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New oral anticoagulants and perioperative management of anticoagulant/antiplatelet agents

Background

The strategy of whether to continue anticoagulation and antiplatelet agents during surgery depends on an evaluation of the thromboembolic risk and haemorrhagic risk of the individual patients. Procedures that carry a significant risk of bleeding may require temporary cessation of the medication.

Objective

We briefly review the use of common oral anticoagulant and antiplatelet agents, including clinical indications and limitations associated with those agents. We also discuss the risks of thromboembolism, and balancing bleeding risk in patients receiving oral anticoagulation therapy, temporary interruption of such therapy and management of such patients undergoing an elective surgical procedure.

Discussion

Generally, patients at high risk of thromboembolism should be considered for a more aggressive perioperative management strategy with bridging therapy. Current recommendations for dual antiplatelet treatment range from 4 weeks in patients undergoing elective stenting with bare metal stents, up to 12 months in patients with drug-eluting stents or patients undergoing coronary stenting for acute coronary syndrome. If a patient is to undergo high-bleeding-risk surgery and an antiplatelet effect is not desired, clopidogrel, prasugrel and ticagrelor should be discontinued 5–7 days before the procedure. Early, effective communication between general practitioners and specialists is useful in managing high-risk patients on anticoagulation/antiplatelet agents during the perioperative periods.

Keywords

perioperative care; anticoagulants; platelet aggregation inhibitors

A large number of patients in general practice take oral anticoagulant or antiplatelet drugs for primary or secondary prevention of arterial or venous thrombosis. There is an increased risk of bleeding when patients take anticoagulant or antiplatelet drugs during surgery. The decision to continue the drug during surgery or not and when to stop and restart involves balancing the risks of arterial or venous thromboembolism against the risk of bleeding.

Case 1

Mr Johnson is 72 years of age and he presents to the surgery for removal of a skin lesion on his right forearm. His medical history includes hypertension, diet-controlled diabetes and persistent atrial fibrillation (AF). He had a stroke 3 years ago without any residual weakness. His medications include perindopril 10 mg daily and rivaroxaban 20 mg daily. An electrocardiogram (ECG) shows atrial fibrillation with a ventricular rate of 57 beats per minute.

- Does Mr Johnson need to stop his rivaroxaban prior to the procedure? If so, how soon before?
- When will you consider restarting Mr Johnson's anticoagulant therapy after the procedure?

Case 2

Mr Smith is 73 years of age and is undergoing an excision of cutaneous lesions with simple flap closure. Following episodes of chronic stable angina, he had a stent inserted in the right coronary artery 2 weeks ago. He is on aspirin and clopidogrel.

- Does he need to stop antiplatelet agents prior to surgery?
- How soon prior to the procedure will you stop them?
- How soon can it be restarted after surgery?

A number of different medications, including oral anticoagulants and antiplatelet agents, are increasingly being used in the treatment of different clinical conditions. Oral anticoagulation in the form of vitamin K antagonists (VKAs) is a well-established treatment for stroke prevention

Table 1. Current PBS-approved indications for NOACs[1]

Prevention of stroke or systemic embolism in a patient with non-valvular atrial fibrillation* who is at moderate-to-high risk of developing stroke or systemic embolism as evidenced by one or more of the following risk factors:

- Age ≥75 years
- Hypertension
- Diabetes mellitus
- Heart failure or left ventricular dysfunction (ejection fraction <40%)
- Previous stroke or transient ischaemic attack or systemic embolism

Prophylaxis of deep vein thrombosis/pulmonary embolism in patients undergoing knee or hip replacement surgery

Treatment of deep vein thrombosis/pulmonary embolism.

*The term valvular AF is used to imply that AF is related to rheumatic valvular disease (predominantly mitral stenosis) or prosthetic heart valves. Rheumatic mitral valve disease with AF carries a 17-fold increased risk of stroke and requires anticoagulation with warfarin. AF in patients with prosthetic valves also requires anticoagulation with warfarin, usually with a higher INR target dependent on type of valve).

in AF. VKAs have also been used extensively over the past 50 years in the treatment and prevention of deep venous thrombosis, pulmonary embolism and for the prevention of thromboembolism in mechanical valves. The new oral anticoagulants (NOACS) offer an alternative to warfarin therapy for selected patients, but as with all anticoagulants, they can potentially cause serious bleeding.

The current indications for NOACs approved by the Pharmaceutical Benefits Scheme (PBS) are listed in *Table 1*.[1] The major positive aspects of these agents are that:

- monitoring is not required
- the risk of adverse interactions with changes in diet or concomitant use of other drugs is reduced

Table 2. Oral anticoagulants and antiplatelet agents[10,11,21]

Drugs	Mechanism of action	Dosage	Stopping medication before surgery
Warfarin	Vitamin K antagonist	Varies across individuals	Withheld for approximately 5 days
Dabigatran	Direct thrombin inhibitors	150 mg twice daily for most patients 110 mg BD for patients aged >75years or with ClCr 30–49 ml/min	24 hours: • low bleeding risk and normal renal function 96 hours • high-bleeding-risk individual and impaired renal function[11]
Rivaroxaban	Factor Xa inhibitor	20 mg daily for most patients 15 mg daily if ClCr 30–49 ml/min Avoid if ClCr <30 ml/min	24–48 hours[11]
Apixaban	Factor Xa inhibitor	5 mg twice daily for most patients 2.5 mg twice daily for age >80 years, weight <60 kg S creat >133 microM/L	24–48 hours
Aspirin	Inhibits thromboxane A_2 synthesis by irreversibly acetylating cyclooxygenase-1 in platelets and megakaryocyte	75–325 mg once daily	Most often can be continued May need to be stopped 5–7 days before surgery
Clopidogrel	Metabolised in the liver to active compounds that bind covalently to ADP receptors on platelets and reduce platelet activation	75 mg daily	5–7 days prior to surgery
Prasugrel	An ADP receptor antagonist	10 mg once daily for adults >60 kg 5 mg once daily for patients <60 kg	5–7 days prior to surgery
Ticagrelor	Reversible, directly acting inhibitor of the ADP receptor P_2Y_{12}	90 mg twice daily	5–7 days prior to surgery

Some variation exists in the recommended time to cease dabigatran between the European Society of Cardiology guidelines[11] and Queensland Health guidelines.[21] The latter guidelines recommend stopping dabigatran for 5 days in patients with CrCl of 31–50 mL/min and greater than 5 days (and not to restart) in patients with CrCl <30 mL/min

ADP, adenosine diphosphate; CrCl, creatinine clearance

- they are effective for prevention of strokes.

The current limitations of NOACS are:

- lack of an effective antidote
- increased risk of bleeding (albeit less than warfarin)
- inability to determine patients' compliance, dose adjustment in renally and hepatically impaired patients
- cost compared with warfarin.

Antiplatelet agents, including aspirin, clopidogrel, ticagrelor and prasugrel, are widely used in Australia for the treatment and prevention of vascular disease.

In view of balancing the risk of thromboembolism and bleeding complications, we will examine the perioperative use of the three NOACs available on the PBS (dabigatran, rivaroxaban and apixaban), warfarin and common antiplatelet agents (*Table 2*).

Oral anticoagulant therapy in the peri-procedural period

Surgical interventions or invasive procedures that carry a significant risk of bleeding may require temporary cessation of the NOACs or warfarin. Trials have previously shown that about one in four patients who need anticoagulation therapy require temporary cessation of their anticoagulants within 2 years.[2] When the anticoagulants are discontinued in high-risk patients, the interval without anticoagulation should be as short as possible, balancing the risk of thromoboembolism against the risk of bleeding.

For patients with non-valvular atrial fibrillation, the $CHADS_2$ score (*Tables 3 and 4*) is a validated clinical prediction score that uses congestive heart failure, hypertension, age >75 years, diabetes and history of stroke or transient ischemic attack in a cumulative manner to estimate expected stroke rate per 100-patient years.[3] Thus, patients with high $CHADS_2$ scores would be considered at high risk of thrombosis. Early data suggest that the $CHADS_2$ score may also be used to predict risk for post-surgical stroke. Kaatz et al showed that in a population-based, retrospective cohort study involving 37 469 patients with AF, 401 (1.1%) developed a stroke within 30 days of non-cardiac surgery, compared with 7260 (0.3%) in 2 228 360 patients without AF (P<0.001). The 30-day risk for post-operative stroke increased with each point score in the $CHADS_2$ score.[4]

Patients with mechanical heart valves are also at increased risk of systemic embolisation and occlusive thrombus of the prosthetic valve orifice during sub-therapeutic levels of warfarin.[5] Older, caged-ball valves are the most thrombogenic, followed by tilting disc valves. Bileaflet valves are the least thrombogenic.[6]

In the absence of anticoagulant therapy, mitral position valves have an annualised risk of thrombosis of 22%, compared with aortic position valves, with an annualised risk of approximately 10–12%.[7]

The anticoagulation strategy selected depends on an evaluation of the thromboembolic risk and the haemorrhagic risk of the surgical

Table 3 – $CHADS_2$ score and adjusted risk of stroke below[3]

C	Congestive heart failure	1 point
H	Hypertension	1 point
A	Age >75 years	1 point
D	Diabetes	1 point
S2	Stroke	2 points
Adjusted risk of stroke for $CHADS_2$ scores		
Score	**Adjusted risk of stroke per year (%)**	
0	1.9	
1	2.8	
2	4	
3	5.9	
4	8.5	
5	12.5	
6	18.2	

Table 4. Risk-stratification for perioperative thromboembolism to guide bridging treatment[7]

Risk category	Atrial fibrillation	Mechanical heart valve	VTE
High (annual risk >10%)	$CHADS_2$ score 5 or 6	Any mechanical mitral valve	Recent VTE (<3 months)
	Recent stroke/TIA (<3 months)	Caged-ball, tilting disk aortic mechanical valve	Severe thrombophilia
	Rheumatic valvular heart disease		Deficiency of protein C/S or antithrombin
Intermediate risk (annual 4–10%)	$CHADS_2$ score 3 or 4	Bileaflet aortic valve with risk factor for stroke	VTE within past 3–12 months
			Recurrent VTE
			Active cancer
Low risk (annual risk <4%)	$CHADS_2$ score 0–2	Bileaflet aortic valve without any risk factor for stroke	VTE >12 months ago

VTE, venous thromboembolism

procedure. The American College of Chest Physician guidelines on antithrombotic therapy suggest a clinically useful thromboembolic risk stratification in the peri-procedural period as shown in *Table 4*.[7]

Low-bleeding-risk procedures

VKAs may be continued with an INR of 1.5–1.8 for minor procedures with a low risk of bleeding.[8] These include excision of skin lesions, cataract surgery and procedures in which the bleeding can be controlled readily by local measures. This approach is not recommended for laparoscopic surgery and ultrasound or CT-guided biopsies.

High-bleeding-risk procedures

The strategy for perioperative anticoagulation in patients undergoing major, high-bleeding-risk surgery is based on the assessment of the risk of thromboembolism versus the risk of haemorrhage (*Table 5*). In the low-thromboembolism-risk group warfarin can be withheld for 5 days before surgery without any bridging anti-coagulation with unfractionated or low-molecular-weight heparin. Generally, high-thromboembolism-risk patients should be considered for more aggressive perioperative management strategy with bridging therapy. With regards to warfarin, a relatively normal zone of haemostasis exists when the INR is 1.0–2.0.[9] Although the INR value at which the risk of bleeding increases is not known, the risk is assumed not to be elevated with INR <1.5 and is elevated with INR >2.0.[7]

When bridging therapy is needed for patients at high risk, unfractionated heparin is preferred when the CrCl <30. In procedures when bridging therapy is required, the usual protocol is to stop warfarin 5 days before the procedure and start low molecular weight heparin at a therapeutic dose once the INR <2.[10] The INR is usually checked on the morning of the procedure while enoxaparin should be last given 24 hours prior to the procedure. Unfractionated heparin on the other hand is usually stopped 4–6 hours before high-risk procedures.[7]

Table 5. Perioperative management

Anticoagulants[7–10]	
1	Evaluate the thromboembolic risk and hemorrhagic risk of the individual patients
2	Consider temporary cessation of the drug in procedures that carry a significant risk of bleeding
3	***Low thromboembolism and bleeding risk*** Warfarin may be continued with relatively low INR 1.5–1.8 for minor procedures
4	***For high bleeding risk with low-thromboembolism-risk group*** Warfarin can be withheld for 5 days before surgery without any bridging anticoagulation with unfractionated or low molecular weight heparin
5	***High-thromboembolism-risk patients*** Generally such patients should be considered for a more aggressive perioperative management strategy with bridging therapy
6	As compared with warfarin, patients on NOACs are less likely to require bridging therapy due to their short half-life
Antiplatelet agents[13–16,20]	
1	Use of DAPT following percutaneous coronary procedures and following acute coronary syndrome are common
2	Current recommendations for DAPT range from 4 weeks in patients undergoing elective stenting with bare metal stents to up to 12 months in patients with drug-eluting stents or patients undergoing coronary stenting for acute coronary syndrome
3	Low-dose aspirin alone does not substantially increase the risk of clinically important bleeding after invasive procedures and can usually be continued during surgery
4	If a patient is to undergo high-bleeding-risk surgery and an antiplatelet effect is not desired, clopidogrel, prasugrel and ticagrelor should be discontinued 5-7 days prior to the procedure
5	Early, effective communication between GPs and specialists is useful in managing high-risk patients on anticoagulant/antiplatelet agents during the perioperative periods

DAPT, dual antiplatelet therapy; NOACs, new oral anticoagulants

NOACs during surgery

Patient factors including renal function, age, history of bleeding complications, concomitant medications and surgical factors should be considered prior to discontinuing the drug. Compared with warfarin, which may need bridging anticoagulation in patients with higher thromboembolic risks (*Table 4*), patients on NOACs are less likely to require bridging therapy.[11] This is explained by the short half-life which allows for properly timed short-term cessation and early re-initiation after surgery.

In the case of emergency, surgery should ideally be deferred for 12–24 hours (since the last dose) if possible. If not possible, a multidisciplinary team approach including surgeon, haematologist and cardiologist should be considered and the risk of bleeding carefully assessed and discussed with the patient and relatives. These should be assessed on a case-by-case basis. The NOACs do not have specific antidotes and management of bleeding is thus largely supportive. It should be remembered that unlike warfarin (where activity of the drug can be monitored by INR) there are currently limited laboratory tests that can predict the risk of bleeding while on a NOAC. Activated partial thromboplastin time (APTT) provides qualitative assessment of the presence of direct thrombin inhibitor (dabigatran). Similarly prothrombin time (PT) may provide qualitative assessment of the presence of factor Xa inhibitors (rivaroxaban, apixaban). Unfortunately, neither of the tests is sensitive for quantitative assessment of NOAC

effect. *Table 2* summarises the perioperative management of anticoagulants as described earlier.

Restarting NOACs after surgery

The timing to restart the NOACS after surgery will depend on multiple factors. These include the factors mentioned above along with the type of surgery and the ability to achieve immediate haemostasis. Again the risk of bleeding should be weighed against the risk of thromboembolism. For procedures with immediate and complete haemostasis, NOACs can be resumed 6–8 hours after intervention.

For many surgical interventions, resumption of anticoagulation within 48–72 hours may carry significant bleeding risk and is therefore better deferred. Once NOACs are restarted, maximal anticoagulation will be obtained within 2 hours.

Factors to consider before switching from warfarin to NOAC after surgery

The NOACs so far tested in clinical trials have all shown non-inferiority when compared with VKAs, as well as better safety, consistently reducing the number of intracranial haemorrhages.[12]

On this basis, the 2012-focused update of the European Society of Cardiology guidelines for the management of atrial fibrillation now recommends NOACs as 'broadly preferable to VKA in the vast majority of patients with non-valvular (*Table 1*) atrial fibrillation'.

Generally, stable patients taking warfarin whose INR is within the targeted therapeutic range, and in whom INR testing does not present a problem, may prefer to continue with warfarin. If a particular patient does have difficulties maintaining INR within the therapeutic range, switching to a new oral anticoagulant may be considered and the post-operative setting may be the perfect opportunity to address the issue. Therefore, factors to consider before switching from warfarin to a NOAC after surgery are:

- **Renal function**

Before switching from warfarin to NOAC, one of the most important considerations should be renal function. Most of the NOACs are contraindicated if there is significant renal impairment (eGFR <30 ml/min). If there is moderate renal impairment, NOACs should be used with caution and, in most cases, dosages need to be reduced.

- **Compliance**

Compliance and adherence to treatment is crucial, especially as these drugs have a relatively short half-life.

- **INR**

When switching from a VKA to a NOAC, the INR should be allowed to fall to <2.0 before starting the NOAC.

Perioperative management of antiplatelet therapy

Dual antiplatelet therapy (DAPT) following percutaneous coronary stenting and acute coronary syndrome (ACS) is common. Antiplatelet medications that are used commonly in Australia include, aspirin, clopidogrel, prasugrel and ticagrelor. Management of patients on DAPT who are referred for surgical procedures depends on the level of emergency and the thrombotic and bleeding risk of the individual patient.

Current recommendations for DAPT range from 4 weeks in patients undergoing elective stenting with bare metal stents (BMS) to up to 12 months in patients with drug-eluting stents (DES) or for patients undergoing coronary stenting for acute coronary syndrome.[13] In some cases of complex stenting (eg bifurcation stenting), continuation of DAPT for longer than 1 year may be necessary. Premature cessation of DAPT is thought to be one of the most important causes of stent thrombosis, which can have fatal consequences.[14]

The current guidelines recommend that elective non-cardiac surgeries be postponed for at least 6 weeks (ideally 3 months) following angioplasty with BMS and for 12 months after DES,[15] as the risk of thrombosis is highest within 6 weeks after the placement of a bare-metal stent and within 3–6 months after the placement of a DES.[16]

Perioperative continuation of aspirin increases bleeding risk slightly but does not increase the risk for bleeding that requires medical or other interventions and therefore can usually be continued.[17,18] On the other hand, perioperative interruption of aspirin confers a 3-fold increased risk for adverse cardiovascular events.[19] If a patient is to undergo surgery with a high risk of bleeding and an antiplatelet effect is not desired, clopidogrel, prasugrel and ticagrelor should be discontinued 5–7 days prior to the procedure.[13,20] Good communication with the treating cardiologist and, in some cases, individualised treatment plans may be necessary in managing such patients in the perioperative periods.

Case study continued

Mr Johnson does not necessarily need to discontinue his NOAC as the risk of bleeding is small. If there were concerns about increased risk of bleeding, then the best approach would be to stop the rivaroxaban 24 hours prior to the procedure and taking the next dose the morning after the procedure.

Mr Smith does not need cessation of his dual antiplatelet therapy. His angioplasty was performed only 2 weeks prior and as the risk of bleeding is low, DAPT should be continued. If the risk of bleeding in his procedure were deemed to be high on DAPT, then the procedure is best postponed until a time when it is deemed safe to stop his clopidogrel.

Conclusion

General practitioners (GPs) undeniably have a major role to play in the management of patients on oral anticoagulants who have to undergo an invasive procedure. The strategy of management of anticoagulation/antiplatelet agents in the perioperative periods is based on the assessment of each patient's thromboembolic and bleeding risks. Most patients having minor procedures can continue to take an anticoagulant, provided that they are closely monitored. Patients at high risk of bleeding should be considered for a more aggressive perioperative management strategy with bridging therapy.

Antiplatelet therapy is usually safe to continue in procedures with a low risk of bleeding. Generally, drugs such as clopidogrel, prasugrel and ticagrelor should be stopped about 5–7 days before any procedure where the risk of bleeding is deemed to be high. Low-dose aspirin alone does not substantially increase the risk of clinically important bleeding after invasive procedures and can usually be continued during surgery. The timing of any non-urgent procedure and stopping of antiplatelet therapy depends on the time frame between insertion of stents and the planned procedure and on the type of stent used.

Early, effective and ongoing communication between GPs and specialists is required to maximise patient safety during perioperative transitions of anticoagulation. Involvement of an accredited pharmacist via a home medicines review may be helpful to facilitate optimal use of anticoagulants at this time of risk.

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