Reversal of direct oral anticoagulants

Direct oral anticoagulants are being increasingly used as the alternative to warfarin for anticoagulation (e.g. Hu et al, 2016). Although many direct oral anticoagulants are associated with lower rates of major bleeding compared to warfarin (Connolly et al, 2009; Granger et al, 2011; Giugliano et al, 2013), such events do occur and managing them can be a challenge given the lack of readily available measurement assays or specific antidotes. Reversal may also be indicated in the context of emergency surgery, invasive procedures or overdose. This article guides the management of patients who are already on a direct oral anticoagulant and who require immediate reversal, and reviews new reversal agents which are currently being developed and approved for use.

The direct oral anticoagulants

Direct oral anticoagulants act by direct inhibition of a coagulation factor. They include rivaroxaban, apixaban, dabigatran and edoxaban. Dabigatran is administered as a pro-drug, dabigatran etexilate, which is absorbed in the gut before conversion to its active form, which acts as a competitive inhibitor of both free and fibrin-bound thrombin. In contrast, the other licensed direct oral anticoagulants competitively inhibit factor Xa thus restricting thrombin generation.

Dr Oliver Cohen, Specialist Registrar in Haematology, Department of Haematology, Royal Free Hospital, London

Dr Lucy-Anne Frank, Specialist Registrar in Elderly Care, Department of Elderly Care, North Middlesex University Hospital, London

Dr Susan Bradley, Consultant, Department of Haematology, Watford General Hospital, Watford

Correspondence to: Dr O Cohen, Specialist Registrar in Haematology, Department of Haematology, University College London Hospital, London NW1 2BU (o.cohen@nhs.net)

The direct oral anticoagulants have relatively short half-lives compared with vitamin K antagonists and are rapidly absorbed with peak plasma levels reached within 2–4 hours. Dabigatran is predominantly renally excreted (80%) in contrast to the other direct anticoagulants for which renal excretion accounts for less than 33% of the total dose (Ieko et al, 2016). These features are summarized in *Table 1*.

Measurement and use of levels of direct oral anticoagulants

A major benefit of the direct oral anticoagulants is their predictable dose–response pharmacokinetics (Hu et al, 2016), which obliterates the need for routine drug-level monitoring. Routine coagulation testing cannot be used as the traditional coagulation parameters do not correlate well with direct oral anticoagulant levels and may be normal despite therapeutic anticoagulation. For example, rivaroxaban influences the prothrombin time but the degree of influence varies between reagents. However, the thrombin time is very sensitive to dabigatran and as such a normal thrombin time can exclude high levels of this drug, which can be beneficial in determining the need for reversal in an emergency. To measure the level of edoxaban, apixaban or rivaroxaban, a quantitative anti-factor Xa assay calibrated for the specific drug being tested may be used. For dabigatran, anti-factor IIa assays, dilute thrombin-based assays or ecarin clotting times may be used to quantify the level (Kitchen et al, 2014).

While there are some circumstances where direct oral anticoagulant measurement may impact upon clinical management, this is unlikely to be useful in the setting of major bleeding as the results are unlikely to be available in a timely fashion. However, a level may be useful in the context of imminent surgery, non-major bleeding, renal impairment, compliance monitoring, dose monitoring in the presence of other medications which interact with a direct oral anticoagulant and treatment failure. There may also be a benefit to monitoring in the setting of overdose in order to establish either a baseline level or confirm when it is safe to re-start the direct oral anticoagulant by confirming a fall to sub-therapeutic levels.

General management of bleeding and the use of prothrombin complex concentrate

The management of major bleeding in patients taking direct oral anticoagulants has presented challenges for clinicians given the previous lack of available reversal agents. Major and minor bleeding are defined in *Table 2*. Despite the introduction of reversal agents, general bleeding cessation measures including administration of agents such as tranexamic acid and use of major haemorrhage protocols should not be compromised by the addition of a new reversal agent to the management strategy. The decision to use a reversal agent is ultimately clinical and will be influenced by the timing of the last dose, factors affecting direct oral anticoagulant clearance such as renal function and the level of bleeding

Table 1. Characteristics of direct oral anticoagulants

Drug	Mechanism	Half life	Renal excretion	Potential lab tests
Dabigatran	Inhibition of factor IIa	14–17 hours	80%	Anti-IIa, ecarin clotting time, thrombin clotting time
Apixaban	Inhibition of factor Xa	10–14 hours	25%	Anti-Xa
Rivaroxaban	Inhibition of factor Xa	7–11 hours	36%	Anti-Xa
Edoxaban	Inhibition of factor Xa	9–11 hours	35%	Anti-Xa

Table 2. Definition of minor *vs* major bleeding as per the International Society on Thrombosis and Haemostasis

Major bleeding is defined as:

1. Fatal bleeding
2. Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular, pericardial, or intramuscular with compartment syndrome and/or
3. Bleeding causing a fall in haemoglobin level of 20 g/litre or more, or leading to a transfusion of 2 or more units of whole blood or red cell

In order for bleeding in a critical organ to be classified as a major bleed, it must also be associated with a symptomatic clinical presentation, especially if there is no associated drop in haemoglobin

A bleeding episode is defined as minor if it does not meet the criteria for major bleeding. This is sometimes also referred to as 'non-life-threatening bleeding' or 'nuisance bleeding'

From Schulman et al (2010)

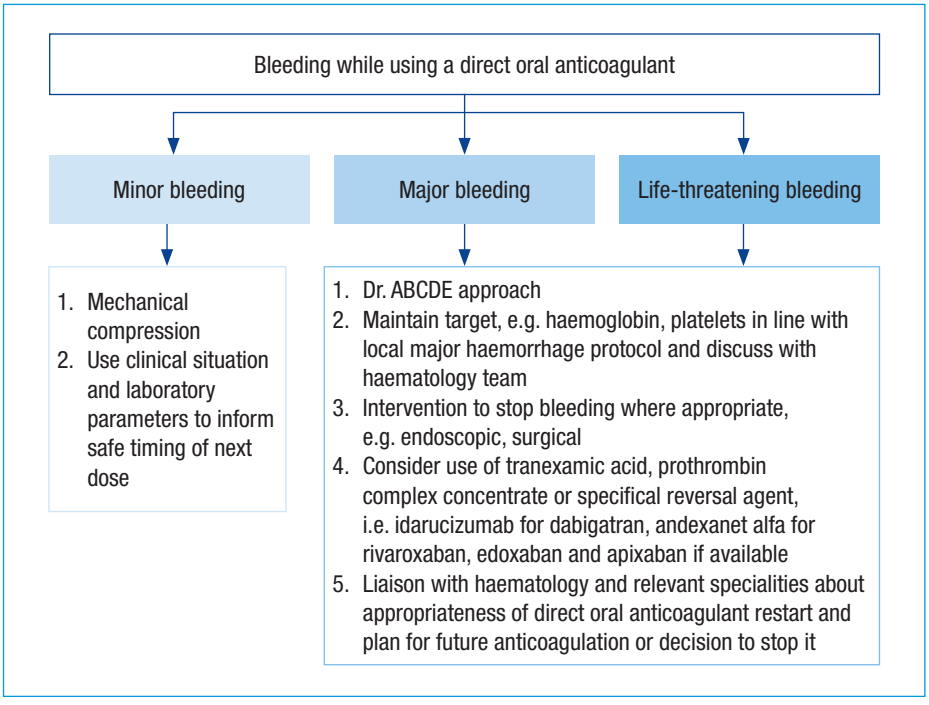

Figure 1. Suggested algorithm for management of bleeding in patients taking direct oral anticoagulants.

(Heidbuchel et al, 2015). It is imperative that the local haematology team be contacted for advice in the case of major bleeding or emergency surgery for a patient taking a direct oral anticoagulant.

Direct oral anticoagulant reversal may also be indicated in patients requiring emergency surgery or following an overdose of a direct oral anticoagulant. In the presence of normal renal function, a direct oral anticoagulant should be stopped for 24 hours before surgery if there is low bleeding risk and for 48 hours if the surgery is high bleeding risk. In the setting of a time-critical surgical emergency, idarucizumab for dabigatran can be used if the bleeding risk is considered to be significant. It should be noted that prothrombin complex concentrate should not be routinely used in patients on direct oral anticoagulants before emergency surgery even if reversal agents are unavailable. Tranexamic acid is likely to reduce bleeding in patients on direct oral anticoagulants where there is any residual anticoagulant effect (Keeling et al, 2016).

Prothrombin complex concentrate is not licensed for direct oral anticoagulant reversal but is suggested based on expert opinion, small clinical trials and case reports in the setting of major or life-threatening bleeding in patients taking direct oral anticoagulants when a specific reversal agent is unavailable (Sartori and Prandoni, 2016). A prospective cohort study of 84 patients on rivaroxaban or apixaban and presenting with major bleeding demonstrated 69.1% efficacy of prothrombin complex concentrate as defined by International Society on Thrombosis and Haemostasis criteria for the assessment of effectiveness of management of major bleeding (Majeed et al, 2017). Prothrombin complex concentrate was less likely to be effective in the setting of intracerebral haemorrhage while two patients developed an ischaemic stroke within 10 days of use of prothrombin complex concentrate. The dose of prothrombin complex concentrate used may vary according to local guidelines but a suggested algorithm for bleeding in patients on direct oral anticoagulants is detailed in *Figure 1*.

Idarucizumab: to reverse dabigatran

Idarucizumab is a humanised mouse monoclonal antibody fragment that binds unbound and thrombin-bound dabigatran and reverses its anticoagulant effect. Once dabigatran is complexed to idarucizumab, the anticoagulant effect of unbound and protein-bound dabigatran and its active metabolites are neutralised. Idarucizumab has no intrinsic procoagulant effect as it does not bind thrombin or its substrates, nor does it activate platelets or convert fibrinogen to fibrin (Eikelboom et al, 2015; Hu et al, 2016).

Idarucizumab is administered by intravenous infusion as two 2.5 g 50 ml bolus infusions within 15 minutes. It has a half-life of 45 minutes. Its features are summarized in *Table 3*. In the phase 1 studies, peak concentrations of idarucizumab were reached immediately after completion of the infusions. The binding of idarucizumab and dabigatran is effectively irreversible. It is absorbed and degraded in the proximal renal tubules and is eliminated within 4 hours of administration (Eikelboom et al, 2015; Hu et al, 2016).

Idarucizumab has been tested in over 200 healthy volunteers and was well tolerated at doses up to 8 g. No serious adverse side effects or severe antidrug antibody reactions have been reported. The most frequently reported symptoms were headache, nasopharyngitis, back pain and skin irritation (Eikelboom et al, 2015).

The REVERSE-AD study is the only phase 3 multicentre, single-arm, prospective, cohort study to establish the efficacy of idarucizumab in reversing the anticoagulation effect of dabigatran irrespective of the indication for taking the drug. A total of

Table 3. Characteristics of agents used for reversal of direct oral anticoagulants

	Idarucizumab	Andexanet alfa
Mechanism of action	Binds free and thrombin-bound dabigatran Renal elimination of the complex	Modified factor Xa decoy protein that binds to active site of factor Xa inhibitors
Dose	Two 2.5 g bolus infusions administered within 15 minutes of one another	Bolus followed by 2-hour infusion. Dose dependent on drug type and timing of ingestion
Half-life	45 minutes	60 minutes
Time to effect	Normalisation of dilute thrombin time and ecarin clotting time minutes after the end of the infusion	2 minutes
Adverse effects	Headache, back pain, skin or nasopharyngeal irritation	Minor gastrointestinal effects, urticarial and flushing. Non-neutralising antibodies can occur
Possible indications	Life-threatening or uncontrolled bleeding or urgent surgery or procedure in patients on dabigatran Overdose of dabigatran	Life-threatening or uncontrolled bleeding or urgent surgery or procedure in patients on rivaroxaban, edoxaban or apixaban Overdose of rivaroxaban, edoxaban or apixaban

TOP TIPS

- In cases requiring urgent direct oral anticoagulant reversal inclusive of bleeding and emergency surgery, contact haematology early for specialist advice.
- Be aware of local policy including major haemorrhage protocol and availability of reversal agents at your trust.
- Idarucizumab should be used for dabigatran reversal if available and indicated.
- In the elective setting, liaise with haematology in a timely fashion in relation to stopping direct oral anticoagulants before planned procedures. The general rule is 24 hours before for low bleeding risk procedures or surgeries and 48 hours before for higher bleeding risk procedures or surgeries assuming normal renal function. However, other risk factors for bleeding must also be taken into account.
- In patients with chronic kidney disease, direct oral anticoagulant clearance will be impaired, which may impact on clinical management.

503 patients were enrolled in the trial. The patients who received idarucizumab were divided into two groups. Group A (301 patients) had life-threatening bleeding judged to require a reversal agent by the treating clinicians. Group B (202 patients) required an urgent procedure within 8 hours. All patients were to receive idarucizumab 5 g as two 50 ml bolus infusions. Only nine of the 503 patients received more than 5 g of idarucizumab because of ongoing bleeding (Pollack et al, 2017).

At baseline, 461 of the 503 patients had elevated dilute thrombin time or ecarin clotting time and 373 patients had prolonged activated partial thromboplastin time. The median maximum percentage reversal of dabigatran was 100% on the basis of either dilute thrombin time or ecarin clotting time. The median time for cessation of bleeding was 2.5 hours. Out of 202 patients in group B, 197 (97.5%) underwent the intended surgery or intervention within a median time of 1.6 hours and normal intraoperative haemostasis was present in 93.4%. At 90 days, thrombotic events had occurred in 6.3% in group A and in 7.4% in group B. The 90-day mortality rate was 18.8% in group A and 18.9% in group B. Measurement of reversal based on activated partial thromboplastin time and thrombin time was similar to the results for dilute thrombin time, which has useful implications for clinical practice as activated partial thromboplastin time and thrombin time are more readily available in most hospital laboratories (Pollack et al, 2017).

In May 2016, the National Institute for Health and Care Excellence approved the use of idarucizumab in patients on dabigatran when rapid reversal is required in the following situations:

- For emergency surgery or urgent procedures
- In the event of life-threatening or uncontrollable bleeding.

Apixaban, rivaroxaban or edoxaban reversal

Andexanet alfa is a recombinant modified factor Xa decoy protein, which binds to the active site of factor Xa inhibitors thus preventing their action. Its features are summarized in *Table 3*. It exhibits rapid onset (within 2 minutes) and effects lasting 1–2 hours (Hu et al, 2016). It is administered as a bolus dose followed by a 2-hour infusion of the drug. The dose used for both the bolus and infusion varies depending on the type of direct oral anticoagulant ingested and time of ingestion (Connolly et al, 2016).

Siegal et al (2015) demonstrated its use in healthy older volunteers taking standard doses of either apixaban 5 mg twice daily or rivaroxaban 20 mg once daily. The study showed thrombin generation was fully restored in 100% of those taking apixaban and 96% of those taking rivaroxaban. Furthermore, anti-factor Xa activity was reduced with apixaban and rivaroxaban by 94% and 92% respectively. Some volunteers received a bolus of andexanet alfa alone while others received a bolus followed by a 2-hour infusion. Using the bolus alone, there was a rebound effect of rising anti-factor Xa activity from the time the bolus finished while the addition of a 2-hour infusion delayed this effect and maintained the reduction in anti-factor Xa activity throughout this period. No severe side effects occurred, specifically no thrombosis, although non-neutralising antibodies were detected in 17%.

The ANNEXA-4 study (Connolly et al, 2016) is a multicentre, prospective, unblinded single arm study whereby andexanet alfa was administered to patients within 18 hours of administration of an anti-factor Xa inhibitor. A preliminary analysis of 67 patients revealed a decrease in anti-factor Xa activity by 89% from baseline in the rivaroxaban patients and 93% in the apixaban patients when measured 2 hours post-infusion. Despite a rebound effect demonstrating rising anti-factor Xa levels towards the pre-treatment baseline at 4–4.5 hours, 79% of patients achieved

a good or excellent clinical response. This suggests that the initial reduction in anti-factor Xa level is usually sufficient to achieve haemostasis. At 30-day follow up, 18% of patients developed thrombosis and 15% died.

Despite this, andexanet alfa shows early promise in the context of major bleeding. While the drug is not yet approved by the Food and Drug Administration, it is recommended for use, if available, before emergency surgery or other invasive procedures in patients taking rivaroxaban, apixaban or edoxaban where a significant bleeding risk exists by a guideline from the British Society of Haematology (Keeling et al, 2016). In the case of low molecular weight heparins, no trial exists comparing the use of protamine sulphate and andexanet alfa for reversal of their anticoagulant, anti-factor Xa effect.

Newer agent in trial

Ciraparantag is a synthetic molecule that binds direct thrombin and direct Xa inhibitors together with both low molecular weight and unfractionated heparin (Hu et al, 2016). Ansell et al (2017) demonstrated full reversal of anticoagulation within 10–30 minutes in healthy volunteers taking edoxaban as determined by whole blood clotting time. Unlike andexanet, ciraparantag showed sustained reversal responses after bolus administration alone without the need for a subsequent infusion. Furthermore, Ansell et al (2016) conducted a phase 1/2 trial using healthy volunteers to demonstrate, by use of whole blood clotting time, that ciraparantag reverses enoxaparin without significant side effects.

Currently, protamine sulphate is the only reversal agent available for low molecular weight heparin, which only leads to a partial reversal hence the potential importance of ciraparantag considering the widespread use of low molecular weight heparin in the hospital setting (Ansell et al, 2016). Two phase 2 trials examining the effect of ciraparantag on rivaroxaban and apixaban are recruiting. While this agent shows promise in phase 2 trials, it will be some time before it may be available for use outside of a trial setting.

Conclusions

While direct oral anticoagulants have clear advantages over traditional anticoagulants, the need for immediate reversal has proved a clinical challenge given the previous lack of available reversal agents. Idarucizumab is now licensed for dabigatran reversal with further agents in development, which are likely to change clinical practice in the coming years. **BJHM**

Conflict of interest: none.

KEY POINTS

- Dabigatran, apixaban, rivaroxaban and edoxaban are the direct oral anticoagulants which are licensed for use in the UK.
- The management of major bleeding in patients taking direct oral anticoagulants has presented challenges for clinicians given the previous lack of available reversal agents.
- The decision to use a reversal agent in a patient taking a direct oral anticoagulant is ultimately clinical, influenced by various factors.
- The National Institute for Health and Care Excellence has approved the use of idarucizumab in patients on dabigatran when rapid reversal is required for emergency surgery or urgent procedures, or in the event of life-threatening or uncontrollable bleeding.
- Andexanet alfa has shown early promise in its ability to reverse the effect of anti-factor Xa agents in major bleeding but is awaiting licensing and approval.
- Until there is an approved licensed reversal agent for rivaroxaban, apixaban and edoxaban, consider use of prothrombin complex concentrate for major or life-threatening bleeding.

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