Management of Bleeding in Adult Patients Taking Oral Anticoagulants

Gloucestershire Hospitals NHS
NHS Foundation Trust

Direct Oral Anticoagulants (DOAC):

Factor Xa inhibitors:
Rivaroxaban
Apixaban
Edoxaban

Direct thrombin inhibitors:
Dabigatran

Vitamin K antagonists (VKA):
Warfarin
Acenocoumarol
Phenindione

MINOR BLEEDING

1. Local haemostatic measures.
2. Mechanical compression.
3. Tranexamic acid topically or orally (1g TDS orally, or 1.5g TDS if weight >100kg. Reduce dose in renal impairment (see p.4).

DOAC: Suspend DOAC until haemostasis achieved.

VKA:

1. Stop VKA and check INR.
2. If INR >5, give 1-3mg Vitamin K (phytomenadione [Konakion® MM 2mg in 0.2mL ampoules]) i.v./po. Repeat dose at 24h if INR still too high. Restart VKA when INR <5.0 if haemostasis achieved.

MAJOR BLEEDING

1. Control haemorrhage:
   - Consider surgical intervention, endoscopy, wound packing or interventional radiology.
   - Tranexamic acid 1g by slow i.v. injection over 10 mins followed by 1g TDS by slow i.v. infusion over 8 hrs (Do not give for GI bleeding). Reduce dose in renal impairment (see p.4)
2. Consider oral activated charcoal if oral anticoagulant taken < 1 hr ago.
3. Consider resuscitation with blood products as per Major Haemorrhage Procedure.

DOAC: LIFE/LIMB/SIGHT THREATENING BLEEDING

Dabigatran:
As for major bleeding
PLUS administer
Idarucizumab (Praxbind®) click here

Apixaban / Edoxaban / Rivaroxaban:

Life threatening **G.I.** bleed?

YES

As for major bleeding
PLUS administer
Andexanet alfa (Ondexxya®) click here

NO

As for major bleeding
PLUS administer
4-factor Prothrombin Complex Concentrate (Octaplex®) by slow I.V. injection (see dosing table on p.3). Obtain from Transfusion.

VKA

1. Stop VKA and check INR (do not delay treatment pending result)
2. Give vitamin K (phytomenadione [Konakion® MM]): 5 to 10mg by slow i.v. injection (over at least 30 seconds). May alternatively be given by i.v. infusion (draw up 0.5 to 1 ml of Konakion® MM and add to a 50ml bag of Glucose 5%). Repeat INR after 6 hrs - if response inadequate; dose may be repeated.
3. If major/life/limb/sight threatening bleeding (including intracranial /rapid onset neurological signs) requiring immediate complete reversal Administer 4-factor Prothrombin Complex Concentrate (Octaplex®) by slow i.v. injection (see dosing table on p.3). Recheck INR ten minutes after administration (consider further dose). Obtain from Transfusion.
4. Advice available to Senior Clinician from on-call Consultant Haematologist, if required.

Direct Oral Anticoagulant (DOAC) Reversal

Apixaban / Edoxaban* / Rivaroxaban – Life-threatening G.I. bleeds only (NICE TA697)

Andexanet alfa (Ondexxya®) may only be prescribed for acute life-threatening G.I. bleeds that are not amenable to standard management including endoscopy, interventional radiology, and blood products. At the discretion of the Consultant Gastroenterologist doing the emergency endoscopy, it may be felt appropriate to administer DOAC reversal prior to the procedure.

Andexanet alfa may only be prescribed for acute life-threatening G.I. bleeds by a senior clinician following Consultant Gastroenterologist authorisation (with Haematologist advice as necessary). Prescription should be placed on EPMA using dedicated order set.

Andexanet alfa may NOT currently be used for non-G.I. bleeds outside of clinical trials

Dose: (see SPC and Medusa for further details)

Low dose (5 x 200mg vials): Initial i.v. bolus 400mg at a rate of 30mg/min
Continuous i.v. infusion 4mg/min for 2 hours

High dose (9 x 200mg vials): Initial i.v. bolus 800mg at a rate of 30mg/min
Continuous i.v. infusion 8mg/min for 2 hours

DOAC to be reversed	DOAC last dose	Timing of last DOAC dose	
		< 8 hours ago or unknown	≥ 8 hours ago
Apixaban	≤5mg	Andexanet alfa x **5 vials**	Andexanet alfa x **5 vials**
	>5mg or unknown	Andexanet alfa x **9 vials**	
Edoxaban*	≤30mg	Andexanet alfa x **5 vials**	Andexanet alfa x **5 vials**
	>30mg or unknown	Andexanet alfa x **9 vials**	
Rivaroxaban	≤10mg	Andexanet alfa x **5 vials**	Andexanet alfa x **5 vials**
	>10mg or unknown	Andexanet alfa x **9 vials**	

To be administered using an infusion pump via an in-line 0.2 or 0.22 micron low-protein filter

If patient develops a reaction (metallic taste, flushing, fever, cough or dyspnoea) – stop infusion and administer Chlorphenamine 10mg iv – restart infusion once reaction settled

List price (BNF June 2024):

- Low dose (5 vials) = £13,875
- High dose (9 vials) = £24,975

Location: Andexanet alfa is stocked in the medication fridge in ED: **GRH** ED Resus
CGH ED Central Nurses' Station Fridge

*Note: Andexanet alfa is not licensed to reverse edoxaban; however, GHNHSFT approves the off-label use of andexanet alfa for reversing edoxaban provided it is used in accordance with the recommendations made within NICE TA697 for apixaban and rivaroxaban. The ANNEXA-4 study showed that for patients taking edoxaban, andexanet alfa significantly decreased anti-factor Xa activity (median decrease 71.3%; 95% CI: 65.2–82.3%) and excellent or good haemostasis at 12 hours was observed in 78.6% (95% CI: 59.0–91.7%) of patients overall.

Dabigatran

Idarucizumab (Praxbind®) may only be prescribed for acute life-threatening bleeds that are not amenable to standard management.

Idarucizumab may only be prescribed by a senior clinician following Consultant Haematologist (or Gastroenterologist for G.I. bleeds) authorisation. Prescription should be placed on EPMA using dedicated order set.

Dose: (see SPC and Medusa for further details)
5g (2 x 2.5g/50ml vials given consecutively via i.v. infusion each over a period of 5-10 minutes).
Administration of a second 5g dose of idarucizumab may be considered if life-threatening bleeding recurs, together with prolonged clotting times.

List price (June 2024):

- 5g = £2,400

Location: Idarucizumab alfa is stocked in the medication fridge in ED: **GRH** ED Resus
CGH ED Central Nurses' Station Fridge

Octaplex® (4-factor Prothrombin Complex Concentrate)

If INR unknown (warfarin patients) or patient on a DOAC:

Body Weight	Octaplex® dose	Volume of reconstituted Octaplex® to administer
<60kg	1500 units	60mL
60-75kg	2000 units	80mL
76-90kg	2500 units	100mL
>90kg	3000 units	120mL

If INR known (patients on warfarin only):

Prothrombin Complex Dosing Chart
Calculated dose of OCTAPLEX to the nearest 500(iu)

	INR	<2.5	2.5-3.0	3.1-3.5	>3.5
	iu/kg	27.5	36.25	43.75	47.5
Patient Weight (kg)	40	1000	1500	2000	2000
	50	1500	2000	2000	2500
	60	1500	2000	2500	3000
	70	2000	2500	3000	3000
	80	2000	3000	3000	3000
	90	2500	3000	3000	3000
	100	3000	3000	3000	3000
	110	3000	3000	3000	3000
	120	3000	3000	3000	3000

DIRECT ISSUE:

Issue Octaplex directly for patients on warfarin presenting with:

1. Intracranial Haemorrhage
2. Significant head injury
3. Gastrointestinal haemorrhage
4. Ruptured aortic aneurysm

For all other possible indications and requests for FFP for warfarin reversal, these require consultation with a clinical Haematologist

Tranexamic Acid – dosing in renal impairment

GFR (ml/min)	I.V. Dose	Oral Dose Note: round to nearest 250mg (half tablet)
20 – 50	10mg/kg (max. 1g) 12 hourly	25mg/kg (max. 1.5g) 12 hourly
10 – 20	10mg/kg (max. 1g) 24 hourly	25mg/kg (max. 1.5g) 12 to 24 hourly
<10	5mg/kg (max. 1g) 24 hourly	12.5mg/kg (max. 1.5g) 24 hourly

Additional Notes:

Bleeding Classification

Major Bleeding:

- A clinically overt bleed causing blood loss > 1500ml/loss of half circulating volume in < 2hrs/ poor response to fluid resuscitation/major trauma with Systolic BP <100mmHg/ HR > 100bpm/penetrating injury
- Symptomatic bleeding into a critical area or organ (i.e. intracerebral, intraocular, intraspinal, intraabdominal, retroperitoneal)
  Life/limb/sight-threatening bleeding: **ACTIVATE ADULT MAJOR HAEMORRHAGE CALL** (click here)

Blood Tests

- Check FBC + coagulation screen including prothrombin time (PT), activated partial thrombin time (aPTT) and fibrinogen assay. G&S + XMatch sample (a second sample will be required for patients with no historical blood group on record)
- Check electrolytes including calcium, renal function, and LFTs. The latter is to consider if other causes of coagulopathy may be present
- Indicate time of last dose of dabigatran, rivaroxaban, apixaban and edoxaban when requesting tests NB half-lives are:
  - Warfarin (40 hours)
  - Acenocoumarol (8-11 hours)
  - Phenindione (5-6 hours)
  - Dabigatran (12-14 hours – 27 hours if CrCl < 30ml/min)
  - Rivaroxaban (5-9 hours – 11-13 hours in the elderly)
  - Apixaban (12 hours)
  - Edoxaban (10-14 hours)

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