Periprocedural management of patients receiving novel oral anticoagulants

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Received 17 August 2016

Revised 18 January 2017

Accepted 6 February 2017

Published Online First

23 February 2017

EAHP Statement 4: Clinical Pharmacy Services

ABSTRACT

Background Non-vitamin K oral antagonists are being increasingly used. However, broad clinical experience with them is lacking.

Objectives To review guidelines and evidence for the use of non-vitamin K oral antagonists in the periprocedural environment.

Results Despite the clear advantages of vitamin K oral antagonists, their use can entail risks owing to the scarcity of reversal agents. Consensus has been reached about postoperative resumption, which is recommended at 24 hours and 48–72 hours, respectively, after low-risk and high-risk bleeding surgery. Bridging with heparin is recommended in patients with a high risk of thrombosis. Urgent interventions should ideally take place 24 hours after the last dose intake. Major discrepancies exist between the American and the European recommendations for neuraxial procedures. The American proposals recommend suspending the drug for five half-lives, whereas the European approaches suggest suspension of just two half-lives. Suggestions for perioperative discontinuation vary widely. Some authors recommend a longer time of resumption for patients with renal impairment. All agree that there should be an increase in the number of days of interruption in high-risk bleeding procedures versus low-risk bleeding procedures.

Conclusions A diverse number of approaches have been suggested for perioperative management of novel oral antagonists. American recommendations tend to be more rigorous than those of Europe. A need for more studies that measure health outcomes after the use of these drugs would be indispensable.

INTRODUCTION

Vitamin K antagonists (VKAs) have been the mainstay of oral anticoagulant therapy for decades. However, VKAs interact with a large number of drugs, have variable interindividual responses and narrow therapeutic indexes, so they require laboratory monitoring.¹ Non-vitamin K oral antagonists (NOACs) include dabigatran, a factor IIa inhibitor, as well as rivaroxaban and apixaban, which are factor Xa inhibitors. They are non-inferior to warfarin in efficacy for stroke prophylaxis in atrial fibrillation (AF) and for the treatment of venous thromboembolism (VTE). The last chest guideline for antithrombotic therapy for VTE disease suggests the use of dabigatran, rivaroxaban or apixaban rather than VKAs as anticoagulant therapy in patients with deep vein thrombosis of the leg or pulmonary embolism and no cancer.² Moreover, these drugs have proved to be at least as safe as warfarin in their effect on major bleeding.³

The Randomized Evaluation of Long-Term Anti-coagulation Therapy (RE-LY) randomised trial demonstrated that both dabigatran and warfarin are associated with similar rates of perioperative bleeding and thrombotic complications, even among patients having urgent or major surgery.⁴ The authors of this study argue that in patients undergoing invasive procedures, one of the key advantages of dabigatran in comparison with warfarin is its short half-life, which enables dabigatran to be continued in many patients up to 24 to 48 hours before the procedure. This ensures adequate haemostasis at the time of surgery, while reducing thromboembolic and heparin bridging complications and associated costs.⁴

Experts find periprocedural management of VKAs to be clear-cut while their opinions about management of NOACs appear to differ, remaining ambiguous and complex.³ It has been reported that NOACs, with their rapid onset and offset of anticoagulant effect due to their short half-lives, should allow for a safer and shorter period of drug cessation before procedures in patients with normal renal and hepatic function.⁵

Mar *et al*³ report that the use of NOACs has advantages over use of VKAs in the periprocedural setting because they provide predictable levels of anticoagulation, they have fewer drug–drug interactions and they are rapidly cleared from the body in a normal renal function setting.⁶

However, there are several uncertainties about the optimal preoperative approach with NOACs: limited data in patients with renal insufficiency and interindividual variability in some pharmacokinetic parameters.⁷ In addition, the use of classic coagulation tests cannot quantify their anticoagulant effect, and experience with reversal agents is limited. As new data from clinical trials are published, several authors have now begun to point out emerging risks with the use of these drugs.^{8,9} Clinical practice in particular patient populations, such as older adults and patients with renal impairment, has shown an increased risk of bleeding and drug interactions.^{10,11}

There is no universal strategy for perioperative anticoagulation with NOAC therapy.¹ It is dependent on bleeding risk, consequences of bleeding, thrombotic risk associated with stopping anticoagulation and its consequences, as well as the effectiveness of the bridging protocol.¹² Bridging anticoagulation refers to the temporary interruption of oral anticoagulation and the introduction of a short-acting anticoagulant, such as low-molecular-weight heparin (LMWH) or unfractionated heparin, to allow surgical or invasive procedures.⁷

To cite: Arias Pou P, González A, Martínez LJP, *et al.* *Eur J Hosp Pharm* 2018;**25**:292–297.

It has been suggested that procedures should be performed when serum drug levels are lowest or, that one dose should be omitted and then medications restarted after the procedure, provided that there are no concerns about bleeding.⁷

The European Heart Rhythm Association (EHRA) recommends 'the development of an institutional guideline and a hospital-wide policy concerning perioperative anticoagulation management in different surgical settings, widely communicated and readily available'.¹³

RISK STRATIFICATION FOR PERIOPERATIVE THROMBOEMBOLISM AND BLEEDING RISK

To determine an overall periprocedural anticoagulant management strategy for a particular patient, the patient's thrombosis and bleeding risk, together with the surgical risks, should be assessed (tables 1 and 2).^{13 13–15}

If the risk of interrupting anticoagulation is higher than the procedural bleeding risk, anticoagulation should not be interrupted or should at least be substituted with LMWH.³ The CHADS₂ score is calculated by scoring one point for each of congestive heart failure, hypertension, age 75 years or diabetes

mellitus, and two points for previous stroke or transient ischaemic attack.⁷

The American College of Chest Physicians stratifies patients for thrombotic risk in three categories: high risk (>10%), moderate risk (5–10%), and low risk (<5%). They suggest that bridging should be used in moderate-risk patients. The British Committee for Standards in Haematology has established two categories, suggesting high-risk patients for bridging.⁷

Perioperative thromboembolism risk depends both on patient characteristics and the type of surgery/procedure.¹ It has been shown that active cancer is an independent predictor of thrombotic recurrence.¹ For the type of surgery, neurological or vascular surgery confers the highest absolute stroke risk, whereas abdominal-pelvic surgery has the lowest risk.¹

Prior bleeding, a mechanical mitral valve, heparin bridging resumed <24 hours after the procedure, and active cancer are independent predictors of periprocedural bleeding.¹ The surgical bleeding risk determines whether anticoagulant therapy needs to be interrupted and the timing of preoperative and postoperative resumption of an OAC.¹⁴ It also determines the timing of the postprocedural resumption of heparin bridging.¹⁴

PREOPERATIVE DISCONTINUATION OF NOACS

The timing of preoperative NOAC interruption to ensure a minimal or non-residual anticoagulant effect at surgery is based on the elimination half-life of the NOAC, patient renal function and its effect on NOAC elimination, and the bleeding risk associated with planned surgery and anaesthesia.^{5 13}

It is critical to ensure that the time of discontinuation for each agent in question is consistent with its delay in drug clearance.³ NOACs should not be used in patients with moderate to severe hepatic impairment owing to a paucity of data about their use in patients with intrinsic coagulation abnormalities.¹⁶ In patients who have developed severe hepatic impairment in the periprocedural setting, NOACs should be discontinued and not restarted in the postoperative setting.³

The latest data suggest that selected minor procedures can be safely performed either without interruption of NOAC therapy or with interruption on the day of the procedure to avoid peak effects.^{5 14} Even dabigatran, which has the longest half-life among NOACs, loses much of its anticoagulation potency 24 hours after the last dose, with drug concentration dropping to approximately 25% of peak serum drug concentration.³

For procedures with a minor bleeding risk, the 'updated EHRA practical guide for the use of non-VKA oral anticoagulants' recommends that the last dose of NOAC be taken 24 hours before the elective procedure in patients with normal kidney function.¹³ In procedures that carry a risk for major bleeding, the recommendation is to take the last NOAC 48 hours before the procedure.¹³ For the three currently available NOACs, the Spanish Forum on Anticoagulants and Anaesthesia proposes a preoperative period withdrawal that covers at least three half-lives of any one of these three drugs.¹⁵

Spyropoulos *et al*¹⁴ suggest an interval of two to three drug half-lives between the last NOAC dose and low-bleeding risk procedures and an interval of four to five drug half-lives when the bleeding risk is high. This means that the last NOAC dose will be taken 2 days before surgery in patients undergoing low-bleeding risk procedures and 3 days before surgery when the bleeding risk is high. An additional 1–2 days of interruption is required in patients receiving dabigatran with an estimated glomerular filtration rate (eGFR) of <50 mL/min.¹⁴ The use of the upper limit of the half-life to calculate the time off for

Table 1 Classification of patient thromboembolic risk

Low	Moderate	High
<ul style="list-style-type: none"> ▶ CHADS₂ score of 0–2 (and no prior stroke or TIA) 	<ul style="list-style-type: none"> ▶ CHADS₂ score of 3 or 4 	<ul style="list-style-type: none"> ▶ CHADS₂ score of 5 or 6 ▶ Recent stroke or TIA (<3 months) ▶ Rheumatic valvular heart disease
<ul style="list-style-type: none"> ▶ Bileaflet mechanical aortic valve without major risk factors for stroke 	<ul style="list-style-type: none"> ▶ Bileaflet mechanical aortic valve with major risk factors for stroke 	<ul style="list-style-type: none"> ▶ Any mechanical mitral valve
<ul style="list-style-type: none"> ▶ VTE more than 12 months ago 	<ul style="list-style-type: none"> ▶ Previous VTE (3–12) months ▶ Recurrent VTE ▶ Non-severe thrombophilia ▶ Active cancer 	<ul style="list-style-type: none"> ▶ Recent VTE (<3 months) ▶ Severe thrombophilia ▶ Deficiency of protein C, protein S or antithrombin ▶ Antiphospholipid antibodies

CHADS₂, cardiac failure, hypertension, age, diabetes, stroke (doubled); TIA, transient ischaemic attack; VTE, venous thromboembolism.

Table 2 Classification of procedural bleeding risk

Low	Moderate	High
<ul style="list-style-type: none"> ▶ Minor dental procedures ▶ Superficial surgery ▶ Cataract and glaucoma surgery ▶ Endoscopy without biopsy 	<ul style="list-style-type: none"> ▶ Bronchoscopy biopsy ▶ Endoscopy with biopsy ▶ Prostate or bladder biopsy ▶ Arthroscopy ▶ Shoulder/foot/hand surgery ▶ Coronary angiography ▶ Abdominal hysterectomy ▶ Laparoscopic cholecystectomy 	<ul style="list-style-type: none"> ▶ Major surgery with intensive tissue injury ▶ Liver/kidney biopsy ▶ Cancer surgery ▶ Urologic or gastrointestinal surgery ▶ Transurethral prostate resection, bladder resection, or tumour ablation ▶ Surgery in highly vascular organs (kidneys, liver, spleen) ▶ Cardiac, intracranial or spinal surgery ▶ Any major operation (procedure duration >45 min)

Table 3 Preoperative interruption of new oral anticoagulants

Preoperative		Low/moderate bleeding risk				High bleeding risk			
Drug	GFR (mL/min)	>80	50–80	30–50	15–30	>80	50–80	30–50	15–30
Dabigatran									
Study		Days to interrupt NOAC							
Spyropoulos <i>et al</i> ¹⁴		1	1	2	*	2	2	3–4	*
Liew <i>et al</i> ¹		1	1	2	*	2	2	3–4	*
Heidbuchel <i>et al</i> ¹³		1	1,5	2	*	2	3	4	*
Cheng and Barillari ¹⁷		1	1–2	2–3	*	2	2–3	4	*
Tran <i>et al</i> ⁶		1	1	2–3	*	2–3	2–3	4	*
Mar <i>et al</i> ³		1	3	4	5	3	3	4	5
GFR (mL/min)		>80	50–80	30–50	15–30	>80	50–80	30–50	15–30
Rivaroxaban									
Study		Days to interrupt NOAC							
Spyropoulos <i>et al</i> ¹⁴		1	1	1	Ind [†]	2	2	2	Ind [†]
Liew <i>et al</i> ¹		1	1	2	*	2	2	3–4	*
Heidbuchel <i>et al</i> ¹³		1	1	1	1,5	2	2	2	2
Cheng and Barillari ¹⁷		1	1	1	1	1 [‡]	1 [‡]	1 [‡]	1 [‡]
Tran <i>et al</i> ⁶		1	1	1	2	2–3	2–3	3	*
Mar <i>et al</i> ³		1	1	1	2	1	1	1	2
GFR (mL/min)		>80	50–80	30–50	15–30	>80	50–80	30–50	15–30
Apixaban									
Study		Days to interrupt NOAC							
Spyropoulos <i>et al</i> ¹⁴		1	1	1	Ind [†]	2	2	2	Ind [†]
Liew <i>et al</i> ¹		1	1	2	*	2	2	3–4	*
Heidbuchel <i>et al</i> ¹³		1	1	1	1,5	2	2	2	2
Cheng and Barillari ¹⁷		1	1	1	1	2	2	2	2
Tran <i>et al</i> ⁶		1	1	2	*	2–3	2–3	3	*
Mar <i>et al</i> ³		1	2	3	*	2	2	3	*

GFR, glomerular filtration rate; NOACs, new oral anticoagulants.

*Not reported; [†]Individualise; [‡]Canada 2–4 days.

each individual drug without using bridging anticoagulation is recommended.⁷ Table 3 shows the different recommendations of selected authors.^{1 3 4 13 14 17}

Some authors lengthen the interruption of dabigatran with an eGFR of <80 mL/min while others recommend lengthening the interruption with an eGFR of <50 mL/min. For rivaroxaban and apixaban, all the authors, with the exception of one, recommend more days of interruption for a patient with renal impairment.

Elective surgery should be postponed for a minimum of 4–6 weeks after bare metal stent implantation (preferably 3 months) and 6 months after drug-eluting stent implantation (preferably 12 months), after which point surgery should proceed.⁷

POSTOPERATIVE REINTRODUCTION OF NOAC

The first dose of NOAC after surgery should be given in the early postoperative period ‘as soon as possible’ when surgical bleeding risk is under control¹⁵ and once haemostasis is restored.^{3 17} Specific recommendations vary from 4–6 hours after surgery in good haemostasis procedures¹⁸ or to restart 6¹³ or 12 hours after surgery.¹²

Several authors agree with the following suggestions: for post-procedural NOAC therapy resumption, wait for approximately 24 hours after low-bleeding risk procedures and 48–72 hours if the bleeding risk is high.^{1 5 7 14 16} In the intervening period, prophylactic LMWH may be given.⁷

URGENT SURGICAL INTERVENTION

NOACs should be discontinued if an emergency intervention is required.¹³ Surgery or intervention should be deferred, if possible, until at least 12 hours¹⁸ and ideally 24 hours after the last NOAC dose.¹³ Surgery with a high-bleeding risk should be postponed for at least one to two drug half-lives.^{7 17} It is very important to know the exact time of the last dose of NOAC.¹⁵ Spinal or epidural anaesthesia should only be used in emergency surgery when there is certainty of no anticoagulant activity.^{5 7}

There is currently only one approved antidote to reverse the effects of dabigatran. The use of concentrated prothrombin complex and recombinant activated factor VII has been suggested for urgent reversal of the anticoagulant effect.¹⁹ Moreover, ‘the use of these pro-haemostatic agents should be restricted to patients with life-threatening bleeding unable to be managed with supportive measures alone’.⁵

PERIOPERATIVE BRIDGING

The decision to bridge patients at high-risk for thromboembolism should be based on individual surgical and patient characteristics, including the risk of bleeding and the length of NOAC interruption.³

The BRIDGE investigators found that in patients with AF who require perioperative interruption of warfarin treatment for an elective procedure, a strategy of discontinuing warfarin treatment without the use of bridging anticoagulation was non-inferior to the use of bridging anticoagulation for the prevention of arterial thromboembolism.²⁰ In addition, bridging conferred a risk of major bleeding that was nearly triple the risk associated with no bridging.²⁰ The findings from the BRIDGE trial as well as from non-randomised studies suggest that the perioperative risk of arterial thromboembolism in patients with AF during interruption of warfarin treatment may have been overstated and may not be mitigated by bridging anticoagulation.²⁰ These investigators state that the trial findings may also apply to the newer agents, such as NOACs.²⁰

In general, perioperative heparin bridging is not needed in NOAC-treated patients who require an elective surgery/procedure because of the rapid offset and onset of NOACs.¹ However, heparin bridging may have a role in patients with high thromboembolic risk, especially where there is impaired intestinal absorption (owing to intestinal surgery) or an inability to take oral medications.¹ When the oral route may not be feasible for several days, especially when the risk of bleeding is low but the risk of thrombosis is high, the use of postoperative bridging with a parenteral anticoagulant should be planned accordingly.³ Patients who are unable to tolerate oral intake can receive prophylactic LMWH.⁵ In cases of severe renal impairment when unprotected times exceed 96 hours owing to interruption, bridging can be considered.³

LMWH is considered the best bridging treatment in most cases. In patients with a GFR of <30 mL/min, the LMWH dose should be reduced, and the monitoring of anti Xa levels is suggested.⁷ Unfractionated heparin (HNF) constituted an alternative to LMWH in patients with renal impairment.⁷

The dose of LMWH (prophylactic or anticoagulant) should be based on the thrombotic risk of each patient.¹⁵ Therapeutic-dose heparin bridging therapy should be reserved for patients with a mechanical heart valve with high thromboembolism risk features and possibly, for a selected group of high-risk patients with AF, comprising those with a recent (within 3 months) stroke/transient ischaemic attack or a CHADS2 score of 5 or 6. Van Veen *et al*⁷ suggest that all patients with mechanical valves, except those with aortic bileaflet valves without other risk factors for stroke, should be considered for bridging.

The French Working Group on Perioperative Hemostasis and the French Study Group on Thrombosis and Hemostasis (GIHP and GEHP) propose that LMWH should be started 12 hours after the last dose of NOAC, if it is to be administered twice a day, or 24 hours after the last dose of NOAC, if it is to be administered daily.¹⁵ The last therapeutic anticoagulant dose of LMWH should be administered 24 hours before surgery and should be half the total dose if it was given once daily.^{12 15} The last dose of thromboprophylactic LMWH should be given 12–24 hours preoperatively.^{15 21}

Given the growing concern about haemorrhagic complications associated with bridging, it is considered that bridging should be used only in patients who are at the highest risk of thrombosis.⁷ In summary, high-risk patients should be considered for bridging; moderate-risk patients may be considered for bridging in procedures that do not have a high bleeding risk; and low-risk patients do not require bridging.⁷

NEURAXIAL PROCEDURES

Patients receiving NOACs, like those who are receiving other anticoagulants, are at risk of developing epidural or spinal haematoma when neuraxial anaesthesia is used. Patients should be monitored carefully for symptoms and signs of neurological impairment.⁵ Given the limited data available concerning NOAC use and epidurals, some authors suggest strict adherence to manufacturer recommendations.³

Procedures such as spinal anaesthesia, epidural anaesthesia, and lumbar puncture are high-risk bleeding procedures and may require complete haemostasis function.¹³ Tran *et al*⁵ state that while there is no evidence regarding the safety of neuraxial anaesthesia in patients therapeutically anticoagulated with a NOAC, it cannot be recommended. In this situation, neuraxial anaesthesia should be avoided until laboratory testing establishes the absence of its anticoagulant effects, where available^{13 18} or

Table 4 European Society of Anaesthesiology recommended intervals before and after interventional pain procedure²¹

Interventional pain procedure	Dabigatran	Rivaroxaban	Apixaban
Recommended interval between discontinuation of drug and procedure (two half-lives), hours	24	22–26	26–30
Recommended interval between procedure and resumption of drug, hours	6	4–6	4–6

five renally adjusted half-lives of the drug have elapsed.⁵ In emergency surgery, neuraxial anaesthesia is contraindicated unless laboratory results have demonstrated the absence of significant anticoagulation.⁷

Factors that increase the risk of spinal haematoma were identified as lack of guidelines, administration of antithrombotic agents, female sex, difficult punctures,²¹ indwelling epidural catheters, concomitant use of drugs that inhibit platelet function, traumatic or repeated epidural or spinal punctures, and a history of spinal deformity or surgery.²²

The risk of haemorrhage is lowest in spinal anaesthesia that uses fine needles and highest in epidural catheter anaesthesia, which requires the largest needle gauges available. Nearly half of all cases of bleeding occur during the removal of an epidural catheter and this procedure must be regarded as critical as catheter insertion. The neuraxial procedure should coincide with the lowest anticoagulant blood level.²¹

The European Society of Anaesthesiology (ESA) establishes the time interval between cessation of medication and neuraxial blockade at twice the elimination half-life of the drug as shown in table 4.²¹

The recommended time intervals apply only to patients with normal renal function; for those known to have reduced renal function, either dose adjustment or longer time intervals are required.²¹

The American Society of Regional Anesthesia and Pain Medicine (ASRA) recommends a five half-life interval between discontinuation of the drug and neuraxial pain procedures. If the risk of VTE is high, then bridge therapy with LMWH may be instituted. 'It should be noted that 25% of the drug still remains in the plasma after two half-lives, but only 3% remains after five half-lives' (table 5).²²

THERAPEUTIC DRUG MONITORING

An accurate, reliable, and widely available assay is not yet available for this class of medication but from a clinical perspective, it would be very useful.³ If diluted thrombin time is available, it is suggested that it be used as a quantitative measurement of the anticoagulant effect of dabigatran.^{1 7 13} The thrombin time is the most sensitive routine coagulation assay for determining

if any dabigatran is present.^{13 17} The prothrombin time is the most sensitive routine coagulation assay for determining rivaroxaban.^{13 17} The drug-specific anti-factor Xa chromogenic assay is necessary for accurately estimating the anticoagulant effect of apixaban.⁵

In a recent review, Hidalgo *et al*¹⁹ stated that routine blood coagulation tests, such as the prothrombin time and activated partial thromboplastin time, have a limited efficacy in the perioperative control of blood coagulation in these patients. Moreover, it has been concluded that there is no evidence for or an established role of NOAC monitoring to improve clinical outcomes in periprocedural settings.^{13 14}

CONCLUSION

The development of local guidelines is essential to manage patients receiving NOACs who either require an elective procedure or surgery, present bleeding, or require urgent surgery. Different perioperative strategies have been suggested for pre- and post-operative management of NOACs, the need to use bridging therapy, and the proper use of NOACs in neuraxial procedures. In general, American guidelines suggest longer cessation intervals of these drugs than the European guidelines. Depending on the source consulted, the recommendations for neuraxial procedures and preoperative interruption of NOAC for patients with renal insufficiency were found to be extremely different. The availability of reversal agents and the development of specific monitoring tests for these drugs will enable safer perioperative management with shorter interruption intervals.

Contributor All authors have contributed significantly to the publication. All authors are aware of the submission and agree with it.

Competing interests None declared.

Provenance and peer review Not commissioned; externally peer reviewed.

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Table 5 The American Society of Regional Anesthesia and Pain Medicine recommended intervals before and after interventional pain procedure²²

Interventional pain procedure	Dabigatran	Rivaroxaban	Apixaban
Recommended interval between discontinuation of drug and procedure (five half-lives), days	4–5 6 (renal disease)	3	3–5
Recommended interval between procedure and resumption of drug, hours	24	24	24

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