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# Haemostasis Part 2: Medications that Affect Haemostasis

**Abstract:** Post-operative haemorrhage is a recognized complication in dental practice. This may be more prevalent in patients taking anti-thrombotic medications. It is important that the dentist understands the mechanism of action of these drugs and how they may affect management of dental patients.

**Clinical Relevance:** Dental professionals must be aware of those medications affecting haemostasis and how they may impact on management. The emergence of different therapeutic regimens has increased the number of such drugs.

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For many years, warfarin has been the most commonly used oral anticoagulant in the United Kingdom; however, as a long term medication it has disadvantages. This has led to the introduction of a number of new anticoagulant regimens that can impact on dental practice. Other medications, such as aspirin, are also used regularly for their anti-thrombotic effect. A clear understanding of oral anticoagulant therapy and the

indications for treatment provision or suitable referral is important.

## Indications for anti-thrombotic therapy

Prescribed medications are used to reduce the risk of a thrombo-embolic event. A thrombus is most likely to occur within a damaged vessel or heart wall. The pathologist Rudolph Virchow adopted a triad of risk factors for thrombo-embolism (Figure 1). These include:

- A hypercoagulable state;
- Vessel wall damage;
- Stasis of blood.

The prevention and treatment of thrombo-embolism is the main indication for anticoagulant use. Table 1 shows the most common examples.

## Types of anti-thrombotic agents

Some consideration should be given to the action of the different therapies available. They can be split into 3 main categories according to their action:

1. Antiplatelet drugs – interfere with

platelet function and adhesion;

2. Anticoagulant drugs – stop the clot formation by interfering with the clotting cascade;
3. Thrombolytic drugs – cause the breakdown of clots that are already formed (predominantly used immediately following a myocardial infarction).

Table 2 shows commonly used examples of each.

Figure 2 shows the coagulation timeline with the point of action of the different anti-thrombotic agent's action shown.

### Antiplatelet drugs

#### *Aspirin (acetylsalicylic acid)*

Aspirin is a non-steroidal anti-inflammatory drug that acts by irreversibly inhibiting cyclo-oxygenase activity. Within platelets this results in a lack of production of thromboxane A<sub>2</sub> (a powerful chemical released by platelets causing aggregation and vasoconstriction). This effect occurs at lower doses than those required for analgesia and lasts for the lifetime of the platelet. Aspirin has been shown to reduce mortality following a myocardial infarction. It is unsuitable for children (causing Reye's

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syndrome) and may cause gastro-intestinal bleeding in adults as a common side-effect.

**Dipyridamole**

Dipyridamole inhibits the aggregation of platelets by reducing thromboxane A2 production. It is generally used as an adjunct to other anticoagulants. It is indicated in the prophylaxis of thrombo-embolism associated with prosthetic heart valves.<sup>1</sup>

**Clopidogrel**

Clopidogrel blocks adenosine diphosphate (ADP) by inhibiting a receptor on platelet cell membranes. ADP is stored

in platelets and causes further platelet activation. Clopidogrel is used mainly for the prevention of ischaemic events in patients with a history of symptomatic ischaemic disease. It is commonly used as long term management for patients who have had a myocardial infarction.

**Prasugrel and ticagrelor**

Prasugrel and ticagrelor are ADP inhibitors used in combination with aspirin. Prasugrel is indicated to treat patients with acute coronary syndrome undergoing percutaneous coronary intervention,<sup>2</sup> whilst ticagrelor was more recently indicated to treat acute coronary syndrome.<sup>3</sup>

**Abciximab, eptifibatide and tirofiban**

Abciximab, eptifibatide and tirofiban are antiplatelet drugs given intravenously. They act as glycoprotein IIb/IIIa inhibitors that block platelet aggregation by stopping fibrinogen binding to receptors on platelets. They are used to treat unstable angina or a non ST-segment-elevation myocardial infarction (NSTEMI).

Table 3 outlines the oral antiplatelet preparations currently available in the UK.

**Dual therapy of antiplatelet medication**

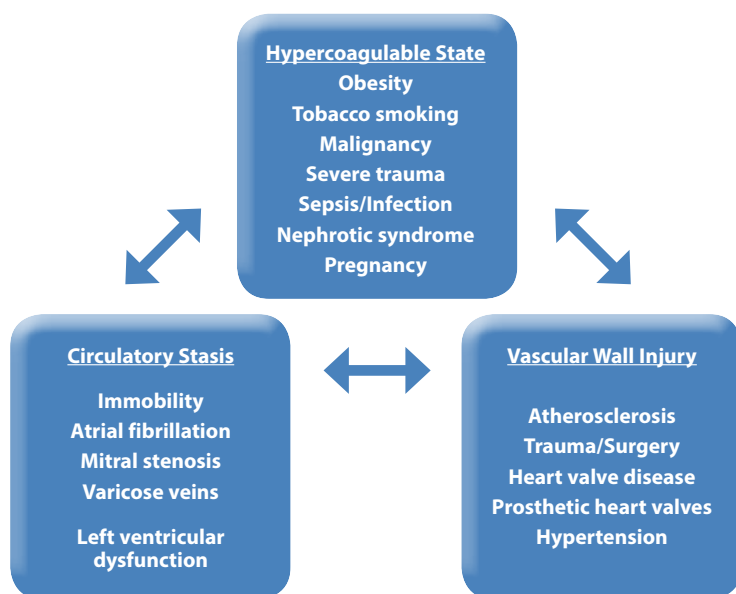
A number of evidence-based indications exist for the appropriate use of dual therapy antiplatelet medications. Clopidogrel and low-dose aspirin are advocated in the management of unstable angina and NSTEMI.<sup>4</sup> Aspirin and dipyridamole are used synergistically to prevent cerebrovascular accidents. A dual therapy of Clopidogrel and aspirin is more likely to cause a post-operative bleed than that of aspirin and dipyridamole.<sup>5</sup> Aspirin is also used in conjunction with prasugrel or ticagrelor in certain situations of acute coronary syndrome.

**Dental implications regarding antiplatelet therapy**

It is imperative that no antiplatelet medication is stopped for any form of dental treatment without direct consultation with the cardiologist in charge of the patient's care. The risk of a thrombo-embolic event following cessation of medication is greater than that of a post-operative bleed.<sup>6</sup>

Antiplatelet medication increases bleeding time but this may not be clinically relevant. The North West Medicines Information Centre has produced guidelines on the *Surgical management of the primary care dental patient on antiplatelet medication*.<sup>5</sup> The most recent update of this document was in August 2010 and its conclusions include:

- Patients are more at risk of permanent disability or death if they stop antiplatelet medication prior to a dental procedure than if they continue it;
- Patients should not have their antiplatelet medication altered or stopped without



**Figure 1.** Thrombo-embolic risk factors (Virchow's Triad).

<p><b>Prophylaxis of:</b></p> <ul style="list-style-type: none"> <li>■ Myocardial infarction (High risk patients and recurrence)</li> <li>■ Venous thrombo-embolism (Including peri-operatively and hospital admission)</li> <li>■ Cardiac thrombo-embolism (Atrial fibrillation, prosthetic heart valve)</li> <li>■ Thrombosis in chemotherapy for stage IV breast cancer</li> </ul> <p><b>Treatment of:</b></p> <ul style="list-style-type: none"> <li>■ Venous thrombo-embolism</li> <li>■ Critical limb ischaemia</li> <li>■ Acute myocardial infarction</li> <li>■ Acute coronary syndrome (ACS)</li> </ul>
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**Table 1.** Indications for oral anticoagulants.<sup>1</sup>

- consulting the interventional cardiologist;
- Bleeding complications following dental procedures, while inconvenient, do not carry the same risks as thrombo-embolic complications;
  - Post-operative bleeding after dental procedures can be controlled using local haemostatic measures in patients taking mono or dual antiplatelet therapy.

There is no reason for this cohort of patients to require referral to a secondary care setting on the basis that they receive antiplatelet therapy. The patient taking

antiplatelet medication may have several co-morbidities (eg liver disease, renal failure, other bleeding disorder) and therefore may justify a referral or have a plan directed by the haematologist. It is important to ask patients about previous 'bleeding experiences', ascertaining how they coped with previous dental surgery or cuts/lacerations. It is appropriate to consider the correct timing of treatment. Patients that are at high risk of post-operative bleeding should be seen in the early morning and preferably at the start of the week. This

allows an increased time period post-operatively for review and the management of any problems, should they arise.

Platelet levels are part of a full blood count and normally range between 150–450x10<sup>9</sup>/L. Levels below 100x10<sup>9</sup>/L indicate the need for haemostatic packs and sutures; levels below 50x10<sup>9</sup>/L may require prophylaxis either by platelet transfusion or systemic steroids, depending upon the underlying cause.

### Oral anticoagulants

Warfarin, acenocoumarol, coumarins and phenindione are oral anticoagulants that antagonize the effects of vitamin K. These drugs take 48–72 hours for their anticoagulant effect to occur fully. Vitamin K is required for the formation of clotting factors II, VII, IX and X. Warfarin is the drug of choice in the UK. It is used to treat deep-vein thromboses, pulmonary embolism and prophylaxis treatment for atrial fibrillation and metallic heart valves.

#### Warfarin

Warfarin was discovered in 1948 and is named after the 'Wisconsin Alumni Research Foundation' (WARF-), with the ending (-ARIN) linking it to the coumarins. It is metabolized by the cytochrome P450 enzymes in the liver.

The dose of warfarin (usually 1–10 mg daily) must be monitored at regular intervals by assessing the INR (International Normalized Ratio). This is a measure of prothrombin time (PT), which assesses the extrinsic pathway of the clotting cascade.

Drug Type	Example
<b>Antiplatelet</b>	<ul style="list-style-type: none"> <li>■ Aspirin</li> <li>■ Dipyridamole</li> <li>■ Clopidogrel</li> <li>■ Prasugrel</li> <li>■ Ticagrelor</li> <li>■ Abciximab/Eptifibatide/Tirofiban (IV preparations)</li> </ul>
<b>Anticoagulant</b>	<ul style="list-style-type: none"> <li>■ Warfarin</li> <li>■ Acenocoumarol</li> <li>■ Phenindione</li> <li>■ Dabigatran</li> <li>■ Rivaroxaban</li> <li>■ Apixaban</li> </ul>
<b>Thrombolytic</b>	<ul style="list-style-type: none"> <li>■ Streptokinase</li> <li>■ Alteplase</li> </ul>

Table 2. Types of anti-thrombotic therapy.

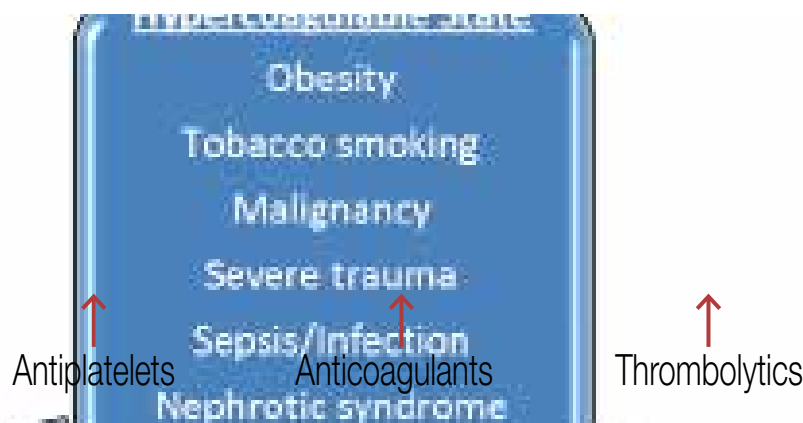


Figure 2. Coagulation timeline and the drug effects.

An INR of over 1.2 (normal range: 0.8–1.2) means that the patient’s coagulation time is increased. The target INR with warfarin is generally between 2 and 4 but is dependent upon the underlying condition being treated. Table 4 shows examples of target INR values.<sup>7</sup>

### Dental implications of warfarin use

National guidelines were

published by the British Committee for Standards in Haematology (BCSH) in 2011<sup>7</sup> regarding dental surgery on patients taking oral anticoagulants.<sup>8</sup> The key points are shown in Table 5.

These guidelines are extremely important; however they must be used with common sense and good clinical judgement. A minor surgical procedure would involve up to three teeth extracted at an appointment.<sup>9</sup> If multiple teeth

require extraction, 2–3 teeth may be removed at a time, preferably within one quadrant.<sup>10</sup> Local haemostatic measures, eg haemostatic packs and sutures are routinely used to control bleeding.

If a pre-existing medical condition that may interfere with coagulation exists alongside oral anticoagulant use or the patient requires more advanced dental surgery, the patient should be referred to a local oral and maxillofacial surgery specialist centre.<sup>10</sup>

History-taking is an essential tool for risk assessment of post extraction haemorrhage. If a patient is on warfarin, he/she will generally be well aware of its implications as a result of the regular INR checks (minimum every 12 weeks). Some useful questions to ask a patient include:

- Do you have your yellow INR book with you today? (Figure 3);
- When was your INR last checked?/When was your last blood test?;
- What is the normal number given to you at the blood test?;
- Is this number stable or does it change regularly?

Ideally, INR should be checked within 24 hours (72 if stable) before any dental surgery. This can be carried out within the dental practice using a portable machine (Figure 4). If this is not possible, an INR check must be arranged at the patient’s general medical practitioner or haematology clinic.

Phenindione and acenocoumarol are less commonly used anticoagulants that antagonize the effects of vitamin K. Clinicians must be aware that they have similar effects on prothrombin time to warfarin, therefore requiring an INR check prior to dental surgery.

### Dual therapy – warfarin and antiplatelet drugs

Antiplatelet medications enhance the anticoagulant effect of warfarin by interfering with the coagulation process at more than one point (Figure 2). Platelet plug formation will be inhibited along with fibrin formation. As discussed above, a pre-operative INR check must be carried out prior to any surgical procedures. Local haemostatic measures should be used to control bleeding as a preventive measure.

<ul style="list-style-type: none"> <li>■ Aspirin (75–300 mg)</li> <li>■ Clopidogrel (Plavix®)</li> <li>■ Dipyridamole (Persantin®, Persantin Retard®)</li> <li>■ Aspirin plus Dipyridamole (Asasantin Retard®)</li> <li>■ Prasugrel (Efient®)</li> <li>■ Ticagrelor (Brilique®)</li> </ul>
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**Table 3.** Oral antiplatelet medications available in the UK.

Target INR of 2.5	Target INR of 3.5
<ul style="list-style-type: none"> <li>■ Venous thrombo-embolism</li> <li>■ Antiphospholipid syndrome</li> <li>■ Atrial fibrillation</li> <li>■ Cardioversion</li> <li>■ Mitral stenosis</li> <li>■ Post-myocardial infarction (if they have clot heart chambers)</li> </ul>	<ul style="list-style-type: none"> <li>■ Recurrent venous thromboembolism (on target INR of 2.5)</li> <li>■ Some mechanical prosthetic heart valves</li> </ul>

**Table 4.** Target INR values with warfarin anticoagulation.

<ul style="list-style-type: none"> <li>■ Patients with an INR &lt;4.0 should not adjust dose to undergo dental treatment. Minor surgical procedures and periodontal treatment can be carried out in primary care if the INR is stable and below 4.0 (ie therapeutic range).</li> <li>■ Although taking warfarin will increase bleeding time, most cases can be managed with local haemostatic measures (surgical or collagen sponges and sutures) and 5% tranexamic acid mouthwashes used four times a day for 2 days.</li> <li>■ The increased risk of a thrombo-embolic event occurring due to stopping the oral anticoagulant outweighs the risk of a post-operative haemorrhage.</li> <li>■ For patients who are stably anticoagulated on warfarin, a check INR is recommended 72 hours prior to dental surgery.</li> <li>■ Patients taking warfarin should not be prescribed non-selective NSAIDs and COX-2 inhibitors as analgesia following dental surgery.</li> <li>■ Inferior alveolar nerve blocks should be given cautiously in patients with INR &lt;3.0. Alternative local anaesthetic techniques should be used when possible.</li> </ul>
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**Table 5.** Guidelines for dental surgery on patients taking warfarin.<sup>8</sup>

## New oral anticoagulant medications

Despite the long-term reliance on vitamin K antagonistic anticoagulants, several new medications are now available. Warfarin has a narrow therapeutic range and requires constant dose monitoring. The new oral anticoagulant medications of interest are dabigatran etexilate (Pradaxa®), rivaroxaban (Xarelto®) and apixaban (Eliquis®). They do not require therapeutic monitoring with the same degree as warfarin and have been licensed for use in some conditions.

### Dabigatran

Dabigatran is a direct thrombin inhibitor with a half-life of 10–17 hours and maximum anticoagulation starts within 2–3 hours. It is metabolized in the liver and excreted in the kidney (80%) or biliary system (20%).<sup>11</sup> It does not require constant therapeutic monitoring of INR, as with warfarin. Dabigatran is not metabolized by cytochrome P450 (CYP450) enzymes in the liver. This may be beneficial in terms of the multiple drug interactions involved with warfarin (Table 6). Some medications do interact with dabigatran (eg rifampicin, carbamazepine and St John's Wort). Drug interactions are discussed later.

Dabigatran has been advocated for the use of prevention of venous thrombo-embolism after knee and hip surgery following NICE guidance on the subject.<sup>12</sup> More recently, NICE has also approved its use for stroke prevention in atrial fibrillation.<sup>13</sup> This has the potential to have a large impact on dental practice. As an oral anticoagulant, dabigatran has the potential to cause post-operative bleeding. The current manufacturers (Boehringer Ingelheim®) have published advice regarding invasive surgery on patients taking dabigatran etexilate.<sup>14</sup> The dental implications are discussed below.

### Rivaroxaban and apixaban

Rivaroxaban and apixaban are direct inhibitors of activated factor X (Xa). Rivaroxaban has a half-life of 4–12 hours. It is metabolized in the liver and excreted via the kidney (67%) and biliary (33%) systems.<sup>11</sup> Apixaban has a longer half-life than rivaroxaban (9–14 hours) and is excreted mainly in the biliary system

(75%). As with dabigatran, these drugs don't require therapeutic monitoring. Rivaroxaban appears to have no effect on CYP450 enzymes, therefore having the same benefit as dabigatran over warfarin.

## Dental implications of the new anticoagulants

In contrast to warfarin, there is very limited literature regarding the impact of dental surgery on patients taking dabigatran, rivaroxaban or apixaban. Nevertheless, all dental practitioners must be aware of these drugs and their

anticoagulant effects. Although INR monitoring is not required, this does not mean that bleeding complications will not occur. It is advised to be aware of co-morbidities regarding post-extraction haemorrhage (including other medications and medical complications). As mentioned in part 1 of this series, a well organized armamentarium of local haemostatic measures should be available if any bleeding complication arises.

BSCCH guidelines<sup>7</sup> on warfarin and the North West medicines information centre guidance on antiplatelet medication<sup>5</sup> both advocate the use of local haemostatic



Figure 3. Yellow INR record book with patient advice leaflet.



Figure 4. Portable INR testing machine.

CYP450 enzyme inducers – **decrease** Warfarin action; **decrease** INR (S-C-R-A-P):

- St John's Wort
- Carbamazepine
- Rifampicin
- Alcohol
- Phenytoin

CYP450 enzyme inhibitors – **increase** Warfarin action; **increase** INR (M-E-A-N-T):

- Metronidazole
- Erythromycin
- Azole antifungals
- NSAIDs
- Tetracyclines

Table 6. Common drug interactions with warfarin.



measures to control the bleeding risk in patients taking these medications. However, the more recently licensed oral anticoagulants (dabigatran, rivaroxaban and apixaban) fall outside the remit of this guidance.

An advice sheet regarding dabigatran etexilate (Pradaxa®) and surgical procedures was sent to dentists in August 2012 from the manufacturers Boehringer Ingelheim. It outlines their advice regarding surgical intervention on patients taking dabigatran.

The main points of the advice sheet<sup>15</sup> state:

- Dabigatran carries a bleeding risk for patients undergoing surgical procedures;
- The risk is higher in patients with renal insufficiency given the slower clearance of the drug (dabigatran is contra-indicated if creatinin clearance is <30);
- In some instances, dabigatran medication should be discontinued prior to surgery and, if possible, any surgical intervention should occur at least 12 hours (time period depends on patient's creatinin clearance) after the last dose;
- Any bleeding risk should be weighed up against the urgency of the intervention;
- Patients on dabigatran should carry a warning/alert card to notify practitioners;
- Similar to warfarin, there may be some procedures which, at the discretion of the dentist, can be carried out with no discontinuation of therapy.

The advice is not specific on types of dental treatment; however, these should be similar to those highlighted as precautionary with warfarin (block anaesthesia and complex dental extractions are likely to be the procedures more at risk in a primary care setting). Some advice should be sought from the medical practitioner involved in prescribing dabigatran or a haematologist prior to any treatment planning. They may consider therapy discontinuation as carrying a higher risk than post-treatment haemorrhage.

Some authors advise the use of local haemostatic measures in patients on dabigatran and rivaroxaban and advise that patients taking dabigatran should be managed similarly to those on low-molecular-weight heparins (LMWH).<sup>11</sup> They suggest that dabigatran may require discontinuation prior to oral/maxillofacial surgery procedures; however, simple

dental treatments (such as uncomplicated extractions) may be managed with local haemostatic measures. Renal impairment and liver disease with coagulopathy are cited as major co-morbidities to bleeding risk. Liver failure is also a contributory factor in rivaroxaban treatment.<sup>11</sup>

There has not been enough experience with these medications to have a concrete plan prior to any surgery or invasive procedure. Therefore, there are currently no published written protocols/guidelines. However, the following suggestions appear reasonable:

- Non-invasive procedures such as routine restorative treatment and non-surgical periodontal therapy can readily be carried out in a primary care setting;
- The prescribing clinician/haematologist should be contacted regarding advice prior to any treatment if there is high risk of bleeding (eg co-existing co-morbidities such as renal failure live disease, thrombocytopenia);
- Following consultation with the prescribing physician, it would be reasonable to omit the medication for one day before the procedure and restart after treatment; once haemostasis is secured (this is practical as their half-life is 10–17 hours and they reach maximum therapeutic range within 2–3 hours following restart);
- Any complicated case should be managed in a dental hospital/maxillofacial ward in liaison with a haematologist for an individual plan;
- **It should be stressed that there is no specific reversal antidote for these new oral anticoagulants, unlike warfarin.**

### Drug interactions of the new oral anticoagulants

Dabigatran etexilate does have several drug interactions that impact on dentistry. Concomitant uses of diclofenac, rifampicin, carbamazepine or ketoconazole are to be avoided. Amiodarone and verapril require the dose of dabigatran to be reduced. Similar drug interactions exist with rivaroxaban and apixaban, with diclofenac and ketoconazole both being contra-indicated. Rifampicin and several antiviral medications must also be avoided when using rivaroxaban or apixaban. The most recent British National Formulary (BNF) available should be consulted prior to commencing treatment or prescribing medication.

### Heparin

Some anticoagulants (eg heparin) are given intravenously for short-term action. Patients suffering from kidney failure are likely to require heparin during renal dialysis. This will impact on the timing of dental treatment. Heparin is a short-acting anticoagulant that binds to antithrombin to cause clot breakdown. It is available in unfractionated and low molecular weight heparin (LMWH), however, LMWHs have a more consistent activity<sup>16</sup> and are now used most regularly. LMWH is given subcutaneously and will not be discontinued prior to most dental treatment. Local haemostatic measures should be used following a dental extraction on a patient taking LMWH. Dialysis will involve heparinization with a loading dose, followed by a maintenance dose throughout the procedure. Any dental treatment carried out on a 'non-dialysis day' is unlikely to cause drug-induced anticoagulation.<sup>17</sup> A dental extraction is best carried out on the day after dialysis to give the longest recovery period before the next heparinization.

### Conclusion

It is crucial that dentists and patients understand that anticoagulant therapy must not be routinely stopped prior to dental surgery. Numerous studies have shown that the risk of continuing anticoagulant therapy is not associated with an increased risk of post-operative bleed. Pre-operative alteration of anticoagulant therapy has been linked to some very serious consequences, including fatalities.<sup>18</sup> Local haemostatic measures are the preferred management of high risk patients. The placement of a *haemostatic pack or gauze* along with a *resorbable suture* is the mainstay measure, with the accompaniment of *tranexamic acid mouthwash* in some hospital units.

Anticoagulant use may be shifting from vitamin K antagonists to newer options. Dental professionals must ensure that they keep up-to-date with the ever-changing field of pharmacology. This issue reiterates the importance of an up-to-date patient medical history and a holistic clinical approach to the management of dental surgery.

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