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Management of patients receiving novel antithrombotic treatment in endodontic practice: Review and clinical recommendations

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Abstract

Cardiovascular diseases are a major component of non-communicable diseases and death, with thrombosis constituting the most common underlying pathosis of the three major cardiovascular disorders: ischaemic heart disease (acute coronary syndrome), stroke, and venous thromboembolism (VTE). The introduction of direct oral anticoagulants (DOACs) in recent years has necessitated a more complex approach to periprocedural and perioperative anticoagulation management and the need for revised management strategies and protocols. Patients taking classic oral anticoagulants are advised to stop taking the drugs and have their INR values checked 72 hours prior to dental surgery (e.g. apical surgery, tooth extraction, periodontal surgery) and checked again 24 hours prior to the procedure to ensure it is within the therapeutic range. However, the current incorporation of these novel DOAC drugs in routine medical practice requires a change in the way patients are managed preoperatively in dentistry, and specifically in endodontic surgery. The methodology of this review consisted of searching relevant articles in the PubMed database using keywords listed in Entree Terms databases. Articles published on human blood clotting mechanism, antithrombotic drugs, as well as treatment guidelines and recommendations for dentistry were retrieved. In addition, textbooks and guidelines that may not have surfaced in the online search were searched manually. The aim of this paper was to review the mechanisms of action of classic and novel antithrombotic medications and their impact on endodontic treatment and current knowledge of local haemostasis in endodontics.

Introduction

Warfarin, a vitamin K antagonist (VKA), has been the most common anticoagulant used for the prevention and treatment of thromboembolic diseases for six decades, but in the last 8 years it has been gradually replaced by novel anticoagulants termed ‘direct oral anticoagulants’ (DOACs) first approved by the US Food and Drug Administration (FDA) in 2010 (Chen *et al.* 2020). Bleeding complications related to these agents during and after minor oral surgery is of concern to dentists. The risks and benefits of these agents must be weighed before initiating such invasive dental procedures.

Blood clotting is a haemostatic mechanism which maintains a balance between tendencies for bleeding and hypercoagulation, known as thrombosis (Fredenburgh & Jeffrey 2018, Iqbal & Jeffrey 2018). This mechanism is triggered following injury of a blood vessel, when a blood clot must form to seal the wall of the injured vessel and prevent continued bleeding. The coagulation process, activated instantaneously following tissue injury, is a cascade resulting in the formation of a fibrin “clot” that seals the site of injury in the endothelium of the blood vessel. The haemostatic system can be divided arbitrarily into three phases: the vascular, platelet, and coagulation phases (Stassen *et al.* 2004, Lippi *et al.* 2009, Fredenburgh & Jeffrey 2018). The first two phases are termed primary haemostasis, and the coagulation phase secondary haemostasis (Gale 2010). However, this division was proposed strictly for didactic purposes, as the soluble factors and cellular components are intertwined with overlap among the three phases during blood vessel injury.

The vascular phase is initiated immediately upon injury to blood vessels, which causes the smooth muscles in the vessel walls to spasm, resulting in retraction of severed arteries, release of mediator molecules from injured endothelial cells and activated platelets (Thromboxan A₂), and nervous system reflexes following activation of local pain receptors (Nordin & Fagius 1995). thereby minimizing immediate blood loss.

The platelet phase includes platelet adhesion and aggregation that lead to the formation of a soft haemostatic plaque (platelet plug) in order to reduce blood loss at the site of injury (Little *et al.* 2018). Binding of platelets to the blood vessel wall occurs with the aid of the Von Willebrand factor (vWF), a specialized binding protein found in the plasma (Ruggeri 2007).

However, the primary platelet plug is not sufficient for the creation of a stable blood clot, and is further reinforced by means of secondary haemostasis, which activates the coagulation cascade (Little *et al.* 2018). The cascade model of clotting, comprises the intrinsic and extrinsic pathways, both of which generate activated factor X (FXa) and converge into the common pathway. The two pathways converge into a “common pathway” which begins with the activation of FX and converting it into FXa. FXa, FVa, and Ca²⁺, thereby leading to the formation of the prothrombinase complex, which, in the presence of membrane phospholipids, converts prothrombin (FII) to thrombin (FIIa). Thrombin also converts (FI) to form fibrin (FIa) and FXIII into FXIIIa, resulting in the end product, namely the formation of a stable fibrin clot (Davie & Ratnoff 1964) (Figure 2-now Figure 1). The fibrinolytic system comprises what is termed tertiary haemostasis. It is initiated to disrupt clotting even as the clot is being formed, thereby maintaining a balance between continued haemorrhaging and hyper coagulation (Collen & Lijnen 1986).

VKAs, mainly warfarin (Acenocoumarol, Coumadin) have been the oral anticoagulants of choice for more than half a century (Pirmohamed 2006). However, the pharmacokinetics of VKAs result in a number of considerable shortcomings such as a low therapeutic index, delayed onset of action, many drug and food interactions, and therefore require constant monitoring and adjustment (De Caterina *et al.* 2013). Direct oral anticoagulants (DOACs) have been introduced into the market since 2010 in order to overcome some of these shortcomings (Table). These novel agents have several advantages over VKAs such as the decreased need for monitoring, fewer food and drug interactions, and a more predictable pharmacodynamic effect (Dentali *et al.* 2012).

However, prothrombin time (PT) expressed as the international normalized ratio (INR), which dentists have become accustomed to over the years in order to assess bleeding risk among patients taking VKAs, is irrelevant when using DOACs (Barrett *et al.* 2010, Lindhoff-Last *et al.* 2013), and a different perioperative strategy must be employed while treating patients on DOAC therapy.

Endodontic surgery as well as root canal treatment are invasive dental procedures and carry a risk for haemorrhage in patients on oral antithrombotic drugs (Witherspoon & Gutmann 1996). While orthograde endodontic treatment is considered a dental procedure that is unlikely to cause bleeding, endodontic surgery, on the other hand, involves the elevation of a flap, ostectomy of overlying bone and the acquisition of a biopsy, and therefore is considered to be a procedure with a higher risk of postoperative bleeding complications (SDCEP 2015). Unfortunately, no specific guidelines for peri-operative management of patients receiving DOACs and undergoing endodontic surgery are available to date.

There is limited literature concerning the risk of bleeding in endodontic procedures. Most of the recommendations available are related to similar procedures in the fields of maxillofacial surgery or periodontology. Thus, the aims of this paper are to review the mechanisms of action of common and novel antithrombotic medications, their impact on endodontic treatment and the current available knowledge of local haemostasis in Endodontics.

Literature search strategy

An electronic literature search was carried out in Medline (PubMed) database using keywords listed in Entree Terms database for articles published in English. The search employed a combined search strategy using the keywords "blood clotting mechanism", "anticoagulant", "anti-platelet", "haemostatic agents in endodontic surgery". This was done to identify articles related to human bleeding mechanisms, antithrombotic drugs and their influence on endodontic treatments and /or in dentistry in general. All titles and abstracts were screened for studies that met the eligibility criteria. Any questionable titles were discussed and the decision to include or exclude was made accordingly once consensus was reached. The published material also included textbooks and guidelines that may not have surfaced in the online

search, which were manually identified along with relevant treatment recommendations for dentistry. Inclusion criteria included studies on humans and animals; exclusion criteria consisted of studies that failed to meet the inclusion criteria, as well as conference proceedings, lectures, and letters to editors.

Review

Drugs interfering with blood clotting

Antithrombotic agents, prescribed to prevent blood clotting and reduce the risk of thromboembolic events, are among the most commonly prescribed drugs by general medical practitioners (Baker *et al.* 2011). There are two main groups of antithrombotic agents: antiplatelet agents, which are usually prescribed to prevent arterial thrombi formation, and anticoagulant agents, which are usually prescribed to prevent venous thrombi formation (Little *et al.* 2002).

Antiplatelet drugs

Aspirin blocks the production of TxA₂ by irreversibly inhibiting cyclooxygenase-1 (COX1), thereby preventing activation and aggregation of platelets (McFadyen *et al.* 2018). It is the first antiplatelet treatment line for acute coronary syndrome (ACS; Lewis *et al.* 1983, Hennekens *et al.* 1997), and in addition, has proven beneficial for secondary prevention and reducing the risk of myocardial infarction (MI) (ISIS-2 1988). Understanding the molecular mechanism of platelet aggregation has led to the development of new antiplatelet drugs (Clopidogrel [Plavix®], Prasugrel [Effient®] and Ticagrelor [Brilinta®]). These new drugs, which prevent platelet aggregation by inhibition of the P2Y₁₂ receptor, are either used alone or in combination with aspirin resulting in antithrombotic effects (ATC 2002) as an abundant number of clinical trials indicate increased reduction of ischaemic events by combining aspirin with P2Y₁₂ blockers (Yusuf *et al.* 2001, Wallentin 2009) (Table 1)

Anticoagulants

Heparin and low molecular weight heparin (LMWH)

Heparin (UFH) is a processed form of a natural polysaccharide that is administered intravenously. It inhibits factors IIa and Xa as well as other factors in the coagulation pathway, thus effectively preventing the formation of the fibrin clot (Brinkhous *et al.* 1939, Lindahl *et al.* 1979), but has two major drawbacks: a wide and unexpected therapeutic window and its intravenous administration. low molecular weight heparin (LMWH, which is administered subcutaneously, enables less constant monitoring as well as treatment in an ambulatory setting (Shaughnessy *et al.* 1995, Gray *et al.* 2008). Therefore, LMWH has replaced UFH as the standard of care, except under certain conditions, specifically kidney failure (Iqbal & Jeffrey 2018).

Warfarin

Warfarin (Cumadin) inhibits the synthesis of vitamin K-dependent clotting factors (II, VII, IX, X) by irreversibly binding to the enzyme epoxide reductase and reducing available vitamin K (Freedman 1992). It is administered orally but has a number of significant drawbacks making it difficult to achieve optimal anticoagulation. It has a long onset time, a narrow therapeutic window, a long half-life, and major drug and food interactions requiring constant monitoring of the patient's international normalised ratio (INR) values (Ansell *et al.* 2008) (Table 2).

The new anticoagulant drugs, Direct Oral Anticoagulants (DOACs).

The drawbacks of the anticoagulants mentioned above have led to the development of a new generation of oral anticoagulants, known as direct oral anticoagulants (DOACs). These newer drugs are characterized by a short onset time, a short half-life, very limited drug and food interactions, and therefore do not require constant monitoring.

Dabigatran etexilate (Pradaxa®, approved 2010), is an active direct thrombin (FIIa) inhibitor that inhibits clot-bound and circulating thrombin (Hauel *et al.* 2002). It is generally given in a fixed dose without monitoring. Its absorption is unaffected by food, and it has a half-life of approximately 12-17 hours in individuals with normal renal function. Maximum anticoagulant effects are achieved within 2-3 hours of ingestion. However, dosing differs according to the clinical indication and the patient's renal function (Burnett *et al.* 2016).

Rivaroxaban (Xarelto®, approved 2011) is a direct FXa inhibitor with a half-life of 5-9 hours. It is generally given in a fixed dose without monitoring,

Apixaban (Eliquis®, approved 2012) is an FXa inhibitor. It is generally given in a fixed dose without monitoring, has a half-life of approximately 12 hours,

Edoxaban (Lixiana®, Savaysa®, approved 2015) is an FXa inhibitor. It is generally given in a fixed dose without monitoring . It has a half-life in the range of 10-14 hours, and its absorption is unaffected by food (Camm & Bounameaux 2011) (Burnett *et al.* 2016) (Table 3).

Perioperative management of patients receiving anticoagulants and/or antiplatelet agents

The management of anticoagulation in patients undergoing surgical procedures is challenging, because interrupting the antithrombotic regimen transiently increases the risk of thrombosis. On the other hand, surgery and invasive procedures have associated bleeding risks that are increased by antithrombotic drugs administered to prevent thrombosis. The decision of whether to modify or temporarily discontinue the patient's antithrombotic regimen depends on the balance between the risk of uncontrolled bleeding and the risk of developing a thrombus (Steed & Swanson 2016).

Thromboembolic risk estimation: A greater risk of a thromboembolic event increases the need to minimize time intervals without anticoagulation. The risk for a thromboembolic event among patients with atrial fibrillation is assessed in accordance with age and comorbidities.

For those with a recent deep vein thrombosis (DVT) or pulmonary embolism (PE), the risk is estimated based on the interval since diagnosis. If thromboembolic risk is transiently increased (i.e. recent stroke or pulmonary embolism), surgery should be delayed until the risk returns to baseline, if possible. For patients with more than one condition that predisposes thromboembolism, the condition with the highest thromboembolic risk takes precedence.

Bleeding risk estimation: A higher bleeding risk confers a greater need for perioperative haemostasis, and hence a longer period of anticoagulant interruption. The risk of bleeding is dominated by the type and urgency of surgery; the patient's comorbidities may also contribute. Procedures with a low risk of bleeding (i.e. simple dental extractions or minor skin surgery) can often be performed without interruption of anticoagulation. The timing of anticoagulant interruption depends on the specific agent the patient is receiving. For example, warfarin requires earlier discontinuation than shorter-acting target-specific oral anticoagulants (i.e. dabigatran, rivaroxaban, and apixaban).

Determining whether to use bridging anticoagulation: For patients receiving warfarin, the interval without an anticoagulant may be as long as 5-6 days, due to the long half-life of warfarin and the time required to reach the therapeutic international normalized ratio (INR). A range of 24-48 hours is sufficient in the case of DOACs. The use of heparin or low molecular weight heparin (LMWH) to reduce the interval without anticoagulation (i.e. bridging anticoagulation) may be appropriate for some patients, especially those who have a high thromboembolic risk and are taking warfarin.

Dental and endodontic considerations

Dental procedures are generally classified into those with high risk of bleeding and those with low risk of bleeding (SDCEP 2015). Low risk procedures such as scaling and/or root planing, restorative treatment, non-surgical endodontic treatment, simple extractions, or minor surgery generally do not require any alteration in the antithrombotic regimen, as the risk of thrombosis far outweighs the risk of uncontrolled haemorrhaging. Procedures associated with

a high risk of bleeding (e.g. surgical extractions, multiple extractions, more complex oral surgery, or head and neck cancer surgery) require a multidisciplinary approach preoperatively to prevent uncontrolled haemorrhaging (Bisbe & Molto 2013, Kozek-Langenecker *et al.* 2017).

Also it should be noted that the evidence and recommendations described below generally refer to patients without other major underlying conditions (a history of liver disease, biliary tract obstruction, malabsorption problems, infectious diseases, genetic coagulation disorders, chronic inflammatory diseases, chronic renal disease, leukaemia or other types of cancer, and whether the patient has received chemotherapy, radiation therapy or has been exposed to large amounts of radiation), which might alter the decision to continue with anticoagulation treatment. Such conditions may have a profound effect both on the patient's baseline tendency of bleeding and on the pharmacokinetics of the antithrombotic agents (Little *et al.* 2018). These complex patients should be closely supervised by the attending haematologist, and may require even more meticulous adjustments to their antithrombotic regimen.

Perioperative management of aspirin and newer antiplatelet drugs. A systematic review (Napeñas *et al.* 2013) found no significant risk of postoperative bleeding complications among patients on either single or dual antiplatelet therapy, who were undergoing invasive dental procedures. A retrospective study (Doganyay *et al.* 2018) supports the current recommendation of the American Dental Association (ADA 2018), stating that in an otherwise healthy individual there is no need to discontinue antiplatelet therapy prior to dental procedures, and the use of local haemostatic measures is sufficient. The attending physician must be consulted prior to treating patients with a higher bleeding tendency. Although dual antiplatelet therapy can theoretically increase the risk of subsequent bleeding, controlled studies have repeatedly and consistently shown that dental surgery in patients receiving dual antiplatelet therapy is safe and local measures for haemostasis are sufficient for controlling bleeding (Napeñas *et al.* 2013, Doganyay *et al.* 2018).

Perioperative management of heparin. Most patients taking heparin are hospitalized, and their medication upon discharge is changed to warfarin. Surgery may be performed 2-4 hours after discontinuation of heparin. Patients taking LMWH (e.g. Enoxaparin, Clexane®) may undergo invasive dental procedures 12 hours following drug discontinuation (Little *et al.* 2002). Local haemostatic measures are to be used in the event of postoperative bleeding. These patients are usually not monitored. LMWH therapy may be restarted after achieving haemostasis (such as Hexakapron®). Another option is to delay elective dental procedures until LMWH therapy is terminated. It is advisable to consult the attending physician prior to choosing one of the above-mentioned options.

Preoperative management of warfarin. The available literature supports continuing warfarin therapy while undergoing minor dental procedures or other invasive dental procedures when INR values do not exceed 3.5 (Iqbal & Jeffrey 2018). A systematic review and meta-analysis (Nematullah *et al.* 2009) did not find increased bleeding risk with continued warfarin therapy, when compared to treatment discontinuation or dose adjustment in patients undergoing single or multiple extractions. Another systematic review (Weltman *et al.* 2015) dealing with the management of patients undergoing extractions and taking warfarin supports this finding. However, the available literature is not as decisive regarding major surgical procedures. For patients with bleeding problems such as liver disease or kidney disease or taking additional drugs (e.g. aspirin, antibiotics, nonsteroidal anti-inflammatory drugs (NSAIDs)) treatment must be planned individually. In general, with reference to all patients taking warfarin the dentist must consult with the haematologist (Little *et al.* 2018).

Perioperative management of DOACs

Dabigatran can be omitted for 2-3 days before a surgical procedure in patients with normal or mildly impaired renal function (i.e. creatinine clearance >50 mL/minute), and 2-4 days before the procedure in those with more severe renal insufficiency (e.g. creatinine clearance between 30 and 50 mL/minute), with longer intervals used for procedures with a greater risk of

bleeding and shorter intervals for surgeries with lower bleeding risks. The last preoperative day on which Dabigatran is administered can be more closely estimated based on the half-life of Dabigatran, which varies according to renal function, namely 12-14 hours in patients with normal renal function (Keeling *et al.* 2016, Tafur & Douketis 2018).

Rivaroxaban can be omitted the day before endodontic surgical procedure. These intervals are based on a half-life elimination of 7-11 hours and apply to individuals with normal renal function or mild renal insufficiency (Keeling *et al.* 2016, Tafur & Douketis 2018). No discontinuation is needed prior to non- surgical endodontic treatment.

Apixaban can be omitted the day before endodontic surgical procedure. These intervals are based on a half-life elimination of 8-12 hours. These intervals apply to individuals with normal renal function or mild renal insufficiency (e.g. creatinine clearance >50 mL/minute), No discontinuation is needed prior to non- surgical endodontic treatment.. (Keeling *et al.* 2016, Tafur & Douketis 2018).

Edoxaban can be omitted the day before endodontic surgical procedure. These intervals are based on a half-life elimination of 10-14 hours. These intervals apply to individuals with normal renal function or mild renal insufficiency (e.g. creatinine clearance >50 mL/minute) No discontinuation is needed prior to non- surgical endodontic treatment. (Keeling *et al.* 2016, Tafur & Douketis 2018) (Table 3).

Elad *et al.* (2016) referred to the DOACs mentioned above with regard to bleeding risks in 18 randomized controlled trials which compared new drugs with conventional anticoagulants or placebo. According to that review, the authors proposed the following options:

- (1) continue the anticoagulant therapy without changes,
- (2) delay the next drug dose (administration following the procedure or skip a dose) or delay the procedure for as long as possible after the last drug dose, and
- (3) temporarily discontinue the drug for 24-48 hours.

Their conclusion was that the first two options are suitable for most dental procedures, but warrant comparative clinical studies to confirm these findings.

A systematic review (Lusk *et al.* 2018) conducted on the management of DOACs in patients in need of procedures with a low (e.g. local anaesthesia, simple exactions, supra-gingival scaling, single tooth extractions) to moderate (e.g. extractions of 2-4 teeth and a local periodontal surgery on up to 5 teeth) risk of bleeding concluded that the frequency of bleeding was low regardless of whether the drug was discontinued or not before the procedure, and that control of bleeding could be achieved with local haemostatic measures. An further systematic review (Chahine *et al.* 2019) that divided the different procedures according to the levels of bleeding, included procedures with a higher risk of bleeding such as a biopsy and endodontic surgery and concluded that for most dental procedures there is no need to discontinue administration of the drug. Nonetheless, a multidisciplinary approach must be taken for patients with a more complex systemic condition and/or procedures with an increased risk of bleeding.

Endodontic surgery

Dental surgery is generally considered a procedure with minor bleeding risk and with the possibility for adequate local haemostasis. Most professional statements on dental surgery advise not to suspend DOACs treatment and avoid the use of NSAIDs.²⁷⁴ However, recommendations are often based on a low quality of evidence and mainly rely on available pharmacological information.²⁷⁵ Endodontic root end resection can generally be performed safely in an outpatient facility by applying local haemostatic measures, without interrupting anticoagulation or by just skipping the morning dose of the DOACs.²⁷⁶⁻²⁷⁹ Periprocedural management includes specific haemostatic techniques including the use of oxidized cellulose or absorbable gelatin sponge, sutures, tranexamic acid mouthwashes, or compressive gauze soaked in tranexamic acid.

Antithrombotic agents and endodontic surgery

Endodontic surgery requires the elevation of a mucoperiosteal flap and osteotomy, and is thus considered a procedure with a high risk of bleeding (Spyropoulos & Douketis 2012). One of the objectives of endodontic surgery is to hermetically seal the root canal system, thereby enabling healing by forming a barrier between the irritants within the confines of the affected root and tissues surrounding the root (von Arx *et al.* 2006). In addition to the primary objective of avoiding excessive blood loss, the ability to achieve sustained tissue haemostasis during endodontic surgery is crucial to the outcome of the procedure. Achieving adequate control of bleeding improves vision in the surgical site, minimizes surgical time, enhances the surgical procedures (root-end resection, preparation, and filling), and reduces surgical blood loss, postsurgical haemorrhage, and postsurgical swelling (Witherspoon & Gutmann 1996). In addition to increased risk of all of the above, inadequate haemostasis may jeopardize the integrity of the root-end filling material (Gutmann & Harrison 1991, Johnson & Fayad 2016).

Primary control of bleeding starts before the incision is made with the injection of a vasoconstrictor local anaesthetic agent, such as 1:50,000 epinephrine with 2% lidocaine (Gutmann 1993). Secondary control of bleeding is achieved by topical haemostats or local haemostatic agents such as bone wax, epinephrine, ferric sulphate, thrombin, calcium sulphate, gelfoam, absorbable collagen, microfibrillar collagen, and surgicel (Kim & Kratchman 2006). Another common haemostatic agent is tranexamic acid. However, studies have not shown any significant decrease in haemorrhage when tranexamic acid is used intraoperatively through mouthwash, irrigation, or soaked gauze (Ramström *et al.* 1993) (Table 4).

A patient taking antithrombotic medication is expected to have a greater tendency to bleed. Nonetheless, no studies were found that investigated whether intra-operative bleeding can be adequately controlled using local haemostatic measures in patients taking anti-thrombotic medication and undergoing endodontic surgery.

Another aspect of endodontic surgery is the management of post-surgical pain and swelling, as surgical endodontic treatment is considered to cause the most post-operative pain among all dental treatments (Seymour *et al.* 1986, Kvist & Reit 2000, Tsesis *et al.* 2003). Both the administration of systemic low-dose corticosteroids or nonsteroidal anti-inflammatory drugs (NSAIDs) can effectively manage post-operative pain and swelling (Lin *et al.* 2006).

However, drug-drug interactions among patients taking antithrombotic agents must be taken into account. Although a 10-day course of prednisolone (0.5 mg/kg per day) induces a procoagulant state in healthy subjects (Majoor *et al.* 2016), there is no evidence indicating that low-dose systemic administration of corticosteroids for shorter periprocedural periods (3-4 days) has any effect on the coagulative state of the patient.

NSAIDs, on the other hand, do affect haemostasis. Whereas aspirin covalently acetylates and irreversibly inhibits cyclooxygenase, other NSAIDs reversibly inhibit cyclooxygenase (Ikeda 1977, Stanford *et al.* 1977). Additionally, ibuprofen and other non-aspirin NSAIDs protect platelets from irreversible inactivation from aspirin, presumably by blocking access of aspirin to the active site of cyclooxygenase (Rao *et al.* 1983). All non-aspirin NSAIDs interfere with platelet function by essentially the same mechanism; the *in vivo* differences among these agents are primarily related to the extent and duration of their effects on the function of platelets. In addition to their antiplatelet function, NSAIDs can affect the pharmacologic action of warfarin through their direct interaction. High protein binding and the cytochrome P450 (CYP)-dependent clearance mechanisms of NSAIDs can affect the serum levels of warfarin (Brouwers & de Smet 1994, Harder & Thurmann 1996, Kvist & Reit 2000, Tsesis *et al.* 2003, van Dijk *et al.* 2004). Accordingly, many case reports describe bleeding complications after NSAIDs were administered along with warfarin (Stading *et al.* 2001, Knijff-Dutmer *et al.* 2003). It has also been reported that both the transient or prolonged combination of NSAIDs with DOACs pose a serious risk of bleeding (Ikeda 1977, Stanford *et al.* 1977, Davidson *et al.* 2014, Kent *et al.* 2018), and it appears there is a low risk of potentiated bleeding for patients concomitantly taking LMWH and NSAIDs (Weale *et al.*

1995). Consequently, the benefits of perioperative NSAIDs must be weighed against the increased risk of unnecessary bleeding complications (Table 3).

Local haemostasis in endodontic surgery

Haemostasis is the process whereby bleeding is controlled (McClanahan *et al.* 2020). Adequate control of bleeding is essential for the success of periapical surgery since it improves visualization of the surgical site, minimizes operating time, and provides a dry field for the placement of retrograde filling material (Witherspoon & Gutmann 1996). Even mild haemorrhaging during endodontic surgery can cause complications during the surgical procedure and therefore jeopardize the success of the treatment. Excessive bleeding which cannot be controlled by local measures in the dental clinic should be referred to the nearest emergency department and managed appropriately (Selim *et al.* 1987). A detailed medical history must be obtained before any surgical procedure in order to avoid uncontrollable bleeding, and this is of even greater importance when treating patients with bleeding disorders or under antithrombotic therapy. Excessive bleeding may occur even if only relatively small blood vessels are damaged during the surgical procedure (Selim *et al.* 1987, Reich *et al.* 2009), and treatment planning and postoperative management should be focused on minimizing the risk of excessive bleeding even in healthy patients (Witherspoon & Gutmann 1996, Kim & Kratchman 2006, Rosen & Tsesis 2016). The preoperative treatment planning of flap design and osteotomy should focus on avoiding anatomical structures such as major blood vessels in the maxillofacial region and the submental and sublingual arteries in the mandible, thus reducing the risk of severe haemorrhaging and massive haematomas (Selim *et al.* 1987, Witherspoon & Gutmann 1996, Reich *et al.* 2009). Thus, more emphasis needs to be placed on patients on anti-thrombotic medication, due to the fact that the ability to modify the patient's antithrombotic regimen and minimize intraoperative bleeding is limited by the risk of a thromboembolic event. Routine measures regarding local haemostasis must be utilized even more effectively and meticulously in such patients in order to avoid uncontrollable

bleeding and maintain an appropriate surgical area. This is achieved first by the use of a vasoconstrictor containing local anaesthetic agent and second by local application of various materials which induce the rapid development of an occlusive clot, either by producing a physical barrier or by enhancing the clotting mechanism and vasoconstriction (or both).

Epinephrine used with local anaesthetics mainly binds to α adrenergic receptors located on the vascular smooth muscles in the oral mucosa, sub-mucosa and periodontium, which result in vasoconstriction (Kim & Kratchman 2006). Thus, the drug's predominant effect in the oral mucosa, sub-mucosa and periodontium is vasoconstriction. Consequently, a high concentration of vasoconstrictor containing anaesthetic, e.g. 1:50,000 epinephrine, is preferred to obtain effective vasoconstriction for lasting haemostasis (Buckley *et al.* 1984, Gutmann 1993, Kim *et al.* 2001). The systemic effects associated with epinephrine are dose and route dependent and it has been shown that the amount and concentrations of epinephrine used in endodontic surgery does not usually elicit dramatic and persistent systemic cardiovascular responses (Vy *et al.* 2004). The currently recommended maximum dosage of epinephrine 1:50,000 in local anaesthetics is 5.5 cartridges and clinicians should use the appropriate dose with an aspirating syringe (Malamed 2020). This dose is recommended for local anaesthesia in the majority of cases but should be lowered with epinephrine-sensitive individuals, often those taking antithrombotic therapy. As a result, consultation with the patient's physician before surgery should be routine and included in the surgery protocol.

Secondary haemostasis after the incision is made and the flap is elevated, is achieved by the application of commonly used topical haemostats. Such materials must provide haemostasis for the entire duration of the procedure, be completely resorbed or easily removed once the procedure is completed, to avoid adversely affecting the healing process, while being cost-effective. Not all local haemostats fulfil the above-mentioned requirements. Although common local haemostatic agents include bone wax, epinephrine, ferric sulphate, thrombin, calcium sulphate, gelfoam, absorbable collagen, microfibrillar collagen and surgicel (Kim &

Kratchman 2006), the two most highly recommended and routinely used are epinephrine pellets and ferric sulphate (Rethnam-Haug *et al.* 2018).

Epinephrine cotton pellets

Commercial cotton pellets containing racemic epinephrine HCl usually provide good local haemostasis during periapical surgery (Vickers *et al.* 2002). There has been concern regarding systemic cardiovascular effects when using such products, as addressed in a number of studies. Besner (Besner 1972) reported that the pulse rate of patients did not change when one Racellet pellet containing an average of 1.15 mg of epinephrine HCl was used during periapical surgery. In a later study, Vickers *et al.* (Vickers *et al.* 2002) measured blood pressure and pulse rate changes in 39 patients when 1-7 racemic-epinephrine cotton pellets (Racellet ® size 3) were left in the bony crypt for two to four minutes, and concluded that there was no evidence of significant cardiovascular changes. These findings were later confirmed by Vy *et al.* (2004) who concluded that placement of 2.25% racemic epinephrine in CollaCote collagen had little or no effect on the blood pressure and pulse rate of patients during surgical endodontics. Based on the available evidence, it appears that the systemic cardiovascular effect of cotton pellets containing epinephrine is minimal. This lack of systemic effects is probably due to the fact that epinephrine used typically causes immediate local vasoconstriction with little absorption in the systemic circulation.

Ferric sulphate

Ferric sulphate or ferric subsulphate is a haemostatic agent which causes agglutination of blood proteins as a result of the reaction of blood with both ferric and sulphate ions and with the acidic pH (0.21) of the solution (Evans 1977). The agglutinated proteins form plugs that occlude the capillary orifices. Because of its low pH, and although this material is very cytotoxic and must be used with caution, systemic absorption of ferric sulphate is unlikely, because the coagulum isolates it from the vascular supply.

Calcium sulphate

Calcium sulphate, also known as plaster of Paris, has been primarily used in dentistry to fill large surgical bone defects, as a barrier material in guided tissue regenerative procedures, and for repair of furcation defects (Gutmann 1993). It has also been recommended as haemostatic material during periapical surgery where it acts as a physical barrier lining the walls of the bony crypt and plugging vascular channels, thus preventing bleeding (Pecora *et al.* 1997, Kim & Kratchman 2006). It is resorbable material and after placing it in the bony crypt, using wet cotton pellets, and packing it against the crypt walls, it can be carved away to allow access to the root-end (Gutmann 1993, Kim & Rethnam 1997, Pecora *et al.* 1997). Calcium sulphate does not affect the healing process which involves the deposition of cementum and osseous healing (Apaydin *et al.* 2004), and is gradually removed from the site of implantation regardless if new bone has formed or not (Clokie *et al.* 2002). After completion of root-end filling, the residual calcium sulphate can be removed or left in the bony crypt.

Collagen-based materials

Various collagen-based haemostatic agents obtained from bovine sources and supplied in sheets and sponge pads are available for use as local haemostatic agents such as Hemopatch (Sealing Hemostat, Baxter AG, Vienna, Austria) (Gutmann 1993). The mechanisms by which collagen products achieve haemostasis involve the stimulation of platelet adhesion, platelet aggregation and release reaction (Kay *et al.* 1977, Kay *et al.* 1977), activation of factor XII (Hageman factor) (Mason & Read 1974, Mason & Read 1975) and mechanical tamponade at the collagen-blood wound interface. Collagen creates minimal interference in the wound healing process, with a limited foreign body reaction (Haasch *et al.* 1989). A study that examined the effects of haemostatic agents on peripheral nerve function in rats concluded that bovine collagen is the most suitable haemostatic agent compared to bone wax, gelatin sponge, and Surgicel (Hunt & Benoit 1976).

Aluminium Chloride

Several studies have shown that aluminium chloride elicits inflammatory tissue reactions (Barr *et al.* 1993, Abdel Gabbar & Aboulazm 1995). To prevent such reactions, it is currently recommended to curette and freshen the walls of the bony crypt with a round bur and rinse the surgical site with saline before wound closure when using aluminium chloride as a haemostatic agent in periapical surgery (von Arx *et al.* 2006). Aluminium chloride in combination with ferric sulphate has proved to be the most effective test material to control bleeding within bony defects. However, in that same study, aluminium chloride demonstrated a foreign body reaction and the presence of giant cells and other inflammatory cells after three weeks and 12 weeks post-surgery (von Arx *et al.* 2006).

Cautery/Electrosurgery

Cautery stops the flow of blood through coagulation of blood and tissue proteins, leaving an eschar that the body attempts to slough (Trent 1993). The effect of cautery in the bony crypt during periradicular surgery has not been studied to date. However, the effect of electrosurgery on alveolar bone has been studied in periodontal surgery demonstrating greater tissue destruction in areas exposed to electrosurgery and delayed healing compared with surgical sites not exposed to electrosurgery (Azzi *et al.* 1983)

Gelfoam

Gelfoam is a gelatin-based sponge that is water insoluble and biologically resorbable (Ibarrola *et al.* 1985, Witherspoon & Gutmann 1996, Kim & Kratchman 2006). It stimulates the intrinsic clotting pathway by promoting platelet disintegration and the subsequent release of thromboplastin and thrombin (Evans 1977). Ibarrola *et al.* compared the response of rat tibias to bone wax, Surgicel, and Gelfoam histologically (Ibarrola *et al.* 1985). At the end of the 120-day experiment period, Gelfoam usually resorbed completely and the bone defects healed adequately.

Surgicel

Surgicel, a chemically sterilized material prepared through oxidation of regenerated alpha cellulose (oxycellulose), and bone wax, a material composed of approximately 88% highly purified bees wax and 12% iso-propyl palmitate, are rarely used today in endodontic surgery. Surgicel has a pH of 3 and if left in the wound can retard healing (Selden 1970, Nappi & Lehman 1980). Use of Surgicel in extraction sockets resulted in greater postoperative pain compared with a control in a split mouth–designed study (Petersen *et al.* 1984). Bone wax is a nonabsorbable material and is known to cause retarded bone healing and predisposition of the infection (Culliford *et al.* 1976, Nelson *et al.* 1990) by producing a chronic inflammatory foreign body reaction (Aurelio *et al.* 1984). Thus, it is not recommended for use in endodontic surgery (Witherspoon & Gutmann 1996, Samudrala 2008, Penarrocha-Oltra *et al.* 2019).

Antithrombotic agents and non-surgical endodontic treatment

Primary and secondary root canal treatment (RCT) can be performed without interruption of antithrombotic medication. In primary RCT complete pulp extirpation is indicated for elimination of pain and the bleeding from the root canal system. In the event of persistent bleeding despite complete pulp extirpation tranexamic acid (Hexakapron®) may be placed in the root canal with a syringe followed by the insertion of a paper point to the measured working length. The procedure may be repeated if haemostasis is not achieved within 5 minutes. If bleeding still cannot be controlled a calcium hydroxide dressing for one week is indicated. The same measures are indicated for secondary RCT following removal of root canal filling material, but only after root perforation has been ruled out.

Vital pulp treatments should also be performed without interruption of antithrombotic medication, and haemostasis should be achieved using cotton pellets soaked with sodium hypochlorite (0.5%–5%) or chlorhexidine (0.2%–2%). If haemostasis cannot be controlled after 5 minutes, additional pulp tissue should be removed (Table 5).

Conclusion

The drawbacks of classic anticoagulants have led to the development of a new generation of oral anticoagulants, known as direct oral anticoagulants (DOACs). These newer drugs are characterized by a short onset time, a short half-life, are not affected by food, have limited drug interactions, do not require constant monitoring and have limited drug interactions. The attending dentist should become familiar with the various drugs on the market, their working mechanisms, and potential interaction with other drugs.

Conflict of interest

The authors have stated explicitly that there are no conflicts of interests in connection with this article.

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Figure legends

1. The platelet mechanism
2. The blood cascade model of clotting comprises of intrinsic and extrinsic pathways and converge into the common pathway

Table 1 – Major characteristics of common antiplatelet agents

Antiplatelet drug	Mechanism of action	Dose (mg)	Half-life (hours)	Time to peak (hours)	Time to recover platelet function after drug withdrawal	Excretion
Aspirin	COX-1 inhibitor	Oral Loading 325mg 75–325 mg daily	Dose-dependent 2-3 h for low doses	2-4	30% at 48 h	Urine (+ sweat, saliva, feces)
Clopidogrel	P2Y12 receptor inhibitor	Oral Loading 300–600 mg 75 mg daily	6-8 h	3-5	40% at 3 days	Urine and bile
Prasugrel	P2Y12 receptor inhibitor	Oral Loading 60 mg 10 mg daily	5-9 h	2-8	2–3 days	Urine (2/3) and feces (1/3)
Ticagrelor	P2Y12 receptor inhibitor	Oral Loading 180 mg 90 mg twice a day	7-9 h	2 (taken with high-fat meal)	57% at 24 h	Bile

Table 2 – Major characteristics of classic anticoagulants

Anticoagulant	Coagulation factors inhibited	Dose	Half-life elimination (hours)	Time to peak (hours)	Excretion
UFH	Thrombin (FIIa), FIXa, FXa, FXIa, FXIIa.	IV: A loading dose of 5000 units followed by continuous administration of 1000-2000 units/hour.	1.5	2-4	Renal (50%)
LMWH	Thrombin (FIIa), FIXa.	SC: 1 mg/kg every 12 hours (therapeutic dosage)	3-7	3-5	Renal (40%)
Warfarin	Vitamin K-dependent coagulation factors (FII, FVII, FIX, FX).	Oral: Customized dosing according to target INR. Doses range from 1-20 mg once daily.	25-60	2-8	Renal (80%) Faeces (20%)

UFH – Unfractionated heparin

LMWH – Low molecular weight heparin

IV – Intravenous

SC – Subcutaneous

Table 3 – Major characteristics of direct oral anticoagulants (DOACs)

Anticoagulant	Coagulation factors inhibited	Dose	Half-life elimination (hours)	Time to peak (hours)	Excretion
Dabigatran	Thrombin (FIIa).	Oral: 110- 150 mg twice a day.	12-17 hours	2 (taken with high-fat meal)	Renal (80%)- unchanged form Biliary (20%)
Rivaroxaban	FXa	Oral: 20 mg /day	5–9 hours (healthy) 9–13 hours (elderly)	2-4	Renal (67%) – 33% in unchanged form Hepatobiliary (33%)
Apixaban	FXa	Oral: 2.5-5 mg twice daily	8–15 hours	3-4	Renal (27–30%) Hepatobiliary (70%) – direct intestinal (major) and biliary (minor)

Edoxaban	FXa	Oral: 30-60 mg/day	10–14 hours	1-2	Renal (50%) – unchanged form Hepatobiliary (50%)
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Table 4 – Systemic and local measures for controlling bleeding during endodontic microsurgery

Systemic Drugs	Local Bleeding
Aspirin – no interruption.	Arresting bleeding from an arterial vessel is possible
Clopidogrel, Ticagrelor – stop 5 days before surgery.	with local pressure for 2 minutes or with the use of a haemostat. Cotton pellets soaked in epinephrine
Prasugrel – stop 7 days before surgery.	1:50,000 or cotton pellets soaked in ferric sulphate
Dual antiplatelet therapy – interruption of non-aspirin drug.	(Astringedent™).
Heparin – stop 2-4 hours before surgery.	
LMWH – stop 12 hours before surgery.	
Dabigatran – 3 days before surgery.	
Warfarin – no interruption with target INR \leq 3.	
All other DOACs – 2 days before surgery.	
* All of the above are according to the individual risks vs. benefits and hematologic consultation.	

Table 5 – Measures for controlling bleeding during non-surgical endodontic treatment

Treatment	Systemic Drugs	Local Bleeding
Primary root canal treatment. Persistent canal bleeding in previously un-treated root canals.	Perform the procedure without interruption of antithrombotic medication.	Complete pulp extirpation and instrumentation is indicated. Tranexamic acid (Hexakapron®) may be dripped into the canal with a syringe, followed by the insertion of a paper point to the measured working length. The procedure may be repeated. If haemostasis is not achieved within 5 minutes, if bleeding still cannot be controlled calcium hydroxide dressing for one week is indicated.
Secondary root canal treatment. Persistent canal bleeding in previously treated root canals.	Perform the procedure without interruption of antithrombotic medication.	The same measures as for primary root canal treatment following removal of root canal filling material, but only after perforation has been ruled out.
Vital pulp treatment	Perform the procedure without interruption of antithrombotic medication.	Haemostasis should be achieved using cotton pellets soaked with sodium hypochlorite (0.5%–5%) or chlorhexidine (0.2%–2%). If haemostasis cannot be controlled after 5 minutes, further pulp tissue should be removed.