# ANTICOAGULANTS

## Novel oral anticoagulants



### BACKGROUND

With an increase in life expectancy and the greater prevalence of chronic diseases, patients who are taking anticoagulants are likely to come for care from dental practitioners. Generally, anticoagulants are used to treat and/or prevent potential thromboembolic diseases. The conventional drugs are vitamin K antagonists (VKAs) such as warfarin, which have been associated with drug interactions and require monitoring. Novel oral anticoagulants (NOACs) have been developed as alternatives. A literature review was done to provide dental professionals with information that can help guide clinical decision making regarding the management of individuals taking these medications.

### METHODS

The PubMed, Medline, and Embase databases were searched for articles published in English. In addition, major dental medicine journals were hand searched, and the ClinicalTrials.gov database was reviewed. The data collected included NOAC pharmacokinetics and pharmacodynamics, implications for dental practitioners treating patients taking these agents, and the risks of interrupting anticoagulant therapy when dental surgery is planned.

### RESULTS

#### High-risk Patients

The coagulation cascade represents a balance between pathways to coagulation, which are called into action by trauma and lead to the formation of a blood clot, and pathways of anticoagulation, which inhibit the former pathways. High-risk patients may be receiving anticoagulants to manage the risk of experiencing future thromboembolic events. A high-risk patient can be defined as one who (1) has a mitral valve prosthesis, any caged-ball prostheses, or a tilting disc aortic valve prosthesis; (2) has had a stroke or transient ischemic attack (TIA) in the past 6 months; (3) has had a venous thromboembolism (VTE) within the past 3 months; (4) suffers from severe thrombophilia; or (5) has a deficiency of protein C, protein S, antithrombin, or antiphospholipid antibodies. These patients can be challenging to define because of the many factors that contribute to their risk of developing a thromboembolic crisis.

#### VKAs

The major VKAs are warfarin and acenocoumarol. These drugs are given orally and act by inhibiting vitamin K epoxide reductase. The process reduces the hepatic synthesis of various coagulation factors and proteins. VKAs characteristics include having adequate oral absorption, an increased affinity for combining with plasmatic proteins, hepatic and renal metabolism, and a half-life of 10 to 24 hours. They also interact with a number of other drugs. Anticoagulant effect is monitored through measurement of the prothrombin time (PT).

#### NOACs

NOACs work primarily by targeting specific coagulation factors in the form of thrombin or activated coagulation factor Xa. The major agents are dabigatran, rivaroxaban, apixaban, and edoxaban. One of their most important advantages is a more rapid onset of action than VKAs, with most NOACs reaching peak concentrations in 1 to 4 hours. NOACs also offer rapid offset of action, which can be essential if patients require surgery. NOACs generally have few interactions with other drugs and are seldom associated with food interactions. NOACs can be given in fixed doses to patients, offering wider therapeutic windows, predictable pharmacokinetic and pharmacodynamics parameters, and freedom from routine monitoring regardless of demographic variations.

Problems associated with NOACs include a lack of clinical experience with these agents, no reversal agent for most of them, and little information regarding their use in specific populations, such as obese individuals, pregnant women, pediatric patients, and low-weight persons. NOACs have not yet been used in patients who have pre-existing conditions associated with an increased risk of thrombophilic states. Caution is required for patients with renal or hepatic insufficiency. Cost and patient compliance can also complicate their use. If the patient does not comply with NOAC administration, he or she may risk thrombosis because of the short half-life of these drugs. It's also difficult to measure anticoagulation effects of NOACs using conventional clotting time tests.

*Dabigatran* is a direct thrombin inhibitor that prevents fibrinogen from converting to fibrin and thereby prevents the formation of a clot. It's used to limit the risk of potential stroke and systemic

embolism for persons who have nonvalvular atrial fibrillation (NVAF). It's poorly absorbed through the gastrointestinal tract unless given as dabigatran etexilate. It prevents numerous cascade events in coagulation. Eighty percent is excreted unchanged through the renal system and 20% undergoes hepatic metabolism. The dosage must be lowered for patients with renal insufficiency. Its advantages include a very low potential for drug-drug interaction and absorption unaffected by the presence of food.

*Rivaroxaban* is used to reduce the risk of stroke and systemic embolism in patients with NVAF who have additional risk factors, such as hypertension, diabetes mellitus, heart failure, or stroke. It can also help to treat and reduce the recurrence of deep vein thrombosis (DVT) and pulmonary embolism (PE). The mechanism of action of rivaroxaban is a direct inhibitory effect on FXa, which blocks prothrombin from being transformed to thrombin. Its characteristics include rapid absorption, reaching peak plasma concentration in about 2.5 to 4 hours, and a terminal half-life that depends on patient age and state of health. About a third of the available rivaroxaban is excreted unchanged in urine, with two thirds excreted in urine and feces as inactive metabolites. Renal and/or hepatic impairment result in increased rivaroxaban levels.

*Apixaban* is used in the treatment of DVT, PE, stroke risk, and the risk of systemic embolism in patients with NVAF. It inhibits FXa, but works reversibly to selectively inhibit free and bound FXa as well as prothrombinase. There are dose-proportional increases in exposure for doses up to 10 mg. In these doses, apixaban has a bioavailability of 50%. Maximum plasma concentration is reached 3 to 4 hours after oral administration, with a half-life of about 12 hours for orally administered apixaban. Given intravenously, its half-life is about 5 hours. Its renal clearance is just 27%. It should not be given with P-glycoprotein and cytochrome P450 3A4 inhibitors. No current coagulation test accurately measures apixaban levels.

*Edoxaban* is a direct and specific inhibitor of FXa administered to prevent venous thromboembolism (VTE) after lower-limb orthopedic surgery. Its oral bioavailability is about 60%, and peak plasm concentration is achieved more rapidly than for any other NOACs, in just 1 to 2 hours. Terminal half-life is about 8 to 10 hours. About a third is eliminated through the renal system and the rest via feces. Edoxaban's effects can be compromised by concomitant medication use. Patients who have moderate to severe hepatic impairment are strongly advised to cease the administration of edoxaban when undergoing surgery with a bleeding risk.

### Reversal Agents

The risk of bleeding complications is a concern even when NOACs are used. Some clinical situations may require an anticoagulant reversal agent. Several are being developed, but idarucizumab is currently the only one available. This monoclonal antibody fragment is a specific reversal agent for the direct thrombin inhibitor dabigatran. It's rapidly eliminated, with a total clearance of 47.0 mL/min, an initial half-life of 47 minutes, and a terminal half-life of 10.3 hours.

## GUIDANCE FOR DENTAL PRACTITIONERS

Although NOACs have shown themselves to be safe and effective and offer several advantages over VKAs, defined management guidelines for oral health care practitioners are lacking. Studies indicate that dentists should obtain detailed histories from patients, noting especially underlying diseases, medical background, medication list, and allergies before beginning any dental treatment. In addition, those taking anticoagulants should be seen in the morning and earlier in the week if possible. Bleeding risk associated with the specific treatment, renal function, and available local hemostatic measures should also be considered. The type of surgery to be done, presence of renal failure, and potential hemostatic alterations should be determined before the decision is made to interrupt NOAC before surgery. Dabigatran and FXa anticoagulants should not be resumed after oral/maxillofacial surgical procedures until postoperative bleeding is under control because of the rapid onset of anticoagulation achieved with NOACs.

If the patient decides to undergo dental surgery, the risk of bleeding should be weighed against the risk for stroke or a potential thromboembolic event. Measures to be taken include the following:

1. The level of bleeding associated with the dental procedure should be determined.
2. If the dental procedure is unlikely to cause bleeding, the discontinuation of NOACs before surgery is probably unnecessary.
3. If the dental procedure is associated with either low or high bleeding risk, the NOAC should be discontinued.
4. The recommended duration of discontinuation will vary depending on the class of anticoagulant, so the dental professional should be familiar with the various options and inform the patient accurately.

### Clinical Significance

NOACs are a promising alternative to warfarin and other traditional anticoagulant agents. Health care professionals need to be better informed about the specifics of the use of these agents so that they can make specific clinical decisions for their patients. Currently, clinical experience with these new agents is lacking, as is published information sufficient to develop guidelines. Dental clinicians in particular should not alter a patient's medications without discussing the situation with the prescribing physician.

5. If NOAC administration is interrupted preoperatively, readministration should begin postoperatively once hemostasis is achieved.

Several specific recommendations have been developed. For dabigatran, the recommended interruption is specific to the patient's creatinine clearance value. Those who have a creatinine clearance of 50 mL/min or more should discontinue dabigatran 24 to 48 hours before surgery. If the creatinine clearance is less than 50 mL/min, discontinuation should be extended for 3 to 5 days preoperatively. In the case of rivaroxaban, any interruption should begin at least 24 hours before any dental procedure associated with a bleeding risk. Apixaban discontinuation should begin 24 hours before procedures with a low risk of bleeding and 48 hours before any procedure with a high bleeding risk.

Fortier K, Shroff D, Reebye UN: Review: An overview and analysis of novel oral anticoagulants and their dental implications. *Gerodontology* 35:78-86, 2018

*Reprints available from* K Fortier, Boston Univ Henry M. Goldman School of Dental Medicine, Boston, MA; e-mail: kevinfortier93@gmail.com

# DENTAL CARIES

## Vitamin D and caries in Korean children



### BACKGROUND

Vitamin D is an important nutrient, active in musculoskeletal and dental health through the regulation of calcium and phosphorus absorption in the small intestine. An excessive intake of vitamin D has health consequences, as does a vitamin D deficiency. In the area of oral health, vitamin D is involved in tooth development, so its deficiency leaves teeth vulnerable to dental caries because of the enamel defects that occur. Vitamin D status is determined by measuring 25-hydroxy vitamin D (25[OH]D) levels. A study in Korean individuals showed Koreans were prone to serious health risks because of deficient 25(OH)D levels and that younger generations were particularly likely to have a vitamin D deficiency. The association between 25(OH)D levels and dental caries in Korean children was investigated.

### METHODS

Data were taken from the Korea National Health and Nutrition Examination Survey performed in 2008-2013. Children age 10 to 12 years were surveyed, with vitamin D intake measured by analyzing 25(OH)D levels. In addition, caries experience in the children's permanent dentition was evaluated using the decayed-missing-filled teeth (DMFT) index and the decayed-missing-filled (DMF) rate. The data were then evaluated statistically.

### RESULTS

Most (61.7%) of the 1688 children had 25(OH)D levels under 50 nmol/L, 51.7% had caries experience, and 49.2% had first molar caries experience. Children with 25(OH)D levels less than 50 nmol/L had a higher proportion of dental caries experience than children with levels of 25(OH)D levels of 50 nmol/L or greater. Groups of children who had higher 25(OH)D levels had lower proportions of children with caries experience and first molar caries experience.

The levels of 25(OH)D and caries experience were not related in multivariate analysis. However, 25(OH)D level and first molar caries experience were significantly associated. When the analysis controlled for sex, household income, age, and frequency of tooth brushing, children with 25(OH)D levels under 50 nmol/L were 1.295 times more likely to have first molar caries experience than those whose 25(OH)D levels were 50 nmol/L or more.

Analysis of the dose-response relationship between 25(OH)D level and dental caries experience indicated a negative correlation. Lower 25(OH)D levels correlated with higher numbers of teeth with caries; however, the association was weak.

### DISCUSSION

The most important insights into the relationship between vitamin D levels and caries were the fact that children with 25(OH)D levels lower than 50 nmol.L were 1.295 times more likely to have first molar caries experience than those whose 25(OH)D levels were over 50 nmol/L. In addition, 25(OH)D levels and dental caries experience were negatively correlated, although that relationship was not strong.

**Clinical Significance**

No causative relationship was found between levels of vitamin D and dental caries. However, an insufficiency of vitamin D may be associated with dental caries. Further study is needed to clarify the relationship.