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## DRUG &amp; THERAPEUTICS LETTER



A Quarterly Bulletin from  
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## Antiplatelet drugs, anticoagulants and elective surgery

depends on the risk of recurrent thrombosis versus bleeding.

### Risk of perioperative bleeding

Clinical studies have shown that patients who have taken aspirin preoperatively have an increased risk of postoperative bleeding after cardiac and non-cardiac surgery. Use of aspirin within seven days of coronary artery bypass grafting has been associated with increased blood loss and the need for re-operation, but this does not increase mortality. However, another study showed that aspirin use in the five days before coronary artery bypass grafting was associated with a lower risk of postoperative mortality, without a concomitant increase in re-operation for bleeding or the need for blood transfusion. This applied to a range of aspirin doses, 100 mg to 975 mg daily. It is generally considered safe to continue aspirin throughout the perioperative period, for both cardiac and non-cardiac surgery, unless there is a significant bleeding risk.

### Introduction

A growing number of patients are taking oral anticoagulant or antiplatelet drugs for primary or secondary prevention of arterial or venous thrombosis. The perioperative management of anticoagulation in these patients at the time of elective surgery is contentious yet important. It involves balancing the risks of arterial or venous thromboembolism (such as ischaemic stroke, myocardial infarction, pulmonary embolism or deep vein thrombosis) if the drug is stopped, against the risk of bleeding if the anticoagulant or antiplatelet drug is continued.

### Antiplatelet therapy

Aspirin irreversibly inhibits platelet function via the acetylation of cyclooxygenase-1. Clopidogrel, a thienopyridine, selectively inhibits adenosine diphosphate-induced platelet aggregation. The effect of both drugs lasts for the lifespan of the platelet (approximately 7–10 days). Although it seems logical to stop either drug 7–10 days before an elective procedure, platelet function is only one of the many important mechanisms of coagulation necessary for adequate haemostasis. Aspirin can be continued for most procedures but whether or not clopidogrel can be safely continued

The use of clopidogrel throughout the perioperative period is more controversial. Some studies have shown an increased risk of major bleeding with the use of clopidogrel within five days of coronary artery bypass grafting. While recognising the increased risk of bleeding complications after coronary artery bypass grafting, some experts recommend a more tailored approach depending on individual risk with respect to ischaemic complications and bleeding. For percutaneous coronary intervention, pretreatment with clopidogrel is recommended before and throughout the perioperative period.

Patients with coronary stents *in situ* have a high thrombotic risk if antiplatelet drug therapy is interrupted. Elective non-cardiac surgery should therefore be avoided after stent placement when patients are most prone to thrombosis. This is during the first six weeks for bare metal stents, and during the first 12 months for drug-eluting stents.

For patients without coronary stents who are not at high risk of cardiac events, clopidogrel can be ceased 5–7 days before surgery. It is often routine clinical practice to consult the patient's cardiologist before stopping the drug. Clopidogrel should be resumed following the procedure as soon as there is adequate haemostasis, usually the morning after surgery.

### Warfarin

The most common indications for oral anticoagulant therapy are atrial fibrillation, the presence of a mechanical heart valve, and venous thromboembolism. Warfarin is the most common oral anticoagulant prescribed for the treatment and prophylaxis of venous or arterial thromboembolism. The mean half-life of warfarin activity is approximately 40 hours and the anticoagulant effect lasts 2–5 days. For most patients, the therapeutic target for the international normalised ratio (INR) range is 2.0–3.0. For patients with a mechanical heart valve, the recommended INR range is 2.5–3.5.

When considering how to manage patients on warfarin who require surgery, it is helpful to weigh up the risk of bleeding versus the risk of thromboembolism. This requires consideration of:

- indication for anticoagulation
- history of any thrombotic events

- type of surgery and its associated risks of bleeding and thromboembolism, particularly with respect to postoperative venous thromboembolism.

The patient's management is guided by the risk of thromboembolism. The options include:

- if low risk, stop warfarin five days before surgery (that is, missing four doses before the day of surgery) to allow the INR to drop to less than 1.5, then resume it on the evening of the procedure if there is no evidence of bleeding
- if high risk, stop warfarin and start heparin (unfractionated heparin infusion or low molecular weight heparin) before and after the surgery, during the period when the INR is below the therapeutic range. This option is referred to as 'bridging' anticoagulation. Heparin is usually started on the third morning after the last dose of warfarin when the INR becomes subtherapeutic.

### Stopping heparin preoperatively

For patients who receive bridging anticoagulation with therapeutic doses of low molecular weight heparin, the last dose should be administered at least 24 hours before the procedure. There is evidence suggesting that there will be a residual anticoagulant effect if low molecular weight heparin is given too close to the time of the procedure. It is recommended that the last preoperative dose be half the usual total daily dose. For unfractionated heparin, it is recommended that the infusion be stopped 4–6 hours before the procedure.

### Resuming heparin postoperatively

The factors that affect the risk of postoperative bleeding include the timing of the anticoagulant dose after surgery, the

dose of anticoagulant and the type of surgery along with its associated bleeding risk. The following recommendations take all of these factors into consideration:

- warfarin can be resumed on the evening of the procedure (regardless of whether the procedure is performed in the morning or afternoon), at the usual maintenance dose (no loading dose)
- low molecular weight heparin or unfractionated heparin can be resumed 12–24 hours following the procedure for minor surgery. For major surgery, the first dose should be 24–72 hours post surgery. The initial dose will vary from the prophylactic dose (for example, enoxaparin 40 mg daily) to the therapeutic dose (for example, enoxaparin 1 mg/kg twice daily) depending on the risk of thrombosis, and the risk of bleeding. This needs to be individualised for each patient.

### Epidural or spinal anaesthesia

In patients receiving bridging anticoagulation with heparin, the last dose of low molecular weight heparin should be given 24 hours before, and unfractionated heparin should be stopped four to six hours before the insertion or removal of the epidural or spinal needle. The procedure should be performed by an experienced anaesthetist. It is preferable to not give therapeutic doses of low molecular weight heparin with catheter *in situ* and to wait at least one hour after removing the catheter before recommencing intravenous unfractionated heparin.

### Dental, dermatological or ophthalmological procedures

It is usually safe to continue aspirin around the time of the procedure. However,

clopidogrel should be stopped 5–7 days before the procedure unless the patient has had a recent stent insertion.

Warfarin can usually be continued in patients having minor dental procedures (single or multiple tooth extraction and root canal procedures), minor dermatological procedures (including excisions of skin lesions) and minor ophthalmological procedures (including cataract extraction). Dentists can consider co-administration of an antifibrinolytic drug such as tranexamic mouth wash.

### Endoscopy

For patients having elective gastroscopy or colonoscopy, the recommendations as for dental, dermatological and ophthalmological procedures can apply. However if the patient requires a biopsy, then follow the recommendations for patients undergoing general surgery.

### Conclusion

The perioperative management of patients taking oral anticoagulant or antiplatelet drugs for primary or secondary prevention of arterial or venous thrombosis is a common and important problem. One must balance the risks of primary or recurrent thromboembolism if these drugs are stopped, against the risk of bleeding if these drugs are continued. For minor procedures, antiplatelet and oral anticoagulant drugs can usually be continued. For other elective cardiac and non-cardiac surgery, aspirin can be continued during the perioperative period. Clopidogrel should usually be withheld for non-cardiac surgery unless the patient is at high risk of cardiac events, and in this case the management should be individualised and discussed with a cardiologist. Warfarin and other oral anticoagulants should be stopped according to their half-lives and bridging anticoagulation with a heparin introduced as indicated.