits of this study are the following: 1) the relatively small sample size; and 2) our findings may not be generalizable to other preparations of LMWH because all patients in Group B had made the bridging therapy with enoxaparin.
In any case, the results obtained are encouraging and this encourages us to go into that with further study on the matter.

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