

GUIDELINES FOR MANAGEMENT OF BLEEDING AND EXCESSIVE ANTICOAGULATION WITH ORAL ANTICOAGULANTS

This guideline covers the management of patients being treated with

- **Vitamin K antagonists (VKA):**
Warfarin
Acenocoumarol
Phenindione
- **Direct oral anticoagulants (DOACs*):**
Apixaban (see also Appendix 2),
Rivaroxaban (see also Appendix 3)
Edoxaban (see also Appendix 4)
Dabigatran (see also Appendix 5)

Management of paediatric patients should be in discussion with their named Consultant

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1. INTERPRETATION OF THE COAGULATION SCREEN

Warfarin/Phenindione/Acenocoumarol

- Prolongs the PT significantly more than the APTT.
- PT/INR is used to monitor anticoagulation

Apixaban/Rivaroxaban/Dabigatran/Edoxaban

- Neither the PT nor the APTT can be used to monitor anticoagulation
- For individual DOAC effects on various clotting measures, individual appendices should be consulted

2. GENERAL NON-PHARMACOLOGICAL MEASURES IN A BLEEDING PATIENT

- **Stop the antithrombotic drug**
- Document the timing and amount of the last drug dose and presence of pre-existing renal or hepatic impairment
- Assess the source of bleeding
- Request full blood count, prothrombin time (PT), activated partial thromboplastin time (APTT), fibrinogen concentration, creatinine and LFTs

- Correct haemodynamic compromise with intravenous fluids and red cells
- Consider transfusion
- Apply mechanical pressure if possible
- Use endoscopic, radiological or surgical measures if possible.
- Do not give further doses of anticoagulant until bleeding is controlled and risk/benefit of further doses has been reviewed, assessed and documented

3. MAJOR/LIFE-THREATENING BLEEDING (irrespective of INR):

(eg. bleeding in a critical area or organ such as intracranial, intraspinal, intra-ocular, bleeding due to major trauma, bleeding leading to haemodynamic instability, or bleeding that is life or limb threatening)

- **STOP THE DRUG**
- **In the event of a major bleed, anticoagulation should not be restarted until the patient is haemodynamically stable and there is stabilisation of haemoglobin (Hb).**
- **Follow drug specific guidance as detailed below**

A. Warfarin (or phenindione/acenocoumarol)

- Give vitamin K (phytomenadione) 5mg IV. (significant correction seen within 6-8 hours)
- Give Beriplex (as per [guidance](#)) in addition to phytomenadione

The dose is dependent on the INR and on the weight of the patient. The dose can be calculated from the table below.

The maximum dose is 5000 units.

INR	2.0 - 3.9	25 units/kg
	4.0 - 6.0	35 units/kg
	> 6.0	50 units/kg

- It is NOT mandatory to discuss use of Beriplex with the Haematology Consultant on call.
- Consider IV tranexamic acid 1g bolus over 10 minutes followed by further 1g (15mg/kg) tds if bleeding persists
- Fresh Frozen Plasma (FFP) can be given (only if Beriplex unavailable)
- **Repeat INR should be done 30 minutes after giving Fresh frozen plasma or Beriplex. If the INR is still raised further doses of beriplex may be needed. This should be discussed with the consultant haematologist on call**

B. Apixaban/Rivaroxaban/Edoxaban

- Consider IV tranexamic acid 1g bolus over 10 minutes followed by further 1g (15mg/kg) TDS if bleeding persists.
- Andexanet alfa is available as an option for reversing anticoagulation from apixaban or rivaroxaban in adults with life-threatening or uncontrolled gastrointestinal bleeding. Discuss with a consultant haematologist before prescribing.
- Alternatively give beriplex 50units/kg (maximum 5000units)

C. Dabigatran

- Idarucizumab (praxbind) is a specific reversal agent for dabigatran and is indicated in adult patients where rapid reversal of anticoagulation is required (life threatening bleeding/emergency surgery, etc).
- Dose is 5g in 100ml idarucizumab iv infusion over 10-20minutes (2 x 2.5g vial in 50ml).
- The drug is available via the emergency cupboard in the pharmacy department at either DRI or BDGH.
- Consider IV tranexamic acid 1g bolus over 10 minutes followed by further 1g (15mg/kg) TDS if bleeding persists.
- Alternatively give beriplex 50units/kg (maximum 5000units).
- Advice should be sought from consultant haematologist.

4. NON-MAJOR BLEEDING

Minor bleeds can be classed further as clinically relevant or not.

A clinically relevant minor bleed is an acute or subacute clinically overt bleed that does not meet the criteria for a major bleed but prompts a clinical response, in that it leads to at least one of the following:

- A hospital admission for bleeding, or
- A physician guided medical or surgical treatment for bleeding, or
- A change in antithrombotic therapy (including interruption or discontinuation of study drug).

Use local measures to control bleeding

Warfarin (or phenindione/acenocoumarol)

- **If INR less than 4.5** – Warfarin should be withheld and the underlying cause investigated in the same manner as for patients not taking warfarin.
- **If INR greater than 4.5** – Withhold warfarin. Give vitamin K 1 to 2mg IV or orally (IV active within 6-8hrs, oral active within 12-24hrs). Repeat INR the next day.

Apixaban/Rivaroxaban/Dabigatran/Edoxaban

- Delay next dose or discontinue as appropriate

5. NO BLEEDING IN PATIENTS ON WARFARIN, PHENINDIONE OR ACENOCOUMAROL WHO ARE OVER-ANTICOAGULATED (BASED ON INR) – TREAT ACCORDING TO INR

- **INR greater than 8** – Withhold warfarin and give vitamin K 1mg IV or orally (IV active within 6-8hrs, oral active within 12-24hrs)
- **INR 4.5 to 8.0** – Withhold warfarin and give vitamin K 1mg orally if patient considered at increased risk of bleeding (e.g. age >65 yrs, previous GI or intracranial bleed, renal or liver failure, anaemia, cancer, recent stroke, or recent surgery, recent head injury)

**6. PATIENTS ADMITTED FOR EMERGENCY SURGERY
([see also Bridging Anticoagulation guidance](#))**

Warfarin (or phenindione/acenocoumarol)

- **Emergency admission for surgery within 8 hours** – Withhold warfarin and give vitamin K 5mg IV and give Beriplex (as per [policy](#))
- **Emergency admission for surgery (which can wait for 8 hours)** – Withhold warfarin and give vitamin K 5mg IV
- **Apixaban/Rivaroxaban/Edoxaban/dabigatran**
 - **Emergency admission for immediate surgery-** For patients taking DOACs (e.g. apixaban, rivaroxaban, dabigatran), the dose should be 50 units/kg.
 - **If Beriplex is to be administered for an indication other than major bleeding on a vitamin K antagonist, then the patient must be discussed with the Consultant Haematologist on call.**
 - **For patients on dabigatran a specific reversal agent (idarucizumab) is now available and may be preferred over beriplex in patients admitted on dabigatran needing urgent reversal – seek Consultant haematologist advice**
 - **If surgery can't be delayed to allow relevant time to have elapsed to ensure reversal of the DOAC as described in the bridging guidance than a consultant haematologist should be contacted to discuss the options for the particular patient concerned**

7. Management of head injury in a patient on anticoagulants

- **Head injuries should be managed as detailed in the NICE guidance on Head injury: assessment and early management (<https://www.nice.org.uk/guidance/cg176>)**
- All patients on anticoagulants presenting to Accident and Emergency departments with head injury should have their INR and clotting measured as soon as possible.
- Adult patients who have sustained a head injury and have presented with a strong suspicion of a bleed (see [NICE guidance](#) for definitions) should have their anticoagulation reversed before the results of any investigations (vitamin K and beriplex for those on warfarin)
- A CT scan should be performed within 1 hour in any patient with risk factors for a bleed (within 1 hour of identification of risk factors)
- For patients who have sustained a head injury with no other indication for a CT head scan other than anticoagulation a CT scan should be performed within 8 hours of the injury (see [NICE guidance](#) for full details)
- Delayed intracranial bleeding can occur in patients on therapeutic anticoagulation even when the initial scan is normal. In view of this, patients with supratherapeutic INR on warfarin should have this corrected into the therapeutic range with IV vitamin K prior to discharge. If the risk of utilising vitamin K to bring an INR back into the therapeutic range is felt to be greater than the risk of bleeding for the individual patient concerned then as a minimum prior to discharge the INR should be rechecked. The patient should only be discharged if the INR has reduced and monitoring arrangements have been made to ensure that this continues
- Following a significant head injury with a normal CT (head injury patient with risk factors including mode of injury/signs and symptoms for intracranial bleed see [NICE guidance algorithm](#)) for patients on warfarin the INR should be more stringently maintained within the desired therapeutic range for 4 weeks following a normal CT scan to minimise the risk of delayed intracranial bleeding. The GP/AMS as appropriate should be informed of the head injury to ensure this is acted on. The Anticoagulation referral form (WPR41040) should be utilised for this and a copy given to the patient detailing doses to be taken until review by their usual team - ideally within the next 72 hours. (Usually the AMS for Doncaster patients and the GP for Bassetlaw patients) The patient/carer as appropriate should be counselled on the doses of warfarin to take until the next blood test and of the need to inform the GP/AMS service of their head injury. The decision as to when to restart/continue the warfarin in a patient on warfarin at the desired therapeutic range with a normal CT is a clinical decision that should be taken by a senior clinician who will consider factors such as the how the head injury occurred, the therapeutic reason for the anticoagulation etc. In some patients it may be appropriate to discontinue the anticoagulant for a period of time. Advice should be taken from the Consultant in charge/Haematologist as needed.
- For patients on DOAC's as with warfarin delayed intracranial bleeding can occur at normal therapeutic doses. To minimise this risk the patient should be maintained on the appropriate dose for their condition ensuring this is appropriate for their renal function, weight etc and that

no interacting drugs are co-prescribed which could increase the exposure to the DOAC concerned. As with warfarin the decision as to when to restart/continue the DOAC is a clinical decision that should be taken by a senior clinician who will consider factors such as the how the head injury occurred, the therapeutic reason for the anticoagulation etc. In some patients it may be appropriate to discontinue the anticoagulant for a period of time. Advice should be taken from the Consultant in charge/Haematologist as needed. It should be noted that when starting/restarting a DOAC the patient will be fully anticoagulated within the day unlike warfarin which may take another 48hours. This needs to be considered when making clinical decisions with respect to anticoagulation.

- In intracranial haemorrhage, anticoagulation should be restarted only after discussions with neurosurgeons.

REFERENCE

Guideline on the management of bleeding in patients on antithrombotic agents – British Committee for Standards in Haematology (BCSH) – 2012*
DOAC (Direct oral anticoagulant) has replaced the acronym NOAC (Novel oral anticoagulant) following some safety alerts where the acronym was misinterpreted. Please be aware both acronyms can be found in the literature

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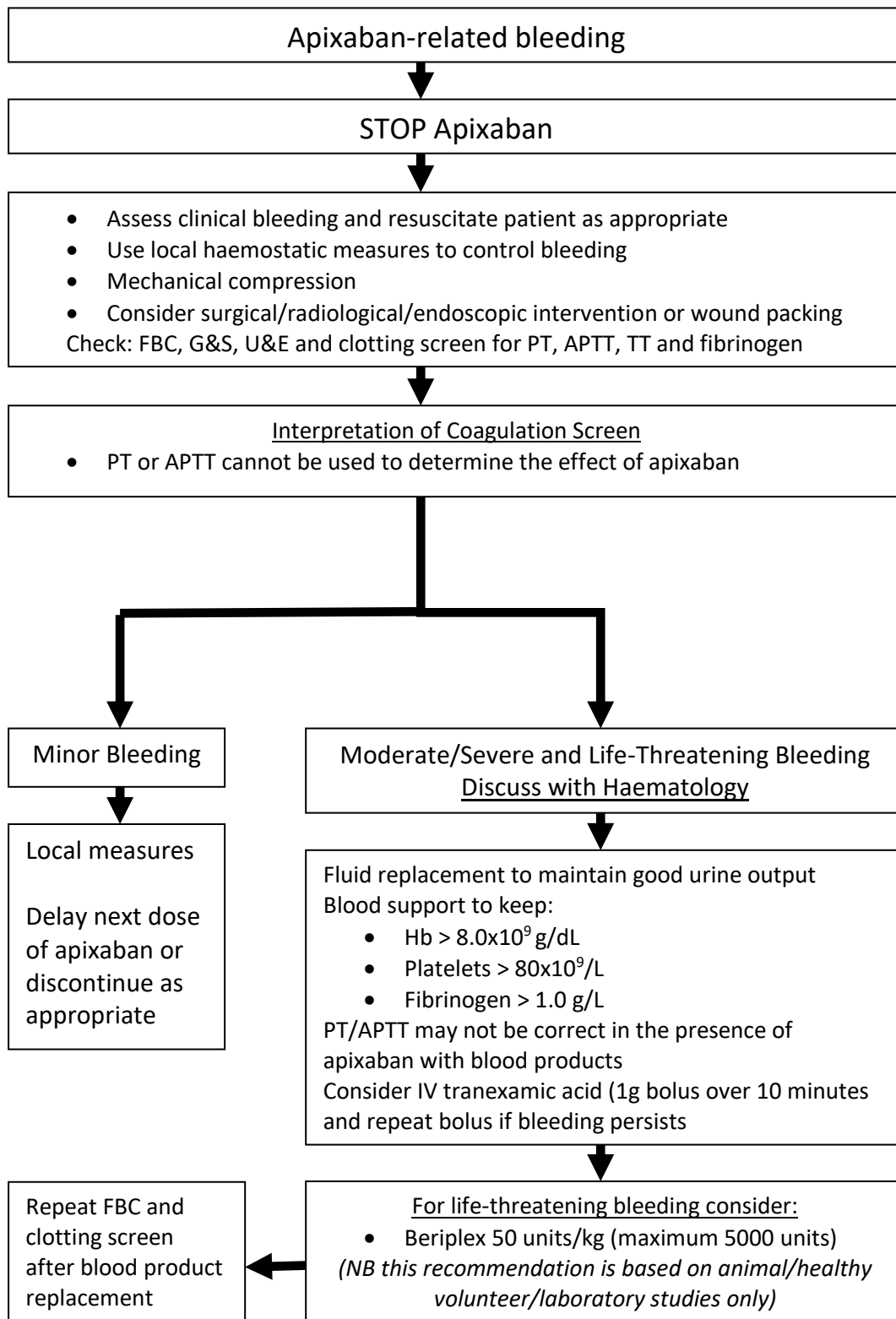
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Appendix 1: Anticoagulant Drug Effect on Routine Laboratory Tests (utilising our instrumentation and reagents)

	PT	APTT	TT	Fgn	DD
Warfarin	+++	+			Low
UFH	+	+++	+++		Low
LMWH		+			Low
Fondaparinux		+			Low
Dabigatran	+	++	+++	-/+	Low
Rivaroxaban	++				Low
Apixaban	+				Low

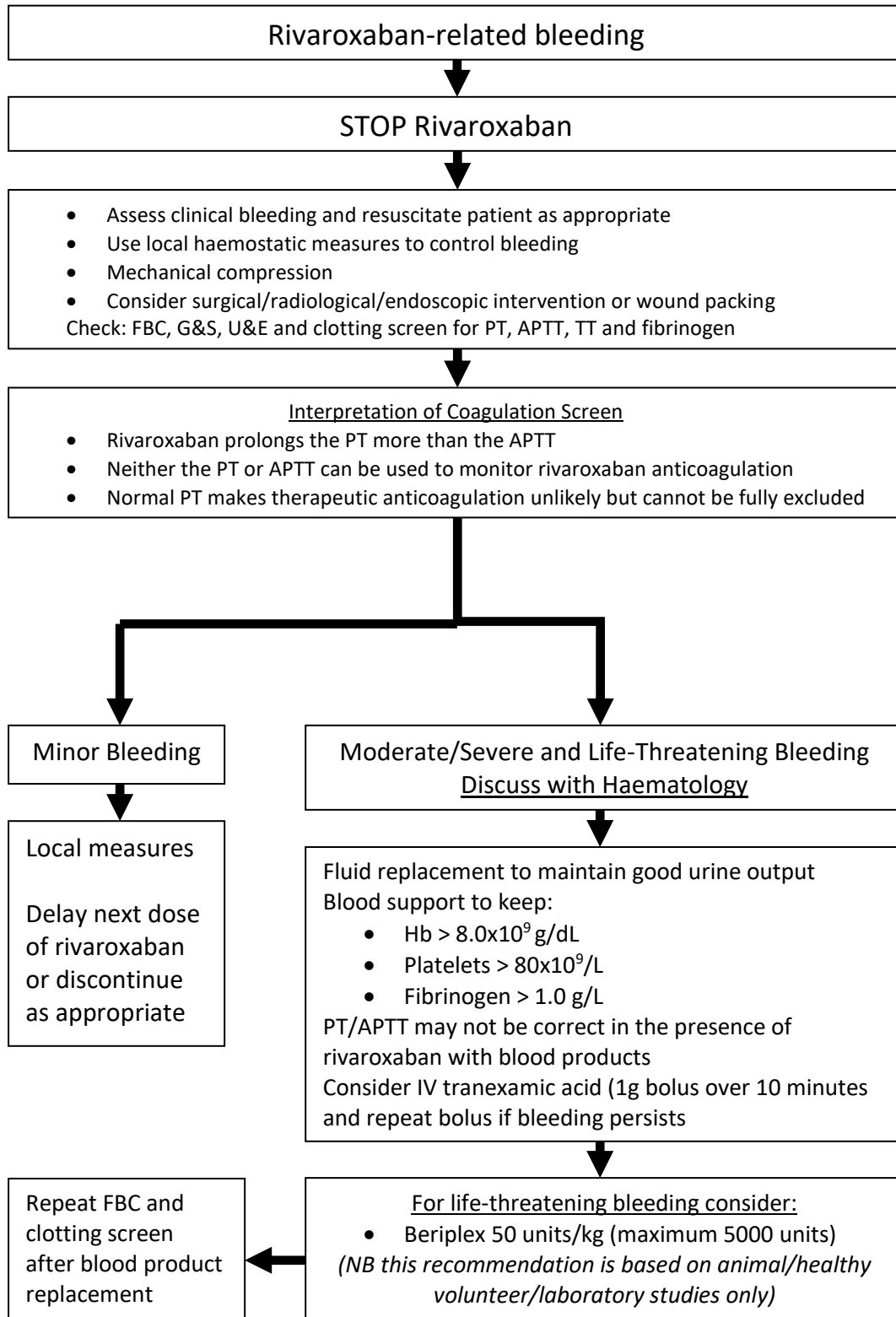
Appendix 2: Guidelines For The Management Of Apixaban-Related Bleeding

- Apixaban is an oral direct factor Xa inhibitor
- Apixaban has a half-life of approximately 12 hours
- Apixaban is metabolised 25% renally and 75% hepatic
- There is NO SPECIFIC REVERSAL agent for apixaban



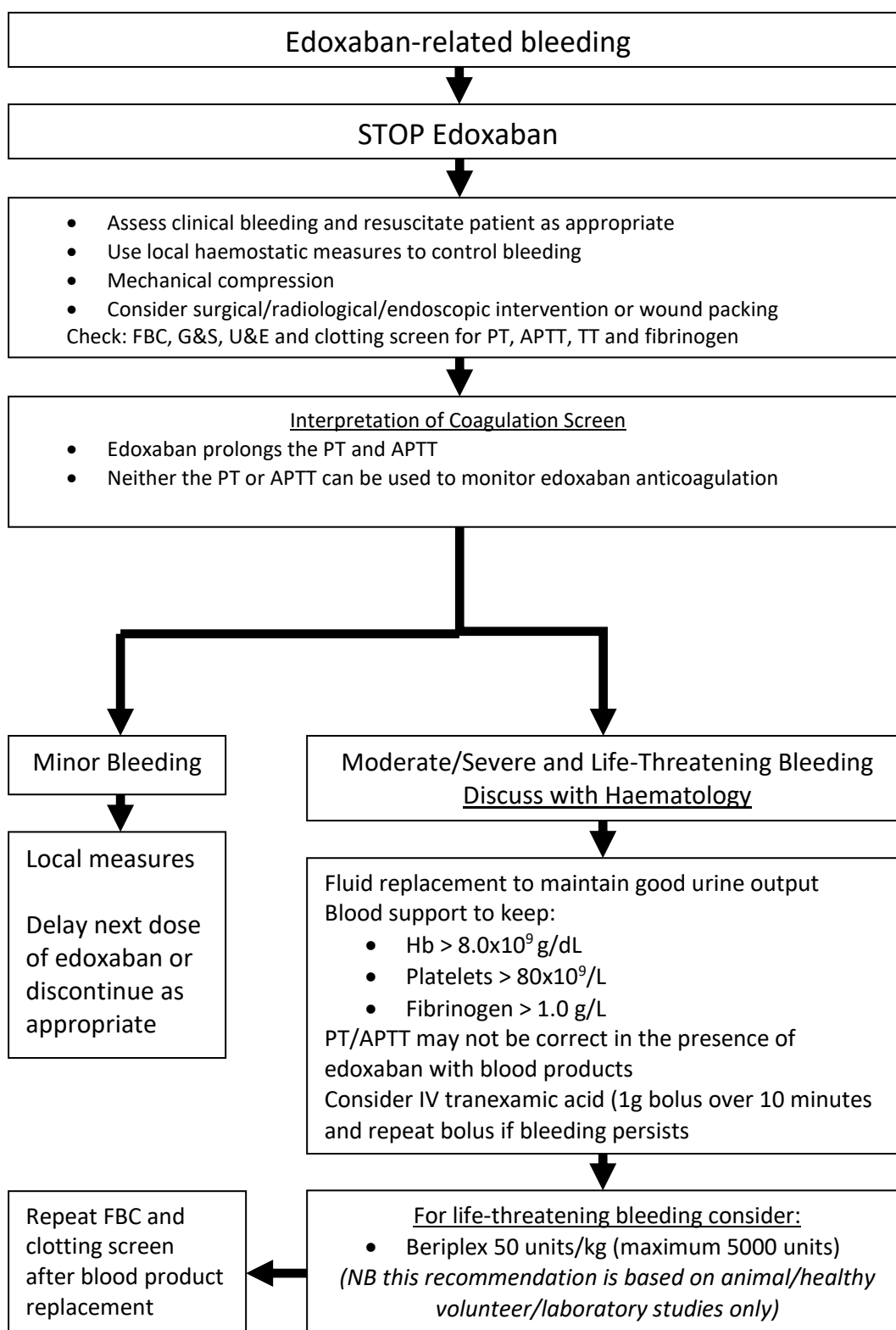
Appendix 3: Guidelines For Management Of Rivaroxaban-Related Bleeding

- Rivaroxaban is an oral direct factor Xa inhibitor
- Rivaroxaban has a plasma half-life of 7 to 9 hours
- Rivaroxaban is metabolised 25% renally and 75% hepatic
- There is NO SPECIFIC REVERSAL agent for rivaroxaban



Appendix 4: Guidelines For Management Of Edoxaban-Related Bleeding

- Edoxaban is an oral direct factor Xa inhibitor
- Edoxaban has a plasma half-life of 10 to 14 hours
- Approximately 50% of edoxaban is excreted unchanged in urine; the remainder is metabolized (minimally by hydrolysis, conjugation, and cytochrome P-450 [CYP] 3A4) and eliminated through biliary and intestinal routes.¹²
- There is NO SPECIFIC REVERSAL agent for edoxaban



Appendix 5: Guidelines For Management Of Dabigatran-Related Bleeding

- Dabigatran is a direct oral thrombin inhibitor with a plasma half-life of 12 to 18 hours
- Dabigatran is primarily renally excreted and the half-life is prolonged in renal impairment. Diuresis must be maintained to promote adequate drug clearance.
- There is now a specific reversal agent for dabigatran (5g idarucizumab; iv infusion over 10-20minutes)

