Perioperative Management of Antithrombotic Agents

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Published 21 April 2026 DOI: 10.28923/atotw.570

KEY POINTS

- Antithrombotic agents are commonly encountered perioperatively requiring careful consideration of patient thromboembolic risk and surgical bleeding risk.
- Certain high-risk groups such as those with recent percutaneous intervention for myocardial infarction, those with recent venous thromboembolism, and recent valve replacement require complex perioperative management strategies.
- Emergency surgery presents additional challenges with little to no time for perioperative optimisation, requiring specific reversal agents sometimes in consultation with haematology.
- Resumption of anticoagulation postoperatively is dependent on bleeding risk and patient thromboembolic risk with most agents generally resumed within 24 hours of surgery.
- A multidisciplinary team approach involving anaesthetics, cardiology, haematology, and surgery is often warranted for high-risk patients for safe decision making.

INTRODUCTION

Antithrombotic agents include agents that inhibit the action of platelets and coagulation factors and are commonly prescribed for the treatment and prevention of coronary thrombosis, stroke, deep venous thrombosis, and pulmonary embolism. New agents have been introduced in recent times, making perioperative management challenging.

Perioperative management must strike the right balance between thromboembolic and surgical bleeding risk. This article discusses considerations for perioperative management of antithrombotic agents, including warfarin, direct oral anticoagulants (DOACs), and antiplatelet agents. Considerations include management of high-risk patient populations (e.g. recent percutaneous coronary intervention for acute coronary syndrome, elective versus emergent surgery, and guidance for postoperative restoration of antithrombotic therapy are discussed. This article will exclude recommendations for neuraxial techniques, which require different management.

Warfarin, Direct Oral Anticoagulants, and Antiplatelets

Numerous antithrombotic agents are available with varying primary and secondary indications and well as differing mechanisms and pharmacokinetics (summarised in table 1). Patients may be prescribed more traditional agents such as warfarin and antiplatelets, or newer agents such as DOACs. Knowledge of the indications and pharmacological profile of these agents is crucial for perioperative management.

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Drug	Indication	Mechanism of Action	Half-life
Warfarin	Prevention of VTE, thromboembolic complications and treatment of AF or cardiac valve replacement, prevention of recurrent myocardial infarction	Reduction of vitamin K dependent coagulation factors II, VII, IX, X	20–60 hr
Dabigatran	VTE prevention and treatment, and thromboembolic complications of non-valvular AF	Factor IIa inhibition	8–15 hr
Rivaroxaban		Factor Xa inhibition	5–13 hr
Apixaban			12 hr
Aspirin	Secondary prevention of MI and CVA	Irreversible inhibition of COX	3–10 hr
Clopidogrel	Prevention and treatment of ACS, secondary prevention of CAD and stent thrombosis CVA	Irreversible P2Y12 antagonist	8 hr

Table 1. Summary of Common Antithrombotic Agents[8]. ACS indicates acute coronary syndrome; AF, atrial fibrillation; CAD, coronary artery disease; COX, cyclooxygenase; CVA, cerebrovascular accident; MI, myocardial infarction; VTE, venous thromboembolism; Xa, xabans

Warfarin

Warfarin is a vitamin K antagonist that blocks carboxyl groups on glutamic acid residues of vitamin K dependent clotting factors II, VII, IX, X, and natural anticoagulants protein C and protein S.[1] It is most commonly indicated for venous thromboembolism (VTE) prevention in nonvalvular atrial fibrillation; however, it is also indicated for VTE prevention and treatment, and for prophylaxis in those with mitral stenosis, and for mechanical heart valves. Limitations of warfarin include requirement for frequent monitoring of the international normalised ratio (INR), transient prothrombotic phase on initiation and cessation due to inactivation and activation of protein C and S that is out of phase with coagulation factors, and unpredictable efficacy due to a plethora of interactions with various food and co-administered medications.[2]

Direct Oral Anticoagulants

Direct oral anticoagulants (DOACs) are commonly indicated for prevention of thromboembolic (TE) complications of non-valvular AF and for VTE prophylaxis and treatment.[1] The most encountered DOACs include: apixaban, rivaroxaban, and dabigatran. Apixaban and rivaroxaban directly inhibit factor Xa, whereas dabigatran inhibits thrombin (factor IIa).[3] Another agent, fondaparinux, has an indirect action through binding and enhancing activity of antithrombin, interrupting thrombin formation through factor Xa neutralization.[3] These relatively newer anticoagulants have become increasingly utilised due to their rapid onset, short half-lives, fewer drug interactions, and lesser requirement for monitoring without compromising efficacy.[1]

Antiplatelet Agents

Antiplatelet agents may be prescribed as monotherapy for long-term secondary prevention of stroke, coronary, and peripheral thrombosis. The monotherapy can also follow a period of dual antiplatelet therapy (DAPT) in patients who have experienced an acute coronary syndrome, percutaneous intervention, or after coronary artery bypass grafting or percutaneous peripheral vascular interventions.[3] DAPT can also be prescribed for the prevention of myocardial infarction, stroke, or for those with complicated atrial fibrillation with high risk of coronary artery disease. DAPT is usually short term and poses important questions in the setting of elective surgery such as risk of heart attack or stroke if perioperative cessation is considered.

The most prescribed agents are aspirin and clopidogrel, offering differing mechanisms of actions with synergic effect. Aspirin irreversibly inhibits the production of thromboxane A_2 in thrombocytes by acetylation of cyclooxygenase 1, thereby inhibiting thrombocyte aggregation. Clopidogrel, on the other hand, inhibit the P2Y12-ADP receptor on thrombocyte surfaces.[4] Other P2Y12 inhibitors include ticagrelor and prasugrel. These agents address some of the limitations of clopidogrel such as interindividual variability; however, they have greater bleeding risk compared to clopidogrel.[5]

Perioperative Management of Antithrombotic Agents

Provoked thromboembolic complications are a common cause of perioperative morbidity and mortality due to venous stasis, hypercoagulable state, and endothelial dysfunction. There are approximately 10 to 12 million people worldwide requiring anticoagulant management as they have a pre-existing risk factors for thromboembolic complications.[6] It is the task of the perioperative physician to balance the inherent risk of perioperative bleeding against the patient's risk of thromboembolsim.[7] This decision often nuanced and complex, requires necessitating multidisciplinary collaboration (anaesthesiology, surgery, medicine, hematology, cardiology) and the necessity to follow local hospital protocols and guidelines such as published by CHEST.[6]

Patient Risk

Assessment of patient risk for TE is vital. Risk of VTE as per the American College of Chest Physician CHEST guidelines can be classified as high, moderate, and low. Presence of mitral stenosis, mechanical heart valve, recent stroke, and deep vein

thrombosis, or haematological conditions or cancer predisposing to thrombophilia usually constitute high risk (risk profile is summarised in Table 2).[6] Perioperative assessment should carefully assess for these factors, alongside other risk factors for bleeding such as low platelet count, previous personal or family history of bleeding, and use of other medications with antiplatelet action such as fish oil and nonsteroidal agents. The HAS-BLED score may be useful in predicting major bleeding in patients with nonvalvular atrial fibrillation receiving anticoagulation, encompassing factors such as hypertension, renal and liver dysfunction, history of stroke and bleeding, labile INR (international normalised ratio), age (>65 years), and use of concomitant drugs and alcohol.[8] If, based on the perioperative assessment, the patient is deemed to be at high risk of TE, multidisciplinary assessment with further specialist input is required where there is high risk of surgical bleeding.

Surgical Risk

Common surgical procedures can be classified as minimal, low to moderate, and high bleeding risk (summarised in Table 3), adapted from the International Society on Thrombosis and Haemostasis Guidance Statements.[6] Generally, procedures involving highly vascularised organs such as the liver, kidney, and spleen carry high bleeding risk independent of antithrombotic drug action.[6] Additionally, whereas intracranial and spinal procedures may not present risk of high-volume bleeding the surgery occurs in uncompliant anatomical spaces and may compromise neural function, and inability to achieve proper wound closure as in urological procedures such as transurethral resection of prostate can have adverse impact.[9]

Warfarin

For surgical procedures with minimal risk of bleeding, warfarin can generally be continued perioperatively if INR is within therapeutic range.[6] With surgical procedures posing low to moderate, and high risk of bleeding, warfarin should be ceased prior to surgery.[6] If the risk of TE is low to moderate, warfarin should be ceased 5 days prior to surgery without requirement for bridging therapy (unless high risk for TE).[6] The purpose of bridging is to provide protection for high-risk TE groups, whereas fully reversing effect of warfarin and allow for the regeneration of vitamin K dependent clotting factors.[2] In this case, the patient's INR should be tested on the day prior to their procedure. If the patient's INR >1.5 it is safe to proceed with the operation (excluding neuraxial techniques); otherwise, vitamin K may be administered prior to the procedure to avoid cancellation.[2] However, use of vitamin K is controversial. CHEST guidelines suggest against routine use of preoperative vitamin K due to uncertainty regarding dosing, availability, and resistance to postoperative re-anticoagulation (conditional recommendation, with very low certainty of evidence).[6]

If the risk of TE is high, in addition to warfarin cessation 5 days prior to surgery, bridging therapy with a short acting anticoagulant such as unfractioned heparin and low molecular weight heparin is typically initiated 3 days prior to the surgery and stopped 24 hours prior to the procedure.[6] Bridging is not recommended for patients undergoing pacemaker insertion or patients with atrial fibrillation (unless high risk for TE).[6] In patients with impaired renal function or procedures with high risk of bleeding, the bridging agent may

Risk	Mechanical Heart Valve	Atrial Fibrillation	VTE
High (>10% yearly risk of ATE or > 10%/monthly risk of VTE)	Mitral valve with major risk factors for stroke. Caged ball or tilting-disc valve in mitral/aortic position. Recent (<3 mo) stroke or TIA	CHA2DS2VASc score ≥ 7 or CHADS2 score of 5 or 6. Recent (<3 mo) stroke or TIA. Rheumatic valvular heart disease	Recent (<3 mo and especially 1 mo) VTE. Severe thrombophilia (deficiency of protein C, protein S or antithrombin; homozygous factor V Leiden or prothrombin gene G20210A mutation or double heterozygous for each mutation, multiple thrombophilias). Antiphospholipid antibodies. Active cancer associated with high VTE risk
Moderate (4%-10% yearly risk of ATE or 4%-10% monthly risk of VTE)	Mitral valve without major risk factors for stroke. Bileaflet aortic valve replacement with major risk factors for stroke	CHA2DS2VASc score of 5 or 6 or CHADS2 score of 3 or 4	VTE within past 3-12 months. Recurrent VTE Non-severe thrombophilia (heterozygous factor V Leiden or prothrombin gene G20210A mutation). Active cancer or recent history of cancer
Low (<4% yearly risk of ATE or <2% monthly risk of VTE)	Bileaflet aortic valve replacement without major risk factors for stroke	CHA2DS2VASc score of 1-4 or CHADS2 score of 0-2 (and no prior stroke or TIA)	VTE > 12 months ago

Table 2. Perioperative Risk Stratification. Adapted From the CHEST Guidelines[6]. ATE indicates arterial thromboembolism; TIA, transient ischemic attack; VTE, venous thromboembolism

Surgical Bleeding Risk	Surgical Procedure
High (30-d risk of major bleed ≥2%)	- Any major operation (procedure duration of >45 min) - Bowel resection - Cancer procedure, including solid tumour resection (lung, oesophagus, gastric, colon, hepatobiliary, pancreatic) - Cardiac, intracranial, or spinal procedure - Colonic polyp resection - Epidural injections - Major procedure with extensive tissue injury - Major orthopaedic procedure (including hip, knee, or shoulder replacement procedure - Major thoracic procedure - Nephrectomy, kidney biopsy - Neuraxial anaesthesia (including spinal and epidural anaesthesia or other neuraxial intervention) - Percutaneous endoscopic gastrostomy placement, endoscopic retrograde cholangiopancreatography - Procedure in highly vascular organs (kidneys, liver, spleen) - Reconstructive plastic procedure - Transurethral prostate resection, bladder resection, or tumour ablation - Urologic or gastrointestinal procedure – including anastomosis procedure
Low-Moderate (30-d risk of major bleed 0%-2%)	- Abdominal hernia repair - Abdominal hysterectomy - Arthroscopy - Cutaneous/lymph node biopsies Low/moderate - Bronchoscopy ± biopsy - Colonoscopy ± biopsy - Coronary angiography - Foot/hand procedure - Gastrointestinal endoscopy ± biopsy - Haemorrhoidal procedure - Laparoscopic cholecystectomy - Small skin grafts
Minimal (30-d risk of major bleed approximately 0%)	- Minor dental procedures (dental extractions, restorations, prosthetics, endodontics), dental cleanings, fillings - Minor dermatologic procedures (excision of basal and squamous cell skin cancers, actinic keratoses, and premalignant or cancerous skin nevi) - Ophthalmological (cataract) - Pacemaker or cardioverter – defibrillator device implantation - Removal of external fixators

Table 3. Surgical Risk Stratification Based on ISTH Guidelines[6]. ISTH indicates International Society on Thrombosis and Haemostasis

need to be stopped earlier than the morning of surgery. Guidelines suggest use of a perioperative warfarin and heparin bridging calendar for patients and medical practitioners to help minimise errors and optimise communication regarding perioperative anticoagulation.[6] An approach to bridging with warfarin therapy is summarised in Table 4.

Direct Oral Anticoagulants

For procedures with low to moderate risk of bleeding DOACs (apixaban and rivaroxaban) can be ceased 1 day before surgery, and 2 days prior to surgeries with high risk for haemorrhage.[6] This period should be extended to for patients with renal impairment, very low body weight, or advanced age.[10] Dabigatran should be ceased 1 day prior to surgeries with low to moderate bleeding risk, 2 days for high surgical bleeding risk, and 4 days prior to high bleeding risk with impaired renal function (creatinine clearance <50 mL/min).[6] Patients requiring cessation of DOAC prior to surgery do not require perioperative bridging due to rapid onset and offset and lack of procoagulant effect compared with warfarin.[10] Routine laboratory testing for DOAC (anti Xa assay) is usually advised against; however, thrombin time is sensitive for the presence of dabigatran and can be used for drug exclusion.[6,9] Guidance differs for neuraxial anaesthesia, in which case DOAC therapy (apixaban and rivaroxaban) should be stopped 72 hours prior, with consideration for checking anti-Xa plasma levels if the interval before the procedure is less than this.[10]

Day	Minimal Bleed Risk	Low–Moderate Bleed Risk	High Bleed Risk
−5	Continue warfarin	Stop warfarin	Stop warfarin
−3 to −1	No bridging	Start LMWH (therapeutic dose) if high thrombotic, last dose morning of −1)	Start LMWH (therapeutic dose) if high thrombotic risk (last dose morning of −1)
0 (Surgery Day)	Continue warfarin	Proceed if INR <1.5. No warfarin or LMWH today	Proceed if INR <1.5. No warfarin or LMWH today
+1 (Post-op, once haemostasis secured)	Continue warfarin	Resume warfarin. Restart therapeutic LMWH 24 hr post-op (if low/moderate bleeding risk) until INR therapeutic	Resume warfarin; restart prophylactic LMWH within 24–72 hr; escalate back to therapeutic LMWH at 48–72 hr post-op if safe

Table 4. Perioperative Management of Warfarin[6]. INR indicates international normalized ratio; LMWH, low-molecular-weight heparin

Antiplatelets

Aspirin can be continued perioperatively in procedures with low bleeding and minimal thromboembolic risk.[10] However, for surgeries with higher bleeding risk, cessation of aspirin is typically advised 7 days prior as platelet inhibition is non reversible and new platelets need to be resynthesized.[6] Ticagrelor should be withheld 3–5 days prior and clopidogrel 5 days prior to surgery.[6] In cases where thromboembolic risk is high, multidisciplinary discussion is warranted to guide management.

Risk of stent thrombosis within the first year after coronary revascularisation is high, requiring the use of DAPT to minimise risk of cardiovascular events and associated mortality. DAPT management requires assessment of timing from stent placement, stent type, and indication (acute coronary syndrome vs stable coronary artery disease).[6] The 2024 American Heart Association guidelines recommend delaying elective noncardiac surgery (NCS) for ≥12 months after drug eluting stent for acute coronary syndrome and ≥6 months for drug-eluting stent for stable CAD.[11] In time-sensitive cases, NCS may be considered after 3 months for drug-eluting stent with percutaneous coronary intervention if delay to surgery outweighs the risk of cardiovascular events.[11] Elective NCS after percutaneous intervention with bare metal stents can proceed after ≥30 days of uninterrupted DAPT, although bare metal stents are rarely placed in the contemporary era.[11] The 2022 European Society of Cardiology guidelines, recommend delaying elective NCS for 12 months post-acute coronary syndrome and 6 months post-stent insertion for stable CAD.[12] In high-risk patients with percutaneous intervention for recent acute coronary syndrome, DAPT should be continued for at least 3 months before time sensitive NCS, with a minimum of 1 month of DAPT for time-sensitive NCS after elective percutaneous intervention.[12] This ultimately requires multidisciplinary decision making between cardiology, haematology, anaesthetics, and surgical teams, with key considerations including thrombotic risk from DAPT interruption, bleeding risk if DAPT is continued, and urgency of the surgery.

Considerations for Emergency Surgery and Reversal of Antithrombotic Agents

Communication between the surgical and anaesthetic teams is vital to coordinate optimal timing of surgical intervention. Elective surgery allows for surgical delay and sufficient opportunity for preoperative evaluation and optimisation. Emergency surgery, on the other hand, is defined as surgery that presents immediate threat to life or limb without surgical intervention. There is often limited to no time for preoperative clinical evaluation (<2–6 hours).[11]

Reversal of Antithrombotic Agents

Warfarin

Management of patients requiring emergent procedures with warfarin requires consideration for the patient's INR levels and surgical bleeding risk. If the patient's INR is ≥1.5, haematology should be consulted for individualised advice. In cases where immediate reversal is required (<6 hours to procedure), such as with major trauma and life-threatening bleeding, warfarin should be omitted and intravenous vitamin K should be administered alongside prothrombin complex concentrate or fresh frozen plasma if prothrombin complex concentrate is contraindicated.[10] Newer Australian guidelines in 2024 have recommended transitioning from 3-factor prothrombin complex concentrate such as Prothrombinex-VF to Beriplex, a four factor prothrombin complex concentrate.[13] Onset of reversal occurs approximately within 5 minutes of infusion for three-factor prothrombin complex concentrate and four-factor prothrombin complex concentrate.[13] In circumstances where none of these therapies are helping, recombinant factor VIIa could be considered.

Direct Oral Anticoagulants

For patients receiving dabigatran, idarucizumab, a monoclonal antibody fragment, can be used to rapidly reverse anticoagulation within minutes.[8] If idarucizumab is unavailable, haemodialysis can be considered.[8] For Apixaban and rivaroxaban, andexanet alfa

has been shown to reverse factor Xa mediated anticoagulation.[8] However, routine use of andexanet alfa is limited by its availability, high cost, and potential for thrombotic complications. Evidence supporting the use of prothrombin complex concentrates in DOAC associated bleeding remains mixed. Nonetheless, in the absence of other reversal agents, four-factor prothrombin complex concentrate may provide partial reversal of anticoagulation.[8] Notably, haemodialysis is not effective for the reversal of apixaban and rivaroxaban due to their high plasma protein binding.[8] A DOAC level <50 ng/mL may not require reversal intervention; however, evidence is limited in this context.[7]

Antiplatelets

In patients who require emergent surgery, platelet transfusion can be considered to restore platelet function; however, data supporting this recommendation is limited.[8] Platelet transfusion is generally not administered preoperatively for patients on aspirin monotherapy; however, a single unit of platelets may reduce surgical bleeding risk on patients receiving DAPT.[8]

Tranexamic Acid

A recent randomized controlled trial comparing use of 1g tranexamic acid to placebo at the start and end of surgery demonstrated significantly reduced incidence of bleeding.[14]

Postoperative Anticoagulation Recommencement

Warfarin

For most patients, warfarin should generally be resumed within 24 hours of their procedure, with most patients suitable for recommencement on the evening of surgery at their usual maintenance dose (excluding neuraxial techniques).[6] Resumption of warfarin therapy may be delayed if there are concerns for inadequate surgical haemostasis and need for additional interventions.[6] Of note, on resuming warfarin, partial anticoagulation usually occurs within 2–3 days, with full anticoagulant effect taking 4–8 days.[6] In patients at high risk of thrombosis low molecular weight heparin or unfractioned heparin can use used, typically commencing 12–24 hours postoperatively at either a prophylactic or therapeutic dose. This regimen is generally continued until therapeutic INR is achieved.[9]

DOACs

DOACs should be resumed 24 hours after surgery for low to moderate bleeding risk and 48–72 hours after high bleeding risk.[7] For patients who are high risk of surgical bleeding with high risk for thromboembolism, prophylactic low-dose low-molecular-weight heparin (LMWH) may be used until DOAC resumption.[7]

Antiplatelets

It is recommended antiplatelets resume within 24 hours of surgery.[6] Aspirin achieves maximal antiplatelet effect within minutes of resumption, whereas clopidogrel may take up to 7 days to achieve maximal effect.[9]

SUMMARY

Antithrombotic agents are frequently encountered in the perioperative setting and research and guidelines are continuously evolving. Management of antithrombotic agents in this setting requires understanding of their indications, pharmacology, and the interplay between patient related and surgical risks.

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