

New oral anticoagulants and their implications for dental patients

Anticoagulation therapy is used in several conditions to prevent or treat thromboembolism. Over the last 40 years, warfarin has been the oral anticoagulant of choice and has been considered the mainstay of treatment. However, its use is limited by a narrow therapeutic index and complex pharmacodynamics, necessitating regular monitoring and dose adjustments.

Recently, two new oral anticoagulants - dabigatran etexilate (a direct thrombin inhibitor) and rivaroxiban (a factor Xa inhibitor) - have been approved for use in North America and Europe. Unlike warfarin, dabigatran and rivaroxiban are relatively small molecules that work as anticoagulants by targeting specific single steps of the coagulation cascade. Their advantages, relative to warfarin, include: predictable pharmacokinetics; limited food and drug interactions; rapid onset of action; and, short half-life. They require no monitoring. However, they lack a specific reversal agent.

The number of patients taking dabigatran and rivaroxaban is increasing. Therefore, it is inevitable that dentists will be required to perform invasive procedures on this cohort of patients. This paper outlines the various properties of the new oral anticoagulants and the most recent guidelines regarding the management of these dental patients taking these medications.

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Introduction

Anticoagulation therapy is indicated in several conditions to prevent, treat, or reduce the recurrence risk of thromboembolism. Included in these conditions are: deep vein thrombosis (DVT); pulmonary embolism (PE); atrial fibrillation; prosthetic and rheumatic heart valves; myocardial infarction; transient ischaemic attacks; and, stroke. Over the last 40 years, the coumarin-derivative, vitamin K antagonist, warfarin has been the oral anticoagulant of choice and has been considered the mainstay of treatment. Indeed, it has, along with other vitamin K antagonists, been the most widely-available, orally-administered anticoagulant.^{1,2} However, like all medicines, warfarin is not

without its disadvantages. Its use is limited by a narrow therapeutic index and complex pharmacodynamics, necessitating regular monitoring and dose adjustments. In addition, it has multiple drug and dietary interactions. These disadvantages created an impetus for the development of novel oral anticoagulants with a wider therapeutic index, less interactions, and a predictable level of anticoagulation at a specific dose. Recently, two new oral anticoagulants, dabigatran etexilate (a direct thrombin inhibitor) and rivaroxiban (a factor Xa inhibitor) have been approved for use in North America and Europe. In Europe, both dabigatran and rivaroxiban are licensed for short-term primary prevention of venous thromboembolic events in adult patients

TABLE 1: Indications for and pharmacology of oral anticoagulants.

	Warfarin	Dabigatran	Rivaroxaban
Indications	DVT, PE Prevention of thrombosis in AF Prevention of recurrent MI MHV	Prevention of CVA in AF VTE prophylaxis in elective THR, TKR	VTE prophylaxis in elective THR, TKR
Dose and regimen	Titrated according to INR Once daily	Range: 110-150mg BD for AF; 220mg daily for THR/TKR	10mg once daily
Site(s) of action	Factors II, VII, IX, and X Proteins C and S	Thrombin	Factor Xa
Oral bioavailability	~100%	3-7%	80-100%
Time to peak plasma concentration (T_{max})	2-8 hours	2-4 hours	2.5-4 hours
Half-life ($T_{1/2}$)	20-60 hours	12-17 hours Up to 28 hours in severe renal impairment	5-13 hours
Metabolism	Primarily CYP2C9 (liver)	Esterase catalyzed hydrolysis in plasma/liver	Liver: CYP3A4, CYP3A5, CYP2J2
Renal elimination	90-100%	80-85%	66%
Need for monitoring	Regular INR	None	None

Abbreviations

<i>AF</i>	atrial fibrillation	<i>CYP</i>	cytochrome P	<i>MI</i>	myocardial infarction
<i>CVA</i>	cerebrovascular accident	<i>DVT</i>	deep venous thrombosis	<i>PE</i>	pulmonary embolus
		<i>INR</i>	international normalised ratio	<i>THR</i>	total hip replacement
		<i>MHV</i>	mechanical heart valve	<i>TKR</i>	total knee replacement

who have undergone elective total hip or knee replacement surgery, while dabigatran is also licensed for prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation, plus one or more additional risk factors. Dabigatran is contra-indicated in patients with a prosthetic heart valve requiring anticoagulant treatment.³ Unlike warfarin, dabigatran and rivaroxaban are relatively small molecules that work as anticoagulants by targeting specific single steps of the coagulation cascade.⁴ In addition, they are reported to have fewer drug-drug interactions, no significant food interactions, and provide predictable anticoagulation at a specific dose, without the need for regular laboratory monitoring and alterations of dose.^{5,6,7} The pharmacologic properties of dabigatran, rivaroxaban, and warfarin are outlined in **Table 1**.

As the number of patients taking dabigatran and rivaroxaban increases, it is inevitable that dentists will encounter them in the near future. It is therefore incumbent on all of us to become familiar with these drugs, their indications and method of action, and in particular

the management of those patients requiring invasive dental procedures, so that these patients are managed in a safe manner. This present paper outlines the various properties of the new oral anticoagulants and the most recent guidelines regarding the management of these patients in dental practice.

Materials and methods**Dabigatran** (Pradaxa[®]; Boehringer Ingelheim)

In October 2010, the Food and Drug Administration (FDA), USA, first approved the use of dabigatran etexilate to reduce the stroke and systemic embolisation risk in patients with non-valvular atrial fibrillation. It is now also used, in the EU and Canada, for thromboembolic prophylaxis in patients who have recently undergone a total hip or knee replacement.^{8,9} Recent studies have shown that dabigatran, given at a fixed dose (owing to predictable pharmacokinetics) does not require monitoring and is as effective as

warfarin in preventing embolic events in patients with atrial fibrillation. The Randomised Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial demonstrated that, compared with warfarin, dabigatran 150mg twice daily is more effective at preventing stroke and systemic embolisation with a similar risk of major bleeding, whereas dabigatran 110mg twice daily is associated with a lower risk of major bleeding and a similar rate of stroke and systemic embolisation.¹⁰ It has also been shown to be equivalent to warfarin in the prevention and management of recurrent venous thromboembolism (VTE) and PE.¹¹ However, significant concerns regarding the lack of a reversal agent, and difficulty in precisely monitoring its anti-coagulant effect remain.

Mechanism of action and pharmacology

It is a specific, reversible, direct thrombin inhibitor that, unlike warfarin, inhibits both free and fibrin-bound thrombin.¹² It binds to the active site on the thrombin molecule (Factor II a) so that fibrinogen cannot be converted into fibrin.⁵

Dabigatran etexilate is a pro-drug which, following oral administration is converted to its active form, dabigatran. When administered orally, the bioavailability is approximately 3-7%. It is rapidly absorbed and is metabolised by the liver. It has a rapid onset of action with a peak plasma concentration at 0.5-4 hours.^{13,14} When administered twice daily, a steady state plasma concentration is reached within two to three days.¹³ The half-life elimination is 12-14 hours in healthy patients, 14-17 hours in the elderly, and up to 27 hours in patients with severe renal impairment (i.e., creatinine clearance <15-30 ml/min). There is no evidence for an alteration in pharmacodynamics in patients with moderate hepatic impairment (Child-Pugh B).¹⁴

Laboratory testing/monitoring

Unlike warfarin, routine monitoring of the anticoagulant effect of dabigatran is not required. However, certain situations such as emergency surgery, intra-cranial/cerebral bleeding, and overdose may require assessment of anticoagulation. The thrombin clotting time (TT), and ecarin clotting time (ECT) are reported to be the most sensitive tests for quantifying the anticoagulant effects of dabigatran. However, the ECT test is not widely available. The activated partial thromboplastin time (aPTT), whilst widely available, is less sensitive particularly at higher dabigatran doses.^{15,16} Most dentists are familiar with the prothrombin time (PT), often expressed as the international normalised ratio (INR). However, this test is less sensitive than others and cannot be relied upon to determine the anticoagulant effect of dabigatran.

Adverse reactions

The RE-LY trial reported that more than 15% of patients experienced gastritis type symptoms.¹⁰ Minor bleeding events were reported in 8-33%, and major bleeding in less than 6%. In addition, it reported drug hypersensitivity (including urticaria, rash, and pruritus), allergic edema, anaphylactic reaction, and anaphylactic shock in less than 0.1% of patients.

Reversal agent

Currently, there is no reversal agent for the dabigatran. However, owing to its short half-life, discontinuation of the drug may be sufficient to resolve minor haemorrhage, with the exception of patients with renal impairment. For more persistent or major bleeding, supportive measures such as pressure, vessel ligation, fluid replacement, and transfusion of blood products can be employed. Recombinant factor VII (rFVIIa), prothrombin complex concentrates, and/or haemodialysis may also be considered.¹⁵

Drug interactions

Unlike Warfarin, it appears that dabigatran has few clinically significant drug and food interactions. Ketoconazole, verapamil, and amiodarone may increase its anticoagulant effect, whilst rifampicin may decrease its effect. The risk of bleeding whilst on dabigatran may be increased by concomitant use of other anticoagulants, antiplatelets, and salicylates.¹² Stangier reported that the concomitant use of the non-steroidal anti-inflammatory drug (NSAID), diclofenac sodium, and dabigatran did not produce a significant interaction.¹⁷ Nevertheless, given that non-cox-selective NSAIDs inhibit platelet aggregation and are associated with gastro-intestinal bleeding and peptic ulcer disease, it may be prudent to avoid their use in patients taking dabigatran. Paracetamol and opioid analgesics are suitable alternatives.¹⁸

Specific dental considerations

Unfortunately, to date, there are no clinical trials supporting specific measures in the event of haemorrhage in dental patients taking dabigatran. The most current information suggests that patients taking dabigatran can undergo invasive dental procedures without alteration of dose. As is the case with all patients, irrespective of coagulation status, local haemostatic measures (absorbable gelatin or oxidized cellulose pellets, sutures, gauze soaked in 5% tranexamic acid, pressure) should be employed in the event of bleeding. Owing to the risk of thromboembolism, dabigatran should never be discontinued without prior consultation with the treating physician. Firriolo and Hupp, studied data from reports on post-extraction bleeding in patients receiving low molecular weight heparin (LMWH).^{5,19,20} In addition, they looked at the recommendations of van Ryn *et al* regarding the discontinuation of dabigatran before elective general surgery, and concluded that there should not be a significant risk for serious bleeding after dental treatment, including most uncomplicated dental extractions, in patients with normal renal function and without other risk factors for bleeding.¹⁵ However, they continue to say that a temporary cessation of dabigatran may be required in patients requiring major oral/maxillofacial surgery. If this is the case, dabigatran should be discontinued (following consultation with the patients physician) at least 24 hours (or longer in renal impairment) before elective surgery. In addition, consideration should be given to performing a TT or aPTT six to 12 hours prior to surgery, which, if normal, indicates that the coagulation is normal and that the anticoagulant effect of dabigatran has resolved.^{5,15,21}

Dabigatran should only be recommended post-operatively once a stable clot has formed, thereby minimising the risk of bleeding. This is particularly important with dabigatran, and indeed rivaroxaban, as unlike warfarin, their onset of effect is predictable and rapid.

If discontinuation of anticoagulation is not considered safe, and extensive oral surgery is required, peri-operative bridging anticoagulation with an appropriate dose of subcutaneous LMWH or unfractionated heparin is recommended.

The RE-LY trial involving over 18,000 patients, looked at (amongst other things) the levels of bleeding in dabigatran versus warfarin.¹⁰ Whilst the level of both major and minor bleeding was lower amongst the cohort taking dabigatran, no significant statistical significance was found.

A secondary analysis of the RE-LY trial showed that 4,591 patients had undergone at least one invasive procedure, with cessation of anticoagulation pre-operatively.²² Interestingly, 10% (460) of these procedures were dental, which was the second most common type of surgery. Dabigatran was discontinued 24-72 hours (average 49 hours) or more pre-operatively, based on renal function and bleeding risk, and warfarin was discontinued an average of 114 hours pre-operatively. The analysis demonstrated similar rates of perioperative bleeding for both dabigatran and warfarin. More specifically, the incidences of major perioperative bleeding were 3.1% with dabigatran 110mg, 5.1% with dabigatran 150mg, and 4.6% with warfarin.⁴⁴ However, despite the fact that approximately 460 dental procedures were included in this study, it is difficult to find specific perioperative measures or guidelines as information regarding the duration and type of procedure are limited. Therefore, it is important to highlight that it is difficult to recommend this study as a guide for the management of patients requiring dental procedures.

Romond *et al.*, in a recent paper, describe the successful management of a patient taking dabigatran who required multiple extractions.²³ As per the recommendations of van Ryn *et al.*, they held the patients' dabigatran 24 hours prior to the procedure, which involved eight extractions, alveoloplasty, and tuberosity reduction.¹⁵ They reported no prolonged post-operative bleeding. Interestingly, they also stated that had the patient required only one to three extractions, consideration would have been given to not stopping the patients' dabigatran. Weitz *et al.*, also suggest that dabigatran does not need to be stopped in cases where the bleeding risk is low and cites dental extractions as an example.²⁴

Rivaroxaban (Xarelto®; Bayer)

Rivaroxaban is an orally-administered, selective, reversible, direct inhibitor of activated factor X (factor Xa), and is currently indicated for prophylaxis of venous thromboembolism (VTE) in adults after hip or knee replacement surgery. A number of studies have demonstrated that rivaroxaban can reduce VTE and all cause mortality in these patients.^{25,26,27}

The ROCKET-AF trial investigated the effectiveness of rivaroxaban, relative to warfarin, in the reduction of ischaemic stroke or systemic embolism in patients with atrial fibrillation.²⁸ However, the FDA has

yet to approve its use in the setting of atrial fibrillation, based on a perceived lack of evidence.²⁹

Mechanism of action and pharmacology

Rivaroxaban is an oxazolidinone derivative that inhibits factor Xa and interrupts both the extrinsic and intrinsic coagulation pathways, thereby inhibiting thrombin formation.¹²

It is rapidly absorbed and has a rapid onset of action of two and a half to four hours. The half-life is five to nine hours in healthy adults, and 11-13 in the elderly (due to decreased total and renal clearance).³⁰ Oral bioavailability is 80-100% and the duration of effect is 10-18 hours.⁴ It is excreted in the urine (66%) and faeces (28%).³¹

Laboratory testing/monitoring

Like dabigatran, routine monitoring of rivaroxaban is not required. However, in an emergency situation, measurement of the level of anticoagulation may be indicated. Anti-factor Xa assay is reportedly the most accurate measurement of the anti-coagulant effect of rivaroxaban (as well as LMWHs).²¹ In addition, some authors suggest that aPTT and PT (with rivaroxaban specific calibration) may also be used.^{32,33} The activated aPTT and HepTest® are prolonged dose-dependently; however, they are not recommended to assess the pharmacodynamic effect of rivaroxaban.³⁰

Adverse reactions

Approximately 1-10% of patients taking rivaroxaban experience an adverse reaction.³⁴ Major bleeding occurs in 1-2%, and minor bleeding in 4-7%. Nausea occurs in 1% of patients.

Reversal agent

Unlike warfarin, there is no specific agent to reverse the anti-coagulant effect of rivaroxaban. However, owing to its short duration of action, discontinuation of the drug should be sufficient to arrest persistent minor haemorrhage. Severe or life-threatening haemorrhage may require the use of blood product transfusion, recombinant Factor VIIa, or prothrombin complex concentrate (PCC).^{35,36}

Drug interactions

Two thirds of rivaroxaban is metabolised by the Cytochrome P450 (CYP) system, especially CYP3A4. In addition, rivaroxaban is also a substrate of P-gp transporters.⁵ Therefore, the concomitant use of rivaroxaban with inhibitors or inducers of CYP3A4 should be avoided.^{35,37} CYP3A4 inhibitors, which can increase the serum concentration of rivaroxaban and therefore the risk of bleeding, include erythromycin, ketoconazole, and amiodarone. Clarithromycin is considered a strong CYP 3A4 inhibitor, and a moderate P-gp inhibitor. However, the increase in peak serum concentration of rivaroxaban when administered with a twice-daily dose of Clarithromycin 500mg was found to be of no clinical relevance in one study.³⁸ Conversely, CYP3A4 inducers such as phenytoin, rifampicin and St Johns wort may increase the metabolism of rivaroxaban, thereby decreasing the level of anticoagulation. Non-steroidal and

opioid analgesics should be used with caution in patients taking rivaroxaban.⁵

Specific dental considerations

Similar to dabigatran, there are currently no clinical trials in the literature offering specific recommendations for the management of dental patients taking rivaroxaban.

Turpie *et al.*, suggest that interruption of rivaroxaban is not required for simple dental extractions.³⁹ The guidelines given above in relation to dabigatran are also applicable to rivaroxaban. Therefore, it is not necessary to discontinue rivaroxaban for uncomplicated extractions and other similar invasive dental procedures in patients with normal renal function. Local haemostatic measures, as described previously, should be employed when necessary. For patients undergoing elective oral/maxillofacial surgery, where the bleeding risk is significant, rivaroxaban should be discontinued (only after consultation with the patients physician) for at least 24 hours before surgery. A longer time period will be required in patients with renal dysfunction.^{4,40}

Warfarin

The guidelines for management of dental patients taking warfarin, have previously been well described in the literature.⁴¹⁻⁴⁴ However, for completeness, a summary of the management of dental patients taking warfarin is included here. Warfarin inhibits the enzyme vitamin K epoxide reductase, therefore inhibiting the formation of vitamin K-dependent coagulation factors II, VII, IX, and X, and proteins C and S. The maximum anticoagulant effect of warfarin takes 48 to 72 hours to develop, with an estimated duration of action of two to five days and a reported half-life of two and a half days. It is important to stress that, owing to the risk of a potentially fatal thromboembolism, cessation of warfarin therapy prior to dental treatment is not recommended. Instead, an INR should be taken 24 to 48 hours pre-operatively to establish the degree of anticoagulation. In general, it is safe to proceed with an invasive dental procedure (including administration of local anaesthesia, periodontal or endodontic surgery, and routine/surgical extractions) if the INR is less than or equal to 3.5. Local haemostatic measures should be employed routinely. If the INR is greater than 3.5, the dentist should liaise with the treating physician in order to safely reduce the warfarin dosage. Due to warfarin's long half-life, a period of three to five days is required for a reduction in the level of anticoagulation, as reflected in a reduced INR. An INR again needs to be taken 24 to 48 hours prior to the procedure to ensure that it is less than or equal to 3.5. Finally, all dentists should be cognisant of the potential interaction between warfarin and other drugs commonly used in dentistry, including azole antifungals, macrolide antibiotics, and NSAIDs.

Discussion

Oral vitamin K antagonists have, for many years, been the mainstay of management for VTE treatment and prevention. Despite their widespread use, they are not without problem. They require regular monitoring and dose titration. In addition, they

have multiple food and drug interactions. Despite this, the availability of an antidote, specifically Vitamin K, is somewhat reassuring. In the event of a significant or life-threatening bleed, prothrombin complex concentrate may also be used. Recently, the search for a better alternative to Vitamin K antagonists has resulted in the production of two new drugs, namely dabigatran etexilate and rivaroxaban. Their advantages, relative to warfarin, include predictable pharmacokinetics, limited food and drug interactions, rapid onset of action, and short half-life. They also require no regular monitoring or dose titration. A Cochrane review of 14 studies, incorporating 27,746 patients, comparing direct thrombin inhibitors to vitamin K antagonists and LMWH showed no statistically significant difference in the risk of bleeding.⁴⁵ However, the lack of a specific reversal agent remains a concern.

The RE-LY trial, which was referred to in the above section on dabigatran, looked at (amongst other things) the levels of bleeding in dabigatran versus warfarin.¹⁰ Whilst the level of both major and minor bleeding was lower amongst the cohort taking dabigatran, no notable statistical significance was found. However, significant concerns have since been raised regarding severe bleeding events (in patients whose anticoagulation was not stopped) and their management (or lack thereof) in patients taking dabigatran.⁴⁶⁻⁴⁷

To our knowledge, there are no randomised controlled trials looking at the peri-operative management of bleeding in dental patients taking dabigatran or rivaroxaban. Romond *et al.* describe the successful management of a patient taking dabigatran who underwent multiple extractions.²²

Van Diermen *et al.* in an extensive literature review and summary of papers dealing with the management of dental patients receiving oral anti-thrombotic medication (including the novel oral anticoagulants) proposed an updated clinical practice guideline for dentists.⁴⁸ They concluded that the evidence does not support cessation of oral antithrombotic medication for simple dental procedures. More specifically, they recommend that novel oral anticoagulant treatment (including dabigatran and rivaroxaban) should not be interrupted to facilitate simple dental procedures (e.g., up to three dental extractions, up to three dental implants, and periodontal surgery).

Most current guidelines are largely based on expert opinion and the pharmacologic properties of the new oral anticoagulants.^{5,12,15,18,22}

Current available information suggests that the risk of bleeding in patients undergoing invasive dental procedures (for example, extractions) is low, provided that local haemostatic measures (suturing, gelatin sponge, gauze soaked 5% tranexamic acid, tranexamic acid mouth rinse) are used and the patient has normal renal function. Indeed, the risk seems to be analogous to patients taking warfarin and with an INR of between two and three. For patients requiring multiple extractions, or oral/maxillofacial procedures, consideration must be given to discontinuation of dabigatran/rivaroxaban, with the duration determined by renal function and bleeding risk.¹⁵ However, as stated previously,

dentists should not discontinue oral anti-coagulants without prior consultation with the patients' physician. If discontinuation is not feasible, due to the risk of VTE, bridging with LMWH or intravenous unfractionated heparin, as per the ACCP guidelines for patients taking vitamin K antagonists, is required.⁴⁹

It is also important to be cognisant of the potential drug interactions between rivaroxaban/dabigatran and the drugs commonly used in dentistry, as outlined previously.

Conclusion

As the number of patients taking dabigatran and rivaroxaban increases, it is inevitable that dentists will encounter them in the near future. It is therefore incumbent on all of us to become familiar with these drugs, their indications and method of action, and, in particular, the management of those patients requiring invasive dental procedures. As our experience with these medicines increases, so will our understanding of appropriate management measures. Currently, no specific protocols are available and further observational studies and randomised controlled trial are required to properly define management guidelines.

Summary of management of dental patients taking dabigatran or rivaroxaban

- ▶ Based on current information, in patients with normal renal function taking dabigatran or rivaroxaban, invasive dental procedures can be carried out without interruption of the medication.
- ▶ All procedures should be performed as late as possible after the most recent dose.
- ▶ Local haemostatic measures should be used routinely in these patients.
- ▶ Patients requiring oral/maxillofacial surgery may need discontinuation of oral anticoagulants for at least 24 hours preoperatively, but always in consultation with treating physician.
- ▶ If stopped pre-operatively, dabigatran and rivaroxaban should only be re-commenced when a stable clot has formed (typically 24-48 hours post-operatively).
- ▶ If post-operative bleeding occurs, stop the oral anticoagulant, employ local haemostatic measures, and contact the patient's physician.
- ▶ For patients taking dabigatran, transfusion with packed red cells (PRC) or fresh frozen plasma (FFP) should be considered, plus haemodialysis +/- rFVIIa if required.
- ▶ For patients taking rivaroxaban, transfuse with PRC, or FFP, and, if available, give prothrombin complex concentrate or rFVIIa.
- ▶ NSAIDs and salicylates should be used with caution with dabigatran. Paracetamol and opioids are acceptable alternatives.
- ▶ NSAIDs, salicylates, macrolide antibiotics (especially erythromycin and clarithromycin), fluconazole, and opioids should be used with caution with rivaroxaban.
- ▶ Avoid ketoconazole, itraconazole, and voriconazole with rivaroxaban.

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