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New antiplatelet drugs and new oral anticoagulants

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Abstract

In our daily anaesthetic practice, we are confronted with an increasing number of patients treated with either antiplatelet or anticoagulant agents. During the last decade, changes have occurred that make the handling of antithrombotic medication a challenging part of anaesthetic perioperative management. In this review, the authors discuss the most important antiplatelet and anticoagulant drugs, the perioperative management, the handling of bleeding complications, and the interpretation of some laboratory analyses related to these agents.

Key words: antiplatelet agents; anticoagulants and haemorrhage; blood coagulation tests

Editor's key points

- Antiplatelet agents significantly increase the risk of bleeding in high-risk surgery.
- A number of anticoagulant drugs that either inactivate factor Xa or directly inhibit thrombin have become available in recent years.
- Current data do not support the use of periperative bridging therapy to cover the withdrawal of oral anticoagulants in patients at low risk of thromboembolism.
- Standard coagulation tests together with assay of factor Xa activity can be used to guide the managment of new anticoagulant drugs in the perioperative setting.

Arterial and venous thrombosis have an important impact on worldwide morbidity and mortality. Worldwide, >10 million deaths per annum are caused by arterial thrombotic events (ischaemic stroke, heart disease, and peripheral gangrene).¹² Platelets are the key prothrombotic element in arterial thrombosis, forming aggregates interconnected by fibrin. Antiplatelet treatment can counteract this process. For decades, aspirin has been the first-line antiplatelet drug of choice; recently, however, alternative antiplatelet substances have been introduced. Half a million deaths related to venous thromboembolism occur in the European Union per year.¹ Venous thrombi consist primarily of fibrin with some cells trapped in between. Anticoagulants are the drugs of choice to prevent or treat these conditions. For decades, warfarin and heparin were the mainstay of treatment, but the development of new anticoagulant drugs is constantly enlarging the pharmaceutical armamentarium.

In this review, the pharmacological properties of the new antiplatelet and new oral anticoagulant drugs, their usage in the perioperative setting, and the management of bleeding complications are discussed.

Antiplatelet agents (Table 1)

Platelet adhesion, activation, and aggregation are mediated by numerous adhesive proteins. The reactions of these proteins underpin the physiological responses to endothelial damage or rupture of atherosclerotic plaques. Amplification of these mechanisms and excessive thrombus formation endanger vascular flow, leading to occlusion of arteries and temporary or persistent ischaemia.³ Blocking such thrombus formation can prevent ischaemic events.

Treatment strategies for prevention or therapy of arterial thrombosis are changing constantly. The duration of treatment,

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Table 1 S <mark>ummary</mark> of the <mark>characterist</mark> i	ics of currently a	available antiplatele	t <mark>drug</mark> s					
Characteristic	Aspirin	Clopidogrel	Prasugrel	Ticagrelor	Cangrelor	Abciximab	Eptifibatide	Tirofiban
Route of administration	Oral once daily, (i.v.)	Oral once daily, (i.v. under investigation)	Oral once daily	Oral twice daily	i.v.	i.v.	i.v.	i.v.
Bioavailability	<mark>68%</mark>	50%	80%	36%				
Plasma peak concentration	3 <mark>0–4</mark> 0 min	$1 \mathrm{h}$	30 min	1.5 h	Seconds	Dose dependent	Dose dependent	Dose dependent
Time to plasma steady state		2–8 h	30 min to 4 h	30 min to 2 h	Seconds	Initial bolus and	Initial bolus and	Initial bolus and
						continuous	continuous	continuous
						application	application 4–6 h	application
								10 min
Plasma half-life	15–30 min	8 h	7 h	7 h	2–5 min	10-15 min	2.5 h	2 h
Plasma protein binding	Strong	Strong	Strong	Strong				
Time from last dose to offset	7–10 days	7–10 days	7–10 days	5 days	60 min	12 h	2–4 h	2-4 h
Reversibility of platelet inhibition	No	No	No	Yes	Yes	Yes	Yes	Yes
Recommended period of	0–5 days	7 days	10 days	7 days	1–6 h	48 h	8 h	8 h
discontinuation before surgical								
intervention (see Fig. 2)								

especially of dual or triple antiplatelet therapy, is highly dependent on the indication for treatment and, for percutaneous coronary intervention, the chemical constitution of any coronary stents (Table 2).⁴⁻⁶

Acetylsalicylic acid (aspirin)

For >50 yr, aspirin has been known to have antithrombotic and anti-inflammatory properties.⁷ Aspirin is a cyclooxygenase (COX) inhibitor that irreversibly inhibits COX1 and, in higher doses, COX2. Inhibition of COX1 is the main antithrombotic mechanism; the formation of prostaglandin H₂ is blocked, thus th<mark>romboxane A2 cannot be synthes</mark>ized. Thromboxane A2 activates platelets and stimulates their aggregation.⁸ The irreversibility of the effect of aspirin causes inhibition for the lifespan of a platelet (7–10 days). After the discontinuation of aspirin intake by a patient, their platelet function can be expected to increase b<mark>y 10–15% per day as</mark> a result of new platelet formation.⁸⁹ Aspirin is a key component of antiplatelet treatment to reduce death attributable to myocardial infarction or stroke.¹⁰ Bleeding risk is smaller with low doses (75–100 mg), which deliver an equivalent antithrombotic impact to higher doses (300 mg).¹¹ Drug interactions with aspirin are scarce, but <u>co-administration of</u> non-selective COX1 inhibitors may impair its efficacy. Owing to potential aggravation of ischaemic heart diseases attributable to selective COX2 inhibitors, these drugs should be avoided in patients with coronary artery disease. About one-third of patients receiving aspirin manifest treatment failure (thrombotic complication or death). Non-compliance is a substantial problem but difficult to quantify, with estimates ranging between 3 and 40%. Adverse events resulting from rebound thrombocyte activation after as<u>pirin withdraw</u>al are frequent. Some patients show biochemical resistance or high platelet reactivity, detected by platelet function assays. Diabetes, cardiac surgery, or acute coronary syndromes, all of which are associated with an inflammatory response, are associated with high platelet reactivity. In addition, genetic polymorphisms (COX1, COX2 alleles, platelet glycoprotein receptors), or increased platelet turnover (bone marrow diseases) can reduce the effect of aspirin. The fact that aspirin has only a single binding site and does not influence

Table 2 Treatment recommendations for antiplatelet agents.^{4–6} BMS, bare metal stent; DES, drug-eluting stent; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease

Condition	Treatment recommendations
Primary prevention	Aspirin
	Risk vs benefit evaluation
A <mark>cute coronary</mark>	PCI: aspirin lifelong plus ticagrelor,
<mark>syndrome</mark>	prasugrel, or clopidogre <mark>l ≥12 months</mark>
	Non-PCI: aspirin lifelong plus
	clopidogrel or ticagrelor ≥12 months
Stable angina or	Aspirin lifelong plus clopidogrel
former myocardial	BMS ≥1 month
infarction	<mark>DES ≥6 months</mark>
Recent s <mark>troke</mark>	Aspirin in high-risk situation plus
	clopidogrel 90 days
Past stroke	Aspirin <mark>or cl</mark> opidogrel
PVD	Aspirin or clopidogrel

other thrombocyte receptors results in aspirin having less antithrombotic effect than many other agents.⁹ ^{12 13}

P2Y₁₂ receptor antagonists

 $P2Y_{12}$ receptors are adenosine diphosphate (ADP) receptors expressed on the surface of thrombocytes, which can be blocked chemically. The overall effect of ADP on platelets, the change of conformation, emergence of pseudopodia, platelet aggregation, and interaction with other cellular or plasma components to promote coagulation, is reduced.¹⁴ Currently, clopidogrel, prasugrel, and ticagrelor are in use, and cangrelor has recently been licensed. Those substances are often prescribed in conjunction with aspirin, i.e. dual antiplatelet therapy (DAPT).¹⁵

Clopidogrel

Clopidogrel is a thienopyridine and a prodrug, of which 85% is hydrolysed to an inactive metabolite. The remaining part is activated via cytochromes P3A4/3A5 and P2B6/1A2/2C9/2C19.6. The active metabolite binds irreversibly to P2Y₁₂. For rapid onset of platelet inhibition, an initial loading dose is necessary.^{8 16} The pharmacological effect lasts for the <u>lifespan_</u>of the affected thrombocytes.¹⁵ The CYP450 dependency makes clopidogrel susceptible to drug interactions. Proton-pump inhibitors can also reduce its effect. No studies have been published proving sufficient evidence that any other drug interactions have any impact on its therapeutic effect.¹⁷ Thirty per cent of patients treated with clopidogrel do not show adequate platelet inhibition. Genetic polymorphisms (CYP2C19, P2Y₁₂ receptor) or altered intracellular signal pathways seem to be causative. Patients, especially if diabetic, may show high platelet reactivity even when receiving dual antiplatelet therapy. However, non-compliance, discontinuation of drug intake, or lack of access to clopidogrel are more frequent causes of inadequate platelet inhibition than pharmacological high platelet reactivity.¹⁵

Prasugrel

Prasugrel, a third-generation oral thienopyridine, is a prodrug, converted by CYP450 enzymes to its active metabolite. It binds irreversibly to P2Y₁₂, inhibiting platelet function for the lifespan of the affected platelets. Prasugrel shows a more reliable conversion to the active drug and <u>more rapid onset</u> of action than clopidogrel. Prasugrel produces <u>more effective platelet inhibition</u> than clopidogrel. Genetic polymorphisms (CYP2C9, CYP2C19) do not influence the metabolism of prasugrel. Drug interactions attributable to CYP-dependent conversion have not been described.⁹

Ticagrelor

Ticagrelor is an oral non-thienopyridine reversible P2Y₁₂-blocking agent. CYP3A4 and CYP3A5 are the enzymes involved in the hepatic metabolism of ticagrelor. One of its active metabolites also has an important platelet-inhibiting effect. Twenty-four hours after the last intake, the antiplatelet effect of ticagrelor has declined by 50%, and 20% of the antiplatelet activity remains after 3 days. CYP3A4, CYP3A5, and CYP2D6 are moderately inhibited by ticagrelor, and drug interactions associated with this effect have been reported. Digoxin concentrations should be monitored in the event of concomitant use. Serum concentrations of some statins (lovastatin and simvastatin) are increased. Concomitant use of CYP3A4 inhibitors (ketoconazole, ritonavir, and clarithromycin) or inducers (rifampicin, phenytoin, carbamazepine, and dexamethasone) should be avoided.¹⁸

Cangrelor

Cangrelor is the most recently (June 2015) approved i.v. non-thienopyridine, reversible_P2Y₁₂-blocking agent. Steady-state concentrations are achieved after 18–24 h of i.v. infusion without a loading dose or a preliminary bolus being recommended. Platelet inhibition is >90%. Cangrelor is inactivated by plasma enzymes, and within 60 min of stopping the infusion the platelet function has recovered to <u>normal.¹⁹</u> These favourable pharmacokinetic properties make cangrelor a <u>promising</u> agent for <u>bridging</u> of high-risk patients in the perioperative setting.²⁰

Glycoprotein IIb/IIIa inhibitors

Glycoprotein IIb/IIIa (GpIIb/IIIa) receptors are the most numerous proteins on the platelet surface. Glycoprotein IIb/IIIa inhibitors block the adhesion of fibrinogen to the activated platelet. preventing the building of interplatelet bridges. Adhesion of fibronectin, von Willebrand factor, and vitronectin are inhibited. The activation of the GpIIb/IIIa receptor is one of the final steps in platelet activation, building cross-linked platelet-fibrinogen complexes. Glycoprotein IIb/IIIa receptors also contribute to a positive feedback mechanism with thrombin and collagen, producing a sustained prothrombotic effect.^{21 22} Abciximab, triofiban, and eptifibatide are i.v. GpIIb/IIIa inhibitors that are currently in use.

<mark>Abciximab</mark>

Abciximab is a humanized monoclonal mouse antibody. It reversibly binds to thrombocytes within 1 min of adminstration. A loading dose is necessary to achieve a >80% receptor blockage. It shows the highest affinity to the GpIIb/IIIa receptor of the three licensed drugs.²³ It has a short plasma half-life, but a long biological activity.

Tirofiban and eptifibatide

Tirofiban and eptifibatide are synthetic GpIIb/IIIa inhibitors that reversibly bind and rapidly dissociate (10–15 s) from the GpIIb/ IIIa receptor. The plasma concentration of these drugs determines the receptor occupancy and extent of platelet inhibition. Both molecules compete with fibrinogen for the binding of the GpIIb/IIIa receptor. The affinity for the receptor is greater for tirofiban than for eptifibatide.²³

Other antiplatelet agents

Cilostazol and dipyridamole are phosphodiesterase inhibitors that interfere with degradation of cyclic adenosine monophosphate and cyclic guanosine monophosphate. In addition to their antiplatelet action, they cause vasodilation because of an effect on vascular smooth muscle.

The protease-activated receptor-1 antagonists, agents such as vorapaxar and atopaxar, inhibit platelet activation through alternative routes, including thrombin-mediated platelet aggregation. Numerous other platelet surface proteins (glycoprotein VI, glycoprotein Ib, prostaglandin E, nitrous oxid, and thromboxane A) are potential targets for inhibitory drugs currently under investigation.^{3 8}

Management of antiplatelet therapy in the perioperative setting (Fig. 1)^{24 25}

Dual antiplatelet therapy is known to reduce significantly the number of arterial thrombotic events in the perioperative period. Discontinuation of antiplatelet agents is associated with a risk of myocardial infarction, stent thrombosis, and death attributable

Risk of a cardiovascular event Risk of perioperative Bleeding	Low to moderate cardiovascular risk	High cardiovascular risk ACS >12 months preop PCI/DES >6 months preop PCI/BMS >1 month preop CABG >6 weeks preop CVA/TIA >1 month preop Peripheral vascular disease	Very high cardiovascular risk ACS <12 months preop PCI/DES <6 months preop PCI/BMS <1 month preop CVA/TIA <1month preop CABG <6 weeks preop
Low bleeding risk e.g. endoscopy, body surface surgery		Continue aspirin	Delay elective surgery to allow management of cardiovascular condition
Moderate bleeding risk e.g. biopsy, therapeutic endoscopy; cardiothoracic, urologic, orthopedic, vascular, visceral, ENT and surgery	Discontinue aspirin 5 days before surgery – to 7 days after surgery	Discontinue P2Y ₁₂ inhibitors	Urgent surgery e.g. cancel surgery requires multidisciplinary dicussion of management. Consider - continuation of aspirin - discontinuation of P2Y ₁₂ inhibitors with/without bridging with tirofiban or cangrelor
High bleeding risk e.g. hepatobiliary and vertebrospinal surgery		Discontinue aspirin 5 days before surgery to 1–2 days after surgery	
Very high i.e. intracranial surgery		Discontinue P2Y12 inhibitors	

Fig 1 Perioperative management of antiplatelet drugs. ACS, acute coronary syndrome; BMS, bare metal stent; CABG, coronary artery bypass graft; CVA, cerebrovascular accident; DES, drug-eluting stent; PCI, percutaneous coronary intervention; postop, postoperative; preop, preoperative; PVD, peripheral vascular disease; TIA, transient ischaemic attack.^{24 25}

to inflammatory-mediated rebound effects of platelet adhesion. Persistent perioperative application is associated with higher risk of bleeding (2.5–20 vs 30–50%) and a 30% higher rate of blood cell transfusion; however, mortality linked to these circumstances is hardly increased. The necessity of elective surgery should be assessed on a patient-by-patient basis. Antiplatelet therapy and treatment for other co-morbidities should be optimized. The relative risks of a thromboembolic event and of bleeding should be weighed. Postoperative restarting of antiplatelet therapy depends on the individual patient's cardiovascular risk profile, the bleeding risks associated with the particular operation, and the pharmacokinetics of each drug. The aim should be to re-establish the antiplatelet regimen as early as is reasonably possible. Hospital discharge without restarting treatment carries substantial risks.¹⁹ ²⁶

For operations with a low bleeding risk, antiplatelet therapy does not need to be interrupted. In procedures with a high risk of bleeding, aspirin should be maintained and other antiplatelet substances discontinued long enough before surgery to allow the antiplatelet effect to have waned. If possible, for example after percutaneous coronary angioplasty, the operation should be delayed until the patient has a lower risk of cardiovascular complications. In patients with a low risk of thromboembolic events who require surgery that carries a high risk of haemorrhage, antiplatelet therapy should be interrupted in the perioperative period. The continuous evaluation of the bleeding should guide intra- and postoperative therapeutic strategies.⁸⁹²⁷ The management of bleeding is discussed below.

In situations where there is a high chance of bleeding and withdrawal of antiplatelet therapy carries a high risk of cardiovascular events, bridging of antiplatelet therapy can be considered. Bridging therapies involve replacing antiplatelet therapy using long-acting P2Y₁₂ antagonists with a short-acting anticoagulant or antiplatelet agent that can be discontinued shortly before surgery. The use of tirofiban and eptifibate has been described. More recently, cangrelor has become available and is recommended as a suitable drug because of its pharmacokinetic profile. In the situation of bridging, treatment with aspirin should be continued and the other oral agent stopped 5–7 days before surgery. A short-acting i.v. agent should be started no more than 72 h after the discontinuation of DAPT. Four to six hours (or 1 h for cangrelor) before surgery, the i.v. drug is discontinued and is restarted 6 h after surgery. The patient's usual DAPT is restarted as soon as the risk of perioperative haemorrhage is negligible.^{28–32}

Heparinoids are sometimes used for bridging. This is based on their known effect in unstable angina and Non-ST-elevation myocardial infarction (NSTEMI); they do not have any protective effect against coronary or stent thrombosis. <u>Heparin</u> is <u>not</u> an <u>appropriate substitute</u> for <u>antiplatelet</u> agents. <u>Non-steroidal</u> anti-inflammatory agents and, in particular, r<mark>eversible COX1</mark> inhibitors c<mark>an be consi</mark>dered as <mark>short-term substitutes</mark>.^{8 26 27}

Th<mark>e management of bleeding</mark>

Antiplatelet drugs have haemorrhage as a common side-effect. Several factors associated with a higher risk of bleeding have been identified, including female sex, advanced aged (>75 yr), impaired renal function, anaemia, low body weight (<60 kg), and a history of transient ischaemic attack or stroke. In a surgical context, complex or urgent operations are considered as high-risk situations for bleeding.

Major surgical bleeding in patients treated with antiplatelet agents increases perioperative morbidity and mortality, as do blood transfusions. A restrictive transfusion management strategy is widely recommended, with transfusion thresholds of the order of a haemoglobin <80 g litre⁻¹ or a haematocrit <25%.³³ No antagonists for antiplatelet agents are available. Management of significant haemorrhage is based on the administration of tranexamic acid, fibrinogen, factor XIII, desmopressin, platelets, and activated factor VIIa. The prothrombotic properties of these agents may pose a risk of major thrombotic complications.^{8 9 34}

Drug monitoring and laboratory tests

Numerous platelet function tests are available (e.g. turbidometric light transmittance, VerifyNow, Thrombelastogram, Multiplate, or Platelet Function Analyser-100). These were often initially designed to identify platelet function disorders (either dysfunction or hyperactivity). With the increasing armamentarium of platelet-inhibiting drugs, many of which display significant intra-individual variation in their efficacy, these assays have become more relevant to drug monitoring, the design of individualized pharmacotherapy, perioperative evaluation, and the planning of surgery. The results of platelet function tests vary between assays and depend on the cut-off values used to define a normal test. A further limitation is the dependency of these assays on haematocrit and platelet count.^{35–37}

Anticoagulant agents (Table 3)

Anticoagulants inhibit the initiation and progress of coagulation and fibrin-clot formation and propagation. Their uses include the treatment or prevention of venous thromboembolism and atrial fibrillation. For acute treatment of venous thromboembolism and during revascularization therapy, immediately acting parenteral anticoagulants are used. Low molecular weight heparins and, recently, parenteral anti-factor Xa agents (fondaparinux) have widely replaced unfractionated heparin.³⁸ ³⁹ Oral anticoagulants are indicated for long-term treatment or prevention of thromboembolic complications of different cardiovascular diseases, such as venous thromboembolism, myocardial infarction, or atrial fibrillation, and after implantation of mechanical valves.³⁸

Parenteral anticoagulants

Unfractionated heparin and low molecular weight heparin Heparins are indirectly acting anticoagulants that bind to and activate antithrombin. After inducing a conformational change in antithrombin, the heparins dissociate and bind to further antithrombin molecules. <u>Activated antithrombin</u> accelerates the <u>inactivation</u> of coagulation <u>factors IIa, IXa, Xa, Xia, and XIIa.</u> Unfractionated heparin dosing depends on the indication for its

Characteristic	Warfarin	Oral					Parentral			
		Dabigatran	Apixaban	Edoxaban	Rivaroxaban	Unfractionated heparin (s.c./i.v.)	Low molecular weight heparins (s. c.)	Fondaparinux (s.c.)	Argatroban (i.v.)	Bivalirudin (i.v.)
Mechanism of action	Vitamin K antagonist	Direct inhibition IIa	Direct inhibition Xa	Direct inhibition Xa	Direct inhibition Xa	Direct inhibition Xa=IIa	Direct inhibition Xa>IIa	Direct inhibition Xa	Direct inhibition IIa	Direct inhibition IIa
Bioavailability (%)	80	9	66	62	80	30	06	100	100	100
Plasma half-life	20-60 h	12–14 h	8–15 h	10–14 h	7-10 h	$1 \mathrm{h}$	4 h	17 h	50 min	24 min
Duration of action from last dose	48–96 h	48 h	24 h	24 h	24 h	Dose dependent (s.c.)	Dose dependent	48–96 h	2-4 h	1 h
Peak plasma concentration	Variable	2 h	2.5-4 h	1–2 h	1–3 h	4 h (s.c.)	3 h	2 h		0.25–2 h
Elimination	Metabolism	80% renal	25% renal	50% renal	50% renal, 50% hepatic	Reticulo- endothelial system	Hepatic metabolism, renal excretion 10%	Renal	65% faeces, 22% urine	20% renal
Drug interaction	CYP2C9, CYP3A4, CYP1A2	P-glycoprotein inhibitors	CYP3Y4, P-glycoprotein inhibitors	P-glycoprotein inhibitors	Strong CYP3A4 inhibitors or inducers and P-glycoprotein inhibitors					

e 3 Summary of the characteristics of currently available anticoagulant drugs

use and is highly variable. Low molecular weight heparins can be used at a fixed dose for prophylaxis and in a weight-adjusted dose for therapeutic anticoagulation.⁴⁰

Fondaparinux

Fondaparinux selectively and <mark>irreversibly binds to antithrombin</mark> III, thus <u>inactivating factor Xa</u> and, in turn, <u>interrupting thrombin</u> formation and thrombus propagation.⁴⁰

Direct thrombin inhibitors

Parenteral direct thrombin inhibitors bind directly, selectively, and <u>reversibly</u> to the <u>active site of thrombin</u>. Fibrin formation and propagation of clot formation are inhibited. Currently, desirudin, argatroban, and bivalirudin are licensed direct thrombin inhibitors. They are the <u>main alternative</u> therapeutic agents in heparin-induced thrombocytopenia.^{40 41}

Oral anticoagulants

Vitamin K antagonists

For more than 80 yr, vitamin K antagonists have been known to have anticoagulant properties and were the most frequently used oral anticoagulant drugs. After the identification of dicoumarol warfarin, phenprocoumon and acenocoumarol were synthesized.⁴² These drugs, the latter mainly used in Europe, hinder the synthesis of vitamin K-dependent clotting factors; vitamin K reductase is blocked, causing a depletion of reduced vitamin K. This is needed for the γ -carboxylation and activation of vitamin K-dependent clotting factors II, VII, IX, and X. Additionally, they inhibit the carboxylation of the anticoagulant <u>proteins C. S. and Z.</u> causing a <u>transient procoagulant</u> state.^{43 44}

Although vitamin K antagonists are highly effective agents they do have numerous limitations.

- Genetic polymorphisms producing variation in patients' sensitivity.
 - Drugs such as warfarin act on the vitamin K epoxide reductase complex 1 (VKORC1). People with the A allele of VKORC1 produce less VKORC1 subunit than those with the more common G allele and require less VKA to produce an anticoagulant effect.
 - Warfarin is metabolized in the liver by CYP2C9. People with the CPY2C9*2 and CPY2C9*3 variants metabolize warfarin less effectively than those with wild-type CPY2C9*1 and require a lower dose to warfarin to achieve effective anticoagulation.
- Non-genetic factors, including age, body weight, dietary vitamin K intake, concomitant diseases, and alcohol consumption, modulate the required dose.
- Vitamin K antagonist drugs show variable pharmacodynamic properties, with slow onset and slow offset of action.
- 4. Vitamin K antagonists are subject to interactions with drugs metabolized by CYP2C9, CYP3A4, and CYP1A2.
- 5. They have a narrow therapeutic window, with the need for constant monitoring.

A <u>>10-fold interpatient variation</u> in the <u>dose necessary</u> to reach the desired anticoagulant effect is observed, leading to a risk of under- or overdosing and causing haemorrhage or thromboembolism. This made the development of alternative drugs attractive.^{38 42 45}

New oral anticoagulants

In 2004, ximelagatran was licensed by the European Medical Agency, thus becoming the first oral thrombin inhibitor to reach the market. As a result of potential hepatotoxicity, it was withdrawn soon after.⁴⁶ Since 2008, further new oral anticoagulants have been introduced. These include the direct thrombin inhibitor, dabigatran, and the direct factor X inhibitors, such as rivaroxaban, apixaban, and edoxaban. Other new oral anticoagulants (NOACs) are currently being tested in clinical trials.

Dabigatran etexilate

Dabigatran etexilate, a low molecular weight prodrug, is a direct thrombin inhibitor. It is converted to its active form, dabigatran, by non-specific esterases in the liver and plasma. It binds directly to the active site of thrombin via ionic interactions. Fibrin-bound thrombin and free thrombin are inactivated competitively and reversibly. Unlike heparins, which cannot inhibit clot-bound factor II, dabigatran can inhibit thrombus expansion triggered by thrombin. The following events in the coagulation cascade are prevented by dabigatran: conversion of fibrinogen into fibrin, positive feedback amplification of coagulation activation, crosslinking of fibrin monomers, platelet activation, and inhibition of fibrinolysis. Co-medication with P-glycoprotein inhibitors, including ketoconazole, amiodarone, verapamil, or quinidine, may increase its plasma concentration. Rifampicin may reduce the plasma concentration because of induction of P-glycoprotein.^{47 48}

<mark>Apixaban</mark>

Apixaban is a direct, selective factor Xa inhibitor that inhibits free and prothrombinase complex-bound factor Xa. It is rapidly absorbed in the stomach and small bowel, independently of food intake. Absorption is mediated by P-glycoprotein, and P-glycoprotein inhibitors can increase absorption. Metabolism is mediated by CYP3A4, and concomitant use of CYP3A4 and P-glycoprotein inducers (carbamazepine, phenobarbital, phenytoin, St John's wort, and rifampicin) cause a decreased concentration of apixaban.^{42 48 49}

<mark>Rivaroxaban</mark>

Rivaroxaban is a direct, highly selective, reversible, competitive inhibitor of free and complex-bound factor Xa. The bioavailability of this lipophilic drug is increased by concomitant food intake, causing more predictable plasma concentrations. Co-treatment with CYP3A4 inhibitors or inducers and P-glycoprotein inhibitors is (relatively) contraindicated, because it may lead to altered plasma concentrations of rivaroxaban.^{42 48 50}

Edoxaban

Edoxaban is a direct, highly selective and competitive inhibitor of factor Xa. It has a bioavailability of 62%. Co-administration of strong P-glycoprotein inhibitors (e.g. ketoconazole, amiodarone, verapamil, or quinidine) cause an increased effect of edoxaban, necessitating a dose reduction of 50%. Dose adjustment in patients with low body weight (<60 kg) or moderate renal impairment is also necessary.⁵¹

The perioperative setting (Table 4)

Of all patients receiving oral anticoagulant treatment, 10% have to interrupt it for invasive procedures at some point.⁵² In current clinical practice, bridging therapy is widely used to cover the temporary withdrawal of oral anticoagulation. <u>Recent data (</u>e.g. <u>BRIDGE Trial, ORBIT-AF</u>) suggest that this approach <u>increases</u>

Drug	Glomerular filtration rate (ml min ⁻¹)	Bleeding risk	Duration of omission before surgery (h)	Recommendations for restarting
Dabigatran	>50	Moderate	36	Decisions on restarting these agents depend on
	50–30		48–72	surgical bleeding risk (see Fig. 1), renal function
	<30		Minimum 72	the indication for anticoagulation, and the
	>50	High	48–72	presence or otherwise of a neuroaxial catheter.
	50–30		96	A pause of at least 6 h after the surgical
	<30		Minimum 120	intervention is recommended
Rivaroxaban		Moderate	18	
<10 mg		High	24	
Rivaroxaban	>50	Moderate	24	
>15 mg	50–30		48	
	<30		Minimum 72	
	>50	High	36	
	50–30		48	
	<30		Minimum 72	
Apixaban	>50	Moderate	24	
	50–30		48	
	<30		Minimum 72	
	>50	High	48	
	50–30		72	
	<30		Minimum 72	
Edoxaban	>50	Moderate	24	
	50–30		48	
	<30		Minimum 72	
	>50	High	48	
	50–30		72	
	<30		Minimum 72	

the risk of perioperative haemorrhage but with little beneficial effect on thromboembolic complications in patients with atrial fibrillation.⁵³⁵⁴ Most importantly, two major aspects need to be considered, as follows: (i) the risk of intervention related haemorrhage (as subdivided in Fig. 1); and (ii) the risk of perioperative thromboembolism, classified as low, medium, or high (as in Table 5).55

A low-risk procedure in a low-risk patient does not require discontinuation of oral anticoagulation. In patients with lone atrial fibrillation or a CHA₂DS₂-VASc ≤4 (CHADS₂, CHADS₂ risk score for stroke in atrial fibrillation based on congestive heart failure, hypertension, age >75 yr, diabetes, and stroke or transient ischaemic attack; CHA2DS2- VASc, updated risk score for stroke in atrial fibrillation including CHADS₂ risk factors plus vascular disease age 65–75 yr and female sex), bridging is of questionable value because haemorrhagic risks exceed the risk of thromboembolic complications in these patients. High-risk procedures or high-risk patients do need bridging therapy to cover withdrawal of vitamin K antagonists. All intermediate-risk patients (CHA2-DS₂-VASc >4) and interventions carrying an intermediate risk of bleeding are likely to require patient-by-patient estimation of the individual bleeding and thromboembolic risk.56

In contrast to the periopertive management of vitamin K antagonists, current data do not support preoperative bridging therapy to cover the perioperative withdrawal of NOACs.^{28 29 57 58} The advice for interruption of NOACs depends on their plasma halflife and the patient's co-morbidities, especially renal function. Two half-lives (remaining drug concentration <25%) are considered as an adequate compromise between the reduction of bleeding risk and the prevention of a thromboembolic event. If there is reduced elimination or a high risk of perioperative haemorrhage,

the time of discontinuation should be increased. For minor surgical procedures, treatment with NOACs can be continued without interruption. Usual haemostatic measures are undertaken, and an awareness of the risk of bleeding is important. For major surgical procedures that carry a high bleeding risk and interventions near delicate structures or in enclosed spaces (e.g. neurosurgery), NOACs should be discontinued.⁵⁹⁶⁰

If emergency surgery is needed, an evaluation of the indication for treatment with a NOAC, and the daily dose, last intake, and renal function allows a rough estimation of the pharmacological activity at the time of planned surgery. If feasible, a delay for at least 24 <u>h from the last dose is advisable.</u>New oral antiocoagulant ingestion less than 2–6 h previously may be treated with activated charcoal. Haemodialysis may be used for dabigatran elimination. The treatment of bleeding is discussed in the next section.^{59 60}

Postoperative resumption depends on the risk of bleeding, the renal function, and the presence of neuroaxial catheters.

Management of bleeding

Bleeding risk is increased in patients aged >75 yr, with concomitant aspirin intake, diabetes mellitus, low body weight (<50 kg), or an elevated plasma concentration of the anticoagulant.⁶¹ Minor bleeding can be treated with basic measures, including compression, sclerotherapy, blood-pressure regulation, and so forth. It usually does not require pharmacological correction of coagulation. Anticoagulation should be interrupted until no further bleeding is detected.58

In the event of major bleeding (>20% of patient's blood volume), potential causes should be identified without delay. General measures should be undertaken, including the avoidance Table 5 An approach to classifying arterial and venous thromboembolic risk in surgical patients. CHADS₂, CHADS₂ risk score for stroke in atrial fibrillation based on congestive heart failure, hypertension, age >75 yr, diabetes, and stroke or transient ischaemic attack; CHA2DS₂ VASc, updated risk score for stroke in atrial fibrillation including CHADS₂ risk factors plus vascular disease age 65–75 yr and female sex,⁵⁵ VTE, venous thromboembolic event

Thromboembolic risk	Risk factors
Low risk	VTE >12 months previously without risk factors for further event
	$CHADS_2 \leq 2$ without cerebrovascular disease
	CHA ₂ DS ₂ -VASc <4
	Bileaflet aortic valve without further risk factors (e.g. diabetes, atrial fibrillation, or congestive heart failure)
Intermediate risk	Recurrent VTE
	Active cancer
	VTE 3–12 months
	Factor V Leiden carrier
	Prothrombin mutation carrier
	CHADS ₂ score 3–4
	CHA ₂ DS ₂ -VASc score <mark>4–5</mark>
	Bileaflet aortic valve disease with further risk factors
High risk	VTE <3 months, severe thrombophilia
	Cerebrovascular accident <6 months previously
	CHADS ₂ score 5–6
	CHA ₂ DS ₂ -VASc score <mark>>5</mark>
	Prosthetic cardiac valve
	Aortic valve replacement with cage ball valve

and correction of acidosis, hypothermia, and hypocalcaemia. Specific reversal agents for NOACs are not yet available. Research on the development of specific reversal agents is in progress (e.g. idarucizumab for dabigatran, and exanet alfa for factor Xa inhibitors, and PER977 for factor Xa and thrombin inhibitors).⁶²

Procoagulant agents may be required. Options include <u>pro-</u> <u>thrombin complex concentrate (25–50 U kg⁻¹)</u> or activated prothrombin complex concentrate (50–100 U kg⁻¹); the latter is more efficient but also more likely to cause thromboembolic complications. Recombinant factor VIIa may be used as rescue medication, but carries a high risk of thromboembolism. Adjuncts such as tranexamic acid or desmopressin may be considered, but there are few clinical data regarding their efficacy. ^{59 60 63}

Drug monitoring and laboratory tests (Fig. 2)⁶⁴

One advantage of NOACs over vitamin K antagonists is the avoidance of the necessity of routine laboratory monitoring. The most frequently used coagulation tests (activated partial thromboplastin time and international normalized ratio) are influenced by <mark>NOACs, </mark>because they <u>directly inhibit f</u>actor <u>IIa or Xa, </u>the <mark>end</mark> points of these assays. The degree of alteration of clotting assays depends on the plasma concentration of the NOAC. Moreover, normal test results indicate a lack of a significant NOAC effect. This is particularly true for the activated partial thromboplastin time test in patients taking dabigatran.^{65–67} Interpretation of drug plasma concentration is difficult because there is no defined range that reflects optimal treatment levels or bleeding risk. In daily clinical practice, routine laboratory testing during NOAC treatment is currently not recommended. A better understanding of their influence on laboratory coagulation tests might allow optimization and individualization of treatment in the future.⁶⁸ Laboratory testing is advisable in patients requiring urgent surgery, those with a rapid decline in renal function, or in bleeding patients. Test results should be interpreted in the context of the time of last drug administration. At present, our ability to state that there is no NOAC effect is probably greater than our ability to quantify any NOAC effect.



Fig 2 Interpretation of laboratory coagulation tests in patients with suspected new oral antiocoagulant treatment. anti-Xa, anti-Xa assay; aPTT, activated partial thromboplastin time; Hemoclot test, Hemoclot[®] thrombin inhibitor assay; PT, prothrombin time; TT, thrombin time.⁶⁴

Concomitant use of antiplatelet agents and new oral antiocoagulants

In clinical routine, the number of patients receiving antiplatelet therapy and NOAC therapy is increasing. Data suggest that NOACs offer benefit in ischaemic events when used concomitantly with a single antiplatelet regimen. Patients on DAPT (aspirin and clopidogrel) who additionally receive a NOAC show a 3-fold increase in the risk of haemorrhage without further reduction of adverse cardiac events. Potentially, the bleeding risk is higher with more potent antiplatelet agents (ticagrelor and prasugrel), although data to confirm this are lacking. An individualized approach is necessary in patients who might be favourably treated with a combination of DAPT (including prasugrel and ticagrelor) and NOACs, balancing the potential benefit against the increased risk of haemorrhage. A dose reduction may be a potential strategy, but research to confirm this is required. The indication for long-term use of NOACs and DAPT in an individual patient should be re-evaluated regularly.⁶⁹

Conclusion

It is essential for anaesthetists to know the properties of new antiplatelet agents and NOACs because their management in the perioperative period or the bleeding patient is crucial. The perioperative period is associated with significant prothrombotic risk because of the inflammatory response to surgery. This risk must be balanced with the likelihood of haemorrhage in patients treated with antiplatelet or anticoagulant drugs. Both situations carry a significant burden of morbidity and mortality. With the increasing use of a broad range of antiplatelet and anticoagulant drugs, most anaesthetists face these dilemmas on a regular basis.

Guidelines are published and updated regularly to enable appropriate, up-to-date treatment, and the anaesthetist should ensure that they are familiar with relevant local and national guidance.^{28 29 67}

Sophisticated laboratory assays are unevenly accessible in emergency situations, but standard laboratory tests, such as activated partial thromboplastin time, international normalized ratio, or basic platelet function tests, are not. These allow adaptation and guidance of treatment strategies (Fig. 2). Multidisciplinary discussion to plan the best treatment in high-risk patients undergoing surgery is essential.

Authors' contributions

The review was conceived by V.K.-O. and M.F.

Declaration of interest

None declared.

References

- 1. Raskob GE, Rosendaal FR. On World Thrombosis Day. Lancet 2014; **384**: 1653–4
- World Health Organisation. Deaths from cardiovascular diseases and diabetes. WHO 2016. Available from http://www. who.int/gho/ncd/mortality_morbidity/en/ (accessed 26 December 2014)
- 3. Patrono C, Andreotti F, Arnesen H, et al. Antiplatelet agents for the treatment and prevention of atherothrombosis. *Eur Heart J* 2011; **32**: 2922–32
- Choudhry NK, Desai NR, Fischer MA et al. 2012. Alosa Foundation, Inc. Available from http://www.alosafoundation.org/ wp-content/uploads/2013/03/Antiplatelet_UnAd.pdf (accessed 21 February 2016)
- 5. Windecker S, Kolh P, Alfonso F, et al. 2014 ESC/EACTS Guidelines on myocardial revascularization: the Task Force on

Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). Eur Heart J 2014; **35**: 2541–619

- Kernan WN, Ovbiagele B, Black HR, et al. Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2014; 45: 2160–236
- 7. Fuster V, Sweeny JM. Aspirin: a historical and contemporary therapeutic overview. Circulation 2011; **123**: 768–78
- Oprea AD, Popescu WM. Perioperative management of antiplatelet therapy. Br J Anaesth 2013; 111(Suppl 1): i3–17
- 9. Hall R, Mazer CD. Antiplatelet drugs: a review of their pharmacology and management in the perioperative period. Anesth Analg 2011; **112**: 292–318
- Antithrombotic Trialists' Collaboration. Collaborative metaanalysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. Br Med J 2002; 324: 71–86
- Ferraris VA, Saha SP, Oestreich JH, et al. 2012 update to the Society of Thoracic Surgeons guideline on use of antiplatelet drugs in patients having cardiac and noncardiac operations. Ann Thorac Surg 2012; 94: 1761–81
- Michelson AD. Advances in antiplatelet therapy. Hematology Am Soc Hematol Educ Program 2011; 2011: 62–9
- Weitz JI, Eikelboom JW, Samama MM, American College of Chest Physicians. New antithrombotic drugs: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2012; 141(2 Suppl): e120S–51S
- 14. Topol EJ, Byzova TV, Plow EF. Platelet GPIIb-IIIa blockers. Lancet 1999; **353**: 227–31
- 15. Wijeyeratne YD, Heptinstall S. Anti-platelet therapy: ADP receptor antagonists. Br J Clin Pharmacol 2011; **72**: 647–57
- Lins R, Broekhuysen J, Necciari J, Deroubaix X. Pharmacokinetic profile of 14C-labeled clopidogrel. Semin Thromb Hemost 1999; 25(Suppl 2): 29–33
- Giorgi MA, Di Girolamo G, González CD. Nonresponders to clopidogrel: pharmacokinetics and interactions involved. Expert Opin Pharmacother 2010; 11: 2391–403
- Dobesh PP, Oestreich JH. Ticagrelor: pharmacokinetics, pharmacodynamics, clinical efficacy, and safety. Pharmacotherapy 2014; 34: 1077–90
- Ortel TL. Perioperative management of patients on chronic antithrombotic therapy. Hematology Am Soc Hematol Educ Program 2012; 2012: 529–35
- Angiolillo DJ, Firstenberg MS, Price MJ, et al. Bridging antiplatelet therapy with cangrelor in patients undergoing cardiac surgery: a randomized controlled trial. JAMA 2012; 307: 265–74
- 21. Patrono C, Bachmann F, Baigent C, et al. Expert consensus document on the use of antiplatelet agents. The task force on the use of antiplatelet agents in patients with atherosclerotic cardiovascular disease of the European society of cardiology. Eur Heart J 2004; 25: 166–81
- Armstrong PC, Peter K. GPIIb/IIIa inhibitors: from bench to bedside and back to bench again. Thromb Haemost 2012; 107: 808–14
- 23. Schneider DJ. Anti-platelet therapy: glycoprotein IIb-IIIa antagonists. Br J Clin Pharmacol 2011; **72**: 672–82
- Filipovic M, Korte W, Rickli H. Thromboseprophylaxe und periinterventionelle antithrombotische Therapie, 5.

Auflage 2014. Available from http://www.kardiologie.kssg. ch/content/dam/dokument_library/container_kardiologie/ Gerinnungskarte/Thromboembolieprophylaxe%20in% 20der%20Chirurgie%2026%2005%202014.pdf.ocFile/ Thromboembolieprophylaxe%20in%20der%20Chirurgie% 2026%2005%202014.pdf (accessed 29 February 2016)

- 25. Douketis JD, Spyropoulos AC, Spencer FA, et al. Perioperative management of antithrombotic therapy: antithrombotic therapy and prevention of thrombosis: American College of Chest Physicians evidence-based clinical practice guidelines (9th edition). Chest 2012; **141**: e326S–50S
- Chassot PG, Marcucci C, Delabays A, Spahn DR. Perioperative antiplatelet therapy. Am Fam Physician 2010; 82: 1484–9
- Benzon HT, Avram MJ, Green D, Bonow RO. New oral anticoagulants and regional anaesthesia. Br J Anaesth 2013; 111 (Suppl 1): i96–113
- The Cardiac Society of Australia and New Zealand. Guidelines for the use of antiplatelet therapy in patients with coronary stents undergoing non-cardiac surgery. 2009. Available from www.csanz.edu.au (accessed 26 October 2015)
- 29. Österreichische Gesellschaft für Anästhesiologie, Reanimation und Intensivmedizin Perioperatives Management von PatientInnen mit Koronarstents unter dualer Antiplättchentherapie bei nicht-kardiochirurgischen Eingriffen. Empfehlungen der Arbeitsgruppe perioperative Gerinnung der ÖGARI. 2013. Available from www.oegari.at (accessed 25 October 2015)
- Kyo S, Imanaka K, Kurosawa H, et al. Guidelines for Perioperative Cardiovascular Evaluation and Management for Noncardiac Surgery. Circ J 2011; 75: 989–1009
- Douketis J, Spyropoulos AC, Spencer FA et al. Perioperative Management of Antithrombotic Therapy 2016. Available from www.chestnet.org (accessed 8 December 2014)
- 32. Rossini R, Musumeci G, Visconti LO, et al. Perioperative management of antiplatelet therapy in patients with coronary stents undergoing cardiac and non-cardiac surgery: a consensus document from Italian cardiological, surgical and anaesthesiological societies. EuroIntervention 2014; 10: 38–46
- Carson JL, Grossman B, Kleinman S, et al. Red blood cell transfusion: a clinical practice guideline from the AABB. Ann Intern Med 2012; 157: 49–58
- 34. Gresele P. Antiplatelet agents in clinical practice and their haemorrhagic risk. Blood Transfus 2013; 11: 349–56
- Wolf Z, Mani H, Lindhoff-Last E. Significance of platelet function tests. Internist 2010; 51: 1095–6
- Sambu N, Curzen N. Monitoring the effectiveness of antiplatelet therapy: opportunities and limitations. Br J Clin Pharmacol 2011; 72: 683–96
- Mahla E, Höchtl T, Prüller F, Freynhofer MK, Huber K. Platelet function: new drugs, new assays: possible impacts on operative medicine? *Anaesthesist* 2012; 61: 483–96
- Weitz JI, Eikelboom JW, Samama MM; American College of Chest Physicians. New antithrombotic drugs: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012; 141(2 Suppl): e120S–51S
- Eikelboom JW, Weitz JI. New anticoagulants. Circulation 2010; 121: 1523–32
- Garcia DA, Baglin TP, Weitz JI, Meyer M. Parenteral anticoagulants: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-

based clinical practice guidelines. Chest 2012; **141**: e24S-43S

- 41. Lee CJ, Ansell JE. Parenteral anticoagulants: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. Br J Clin Pharmacol 2011; 72: 581–92
- Scaglione F. New oral anticoagulants: comparative pharmacology with vitamin K antagonists. Clin Pharmacokinet 2013; 52: 69–82
- 43. Ansell J, Hirsh J, Hylek E, Jacobson A, Crowther M, Palareti G; American College of Chest Physicians. Pharmacology and management of the vitamin K antagonists: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 2008; 133(6 Suppl): 160S–98S
- 44. 2005. Available from http://www.drugbank.ca/drugs/DB00682 (accessed 25 October 2015))
- 45. Bauer KA. Pros and cons of new oral anticoagulants. Hematology Am Soc Hematol Educ Program 2013; **2013**: 464–70
- 46. Keisu M, Andersson TB. Drug-induced liver injury in humans: the case of ximelagatran. Handb Exp Pharmacol 2010; **196**: 407–18
- 47. Hankey GJ, Eikelboom JW. Dabigatran etexilate: a new oral thrombin inhibitor. Circulation 2011; **123**: 1436–50
- Dempfle CE. Direct oral anticoagulants—pharmacology, drug interactions, and side effects. Semin Hematol 2014; 51: 89–97
- Nutescu E. Apixaban: a novel oral inhibitor of factor Xa. Am J Health Syst Pharm 2012; 69: 1113–26
- Gulseth MP, Michaud J, Nutescu EA. Rivaroxaban: an oral direct inhibitor of factor Xa. Am J Health Syst Pharm 2008; 65: 1520–9
- Lip GYH, Agnelli G. Edoxaban: a focused review of its clinical pharmacology. Eur Heart J 2014; 35: 1844–55
- 52. Douketis JD, Woods K, Crowther MA. Anticoagulant Management of Patients Undergoing Elective who Require Temporary Interruption of Warfarin Therapy. 2005. Available from http://fhs.mcmaster.ca/surgery/documents/Handout2for VTEProphylaxisof02Sep2009byDr.M.Crowther.pdf (accessed 2 October 2015)
- Douketis JD, Spyropoulos AC, Kaatz S, et al. Perioperative bridging anticoagulation in patients with atrial fibrillation. N Engl J Med 2015; 373: 823–33
- 54. Steinberg BA, Peterson ED, Kim S, et al. Use and outcomes associated with bridging during anticoagulation interruptions in patients with atrial fibrillation: findings from the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF). Circulation 2015; 131: 488–94
- 55. January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the Heart Rhythm Society. Circulation 2014; 130: 2071–104
- Rechenmacher SJ, Fang JC. Bridging anticoagulation: primum non nocere. J Am Coll Cardiol 2015; 66: 1392–403
- CoaguSave 2015. Available from http://www.girard.li/ girardDev/index_light_slider.html (accessed 25 October 2015)
- Beyer-Westendorf J, Gelbricht V, Förster K, et al. Peri-interventional management of novel oral anticoagulants in daily care: results from the prospective Dresden NOAC registry. Eur Heart J 2014; 35: 1888–96
- Baron TH, Kamath PS, McBane RD. Management of antithrombotic therapy in patients undergoing invasive procedures. N Engl J Med 2013; 368: 2113–24
- 60. Kozek-Langenecker SA. Perioperative management issues of direct oral anticoagulants. Semin Hematol 2014; **51**: 112–20

- 61. Palareti G. Direct oral anticoagulants and bleeding risk (in comparison to vitamin K antagonists and heparins), and the treatment of bleeding. *Semin Hematol* 2014; **51**: 102–11
- Vanden Daelen S, Peetermans M, Vanassche T, et al. Monitoring and reversal strategies for new oral anticoagulants. Expert Rev Cardiovasc Ther 2015; 13: 95–103
- Siegal DM, Cuker A. Reversal of novel oral anticoagulants in patients with major bleeding. J Thromb Thrombolysis 2013; 35: 391–8
- 64. Tran H, Joseph J, Young L, et al. New oral anticoagulants: a practical guide on prescription, laboratory testing and peri-procedural/bleeding management. Australasian Society of Thrombosis and Haemostasis. Intern Med J 2014; 44: 525–36
- van Ryn J, Baruch L, Clemens A. Interpretation of point-ofcare INR results in patients treated with dabigatran. Am J Med 2012; 125: 417–20

- 66. Thrombosis Canada. New/Novel Oral Anticoagulants (NOACs) Perioperative Management 2015. Available from http:// thrombosiscanada.ca/wp-content/uploads/2015/01/NOACs-Peri-Operative-Management-2015Jan22-FINAL.pdf (accessed 25 October 2015)
- 67. Heidbuchel H, Verhamme P, Alings M, et al. EHRA practical guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation: executive summary. Eur Heart J 2013; 34: 2094–106
- 68. Ten Cate H. New oral anticoagulants: discussion on monitoring and adherence should start now! Thromb J 2013; 11: 8
- 69. Oldgren J, Wallentin L, Alexander JH, et al. New oral anticoagulants in addition to single or dual antiplatelet therapy after an acute coronary syndrome: a systematic review and metaanalysis. Eur Heart J 2013; 34: 1670–80

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