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# New agents for DOAC reversal: a practical management review

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**Bleeding is the commonest and most concerning adverse event associated with anticoagulants. Bleeding, depending on the severity, is managed in various ways, and for severe or life-threatening bleeding, specific antidotes are indicated and recommended. This review provides guidance relating to specific direct oral anticoagulant (DOAC) reversal agents, the antidotes. We discuss their indications for use, dosing, and potential side effects.**

## Introduction

Anticoagulation is utilised in the management of venous thromboembolism and to prevent thrombotic complications in patients with cardiac comorbidities, e.g. atrial fibrillation (AF), valvular heart disease, congenital heart disease, and other indications. Direct oral anticoagulants (DOACs), also known as NOACs (non-vitamin K antagonist oral anticoagulants), have shown superior efficacy, safety, adherence and tolerability over traditional anticoagulants, such as vitamin K antagonists and low-molecular weight heparins, and this has resulted in a paradigm shift with DOACs as the preferred options for most patients with thrombotic disorders.[1-3]

DOACs can be subclassified as inhibitors of clotting factor Xa (FXa) such as rivaroxaban, apixaban and edoxaban, and inhibitors of clotting factor IIa (FIIa) such as dabigatran etexilate. National Institute for Health and Care Excellence (NICE) guidance recommends DOACs (apixaban, edoxaban, rivaroxaban and dabigatran) for AF with a $CHA_2DS_2$-VASC score ≥2 and to consider anticoagulation with a score of 1.[4] A vitamin K antagonist is advised if a DOAC is contraindicated or not tolerated, and, for those established on warfarin, a transition to a DOAC should be offered.

Similarly, for suspected venous thromboembolism


(VTE), DOACs are initiated while awaiting a confirmatory scan, in preference to low-molecular-weight heparin, in the absence of any contraindication, and are the agent of choice for a confirmed VTE, including in cancer patients.[5] Furthermore, DOACs are utilised in specific settings for prophylaxis during periods of particularly high risk, such as following orthopaedic surgery.[6]

## Bleeding – incidence and risk factors

Bleeding is the primary risk with any anticoagulant therapy, but compared with traditional vitamin K antagonists (such as warfarin), the risk is generally thought to be lower with DOACs due to their shorter half-lives (ranging from 5 to 17 hours), more predictable pharmacokinetics, and reduced food/drug interactions. Superior safety outcomes were demonstrated in the DOAC versus vitamin K antagonist phase III trials in patients with non-valvular AF and VTE. The bleeding incidence varies according to the severity of bleeding (major, clinically relevant non-major or minor bleeding), the type of DOAC, the indication, and individual risk factors.

### Bleeding incidence and mortality in trials and observational data

The risk of bleeding with DOACs in patients with AF (rates per 100 patient-years) versus vitamin K antagonists were compared in separate studies. These data showed a range for major bleeding of 1.6–3.6 versus 3.1–3.6; major plus clinically relevant

non-major bleeding 4.1–20.1 versus 3.0–20.3; intracranial haemorrhage (ICH) 0.2–0.5 versus 0.7–0.9; and major gastrointestinal (GI) bleeding 0.8–3.2 versus 0.9–2.2. [7] The risk of major bleeding with oral anticoagulants in patients with VTE is 2% to 3% per year. In patients with VTE, after the first three months, bleeding rates per 100 patient-years for major bleeding are 2.7 and for ICH 0.65.[8]

Observational data in the UK have shown the standardised risk rate for major bleeding per 1,000 person-years is 21.8 for dabigatran, 26.5 for rivaroxaban and 15.4 for apixaban. The use of DOACs is increasing in the UK.[9] For DOAC-related major bleeds, around 30% to 50% of bleeds occur in the GI tract, and around 10% to 25% of major bleeding events are ICHs.[10-12] Mortality from major bleeding associated with DOAC use is 7.6% (*vs.* 11% on VKA).[13] For DOACs, ICH-related 30-day mortality ranges from 45% to 48%.[14,15]

Bleeding risk scores have previously been developed for AF indications, such as HAS-BLED, ABC, ORBIT, ATRIA and HEMORR$_2$HAGES. Other scores have been developed for VTE. A high score should trigger a review of the indication, risks and benefits, the duration of therapy in the VTE setting and addressing any modifiable factors to ameliorate bleeding risk.[2] Risk factors can be classified into modifiable, potentially modifiable and non-modifiable.[2] Most of the risk factors are more prevalent with increasing age. Routine monitoring of DOACs is not required in the same way that it is with vitamin K antagonists, but patients should be counselled regarding bleeding risk, including signs and symptoms of occult bleeding. Patients should be regularly examined for bleeding, anaemia and modifiable risk factors.

### Modifiable bleeding risk factors

These include systemic hypertension (especially with systolic blood pressure >160 mmHg), alcohol excess (>8 units/week) and medications predisposing to bleeding, such as antiplatelet therapy, non-steroidal anti-inflammatory drugs (NSAIDs) and selective serotonin reuptake inhibitors (SSRIs). Antiplatelet agents are often used in combination with DOACs, usually in the setting of arterial vascular disease, such as acute coronary syndromes, and data show concomitant use escalates the bleeding risk and, hence, the risk–benefit needs to be assessed. Other medications, such as strong inhibitors of P-glycoprotein or CYP3A4 can potentiate DOAC levels and increase the risk of bleeding. These need to be reviewed before starting a DOAC, and carefully considered if commenced while on DOAC treatment, particularly if long-term anticoagulation is indicated.[2]

### Potentially modifiable bleeding risk factors

Renal dysfunction increases bleeding risk, the greater the dysfunction the higher the bleeding risk (6.8% *vs.* 3.8% for moderate *vs.* mild), and worsening renal function is associated with higher drug concentrations due to poor excretion,[12] the dosing of DOACs reflects this. Liver and platelet dysfunction, anaemia and very low body weight can also increase the bleeding risk, and DOAC levels should be considered in these patients.

### Non-modifiable risk factors

Age is the most important non-modifiable risk factor associated with an increased risk of bleeding. Paradoxically, this category also benefits more from anticoagulation to prevent thrombotic complications. A prior history of bleeding, genetic factors, dialysis dependence/kidney transplant, previous stroke, liver cirrhosis and malignancy also increase the bleeding risk.[2]

## Bleeding – classification

Defining the severity and extent of the bleed can help direct treatment, definitions are often subjective.

**Mild bleeding** includes most milder, often self-limiting presentations of epistaxis, ecchymosis, mucosal bleeding, menorrhagia and haematuria. Management consists of temporarily discontinuing the DOAC, using appropriate local measures to stop the bleeding, supportive care and ensuring haemodynamic stability.

**Moderate bleeding** is bleeding that will result in a clinical review usually requiring intervention and/or hospitalisation. Examples include bleeding from the upper and lower GI tract, the respiratory tract and the urogenital tracts that does not require transfusion and is not associated with significant anaemia. The DOAC should be stopped and supportive measures instituted such as haemodynamic support, volume replacement, specific interventions (e.g. endoscopic or surgical haemostasis) and maintaining diuresis.

**Major bleeding.** There are a number of definitions for major bleeding, varying in sensitivity. One of the most sensitive is the International Society on Thrombosis and Haemostasis (ISTH) definition of major bleeding:[16]

- Fatal bleeding, and/or
- Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intra-ocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome, and/or
- Bleeding causing a fall in haemoglobin level of 20 g/L (1.24 mmol/L) or more, leading to transfusion of two or more units of whole blood or red cells.

The DOAC should be stopped. Ideally the specific reversal agents are used, but if not available, then prothrombin complex concentrate (PCC) at 50 IU/kg (hospitals usually have a cap on dosing) should be given and haemodialysis should be considered for dabigatran.

Once the bleeding has stopped, the patient should be re-assessed for suitability of the DOAC and when to restart it. Patients experiencing DOAC-associated bleeding are also at increased risk of developing subsequent thrombotic events, with those experiencing ICH being most at risk. Often the changes/interruptions in antithrombotic treatment can contribute to this risk.

## Management of bleeding

### General measures

All DOAC-associated bleeding should be initially managed in the same way, after this, specific management depends on the severity of bleeding. DOACs have short half-lives, so a conservative approach only may be needed. The DOAC should be stopped, and the amount of DOAC onboard should be established by considering the dose, when it was last taken, the age of the patient, renal and liver function, along with considering other drugs and comorbidities, to establish the full bleeding potential.

**Table 1. Investigations for patients with moderate-to-severe direct oral anticoagulant (DOAC)-associated bleeding**

| Laboratory test | Initial assessment | Repeat after reversal |
|---|---|---|
| Creatinine & urea | • | |
| Ionised calcium | • | • |
| Liver function | • | |
| Full blood count | • | • |
| Prothrombin time (PT) | • | • |
| Activated partial thromboplastin time (APTT) | • | • |
| Dilute thrombin time (dTT) | • | • |
| DOAC level | • | • |
| Fibrinogen | • | • |
| Group and screen | • | |

A full set of bloods should be taken (**table 1**) at initial assessment along with a DOAC level, coagulation profile (activated partial thromboplastin time [APTT], prothrombin time [PT], fibrinogen) and a group and screen. Some of these blood tests will need to be repeated, dependent on the treatment the patient receives.[17]

The dilute thrombin time is useful in assessing how much dabigatran is onboard: if normal or measurable it suggests low levels of dabigatran. A dabigatran-calibrated assay is available in some hospitals. The APTT/PT are not very useful in determining the amount of FXa inhibitor, as their sensitivity depends on which reagents are used, so it is laboratory specific. DOAC-calibrated assays are now available in many institutions, and these give a good idea of how much anticoagulation is onboard. A coagulation profile is a useful baseline test to have, especially if the patient is going to receive a large amount of blood, and fresh frozen plasma/cryoprecipitate may need to be given later as part of the major haemorrhage protocol.

A basic life support approach of ABC (airway, breathing, circulation) with fluid resuscitation, blood transfusion, triggering of the major haemorrhage protocol, if needed, and attempting local haemostasis, for example applied pressure. Tranexamic acid should be given if appropriate. Removal of the oral anticoagulant with gastric lavage, oral charcoal (if <2 hours since ingestion) or dialysis for dabigatran can be considered. However, these methods are rarely used as DOACs are absorbed rapidly after oral administration, also now that idarucizumab is available, dialysis is uncommon and activated charcoal is rarely used.[18] Activated charcoal can also make management of the airway difficult if endoscopy is needed as it can be emetogenic.

Investigations to determine the site/cause of bleeding should be undertaken and then endoscopic, surgical or radiological measures implemented to stop the bleeding at source. This should be running in parallel with haemostatic support and reversal of the DOAC, if needed.

## Reversal agents and antidotes

Specific treatment depends on the severity of the bleeding and the DOAC. There are two specific reversal agents (antidotes) approved for reversal of a DOAC: idarucizumab is approved for reversal of the direct thrombin inhibitor dabigatran, and andexanet alfa is approved for reversal of the direct FXa inhibitors apixaban and rivaroxaban (**table 2**).[18,19] There are currently no approved reversal agents for the other direct FXa inhibitors; edoxaban and betrixaban. LMWH can be reversed by protamine, which is a highly cationic peptide that binds unfractionated heparin completely or LMWH partially, to form a stable inactive salt pair that has no anticoagulant activity.

## Prothrombin concentrate complex (PCC)

PCC has been developed to contain highly concentrated coagulation factors (II, IX, X in three-factor [3-F] PCC and II, VII, IX and X in four-factor [4-F] PCC) to help replenish coagulation factor deficits in warfarin and haemophilia patients. However, the clinical trial evidence did not show an effect on important clinical outcomes to support their use for vitamin K antagonist-related bleeding. Sarode *et al.* compared 4-F PCC with plasma for urgent vitamin K antagonist reversal in bleeding patients and found there was no statistically significant difference in effective haemostasis between the two interventions. The only finding was that 4-F PCC did achieve international normalised ratio (INR) correction more rapidly than those in the plasma group.[20]

PCC have been used for DOAC-associated bleeding, in an off-label fashion, before the specific reversal agents appeared. They are now used if specific reversal agents are not available or if there is no specific reversal agent approved, such as with edoxaban. Their aim is to boost factor levels and, thereby, 'overwhelm' the inhibitors. However, they do not directly inhibit the DOAC, nor do they affect FXa levels.[21] 4F-PCC also do not reverse inhibition of thrombin generation (TG) by DOACs in therapeutic or supratherapeutic levels that are usually seen in DOAC-related bleeding. 4F-PCC are only able to normalise TG over a low and narrow range of FXa inhibitor concentrations (<75 ng/ml).[22]

## Dabigatran reversal

Idarucizumab is a humanised monoclonal antigen binding fragment (Fab) antibody that binds dabigatran with 350 times more avidity than thrombin, and rapidly reverses its anticoagulant effect. It has no intrinsic activity in the coagulation system, providing immediate, complete and sustained reversal of the dabigatran effect.[18]

The patient is given a 5 g dose, given as two 50 ml bolus infusions of 2.5 g, no more than 15 minutes apart. Idarucizumab can re-enter the circulation from the extravascular space between 12 and 24 hours after reversal, so if a patient shows new/recurrent bleeding/needs further surgery with a prolonged clotting time, a further dose should be considered. No dose adjustment is required in the elderly, those with renal or hepatic impairment. There are no data on pregnant women or breast feeding.

It has been licensed by the European Medicines Agency (EMA) and Food and Drug Administration (FDA) in the USA for emergency surgery/urgent procedures, and in life-threatening or uncontrolled bleeding. Licensing was based on the phase III RE-VERSE AD (A Study of the RE-VERSal Effects of Idarucizumab on Active Dabigatran) trial.[18] There were no serious adverse safety signals and at 90 days thromboembolic events

**Table 2. Characteristics of specific DOAC antidotes**

| | Andexanet alfa (Ondexxya® ▼)[19] | Idarucizumab (Praxbind®)[18] |
|---|---|---|
| Reversal agent for | Factor Xa (FXa) inhibitor (apixaban, rivaroxaban) | Dabigatran |
| Mechanism | • Recombinant inactive form of human FXa<br>• Binds and sequesters FXa inhibitor molecules<br>• Rapidly reduces anti-FXa activity | • Humanised monoclonal antibody fragment<br>• Binds dabigatran with high affinity and specificity |
| Trials | ANNEXA-A and -R, ANNEXA-4 | RE-VERSE AD |
| Dose | Low dose: 400 mg (rate 30 mg/min) bolus and 4 mg/min for 120 mins infusion<br><br>High dose: 800 mg (rate 30 mg/min) bolus and 8 mg/min for 120 mins infusion | 5 g (2 vials of 2.5 g/50 ml) and second dose can be given if needed |
| Administration | See **tables 3 and 4** | Intravenous infusion over 5–10 minutes or bolus injection |
| Indications | Life-threatening or uncontrolled bleeding on apixaban or rivaroxaban | Life-threatening or uncontrolled bleeding on dabigatran |
| Contraindications | Hypersensitivity to ingredients or known allergic reaction to hamster proteins | None |
| Storage | Three-year storage if refrigerated (2–8°C), do not freeze | Refrigerated (2–8°C), do not freeze. Can be kept at room temperature for 48 hours |
| Adverse reactions | Infusion-related common, e.g. flushing, hot, urticaria, dizziness, headache, cough | Hypersensitivity, e.g. rash, allergic reactions including anaphylaxis (very rare) |
| Safety* | 10% thrombotic event within 30 days | 4.8% thrombotic event within 30 days |
| Recommendations | Accepted by SMC for life-threatening or uncontrolled bleeding<br><br>Recommended by NICE for life-threatening/uncontrolled GI bleeds. It is recommended only in research in ICH (ANNEXA-I trial) but not other major bleeds | Accepted by SMC for life-threatening or uncontrolled bleeding |
| NHS cost | £11,100 per pack (4 × 200 mg vials) | £2,400 per 5 g (2 × 2.5 g/50 ml) |

* The safety profile between andexanet alfa and idarucizumab is not directly comparable due to differing populations in the studies.

**Key:** GI = gastrointestinal; ICH = intracranial haemorrhage; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; SMC = Scottish Medicines Consortium

**Table 3. Summary of dosing reversal based on timing and size of last dose**

| Factor Xa inhibitor | Last dose | Timing of last dose before andexanet alfa initiation | |
|---|---|---|---|
| | | <8 hours or unknown | ≥8 hours |
| Apixaban | ≤5 mg | Low dose | Low dose |
| | >5 mg/unknown | High dose | |
| Rivaroxaban | ≤10 mg | Low dose | Low dose |
| | >10 mg/unknown | High dose | |

occurred in 6.3% of patients reversed for haemorrhage and in 7.4% of those having emergency surgery. In the haemorrhage arm, greater than 90% of these complications occurred in patients who did not have re-initiation of their anticoagulant therapy.

## Factor Xa inhibitor reversal

Andexanet alfa is the specific antidote for FXa inhibitors, apixaban and rivaroxaban, and is a truncated form of enzymatically inactive FXa. It is a recombinant protein that lacks the membrane-binding Y-carboxyglutamic acid (GLA) domain, so it has no biologic activity in the coagulation cascade. A mutation in the catalytic domain also removes its intrinsic procoagulant activity. It retains the ability of native FXa to bind direct and indirect FXa inhibitors and sequester them, thereby acting as a decoy to neutralise the anticoagulant effects of FXa inhibitors by preventing the inhibitors from binding endogenous FXa. As well as rapidly reducing anti-FXa activity, a measure of the anticoagulant effect of FXa inhibitors, it also reduces the unbound fraction of the plasma level of FXa inhibitor.[19]

The dose of andexanet alfa must be tailored to the molar concentration of the anticoagulant and an infusion must be maintained to continue the competitive blockade of the anticoagulant. As in the ANNEXA-4 (Andexanet Alfa, a Novel Antidote to the Anticoagulation Effects of Factor Xa Inhibitors) study, the bolus dose of andexanet alfa must be followed by a two-hour infusion to avoid rebound FXa activity.[19] The recommended dosing of andexanet alfa depends on the specific FXa inhibitor, the dose of FXa inhibitor and the time since the patient's last dose of FXa inhibitor (**tables 3 and 4**). The efficacy and safety of repeated administration of andexanet alfa after this has not been established.

Andexanet alfa has been approved by the EMA and FDA for patients treated with apixaban or rivaroxaban, when reversal of anticoagulation is needed owing to life-threatening or uncontrolled bleeding. The EMA note there is not enough evidence on the use of andexanet alfa to reverse the effects of edoxaban, another FXa inhibitor. This licensing is based on a series of pivotal studies. ANNEXA-A and ANNEXA-R were studies to evaluate the safety and ability of andexanet

**Table 4. Dosing regimens for andexanet alfa**

| | Initial intravenous bolus | Continuous intravenous infusion | Total number of 200 mg vials needed |
|---|---|---|---|
| Low dose | 400 mg at a target rate of 30 mg/min | 4 mg/min for 120 minutes (480 mg) | 5 |
| High dose | 800 mg at a target rate of 30 mg/min | 8 mg/min for 120 minutes (960 mg) | 9 |

alfa to reverse the anticoagulation effect of apixaban and rivaroxaban, respectively.[23] The ANNEXA-4 study was the phase III study in patients with acute major bleeding. Andexanet alfa is not licensed prior to urgent surgery for reversal of anti-FXa inhibitors, however, a study is planned (ANNEXA-S). A further randomised-controlled trial of andexanet alfa versus standard care in ICH is currently being undertaken (ANNEXA-I).

No dose adjustment is needed for the elderly, renal or hepatic impairment. Hypersensitivity reactions are possible if the patient has a known allergic reaction to hamster proteins.

## Conclusion

DOACs are the first-line option for anticoagulation in AF and VTE. DOACs have a favourable bleeding profile compared with vitamin K antagonists, but can nonetheless be associated with critical site major bleeding, uncontrolled bleeding requiring transfusion, and fatal bleeding. Andexanet alfa and idarucizumab are targeted reversal agents that can be used in life-threatening or uncontrolled bleeding with rivaroxaban/apixaban or dabigatran, respectively. They should be used in conjunction with general haemostatic measures and definitive management of the bleeding source. For non-clinically significant or non-major bleeding we do not advise use of either of these drugs. Clinicians involved in managing major haemorrhage should familiarise themselves with storage locations and administration of both reversal drugs

### Conflicts of interest

ATC has received research support from Alexion Pharmaceuticals, Bayer, Boehringer Ingelheim, Bristol-Myers-Squibb, Daiichi-Sankyo, Johnson & Johnson, Pfizer, Portola Pharmaceuticals, and Sanofi. He has received consultancy fees and/or honoraria from Abbott, AbbVie, ACI Clinical, Alexion Pharmaceuticals, Aplagon, Aspen, Bayer, Boehringer Ingelheim, Boston Scientific, Bristol-Myers Squibb, BTG, Daiichi-Sankyo, EmstoPA Ltd, EPG Health, GLG, Guidepoint Global Gulf Coast Developments, Janssen, Johnson & Johnson, JP Morgan, Leo Pharma, Lifesciences Consulting, McKinsey, Medscape, Navigant, Northstar Communications, Ono, Pfizer, Portola Pharmaceuticals, Sanofi, Temasak Capital, Total CME, TRN, and Windrose Consulting Group. KW and UF: none declared.

## Key messages

- Direct oral anticoagulants (DOACs) are the first-line option for anticoagulation in atrial fibrillation (AF) and venous thromboembolism (VTE)
- While DOACs have a favourable bleeding profile compared with vitamin K antagonists, they can be associated with major bleeding events
- Andexanet alfa and idarucizumab are targeted reversal agents that can be used in life-threatening or uncontrolled bleeding with rivaroxaban/apixaban or dabigatran, respectively
- They should be used in conjunction with general haemostatic measures and definitive management of the bleeding source

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