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Bleeding on oral anticoagulants: overview of reversal strategies

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Summary

Oral anticoagulants (antivitamin K, direct oral anticoagulants) are routinely prescribed for the prevention or treatment of thromboembolic events, and many patients are now on long-term anticoagulant therapy. However, this complicates the management of urgent surgical conditions or major bleeding. Various strategies have been developed to reverse the anticoagulant effect and this narrative review provides an overview of the wide range of therapies currently available.

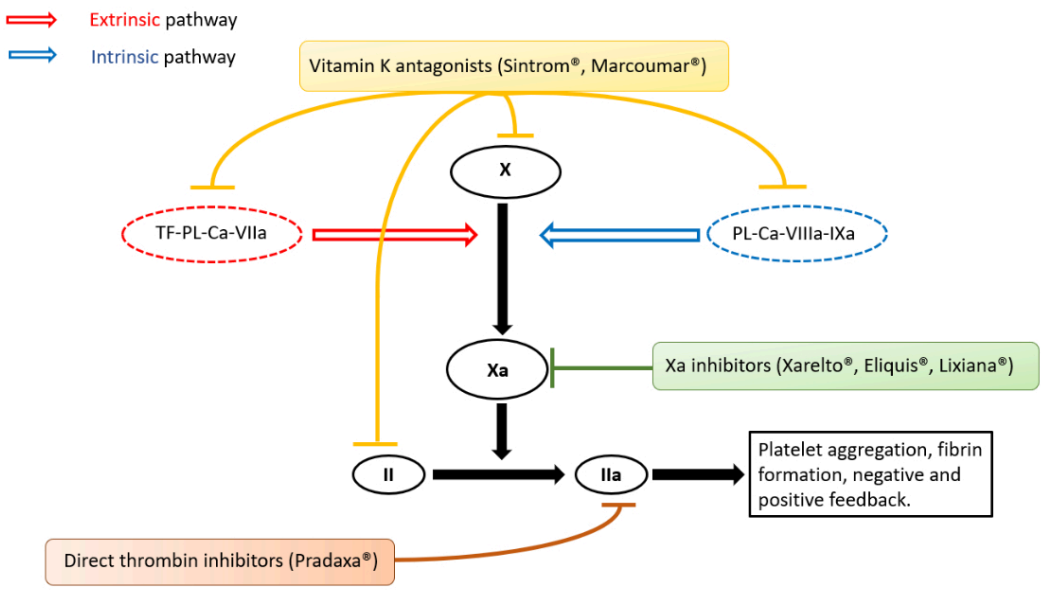
Introduction

Since their introduction more than 10 years ago, direct oral anticoagulants (DOACs) are now routinely prescribed in Switzerland. Rivaroxaban (Xarelto®, Bayer Vital GmbH Deutschland), a coagulation factor Xa inhibitor, was introduced in 2009 and approved in 2012 [1], followed a few years later by apixaban (Eliquis®, Bristol-Myers Squibb SA) and edoxaban (Lixiana®, Daiichi Sankyo), also factor Xa inhibitors (fig. 1).

Dabigatran (Pradaxa®, Boehringer Ingelheim Pharmaceuticals), a thrombin inhibitor (or direct factor IIa inhibitor) (fig. 1), also appeared in 2012 and completes the therapeutic range for stroke prevention in the context of atrial fibrillation, treatment of pulmonary embolism or deep vein thrombosis. Due to ease of prescribing and a better safety profile than vitamin K antagonists [2], the prescription of DOACs is becoming more important every year. However, major haemorrhage under anticoagulant therapy remains a dreaded complication for physicians faced with emergencies. The aim of this article is to provide an overview of the measures to be adopted by any physician confronted with these situations, based on current recommendations and the published literature.

The Medline database was searched for articles published since 1998 in English and dealing with topics in haema-

Figure 1: Simplified coagulation cascade (extrinsic and intrinsic) with targets of different anticoagulants.



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tology, and Google Scholar was searched for the literature in French language. The terms used were “major bleeding”, “anticoagulation reversal”, “laboratory measurement of anticoagulation” and “direct oral anticoagulants”.

Definition of acute situations requiring anticoagulation neutralisation

In an emergency, two situations must prompt rapid and effective neutralisation of anticoagulation: a major haemorrhage or surgery that cannot be delayed.

Severity of bleeding is defined according to the criteria of the International Society of Thrombosis and Hemostasis, published in 2005 and valid today [3, 4]. Major haemorrhage is defined as follows: fatal haemorrhage; haemorrhage in a critical area or organ; and haemorrhage that has resulted in a fall in haemoglobin of at least 20 g/l or has required the transfusion of more than two units of packed red blood cells in less than 1 hour [3, 4] (table 1).

It is important to recall that gastrointestinal haemorrhage should not be considered as a critical organ haemorrhage and it is the combination of the other criteria for severity of bleeding that should prompt coagulation correction. The anticoagulation control does not replace, but rather complements, the usual measures for treating haemorrhagic shock. Examples include external compression manoeuvres if the haemorrhage is external, tourniquet placement for major limb bleeding, pelvic girdling in the case of an unstable pelvic fracture, prevention of hypothermia, oxygen therapy, controlled and effective volume resuscitation and early administration of tranexamic acid if indicated [5]. In the case of surgery for certain conditions that cannot be deferred (e.g., open fracture, intracranial bleeding, amputation, intestinal perforation) [6], neutralisation of the anticoagulant must be discussed on a case-by-case basis by a multidisciplinary team (emergency doctor, surgeon, anaesthetist, other specialist), depending on the balance between the risks of bleeding and of thrombosis.

Coagulation monitoring and target values in the case of neutralisation

Conventional coagulation tests are used to determine the patient's degree of anticoagulation and to monitor the effectiveness of the treatment. Various tests (prothrombin time [PT], international normalised ratio [INR], partial thromboplastin time [PTT] or anti-Xa) should be considered, depending on the anticoagulant prescribed and the analytical resources available to the hospital (table 2).

It takes some time to obtain the results of these classical coagulation tests. Rotational thromboelastometry (ROTEM®, Rotem Medical) or thromboelastography (TEG®, Haemonetics) are whole blood analysis techniques that can be monitored in real time at the patient's bedside or at the point of care and thus allow a rapid assessment of the coagulation status and guidance for therapy based on the results. Of note, although they are now routinely used in the operating theatre, few emergency departments have access to them.

In cases of major bleeding (table 1) in patients on anticoagulants, rapid neutralisation of the anticoagulant effect without waiting for laboratory results is essential, regardless of the indication for treatment. It is important to emphasise that if a haemostatic procedure is required to control the bleeding, priority should be given to organising and performing the procedure [7]. Recognition of the severity of the bleeding and its origin is therefore essential. In a patient with a mechanical heart valve and a major haemorrhage, neutralisation of the anticoagulant should also be carried out while assessing the thrombotic risk associated with the delay before reintroduction of the anticoagulant [8]. Although activated charcoal is effective in reducing plasma concentrations of anticoagulants, its administration is not recommended in international guidelines in cases of major bleeding.

Vitamin K antagonists

With treatment with acenocoumarol (Sintrom®, Merus Labs International, plasma elimination half-life 8–11 hours), warfarin (Coumandine®, Bristol-Myers Squibb, plasma elimination half-life 35–45 hours) or phenprocoumone (Marcoumar®, Meda, plasma elimination half-life 160 hours), the degree of anticoagulation is quantitatively reflected by prolongation of the PT (in seconds), most often reported as the prothrombin rate expressed as a percentage (PT%), or the INR, which increases when the PT% is lowered [8] . Many protocols rely on INR results to guide anticoagulation neutralisation. Biologically, neutralisation of anticoagulation with vitamin K antagonists is considered effective when the INR is less than 1.3 [9, 10]. It is advisable to check the INR 30 minutes after a reversal and periodically thereafter, with the frequency determined by the severity of bleeding.

Direct oral anticoagulants

For patients on DOACs, conventional tests only randomly reflect effective anticoagulation. Specific tests have been developed and can be incorporated into routine practice (table 3) [9, 11, 12].

Table 1:
Criteria for major bleeding as defined by the Control of Anticoagulation Subcommittee of the International Society on Thrombosis and Hemostasis.

Fatal haemorrhage
Symptomatic bleeding into a critical organ or area such as the intracranial, intraspinal, intraocular, retroperitoneal, intraarticular, or pericardial space or intramuscular space with the development of compartment syndrome
Haemorrhage with a decrease in haemoglobin of at least 20 g/l (1.24 mmol/l) or requiring the transfusion of at least two units of packed red blood cells

Table 2:
Coagulation tests.

Coagulation tests	Abbreviations	Normal values
International normalised ratio	INR	0.8–1.2
Prothrombin time	PT	11 to 13.5 seconds
Activated partial thromboplastin time	aPTT	26–37 seconds
Diluted thrombin time	dTT	<20 seconds
Ecarin clotting time	ECT	22.6-29 seconds
Thrombin time	TT	14–19 seconds

Direct factor Xa inhibitors

For rivaroxaban (Xarelto®), apixaban (Eliquis®) or edoxaban (Lixiana®), the reference for assessing anticoagulation is the measurement of anti-Xa activity expressed in ng/ml and calibrated to the anticoagulant (table 3) [11, 13]. This allows an anticoagulant to be detected and its concentration to be determined. To achieve what is considered effective neutralisation, a result of less than 30 ng/ml in the case of invasive procedures or 50 ng/ml in the case of major bleeding is required [10, 14]. Although these tests can be performed in almost all Swiss hospitals, the time taken to obtain the results sometimes leads to the use of conventional tests. For example, a decrease in PT% or an increase in INR may indicate the presence of the molecule without giving any indication of its concentration. It should be recalled that normal results for these tests do not exclude the presence of effective anticoagulation [4, 11]. Direct determination by liquid chromatography-mass spectrometry or mass spectrometry is an alternative [14, 15].

Direct factor IIa inhibitor

For dabigatran (Pradaxa®), two assays are used to measure its concentration and correlate it with the level of anticoagulation: the diluted thrombin time (dTT) or the ecarin clotting time (ECT) expressed in seconds and converted in ng/ml. A result of less than 30 ng/ml in the case of invasive procedures or 50 ng/ml in the case of major bleeding is considered satisfactory for neutralising the anticoagulant effect of dabigatran [10, 11, 14]. Other less specific tests may reflect the presence of the drug in the blood without determining its concentration. A prolongation of the activated PTT (aPTT) expressed in seconds indicates significant anticoagulation but it is not excluded in the case of a normal result. As the TT is extremely sensitive to dabigatran, a normal value excludes the presence of the anticoagulant in the blood (table 3) [11, 12].

For each class of anticoagulant, a neutralisation strategy

Although bleeding on anticoagulants is a known problem, few randomised studies have been carried out on large populations [13, 16] and even fewer with a control arm [17, 18], mainly because of the difficulty of carrying out such studies in extreme emergencies. Therefore, strategies for anticoagulation neutralisation are based mainly on expert consensus [4, 6]. Regardless of the strategy chosen (table 4), it is usually recommended that coagulation tests be repeated after administration of the various therapies, with the timing depending on the type of antidote administered [19], and that the efficacy of the treatment instituted be reassessed at short intervals (table 5). However, the clinician must be careful with specific antidotes. For example commercial anti-FXa-activity assays are unsuitable for measuring anti-FXa activity following administration of andexanet alfa as these assays result in erroneously elevated anti-FXa activity levels, thereby causing a substantial underestimation of the reversal activity of andexanet alfa.

Vitamin K antagonists

In the case of vitamin K antagonist anticoagulation, neutralisation consists of the administration of 10 mg oral or intravenous vitamin K1 (phytomenadione; Konakion®, Neon Healthcare Ltd.) (table 5). However, the peak effect of vitamin K1 has a delay of 4-6 hours after administration, with maximum efficacy at 24–48 hours [20]. Thus, it is recommended to administer prothrombin complex concentrate (PCC) (Beriplex® CSL Behring AGP, Octaplex® Octapharma AG or Prothromplex® Takeda Pharma AG) at the same time in order to supplement coagulation factors during the first 6–10 hours, with a dosage adapted to the initial measured prothrombin rate, the target prothrombin rate after administration of the product, and the patient's weight (according to the formula for PCC: dose (IU) = body weight x 40 x [targeted − measured prothrombin rate]/100). An alternative strategy is to adjust the dose of PCCs solely to the baseline INR value (table 6) [21].

Table 3:
Laboratory results indicating the presence of an anticoagulant effect according to laboratory results and type of anticoagulation.

	INR	aPTT	anti-Xa activity	dTT or ECT	TT
Anti-vitamin K (Marcoumar®, Sintrom®)	>1.8, correlated with concentration	>37 s	–	–	–
Anti-Xa (Xarelto®, Eliquis®, Lixiana®)	Normal or increased	Normal or increased	>30–50 ng/ml, correlated with concentration	–	–
Anti-IIa (Pradaxa®)	Normal	Normal or increased	–	>50 ng/ml, correlated with concentration	Increased, but not quantitative

PT: prothrombin time; INR: International normalised ratio; aPTT: activated partial thromboplastin time; dTT: diluted thrombin time; ECT: ecarin clotting time; TT: thrombin time

Table 4:
Management strategy for major bleeding according to anticoagulant.

Molecules		Strategies	
		1	2
Anti-vitamin K	Acenocoumarol (Sintrom®)	Prothrombin complex concentrate + vitamin K	Fresh frozen plasma + vitamin K
	Warfarin (Coumadine®)		
	Phenprocoumone (Marcoumar®)		
Direct factor IIa inhibitor	Dabigatran (Pradaxa®)	Idarucizumab	Prothrombin complex concentrate
Direct factor Xa inhibitors	Rivaroxaban (Xarelto®)	Andexanet alfa (Rivaroxaban, Apixaban): if critical and available!	Prothrombin complex concentrate
	Apixaban (Eliquis®)		
	Edoxaban (Lixiana®)		

If an INR is not available at the start of management, a dose of 25 IU/kg is recommended. The maximum dose is set at 3000 IU intravenously but will usually vary between 1000 and 2500 IU intravenously, administered at a rate of 8 ml/min – 200 IU/min (Beriplex®), 3 ml/min – 75 IU/min (Octaplex®) or 1 ml/min – 30 IU/min (Prothromplex®) [19].

Fresh frozen plasma (FFP) is no longer used as a first-line treatment for anticoagulation neutralisation because of the risk of adverse effects related to the amount of fluid administered, delay in delivery, risks of transfusion and its lack of

Table 5:
Drugs administered to neutralise anticoagulation of different anticoagulants and the effective cost of drugs administered for a 70 kg adult patient.

	Indication	Dosage	Major contraindications	Major side effects	Pharmacology	Cost for reversal
Vitamin K (Phytomenadione, Konakion®)	Anticoagulation with VKA	10 mg IV over 20 minutes	Component-related anaphylactic reaction	Anaphylactic reaction associated with a component	Synthesis of factors II, VII, IX and X	Approx. CHF 3
				No effective anticoagulation for the next 2 weeks	Onset usually 1 to 2 hours after medication, peak after 4 to 6 hours	
					Hepatic absorption	
PCC (Beriplex®, Octaplex®, Prothromplex®)	Anticoagulation with VKA, anti-Xa or anti-IIa	If VKA: According to the formula Dose (IU) = body weight x 40 x [Targeted - measured prothrombin rate]/100 -> if no INR available: 1750 IU (25 IU/kg)	Component-related anaphylactic reaction	Increased risk of thromboembolic events	Supplementation of human factors II, VII, IX and X	Approx. CHF 1180 for 1750 IU
		If anti-Xa: 2100–3500 IU (30 or 50 IU/kg depending on clinical context)	Heparin-induced thrombocytopenia	Headache	Half-lives vary from 4 hours (factor VII) to 60 hours (factor II)	Approx. CHF 1420 for 2100 IU
		If anti-IIa: 2100–3500 IU (30 or 50 IU/kg depending on clinical context)	Caution in patients with a history of disseminated intravascular coagulopathy, pulmonary embolism or myocardial infarction			Approx. CHF 2360 for 3500 IU
FFP	VKA anticoagulation in the absence of PCC	700–1050 ml total (10–15 ml/kg)	Patients with circulating anti-IgA antibodies	Hypervolaemia associated with transfusion	Supplementation of plasma proteins and factors	Approx. CHF 400 for 700 ml
				Cardiac decompensation in heart disease	Half-lives vary according to different coagulation factors	Approx. CHF 570 for 1050 ml
				Post-transfusion respiratory distress		
Andexanet alfa (Ondexxya®)	Anticoagulation with rivaroxaban (Xarelto®), apixaban (Eliquis®)	Low dose: Rivaroxaban ≤10 mg, apixaban ≤5 mg, Elapsed time >8 h regardless of dose: bolus 400 mg at 30 mg/min, then infusion 480 mg at 4 mg/min	Component-related anaphylactic reaction	Increased risk of thromboembolic events	Reversible binding of factor Xa	Approx. CHF 12,300 for low-dose therapy
		High dose: Rivaroxaban >10 mg; apixaban >5 mg with elapsed time <8 h: bolus 800 mg at 30 mg/min, then infusion 960 mg at 8 mg/min		Common infusion reactions	Half-life of 4–7 h	Approx. CHF 22,200 for high-dose therapy
					Low renal elimination	
					Degraded by endogenous proteases	
Idarucizumab (Praxbind®)	Anticoagulation with dabigatran (Pradaxa®)	2 boluses of 2.5 mg at 15 min interval	Component-related anaphylactic reaction	Increased risk of thromboembolic events	Irreversible binding of dabigatran	Approx. CHF 4000
					Half-life of 9.5–10.8 h	
					Hepatic metabolism and renal elimination	
rFVIIa (Novoseven®)	Failed first-line therapies	6300 µg administered over 5 min (90 µg/kg)	Component-related anaphylactic reaction	Increased risk of thromboembolic events	Activated factor VII	Approx. CHF 5270
					Half-life approx. 2.5 h	
FXIII (Fibrogammin®)	Failed first-line therapies	1050–1400 IU maximum dose 250 IU/min	Component associated anaphylactic reaction	Increased risk of thromboembolic events	Factor XIII	Approx. CHF 910 for 1050 IU
					Half-life approx. 6–8 days	Approx. CHF 1130 for 1400 IU

VKA: vitamin K antagonist; PT: prothrombin time; INR: International normalised ratio; FFP: fresh frozen plasma; aPTT: activated partial thromboplastin time; dTT: diluted thrombin time; ECT: ecarin clotting time; TT: thrombin time; PCC: prothrombin complex concentrate

Table 6:
Administration of prothrombin complex concentrate (PCC) according to baseline international normalised ratio (INR) value in major bleeding on vitamin K antagonists.

Baseline INR	Value PCC dose in IU/kg
2–4	25
4–6	35
>6	50

efficacy in restoring normal haemostasis, as well as the risk of thromboembolic events [20, 22]. Thus, if PCC is available, the use of FFP is not recommended. In the absence of available PCCs, however, 10–15 ml/kg of FFP can be administered (i.e., for a 70 kg patient, usually 3–4 units) [20] (table 4).

Direct oral anticoagulants

Several antidotes to oral anticoagulants are now available. Other promising therapies are currently under development, such as ciraparantag, a synthetic molecule that reverses all DOACs. In the absence of sufficient data, they are not developed here.

Direct factor Xa inhibitors

Since the end of 2020, andexanet alfa (Ondexxya®, AstraZeneca AG) has been approved in Switzerland as an antidote to rivaroxaban (Xarelto®, Bayer (Schweiz) AG) and apixaban (Eliquis®, Bristol-Myers Squibb SA), following the results of the ANNEXA-4 study. This drug is an inactive recombinant of coagulation factor Xa that neutralises the activity of factor Xa inhibitors. This study showed a significant decrease in anti-Xa activity and excellent haemostasis in patients receiving andexanet alfa [18], but further studies are needed owing to the small number of patients enrolled.

The dosage of the antidote varies according to the dose and the time since the last anticoagulant dose [6, 23] (table 5). If the last dose is low (rivaroxaban ≤10 mg or apixaban ≤5 mg) or the time is >8 hours regardless of the dose, andexanet alfa can be given at a low dosage (400 mg bolus at a rate of 30 mg/min, followed by a 480 mg infusion at a rate of 4 mg/min). If the last dose of anticoagulant is high (rivaroxaban >10 mg or apixaban >5 mg) with a delay of <8 hours, the dosage of andexanet alfa will be high (bolus of 800 mg at a rate of 30 mg/min, followed by an infusion of 960 mg at a rate of 8 mg/min). Some hospitals also adjust the regimen according to specific anti-Xa activity (low dose if anti-Xa 100–200 ng/ml; high dose if anti-Xa >200 ng/ml). It is important to note that the measurement of anti-Xa activity after administration of andexanet alfa is not reliable [24].

However, this antidote is extremely expensive and carries a significant thromboembolic risk, and it is not yet widely used in all Swiss hospitals. The indications are strictly limited to severe bleeding and defined by each institution. In cases where the antidote is not available or where bleeding is excluded from the restrictive criteria, first-line administration of PCC is recommended at a dosage of 30–50 IU/kg [4, 6, 23] (table 5). In Switzerland, Swissmedic has not yet given its approval for the use of this antidote in patients treated with edoxaban (Lixiana®) in the absence of formal studies, despite the fact that its action profile is similar to that of other molecules [25].

Direct factor IIa inhibitor

An antidote to dabigatran (Pradaxa®, Boehringer Ingelheim GmbH) has been available in Switzerland since 2016. Idarucizumab (Praxbind®, Boehringer Ingelheim Pharmaceuticals) is a humanised monoclonal antibody fragment that binds to dabigatran with high affinity and rapidly reverses its anticoagulant effect (nonrandomised prospective REVERSE-AD study) [17]. Idarucizumab should be administered in two boluses of 2.5 mg intravenously at an interval of no more than 15 minutes [17, 20] (table 5). In the absence of idarucizumab, the administration of PCC at a dose of 30–50 IU/kg is recommended [20] (table 6). Despite a good safety profile, the cost of this treatment is not negligible and it seems reasonable to use Idarucizumab in life-threatening situations [25]. Note that dabigatran is predominantly eliminated by the kidneys. However, haemodialysis is no longer a first-line option for neutralising since the development of the specific antidote [26].

In the case of failure of first- and second-line treatment

Recombinant activated factor VII (rFVIIa; eptacog alfa, Novoseven®, Novo Nordisk Inc.) can be considered as an option when a first neutralisation strategy has not improved haemostasis. Only a few studies have evaluated the use of off-label prescription of rFVIIa for anticoagulation neutralisation. Despite good results in rapidly improving INR and haemostasis, the high risk of thrombotic events and the lack of data make rFVIIa a drug of last resort [26]. If necessary, rFVIIa at a dose of 90 µg/kg over 5 minutes is proposed, with the possibility of repeat dosing (table 5).

Human recombinant factor XIII (FXIII, Fibrogammin®, CSL Behring AG) can also be offered as an off-label treatment in situations where the first lines of neutralisation have failed. A dose of 15–20 IU/kg is recommended with intravenous administration and a maximum dose per minute of 250 IU (table 5).

Conclusions

Anticoagulation neutralisation for DOACs has made significant progress in recent years. The development of specific tests and the introduction of various antidotes now make it possible to optimise and codify the management of patients requiring urgent neutralisation. The formal indications and strategies for emergency reversal according to the molecules (and their pharmacokinetics) must be known. Neutralisation of the anticoagulant effect must always be weighed against the risk/benefit balance, bearing in mind the undesirable effects, particularly thrombo-embolic, and the considerable costs of these antidotes. It is certain that these recommendations will evolve over time. They will have to be adapted with the marketing of new molecules and future studies.

Practical implications

- Emergency anticoagulation reversal is necessary in the case of major bleeding or when surgical management cannot be delayed.
- Specific tests are available for different anticoagulants: PT/INR for vitamin K antagonists, anti-Xa activity for direct factor Xa inhibitors, and ECT or dTT for direct factor IIa inhibitor.
- Each anticoagulation has its own antidote: vitamin K and PCC for vitamin K antagonists; andexanet alfa or PCC for direct factor Xa inhibitors (rivaroxaban and

apixaban only); idarucizumab or PCC for direct factor IIa inhibitor.

– If first-line treatments fail, recombinant factor VIIa or factor XIII may be considered.

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