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A New Generation of Antiplatelet and Anticoagulant Medication and the Implications for the Dental Surgeon

Abstract: The management of dental patients taking either antiplatelet medication, anticoagulant medication or both has been well established in the previous literature. Recently, new generations of drugs have emerged which are becoming increasingly common, including direct thrombin inhibitors, factor X inhibitors and a new class of oral thienopyridines. The implications of these drugs for the dental surgeon are not yet fully known. Awareness remains low and there is very little information available within the literature on safe use during surgery. This review paper aims to provide some guidance for dental practitioners performing invasive procedures.

CPD/Clinical Relevance: A new generation of anticoagulant and antiplatelet drugs have serious implications for patients undergoing surgery and their use is increasing.

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Invasive procedures in dentistry generally consist of relatively minor, non life-threatening surgery. One complication which leads to intra- and post-operative disturbance to patient care is haemorrhage. A patient's ability to achieve haemostasis can be disrupted by a wide variety of congenital or acquired disorders of blood vessels, platelet function and/or number and the coagulation system. This review will focus on the management of antiplatelet and anticoagulant drug-induced increased risk of bleeding intra- and post-operatively, briefly looking at the more commonly used drugs at present, followed by a more detailed outline of the new generation of drugs which have emerged in the last decade, exploring the implications of each for dental surgery.

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Haemostasis and traditional drugs

The components of coagulation are present within the circulating blood and, in health, remain in an inactivated state until injury is incurred. When the endothelium of a blood vessel is breached, vasoconstriction (the vascular component of haemostasis) ensues in order to reduce blood loss and assist in platelet adhesion. This adhesion is reliant upon von Willebrand factor within the subendothelium and leads to platelet activation and changes in cell morphology. Platelet agonists, such as adenosine diphosphate (ADP) and thromboxane A_2 are then released. Fibrinogen binds to receptors on the platelet membrane, cross-linking the platelets in a process called platelet aggregation, forming the primary platelet plug and thus completing primary haemostasis.[1] Three common antiplatelet drugs used in the prevention of thrombo-embolic disease act by reducing platelet aggregation via different mechanisms of action:

1. Aspirin, a non-steroidal anti-inflammatory, irreversibly inhibits the cycloxygenase (COX) enzyme which in turn reduces thromboxane A_2 production;[2]
2. Dipyridamole inhibits a phosphodiesterase resulting in a reduction in the breakdown, and subsequent intracellular accumulation of cAMP, ending with the inhibition of ADP;[3] and
3. Clopidogrel inhibits the $P2Y_{12}$ platelet receptor (a subtype of ADP receptor).[4]

Secondary haemostasis (which occurs simultaneously with primary haemostasis, rather than in sequence[5]) is reliant on the conversion of fibrinogen to fibrin, with cross-linking of this fibrin to form polymers and thus a blood clot.[1]

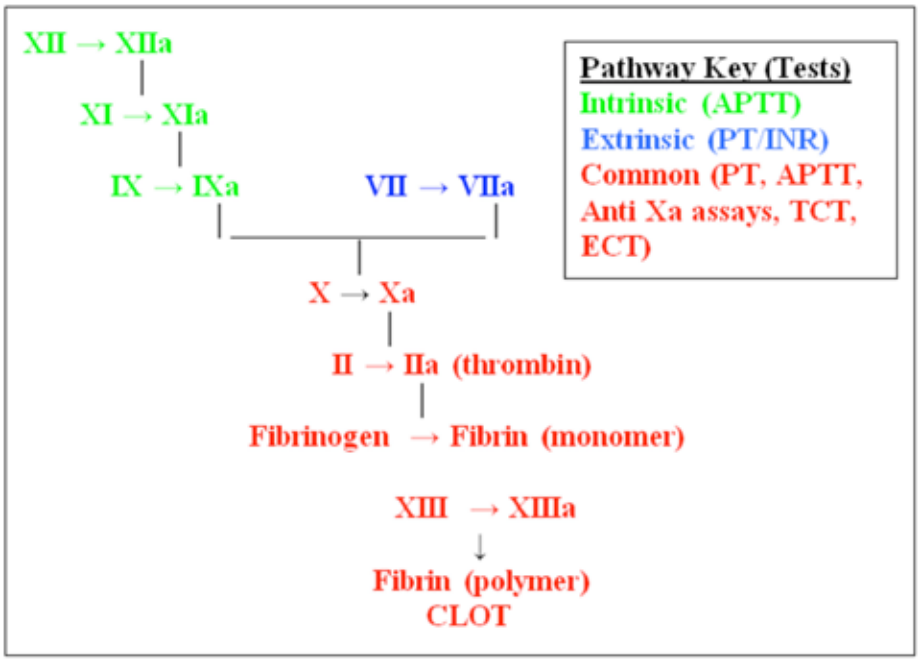

Figure 1. Simplified coagulation cascade.

Figure 1 provides a simplified summary of the coagulation cascade, the process which facilitates the latter conversion. The letter 'a' represents the activated form of the factor and many of these activated factors are proteases for the next stage in the process, hence the name *cascade*. Synthesis of factors II, VII, IX and X is vitamin K dependent. The most common oral anticoagulant, warfarin, binds to vitamin K and therefore subsequently affects the intrinsic, extrinsic and common pathways of the coagulation cascade. Heparin, a commonly prescribed anticoagulant, affects the common pathway by indirectly inhibiting both factor Xa and factor IIa to varying degrees.

Generally, features which affect the extrinsic pathway can be monitored by measuring prothrombin time (PT) and those affecting the intrinsic pathway via activated partial thromboplastin time (APTT). Although warfarin affects all three components of the coagulation cascade, PT will provide the most accurate assessment of coagulation as the extrinsic pathway is the shortest and therefore the first to exhibit signs of any disruption. The International Normalized Ratio (INR) test is a method used to standardize the measurement of PT and is widely used for warfarin monitoring. Prophylactic use of unfractionated heparin (UH) generally does not require monitoring where therapeutic doses can be titrated using APTT as a measure.[6] Low molecular weight (LMWH) does not normally require monitoring but an anti-Xa assay can be used in specific circumstances with careful laboratory validation, and if results are interpreted with caution.[6]

Antiplatelet or anticoagulant medications are most commonly used in the prevention of clot formation in patients with:

- Atrial fibrillation (AF);
- Prosthetic or damaged heart valves;
- A history of stroke; transient ischaemic attacks (TIA) or ischaemic heart disease and following placement of coronary artery stents; and
- In the prevention or treatment of venous thrombo-embolism (VTE) such as deep vein thrombosis (DVT) or pulmonary embolism (PE).[7–13]

The mono- and dual-antiplatelet therapies currently used (for example, in the management of acute coronary disease), have sub-optimal features, such as a modest antiplatelet effect, delayed onset of action and variable outcomes.[14] Although warfarin has been a popular oral anticoagulant drug for over 60 years, it has limitations, such as dietary and drug interactions, narrow therapeutic range and the need for monitoring.[15] One of the major drawbacks of heparin is the need for parenteral administration.[13] Therefore, in the past decade novel oral antiplatelets (NOAPs) and novel oral anticoagulants (NOACs) have been introduced which claim to have improved safety and superior therapeutic value compared with their predecessors. A third category of drug, the thrombolytics, which degrade an established fibrin clot, are not discussed in this paper.

New oral antiplatelet medication

Prasugrel (Efient®) is an oral thienopyridine which, like clopidogrel, irreversibly binds to the $P2Y_{12}$ platelet receptor but with a faster onset, more potent antiplatelet effect, reduced variability and fewer drug interactions.[16] Wiviott *et al* studied over 13,000 patients and found that, although prasugrel reduced the risk of ischaemic events, it was associated with a higher risk of major bleeding.[14] In another trial of 7243 patients, no difference in overall clinical effectiveness or major bleeding was found between prasugrel and clopidogrel, but the former did reduce the risk of multiple ischaemic events.[17]

Another NOAP, ticagrelor (Brilique™) also acts on the $P2Y_{12}$ platelet receptor but binds reversibly, which allows a rapid offset as well as onset.[16] In a multi-centre double-blinded study of over 18,000 patients, ticagrelor showed reduced death rate from MI, stroke or vascular causes compared with clopidogrel, without an increase in bleeding events.[18]

The National Institute for Health and Care Excellence (NICE) has produced recommendations on the use of prasugrel or ticagrelor, but only when in combination with aspirin and only in the management of a subset of patients with acute coronary syndromes.[19,20] Therefore, due to the limited indications, their use will, for the time being at least, be uncommon whilst clinical trials of each are ongoing.

New oral anticoagulant medication

Dabigatran, a direct thrombin

inhibitor (DTI) and rivaroxaban and apixaban, both direct factor Xa inhibitors, target one specific factor in the coagulation cascade directly. These drugs have been developed recently, are becoming increasingly widely prescribed, and their use has significant implications for the management of patients requiring anticoagulation. The most striking difference compared to drugs used in the past is the elimination of the need for monitoring, even if the patient is to undergo surgery. These drugs are administered orally at a constant daily dose, making patient compliance more straightforward. Worryingly, however, an agent for reversal for each of the NOACs in the emergency situation has not yet been developed.

NICE recommend dabigatran as an option for use in the prevention of DVT and PE in patients undergoing hip or knee surgery, and in the management of non-valvular AF,[21,22] and have recommended rivaroxaban and apixaban as options for use in the management of AF and the prevention and treatment of both DVT and PE in patients undergoing total hip or knee replacement.[23-28] Of the three main NOACs mentioned so far, rivaroxaban now has the most indications for use.

Direct thrombin inhibitors: dabigatran

Dabigatran etexilate (Pradaxa®) is the first drug of its kind to be developed to a level in medicine to be in a position of valuable clinical purpose.[29] Although other DTIs exist (argatroban, bivalirudin, desirudin and lepirudin), they are administered parenterally and tend to be reserved for patients with, or at risk of, heparin-induced thrombocytopenia.[30] Dabigatran is the only oral preparation which has been licensed for human use[31] and, although gastric upset and hypersensitivity have been described,[32] it has generally been satisfactorily tolerated.[33,34]

DTIs cause direct reversible inhibition of both free and fibrin-bound thrombin, a potent agonist of platelet activation and aggregation, sparing a small amount of free enzymatically active thrombin for haemostasis.[34] Dabigatran is predictable, reaching its peak concentration around 2 hours after taking the drug, which allows a fixed-dose regimen without monitoring.[29] Consequently, dabigatran is more cost-effective than warfarin.[35-37] In hepatic failure, the absorption and excretion of dabigatran is unaffected, with slightly less rapid bioconversion of the prodrug to dabigatran within the liver.[38] Moderate and severe renal failure leads to drug accumulation[34] and therefore caution needs to be adopted, not only when prescribing dabigatran, but also when considering a period of discontinuation prior to invasive surgery, ensuring sufficient time has elapsed to reduce the plasma concentration enough to reduce bleeding risk appropriately. The latter is discussed further below.

The benefits of dabigatran over warfarin in the management of AF were demonstrated by the RE-LY (Randomized Evaluation of Long-term anticoagulant therapY) multicentre trial of 951 patients, where the dabigatran group had fewer thrombo-embolic events and a reduced bleeding risk.[39] It has also been shown to be as effective as LMWH and warfarin in the prevention of venous thrombo-embolism following hip and knee replacement surgery.[33,40] Circumstances may arise where it would be useful to establish the level of anticoagulation in a patient taking dabigatran, for example following an overdose or where the patient presents with bleeding. It is important before testing to establish exactly when the drug was taken as the concentration varies substantially at different times after administration. Measuring INR gleans little information as dabigatran has little effect on PT. Testing APTT may be useful in establishing excess anticoagulant activity in emergency situations or in centres where other tests are not available, but must be interpreted with caution. Thrombin clotting time (TCT) and ecarin clotting time (ECT) are more sensitive methods of testing anticoagulation in DTIs but are not widely available. TCT directly assesses the activity of thrombin in plasma and ECT assays use ecarin, a snake venom which activates prothrombin and produces a precursor to thrombin (meizothrombin), allowing a direct measurement of DTI activity.[41]

Finally, the anticoagulant effect from inhibiting thrombin is understood but it is not clear whether DTIs will also interfere with the other processes in which thrombin plays a part, such as angiogenesis, the immune response, infection, tumour growth and endothelial function.[38]

Direct factor Xa inhibitors: rivaroxaban and apixaban

Another group of NOACs have been developed which reversibly bind to and inhibit free and clot bound factor Xa directly, thus indirectly inhibiting thrombin production and clot development. Rivaroxaban (Xarelto®) and apixaban (Elequis®) reach peak plasma concentration at around 3 hours and are well tolerated, exhibiting fewer side-effects than dabigatran.[42,43] Owing to the mechanisms of elimination, both drugs should be avoided in hepatic failure but can be used in mild to moderate renal failure.[44,45] Apixaban can be used safely at a reduced dose in severe renal failure.[46,47] Apixaban and rivaroxaban prolongs PT (and therefore increases INR) and increases APTT, but does so to varying degrees.[47] Therefore, to achieve an accurate assessment of anticoagulant effect, chromogenic anti Xa assays are required.[48,49]

Early trials demonstrated that rivaroxaban and apixaban were as effective as warfarin in the management of non-valvular AF with fewer bleeding complications.[43,50] Both drugs have also been shown to be as effective as LMWH in the prophylaxis of venous thrombo-embolism (VTE) in orthopaedic surgery patients and, again, fewer bleeding issues were observed.[42,51,52] Enoxaban is another direct Xa inhibitor which may show promise in the future but has not yet been fully researched or approved for use.[43,53]

Oral surgery in patients taking antiplatelet/anticoagulant medication – current practice

It is often perceived that the risk of bleeding during surgery outweighs the risk of a thrombo-embolic event if medication is discontinued. Rossini *et al* found premature discontinuation of antiplatelet medication following stent placement in over one in ten patients and one of the most common reasons given was that the patient underwent a surgical or dental procedure.[54] Patients are more likely to develop a permanent disability or die as a result of stopping an antiplatelet medication than they are from bleeding

following surgery[55] and the most reliable predictor for the development of a stent thrombus (and possible subsequent MI and/or death), is the premature cessation of clopidogrel.[8]

Bleeding time in patients taking aspirin is increased but this does not translate into increased blood loss during oral operative procedures,[12] and minor oral surgery procedures have been demonstrated as safe when the drug is continued.[7,56-59] Indeed, aspirin has been shown to be effective in the management of post-operative pain following third molar removal with no increased bleeding tendency.[60] Patients taking aspirin plus clopidogrel, however, may have a higher tendency for immediate (within one hour of surgery) post-operative bleeding but no difference intra-operatively or during the late post-operative period.[7] Bleeding encountered in patients on dual therapy with aspirin plus clopidogrel tends to be manageable with simple local measures.[61] Aspirin in combination with dipyridamole poses a similar surgical risk compared with monotherapy.[55] Cessation of antiplatelet medication is unnecessary as local measures can be adopted to manage such issues effectively.[62-64]

The bleeding risk for patients taking warfarin is significantly higher than in those taking single or dual antiplatelet medication.[7] Nevertheless, reports of significant bleeding following dental procedures in warfarinized patients are exceedingly rare, with many of the problems dating back prior to effective testing of a patient's coagulation state.[12] Providing the patient has an INR of 4.0 or less, it is considered safe to continue with surgery, assuming there are no additional bleeding risk factors.[65] The INR should be tested as close to surgery as possible and certainly no more than 72 hours prior to the procedure as fluctuations can occur, even in the apparently stable patient, due to, for example, dietary interactions with warfarin. In a comprehensive review of literature by Dunn and Turpie in 2003, it was found that 'serious' bleeding occurred after dental surgery in patients taking oral anticoagulants in only 0.6% of cases and two-thirds of these occurred when the INR was higher than the recommended therapeutic level.[59] On this basis, providing the INR is checked, serious bleeding should be encountered only once in every 500 encounters with warfarinized patients.

The use of LMWH is common in the hospital setting in the prophylaxis of deep vein thrombosis (DVT) and pulmonary embolism (PE). These drugs, such as dalteparin, have little impact on peri-operative bleeding and are often continued safely even in major surgery. If surgery is planned for a patient using therapeutic heparin or prophylactic heparin in the outpatient setting, it is advisable to consult the patient's physician to arrange the most appropriate time to carry out surgery and decide whether any modifications to the patient's regimen are required. However, following minor procedures (forceps extraction of 1–3 teeth), bleeding tendency will often be insignificant to the dental surgeon.[62]

Simple measures, such as the use of adrenaline containing local anaesthetic, treating patients earlier in the working week and in the morning, are advisable if there is an increased risk of bleeding.[62] Concurrent use of non-steroidal anti-inflammatory drugs (NSAIDs) should be avoided and the patient should be advised accordingly.[66] Any surgery carried out should aim to reduce unnecessary trauma. For example, removal of an impacted third molar ought to be approached without lingual retraction and tooth sectioning in preference to bone removal, if feasible.[67] Blinder *et al* found that the combination of absorbable haemostatic dressing and suturing was sufficient in achieving haemostasis and advocated meticulous curettage of infected extraction sites.[68] If persistent bleeding is encountered, 4.8% tranexamic acid may also be of value if used as a mouthwash by the patient for 7–10 days post-operatively.[62] Unfortunately, however, the latter is not included in the *Dental Practitioners Formulary*[69] and therefore can only be prescribed on a private prescription, making it costly for the patient. Additionally, tranexamic acid is not licensed for use as a mouthwash and can only be obtained from a few manufacturers.[70]

Oral surgery and new generation oral antiplatelets

The literature available regarding surgery in patients taking NOAPs relates mainly to cardiac surgery, therefore making it difficult to draw conclusions regarding bleeding risk in oral surgery. Very little evidence specific to NOAPs and oral surgery exists.[71] One case report described prolonged gingival bleeding following dental scaling in a patient taking prasugrel which was successfully managed with simple local measures.[72] The manufacturer of ticagrelor and prasugrel both advise discontinuing the drug for 7 days prior to surgery,[73,74] but do not give any details of the type of surgery which would necessitate this action.

After discontinuing prasugrel it takes approximately 7 days for the platelets to return to normal,[75] whereas ticagrelor is reported to take around 5 days.[76] This may be more relevant prior to major surgery than in minor oral surgery where stopping the drug, as with the older antiplatelet medications, may not be in the patient's best interests. Given the similarities between clopidogrel and prasugrel, one could assume that they would be treated in a similar fashion clinically, but there is currently no evidence to support this. Strategies for the reversal of the effects of dual aspirin and clopidogrel therapy prior to surgery have been trialled[77] but to-date no such research has been carried out on the NOAPs.

Oro-facial side-effects documented for prasugrel and ticagrelor include angiodema and gingival bleeding[78,79] and both have several interactions with drugs used in dentistry, as shown in Appendix 1.

Oral surgery and new generation anticoagulants

The limited information available on patients taking NOACs undergoing oral surgery tends to focus on dabigatran. The manufacturer of dabigatran recommends temporary discontinuation of the drug prior to surgery and highlights that the patient's renal function will have an impact on clearance and therefore an impact on duration of discontinuation.[80] In a healthy patient with creatinine clearance of >80 mL/min undergoing 'standard risk' surgery, which presumably encompasses minor oral surgery procedures, dabigatran should be stopped 24 hours prior to the procedure. This should increase to 24–48 hours and

>48 hours with a creatinine clearance of 50–80 mL/min and 30–50 mL/min, respectively.[41,80]

One recent case report described surgical removal of eight maxillary teeth, alveoloplasty and tuberosity reduction in a patient taking dabigatran. As instructed by the manufacturer's guidelines, and in conjunction with the patient's physician, the dabigatran was temporarily discontinued 24 hours prior to surgery and neither excessive bleeding nor thrombo-embolic complications were encountered. Resorbable gelatin sponges were placed in the sockets, the wound was sutured and an immediate denture with soft lining was also fitted, which may also have aided the maintenance of haemostasis.[81]

Data captured by the RE-LY trial were used to compare bleeding complications in surgical patients taking either dabigatran or warfarin.[82] Around 10% of procedures in the latter study were categorized as 'dental procedures'. The group concluded that the two drugs showed no significant difference in peri-operative bleeding in both minor and major surgery, as well as similar rates of throbo-embolic complications. Dabigatran patients were, however, able to get more prompt surgery safely due to the short half-life of the drug.[82] One methodological flaw in this study was that a procedure was deemed to be major simply if it lasted for more than one hour. 'Dental procedures' encompasses a wide variety of surgery, potentially including situations where the operation can take less than one hour but carries a significant risk of bleeding and vice versa. Weitz *et al* recommended continuing dabigatran for dental cleaning and dental extractions but gave no reference source.[83]

Treating the patient taking dabigatran is thought to be clinically equivalent to treating a warfarinized patient with an INR of between 2.0 and 3.0,[30] which suggests discontinuation may be unnecessary in minor oral surgery procedures. It is worthwhile noting that the combination of dabigatran and aspirin has been shown to enhance bleeding tendency similar to any other anticoagulant, so further caution may be taken in such a scenario.[41] Taking into account the short half-life of dabigatran, it is recommended that surgery should be carried out as long after the previous dose as possible,[30] a theory which should also apply to the direct Xa inhibitors. This, however, conflicts with the existing good practice advice to treat patients at risk of bleeding early in the morning to allow time to manage bleeding in normal working hours. In a recent review paper published in the *British Dental Journal*, Rider and Rider recommended seeking guidance from the patient's physician with a view to discontinuing dabigatran for standard risk procedures (which included extractions in this paper), putting the patient at only a very low risk of a thrombo-embolic event given the rapid recommencement.[66]

The manufacturer of rivaroxaban simply states that if patients are to undergo any invasive procedures (including dental procedures) they should inform their healthcare professional and discontinue the drug at least 24 hours before surgery, recommencing as soon as haemostasis is established,[46] with no further details on the discontinuation of the drug or expansion on the type of procedure.[84] Apixaban requires discontinuation 24 hours and 48 hours prior to low and moderate to severe risk surgery, respectively, and again, it is recommended to restart the drug as soon as possible after haemostasis is established.[47] Spyropoulos and Douketis suggested a more cautious approach to the surgery, discontinuing dabigatran, rivaroxaban or apixaban two days prior to minor surgery (increasing to three days for major surgery) in patients with good renal function, recommencing 24 hours post-operatively for low risk procedures (increasing to between 48–72 hours for high risk operations).[85]

In 2012, Firriolo and Hupp made a comparison between the similar half-lives of dabigatran and rivaroxaban to enoxaparin (a LMWH) and suggested that discontinuation of these new generation drugs is not necessary in patients with normal renal function undergoing straightforward extractions.[31] Little also drew similar conclusions after studying the literature.[86] The guidance for each of the NOACs is based on clinical trials of patients undergoing various surgical procedures where patients discontinued the drug

Drug	Interaction (lesser effect)	Effect
Dabigatran	Aspirin (and NSAIDs) Ketoconazole (or Itraconazole) Clarithromycin (or erythromycin) Tacrolimus Carbamazepine	Increased bleeding risk Increased dabigatran effect Increased dabigatran effect Increased dabigatran effect Decreased dabigatran effect
Rivaroxaban	IV Diclofenac (other NSAIDs) Ketoconazole (other -azoles) (Erythromycin + Clarithromycin) Carbamazepine	Increased bleeding risk Increased rivaroxaban effect Increased rivaroxaban effect Decreased rivaroxaban effect
Apixaban	IV Diclofenac (other NSAIDs) Ketoconazole/Itraconazole Carbamazepine	Increased bleeding risk Increased apixaban effect Decreased apixaban effect
Prasugrel	(NSAIDs) (Lansoprazole) (–azole antifungals) (Clarithromycin)	Increased bleeding risk Reduced uptake time Decreased prasugrel effect Decreased prasugrel effect
Ticagrelor	(NSAIDs) Ketoconazole (Fluconazole) Clarithromycin (Erythromycin) Dexamethasone Carbamazepine, Phenytoin	Increased bleeding risk Increased ticagrelor effect Increased ticagrelor effect Decreased ticagrelor effect Decreased ticagrelor effect

Appendix 1: NOAP and NOAC interactions encountered in dentistry and oral surgery.

irrespective of the perceived bleeding risk, with the duration of cessation guided by pharmacological data. Clinical trials are required which compare the effects of continuing versus discontinuing NOACs prior to dental surgery.

Aside from post-operative bleeding risk, rivaroxaban and apixaban have both been associated with gingival bleeding, and rivaroxaban-induced xerostomia has also been documented, as well as potential interactions between each NOAC with drugs used in dentistry as shown in Appendix 1.[3,46,47,78,79,87]

The management of bleeding in patients taking NOACs is yet to be fully established. In minor bleeds, simply stopping dabigatran is usually sufficient given the short half-life.[41] To-date an antidote has not been developed so, in more serious haemorrhage techniques, such as using recombinant activated factor VII, fresh frozen plasma or activated prothrombin complex concentrated have been experimented with, but further work is required to establish their effectiveness.[29,88] Presently, the management of over-coagulation with dabigatran is confined to a handful of interventions:

- The use of charcoal if ingestion time is less than 2 hours previously or possibly haemoperfusion through a charcoal filter;
- Maintenance of good renal function to ensure clearance;
- Discontinuation of the drug; and
- Possibly haemodialysis.[41]

Concerns have been raised regarding dabigatran patients presenting to emergency departments with non-surgical bleeding,[29,89] however, the Food and Drug Administration (USA) published a statement to alleviate these concerns after carrying out an assessment of their own.[90] Both the FDA and the UK-based Medicines and Healthcare Products Regulatory Authority (MHRA) have, however, recommended to avoid dabigatran in patients with mechanical prosthetic heart valves, as they were more likely to suffer a stroke or MI and thrombus formation on the prosthesis following phase II of the RE-ALIGN drug trial.[44,91,92] Also, in a recent meta-analysis, Artang *et al* found an increased risk of MI in patients taking dabigatran compared to warfarin in the management of AF.[45]

There is little evidence to support the use of charcoal or fresh frozen plasma (FFP) in the reversal of the effects of rivaroxaban, and haemodialysis is unlikely to have any effect as the drug is highly protein bound. Prothombin complex concentrate (PCC) has been shown to normalize PT in human subjects but with no indication of effect on actual haemostasis, and animal models have shown recombinant activated factor VIIa (rVIIa) to be effective in reducing bleeding times.[29] Very little is known about the reversal of apixaban, therefore the techniques for reversal of dabigatran or rivaroxaban cannot be recommended until studied further.[29] The drug manufacturer, however, recommends administering activated charcoal within 2–6 hours of apixaban consumption in the emergency situation.[47] It is worth noting that the half-life of rivaroxaban is 5–9 hours, whereas apixaban has a half-life of 9–14 hours, which will have implications for management of haemorrhage.[43]

Summary

There is a concerning lack of evidence and guidance on NOAP use in surgical patients. As a result, the oral surgeon is currently reliant on the prescribing physician for advice. It cannot be assumed that prasugrel and ticagrelor behave as benignly as their older relatives in dental/oral surgery, both intra- and post-operatively. Further evidence is required to establish whether a period of discontinuation, and subsequent increased risk of a thrombo-embolic event, is necessary for minor oral surgery procedures.

Eliminating the requirement for monitoring in patients taking new oral anticoagulants is convenient for both the surgeon and the patient. Despite encouraging early findings, there is still concern over the true risk of bleeding during oral surgery. The lack of a reversal agent and guidance on the management of haemorrhage is an area of ongoing research. Provisional findings suggest uncomplicated extractions and other minimally invasive procedures may not necessitate a break in dabigatran. Dabigatran, rivaroxaban and apixaban should all be discontinued for 24 hours prior to invasive dental procedures, or for longer in patients taking dabigatran with renal failure.

Local surgical measures to assist haemostasis should be adopted for all patients taking NOAPs and NOACs until sufficient evidence is available to draw up guidance on best practice.

References

1. Davie EW. A brief historical review of the waterfall/cascade of blood coagulation. *J Biol Chem* 2003; **278**(51): 50819–50832.
2. Vane JR. Inhibition of prostaglandin synthesis as a mechanism of action for aspirin-like drugs *Nat New Biol* 1971; **231**(25): 232–235.
3. Boehringer Ingelheim Limited. *Persantan/Persantan Retard Summary of Product Characteristics, 2012.* Available at: **www.emc.medicines.org.uk** Accessed November/30, 2013.
4. SANOFI. *Plavix (Clopidogrel) Summary of Product Characteristics, 2013*. Available at: **www.emc.medicines.org.uk** Accessed November 30, 2013.
5. Scully C. *Haematology: Haemostasis. Medical Problems in Dentistry* 6th edn. Oxford: Elsevier, 2010: pp177–180.
6. Baglin T, Barrowcliffe TW, Cohen A, Greaves M. Guidelines on the use and monitoring of heparin. *Br J Haematol* 2006; **133**(1): 19–34.
7. Napenas JJ, Oost FC, DeGroot A, Loven B, Hong CH, Brennan MT *et al.* Review of postoperative bleeding risk in dental patients on antiplatelet therapy *Oral Surg Oral Med Oral Pathol Oral Radiol* 2013; **115**(4): 491–499.
8. Grines CL, Bonow RO, Casey DE, Gardner TJ, Lockhart PB, Moliterno DJ *et al*. Prevention of premature discontinuation of dual antiplatelet therapy in patients with coronary artery stents. A Science Advisory from the American Heart Association, American College of Cardiology, Society for Cardiovascular Angiography and Interventions, American College of Surgeons, and American Dental Association, with representation from the American College of Physicians. *Cathet Cardiovasc Interv* 2007; **69**(3): 334–340.
9. Hennekens C, Dalen J. Aspirin in the treatment and prevention of cardiovascular disease: past and current perspectives and future directions. *Am J Med* 2013; **126**(5): 373–378.
10. CAPRIE Steering Committee. A randomised, blinded trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE) *The Lancet* 1996; **348**(9038): 1329–1339.
11. National Institute for Health and Care Excellence (NICE). Clopidogrel and modified-release dipyridamole for the prevention of occlusive vascular events: TA210 Guidance, 2012. Available at: **http://publications.nice.org.uk/clopidogrel-and-modified-release-dipyridamole-for-the-**

prevention-of-occlusive-vascular-events-ta210 Accessed 12/11/2013, 2013.
12. Lockhart PB, Gibson J, Pond SH, Leitch J. Dental management considerations for the patient with an acquired coagulopathy. Part 2: Coagulopathies from drugs. *Br Dent J* 2003; **195**(9): 405–-501.
13. Quader M, Stump L, Sumpio B. Low molecular weight heparins: current use and indications. *J Am Coll Surg* 1998; **187**(6): 641–658.
14. Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S *et al*. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2007; **357**(20): 2001–2015.
15. Lin PJ. Reviewing the reality: why we need to change. *Eur Heart J* 2005; **7**(Suppl E): 15–20.
16. Capodanno D, Ferreiro JL, Angiolillo DJ. Antiplatelet therapy: new pharmacological agents and changing paradigms. *J Thromb Haem* 2013; **11**: 316–329.
17. Roe MT, Armstrong PW, Fox KA, White HD, Prabhakaran D, Goodman SG *et al*. Prasugrel versus clopidogrel for acute coronary syndromes without revascularization. *N Engl J Med* 2012; **367**(14): 1297–1309.
18. Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C *et al*. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2009; **361**(11): 1045–1057.
19. National Institute for Health and Care Excellence (NICE). Prasugrel for the treatment of acute coronary syndromes with percutaneous coronary intervention: TA182 Guidance, 2012. Available at: **http://publications.nice.org.uk/prasugrel-for-the-treatment-of-acute-coronary-syndromes-with-percutaneous-coronary-intervention-ta182** Accessed 12/11/2013, 2013.
20. National Institute for Health and Care Excellence (NICE). Ticagrelor for the treatment of acute coronary syndromes: TA236 Guidance, 2011. Available at: **http://publications.nice.org.uk/ticagrelor-for-the-treatment-of-acute-coronary-syndromes-ta236** Accessed 12/11/2013, 2013.
21. National Institute for Health and Care Excellence (NICE). Dabigatran etexilate for the prevention of venous thromboembolism: TA157 Guidance, 2008. Available at: **http://publications.nice.org.uk/dabigatran-etexilate-for-the-prevention-of-venous-thromboembolism-after-hip-or-knee-replacement-ta157** Accessed 11/30/2013, 2013.
22. National Institute for Health and Care Excellence (NICE). Dabigatran etexilate for the prevention of stroke and systemic embolism in atrial fibrillation: TA249 Guidance, 2012. Available at: **http://publications.nice.org.uk/dabigatran-etexilate-for-the-prevention-of-stroke-and-systemic-embolism-in-atrial-fibrillation-ta249** Accessed 11/30/2013, 2013.
23. National Institute for Health and Care Excellence (NICE). Rivaroxaban for treating pulmonary embolism and preventing recurrent venous thromboembolism: TA287 Guidance, 2013. Available at: **http://publications.nice.org.uk/rivaroxaban-for-treating-pulmonary-embolism-and-preventing-recurrent-venous-thromboembolism-ta287** Accessed 12/6/2013, 2013.
24. National Institute for Health and Care Excellence (NICE). Rivaroxaban for the prevention of venous thromboembolism after total hip or total knee replacement in adults: TA170 Guidance, 2012. Available at: **http://publications.nice.org.uk/rivaroxaban-for-the-prevention-of-venous-thromboembolism-after-total-hip-or-total-knee-replacement-ta170** Accessed 12/6/2013, 2013.
25. National Institute for Health and Care Excellence (NICE). Rivaroxaban for the prevention of stroke and systemic embolism in people with atrial fibrillation: TA256 Guidance, 2012. Available at: **http://publications.nice.org.uk/rivaroxaban-for-the-prevention-of-stroke-and-systemic-embolism-in-people-with-atrial-fibrillation-ta256** Accessed 12/6/2013, 2013.
26. National Institute for Health and Care Excellence (NICE). Rivaroxaban for the treatment of deep vein thrombosis and prevention of recurrent deep vein thrombosis and pulmonary embolism: TA261 Guidance, 2012. Available at: **http://publications.nice.org.uk/rivaroxaban-for-the-treatment-of-deep-vein-thrombosis-and-prevention-of-recurrent-deep-vein-ta261** Accessed 12/6/2013, 2013.
27. National Institute for Health and Care Excellence (NICE). Apixaban for preventing stroke and systemic embolism in people with nonvalvular atrial fibrillation: TA275 Guidance, 2013. Available at: **http://publications.nice.org.uk/apixaban-for-preventing-stroke-and-systemic-embolism-in-people-with-nonvalvular-atrial-fibrillation-ta275** Accessed 12/6/2013, 2013.
28. National Institute for Health and Care Excellence (NICE). Apixaban for the prevention of venous thromboembolism after total hip or total knee replacement: TA245 Guidance, 2012. Available at: **http://publications.nice.org.uk/apixaban-for-the-prevention-of-venous-thromboembolism-after-total-hip-or-knee-replacement-in-adults-ta245** Accessed 12/6/2013, 2013.
29. Kaatz S, Kouides P, Garcia D, Spyropolous A, Crowther M, Douketis J *et al*. Guidance on the emergent reversal of oral thrombin and factor Xa inhibitors. *Am J Hematol* 2012; **87**(S1): S141–145.
30. Davis C, Robertson C, Shivakumar S, Lee M. Implications of dabigatran, a direct thrombin inhibitor, for oral surgery practice. *J Can Dent Assoc* 2013; **79**: d74.
31. Firriolo FJ, Hupp WS. Beyond warfarin: the new generation of oral anticoagulants and their implications for the management of dental patients. *Oral Surg Oral Med Oral Pathol Oral Radiol* 2012; **113**(4): 431–441.
32. Wallentin L, Yusuf S, Ezekowitz M, Alings M, Flather M, Franzosi M *et al*. Efficacy and safety of dabigatran compared with warfarin at different levels of international normalised ratio control for stroke prevention in atrial fibrillation: an analysis of the RE-LY trial. *The Lancet* 2010; **376**(9745): 975–983.
33. Burness CB, McKeage K. Dabigatran etexilate: a review of its use for the prevention of venous thromboembolism after total hip or knee replacement surgery. *Drugs* 2012; **72**(7): 963–986.
34. Stangier J. Clinical pharmacokinetics and pharmacodynamics of the oral direct thrombin inhibitor dabigatran etexilate. *Clin Pharmacokinet* 2008; **47**(5): 285–295.
35. Sorensen SV, Peng S, Monz BU, Bradley-Kennedy C, Kansal AR. A comparative analysis of models used to evaluate the cost-effectiveness of dabigatran versus warfarin for the prevention of stroke in atrial fibrillation. *Pharmacoeconomics* 2013; **31**(7): 589–604.
36. Harrington AR, Armstrong EP, Nolan PE, Malone DC. Cost-effectiveness of apixaban, dabigatran, rivaroxaban, and warfarin for stroke prevention in atrial fibrillation. *Stroke* 2013; **44**(6): 1676–1681.
37. Chang AM, Ho JC, Yan BP, Yu CM, Lam YY, Lee VW. Cost-effectiveness of dabigatran compared with warfarin for stroke prevention in patients with atrial fibrillation – a real patient data analysis in a Hong Kong teaching hospital. *Clin Cardiol* 2013; **36**(5): 280–285.
38. Hankey GJ, Eikelboom JW. Dabigatran etexilate: a new oral thrombin. inhibitor. *Circulation* 2011; **123**(13): 1436–1450.
39. Connolly S, Ezekowitz M, Yusuf S, Eikelboom J, Oldgren J, Parekh A *et al*. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2009; **361**(12): 1139–1151.
40. Salazar C, Malaga G, Malasquez G. Direct thrombin inhibitors versus vitamin K antagonists or low molecular weight heparins for prevention of venous thromboembolism following total hip or knee replacement. *Cochrane Database Syst Rev* 2010; 4: CD005981.
41. van Ryn J, Stangier J, Haertter S, Liesenfeld K-, Wienen W, Feuring M *et al*. Dabigatran etexilate – a novel, reversible, oral direct thrombin inhibitor: interpretation of coagulation assays and reversal of anticoagulant activity *Thromb Haemost* 2010; **103**(6): 1116–1127.
42. Thomas T, Ganetsky V, Spinler S. Rivaroxaban:

an oral factor Xa inhibitor. *Clin Ther* 2013; **35**(1): 4–27.

43. Mohammed I, Syed W. Oral anticoagulants to reduce the risk of stroke in atrial fibrillation: how should a clinician choose? *Clin Cardiol* 2013; **36**(11): 663–670.
44. Van de Werf F, Brueckmann M, Connolly S, Friedman J, Granger C, Härtter S *et al*. A comparison of dabigatran etexilate with warfarin in patients with mechanical heart valves: The Randomized, phase II study to Evaluate the sAfety and pharmacokinetics of oraL dabIGatran etexilate in patients after heart valve replacemeNt (RE-ALIGN). *Am Heart J* 2012; **163**(6): 931–937.
45. Artang R, Rome E, Nielsen J, Vidaillet H. Meta-analysis of randomized controlled trials on risk of myocardial infarction from the use of oral direct thrombin inhibitors. *Am J Cardiol* 2013; **112**(12): 1973–1979.
46. Bayer PLC. Xarelto 10 mg film-coated tablets – Summary of Product Characteristics, 2013. Available at: **http://medicines.org.uk/emc/medicine/21265/SPC/Xarelto+10+mg+film-coated+tablets/** Accessed 12/8/2013, 2013.
47. Bristol-Myers Squibb-Pfizer. Eliquis 5 mg film-coated tablets – Summary of Product Characteristics (SPC) – (eMC) 2013. Available at: **http://medicines.org.uk/emc/medicine/27220/SPC/Eliquis+5+mg+film-coated+tablets/** Accessed 12/8/2013, 2013.
48. Becker R, Yang H, Barrett Y, Mohan P, Wang J, Wallentin L *et al.* Chromogenic laboratory assays to measure the factor Xa-inhibiting properties of apixaban – an oral, direct and selective factor Xa inhibitor. *J Thromb Thrombolysis* 2011; **32**(2): 183–187.
49. Samama M, Guinet C, Flem L, Ninin E, Debue J. Measurement of dabigatran and rivaroxaban in primary prevention of venous thromboembolism in 106 patients, who have undergone major orthopedic surgery: an observational study. *J Thromb Thrombolysis* 2013; **35**(2): 140–146.
50. Patel M, Mahaffey K, Garg J, Pan G, Singer D, Hacke W *et al.* Rivaroxaban versus Warfarin in nonvalvular atrial fibrillation. *N Engl J Med* 2011; **365**(10): 883–891.
51. Lassen M, Gallus A, Raskob G, Pineo G, Chen D, Ramirez L. Apixaban versus enoxaparin for thromboprophylaxis after hip replacement. *N Engl J Med* 2010; **363**(26): 2487–2498.
52. Lassen M, Raskob G, Gallus A, Pineo G, Chen D, Hornick P. Apixaban versus enoxaparin for thromboprophylaxis after knee replacement (ADVANCE-2): a randomised double-blind trial. *The Lancet* 2010; **375**(9717): 807–815.
53. Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL *et al*. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2013; **369**(22): 2093–2104.
54. Rossini R, Capodanno D, Lettieri C, Musumeci G, Nijaradze T, Romano M *et al*. Prevalence, predictors, and long-term prognosis of premature discontinuation of oral antiplatelet therapy after drug eluting stent implantation. *Am J Cardiol* 2011; **107**(2): 186–194.
55. North West Medicines Information Centre. Surgical management of the primary care dental patient on antiplatelet medication, 2007. Available at: **http://www.ukmi.nhs.uk/med_info/documents/Dental_Patient_on_Antiplatelet_Medication.pdf** Accessed November/30, 2013.
56. Madan GA, Madan SG, Madan G, Madan AD. Minor oral surgery without stopping daily low-dose aspirin therapy: a study of 51 patients. *J Oral Maxillofac Surg* 2005; **63**(9): 1262–1265.
57. Dudek D, Helewski K, Wyrobiec G, Harabin-Slowinska M, Kowalczyk-Ziomek G, Zaba M *et al*. Therapy with acetylsalicylic acid does not interfere with oral surgery. *Cent Eur J Med* 2013; **8**(4): 392–397.
58. Cieslik-Bielewska A, Pelc R, Cieslik T. Oral surgery procedures in patients on anticoagulants. Preliminary report. *Kardiol Pol* 2005; **63**(2): 137–141.
59. Dunn AS, Turpie AG. Perioperative management of patients receiving oral anticoagulants: a systematic review. *Arch Intern Med* 2003; **163**(8): 901–908.
60. Seymour RA, Hawkesford JE, Sykes J, Stillings M, Hill CM. An investigation into the comparative efficacy of soluble aspirin and solid paracetamol in postoperative pain after third molar surgery. *Br Dent J* 2003; **194**(3): 153–157.
61. Lillis T, Ziakas A, Koskinas K, Tsirlis A, Giannoglou G. Safety of dental extractions during uninterrupted single or dual antiplatelet treatment. *Am J Cardiol* 2011; **108**(7): 964–967.
62. Scully C, Wolff A. Oral surgery in patients on anticoagulant therapy. *Oral Surg Oral Med Oral Pathol Oral Radiol Endodont* 2002; **94**(1): 57–64.
63. Lockhart PB, Gibson J, Pond SH, Leitch J. Dental management considerations for the patient with an acquired coagulopathy. Part 1: Coagulopathies from systemic disease. *Br Dent J* 2003; **195**(8): 439–445.
64. Wahl MJ. Dental surgery and antiplatelet agents: bleed or die. *Am J Med* 2014; **127**(4): 260–267.
65. Joint Formulary Committee. *Prescribing in Dental Practice: Thromboembolic Disease*. British National Formulary 67th edn. BMJ Group and Pharmaceutical Press, 2014: p31.
66. Rider OJ, Rider EB. The changing face of oral anticoagulants. *Br Dent J* 2013; **215**(1): 17–20.
67. Scully C. Haematology: anticoagulant treatment. In: *Medical Problems in Dentistry* 6th edn. Oxford: Elsevier, 2010: pp192–198.
68. Blinder D, Manor Y, Martinowitz U, Taicher S. Dental extractions in patients maintained on continued oral anticoagulant: comparison of local hemostatic modalities. *Oral Surg Oral Med Oral Pathol Oral Radiol Endodont* 1999; **88**(2): 137–140.
69. Joint Formulary Committee. *Dental Practitioners Formulary* 67th edn. BMJ Group and Pharmaceutical Press, 2014: pp1062–1063.
70. North West Medicines Information Centre. Surgical management of the primary care dental patient on warfarin, 2007. Available at: **http://www.ukmi.nhs.uk/med_info/documents/Dental_Patient_on_Warfarin.pdf** Accessed September/12, 2014.
71. Martinez-Lopez F, Onate-Sanchez R, Arrieta-Blanco J, Onate-Cabrerizo D, Cabrerizo-Merino M. Clinical diseases with thrombotic risk and their pharmacologycal treatment: how they change the therapeutic attitude in dental treatments. *Med Oral Patol Oral Cir Bucal* 2013; **18**(6): e888–895.
72. Lin L, Nizam SI, Fatahzadeh M. The impact of Prasugrel, a new anti-platelet agent, on dental care of patients. *Quintessence Int* 2013; **44**(5): 433–438.
73. Eli Lilly and Company Ltd. Effient® (prasugrel) – official site – safety and side effects, 2013. Available at: **http://www.effient.com/Pages/effient-side-effects.aspx** Accessed 12/11/2013, 2013.
74. AstraZeneca UK Limited. Safety and side effects of Brilique, 2013. Available at: **http://www.brilique.com/about-brilique/safety-and-side-effects.html#question_and_answer11** Accessed 12/11/2013, 2013
75. Price M, Walder J, Baker B, Heiselman D, Jakubowski J, Logan D *et al*. Recovery of platelet function after discontinuation of prasugrel or clopidogrel maintenance dosing in aspirin-treated patients with stable coronary disease. *J Am Coll Cardiol* 2012; **59**(25): 2338–2343.
76. Gurbel PA, Bliden KP, Butler K, Tantry US, Gesheff T, Wei C *et al*. Randomized double-blind assessment of the ONSET and OFFSET of the antiplatelet effects of ticagrelor versus clopidogrel in patients with stable coronary artery disease: the ONSET/OFFSET Study.*Circulation* 2009; **120**(25): 2577–2585.
77. Thiele T, Sumnig A, Hron G, Muller C, Althaus K, Schroeder HWS *et al*. Platelet transfusion for reversal of dual antiplatelet therapy in patients requiring urgent surgery: a pilot study. *J Thromb Haem* 2012; **10**(5): 968–971.
78. AstraZeneca UK Limited. Brilique 90 mg

film coated tablets – summary of product characteristics, 2013. Available at: **http://www.medicines.org.uk/emc/medicine/23935/SPC/Brilique+90+mg+film+coated+tablets/** Accessed 12/11/2013, 2013.

79. Eli Lilly and Company Ltd Daiichi Sankyo UK Limited. Efient 5 mg and 10 mg film-coated tablets – summary of product characteristics, 2013. Available at: **http://www.medicines.org.uk/emc/medicine/21504/SPC/Efient+5mg+&+10mg+film-coated+tablets+(Eli+Lilly+and+Company+Ltd+Daiichi+Sankyo+UK+Limited)/#CLINICAL_PRECAUTIONS** Accessed 12/11/2013, 2013.
80. Boehringer Ingelheim Limited. Pradaxa (dabigatran etexilate) prescriber guide for stroke prevention in atrial fibrillation, 2013. Available at: **http://www.pradaxa.co.uk/downloads/spaf-prescriber-guide.pdf** Accessed November, 2013.
81. Romond K, Miller C, Henry R. Dental management considerations for a patient taking dabigatran etexilate: a case report. *Oral Surg Oral Med Oral Pathol Oral Radiol* 2013; **116**(3): 191–195.
82. Healey JS, Eikelboom J, Douketis J, Wallentin L, Oldgren J, Yang S *et al.* Periprocedural bleeding and thromboembolic events with dabigatran compared with warfarin: results from the randomized evaluation of long-term anticoagulation therapy (RE-LY) randomized trial. *Circulation* 2012; **126**(3): 343–348.
83. Weitz JI, Quinlan DJ, Eikelboom JW. Periprocedural management and approach to bleeding in patients taking dabigatran. *Circulation* 2012; **126**(20): 2428–2432.
84. Bayer Healthcare. XARELTO® (rivaroxaban): stroke risk reduction in NVAF, DVT and PE risk reduction and prophylaxis, 2013. Available at: **http://www.xareltohcp.com/sites/default/** Accessed 12/8/2013, 2013.
85. Spyropoulos AC, Douketis JD. How I treat anticoagulated patients undergoing an elective procedure or surgery. *Blood* 2012; **120**(15): 2954–2962.
86. Little J. New oral anticoagulants: will they replace warfarin? *Oral Surg Oral Med Oral Pathol Oral Radiol* 2012; **113**(5): 575–580.
87. Joint Formulary Committee. *British National Formulary*. BMJ Group and Pharmaceutical Press, 2014.
88. Schulman S, Bijsterveld NR. Anticoagulants and their reversal. *Transfus Med Rev* 2007; **21**(1): 37–48.
89. Cotton B, McCarthy J, Holcomb J. Acutely injured patients on dabigatran. *N Engl J Med* 2011; **365**(21): 2039–2040.
90. Food and Drug Administration (USA). FDA Drug Safety Communication: Update on the risk for serious bleeding events with the anticoagulant Pradaxa (dabigatran), 2012. Available at: **http://www.fda.gov/Drugs/DrugSafety/ucm326580.htm** Accessed 12/1/2013, 2013.
91. Food and Drug Administration (USA). FDA Drug Safety Communication: Pradaxa (dabigatran etexilate mesylate) should not be used in patients with mechanical prosthetic heart valves, 2012. Available at: **http://www.fda.gov/Drugs/DrugSafety/ucm332912.htm** Accessed 12/1/2013, 2013.
92. Medicines and Healthcare Products Regulatory Authority. Dabigatran (Pradaxa): contraindicated in patients with prosthetic heart valve(s) requiring anti-coagulant treatment, because of the risk of thrombosis and haemorrhage. *Drug Safety Update* 2013; **6**(8): A1.