Implications of direct oral anticoagulation and antiplatelet therapy in intensive care

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Anticoagulation is essential for treating venous thromboembolism (VTE) and preventing systemic embolism in many cardiovascular conditions.

Until recently, vitamin K antagonists such as warfarin were the only available oral anticoagulants despite their poorly predicted pharmacokinetic profiles and frequent interactions with concomitant medications and food.[1] In the past decade, two new classes of agents, collectively known as direct oral anticoagulants (DOACs), have largely surpassed warfarin in terms of efficacy, safety and ease of use. In addition, novel antiplatelet agents have emerged, which are often used in addition to or as alternatives to aspirin. Increasing numbers of patients are taking these agents for prolonged periods, and thus clinicians in the critical care setting must be familiar with their use.

This article outlines the indications, actions, clearance and metabolism of these agents and provides a pragmatic approach to both DOAC-related major bleeding and perioperative planning for intensive care clinicians.

Anticoagulation with direct oral anticoagulants in patients in the intensive care unit (ICU)

Indication and mechanism of action of direct oral anticoagulants

In Australia, there are three available DOACS comprising two categories: the direct thrombin inhibitors (dabigatran) and the direct factor Xa inhibitors (apixaban and rivaroxaban). Both classes have predictable anticoagulant effects, rapid onset, ease of oral administration, relatively short half-life,

Figure 1. Coagulation pathway in normal haemostasis

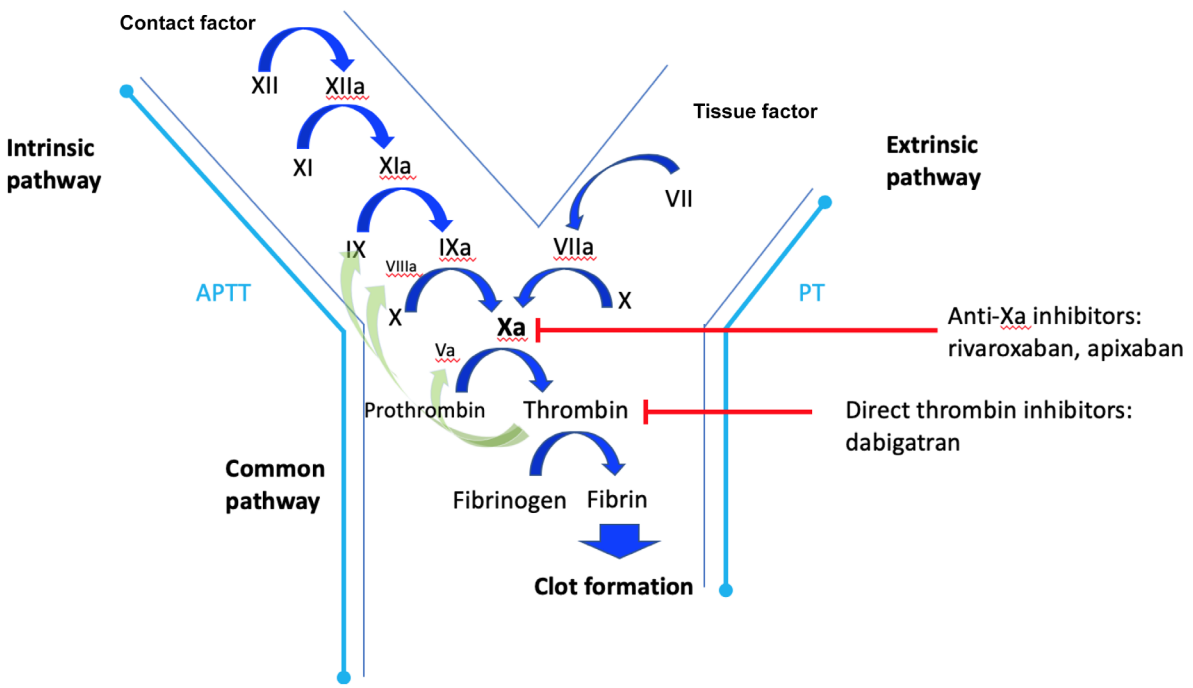

Table 1. Summary of the direct oral anticoagulants

	Dabigatran	Rivaroxaban	Apixaban
Method of action	Direct thrombin (IIa) inhibition	Direct anti-Xa	Direct anti-Xa
Clinical Indication	Prevention of stroke and systemic embolism in non-valvular AF	Prevention of stroke and systemic embolism in non-valvular AF	
	Prevention of VTE after TKR and THR	Treatment and prevention of DVT and PE	
	Treatment of DVT and PE/ Prevention of recurrent VTE (non-PBS indicated)		
Dose	150 mg twice a day	AF: 20 mg per day	AF: 5 mg twice a day
	CrCl 30–50 mL/min, patients aged > 75 years, or patients with increased risk of major bleeding; reduce dose to 110 mg twice a day	CrCl 30–49 mL/min: reduce dose to 15 mg per day	If two or more of the following: weight < 60 kg, age > 80 years, Cr > 33 μmol/L, then reduce dose to 2.5 mg twice a day
		VTE treatment: 15 mg twice a day for 21 days, followed by 20 mg per day thereafter	VTE treatment: 10 mg twice a day for 7 days, followed by 5 mg twice a day thereafter
		Long term thromboprophylaxis: 10 mg per day	Long term thromboprophylaxis: 2.5 mg twice a day
Half-life	12–17 h	5–13 h	8–15 h
Excretion	80% renal excretion	Renal excretion: ~70% (30% unchanged, 40% inactive)	25–27% Renal excretion
		Remaining 30% faecal excretion	
Metabolism	Substrate for P-gp	Substrate for P-gp CYP3A4 and CYP2J2	Substrate for transporter P-gp CYP3A4/5 (major)
Interactions	Inhibitors of P-gp: ketoconazole, quinidine, ciclosporin, verapamil, amiodarone, itraconazole	Strong inhibitors of CYP3A4: ketoconazole, clarithromycin, ritonavir and other HIV protease inhibitors	
	Inducers of P-gp: rifampicin	CYP3A4 inducers: rifampicin	
Reversal agents	Idarucizumab (5 g intravenous)	Andexanet (a decoy modified human factor Xa) recently approved in the United States, not currently available in Australia[3]	
		Consider use of PCC, such as Prothrombinex, or APCC, such as FEIBA	

AF = atrial fibrillation; APCC = activated prothrombin complex concentrate; Cr = creatinine; CrCl = creatinine clearance; DVT = deep vein thrombosis; FEIBA: factor eight inhibitor bypassing agent; HIV = human immunodeficiency virus; PCC = prothrombin complex concentrate; PBS = Pharmaceutical Benefits Scheme; PE = pulmonary embolism; P-gp = P-glycoprotein; THR = total hip replacement; TKR = total knee replacement; VTE = venous thromboembolism.

infrequent interactions with medications or foods, and no need for therapeutic monitoring[1,2] (Figure 1 and Table 1).

In treating VTE, DOACs are non-inferior to warfarin and may be associated with lower risks of bleeding.[4-7] In patients with atrial fibrillation, they are superior to warfarin in reducing stroke risk, all-cause mortality, and risk of intracranial and fatal bleeding.[8-10] Compared with warfarin, DOACs had 28% lower rates of major bleeding and 50% lower rates of intracranial and fatal haemorrhage.[11]

Dabigatran is a prodrug, and hydrolysis of the etexilate moiety leaves a specific but reversible direct thrombin inhibitor that inhibits both free and fibrin-bound thrombin[12,13] (Figure 1). When activated, thrombin converts fibrinogen to fibrin and activates platelets as well as factors V, VIII and XI, which positively feed back to further augment thrombin response[14] (Figure 1).

Factor Xa facilitates conversion of prothrombin to thrombin and is the rate-limiting step in thrombin generation and amplification. As such, direct factor Xa inhibitors, which bind to the active site of factor Xa, inhibit the activity of the prothrombinase complex (Figure 1), dramatically affecting clot formation.[15]

Clearance and metabolism of direct oral anticoagulants

In patients with normal organ function, DOACs display predictable pharmacokinetic and pharmacodynamic profiles.[15] Dabigatran is predominantly renally excreted (70–80%), and acute renal dysfunction can markedly extend the drug's half-life to potentially more than 30 hours.[16] Dabigatran is neither metabolised nor induced by cytochrome p450 but may interact with drugs utilising P-glycoprotein pathways[13] (Table 1).

Elimination of apixaban and rivaroxaban is less renally reliant (25% and 33% respectively),[15] although renal failure may prolong anticoagulant activity.[17] All three agents are contraindicated in patients with significantly impaired renal function (estimated glomerular filtration rate < 30 mL/min with rivaroxaban and dabigatran and 25 mL/min with apixaban).[17,18]

Direct Xa inhibitors are mostly hepatically cleared,[15] although little is known about the activity and elimination of these drugs in hepatic failure or cirrhosis.[19] Direct factor Xa inhibitors rely on the cytochrome p450 pathway and are susceptible to interactions with strong inhibitors or inducers of this pathway[15] (Table 1).

Laboratory investigations

The appropriate laboratory assay to assess anticoagulation is determined by the agent prescribed and the clinical objective. Anticoagulant concentrations may be measured in the context of acute bleeding, emergent surgery, thrombolytic therapy, major trauma, overdose of the agent or profound organ dysfunction. Furthermore, interpretation of traditional coagulation assays can be challenging due to a propensity for confounders, such as disseminated intravascular coagulopathy or transfusion-associated coagulopathy.

Unfortunately, conventional coagulation assays, such as activated partial thromboplastin (aPTT), prothrombin time (PT) and the international normalised ratio (INR), are variably and non-specifically affected by DOACs.[17-21] Typically, dabigatran will prolong aPTT, while the direct Xa inhibitors invariably prolong the PT (Figure 1). As such, routine coagulation testing may be helpful to broadly determine residual anticoagulant effect when specialised assays such as anti-Xa or HEMOCLOT (HYPHEN BioMed, France) are not available[2,17,18] (Table 2).

Specialised assays are increasingly available, which more accurately assess the presence and impact of these agents. Indirect measures, such as thrombin clotting time (TCT), dilute thrombin clotting time (HEMOCLOT) and ecarin clotting time, are functional clot-based assays sensitive for the presence of dabigatran.

Anti-Xa activity is a functional chromogenic assay used to measure factor Xa inhibition in a patient's sample. The anticoagulant present in the patient's plasma either binds the excess added factor Xa directly or inhibits it via antithrombin (in the case of heparin). The residual Xa activity is inversely proportionate to the concentration of the anticoagulant in the plasma sample and can be compared with a reference curve (calibrated specifically for each agent) to determine a drug concentration. Limited data are available on the relationship between DOAC levels and clinical outcomes. While published therapeutic ranges remain poorly defined, broad ranges of drug peak and trough levels have been described based on observational data from large numbers of patients receiving therapy[18] (Table 2).

Rotational thromboelastometry (ROTEM) and thromboelastography (TEG) detect significant amounts of residual DOAC in the systemic circulation. A number of small studies in vitro and in healthy volunteers have correlated reaction time (R time) — the time taken from the start of the assay to fibrin formation — with anticoagulant concentration,[21,22] although further studies in larger patient populations are needed.

Table 2. Summary of laboratory investigations to guide direct oral anticoagulants use

	Direct thrombin inhibitors (dabigatran)	Direct Xa inhibitors (rivaroxaban and apixaban)
Expected patterns in traditional coagulation testing		
Anticoagulant effect present	TCT prolonged and APTT prolonged	PT prolonged
Significant anticoagulant effect unlikely present	APTT and PT normal	PT normal
Confirmatory assay	Dilute thrombin clotting time (HEMOCLOT) TCT — highly sensitive	Modified anti-Xa assay

APTT = activated partial thromboplastin time; TCT = thrombin clotting time; PT = prothrombin time.

Direct oral anticoagulant-related major bleeding

Treatment of DOAC-related major bleeding should be underpinned by the general principles of managing significant bleeding from any cause and with astute anticipation of potential transfusion requirements. Specific management includes cessation of the drug, avoidance of additional absorption, optimisation of organ function (particularly renal function) and monitoring DOAC activity with an appropriate assay.[23] Early administration of activated charcoal within 2–6 hours of ingestion may be helpful in reducing the absorption or enterohepatic recirculation after ingestion of dabigatran and apixaban, but its role in other DOACs is unclear.[24,25]

In major life-threatening haemorrhage partial reversal of the anticoagulant activity and restoration of thrombin generation can be achieved with a prothrombin complex concentrate such as Prothrombinex (25–50 IU/kg).[3,23,26] However, uncertainty exists regarding the efficacy of this approach and the potential for thromboembolic complications.[17,23] Fresh frozen plasma does not restore thrombin potential but can be used as part of general resuscitation and massive transfusion guidelines.

Dabigatran is the only DOAC currently with a safe and effective reversal agent, idarucizumab,[27] which is indicated in the setting of life-threatening bleeding.[28] Specific reversal agents for the factor Xa-inhibitors are currently only available in clinical trials.[29,30]

There is no role for renal replacement therapy with either intermittent haemodialysis or continuous renal replacement in bleeding associated with factor Xa-inhibitors owing to significant drug–protein binding.[23] Dialysis may be considered in major bleeding associated with dabigatran if idarucizumab is unavailable,[2,17,31] but its role remains controversial.

No data exist on the use of antifibrinolytics such as tranexamic acid in DOAC-associated bleeding. Nevertheless, given their utility in other bleeding scenarios,[32,33] most expert guidelines suggest they be considered in the context of significant bleeding where no contraindications exist.[17,34]

ICU-related procedures and direct oral anticoagulants

While invasive surgical interventions require temporary discontinuation of a DOAC, less invasive procedures may not necessarily require discontinuation.[2,17,31] For invasive procedures that carry high risk of bleeding, it is generally recommended that the last DOAC dose be at least 24–48 hours before the procedure.[2,17,31,35] Nevertheless, clinicians must always weigh the risk of bleeding with potential complications of delaying procedures and prolonged cessation of anticoagulation. Central arterial and venous access should be placed as required, although preferably in compressible sites.

Emergency surgery

If a patient requires emergency surgery, the DOAC should be discontinued. If the procedure must be done immediately, reversal of the effects of anticoagulation as outlined above should be considered, but there is a paucity of evidence for efficacy and safety in these scenarios.[3,23,26,35] If the procedure can be deferred for 12–24 hours, reversal agents and prothrombin complex concentrates may be avoided if renal clearance is adequate.

Coagulation tests and drug plasma levels may assist in guiding these decisions. Expert consensus is that a normal aPTT and PT may rule out high plasma levels of dabigatran and rivaroxaban–apixaban respectively.[17,35] However, normal routine coagulation profiles do not exclude the presence of therapeutic plasma drug levels. Where possible, more specific testing relevant for the agent in question, such as anti-Xa assay in the case of apixaban or rivaroxaban or dilute TCT (HEMOCLOT) in the case of dabigatran, should be performed (Table 2).[18,28,35,36]

In the case of neuraxial blockade or diagnostic lumbar puncture, the British guidelines suggest cessation of therapeutic doses of apixaban, rivaroxaban and dabigatran for 48 hours prior.[37] The European and North American guidelines are more conservative and suggest interruption of all DOACs for at least 72 hours prior.[38,39] Such recommendations are based on expert opinion and the pharmacokinetics of these agents. Longer duration of cessation is recommended for patients who are older or have compromised renal function.[37] In such cases, anti-Xa assay or dilute TCT before the procedure is suggested where possible.

Recommencement of anticoagulation depends on the underlying indication for anticoagulation and the patient's ongoing risk for bleeding. Once the DOAC is cleared, alternative anticoagulation options may be considered. Unfractionated heparin infusions have the benefit of a very short half-life, but they can be challenging to maintain within an optimal therapeutic window. Low molecular weight heparin is an alternative that affords subcutaneous administration and monitoring assays, although it must be dose-adjusted for renal dysfunction.

Antiplatelet therapy in ICU patients

Indications for and mechanisms of action of antiplatelet therapy

Antiplatelet therapies are commonly seen in patients in the ICU due to their frequent multitude of comorbidities. Although antiplatelet agents generally have short half-lives, they often have protracted biological impact owing to

Table 3. Summary of the antiplatelet therapy

	Aspirin	Clopidogrel	Prasugrel	Ticlopidine	Ticagrelor	Cangrelor	Abcix-imab	Tirofiban
Class	Non-steroi-dal anti-in-flammatory	Thienopyridine prodrug	Thienopyridine prodrug	Thieno-pyridine prodrug	Nucleoside/ nucleotide derivative	Nucleoside/ nucleotide derivative	GPIIb/IIIa inhibitors	GPIIb/IIIa inhibitors
Method of action	COX-2 inhi-bition*	Blocks $P2Y_{12}$†	Blocks $P2Y_{12}$†	Blocks $P2Y_{12}$†	Blocks $P2Y_{12}$†	Blocks $P2Y_{12}$†	Blocks platelet integrin GPIIb/IIIa	Blocks platelet integrin GPIIb/IIIa
Inhibition	Irreversible	Irreversible	Irreversible	Irreversible	Reversible	Reversible	Irreversible	Reversible
Route	Oral	Oral	Oral	Oral	Oral	Intravenous	Intrave-nous	Intravenous
Frequency	Daily	Daily	Daily	Twice a day	Twice a day	Infusion	Infusion	Infusion
Half-life	15–20 min	6 h	7 h	4–5 days	1.5 h	3–6 min	30 min	2 h
Time to peak	20 min	4–6 h	1 h	1–3 h	2 h	2 min	10–30 min	10–30 min
Metabolism	Hepatic	Hepatic	Hepatic	Hepatic	na	na	na	na
Excretion	Renal	Renal/biliary	Renal	Renal/biliary	Biliary	Biliary	Renal	Renal
Duration of cessation before elective surgery	5–7 days	7–10 days	7–10 days	7–10 days	7–10 days	30 min	12–48 h	3–6 h
Reversal agents					Monoclonal antibody — PB2452‡			

COX-2 = cyclooxygenase 2; GPIIb/IIIa = glycoprotein IIb/IIIa; na = not applicable. * Preventing the conversion of arachidonic acid to thromboxane A2, a potent inducer of platelet aggregation. † $P2Y_{12}$ normally mediates sustained activation of the major platelet adhesion receptor GPIIb/IIIa. ‡ Currently only available in clinical trials.

irreversible platelet inhibition (Table 3). In addition, critically ill patients frequently have multifactorial thrombocytopenia, which can compound bleeding risk.

Aspirin (acetylsalicylic acid) is a non-selective and irreversibly inhibitor of cyclooxygenase 1 (COX-1) and 2 (COX-2), preventing the conversion of arachidonic acid to thromboxane A2, a potent inducer of platelet aggregation.[40] Aspirin is effective as secondary prophylaxis for preventing both recurrent myocardial infarction and stroke.[32] Recently, aspirin has been increasingly used in combination with other antiplatelet therapies or anticoagulation. Its role in primary prevention, particularly in older patients, has recently come under scrutiny due to the relatively high rates of major bleeding.[41,42]

Alternative antiplatelet agents include $P2Y_{12}$ inhibitors, and to a lesser extent, glycoprotein IIb/IIIa (GPIIb/IIIa) inhibitors (abciximab) and PAR-1 inhibitors (vorapaxar) are now available.[34,43] The $P2Y_{12}$ receptor mediates sustained activation of the major platelet adhesion receptor, GPIIb/IIIa, in response to ADP stimulation resulting in potent antithrombotic effects.[43] The $P2Y_{12}$ inhibitors comprise two classes of drugs: the thienopyridines (clopidogrel, prasugrel and ticlopidine) and the nucleoside/nucleotide derivatives (cangrelor and ticagrelor).[43] All thienopyridines are prodrugs that are converted, via hepatic metabolism or plasma-based esterases, to an active metabolite. In contrast, the nucleoside/nucleotide derivatives directly inhibit the $P2Y_{12}$ receptor, resulting in faster and more predictable antiplatelet activity.[43]

Multiple trials have demonstrated that combination dual antiplatelet therapy (DAPT) involving aspirin and a $P2Y_{12}$ inhibitor reduces ischaemic events when compared with aspirin alone,[44-46] and current guidelines recommend DAPT for patients with acute coronary syndrome and for those undergoing percutaneous coronary intervention.[47,48] Use of GPIIb/IIIa inhibitors, such as abciximab, tirofiban and eptifibatide, is restricted to a small number of high risk patients with myocardial infarction undergoing percutaneous coronary intervention without pre-treatment with a $P2Y_{12}$ antagonist, due to its propensity to cause bleeding in up to 50% of patients.[48,49]

Clearance and metabolism of antiplatelet therapies

Aspirin is rapidly hydrolysed to salicylic acid, which is metabolised primarily in the liver and excreted through the kidney as free salicylic acid or salicyluric acid.[40] While the half-life of aspirin is only 20 minutes, the inhibitory effects last the lifetime of the platelet, as binding is irreversible and COX cannot be regenerated within the platelet.[34,40,43] On cessation of aspirin, restoration of haemostatic activity requires regeneration of new platelets and thus takes around 5–7 days.[34]

Most thienopyridine derivatives are metabolised via the hepatic cytochrome p450 pathway to generate an active metabolite, which irreversibly binds to the $P2Y_{12}$ receptor by forming disulphide bridges between extracellular cysteine residues to prevent ADP-induced platelet activation.[40,43] Metabolism of these drugs demonstrates considerable interpatient variability. Metabolites of this class of drugs are extensively bound to serum proteins and elimination is generally via the faeces (50–70%) and urine (30–50%).[40]

The nucleoside/nucleotide derivatives such as ticagrelor are potent $P2Y_{12}$ inhibitors, with a half-life of around 8–12 hours.[34] There antiplatelet activity can persist for 3–5 days. By comparison, cangrelor has an ultra-short half-life (3–6 min), making it appropriate for clinical scenarios where rapid onset and offset is required[43] (Table 3).

Antiplatelet-related bleeding

Bleeding risk associated with antiplatelet therapy is affected by a number of factors, including age, gender, comorbidities and the use of concomitant antithrombotic agents.[44,49,50] In addition, major bleeding is an independent risk factor for recurrent ischaemic event, stroke and death in this patient group.[51,52] Table 3 outlines the duration of cessation of each agent in elective surgery.

The general principles of managing major bleeding related to antiplatelet therapy involve cessation of the drug, resuscitation and consideration of intervention where appropriate.[53] Thrombosis of drug-eluting coronary stents have long been a concern in the cessation or interruption of DAPT in critically ill or bleeding patients. Current data support the use of 6 months over 24 months of DAPT in patients with second-generation drug-eluting stents.[54] Nevertheless, premature cessation can result in life-threatening stent thrombosis, particularly within the first month.[55] Accordingly, careful deliberation and consultation with cardiology before early cessation of DAPT is required.

The antiplatelet effect of aspirin, clopidogrel and ticagrelor can persist for 5–7 days after drug cessation.[41,56] In the absence of specific reversal agents, platelet transfusion is frequently used in an attempt to restore normal haemostasis. Due to the short half-life of aspirin, platelet transfusion can be relatively effective in overcoming the haemostatic defect.[34,56] $P2Y_{12}$ inhibitors, such as clopidogrel, prasugrel and ticagrelor, have longer half-lives, and residual systemic active drug may have an impact on the activity of transfused platelets, necessitating higher volumes of transfusion to restore haemostasis.[34,56,57] A ticagrelor-specific reversal agent has recently been developed, which, in healthy volunteers, has been shown to provide immediate and sustained reversal of the antiplatelet effects of this agent.[58] However, further trials are required before this is available for use in clinical practice.

Although desmopressin restores platelet activity in healthy volunteers administered either aspirin or clopidogrel,[59,60] its role in ICU patients remains contentious. A meta-analysis in 2016 concluded that desmopressin may be useful and safe in patients receiving antiplatelet therapy undergoing cardiac surgery,[61] but concerns about adverse events, including thrombosis, hypertension and profound hyponatraemia, continue to limit its clinical use in these scenarios.

Conclusions

DOACs and antiplatelet therapy are widely used throughout our community. However, a paucity of data exists with regard to optimal management of such patients in an acute care setting. Additional studies are required to delineate how to best monitor and manage patients anticoagulated with DOACs, particularly in the setting of acute life-threatening bleeding. Careful deliberation to balance individual patients' risk of thrombosis versus bleeding, with input from relevant specialists, is integral to optimising patient outcomes in adverse scenarios.

Competing interests

None declared.

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