

# *Perioperative Management of Anticoagulants and Anti-Platelets*

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## **Introduction**

The perioperative management of patients on long-term warfarin therapy poses particular problems. This situation is exacerbated by the absence of randomized trials. The strategy used is based on the assessment of each patient's thromboembolic and bleeding risks. These determine the need for withholding warfarin and switching to heparin. Most patients having minor procedures can continue to take warfarin, provided that they are closely monitored and local measures are used to ensure adequate haemostasis.<sup>1</sup>

The most common indications for long-term oral anticoagulation with warfarin are venous thromboembolism, mechanical cardiac valves and atrial fibrillation. When patients with these conditions need surgery, the perioperative management of their warfarin therapy poses a major problem. Withholding warfarin increases the risk of thromboembolism, particularly in the context of surgery which itself increases the thrombotic risk. To minimize the risk of perioperative thrombosis, alternate anticoagulation with heparin is often used. Perioperative anticoagulation is accompanied by an increased risk of postoperative bleeding. There is no consensus on the optimal approach to anticoagulation in the perioperative period. In each individual patient, rational decisions must be made after weighing up the haemorrhagic and thrombotic risks.<sup>1</sup>

In cases with a low risk of bleeding, oral anticoagulation can usually be continued. In contrast, for larger interventions with a moderate to high risk of bleeding, a discontinuation of warfarin with temporary bridging is required. In this case it is common practice to discontinue warfarin 7-9 days preoperatively and administer heparin mostly in the form of low molecular weight heparin (LMWH) depending on the international normalized ratio (INR). In contrast perioperative management of direct oral anticoagulants (DOAC) is discussed controversially. Based on the pharmacokinetics of the DOAC, the recommendations are to minimize the anticoagulation-free interval to 2-4 half-lives (HWZ) preoperatively (1-5 days) and early postoperative restart. In this case no bridging is necessary. On the other hand, an

early interruption of DOAC 5 days prior to surgery to a minimum of 2 days postoperatively is favored by some surgeons to assure an adequate perioperative hemostasis. Depending on the risk of thromboembolism, bridging is required. These recommendations are justified by limited clinical experience and the absence of antagonism.<sup>2</sup>

### **Clinical guidelines**

The American College of Chest Physicians proposed guidelines for antithrombotic prophylaxis in patients with different risk factors, and it recommends that if the annual risk for thromboembolism is low, warfarin therapy can be withheld for 4-5 days before the procedure without bridging.<sup>3,4</sup>

Currently, it is generally recommended that patients with the highest risk of arterial or venous thromboembolism, who require interruption of oral anticoagulant therapy for surgery, should receive therapeutic-dose heparin therapy (e.g., unfractionated heparin [UFH], low molecular weight heparin [LMWH]) during much of the interval when the international normalized ratio (INR) is subtherapeutic.<sup>5</sup>

Usually, unless accompanied by significant cardiomyopathy or recent arterial embolus, patients with atrial fibrillation can have their Coumadin stopped 4 days prior to surgery, then resumed at the usual dose the night of surgery.<sup>6</sup>

Patients with prosthetic heart valves usually are treated with perioperative LMWH, although randomized controlled trials validating this method are lacking. Coumadin can be stopped 4-5 days preoperatively, with LMWH started the next day at a therapeutic dose. The last dose should be 12 hours preoperatively. LMWH and Coumadin can be re-titrated the evening of the operative day. LMWH is stopped when the Coumadin reaches the target range. For patients at higher risk of valve thrombosis (ie, patients with 2 prosthetic valves or with caged-ball type of valves), whether LMWH provides adequate anticoagulant protection is unclear. For these patients, consider use of perioperative UFH instead of LMWH. Preoperatively, the heparin should be stopped 6 hours before the procedure. Postoperatively, the heparin can be restarted when the surgeon agrees that it is safe, usually 6-12 hours postoperatively.<sup>6</sup>

### **Risk stratification for thrombosis in patients with a mechanical heart valve or atrial fibrillation or venous thromboembolism (VTE):**

- At high risk for thromboembolism, bridging anticoagulation is recommended with therapeutic-dose subcutaneous (SC) low-molecular-weight heparin (LMWH) or

intravenous unfractionated heparin (UFH) rather than no bridging during temporary interruption of vitamin K antagonist (VKA) therapy.

- At moderate risk for thromboembolism, it's proposed to use bridging anticoagulation with therapeutic-dose SC LMWH, therapeutic-dose IV UFH, or low-dose SC LMWH over no bridging during temporary interruption of VKA therapy.
- At low risk for thromboembolism, low-dose SC LMWH or no bridging over bridging with therapeutic-dose SC LMWH or IV UFH is recommended.<sup>5</sup>

**Table (1):** Risk stratification for thrombosis in patients with a mechanical heart valve or atrial fibrillation or venous thromboembolism (VTE).<sup>5</sup>

Which patients on warfarin should receive heparin bridging before surgery?

High risk for thromboembolism: bridging advised	Intermediate risk for thromboembolism: bridging on a case-by-case basis	Low risk for thromboembolism: bridging not advised
<ul style="list-style-type: none"> <li>◆ Known hypercoagulable state as documented by a thromboembolic event and one of the following: Protein C deficiency Protein S deficiency Antithrombin III deficiency Homozygous factor V Leiden mutation Antiphospholipid-antibody syndrome</li> <li>◆ Hypercoagulable state suggested by recurrent (two or more) arterial or idiopathic venous thromboembolic events (not including primary atherosclerotic events, such as stroke or myocardial infarction due to intrinsic cerebrovascular or coronary disease)</li> <li>◆ Venous or arterial thromboembolism within the preceding 1-3 months</li> <li>◆ Rheumatic atrial fibrillation</li> <li>◆ Acute intracardiac thrombus visualized by echocardiogram</li> <li>◆ Atrial fibrillation plus mechanical heart valve in any position</li> <li>◆ Older mechanical valve model (single-disk or ball-in-cage) in mitral position</li> <li>◆ Recently placed mechanical valve (&lt;3 mo)</li> <li>◆ Atrial fibrillation with history of cardioembolism</li> </ul>	<ul style="list-style-type: none"> <li>◆ Cerebrovascular disease with multiple (2 or more) strokes or transient ischemic attacks without risk factors for cardiac embolism</li> <li>◆ Newer mechanical valve model (eg, St. Jude) in mitral position</li> <li>◆ Older mechanical valve model in aortic position</li> <li>◆ Atrial fibrillation without a history of cardiac embolism but with multiple risks for cardiac embolism (eg, ejection fraction &lt;40%, diabetes, hypertension, nonrheumatic valvular heart disease, transmural myocardial infarction within preceding month)</li> <li>◆ Venous thromboembolism &gt;3-6 months ago*</li> </ul>	<ul style="list-style-type: none"> <li>◆ One remote venous thromboembolism (&gt;6 mo ago)*</li> <li>◆ Intrinsic cerebrovascular disease (eg, carotid atherosclerosis) without recurrent strokes or transient ischemic attacks</li> <li>◆ Atrial fibrillation without multiple risks for cardiac embolism</li> <li>◆ Newer model prosthetic valve in aortic position</li> </ul>

\* For patients with a history of venous thromboembolism undergoing major surgery, consideration can be given to postoperative bridging therapy only (without preoperative bridging).

**The 8th and 9th edition of the American College of Chest Physicians Evidence-Based Clinical Practice Guidelines included the following key recommendations:<sup>7</sup>**

1. In patients who require temporary interruption of a VKA before surgery, we recommend stopping VKAs approximately 5 days before surgery *instead of* stopping VKAs a shorter time before surgery.

2. In patients who require temporary interruption of a VKA before surgery, we recommend resuming VKAs approximately 12 to 24 h after surgery (evening of or next morning) and when there is adequate hemostasis *instead of* later resumption of VKAs .
3. In patients with a mechanical heart valve, atrial fibrillation, or VTE at high risk for thromboembolism, we suggest bridging anticoagulation *instead of* no bridging during interruption of VKA therapy. *Remarks:* Patients who place a higher value on avoiding perioperative bleeding than on avoiding perioperative thromboembolism are likely to decline heparin bridging.
4. In patients with a mechanical heart valve, atrial fibrillation, or VTE at low risk for thromboembolism, we suggest no bridging *instead of* bridging anticoagulation during interruption of VKA therapy.
5. In patients with a mechanical heart valve, atrial fibrillation, or VTE at moderate risk for thromboembolism, the bridging or no-bridging approach chosen is, as in the higher- and lower-risk patients, based on an assessment of individual patient- and surgery-related factors.
6. In patients who require a minor dental procedure, we suggest continuing VKAs with co-administration of an oral prohemostatic agent or stopping VKAs 2 to 3 days before the procedure *instead of* alternative strategies.
7. In patients who require minor dermatologic procedures and are receiving VKA therapy, we suggest continuing VKAs around the time of the procedure and optimizing local hemostasis *instead of* other strategies.
8. In patients who require cataract surgery and are receiving VKA therapy, we suggest continuing VKAs around the time of the surgery *instead of* other strategies.
9. In patients who are receiving ASA for the secondary prevention of cardiovascular disease and are having minor dental or dermatologic procedures or cataract surgery, we suggest continuing ASA around the time of the procedure *instead of* stopping ASA 7 to 10 days before the procedure.
10. In patients at moderate to high risk for cardiovascular events who are receiving ASA therapy and require non cardiac surgery, we suggest continuing ASA around the time of surgery instead of stopping ASA 7 to 10 days before surgery. In patients at low risk for cardiovascular events who are receiving ASA therapy, we suggest stopping ASA 7 to 10 days before surgery instead of continuation of ASA .

11. In patients who are receiving ASA and require CABG surgery, we suggest continuing ASA around the time of surgery *instead of* stopping ASA 7 to 10 days before surgery.
12. In patients who are receiving dual antiplatelet drug therapy and require CABG surgery, we suggest continuing ASA around the time of surgery and stopping clopidogrel/prasugrel 5 days before surgery *instead of* continuing dual antiplatelet therapy around the time of surgery.
13. In patients with a coronary stent who are receiving dual antiplatelet therapy and require surgery, we recommend deferring surgery for at least 6 weeks after placement of a bare-metal stent and for at least 6 months after placement of a drug-eluting stent *instead of* undertaking surgery within these time periods.
14. In patients who require surgery within 6 weeks of placement of a bare-metal stent or within 6 months of placement of a drug-eluting stent, we suggest continuing dual antiplatelet therapy around the time of surgery *instead of* stopping dual antiplatelet therapy 7 to 10 days before surgery.
15. In patients who are receiving bridging anticoagulation with therapeutic-dose IV UFH, we suggest stopping UFH 4 to 6 h before surgery *instead of* closer to surgery. *Remarks:* Patients who are more concerned about avoiding the unknown, but potentially large increase in bleeding risk associated with the perioperative continuation of dual antiplatelet therapy than avoiding the risk for coronary stent thrombosis are unlikely to choose continuation of dual antiplatelet therapy.
16. In patients who are receiving bridging anticoagulation with therapeutic-dose SC LMWH, we suggest administering the last preoperative dose of LMWH approximately 24 h before surgery *instead of* 12 h before surgery.
17. In patients who are receiving bridging anticoagulation with therapeutic-dose SC LMWH and are undergoing high-bleeding-risk surgery, we suggest resuming therapeutic-dose LMWH 48 to 72 h after surgery *instead of* resuming LMWH within 24 h after surgery.

#### **Perioperative bridging of anticoagulation**

- In patients with previous arterial embolism, or the patient had a recent arterial thromboembolism within a month of surgery, only 4 daily doses of warfarin should be withheld preoperatively and the INR should be measured the day before surgery to determine if a small dose of vitamin K is needed to accelerate the reversal of anticoagulation. If the INR is more than 1.7 on the day before surgery, administer 1 mg of [vitamin K](#) subcutaneously and repeat the INR the morning of the surgery. If on the day

of surgery the INR is 1.3-1.7, administer 1 unit of [frozen plasma](#); administer 2 units of frozen plasma if the INR is 1.7-2. The active reversal of oral anticoagulants should be discouraged in patients with mechanical valves, especially with the use of fresh frozen plasma and start intravenous UFH when the INR drops to less than 2 to minimize the risk of recurrent embolism. Discontinue the intravenous heparin 6 hours before surgery.<sup>8</sup>

- After an acute episode of venous thromboembolism (VTE), defer surgery, if feasible, until patients have received at least 1 month, and preferably 3 months, of anticoagulation. If surgery must be performed within 1 month of an acute VTE, Warfarin should be withheld for only 4 doses if the most recent episode of VTE occurred 1-3 months before surgery. If the patient has been anticoagulated for 3 or more months, 5 doses of warfarin can be withheld before surgery. Preoperatively, subcutaneous UFH or LMWH is needed only for immobilized inpatients with an INR of less than 1.8, intravenous heparin may be withheld 6 hours preoperatively and 12 hours postoperatively, if the surgery is short. If the acute event was within 2 weeks of major surgery and/or patients have a higher risk of postoperative bleeding, a vena caval filter should be inserted preoperatively or intraoperatively.<sup>9</sup>

### **Perioperative management of patients on new oral anticoagulants**

Novel oral anticoagulants (NOACs) offer an alternative to warfarin for preventing stroke in patients with atrial fibrillation. Management of NOACs in elective and emergency conditions requires knowledge of time of last intake of drug, current renal function, and the planned procedure in order to assess the overall risk of bleeding.<sup>10</sup>

### **NOACs during surgery**

Patient factors including renal function, age, and 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, patients on NOACs are less likely to require bridging therapy. This is explained by the short half-life which allows for properly timed short-term cessation and early re-initiation after surgery.<sup>11</sup>

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) summarizes the perioperative management of anticoagulants as described earlier.<sup>12</sup>

**Table (2):** Perioperative management of NOAC.

<b>Drugs</b>	<b>Mechanism of action</b>	<b>Dosage</b>	<b>Stopping medication before surgery</b>
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: <ul style="list-style-type: none"> <li>• low bleeding risk and normal renal function</li> <li>• 96 hours</li> <li>• high-bleeding-risk individual and impaired renal function<sup>11</sup></li> </ul>
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 <sup>11</sup>
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

Some variation exists in the recommended time to cease dabigatran between the European Society of Cardiology guidelines and Queensland Health guidelines. 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.<sup>11</sup>

### **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.<sup>12</sup>

The first of several NOAC reversal agents, idarucizumab (Praxbind), was approved by the FDA in October 2015. Idarucizumab is a monoclonal antibody that binds specifically to dabigatran (it does not affect other NOACs). It is approved for patients treated with dabigatran when reversal of the anticoagulant effects are needed for emergency surgery or urgent procedures, or in the event of life-threatening or uncontrolled bleeding. Other NOAC reversal agents are currently in clinical trials or awaiting FDA approval (e.g. andexanet alfa, PER977).

Accelerated approval for idarucizumab was based on interim analysis of the Re-VERSE AD trial. Investigators found that, among 39 patients who had been receiving dabigatran and required an urgent procedure were then given idarucizumab, 36 underwent their urgent procedure with 33 (92%) having normal hemostasis during the event. Two of the remaining patients had mildly abnormal bleeding (with slight oozing), while just one had moderately abnormal yet controlled bleeding. Among 35 of 51 patients who had serious bleeding were able to be assessed, hemostasis, as determined by local investigators, was restored at a median of 11.4 hours.<sup>13</sup>

### **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.<sup>14</sup>

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. In some cases of complex stenting (e.g. 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.<sup>15</sup>

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, 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.<sup>16</sup>

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.<sup>17</sup>

On the other hand, perioperative interruption of aspirin confers a 3-fold increased risk for adverse cardiovascular events. 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. Good communication with the treating cardiologist and, in some cases, individualized treatment plans may be necessary in managing such patients in the perioperative periods.<sup>18</sup>

**Table (3):** Perioperative management of antiplatelets.<sup>18</sup>

Aspirin	Inhibits thromboxane A <sub>2</sub> 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	Metabolized 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 <sub>2</sub> Y <sub>12</sub>	90 mg twice daily	5–7 days prior to surgery

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