

Novel oral anticoagulants and exodontia: the evidence

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In brief

Presents an overview on the use and pharmacology of anticoagulant medications.

Explores the current evidence-based management of patients on novel oral anticoagulants during oral surgical treatments.

Outlines recommendations for practice for the management of patients on novel oral anticoagulants in primary and secondary care settings.

Background Haemostasis is crucial for the success of oral surgical treatment as bleeding problems can cause complications both pre- and post-operatively. Patients on anticoagulant drugs present a challenge due to their increased risk of bleeding. **Aims** To review the evidence for the management of oral surgery patients on novel oral anticoagulant therapy. **Methods** A literature review was conducted in May 2016 of free-text and MESH searches (keywords: apixaban, dabigatran, rivaroxaban and dental extractions) in the Cochrane Library, PubMed and CINAHL. Trial registers, professional bodies for guidelines and OpenGrey for unpublished literature were also searched. Studies were selected for appraisal after limits were applied (adult, human and English only studies) and inclusion/exclusion criteria imposed. **Results** Five studies were identified for critical appraisal using the CASP tools. These were a combination of systematic reviews and case series. Two case series were excluded due to low quality evidence. Curtin *et al.*, Davis *et al.* and Constantinides *et al.* together with guidelines from the Scottish Dental Clinical Effectiveness Programme, have highlighted a protocol in managing these patients in a dental surgical setting. **Conclusion** Patients on novel anticoagulant therapy requiring dental surgery can be managed appropriately either without discontinuation of therapy or a delay in dose. For those patients at higher risks of postoperative bleeding complications, it is advised to liaise with the specialist physician.

Background

Warfarin (a coumarin derivative) is the most widely used anticoagulant in the world. It is a vitamin K antagonist and inhibits vitamin K dependent synthesis of clotting factors (VII, IX, X and prothrombin II) affecting formation of fibrin clot. These factors are synthesised in the liver in precursor form and activated by carboxylation of specific glutamic acid residues which require vitamin K in its reduced form as a cofactor. Warfarin more specifically acts by inhibiting the reduction that converts the epoxide form of vitamin K to its reduced form by competitive antagonism due to molecular similarity between warfarin and vitamin K.¹

In the UK it is estimated that at least 1% of the population and 8% of the over-80s are taking it regularly.² It was first used in 1955 to treat American president Dwight D. Eisenhower for a coronary event. It is currently used in:

1. Prevention of venous thrombosis and embolism in rheumatic heart disease and atrial fibrillation (AF)
2. Treatment and prophylaxis of deep vein thrombosis (DVT) and pulmonary embolism (PE)
3. Stroke prophylaxis
4. AF and valvular heart disease (International Normalised Ratio [INR] target 23)
5. Mechanical heart valves (INR target 34)

However, in recent years the advent of novel oral anticoagulants (NOACs), comprising:

- Factor Xa inhibitors: rivaroxaban (Xarelto), apixaban (Eliquis), edoxaban (Lixiana) and direct thrombin (factor IIa) inhibitor: dabigatran (Pradaxa), have been used as an alternative to warfarin to treat patients with non-valvular AF, and in the prevention of stroke and systemic embolism.

NOACs were first developed in order to improve the characteristics of an ideal oral anticoagulant (Table 1).

Rivaroxaban

Rivaroxaban is an oxazolidinone derivative and a highly selective direct Factor Xa inhibitor with good oral bioavailability. Inhibition of Factor Xa interrupts the intrinsic and extrinsic pathway of the haematological coagulation cascade (Fig. 1), inhibiting both thrombin formation and development of thrombi. Rivaroxaban does not inhibit thrombin and therefore has no effects on platelets.³ It is a drug which is taken once daily in 10 mg, 15 mg or 20 mg doses. It has a rapid onset of action of approximately 2.5–4 hours, and a half-life of 5–9 hours (increased in older patients). It is contra-indicated in patients with creatinine clearance of <15 ml/min, whereby creatinine clearance is an assessment of the rate and efficiency of kidney filtration. It can be measured by serum or urine creatinine, but most commonly by the amount of creatinine present

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Table 1 Comparison between warfarin and NOACs

	Warfarin	NOACs
Dose changes	Can be unstable and require dose changes	Stable anticoagulation at a fixed dose, requiring minimal dose changes
Routine monitoring	Yes, INR	None required (for emergency setting: thrombin time, Ecarin clotting time and activated partial thrombin time for dabigatran. For rivaroxaban, antifactor Xa more sensitive)
Onset	Slow	Rapid
Half life	Long	Short
Therapeutic margin	Narrow	Wide
Side effects	Many, as involves P450 metabolism pathway	Few, as does not fully involve P450 pathway
Drug interactions	Many, as cytochrome P450 involved in metabolism (for example,azole antifungals, metronidazole, carbamazepine)	Dabigatran > rivaroxaban/apixaban (for example, carbamazepine)
Food interactions	Some food interactions (for example, alcohol, grapefruit/cranberry juice)	None significant
Antidote/reversal agent	Vitamin K, fresh frozen plasma	Praxbind for dabigatran Recombinant factor Xa for rivaroxaban/apixaban (currently under development)

in a urine sample collected over 24 hours. Normal values for men is 97–137 ml/min and 88–128 ml/min for females (although this can be reduced in patients older than 50 years). Reduced creatinine clearance values can be indicative of kidney disease or damage (for example due to heart failure or cancer).

Thereafter in 2011, the United States Food and Drug Administration (US FDA) approved rivaroxaban for prophylaxis and treatment of DVT, which may lead to PE, in adults undergoing hip and knee replacement surgery⁴ and for stroke prevention in people with non-valvular AF.⁵ In 2012, the National Institute for Health and Clinical Excellence (NICE) recommended rivaroxaban for the prevention and treatment of venous thromboembolism (VTE).⁶

Apixaban

Apixaban, like rivaroxaban is a direct Factor Xa inhibitor and similarly modulates the formation of the prothrombinase complex. Apixaban does not inhibit thrombin and has no effects on platelets. It is a drug which is taken twice daily in 2.5 mg or 5 mg doses. It has a rapid onset of approximately 1–3 hours, and its half-life is 12 hours. It is contra-indicated in patients with creatinine clearance of <15 ml/min. It was approved by NICE in February 2013 for the prevention of stroke and systemic embolism in people with non-valvular AF.

Other NOACs have become available to use, such as Edoxaban (Lixiana®) which was approved by NICE in September 2015 for the same indications. There is limited data on this

drug at present therefore it will not form part of the literature search within this article.

Dabigatran

Dabigatran is administered orally as the prodrug dabigatran etexilate, which is rapidly and completely converted to dabigatran after ingestion, through esterase-catalysed hydrolysis in plasma.⁷ It is a selective and reversible direct thrombin (factor IIa) inhibitor, which binds to the active site of the free and clot-bound thrombin molecule, so it cannot transform fibrinogen into fibrin. Dabigatran has an indirect effect on platelet formation by reducing the thrombin mediated activation of platelets.⁸ It is a drug which is taken twice daily in 110 mg or 150 mg doses, depending on the patient's renal function. It has a quick onset of approximately 0.5–4 hours, and its half-life is 12–15 hours (increased in patients with reduced renal functions). It is contra-indicated in patients with creatinine clearance of <30 ml/min due to a risk of overdose. Dabigatran was approved by NICE in March 2012 as a treatment to prevent stroke and systemic embolism in people with non-valvular AF. Anticoagulation is determined with the use of:

- aPTT (activated partial thrombin time) provides a qualitative indication of anticoagulation but is not suitable for quantification of effect
- TT (thrombin time) has a linear dose response relationship with dabigatran
- Ecarin clotting time allows direct measurement of dabigatran activity but is not widely used.

Dabigatran has little effect on INR. In October 2015 the US FDA approved idarucizumab, a monoclonal antibody fragment (Praxbind, Boehringer Ingelheim Pharmaceuticals, Inc., Germany) as a reversal agent for patients on Dabigatran in emergency surgery, or in life-threatening or uncontrolled bleeding.⁸

Careful patient selection is important before considering prescribing NOACs. Patients are prescribed NOACs for prevention of stroke and systemic embolism with non-valvular AF, and at least one or more of the following:

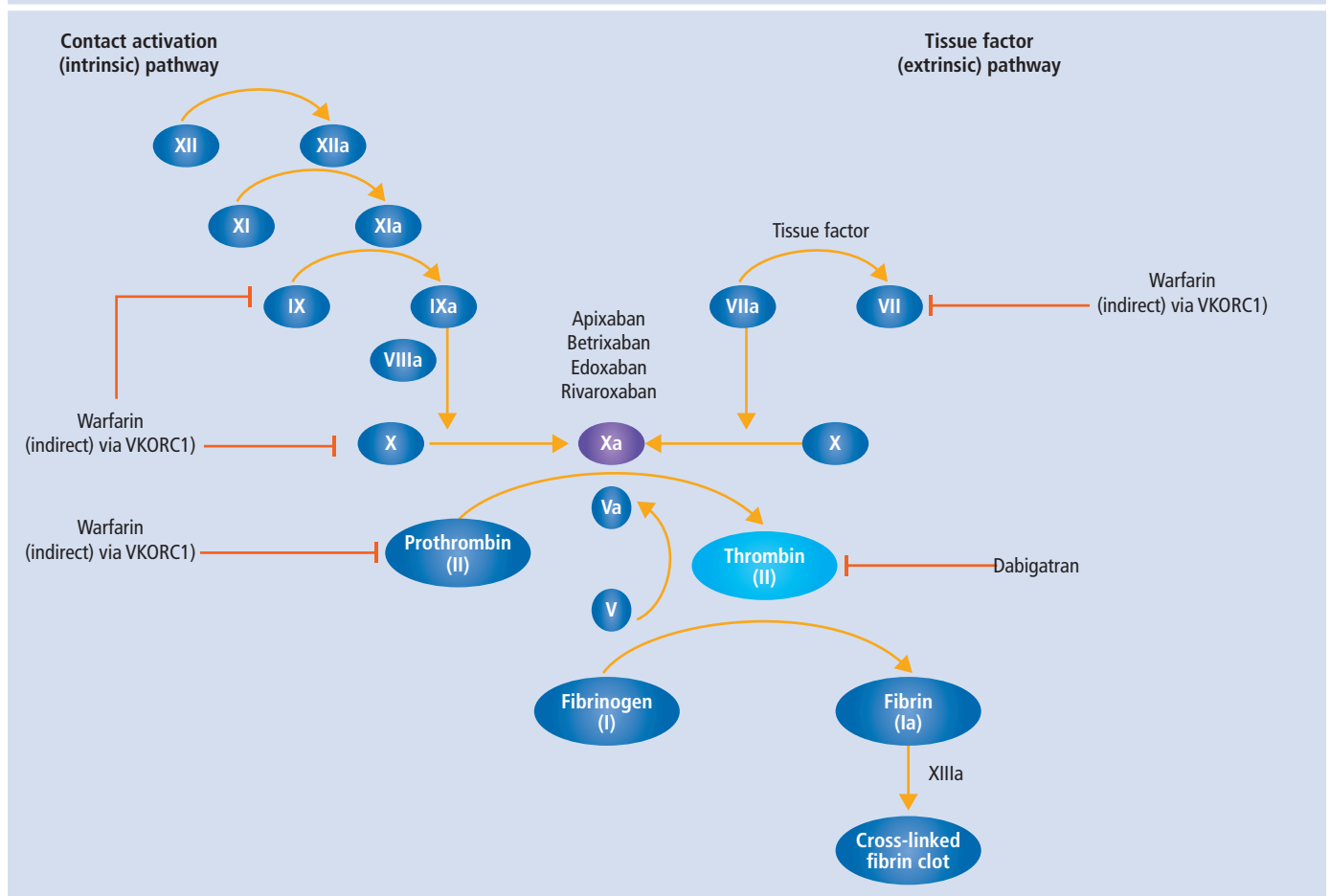
- Have had a stroke or transient ischaemic attack (TIA) in the past
- Are aged 75 or older
- Have high blood pressure
- Have diabetes
- Have heart failure with symptoms.

NOACs should be avoided in patients with severe renal impairment, clinically significant active bleeding, pregnancy and breast feeding, hepatic impairment or liver disease expected to have any impact on survival, concomitant treatment with systemic ketoconazole, cyclosporin, itraconazole, tacrolimus, voriconazole and dronedarone.

The current management of these patients, as with patients on other anticoagulant and anti-platelet therapy, is clinician dependent. Different surgeons provide different pre-operative advice regarding cessation or delaying of these drugs. This can provide a number of difficulties:

- Confusion among patients regarding pre-operative preparation
- Inconsistencies among operating staff
- Attendance at hospital accident and

Fig. 1 Mechanism of action of warfarin and NOACs. Reproduced with permission from I. Sabir *et al.* Oral anticoagulants for Asian patients with atrial fibrillation, *Nat Rev Cardiol* 2014; 11: 290–303, Springer Nature



emergency departments with postoperative haemorrhage

- Delays in treatment as clinicians attempt to contact physicians regards drug management.

The aim of this paper is to clarify, with the aid of evidence-based literature, protocols for the management of patients on NOACs.

Method

A literature review was conducted in May 2016 of free-text and MESH searches with the keywords: apixaban, dabigatran, rivaroxaban and dental extractions, in the Cochrane Library, PubMed and CINAHL. Trial registers, professional bodies for guidelines and OpenGrey for unpublished literature were also searched. Singular and plural forms of words, synonyms, acronyms, different spellings, brand and generic names, truncation, and lay and medical terminology were all used in the PICO analysis. Boolean operators 'OR', 'AND' and 'NOT' were all applied. Studies were

selected for appraisal after limits applied (adult, human and English only studies and inclusion/exclusion criteria imposed).

Results

A review of the literature has identified five studies and one guideline for general dental practitioners in the Scottish Dental Clinical Effectiveness Programme (SDCEP). Of the five studies, two were excluded (case studies).

Curtin *et al.*¹¹ highlight the lack of guidance for patients on these medications requiring dental extractions from manufacturers. General recommendations for rivaroxaban and apixaban include drug cessation for 24–48 hours before surgery dependent on the bleeding risk of the procedure. This should be followed by recommencing the drug as soon as haemostasis has been achieved. The recommendations stipulate the need to make an individual assessment with an account for the risk of bleeding versus systemic embolism. For dabigatran, manufacturer recommendations stipulate the need to measure renal function

to indicate preoperative drug cessation,¹² with the drug restarted soon after haemostasis. The paper highlights the adoption of this protocol by the Thrombosis Guidelines Group, which recommends dental surgical procedures should be performed 12 hours after the last dose of dabigatran, extractions performed with minimal trauma and with the use of postoperative local haemostatic measures.

NICE Clinical Knowledge Summaries advise that extraction of up to three teeth, periodontal or implant surgery is considered to have 'no clinically important bleeding risk' and recommend any procedures be carried out before the next dose of NOAC is due or 18–24 hours after the last dose (which may require missing a dose of the twice daily NOACs; dabigatran and apixaban). The drugs can be restarted six hours after haemostasis has been achieved with the use of local haemostatic measures.

Constantinides *et al.*⁷ is a systematic review of the literature. The RELY (Randomised Evaluation of Long-Term Anticoagulation Therapy) trial in 2009 highlighted the efficacy

Table 2 Factors affecting bleeding risk

Patient factors	Surgical factors
Age	Invasiveness
Renal functionality	Difficulty of surgery
Acquired or congenital coagulation defects	
Antiplatelet/anticoagulant therapies (including drug interaction)	
Haematological malignancy	
Ongoing cancer treatment (chemotherapy)	

of dabigatran against warfarin. The study included 18,113 patients who were taking dabigatran for AF, 4,591 whom underwent invasive procedures (10% of which included dental procedures). The anticoagulant was stopped in these patients according to renal function. The incidence of major bleeding risk peri-operatively for invasive surgical procedures was similar for patients on dabigatran and warfarin (3.8% for 110 mg–5.1% for 150 mg dabigatran; 4.6% warfarin). However, in patients on 110 mg dabigatran twice daily there was a statistically reduced rate of major bleeding.

There was an increased risk of bleeding in those requiring emergency surgery or bridging anticoagulation. Similarly, there was 1.2% risk of thromboembolic event in both anticoagulant therapies.

The paper suggests the level of anticoagulation achieved by dabigatran is similar to warfarin at an INR of 2–3. To minimise bleeding risk (where dabigatran is continued) the recommendation is to perform surgery as late as possible after the last dose and use local haemostatic measures postoperatively. In the case of elective surgery (multiple surgical extraction), there should be consideration of drug cessation which is reliant on:

- Patient's renal function
- The risk of bleeding (Table 2).

Constantinides *et al.*⁷ also highlight that TT or aPTT performed before surgical treatment can indicate, if normal, that the anticoagulant effect of dabigatran has resolved. Due to rapid onset of the drug, dabigatran can

be commenced after formation of a stable clot or as soon as reasonably possible due to the increased risk of stroke should it be discontinued.

In 2010, the ROCKET-AF study discovered a significant reduction in the number of TIAs and systemic embolic events with rivaroxaban compared with warfarin in patients with AF. The rate of major bleeding associated with an invasive procedure was 2.3% and was similar with the two anticoagulants.

As with dabigatran, the authors conclude the same protocol be followed for rivaroxaban, with discontinuation to be discussed with the patient's physician. Therefore, for uncomplicated dental extractions rivaroxaban can be continued in patients with normal renal function (where local haemostatic measures are used). Where there is an increased risk of bleeding or impaired haemostasis, like dabigatran, rivaroxaban should be discontinued 24 hours before surgery (with need for increased discontinuation if there is reduced renal function). Due to its rapid onset of action, continuation should be 24–48 hours after surgery.

The ARISTOTLE trial (apixaban versus warfarin) showed similar results of bleeding (1.6% versus 1.9%) for dental extractions, colonoscopy, and ophthalmologic surgery. Constantinides *et al.*⁷ conclude there is limited data to make reliable suggestions with regards to management of these patients, but to follow the protocol outlined above until further studies can be performed.

Davis *et al.*¹³ reviews the literature in relation to dabigatran in patients requiring oral surgery. The paper considers a Cochrane review

comparing NOACs with low molecular weight heparin and warfarin, which showed no statistically significant increased risk of bleeding (although studies were flawed in the classification of bleeding). As per Constantinides *et al.*,⁷ the anticoagulation effects of dabigatran are comparable to warfarin with an INR of between 2–3. The authors recommend for simple extractions that the risk of postoperative bleeding is low with local haemostatic measures. For multiple/surgical extractions or significant oral and maxillofacial procedures, clinicians should consider discontinuation of dabigatran before the procedure with timing to be determined by the patient's renal function. In patients where discontinuation is not appropriate and extensive oral surgery procedures are planned, bridging to low molecular weight heparin is advised.

Finally, the Scottish Dental Clinical Effectiveness Programme¹⁴ have described a protocol for the dental management of patients on NOACs. Dental procedures are categorised according to 'low risk of postoperative bleeding complications' and 'high risk of postoperative bleeding complications'. For the low risk procedures, the NOACs need not be discontinued or delayed. For high risk procedures, it is suggested that patients delay or miss a dose (dependent on NOAC taken). For example, if a patient on rivaroxaban requires a high risk procedure, it may not be necessary to stop the medication at all, as it is taken once daily, as long as the procedure is performed as late as possible after the last dose. If a patient on apixaban requires a high risk procedure, it may be necessary to miss the morning/evening dose of the medication (Table 3). It is thereafter advised that NOACs may be continued no sooner than four hours after haemostasis has been achieved.

Discussion

Despite the limited evidence and lack of robust long-term clinical data on the effects of NOACs on postoperative bleeding following dental extractions, the literature review has highlighted that patients on NOACs can be

Table 3 Suggested NOAC regimen for day of treatment

NOAC	Usual drug schedule	Morning dose (pre-treatment)	Post-treatment dose
Apixaban or Dabigatran	Twice a day	Miss morning dose	Usual time in evening
Rivaroxaban	Once a day, morning	Delay morning dose	4 hours after haemostasis
	Once a day, evening	Not applicable	Usual time in evening/4 hours after haemostasis

Table 4 Evidence-based protocol identified according to anticipated risk of postoperative bleeding

Minor surgical procedures (low risk of bleeding)	Intermediate surgical procedures (moderate risk of bleeding)	Major surgical procedures (high risk of bleeding)
Simple extraction <3 teeth, incision and drainage of dental abscess	multiple extractions >3 teeth, surgical extractions (flap raising procedures), skin cancer excision/reconstruction, jaw cysts, implant placement, biopsies	oral and maxillofacial surgery (orthognathic, salivary, trauma, cancer)
DO NOT discontinue daily dose If possible, perform surgery as long as possible after last dose Local haemostatic measures	Delay or miss the morning dose Restart 4 hours after haemostasis has been achieved Local haemostatic measures	Discontinue before surgery depending on renal function and physician consult (>24 hours preoperatively) Restart postoperatively as per specialist advice (>24 hours postoperatively)

managed appropriately with local haemostatic measures postoperative to dental extractions. Discontinuation of these drugs should only be considered in conjunction with the prescribing physician, due to the individual pharmacokinetic variability which is dependent on liver/renal function, sex, weight, age, drug interference and genetics. These factors will influence whether a drug should be interrupted or continued, as well as the potential risks of thromboembolic event which are considered on a case by case basis.

All papers conclude that the management of these patients should include the following (Table 4):

- Assess the surgical and patient factors (Table 2)
- Categorise the procedure into low, moderate or high risk of postoperative bleeding
- For minor surgical procedures there is no need to discontinue the anticoagulant medication as the risk of thrombotic event outweighs the risk of post-operative haemorrhagic complications
- If possible, perform the surgery as long as possible after the last dose
- Consider local factors (such as inflammation of soft tissues)
- Application of local haemostatic measures, including pressure application with gauze, use of gelatin sponge/oxidised-cellulose mesh (for example, Surgicel), suturing and the use of 5% tranexamic mouthwash four times daily for five days postoperatively (where available)
- For intermediate surgical procedures (multiple extractions, surgical extractions) it is necessary to stop, miss a dose or delay the NOAC dose
- For major surgical procedures (head and neck surgery, extensive oral and maxillofacial procedures), NOAC cessation is dependent on the patient's renal function and followed by discussion with the

patient's physician/cardiologist (who may consider bridging anticoagulation). It may be necessary to ensure the effect of the drug is reduced by pre-operative aPTT or TT, which if still raised may require an increased period of drug cessation

- Assessment of the risk of thromboembolic event, with high risk patients including any mitral valve prosthesis, stroke, cardioembolic event, venous thromboembolism <3 months, severe thrombophilia or active cancer (diagnosed <6 months or undergoing treatment). Lower risk patients include aortic-valve prosthesis in patients without AF/prior to stroke, and venous thromboembolism >12 months (with no other risk factors).

Recommendations for practice

Limited data is available regarding the management of dental patients on NOACs, and remains a concern among clinicians. Further studies are encouraged to determine the true risks of bleeding after oral surgical procedures and to provide an evidence-based approach in their management.

Based on the findings of the articles appraised and pharmacological profiling of the drugs discussed, the following recommendations can be made (Table 4):

- Ensure a detailed and current medical history is noted
- Explain the risks and benefits of performing any dental treatment in patients on NOACs whether therapy is/is not continued
- Assessment of surgical complexity (clinical and radiographic) that would suggest simple extraction (for example periodontally compromised teeth) versus surgical extraction (for example bulbous root morphology)
- Appointments for extractions to be made in the morning and early in the week so that

postoperative bleeding complications can be arrested before the weekend

- Bleeding should be managed with local haemostatic measures in this group of patients, such as gelatin sponge/oxidised cellulose mesh, sutures and gauze pressure packs
- Consider staged extractions for the control of intra-operative bleeding
- Avoid the concomitant use of drugs that may interfere with peak plasma concentrations of NOACs (for example non-steroidal anti-inflammatories for pain control)
- Discontinuation of NOACs is not necessary for uncomplicated/simple dental extractions and procedures (where the patient has normal renal function and there is only a standard bleeding risk)
- In patients where there is a concern of increased intra-operative or postoperative bleeding, NOACs can be discontinued/dose delayed
- Consider delay of any invasive dental procedures for patients on a time limited course of therapy, or in patients at the start of therapy (where initial doses may be higher)
- For high risk surgical interventions, treatment should be delayed until discontinuation of the NOAC has been prepared and arranged accordingly with the patient's cardiologist, and based on their renal function (especially for general anaesthesia cases where staged extractions are not feasible)
- Patients must be instructed on when to commence their NOAC therapy as part of the postoperative instruction
- Severe postoperative bleeding can be managed with application of mechanical pressure, haemostatic measures, and maintenance of intravascular volume with fluid replacement (and consideration of haemodialysis in emergency situations). Where available reversal agents identified previously should be considered.

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