MIL

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This Medicines Information Leaflet is produced locally to optimise the use of medicines by encouraging prescribing that is safe, clinically appropriate and cost-effective to the NHS.

Management of bleeding, emergency surgery and overdose in adult inpatients on Direct Oral Anticoagulants (DOACs)

This MIL covers bleeding, surgery and overdose in patients on Direct Oral Anticoagulants (DOACs). Related guidance on the management of oral anticoagulation in head injury can be found here.

Direct oral anticoagulants (DOACs)

These include factor Xa inhibitors rivaroxaban, apixaban and edoxaban and the direct thrombin inhibitor dabigatran. These agents have short half-lives and do not require monitoring in normal circumstances. The anticoagulant effect of DOACs can be estimated by the dose, timing of the last dose and renal function. The DOACs are all renally cleared to some degree and the half-life will be prolonged in renal impairment.

Measuring the effect of DOACs

Standard clotting tests may not detect DOACs. In some instances, DOACs can prolong standard coagulation tests but in general they do not provide an accurate or reliable indication of the intensity of anticoagulation. A normal activated partial thromboplastin time (APTT) and prothrombin time (PT) do not exclude the presence of significant concentrations of DOAC in a sample (table 1).

Table 1: Usefulness of standard clotting tests

DOAC	Effect on coagulation screen	Thrombin Time (TT)
Apixaban	Normal or slight ↑APTT Normal or slight ↑PT	Normal
Rivaroxaban	Normal or ↑APTT Normal or ↑PT	Normal
Dabigatran	Usually ↑APTT Normal or ↑PT	↑↑
Edoxaban	Normal or ↑APTT Normal or ↑PT	Normal

Measuring DOAC levels

DOAC levels can be measured in the laboratory (table 2). **However, in the emergency setting do not wait for the laboratory result to guide treatment.** Current guidance from the Scientific and Standardisation Committee of the International Society for Thrombosis and Haemostasis (ISTH) recommends when interpreting drug concentrations, it is important to consider when the last dose of the DOAC was taken to determine whether the levels are likely to increase or fall over time.

Table 2: DOAC trough and peak levels (micrograms/L)

	Trough	Peak
Apixaban 5mg bd	103 (41-230)	171 (91-321)
Apixaban 2.5mg bd	79 (34-162)	123 (69-221)
Dabigatran 150mg bd	91 (40-215)	175 (74-383)
Edoxaban 30mg od	27 (15-45)	85 (55-120)
Edoxaban 60mg od	36 (19-62)	170 (125-245)
Rivaroxaban 20mg od	44 (12-137)	249 (184-343)

There is insufficient available information to provide levels for dabigatran 110mg bd or rivaroxaban 15mg od.

Reversal agents for DOACs

Specific reversal agents should be used for major bleeding and for emergency surgery when available.

Idarucizumab

This binds specifically to dabigatran and its metabolites and will not reverse the effects of any other anticoagulant. Idarucizumab is licensed and NICE-approved for dabigatran reversal in adult patients when rapid reversal of its anticoagulant effects is required either for emergency surgery/urgent procedures or in major bleeding.

Andexanet alfa (andexanet)

This binds to and sequesters Xa inhibitors including DOACs but also LMWH and UFH. It is prothrombotic through inhibition of TFPI (Tissue Factor Pathway Inhibitor). This binds with high affinity to apixaban and rivaroxaban resulting in a neutralization of anticoagulant effect. Andexanet is licensed and NICE-approved for the reversal of apixaban and rivaroxaban **(NOT edoxaban)** in life threatening or uncontrolled GI bleeding ONLY.

Outside of these indications, prothrombin complex concentrate (4 factor PCC) can be used to counteract the effects from apixaban, rivaroxaban and edoxaban when rapid reversal of anticoagulant effect is required, either for emergency surgery/urgent procedures or in major bleeding.

A haematologist does not need to authorise the use of idarucizumab or 4 factor PCC. Andexanet can only be authorised for use by ED, Medicine, Gastroenterology or Haematology ST3 and above. Both idarucizumab and andexanet are available in the emergency drug cupboard fridges on the JR and Horton sites. PCC must be requested from JR or Horton blood bank or can be found in the JR ED and CH theatres.

In all cases of over anticoagulation

1. Identify the precipitating cause
2. Establish whether it is temporary (for example, other medications) or permanent (for example liver failure)
3. Review the need for ongoing anticoagulation.

a) Major / life threatening bleeding requiring immediate complete DOAC reversal

Major bleeds are defined as those which are fatal, life-threatening or may cause chronic sequelae. This includes:

- symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome and/or
- bleeding causing a fall in haemoglobin level of 20 g/L or more, or leading to transfusion of two or more units of whole blood or red cells, and/or
- cardiovascular shock secondary to bleeding.

These patients need urgent clinical assessment of haemostasis. **See Figures 1 and 3 for summary flowsheet.**

1. Discontinue oral anticoagulant
2. Document time of last dose of DOAC.
3. Send urgent samples for FBC, renal and liver function, PT, APTT, fibrinogen, (and add thrombin time, TT, if patient taking dabigatran).
4. Take a DOAC level.
   In the emergency setting do not wait for the laboratory result to guide treatment. However, if the TT is normal then a reversal agent for dabigatran will not be needed.
5. Provide supportive measures: resuscitation and haemostatic control and treat active bleeding according to the OUH major haemorrhage protocol.
6. Give tranexamic acid 1g IV in non-GI haemorrhage
7. **Dabigatran** reversal:
   a. For major bleeding use idarucizumab.
   b. Idarucizumab is available in emergency drug cupboard fridges on the JR and Horton sites.
   c. Administer idarucizumab 5g IV (given as two 2.5g doses by slow bolus). Please see the injectables monograph for idarucizumab, available from the pharmacy injectables intranet site

Reversal of dabigatran must be assessed clinically but also with TT and dabigatran levels. Monitor coagulation/ dabigatran concentrations every six hours for at least 36 hours after idarucizumab administration. Further doses of idarucizumab may be required in which case discuss with the Haemostasis SpR (bleep 5529 or via switchboard)

8. **Apixaban/Rivaroxaban reversal in life threatening or uncontrolled gastrointestinal bleeding: use andexanet.** Andexanet is found in the emergency drug cupboard fridges on the JR and Horton sites and must be prescribed by **ED, Medicine or Gastroenterology ST3 and above, or following advice of Haematology ST3 and above.** Maximal anti-factor Xa activity after administration of andexanet is 2-5 minutes post bolus. However, administration must not be delayed for endoscopic procedures or surgery.

Dosing regimen for andexanet alfa

To determine the dosing regimen, first establish the dose of apixaban or rivaroxaban the patient was taking and the time since the patient's last dose (table 3). The dose of andexanet is administered as an initial IV bolus followed by a continuous IV infusion (table 4):

Table 3: Dose of andexanet to be prescribed

FXa inhibitor	Last dose	Timing of last dose before andexanet initiation	
		Less than 8 hrs or unknown	8 hours or more
Apixaban	2.5mg or 5mg	Low dose	Low dose
	10mg or unknown	High dose	
Rivaroxaban	2.5mg, 10mg	Low dose	Low dose
	15 mg, 20mg or unknown	High dose	

Table 4: Administration of andexanet

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

CAUTION: Andexanet **should not** be used in settings other than GI bleeding.

- ❖ Avoid use if there is evidence of Disseminated Intravascular Coagulopathy (DIC) or arterial or venous thrombosis in the last 2 weeks

- ❖ Avoid if there has been use PCC/Andexanet/rFVII (Novoseven) in the last week and discuss with the Haemostasis SpR and consider use of PCC instead
- ❖ DO NOT use if treatment dose LMWH or UFH required for surgery.

Successful reversal of apixaban and rivaroxaban must be assessed **clinically** after administration. Send repeat FBC, PT, APTT and fibrinogen. Anti-factor Xa levels SHOULD NOT BE USED to monitor efficacy after reversal as andexanet will interfere with the assay. If bleeding continues despite haemostatic measures or restarts, please contact the Haemostasis SpR, (bleep 5529) or via switchboard.

Andexanet alpha is potentially pro-thrombotic and patients should be monitored for arterial and venous thrombotic events post administration. Conversely, unlike idarucizumab, the DOAC will not be bound and eliminated by andexanet. **Therefore, there is a risk of re-elevation or incomplete reversal of anti-factor Xa activity** - patients must be monitored for bleeding, especially in those with renal dysfunction, for 24-48 hours post administration.

9. **Apixaban/Rivaroxaban/Edoxaban reversal in major/life threatening non-GI bleeds: PCC to be given at a dose of 50 units/kg to a maximum dose of 3000 units.** Trauma associated coagulopathy and intracranial haemorrhage have distinct differences in their patho-physiology and management to GI bleeding. If bleeding continues despite haemostatic measures or restarts, please contact the Haemostasis SpR, (bleep 5529) or via switchboard.

b. Non-major bleeding

1. Delay next DOAC dose or discontinue treatment
2. Local haemostatic measures e.g. mechanical compression
3. Consider 1g tranexamic acid PO/IV

c. Emergency surgery

There are few data on the management of emergency surgery in patients receiving DOACs. If an anticoagulant effect cannot be excluded neuraxial anaesthesia should be avoided. When possible, surgery should be delayed allowing the plasma level of the drug to fall. **See Figures 2 and 4 for summary flowsheet.** The ability to make predictions regarding haemostasis at surgery in patients taking DOACs is limited by uncertainty in the concentration of each drug that is associated with haemostatic safety.

- If delay is not possible and anticoagulant effect is still present, tranexamic acid may reduce bleeding.
- Idarucizumab should be used to reverse dabigatran therapy prior to emergency surgery where the bleeding risk is considered significant.
- If a patient taking a Factor Xa inhibitor such as apixaban/rivaroxaban/edoxaban needs emergency surgery, please discuss management with haematology. Andexanet should not be used in this setting.

d. Overdose

1. Discontinue oral anticoagulant medication.
2. Document time of last dose of DOAC.
3. Consider 50g activated charcoal if:
   Dabigatran- 13 mg/kg or more dabigatran has been ingested by a naive patient within 1 hour. In patients who take dabigatran therapeutically, consider activated charcoal if they have ingested twice their daily dose or more, providing it is safe to do so and the airway can be protected.
   Apixaban/Rivaroxaban/Edoxaban - if within 1 hour of ingestion of a toxic dose (apixaban 0.5 mg/kg, rivaroxaban 1 mg/kg, edoxaban 3 mg/kg).
   Refer to Toxbase for more detailed information.
4. Send urgent samples for FBC, renal and liver function, PT, APTT (and TT for dabigatran).
5. If patient is bleeding, follow guidance in previous sections.
6. Review need for oral anticoagulation.

Safe medication practice

Thromboprophylaxis and/or resumption of anticoagulation should be considered as soon as medically appropriate. Therapeutic anticoagulation (at full treatment dose) should be withheld for at least 48 hours and only restarted once haemostasis is secured.

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Figure 1: Dabigatran Haemorrhage Protocol

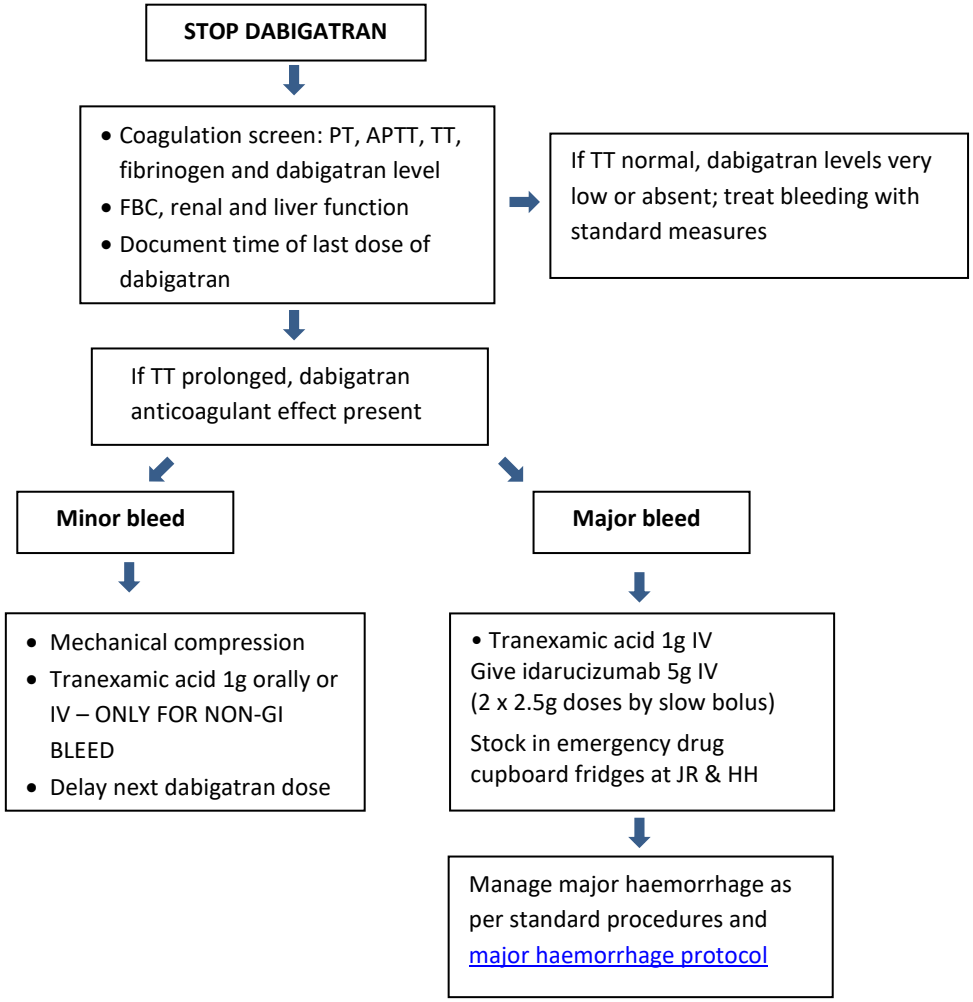

Figure 2: Dabigatran Emergency Surgery Protocol

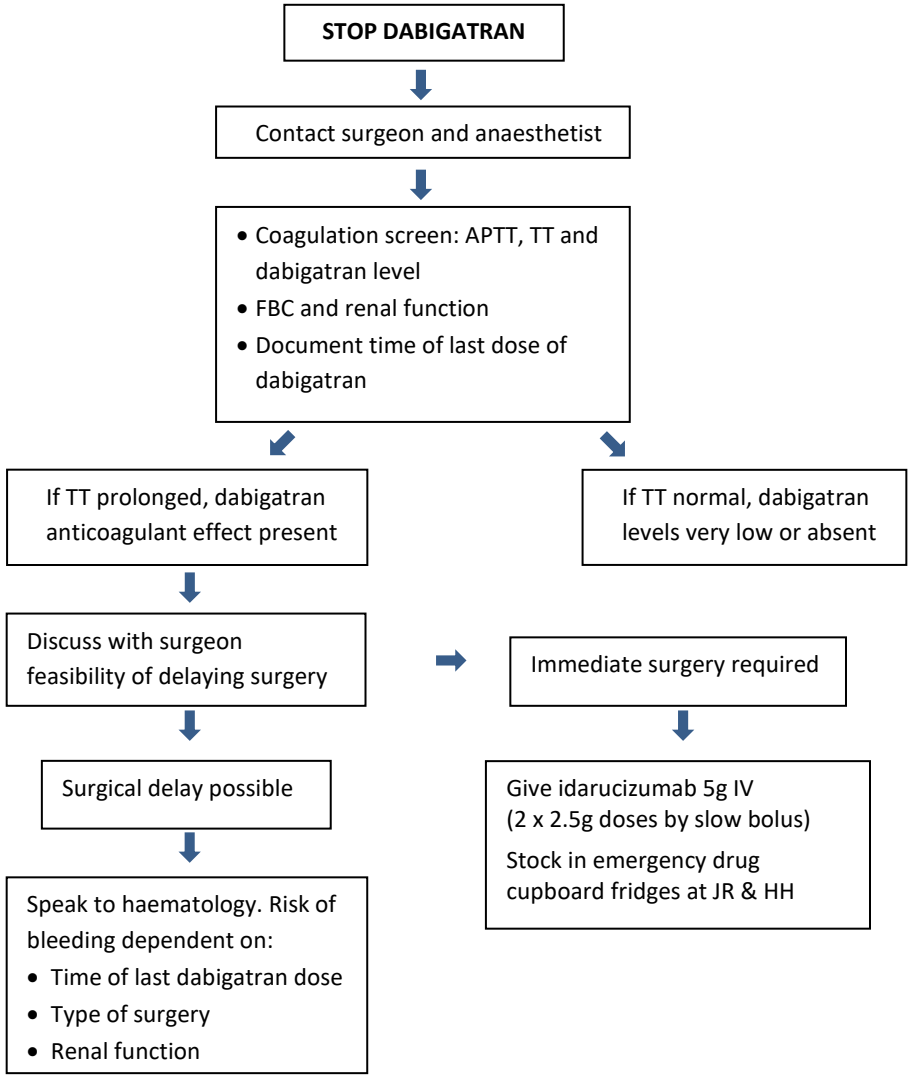

Figure 3: Apixaban, Edoxaban and Rivaroxaban Haemorrhage Protocol

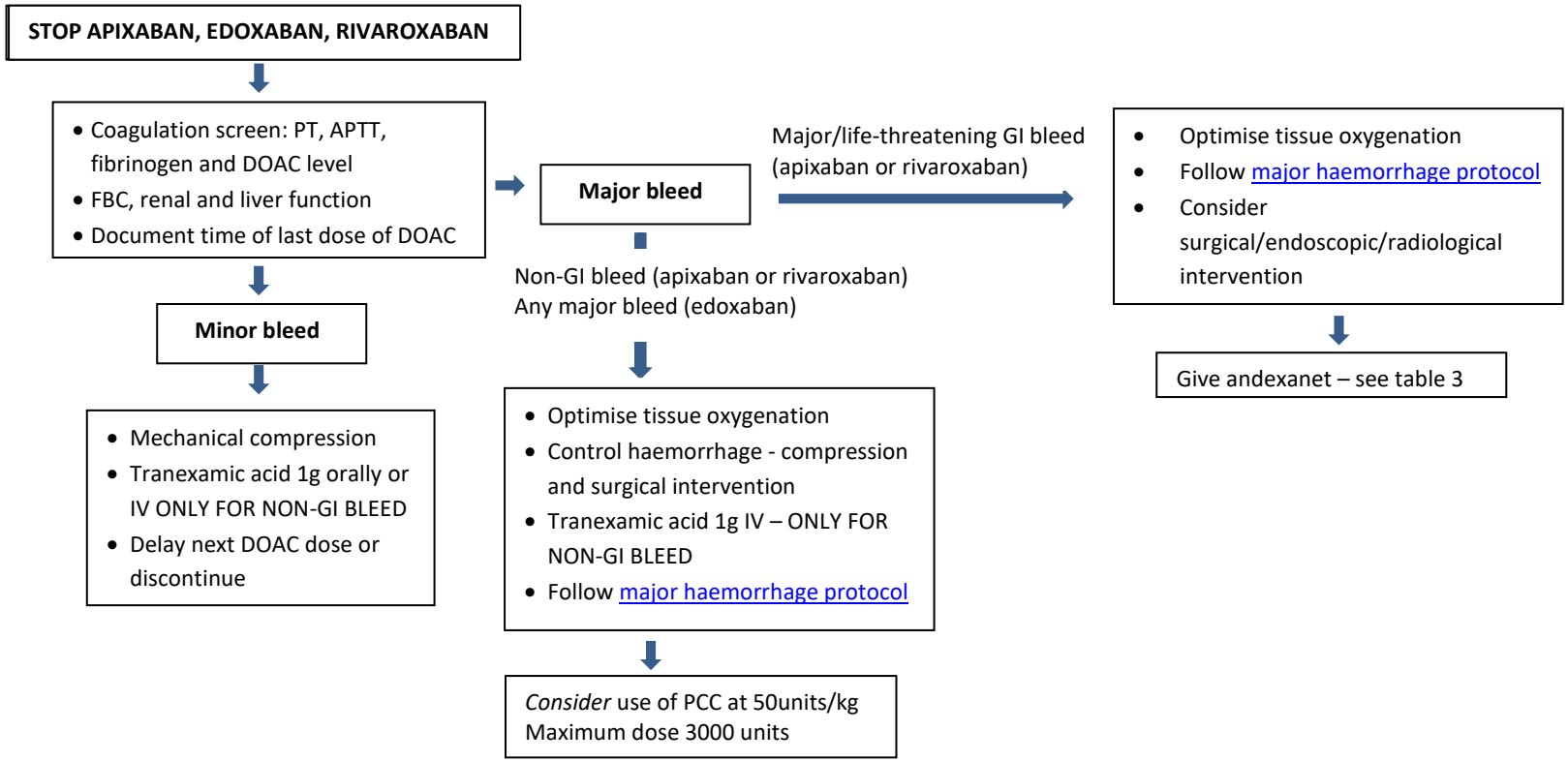

Figure 4: Apixaban, Edoxaban and Rivaroxaban Emergency Surgery Protocol