Chapter 12
Perioperative Management of Anticoagulation and Antiplatelet Therapy

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Abbreviations

AC	Anticoagulation
ADP	Adenosine diphosphate
AF	Atrial fibrillation
ASA	Acetylsalicylic acid
CABG	Coronary artery bypass grafting
CCS	Canadian Cardiovascular Society
CHF	Congestive heart failure
CHADS2	Score system for anticoagulation in atrial fibrillation
CHA2DS2-VASc	Score system for anticoagulation in atrial fibrillation
COX-1/2	Cyclooxygenase-1/2
CVA	Cerebrovascular accident
DES	Drug eluting stent
DOACs	Direct oral anticoagulants
DVT	Deep vein thrombosis
HIT	Heparin-induced thrombocytopenia
ICH	Intracranial hemorrhage
ICD	Implantable cardioverter-defibrillator

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INR	International normalized ratio
LMWH	Low-molecular-weight heparin
LN	Lymph node
M	Month
PCC	Prothrombin complex concentrate
PE	Pulmonary embolism
PT	Prothrombin time
PTT	Partial thromboplastin time
TIA	Transient ischemic attacks
UFH	Unfractionated heparin
VKA	Vitamin K antagonist
VTE	Venous thromboembolism

Introduction

The purpose of this chapter is to suggest an approach to the perioperative management of anticoagulation and antiplatelet therapy based on the current guidelines and available data.

Anticoagulants

The term *bridging* is often used to refer to the use of short-acting anticoagulant before and after elective surgery to ensure the continuity of anticoagulation and reduce thromboembolic risks.

The two variables that interplay in the decision to continue on anticoagulation, temporarily discontinue anticoagulation, or bridge with short-acting preparations are (1) patients' thromboembolic risk and (2) patients' bleeding risk [1–5].

1. *Patient's thromboembolic risks*: The most common indications for anticoagulation are venous thromboembolism, AF, and mechanical valve and heart failure with sinus rhythm. Patients with recent (embolic) cerebrovascular events (CVA) or transient ischemic attacks (TIA). The thromboembolic risk of each of these indications is stratified in Fig. 12.1.
2. *Patient's bleeding risk* is mainly dependent on the type of procedure and patient's history and bleeding risks and is highlighted in Fig. 12.2.

The approach to anticoagulation (AC) bridging is therefore based on the patients' thrombotic risk and the intrinsic as well as operative risks of bleeding.

1. Wafrarin

Figure 12.3 illustrates the approach to bridging when using warfarin. Bridging is achieved with unfractionated heparin (UFH) or low-molecular-weight heparins (LMWH).

	Indication for anticoagulation			
Risk	**VTE**	**AF**	**Valvular**	**CHF-SR**
High risk	Recent <3M DVT/PE Recent <3M Prior clot with anticoagulation interruption VTE while on therapeutic anticoagulation Active cancer Severe congenital thrombophilia (S or C deficiency) Antiphospholipid syndrome	CHA2DS2-VASc score > 6 CHADS2 4–6 Previous stroke <3M Previous stroke+3 or more CHF Hypertension >75 years DM	Mechanical mitral valve Tricuspid prosthesis Old aortic valve Bileaflet valve and additional risk Rheumatic valve disease	Current or < 3M mural thrombus <3M stroke or TIA
Intermediate risk	Previous VTE 3–12M	CHAD2DS2-VASc score 5–6 Prior stroke/ TIA > 3M	Bileaflet aortic valve with AF Bioprosthetic aortic valve with AF	History of stroke/TIA History of mural thrombus
Low risk	Prior VTE >12M	CHAD2DS2-VASc Score 1–4 CHADS2 0–3 Chronic AF	Bileaflet aortic valve with no AF or other risks	No history of mural thrombus

AF CHF Congestive heart failure, *CHAD2DS2-VASc/CHAD2* Score system for *Atrial fibrillation, anticoagulation in atrial fibrillation, DVT* Deep vein thrombosis, *PE* Pulmonary embolism, *VTE* Venous thromboembolism, *TIA* Transient ischemic attack

Fig. 12.1 Risk stratification based on the indication of anticoagulation

Risk	Surgical/procedure	Patient's factors
High risk	Neuraxial anesthesia Neurosurgery Cardiac surgery (CABG/valve) Vascular surgery Major orthopedic surgery Major pulmonary surgery Major cancer surgery Major intra-abdominal or gynecological surgeries and bowel anastomosis Invasive biopsies	Major bleeding <3M ICH < 3M
Intermediate risk	Laparoscopic maneuvers Other invasive surgeries including breast Non-cataract eye Gastroscopy/colonoscopy with biopsy	Platelet abnormalities and use of antiplatelet agents INR is above the therapeutic range Prior bleeding with bridging

Fig. 12.2 Bleeding risk stratification

(continued)

Risk	Surgical/procedure	Patient's factors
Low risk	Coronary angiography Cardiac procedures Pacemaker ICD placement Bone marrow and LN biopsies, thoraco-, para-, and arthrocentesis Multiple tooth extractions Dental, dermatologic, cataract, and minor ENT procedures Endoscopies without polyp removal Dental extractions (2)	
Very low risk	Root canal and periodontal surgery Skin biopsies Cataract removal	

CABG Coronary artery bypass grafting, *DVT* Deep vein thrombosis, *ICH* Intracranial hemorrhage, *ICD* Implantable cardioverter/defibrillator, *LN* Lymph node, *M* Month, *PE* Pulmonary embolism, *VTE* Venous thromboembolism, *TIA* Transient ischemic attack

Fig. 12.2 (continued)

Risk	Bleeding risk			
Thrombotic	**High**	**Intermediate**	**Low**	**Very low**
High	*Plan-A bridging* Start AC 48–72 hours after surgery Or low dose AC or resume VKA after 12–24 hours	*Plan-B bridging* Start AC 24–48 hours after surgery	*Plan-C bridging* Start AC 12–24 hours after surgery	*Continue on anticoagulation*
Intermediate[a]	Individualized *Plan-A bridging* decision Start AC 48–72 hours after surgery Or low dose AC or resume VKA after 12–24 hours *OR*	Individualized *Plan-B bridging* decision Start AC 24–48 hours after surgery *OR*	Individualized *Plan-C bridging* decision Start AC 12–24 hours after surgery *OR*	*Continue on anticoagulation*
	No bridging *Temporary discontinuation*	*No bridging* *Temporary discontinuation*	*Continue on anticoagulation*	
Low	*No bridging* *Temporary discontinuation*	*No bridging* *Temporary discontinuation*	*Continue on anticoagulation*	*Continue on anticoagulation*

[a]The approach to intermediate bleeding risk patients is left to the discretion of the physician to adopt high-risk or low-risk approach

Fig. 12.3 Approach to anticoagulation management based on thromboembolic and bleeding risks

1. *When warfarin and other vitamin k antagonists (VKA) are used, the following action plans can be implemented* [1–5]:

Plan A – Bridging (High and Intermediate Thrombotic Risks with High Bleeding Risk)

- *Day −5:* Stop VKA.
- *Day −3:* Start UFH or subcutaneous LMWH.
- Day *−1:*
  - INR >1.5 – Administer 1–2 mg of vitamin K orally.
  - Stop LMWH on the morning of surgery (omit evening dose in bid) or reduce daily dose 50% in OD dose.
- *Day 0:* Stop UFH 4 hours prior.
- Day *+1/+3:* Assess postoperative hemostasis and could start low dose LMWH or resume VKA.
- Day *+5/+6:* Ensure that INR is therapeutic.

Plan B – Bridging (High and Intermediate Thrombotic Risks with Intermediate Bleeding Risk)

- *Day −5:* Stop VKA.
- *Day −3:* Start UFH or subcutaneous LMWH.
- *Day −1:*
  - INR >1.5 – Administer 1–2 mg of vitamin K orally.
  - Stop LMWH on the morning of surgery (omit evening dose in bid) or reduce daily dose 50% in OD dose.
- *Day 0:* Stop UFH 4 hours prior.
- *Day +1/+2:* Therapeutic dose UFH/LMWH, start VKA.
- *Day +5/+6:* Stop UFH or LMWH when INR is therapeutic.

Plan C – Bridging (High and Intermediate Thrombotic Risks with Low Bleeding Risk)

- *Day −5:* Stop VKA.
- *Day −3:* Start UFH or subcutaneous LMWH.
- *Day −1:*
  - INR >1.5 – Administer 1–2 mg of vitamin K orally.
  - Stop LMWH on the morning of surgery (omit evening dose in bid) or reduce daily dose 50% in OD dose.

- *Day 0:* Stop UFH 4 hours prior – Resume UFH/LMWH 12 hours postoperative.
- *Day +1:* Resume VKA.
- *Day +5/+6:* Stop UFH or LMWH when INR is therapeutic.

No Bridging (Low Thrombotic Risks with High or Intermediate Bleeding Risk)

- *Day −5*: Stop VKA.
- *Day −1*: INR >1.5 – Administer 1–2 mg of vitamin K orally.
- *Day 0*: Resume VKA on the evening if oral feeding allowed.
- *Day +1/+5*: Resume VKA and ensure that INR is therapeutic.

Emergency and Urgent Surgical Interventions on VKA

- *Day −1/0:*
  - Vitamin K 2.5–5 mg IV
  - If needed four-factor prothrombin complex concentrate at a dose of 25–50 IU/kg (average 30 IU/kg) and check INR.
- *Day +1/+5:* UFH/LMWH and resume VKA as per thrombotic/bleeding risk stratification approach.
- (See chapter on anticoagulation reversal for full details.)

For switching to and from other parenteral or oral agents, please refer to the specific agent.

2. Heparin and LMWH

- Stop UFH 4 hours prior to surgery.
- Stop LMWH on the morning of surgery (omit evening dose in bid) or reduce daily dose 50% in OD dose.
- Resume UFH/LMWH 12 hours postoperatively after ensuring that hemostasis is achieved.

3. Hirudin

- Prior to surgical procedure, the medication can be stopped for 4 hours and resumed 12 hours postoperatively after ensuring that hemostasis is achieved.

Transition to Warfarin [6, 7]

- Warfarin initiated only after substantial recovery from HIT has occurred with lepirudin therapy.
- Reduce dosage gradually until the aPTT ratio is just above 1.5, and then initiate therapy with warfarin avoiding loading dose and with modest doses.
- Overlap lepirudin and warfarin therapy for a minimum of 4–5 days until the target INR is reached.

4. Argatroban

- Prior to surgical procedure, the medication can be stopped for 4 hours and resumed 12 hours postoperatively after ensuring that hemostasis is achieved.

Transition to Warfarin [8–10]

- Warfarin initiated only after substantial recovery from HIT has occurred with argatroban therapy.
- If dose is <2 mcg/kg/min D/C when INR is >4 on combined therapy and remeasure INR in 4–6 hours.
- Restart argatroban if INR is below range and repeat until the desired INR is achieved.
- If dose is >2 mcg/kg/min, decrease rate to 2 mcg/kg/min and measure INR at 4–6 hours and proceed accordingly.
- A formula was developed to calculate INR attributable to warfarin when argatroban is given at 2 mcg/kg/min.

$$\mathrm{INR}_{\mathrm{warfarin}} = 0.19 + \left(0.57 \times \mathrm{INR}_{\mathrm{cotherapy}}\right).$$

With the use of direct oral anticoagulants (DOACs), which include the direct thrombin inhibitor, dabigatran, or the anti-Xa inhibitors, bridging takes a different perspective.

5. Dabigatran [11, 12]

In clinical trials (RE-LY), treatment was discontinued in the context of procedures with an incidence of major bleeding ranging between 3.8 percent and 5.1 percent for dabigatran doses of 110 milligrams and 150 milligrams, respectively, with a risk of systemic embolization in the range of 0.5 percent [12].

The following table illustrates the suggested time of discontinuation (in hours) of the medication prior to procedures based on creatinine clearance and suggested restarting does and timing.

Discontinuation		*Timing (hours)*	*Timing (hours)*
Creatinine clearance ml/min	*Half-life in hours*	*Low bleeding risk*	*Moderate and high bleeding risk*
> = 80	13	24	48
> = 50–80	15	24–48	48–72
> = 30- <50	18	48–72	96
Restarting	*Dose (mg)*	*Timing (hours)*	
Minor procedures	75 escalating to 110	Evening of procedure	
Major procedures	Full dose 110–150	48–72	

Bridging with LMWH was done only in a minority of cases in a clinical trial involving high thrombosis risk patients before DOACs are reintroduced.

NB: Normal prothrombin time (PT) and partial thromboplastin time (PTT) do not exclude a significant concentration of dabigatran in the circulation. A normal thrombin time, however, excludes the presence of dabigatran.

If the anticoagulant effect cannot be ruled out completely, neuraxial or celiac block anesthesia should be avoided.

Emergency Surgery: Dabigatran is minimally protein bound and can be removed by dialysis if a procedure can be delayed enough for this to take place.

Tranexamic acid is likely to reduce bleeding in patients who have a residual anticoagulant effect and can be used.

Idarucizumab (Praxbind), a monoclonal antibody to dabigatran, given at a dose of 5 grams (2 × 2.5 g vials) could be used to dose restore hemostasis (see chapter on reversal for full details) [13].

Conversion to Warfarin
When converting from dabigatran to warfarin, adjust the starting time of warfarin based on creatinine clearance as follows:

- For CrCl ≥50 mL/min, start warfarin 3 days before discontinuing dabigatran.
- For CrCl 30–50 mL/min, start warfarin 2 days before discontinuing dabigatran.
- For CrCl 15–30 mL/min, start warfarin 1 day before discontinuing dabigatran.
- For CrCl <15 mL/min, no recommendations can be made.

Converting from or to Parenteral Anticoagulants
- For patients currently receiving a parenteral anticoagulant, start dabigatran 0–2 hours before the next scheduled dose of the parenteral drug or at the time of discontinuation of a continuously administered parenteral drug.
- For patients currently taking dabigatran, wait 12 hours (CrCl ≥ 30 mL/min) or 24 hours (CrCl < 30 mL/min) after the last dose before initiating treatment with a parenteral anticoagulant.

6. *Rivaroxaban (Xarelto)* [14]

Data from large clinical trials showed that the discontinuation of rivaroxaban for more than 3 days to allow surgery or invasive procedure did not result in any significant major hemorrhage or embolization.

The manufacturer's recommendation is to discontinue for over 24 hours and 48 hours for low and high bleeding risks, respectively.

There is no fixed protocol for pre-procedure discontinuation.

Discontinuation		*Timing (hours)*	*Timing (hours)*
Creatinine clearance ml/min	*Half-life in hours*	*Low bleeding risk*	*Moderate and high bleeding risk*
> = 30	9	24	48
<30		48	72
Restarting	*Dose (mg)*	*Timing (hours)*	
Minor procedures	20	6–12	
Major procedures	20	Adequate hemostasis – 48	

In patients with high thrombosis risk, it is appropriate to consider prophylactic doses of anticoagulation with LMWH before reintroducing full therapeutic dose of DOACs.

NB: Normal PT and PTT do not exclude a significant concentration of rivaroxaban in the circulation.

- If the anticoagulant effect cannot be ruled out completely, neuraxial or celiac anesthesia should be avoided.

Emergency Surgery: Few data support the use of PCC in the management of emergency surgery, and it should not be used routinely.

Tranexamic acid is likely to reduce bleeding in patients who have a residual anticoagulant effect and can be used.

Andexanet alfa: No data in patients undergoing surgery but promising data on reversal. When available, it should be used for reversal prior to emergency invasive procedures and surgery where bleeding risks are considered significant (see Chap. 12 for full details) [15].

When neuraxial (epidural/spinal) anesthesia or lumbar puncture is performed, patients treated with antithrombotics for prevention of thromboembolic complications are at risk for developing an epidural or spinal hematoma.

The risk of these events is even further increased by the use of indwelling epidural catheters or the concomitant use of drugs affecting hemostasis. Accordingly, the use of rivaroxaban, at doses greater than 10 mg, is not recommended in patients

undergoing anesthesia with postoperative indwelling epidural catheters. The risk may also be increased by traumatic or repeated epidural or lumbar puncture. If traumatic puncture occurs, the administration of rivaroxaban should be delayed for 24 hours.

Switching from Parenteral Anticoagulants to Rivaroxaban

- Rivaroxaban can be started when the infusion of full-dose intravenous heparin is stopped or 0–2 hours before the next scheduled injection of full-dose subcutaneous LMWH or fondaparinux.
- In patients receiving prophylactic heparin, LMWH, or fondaparinux, it can be started 6 or more hours after the last prophylactic dose.

Switching from Rivaroxaban to Parenteral Anticoagulants

- Discontinue rivaroxaban and give the first dose of parenteral anticoagulant at the time that the next rivaroxaban dose was scheduled to be taken.

Switching from Vitamin K Antagonists (VKA) to Rivaroxaban

- Stop the VKA and determine the INR.
- If the INR is ≤2.5, start rivaroxaban at the usual dose.
- If the INR is >2.5, delay the start until the INR is ≤2.5.

Switching from Rivaroxaban to a VKA

- Rivaroxaban should be continued concurrently with the VKA until the INR is ≥2.0.
- For the first 2 days of the conversion period, the VKA can be given in the usual starting doses without INR testing.
- Thereafter, while on concomitant therapy, the INR should be tested just prior to the next dose of rivaroxaban, as appropriate. Xarelto can be discontinued once the INR is >2.0.
- Once it is discontinued, INR testing may be done at least 24 hours after the last dose reflecting the anticoagulant effect of the VKA.

7. *Apixaban (Eliquis)* [16]

Data from large clinical trials pointed to the discontinuation of apixaban for 2–5 days to allow surgery or invasive procedure.

The manufacturer's recommendation is to discontinue for over 24 hours and 48 hours for low and high bleeding risks, respectively.

There is no fixed protocol for pre-procedure discontinuation.

Discontinuation		*Timing (hours)*	*Timing (hours)*
Creatinine clearance ml/min	*Half-life in hours*	*Low bleeding risk*	*Moderate and high bleeding risk*
> = 30	8	24	48
<30		48	72
Restarting	*Dose (mg)*	*Timing (hours)*	
Minor procedures	2.5–5	6–12	
Major procedures	2.5–5	Adequate hemostasis – 48	

In patients with high thrombosis risk, it is appropriate to consider prophylactic doses of anticoagulation with LMWH before reintroducing full therapeutic dose of DOACs.

NB: Normal PT PTT do not exclude a significant concentration of apixaban in the circulation.

- If the anticoagulant effect cannot be ruled out completely, neuraxial or celiac anesthesia should be avoided.

Emergency Surgery: Few data support the use of PCC in the management of emergency surgery, and it should not be used routinely.

Tranexamic acid is likely to reduce bleeding in patients who have a residual anticoagulant effect and can be used.

Andexanet alfa: No data in patients undergoing surgery but promising data on reversal. When available, it should be used for reversal prior to emergency invasive procedures and surgery where bleeding risks are considered significant (see Chap. 12 for full details) [15].

Switching from or to Parenteral Anticoagulants

- In general, switching treatment from parenteral anticoagulants to apixaban (or vice versa) can be done at the next scheduled dose.

Switching from Vitamin K Antagonists (VKA) to Apixaban

- When switching patients from a VKA, such as warfarin, to apixaban, discontinue warfarin or other VKA therapy.
- Start apixaban when the international normalized ratio (INR) is below 2.0.

Switching from Apixaban to VKA

As with any short-acting anticoagulant, there is a potential for inadequate anticoagulation when transitioning from apixaban to a VKA. It is important to maintain an adequate level of anticoagulation when transitioning patients from one anticoagulant to another.

- Apixaban should be continued concurrently with the VKA until the INR is ≥2.0.
- For the first 2 days of the conversion period, the VKA can be given in the usual starting doses without INR testing.
- Thereafter, while on concomitant therapy, the INR should be tested just prior to the next dose of apixaban, as appropriate.
- The medication can be discontinued once the INR is >2.0.
- Once discontinued, INR testing may be done at least 12 hours after the last dose and should then reliably reflect the anticoagulant effect of the VKA.

8. Edoxaban (Lixiana) [17, 18]

Edoxaban is excreted only 50% by the kidney.

The manufacturer's recommendation is to discontinue the medication for at least 24 hours before the procedure.

There is no fixed protocol for pre-procedure discontinuation.

Discontinuation		*Timing (hours)*	*Timing (hours)*
Creatinine clearance ml/min	*Half-life in hours*	*Low bleeding risk*	*Moderate and high bleeding risk*
> = 30	10–14	24	48
<30		48	72
Restarting	*Dose (mg)*	*Timing (hours)*	
Minor procedures	30–60	Evening of procedure	
Major procedures	30–60	Adequate hemostasis – 24	

The usual restarting dose is 60 mg. Dose reduction to 30 mg is recommended in the presence of kidney impairment, a low body weight of less than 60 kg, or the concomitant intake of P-gp inhibitors.

In patients with high thrombosis risk, it is appropriate to consider prophylactic doses of anticoagulation with LMWH before reintroducing full therapeutic dose of DOACs.

NB: Normal PT PTT do not exclude a significant concentration of apixaban in the circulation.

- If the anticoagulant effect cannot be ruled out completely, neuraxial or celiac anesthesia should be avoided.

Emergency Surgery: Few data support the use of PCC in the management of emergency surgery, and it should not be used routinely.

Tranexamic acid is likely to reduce bleeding in patients who have a residual anticoagulant effect and can be used.

Andexanet alfa: No data on edoxaban and in patients undergoing surgery but promising data on reversal. When available, it should be used for reversal prior to emergency invasive procedures and surgery where bleeding risks are considered significant (see Chap. 13 for full details) [15].

From Unfractionated Heparin
- Stop the infusion and start edoxaban 4 hours later.

Switching from Warfarin to Edoxaban
- Discontinue warfarin and start edoxaban when INR is 2.5 or less.
- From non-warfarin anticoagulant (oral or parenteral, e.g., LMWH, rivaroxaban, dabigatran, apixaban) to edoxaban: start edoxaban at the time the next scheduled dose of the non-warfarin anticoagulant was to be administered.

From Edoxaban to Warfarin
- Start warfarin and administer edoxaban at half the prescribed dose (either 30 mg or 15 mg for those on a reduced dose for one or more of the following: CrCl 15–50 mL/min; <60 kg; use with P-gp inhibitor except amiodarone or verapamil).
- Once INR is 2 or greater, discontinue edoxaban. NOTE: Edoxaban can affect INR; therefore, when starting warfarin, INR may be unreliable. If possible, checking INR just prior to next edoxaban dose may better reflect the anticoagulant effect of warfarin.

From Edoxaban to Non-warfarin Anticoagulants (Oral or Parenteral) (e.g., LMWH, Apixaban, Rivaroxaban, Dabigatran)
- Discontinue edoxaban and give first dose of non-warfarin anticoagulant at the time the next dose of edoxaban is due.

Antiplatelet Agents [19–23]

Acetylsalicylic Acid (Aspirin) (ASA) [19–23]

Aspirin irreversibly inhibits COX-1 to decrease thromboxane and inhibits platelets for 7–10 days. Slow recovery of overall platelet function occurs at 10% per day due to new platelet formation. The doses required for anti-inflammatory effects through COX-2 inhibition are much higher than the doses required for antiplatelet effects (75–100 mg/day). Aspirin has a half-life of 15–20 minutes.

The only randomized trial in noncardiac surgery to assess perioperative antiplatelet management is the Perioperative Ischemic Evaluation-2 (POISE-2) trial. Data from POISE-2 have demonstrated that continuing ASA perioperatively has no protective effect on MI or all-cause mortality (HR 0.99, 95% CI 0.86–1.15) but does increase the risk of major bleeding (HR 1.23, 95% CI 1.01–1.49). However, patients with recent coronary artery stenting or those undergoing carotid endarterectomy were excluded, and only 4% of patients overall had a coronary stent. Consequently, to minimize bleeding risks, ASA is typically withheld for 3 days preoperatively and restarted after 8–10 days postoperatively.

In patients with recent coronary artery stenting (typically 1 month for bare-metal stents and 3 months for drug-eluting stents), elective surgeries should be delayed as interruption of dual antiplatelet therapy in this setting has a high risk of stent thrombosis. Aspirin should be continued in post-PCI patients having noncardiac surgery, while $P2Y_{12}$ therapy is interrupted.

If the patient is not already on ASA, it should not be initiated for the prevention of perioperative cardiac events.

Discontinuation	*Timing*
Undergoing carotid endarterectomy	Continue perioperatively
Elective noncardiac surgery with previous BMS or DES coronary artery stents	Continue perioperatively
Elective noncardiac surgery without previous coronary artery stents	3 days[a]
ACS requiring CABG	Continue perioperatively
Restarting	*Timing*
Major noncardiac surgery	8–10 days[b]

[a]Perioperative ASA continuation may be reasonable to prevent local thrombosis for some surgical interventions (e.g., free flap, acute limb ischemia)
[b]When a patient suffers an MI or thrombotic event postoperatively in the absence of bleeding, there might be a net benefit to restarting ASA sooner after surgery

Emergency Surgery: In emergent surgeries, platelet transfusion can be given to counteract the effect of ASA on thrombocytes, although newer literature suggests this does not reverse the effects of other antiplatelet agents due to their longer half-lives. Platelets should be transfused at least 2 hours after the last dose of ASA. *The indications for restoring platelet function in the setting of bleeding are controversial, and the net benefit is uncertain.* Platelet transfusions can put the patient at risk for stent thrombosis, and a risk–benefit analysis should be performed prior to making this decision.

Intravenous desmopressin has been shown to restore platelet activity in ASA-induced platelet dysfunction, but little clinical data is available.

Clopidogrel (Plavix) [19, 20]

Clopidogrel specifically and irreversibly inhibits the $P2Y_{12}$ subtype of ADP receptor, leading to irreversible platelet inhibition. Clopivdogrel is a prodrug requiring activation by hepatic P450 enzymes, and there exists significant interpatient variability of antiplatelet activity. Clopidogrel is eliminated in both the feces and urine

and does not require dose adjustment in hepatic or renal disease. Peak plasma concentration is reached 2 hours after oral ingestion. Clopidogrel has a half-life of 7–9 hours.

Clopidogrel is typically used in addition to ASA after PCI, but may be seen as monotherapy in the setting of cerebrovascular disease.

Discontinuation	*Timing*
Elective noncardiac surgery with previous BMS coronary artery stent, less than 1 month ago	*Delay surgery*
Elective noncardiac surgery with previous DES coronary artery stent, less than 3 months ago	*Delay surgery*
Semi-urgent noncardiac surgery with previous DES coronary artery stent, less than 1 month ago	*Delay surgery*
Elective noncardiac surgery with previous BMS coronary artery stent, more than 1 month ago	5–7 days
Elective noncardiac surgery with previous DES coronary artery stent, more than 3 months ago	5–7 days
Semi-urgent noncardiac surgery with previous DES coronary artery stent, more than 1 month ago	5–7 days
ACS requiring semi-urgent CABG	Minimum 48–72 hours
ACS requiring elective CABG	5 days
Minor procedures with low risk of bleeding	Continue perioperatively[a]
Restarting	*Timing*
Noncardiac surgery	Restart maintenance dose after surgery, as soon as it is deemed safe by the surgeon

[a]The risk and consequences of perioperative bleeding will vary considerably depending on the type of surgery performed. Some minor surgical procedures carry a low risk of bleeding, whereas others a very high risk of bleeding. For example, some dental, ophthalmological, and endoscopic procedures carry a low risk of bleeding and can be performed without stopping antiplatelet therapy

Emergency Surgery: In emergent surgeries, platelet transfusion can be given to counteract the effect of clopidogrel on thrombocytes, although newer literature suggests this does not reverse the effects of non-ASA antiplatelet agents due to their longer half-lives. Platelets should be transfused at least 12–24 hours after the last dose of clopidogrel. *The indications for restoring platelet function in the setting of bleeding are controversial.* Platelet transfusions can put the patient at risk for stent thrombosis, and a risk–benefit analysis should be performed prior to making this decision.

Bridging with unfractionated or low-molecular-weight heparin has relatively minor effects on platelets and is not recommended. Bridging with short-acting glycoprotein IIb/IIIa inhibitors can be considered in the period of ADP receptor antagonist withdrawal, but not mentioned in the latest CCS guidelines.

Ticagrelor (Brilinta) [24]

Unlike clopidogrel and prasugrel, ticagrelor is a reversible noncompetitive antagonist of the $P2Y_{12}$ subtype of ADP receptor, leading to reversible platelet inhibition. It has a more rapid onset of action and is more potent than either clopidogrel or prasugrel. Ticagrelor is eliminated in the feces. Ticagrelor requires dose adjustment in hepatic dysfunction, but not in renal dysfunction. Ticagrelor has a half-life of 7–9 hours.

Discontinuation	*Timing*
Elective noncardiac surgery with previous BMS coronary artery stent, less than 1 month ago	*Delay surgery*
Elective noncardiac surgery with previous DES coronary artery stent, less than 3 months ago	*Delay surgery*
Semi-urgent noncardiac surgery with previous DES coronary artery stent, less than 1 month ago	*Delay surgery*
Elective noncardiac surgery with previous BMS coronary artery stent, more than 1 month ago	5–7 days
Elective noncardiac surgery with previous DES coronary artery stent, more than 3 months ago	5–7 days
Semi-urgent noncardiac surgery with previous DES coronary artery stent, more than 1 month ago	5–7 days
ACS requiring semi-urgent CABG	Minimum 48–72 hours
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Noncardiac surgery	Restart maintenance dose after surgery, as soon as it is deemed safe by the surgeon

[a]The risk and consequences of perioperative bleeding will vary considerably depending on the type of surgery performed. Some minor surgical procedures carry a low risk of bleeding, whereas others a very high risk of bleeding. For example, some dental, ophthalmological, and endoscopic procedures carry a low risk of bleeding and can be performed without stopping antiplatelet therapy

Emergency Surgery: In emergent surgeries, platelet transfusion can be given to counteract the effect of ASA and clopidogrel on thrombocytes, although newer literature suggests this does not reverse the effects of non-ASA antiplatelet agents due to their longer half-lives. Platelets should be transfused at least 12–24 hours after the last dose of ticagrelor. *The indications for restoring platelet function in the setting of bleeding are controversial.* Platelet transfusions can put the patient at risk for stent thrombosis, and a risk–benefit analysis should be performed prior to making this decision.

Bridging with unfractionated or low-molecular-weight heparin has relatively minor effects on platelets and is not recommended. Bridging with short-acting glycoprotein IIb/IIIa inhibitors can be considered in the period of ADP receptor antagonist withdrawal, but not mentioned in the latest CCS guidelines [19].

Prasugrel (Effient) [25]

Prasugrel specifically and irreversibly inhibits the $P2Y_{12}$ subtype of ADP receptor, leading to irreversible platelet inhibition. No dose adjustment is required for hepatic or renal dysfunction. Peak plasma concentration is reached 30 minutes after oral ingestion. Prasugrel is faster and more effective in achieving platelet inhibition than clopidogrel. The FDA recommends lower doses of prasugrel be used in patients ≥75 years of age, weighing <60 kg, or with a previous history of TIAs. Prasugrel has a half-life of 7 hours.

Discontinuation	*Timing*
Elective noncardiac surgery with previous BMS coronary artery stent, less than 1 month ago	*Delay surgery*
Elective noncardiac surgery with previous DES coronary artery stent, less than 3 months ago	*Delay surgery*
Semi-urgent noncardiac surgery with previous DES coronary artery stent, less than 1 month ago	*Delay surgery*
Elective noncardiac surgery with previous BMS coronary artery stent, more than 1 month ago	7–10 days
Elective noncardiac surgery with previous DES coronary artery stent, more than 3 months ago	7–10 days
Semi-urgent noncardiac surgery with previous DES coronary artery stent, more than 1 month ago	7–10 days
ACS requiring semi-urgent CABG	5 days
ACS requiring elective CABG	7 days
Minor procedures with low risk of bleeding	Continue perioperatively[a]
Restarting	*Timing*
Noncardiac surgery	Restart maintenance dose after surgery, as soon as it is deemed safe by the surgeon

[a]The risk and consequences of perioperative bleeding will vary considerably depending on the type of surgery performed. Some minor surgical procedures carry a low risk of bleeding, whereas others a very high risk of bleeding. For example, some dental, ophthalmological, and endoscopic procedures carry a low risk of bleeding and can be performed without stopping antiplatelet therapy

Emergency Surgery: In emergent surgeries, platelet transfusion can be given to counteract the effect of ASA and clopidogrel on thrombocytes, although newer literature suggests this does not reverse the effects of non-ASA antiplatelet agents due to their longer half-lives. Platelets should be transfused at least 12–24 hours after the last dose of prasugrel. *The indications for restoring platelet function in the setting of bleeding are controversial.* Platelet transfusions can put the patient at risk for stent thrombosis, and a risk–benefit analysis should be performed prior to making this decision.

Bridging with unfractionated or low-molecular-weight heparin has relatively minor effects on platelets and is not recommended. Bridging with short-acting glycoprotein IIb/IIIa inhibitors can be considered in the period of ADP receptor antagonist withdrawal, but not mentioned in the latest CCS guidelines [19].

References

1. Peri-operative management of patients who are receiving warfarin © 2013 Thrombosis Canada, 2013. http://www.thrombosiscanada.ca/guides/pdfs/Warfarin_perioperative_management.pdf.
2. Warfarin: Peri-operative management. © 2016 Thrombosis Canada http://thrombosiscanada.ca/wp-content/uploads/2016/09/14_Warfarin-Peri-Operative_2016Sept15-2.pdf.
3. Guideline for the management of oral anticoagulation before and after elective surgery or procedures. http://anesthesiology.queensu.ca/assets/Clinical_Policies/Guidelines_for_Bridging_Anticoagulation_-_Oct_2013.pdf.
4. Rechenmacher SJ, Fang JC. Bridging anticoagulation: primum non nocere. J Am Coll Cardiol. 2015;66(12):1392–403.
5. Doherty JU, Gluckman TJ, Hucker WJ, Januzzi JL Jr, Ortel TL, Saxonhouse SJ, Spinler SA. A report of the American College of cardiology clinical expert consensus document task force 2017 ACC expert consensus decision pathway for periprocedural management of anticoagulation in patients with nonvalvular atrial fibrillation. J Am Coll Cardiol. 2017;69(7):871–98.
6. Greinacher A, Volpel H, Janssens U, et al. Recombinant hirudin (lepirudin) provides safe and effective anticoagulation in patients with heparin-induced thrombocytopenia. Circulation. 1999;99:73–80. [PubMed 9884382].
7. Messmore HL, Jeske WP, Wehmacher WH, et al. Benefit-risk assessment of treatments for heparin-induced thrombocytopenia. Drug Saf. 2003;26:625–41.
8. Ansara AJ, Arif S, Warhurst RD. Weight based argatroban dosing nomogram for treatment of heparin-induced thrombocytopenia. Ann Pharmacother. 2009;43:9–18.
9. Argatroban package insert, GlaxoSmithKline September, 2009.
10. Argatroban, Pfizer Canada, revision June 25, 2013.
11. PRODUCT MONOGRAPH Pr PRADAXA® Dabigatran Etexilate Capsules 75 mg, 110 mg and 150 mg Dabigatran Etexilate, (as Dabigatran Etexilate Mesilate) Anticoagulant Boehringer