Guidance for Management of Bleeding and Emergency Surgery in Patients Taking Direct Oral Anticoagulants (DOACs)

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Approved by:	***Medicines Management Board***
Approval Date:	***July 2024***
Review Date:	***July 2026***
Document No:	***CID1854***

1 Introduction

The direct oral anticoagulants currently available inhibit thrombin (dabigatran) or factor Xa (rivaroxban, apixaban and edoxaban). They are licensed for the treatment and prevention of venous thrombo-embolism and prevention of stroke in patients who have non-valvular atrial fibrillation. With the exception of dabigatran, at present there are no direct means of reversing their anti-coagulant effect.

Dabigatran can be reversed by the administration of a monoclonal antibody idarucizumab (Praxbind®). For other direct oral anticoagulants, prothrombin complex concentrate has been shown to correct reduced thrombin generation in healthy volunteers and *in vitro* studies, but studies demonstrating a reduction in bleeding are lacking. The fXa specific reversal agent, andexanet alfa (Ondexxya®) has recently been approved for the reversal of apixaban and rivaroxaban (not edoxaban) within the EU. Although there are no direct comparisons with PCC, indirect comparison has shown andexanet to reduce mortality in GI and cerebral haemorrhage, but has no impact on long term disability in cerebral haemorrhage. A recent study, the ANNEXA-I study highlighted the efficacy of andexanet in reversing anti-Xa activity, and preventing hematoma expansion in intracranial hemorrhage on DOAC's when compared to usual standard of acre (primarily PCC). But there is uncertainty around it's benefit in relation to mortality and morbidity. Clinicians should however be aware of the risk of subsequent thrombotic events, with the recent ANNEXA-I study showing a 10.5% rate of thrombotic events after administration, with a 6.5% rate of ischemic stroke. As a result, NICE have appraised the agent, and approved its use in the management of life-threatening GI bleed, associated with apixaban and rivaroxaban use only. Clinicians should however be aware of the risk of subsequent thrombotic events, with the recent An However, given the absence of high quality comparative data, the measures outlined in this guideline cannot be guaranteed to completely reverse the anti-coagulant effect.

2 Guidance

Firstly it is important to establish when the patient last ingested any medication. In the setting or normal renal function, 24 hours is likely to be sufficient for clearance of the of apixaban, edoxaban and rivaroxaban and 24-48 hours for dabigatran. If surgery or other invasive procedure is required, if possible this should be delayed for at least 24 hours. If a delay is not possible, or there is bleeding which threatens serious harm, proceed as outlined in Figure 1 for dabigatran and Figure 2 for rivaroxaban, apixaban and edoxaban.

Figure 1

Emergency reversal of dabigatran

Take blood samples for FBC, Group and Screen, PT, APTT, Fibrinogen, TCT and dabigatran level, renal function and liver function. State clearly on request form "Bleeding on dabigatran."

NB: A normal TCT indicates negligible amounts of dabigatran are present and no further action is required to reverse the effect. Drug levels will be processed during normal working hours.

Ingestion within preceding 2 hours?
If "yes," consider administering oral activated charcoal

General measures:
Stop drug
Apply local pressure
Administer tranexamic acid 1g iv (NOT if bleeding from renal tract)
Consider involvement of interventional radiology to embolise bleeding point

Life threatening bleeding or emergency surgery which can not be delayed:
Administer 5 g of idarucizumab iv (see appendix 2 for dosing)*
Repeat APTT and TCT post administration; if these remain abnormal, consider a second 5 g dose if there is ongoing bleeding or the risk of bleeding remains high.
***Discuss with on-call Haematologist via consultant to consultant discussion**
Accessed via Morriston A+E Omnicell
Accessed via emergency cupboard in Singleton/NPT

Figure 2

Emergency reversal of oral direct Xa inhibitors

Take blood samples for FBC, Group and Screen, PT, APTT, Fibrinogen, drug level, renal function and liver function. State clearly on request form "Bleeding on rivaroxaban," "Bleeding on apixaban," or "Bleeding in edoxaban" as appropriate.

NB An abnormal PT means there is likely to be a therapeutic amount of the drug present; a normal PT does not exclude it. Drug levels will be processed during normal working hours.

General measures:
Stop drug
Apply local pressure
Administer tranexamic acid 1g iv (NOT if bleeding from renal tract)
Consider involvement of interventional radiology to embolise bleeding point

Life threatening *GI* bleeding on apixaban or rivaroxaban:

Consider andexanet alfa (see appendix 2 for dosing) *
***Discuss with on-call Haematologist via consultant to consultant discussion considering risks and benefits of treatment**
Accessed via Morriston Emergency Cupboard Omnicell

Other life-threatening bleeding or emergency surgery which cannot be delayed:

Give 50 units/Kg prothrombin complex concentrate (max 3000 Units) (see appendix 3)*
****Discuss with on-call Haematologist via consultant to consultant discussion**

Appendix 1: Administration of Idarucizuma (Praxbind®):

Idarucizumab is available from the Morriston A+E Omnicell, and can only be accessed following approval from the on-call hematology consultant

Praxbind is a specific reversal agent for dabigatran and is indicated in adult patients treated with Pradaxa (dabigatran etexilate) when rapid reversal of its anticoagulant effects is required:

• For emergency surgery/urgent procedures;

• In life-threatening or uncontrolled bleeding

***Step 1**: Prescribe the required dose as per the below table*

DOSE:

5g (i.e. two vials of 2.5g/50ml)

***Step 2**: Prepare the product and administer*

Reconstitution of vial: The product is available as a ready to administer solution, and has an integrated hanger to facilitate administration

Administration:

- **IV injection**: Give the contents of two vials consecutively, each over a period of 3-5 minutes

OR

- **IV infusion**: Give the contents of two vials consecutively, each over a period of 5-10 minutes

***Step 3**: Repeat if indicated*

Administration of a second 5 g dose of idarucizumab may be considered in the following situations:

• recurrence of clinically relevant bleeding together with prolonged clotting times, or

• if potential re-bleeding would be life-threatening and prolonged clotting times are observed, or

• patients require a second emergency surgery/urgent procedure and have prolonged clotting times

***Step 4**: Consider when oral anticoagulation to re-start*

Pradaxa (dabigatran etexilate) treatment can be re-initiated 24 hours after administration of idarucizumab, if the patient is clinically stable and adequate haemostasis has been achieved.

After administration of idarucizumab, other antithrombotic therapy (e.g. low-molecular weight heparin) can be started at any time, if the patient is clinically stable and adequate haemostasis has been achieved.

Appendix 2: Administration of andexanet alfa (Ondexxya):

Andexanet alfa is available from the Morriston A+E Omnicell, and can only be accessed following approval from the on-call hematology consultant

***Step 1**: Calculate whether a HIGH or LOW dose regime is required*

For apixaban:

FXa inhibitor	Last dose	Timing of last dose before Ondexxya initiation	
		< 8 hours or unknown	≥ 8 hours
Apixaban	≤ 5 mg	Low dose	Low dose
	> 5 mg/ Unknown	High dose	

For rivaroxaban:

FXa inhibitor	Last dose	Timing of last dose before Ondexxya initiation	
		< 8 hours or unknown	≥ 8 hours
Rivaroxaban	≤ 10 mg	Low dose	Low dose
	> 10 mg/ Unknown	High dose	

***Step 2**: Prescribe the required dose as per the below table*

Table 1: Dosing regimens

	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

***Step 3**: Prepare the product*

***Reconstitution of vial:** Reconstitute each vial using 20ml water for injections, using 20 gauge (or larger) needles, aiming the flow to the inside wall of the vial to minimise foam. Swirl for 3 to 5 minutes. (DO NOT SHAKE)*

***Administration:** May be via a syringe pump or an IV bag with infusion pump using a 0.2 or 0.22 micron in-line polyethersulfone (PES) or equivalent low protein- binding filter*

- ***For administration using a syringe pump:** Withdraw the required volume of the reconstituted solution into a 50mL syringe. For high dose therapy, you may need two syringes for the loading dose and two for the maintenance dose.*
- ***For administration using an IV bag:** Use large volume syringes to transfer the reconstituted dose into an empty polyolefin (PO) or PVC infusion bag (150mL or larger). A separate bag is recommended for the loading and maintenance dose*

Appendix 3: Administration of Human prothrombin complex (Octaplex)

Octaplex is available from the Blood Bank, and can only be accessed following approval from the on-call hematology consultant

N.B. This is a blood product. Refer to SBU guidance on consent in relation to receiving blood products

Step 1*: Check Contraindications*

- Hypersensitivity to the active substance or to any of the excipients listed in the SmPC
- Known allergy to heparin or history of heparin induced thrombocytopenia.
- Individuals who have IgA deficiency with known antibodies against IgA

Step 2*: Prescribe the required dose*

SUGGESTED DOSE:

50 units/Kg prothrombin complex concentrate (max 3000 Units)

Step 3: *Reconstitute the product as per the guidance in the product leaflet.*

The product should be supplied with a vial of power and a vial of solvent. The powder dissolves quickly at room temperature to form a colourless to slightly blue solution containing 25units in 1mL of human prothrombin complex. If the powder fails to dissolve completely or an aggregate is formed, do not use the preparation.

Step 4*: Administer the product*

Administer at a rate of 1mL per minute initially, followed by 2-3mL per minute. An infusion pump may be used if the clinical situation allows

No blood must flow into the syringe due to the risk of formation of fibrin clots.

Do not administer with any other medications or blood products. Administer via a separate line

Step 5*: Record for tractability purposes*

The patient details and batch number should be recorded via blood bank

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PLEASE ENSURE THAT ALL QUESTIONS ARE ANSWERED – IF NOT APPLICABLE PLEASE PUT N/A

COIN ID.	CID1854
Document Title.	Guidance for the Management of Bleeding and Emergency Surgery in Patients taking Direct Oral Anticoagulants (DOACs)
Name of Author.	Thrombosis and Anticoagulation Committee
Name of Lead Pharmacist.	 Principal Pharmacist
Is the document New, Revised or a Review of a previous version.	Revised
Where on COIN do you want the document to be published.	Anticoagulation/Haematology/Surgery/Anaesthetics
Is the document relevant to the GP Portal.	Yes
Sign to confirm that the document has been authorised by an approved governance process in a specialty or delivery unit.	Thrombosis and Anticoagulation Committee Medicines Management Operational Board
If NICE guidance been considered/referenced when producing this document, please provide the title or reference number.	No
Please provide a brief description/abstract of the document.	Anticoagulation, Reversal , DOAC, Idarucizumab, Andexanet Alfa, Bleeding.
Equality Statement. *(All policies and procedures need to comply with CID76 Policy for the Management of Heath Board Wide Policies, Procedures and other Written Control Documents (WCD).*	No potential negative equality impact.
Published Date.	September 2016
Last Reviewed Date.	September 2024
Next Review Due/Expiry Date.	July 2026