Perioperative management of antithrombotic therapies

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Purpose of review
Perioperative coagulation management is becoming increasingly frequent in the daily routine of the anesthesiologist and with the plethora of new substances on the market also increasingly complex. The perioperative setting poses unique challenges requiring an individualized evaluation and management of antithrombotic therapy. This review shall summarize the newest developments in this domain.

Recent findings
New data in patients with atrial fibrillation have led to a paradigm change in the perioperative management of antithrombotics. The role of bridging therapy has been downgraded in the guidelines, which only foresee bridging in patients with high thromboembolic risk. Furthermore, direct oral anticoagulants are now a cornerstone in antithrombotic therapy, calling for specific perioperative management. The new reversal agents idarucizumab, and potentially in the future andexanet alfa and ciraparantag, will play an increasingly important role in the treatment of major bleeding in this group of patients.

Summary
With the new evidence and treatment options available, perioperative coagulation management is experiencing a Renaissance, opening many interesting new doors, but also presenting the clinician with new challenges.

Keywords
bridging management, direct oral anticoagulants and reversal agents, new antiplatelets

The introduction of new antithrombotic agents has led to a paradigm change in the management of antithrombotic therapy (AT). With the increasing polymorbidity of patients and the widespread adoption of new antithrombotic agents, anyone shaping the perioperative care of patients must be familiar with the pharmacology, management, and possibilities for reversal of these agents. In this review, we summarize the new developments in the domain of antithrombotic agents.

THE YIN AND YANG OF PERIOPERATIVE COAGULATION MANAGEMENT

The use of AT necessitates a risk-benefit analysis weighing the risk of thrombotic events against the risk of bleeding complications; however, the perioperative setting presents unique challenges in this respect. Surgery causes a systemic inflammatory response with activation of the coagulation system, disturbing preoperative homeostasis and predisposing patients to thrombotic complications. On the other hand, AT increases the risk of bleeding. The goal of perioperative coagulation management is to find the optimum balance between the risk of

thrombosis and bleeding while keeping perturbations of the coagulation system to a minimum. The danger of overzealous coagulation management is the development of an ever-increasing pendulum between bleeding and thrombotic complications, with each swing necessitating even more drastic measures and pushing the pendulum further in the other direction.

AGENTS AFFECTING PLATELET ACTIVATION AND AGGREGATION

Besides the commonly used irreversible COX1/2-inhibitor aspirin, $P2Y_{12}$-receptor antagonists ($P2Y_{12}$-RA) act through inhibition of the $P2Y_{12}$-receptor. The prodrugs clopidogrel and prasugrel

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KEY POINTS

- Every patient requires an individualized evaluation of their perioperative thrombotic and bleeding risk.

- Bridging therapy requires a clear indication and is not supported in patients with low or intermediate thromboembolic risk, or in patients on direct oral anticoagulants.

- Dabigatran can be reversed selectively with idarucizumab and further reversal agents for anticoagulants are on the horizon.

are thienopyridines requiring activation by cytochrome-P450 (CYP) 3A4/5. Both are established in dual antiplatelet therapy (DAPT) together with aspirin for treatment of acute coronary syndrome (ACS) and/or patients undergoing percutaneous coronary intervention (PCI). Prasugrel leads to a greater reduction in ischemic events and stent-thrombosis than clopidogrel, however with an increased risk of bleeding [1,2]. Thirty percent of patients on clopidogrel show inadequate platelet inhibition because of genetic polymorphisms of CYP2C19 [3,4]. Following discontinuation, platelet function recovers after 5–10 days as a result of new platelet formation. In contrast, ticagrelor is a cyclopentyl-triazolopyrimidine not requiring activation. Platelet aggregation is blocked by reversible and noncompetitive antagonism of $P2Y_{12}$ receptors. Compared with clopidogrel, ticagrelor was not only shown to be advantageous in patients with ACS undergoing PCI but also in those treated noninvasively [5]. Ninety percent regeneration can be expected within 5 days [6]. Recently cangrelor, an intravenous nonthienopyridine which blocks the $P2Y_{12}$-receptor reversibly, has been approved. Its antiplatelet properties develop within minutes and last for up to one hour after cessation of infusion, after which the risk of major bleeding returns to baseline. These favorable pharmacological properties make cangrelor a promising agent for the perioperative management of patients requiring antiplatelet therapy [7–9].

GPIIb/IIIa inhibitors block adhesion of fibrinogen to activated platelets, preventing the formation of interplatelet bridges and are used as adjunctive therapy during acute PCI. Abciximab is a monoclonal antibody fragment with short onset of action, short plasma half-life, but long biological activity (>24 h). In contrast, tirofiban and eptifibatide are smaller molecules with reversible binding to the GPIIb/IIIa receptor. Their effect on platelet aggregation disappears within hours after cessation of infusion [10–12] (Table 1).

Protease-activated-receptor-1 antagonists, a new class of antiplatelets not yet licensed, block thrombin-induced platelet activation without interfering with plasmatic coagulation [15]. Voraxapar and atoxapar cause prolonged inhibition of platelet function, lasting up to four weeks after discontinuation [16]. A phase-4 trial investigating voraxapar in postmyocardial infarction patients is underway.

PERIOPERATIVE MANAGEMENT OF DUAL ANTIPLATELET THERAPY

Antiplatelet drugs are mainstays in the primary and secondary prevention of thrombotic events such as stroke, myocardial infarction (MI), ACS or particularly but not exclusively after PCI. DAPT leads to a clear reduction of stent-thrombosis after PCI [17–19], with discontinuation being associated with increased risk for stent-thrombosis, MI, and death [20■,21–23]. Current guidelines of the *American Heart Association* and the *American College of Cardiology* recommend DAPT for 12 months in patients with ACS [24■] (Table 2).

Perioperative management of antiplatelet agents is challenging. In elective surgery with intermediate to high bleeding risk necessitating discontinuation of AT, the risk of cardiac events must be

Table 1. Characteristics of antiplatelet agents

	Mechanism of action/target molecule	Route of administration	Discontinuation before surgery
Aspirin	Irreversible inhibition of COX-1 and COX-2	Oral/i.v. bolus	0–5 days
Clopidogrel	Irreversible inhibition of $P2Y_{12}$ ADP receptor	Oral	7 days
Prasugrel	Irreversible inhibition of $P2Y_{12}$ ADP receptor	Oral	10 days
Ticagrelor	Reversible inhibition of $P2Y_{12}$ ADP receptor	Oral	5–7 days
Cangrelor	Reversible inhibition of $P2Y_{12}$ ADP receptor	i.v. continuous	1–6 h
Abciximab	Reversible inhibition of GP IIb/IIIa receptor	i.v. bolus + continuous	48 h
Eptifibatide	Reversible inhibition of GP IIb/IIIa receptor	i.v. bolus + continuous	8 h
Tirofiban	Reversible inhibition of GP IIb/IIIa receptor	i.v. bolus + continuous	8 h

Adapted with permission from [3,13,14].

Table 2. Treatment recommendations for antiplatelet agents

Condition	Treatment recommendations
Primary prevention	Aspirin in general not recommended
ACS without PCI	Aspirin lifelong + ticagrelor (or clopidogrel) ≥ 12 months
ACS with PCI (DES or BMS)	Aspirin lifelong + prasugrel or ticagrelor (or clopidogrel) ≥ 12 months
SIHD after DES	Aspirin lifelong + clopidogrel ≥ 6 months
SIHD after BMS	Aspirin lifelong + clopidogrel ≥ 1 month
Recent stroke	Aspirin and/or clopidogrel
Past stroke	Aspirin (clopidogrel)
PVD	Aspirin (clopidogrel)

ACS, acute coronary syndrome; BMS, bare metal stent; DES, drug eluting stent; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease; SIHD, stable ischemic heart disease.
Modified from Levine et al. [24▪] and Koenig-Oberhuber et al. [25▪].

evaluated [25▪]. With high cardiovascular risk, DAPT should be continued and surgery rescheduled if possible [13,26,27]. If cardiovascular risk is low, AT should be discontinued in a timely fashion [28–30]. Due to their long biologic half-life, antiplatelet agents should be discontinued 7–10 days before intervention [14,31,32]. If bleeding risk is low, treatment with antiplatelet agents can be continued [33,34]. However, thrombotic risk depends more on the underlying condition of former PCI (ACS versus stable ischemic heart disease) as well as the time interval between PCI and surgery than on the presence of DAPT per se [35▪▪]. Accordingly, DAPT does not protect against cardiovascular events in high-risk situations [36].

Antiplatelet agents should be restarted as soon as possible, considering the pharmacology of the antiplatelet and the risk of postoperative bleeding [30,37]. In patients with high risk for cardiovascular events and conditions not allowing postponement of surgery, the bridging of the oral P2Y$_{12}$ receptor inhibitor with short-acting intravenous agents like eptifibate and tirofiban must be considered [38]. In bridging thienopyridines prior to cardiac surgery, cangrelor led to superior platelet inhibition compared to placebo [7]. When bridging DAPT, aspirin should be continued and the second long-acting antiplatelet agent paused 5–7 days preoperatively. The short-acting agent should be initiated within 72 h of discontinuation of the long-acting agent and maintained until 4–6 h preoperatively (1 h for cangrelor). In general, DAPT should be restarted as soon as possible, considering the postoperative bleeding risk and the presence of neuraxial or nerve catheters. Due to lack of evidence of any efficacy, heparinoids

have no place in the bridging of DAPT. The role of platelet function monitoring in guiding timing of discontinuation of antiplatelet therapy remains unclear [39].

Not only in patients treated with DAPT, but also in those on aspirin monotherapy, ischemic versus bleeding risk has to be considered. If the bleeding risk is high and/or the ischemic risk low to intermediate, aspirin should be stopped, as the recently published POISE-2 trial showed no benefit but increased risk of bleeding in this group of patients [28].

Lastly, in patients suffering a postoperative ACS necessitating DAPT, any indwelling neuraxial catheters must be removed prior to commencement of therapy. Alternatively, the use of cangerelor or a short-acting GPIIb/IIIa inhibitor can be considered. Aspirin can be given in most circumstances without delay.

NEW PLASMATIC ANTICOAGULANTS

The direct oral anticoagulant (DOAC) dabigatran-etexilate is an oral, reversible, direct thrombin-inhibitor. Its anticoagulant effect peaks after 2–3 h, lasting for 12–24 h. Elimination depends strongly on renal function. Normalized INR/PT do not rule-out the presence of the agent. Normal thrombin time indicates lack of clinically relevant dabigatran activity [40–43].

Other DOACs include the direct factor-Xa-inhibitors rivaroxaban, apixaban, and edoxaban. Monitoring of anti-Xa levels predictably detects anticoagulant effect. Rivaroxaban, edoxaban, and apixaban are only partially renally eliminated.

DOACS are licensed for prevention of ischemic events in patients with nonvalvular atrial fibrillation, and for the treatment of deep vein thrombosis and pulmonary embolism. Some substances are also approved for prevention of thromboembolism after major orthopedic surgery (not all substances in all countries). The main advantage of DOACs compared with vitamin K-antagonists (VKAs) in patients with atrial fibrillation is the reduction of the occurrence of intracranial bleeding [44]. Accordingly, DOACs are now the recommended first-line treatment in this group of patients [45,46] (Table 3).

PERIOPERATIVE MANAGEMENT OF PATIENTS UNDER DIRECT ORAL ANTICOAGULANTS OR VITAMIN K-ANTAGONISTS

As in patients on antiplatelet therapy, the management of patients on DOACs or VKA requires consideration of the individual risk of thrombotic

Table 3. Characteristics of anticoagulants

	Mechanism of action/target molecule	Route of administration	Renal elimination	Approximate elimination half-life	Duration of action since last intake
Warfarin	Vitamin-K antagonist	Oral	No	35–45 h	2–4 days
Phenprocoumon	Vitamin-K antagonist	Oral	No	100–270 h	5–7 days
Dabigatran	Direct IIa inhibition	Oral	80%	12–17 h	48 h
Apixaban	Direct Xa inhibition	Oral	25%	8–15 h	24 h
Edoxaban	Direct Xa inhibition	Oral	50%	10–14 h	24 h
Rivaroxaban	Direct Xa inhibition	Oral	33% unchanged	7–12 h	24 h
UFH	Indirect inhibition Xa = IIa	s.c./i.v.	No	1–3 h	Dose dependent
LMWH	Indirect inhibition Xa > IIa	s.c.	Yes, drug dependent	4–8 h	Dose dependent
Fondaparinux	Indirect Xa inhibition	s.c.	100%	18 h	48–96 h
Argatroban	Direct IIa inhibition	i.v.	No	50 min	2–4 h
Bivalirudin	Direct IIa inhibition	i.v.	20%	25 min	1 h

LMWH, low molecular weight heparin; UFH, unfractionated heparin.
Adapted with permission from [40,44,47].

events weighted against the bleeding risk of the planned procedure.

In patients with atrial fibrillation, the CHA_2DS_2-VASc score can aid in estimating thromboembolic risk [48,49]. Importantly, this score has not been validated for prediction of thrombotic complications in the perioperative setting [48,50,51]. In patients with past venous thromboembolic events, the time elapsed since the event is the most important prognostic factor, with the highest risk for recurrence in the first 3 months [52■■]. The thromboembolic risk of patients with mechanical heart valves depends on the position of the valve, the mitral position bearing a particularly high thromboembolic risk. The risk of patients with mechanical valves in the aortic position is only high in the presence of additional risk factors, for example, atrial fibrillation, reduced ejection fraction, or history of thrombotic events. In addition, any caged-ball or tilting-disc mechanical heart valve carries a high thromboembolic risk (Table 4).

Table 4. Conditions conferring high thromboembolic risk

High thromboembolic risk
AF and recent stroke or CHA_2DS_2-VASc Score >6
Recent history of deep vein thrombosis (<3 months)
Mechanical mitral valve prosthesis
Mechanical aortic valve prosthesis and additional risk factors (AF, history of thromboembolic event, reduced ejection fraction)
Caged ball or tilting-disc cardiac valves

AF, atrial fibrillation; CHA2-DS2-VASc, congestive heart failure, hypertension, age >75 years (doubled), diabetes mellitus, prior stroke or transient ischemic attack or thromboembolism (doubled), vascular disease, age 65–74 years, sex category.
Adapted with permission from [48,52■■].

As already discussed, the perioperative management of patients on VKA or DOACs depends on the peri-interventional risk of bleeding and the thromboembolic risk. If the risk of bleeding is low (i.e., for most dental procedures, or for implantation of cardiac pacemakers or internal defibrillators) discontinuation of AT is unnecessary. In patients with higher bleeding risk but low to intermediate thromboembolic risk, temporary discontinuation of anticoagulation without bridging is the correct approach [53,54■]. In this group of patients, bridging does not prevent thromboembolic events but increases the risk of bleeding [53]. Bridging is only indicated in patients with high thrombotic risk treated with VKA (see in the succeeding text).

MANAGEMENT OF DIRECT ORAL ANTICOAGULANT

Discontinuation of DOACs should be timed based on their elimination half-life and relevant comorbidities such as renal impairment [47,55]. An acceptable compromise between risk of bleeding and of thrombotic events may be achieved by waiting approximately two to three half-lives [56]. If bleeding risk is increased or elimination impaired, the duration of discontinuation should be extended. Low-risk surgery does not generally require discontinuation of DOACs. With increased bleeding risk, DOACs should be discontinued in a timely fashion based on their pharmacology. In case of emergent surgery, accurate history of intake and dosage needs to be obtained, and renal function evaluated to estimate the pharmacological activity of DOACs [57■]. Generally, delaying surgery for ≥24 h is advisable (Table 5).

Table 5. Timing of preoperative interruption of direct oral anticoagulants

	eGFR (ml/min)	Bleeding risk *low to moderate* (h)	Bleeding risk *high* (h)
Dabigatran	≥50	≥24	48
	30–50	48	72
	<30	≥72	≥120
Factor Xa-inhibitors (rivaroxaban, apixaban, edoxaban)	≥30	≥24	48
	<30	≥72	≥72

eGFR, estimated glomerular filtration rate.
Adapted with permission from [47,55].

Laboratory testing of DOAC activity is feasible, but rarely helpful. Laboratory measurements to assess the activity of DOACs depend on the specific agent. In general, the correlation of the commonly used coagulation tests with DOAC activity is low. Furthermore, the interpretation of plasma levels of DOACs is difficult due to a wide range of and lack of 'safe' lower limits [58■]. In patients treated with factor-Xa-inhibitors, measurement of anti-Xa using drug-specific calibrators has high sensitivity [59].

MANAGEMENT OF VITAMIN K-ANTAGONISTS

In contrast to DOAC, in high-risk patients undergoing procedures with moderate to high bleeding risk and taking VKA, bridging is recommended. Conditions conferring high thromboembolic risk are summarized in Table 4.

These patients should be bridged with short-acting anticoagulants, for example, low molecular weight heparin (LMWH), while ensuring adequate intervals to surgery, particularly in renal insufficiency. Phenprocoumon should be stopped 5–8 days and warfarin 3 days preoperatively [44]. Low dose vitamin K substitution is indicated if preoperative duration of discontinuation is too short or INR still elevated.

Bridging with LMWH should be started as soon as the INR has dropped under 2 and discontinued 24 (-36) hours preoperatively. If surgical or anesthetic bleeding risk is elevated, an anti-Xa level should be determined. If estimated glomerular filtration rate is under 30 ml/h, bridging should be performed with unfractionated heparin and discontinued 4 h preoperatively. A normal aPTT or prothrombinase-induced coagulation time confirms normalization of the coagulatory state [60–63]. Postoperatively, treatment with LMWH or unfractionated heparin is restarted at the earliest 6 h following end of surgery, initially at a reduced dose which is then increased in a stepwise fashion based on clinical bleeding and risk of hemorrhage. If risk of bleeding is elevated, AT can be suspended for 1–2 days [49] to avoid postoperative hemorrhagic complications [64]. Once postoperative bleeding is unlikely, VKA or a DOAC can be restarted.

MANAGEMENT OF BLEEDING

Minor bleeding can be controlled with compression, sclerotherapy, or lowering of systolic blood pressure; however, resumption of AT should be postponed until bleeding has stopped. Acidosis, hypothermia, and hypocalcemia should be avoided and corrected.

ANTIPLATELET AGENTS

Major hemorrhage in patients taking antiplatelet agents can be managed by the administration of tranexamic acid and fibrinogen. Replacement of coagulation factor XIII and von Willebrand factor can also be considered, however data are lacking. Some centers use desmopressin. If hemostasis cannot be achieved, platelets must be transfused.

REVERSAL OF DIRECT ORAL ANTICOAGULANTS

Until recently, there were no specific reversal agents for DOACs. A just-released, cutting-edge scientific statement and review by the *American Heart Association* summarizes the pharmacology, laboratory testing, indications, and perioperative management of DOACs, with an emphasis on the management of specific bleeding complications, including intracranial hemorrhage (traumatic and nontraumatic), traumatic hemorrhage, and gastrointestinal bleeding [65■■]. Within 2–3 h of DOAC intake, activated charcoal is recommended, and for dabigatran hemofiltration can be considered. In case of severe hemorrhage, the administration of prothrombin complex concentrates is recommended. Recently, idarucizumab was approved for reversal of dabigatran.

Idarucizumab is a monoclonal antidabigatran antibody fragment with a higher affinity for dabigatran than thrombin, thereby neutralizing its anticoagulant effect. Peak plasma concentrations are reached within five minutes of infusion, lasting 24 h [66–68]. Ecarin clotting time and diluted thrombin time were normalized in 88–98% of patients within several minutes, without any detectable tendency to thrombotic adverse effects [69].

Specific agents for antagonizing the effect of Xa-inhibitors are currently under investigation

but are not yet licensed. Andexanet alfa is a recombinant and inactive factor-Xa receptor which binds free factor-Xa-inhibitors, preventing their inhibition of factor-Xa. Therefore, andexanet alfa is capable of reversing the anticoagulant effect of apixaban, rivaroxaban, edoxaban and LMWH. Normalization of anti-Xa activity confirms the antagonized effect of factor-Xa-inhibitors [70]. Phase II studies showed a neutralization of factor-Xa inhibition after 2–5 min in participants treated with rivaroxaban respectively apixaban, without an increase of thrombotic events [71]. However, 18% of patients enrolled in a phase III study sustained a thrombotic event after treatment with andexanet alfa, albeit without thrombotic prophylaxis postintervention [72■].

Ciraparantag, formerly aripazine (PER997), strives to be a universal antidote, but is still under investigation. It is a small, water-soluble, synthetic molecule, which prevents heparins from binding to their target molecules factor-II and Xa, and also inhibits DOACs [73–74]. Phase II studies have shown a reversal of anticoagulation in patients treated with edoxaban, devoid of thrombotic complications [75■■].

CONCLUSION

Balancing the perioperative risk of major bleeding with that of thrombotic events in increasingly polymorbid patients can be a challenge, making an interdisciplinary, holistic approach to perioperative coagulation management more important than ever before. With the undeniable convenience of DOACs comes a price—namely the need for new ways of monitoring of their therapeutic effect and new approaches to major bleeding in patients taking these substances.

Conflicts of interest
There are no conflicts of interest.

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