

Perioperative management of anticoagulant and antiplatelet therapy

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INTRODUCTION

Long-term oral anticoagulant therapy is often used in patients with atrial fibrillation (AF), a mechanical heart valve (MHV) or venous thromboembolism. The perioperative management of patients who are receiving anticoagulant therapy is already a frequently encountered clinical scenario, likely to increase due to an ageing population. Older people are both more likely to need anticoagulation and to require more surgeries or procedures than younger people. Moreover, anticoagulant use is also increasing due to the availability of the direct oral anticoagulants (DOACs),¹ which are easier to administer than vitamin K antagonists (VKA) such as warfarin. Thus, it is estimated that in patients with AF, which is the dominant clinical indication for long-term anticoagulant therapy, 10%–15% will require treatment interruption annually for an elective surgery/procedure based on data from recent randomised trials of patients with AF.^{2,3}

In warfarin-treated patients who need periprocedural treatment interruption, warfarin is typically stopped 5 days prior to a surgery/procedure to allow its anticoagulant effect to dissipate and is resumed within 24 hours postprocedure. During this periprocedural period, patients will have subtherapeutic anticoagulation for 10–15 days, raising the question of whether pre and postprocedure bridging anticoagulation is warranted to shorten the subtherapeutic anticoagulation interval with the intent of mitigating the risk for perioperative thromboembolism. However, there has been uncertainty as regards the putative therapeutic benefits of heparin bridging when weighed against the potential bleeding risks.^{4,5} Recently completed and ongoing randomised trials have assessed the therapeutic benefits and risks of heparin bridging and have helped to inform best practices regarding 'how to bridge' and, perhaps, more importantly 'whether or not to bridge'.^{6,7} For patients who are receiving a DOAC, the ongoing Perioperative Anticoagulant Use for Surgery Evaluation (PAUSE) study (NCT02228798) will assess the safety of a standardised periprocedural management protocol for patients who need an elective surgery/procedure.⁸ Another unmet clinical need in perioperative patient care is how to manage patients who have coronary artery disease, who are receiving dual antiplatelet therapy with aspirin and P2Y₁₂ inhibitor.⁹

Against this background, the objective of this narrative review is to provide a practical but evidence-based approach to the periprocedural management. The stepwise approach described herein aims to reflect how we assess patients in

Learning objectives

- ▶ To underscore clinical scenarios when anticoagulation interruption is not needed.
- ▶ To explain the how to bridge Coumadin when interruptions are needed.
- ▶ To present a pharmacodynamic strategy to the interruption of direct oral anticoagulants.

everyday practice who require perioperative anticoagulant or antiplatelet management.

Is the interruption of anticoagulant therapy specific to a minor surgery or procedure?

The first step in assessing patients for periprocedural anticoagulant management is to determine if a surgery/procedure can be safely done without anticoagulant interruption, with the aim of avoiding the potential risks, costs, and inconvenience of anticoagulant interruption and resumption and possible heparin bridging. An example of such a clinical scenario is depicted in the BRUISE-CONTROL study.¹⁰ In this randomised controlled trial of 681 warfarin-treated patients with AF who had pacemaker implantation, management with uninterrupted anticoagulation was compared with warfarin interruption and therapeutic-dose low molecular weight heparin (LMWH) bridging (eg, enoxaparin, 1 mg/kg twice daily). Patients who continued warfarin had a lower rate of pocket haematoma than those who had LMWH bridging (3.5% vs 16%, $P<0.01$). Conversely, rates of thromboembolism, cardiac tamponade or death were not different with the two management approaches. Continuation of warfarin can also be considered for patients with AF who are having atrioventricular (AV) node ablation procedures. Thus, in the Role of Coumadin Preventing Thromboembolism in Atrial Fibrillation Patients Undergoing Catheter Ablation (COMPARE) study continuation of warfarin was assessed in patients with AF who had AV node ablation.¹¹ In this randomised trial, 1584 patients were allocated to continue warfarin, or to interrupt warfarin and receive therapeutic-dose LMWH bridging preprocedure. There were more thromboembolic events in patients who interrupted warfarin (5.0% vs 0.25%, $P<0.001$), and the rate of major bleeding was not different between the two groups (0.76% vs 0.38%, $P=0.31$). Other procedures that can be performed without interrupting warfarin include minor dental procedures (uncomplicated tooth extraction, root canal), cataract surgery (largely avascular procedure), coronary



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angiography (especially with radial artery cannulation) and minor dermatologic procedures (skin biopsy), based on some randomised trials but mainly observational studies that assessed warfarin continuation in patients having specific procedures.^{4 5 12 13}

In the The Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF) registry, 38% (2803 of 7327) of warfarin-treated patients required treatment interruption, of which approximately 20% were for such dental, cataract, cardiac device or AV node ablation procedures.¹⁴

The safety of continuing DOACs around minor procedures is less certain as the available evidence is derived entirely from observational studies. An ongoing German registry has, to date, assessed 2179 DOAC-treated patients (76% on rivaroxaban), of whom 7% had an elective procedure.¹⁵ In 187 patients who had minor procedures, DOAC therapy was continued and there were no major bleeds reported. In patients with AF undergoing AV node ablation who did not have periprocedural anticoagulant interruption, registry data suggest that bleeding rates were similar in rivaroxaban and apixaban-treated patients when compared with those on warfarin.^{16 17} Additional studies are needed to address the safety of not interrupting DOAC therapy for electrophysiological procedures and ongoing randomised trials such as the BRUISE-CONTROL-2 trial (NCT01675076) will better inform this issue.

Taken together, there is emerging, but mostly lower quality, evidence that selected very low bleeding risk procedures can be done without interrupting anticoagulation. Postprocedure clinical follow-up is important as such patients are managed without hospitalisation and if bleeding occurs patients need to be aware to report such bleeding so it can be promptly addressed.

For warfarin-treated patients with AF, is perioperative bridging needed?

After deciding that perioperative anticoagulation interruption is necessary, the next step is to determine if heparin bridging is preferred. This question of 'whether or not to bridge?' has been only recently addressed by the Bridging Anticoagulation in Patients who Require Temporary Interruption of Warfarin Therapy for an Elective Invasive Procedure or Surgery (BRIDGE) study.⁷ In this randomised, double-blind, placebo-controlled trial, approximately 1800 patients with AF or atrial flutter were allocated to receive pre and postprocedure therapeutic-dose LMWH (dalteparin, 100 IU/kg twice daily) or no perioperative bridging and had 30 days of follow-up postprocedure. Foregoing bridging did not affect the risk for arterial thromboembolism (0.4% vs 0.3%; mean between-group difference 95%CI -0.6 to 0.8) and conferred lower risks for major bleeding (1.3% vs 3.2%, $P<0.01$) and minor bleeding (12.0% vs 20.9%, $P<0.01$). In addition, there was no difference on the rate of myocardial infarction and venous thromboembolism. Based on these results, LMWH

bridging appears unnecessary for most warfarin-treated patients with AF. A potential criticism of this trial was that high-risk patients with a (within 3 months) history of stroke were excluded, and only 3% of patients had a Congestive heart failure, Hypertension, Age > 75, Diabetes mellitus, Stroke (CHADS₂) score ≥ 5 . However, in the BRIDGE trial 17% of patients had a history of stroke or transient ischaemic attack (though not within 3 months) and the patient population mean CHADS₂ score (2.3%) was comparable to that of other randomised trials and observational studies (2.1%–2.7%) involving patients with AF,^{18 19} thereby supporting the generalisability of the BRIDGE trial results to everyday practice.

The BRIDGE trial also informs the question of 'how to bridge', for those patients in whom LMWH bridging is undertaken, as rates of periprocedural bleeding were low. With the bridging protocol used in the trial (figure 1), the last LMWH dose was given 24 hours preprocedure and was resumed 24 hours postprocedure in patients at low bleeding risk and 48–72 hours postprocedure in those at high bleeding risk.²⁰ It is noteworthy that postprocedure, the mean time that was required to re-establish therapeutic anticoagulation, defined by an international normalised ratio (INR) ≥ 2.0 , was approximately 8 days, thereby suggesting that the perioperative milieu may be associated with resistance to reanticoagulation. This observation may lead clinicians to consider a loading dose of warfarin when it is resumed postoperatively, for example, doubling a patient's usual warfarin dose for the initial 1–2 postprocedure days.²¹

In observational studies involving warfarin-treated patients who received LMWH bridging, rates of major bleeding appeared lower if patients do not receive bridging.^{22–24} The HASBLED (Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile INR, Elderly, Drugs/Alcohol Concomitantly) and Bleed-MAP (Bleeding history, Mechanical mitral heart valve, Active Cancer, low Platelets) scores have been proposed to estimate the perioperative bleeding risk; however, there are no prospective data using these scores to decide against bridging. Bleeding risk factors specific to the perioperative period include: a history of cancer, thrombocytopenia, prior major bleeding, more extensive surgery and spinal anaesthesia.^{12 22 25 26}

Overall, there is increasing evidence that in most anticoagulated patients with AF who require treatment interruption for an elective surgery/procedure, LMWH bridging can be avoided, thereby simplifying the periprocedural anticoagulant management for a large number of such patients.

How to manage perioperative anticoagulation for patients with an MHV

There are no published randomised trials evaluating whether pre and postprocedure LMWH bridging is needed for patients with an MHV. In the meantime, data from observational studies suggest

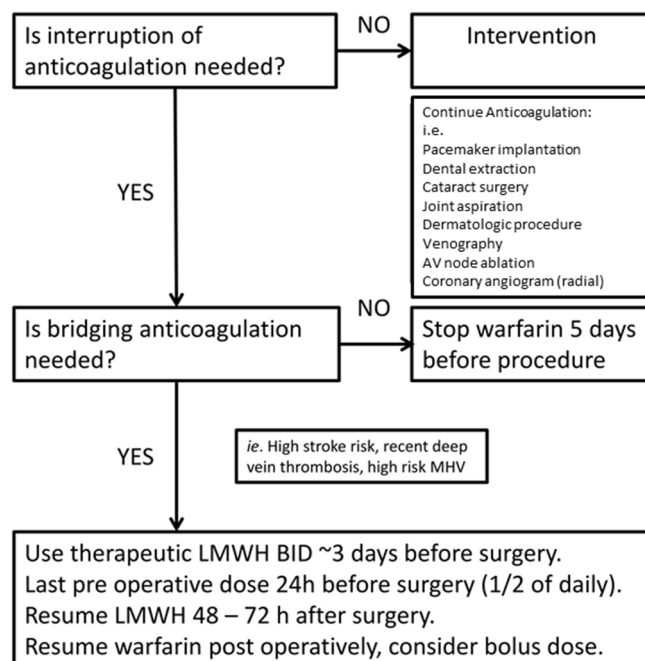


Figure 1 Suggested perioperative bridging protocol for patients on warfarin. Final action plan shall also consider bleeding risk including renal function. Venous thromboembolism prevention as needed in all patients. AV, atrioventricular; LMWH, low molecular weight heparin; MHV, mechanical heart valve.

that perioperative bridging may not be needed in selected patients with a bileaflet aortic MHV and no additional stroke risk factors.²⁷ For most other patients with an MHV, it is reasonable to adopt a perioperative LMWH bridging strategy until randomised trials better inform this question.

The issue of LMWH bridging is also pertinent for patients with a newly implanted MHVs who are initiated on a VKA. Thus, a meta-analysis of 23 studies totalling 9534 patients postimplantation of an MHV assessed management with therapeutic-dose LMWH bridging or no bridging during VKA initiation.²⁸ The rate of thromboembolism appeared higher in patients who received no bridging (2.1% vs 1.1%, $P=0.035$); however, the incidence of this outcome did not differ depending on whether patients received early (<48 hours) or late (>48 hours) postoperative anticoagulation initiation. Postoperative LMWH bridging was associated with more bleeding compared with initiation of oral anticoagulation alone (5.6% vs 0.8%, $P=0.004$). As in other studies, the rate of bleeding did not differ as to whether LMWH or unfractionated heparin was used as a bridging agent: 5.5% (95% CI 2.9 to 10.4) vs 5.2% (95% CI 2.1 to 12.4).^{29,30} Given the potential for increased bleeding with therapeutic-dose LMWH bridging, this approach was compared with use of low-dose LMWH as a bridging agent in an observational study of 1777 patients who had MHV surgery.³¹ There was no difference in the rate of thromboembolism in patients who received therapeutic-dose and prophylactic-dose bridging (OR 0.9; 95% CI 0.4 to 2.2). However, patients who received therapeutic-dose bridging were at higher risk for

major bleeding (OR 3.2; 95% CI 1.6 to 6.6). Thus, among patients having implantation of an MHV, use of a prophylactic-dose LMWH as a bridge to therapeutic anticoagulation with warfarin may be reasonable, but requires further validation.

How to manage DOAC-treated patients who need an elective procedure or surgery

The optimal timing of DOAC interruption prior to a surgery/procedure is a topic of ongoing discussion.^{32,33} A pharmacokinetic-based approach has been used to determine when to stop VKAs, LMWH and unfractionated heparin before a procedure and it may be argued that the same approach can be applied to the DOACs, based on knowledge of their elimination half-lives of 9–14 hours (18–24 hours for patients on dabigatran with impaired renal function).³² A suggested, patient-centred approach to DOAC interruption that is anchored on the procedure-related bleed risk, DOAC type and patient renal function is shown in [table 1](#). The ongoing PAUSE study aims to validate this approach, and can be summarised by the following approach: 1 full day off DOAC if low bleed risk (corresponding to a 32–40 hour interruption interval); 2 full days off DOAC if high bleed risk (corresponding to a 56–64 hour interruption interval), in addition to no DOAC intake on the procedure day.³⁴ The post-procedure resumption of DOAC mirrors pre-procedure management in that the DOAC is resumed after 1 day (ie, at least 24 hours) after a low bleed risk procedure, and resumed after 2 days (ie, at least 48 hours) after a high bleed risk procedure. The initiation of a prophylactic dose anticoagulant (LMWH or DOAC) can be considered in patients at high bleeding risk in whom a delay of full-dose anticoagulation is warranted.

A prospective cohort study of 541 dabigatran-treated patients who were having an elective surgery/procedure assessed the safety of a standardised interruption protocol with last dose of dabigatran taken 24 hours before a low bleed risk procedure and 48 hours before a high bleed risk procedure.³⁵ This management protocol was associated with low rates of major bleeding (1.8%) and thromboembolism (0.6%). However, in a subgroup analysis of 181 patients who had a blood sample drawn just before the procedure, there was evidence of a residual anticoagulant effect, defined by a dilute thrombin time >30 ng/mL, in 25% of patients having a low bleed risk procedure and in 10% of patients having a high bleed risk procedure.³⁶ Further analysis of this subgroup suggested that a slightly longer dabigatran interruption interval, corresponding to 1 full day off dabigatran before a low bleed risk procedure and 2 full days off before a high bleed risk procedure, would yield a higher proportion (ie, >95%) of patients with no detectable residual anticoagulant effect at the time of the surgery/procedure.³² Taken together, these data support an extended DOAC interruption interval, as is being assessed in the PAUSE study ([figure 2](#)).

Table 1 Anticoagulation management of direct oral anticoagulants*

Procedure-related bleeding risk	Patient creatinine clearance		DOAC pharmacokinetics†
	≥50 mL/min	30–50 mL/min	
High bleeding risk	All DOACs Hold for 2 days preprocedure	Dabigatran Hold for 4 days preprocedure All oral Xa inhibitors‡ Hold for 2 days preprocedure	Dabigatran $t_{1/2}$ CrCl >50; 12–18 hours $t_{1/2}$ CrCl 30–50; 13–23 hours Rivaroxaban $t_{1/2}$ CrCl >50; 7–10 hours $t_{1/2}$ CrCl 30–50; 9–13 hours
Low bleeding risk	All DOACs Hold for 1 day preprocedure	Dabigatran Hold for 2 days preprocedure All oral Xa inhibitors Hold for 1 day preprocedure	Apixaban $t_{1/2}$ CrCl >50; 7–10 hours $t_{1/2}$ CrCl 25–50; 9–13 hours Edoxaban $t_{1/2}$ CrCl 50–95; 10–14 hours *Dose reduced 30–50 CrCl

*No DOAC taken on the day of the procedure.

†Timing of DOAC interruption corresponds to at least three to four drug half-lives elapsed prior to low bleed risk procedures and four to five drug half-lives elapsed before high bleed risk procedures.

‡Rivaroxaban, apixaban, edoxaban.

CrCl, creatinine clearance; DOAC, direct oral anticoagulant.

An important but unresolved issue is determining whether preprocedure laboratory testing is needed to guide management in DOAC-treated patients.^{8,37} Such testing may be considered for selected patients who have VKA interruption, for example, measuring the INR on the day before a major surgery with neuraxial anaesthesia. On the other hand, laboratory testing for DOACs is problematic because it is uncertain which assay cut-points correspond to a safe residual anticoagulation level. Moreover, measuring DOAC levels involves assays (dilute thrombin time for dabigatran, DOAC-calibrated anti-Xa levels for oral factor Xa inhibitors) that are not available for routine clinical use. Overall, more research is needed to determine the role, if any, of laboratory testing in DOAC-treated patients who need an elective surgery/procedure.

Another related issue is whether LMWH bridging is needed during the periprocedural interruption of DOAC therapy. In an observational study that assessed dabigatran-treated patients who were bridged or not bridged during perioperative dabigatran interruption, patients in the bridged group had significantly more major bleeding (6.5% vs 1.8%, $P < 0.01$) and there was no significant difference in thromboembolic events (0.5% vs 0.3%, $P = 0.46$) between these two groups.³ In the Dresden registry, 21% (179/863) of DOAC-treated patients who had an elective procedure received perioperative LMWH.¹⁵ The incidence of cardiovascular events was low in all patients (1.0%; 95% CI 0.5 to 2.0) but major bleeding was more frequent in bridged compared with non-bridged patients (2.7% vs 0.5%, $P = 0.01$). Similarly, because of the rapid offset of DOACs, the use of antidotal therapy prior to surgery is currently reserved for bleeding complications or urgent interventions.^{38,39}

Discontinuation of DOAC Flow Diagram

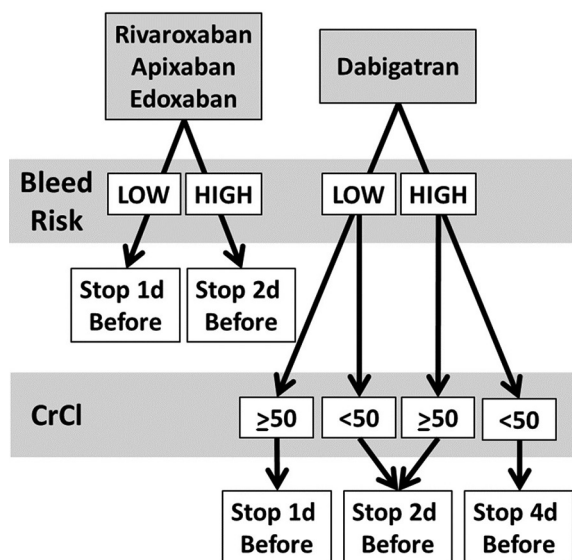


Figure 2 Suggested DOAC interruption schema based on pharmacodynamic approach. CrCl, creatinine clearance; DOAC, direct oral anticoagulant.

How to manage patients who are receiving antiplatelet therapy and require non-cardiac or cardiac surgery

In patients who require an elective surgery/procedure and are receiving an antiplatelet drug that irreversibly inhibits platelet function (ie, Aspirin, clopidogrel, ticlopidine or prasugrel), 7–10 days of treatment interruption, corresponding to the average platelet lifespan, has been recommended to allow full normalisation of platelet function.⁴⁰ Concerns about such treatment interruptions relate to whether this exposes patients to an increased risk for myocardial infarction.⁴¹ A key predictor of major adverse cardiac and cerebrovascular events (MACCE) appears to be the time elapsed between coronary stent implantation and surgery. In a linked administrative database study involving 20 590 patients with coronary stents and 41 180 control patients without stents who had non-cardiac surgery, the incidence of MACCE was highest

Key messages

- Consider whether there is a real need to stop anticoagulation for the scheduled procedure.
- Do not use low molecular weight heparin (LMWH) to bridge direct oral anticoagulants.
- Do not use therapeutic LMWH the night before the procedure.
- When bridging, use a delayed initiation of full-dose anticoagulation in high-risk patients.

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in the initial 6 weeks after surgery but remained significantly higher than in the control group until 6 months postsurgery.⁴² These results are expanded by those of a Danish cohort of 22 590 patients with drug-eluting coronary stents in which 4303 patients with surgery within 1 year were frequency matched by surgery type with 20 232 controls. In this study, there was confirmation of a higher rate of myocardial infarction among patients who underwent surgery within 1 month (OR 14.3; 95% CI 7.5 to 27.4), but there was a strong effect modification if the surgery was emergent as opposed to elective (OR 26.6; 95% CI 11.2 to 62.8).⁴³ Taken together, these studies suggest waiting at least 6 weeks and preferably 6 months after stent implantation before non-cardiac surgery, and such guidance is consistent with clinical practice guidelines.^{44 45}

These observational studies, however, did not address whether antiplatelet therapy should be interrupted. In patients on antiplatelet therapy having coronary artery bypass graft surgery, the Aspirin and Tranexamic Acid For Coronary Artery Surgery (ATACAS) trial addressed perioperative antiplatelet interruption. There were 1047 patients randomised to ASA and 1053 to placebo,⁴¹ in which there was no difference on the primary outcome (non-fatal myocardial infarction, stroke, pulmonary embolism, renal failure or bowel infarction) between groups (relative risk=0.94; 95% CI 0.80 to 1.12). The rates of bleeding leading to reoperation and cardiac tamponade were similar between groups. Thus, even in this high-risk intervention, the likelihood of added thromboembolic protection from perioperative ASA is not evident and discontinuation in high bleeding risk non-cardiac interventions is likely safe as well.

The management of patients who are receiving dual antiplatelet therapy and are undergoing urgent non-cardiac surgery after recent (within

6–12 weeks) stent implantation is challenging.⁴⁶ The management options for such patients include continuing aspirin and interrupting the P2Y₁₂ inhibitor 5–7 days before surgery.⁴⁷ In patients receiving ticagrelor, which is a reversible P2Y₁₂ inhibitor, this can be interrupted 2–3 days before surgery as observational studies in patients having cardiac surgery suggest this is a safe interruption interval.⁴⁸ Another option would be to interrupt both antiplatelet drugs and administer an antiplatelet bridging agent. Thus, cangrelor, which is an intravenously administered P2Y₁₂ inhibitor with a very short half-life (<10 min), has been assessed in the perioperative setting as an antiplatelet bridging agent and can effectively maintain platelet inhibition during antiplatelet drug discontinuation.⁴⁹ A third management option involves continuing dual antiplatelet therapy and administering a platelet transfusion just before the surgery to provide fully functional, uninhibited platelets to optimise hemostasis.⁵⁰

SUMMARY

The identification of patients who may be continued on anticoagulation is an important first step in the perioperative management of anticoagulated patients. Among patients with AF who are receiving VKAs, most can safely interrupt and resume warfarin without LMWH bridging whereas most patients with an MHV should be bridged until further research better informs management. In patients with AF who are receiving a DOAC, simple interruption and resumption protocols are available but require validation in prospective studies. Finally, while continuation of aspirin appears safe for cardiac surgery, high-quality data are lacking to discern which the best perioperative strategy is for patients on other antiplatelet agents or DOACs.

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Author note References which include a * in the reference list have been identified as a key reference.

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