Guideline Number & Full Title:	2805—Guideline for management of patients receiving factor Xainhibitors Apixaban (Eliquis®), Edoxaban (Lixiana®), or Rivaroxaban (Xarelto®) who are bleeding or require emergency surgery
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Division & Speciality:	Cancer and Associated Specialties (CAS) Clinical Haematology Haemostasis & Thrombosis
Version:	Version 5
Ratified by:	Haemostasis and Thrombosis Service Drugs and Therapeutics Committee (DTC)
Scope ***(Target audience, state if Trust wide):***	Trust wide
Review date ***(when this version goes out of date):***	December 2024
Explicit definition of patient group to which it applies ***(e.g. inclusion and exclusion criteria, diagnosis):***	Patients receiving factor Xa inhibitors Apixaban (Eliquis®), Edoxaban (Lixiana®), or Rivaroxaban (Xarelto®) who are bleeding or require emergency surgery
Changes from previous version ***(not applicable if this is a new guideline, enter below if extensive):***	Edited to clarify the tests required to measure levels of Apixaban, Edoxaban or Rivaroxaban.
Summary of evidence base this guideline has been created from:	National guidance and consensus expert opinion
This guideline has been registered with the trust. However, clinical guidelines are guidelines only. The interpretation and application of clinical guidelines will remain the responsibility of the individual clinician. If in doubt contact a senior colleague or expert. Caution is advised when using guidelines after the review date or outside of the Trust.	

Guideline for management of patients receiving factor Xa inhibitors Apixaban (Eliquis®), Edoxaban (Lixiana®), or Rivaroxaban (Xarelto®) who are bleeding or require emergency surgery

Contents

Background

Apixaban, Edoxaban and Rivaroxaban are direct oral anticoagulants (DOACs) which are licenced for use in the contexts of prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation, treatment of DVT/PE, and prevention of recurrence of DVT/PE.

Further information about this medications can be found on the APC website www.nottsapc.nhs.uk and the Nottinghamshire Joint Formulary.

This guideline is intended to assist clinicians in managing patients receiving Apixaban, Edoxaban or Rivaroxaban who require emergency surgery or suffer from bleeding.

There is separate guidance available for patients who require emergency surgery or suffer from bleeding whilst taking Dabigatran (another DOAC) or a vitamin K antagonist (eg Warfarin).

There is also separate guidance available for the management of patients taking Apixaban, Edoxaban or Rivaroxaban who require an elective invasive procedure or surgical intervention. See **'Guideline for the management of adult patients taking Direct Oral Anticoagulants (DOAC's) for elective, non cardiac, non neurosurgical procedures' (**http://nuhnet/nuh_documents/Guidelines/Cancer%20and%20Associated%20Specialties/Clinical%20Haematology/2782.pdf)

Andexanet alfa is the only agent available for the reversal of factor Xa inhibitors, but it is currently only approved for use in the UK in the context of gastrointestinal bleeding in patients taking Apixaban or Rivaroxaban.
For patients who suffer from gastrointestinal bleeding whilst taking Edoxaban, bleeding elsewhere in the body (irrespective of which medication the patient is taking) or in the context of needing to facilitate emergency surgery, consideration can be given to the use of Prothrombin complex concentrate in order to try and mitigate the effect of anticoagulation.

For patients presenting with overdose of Apixaban, Edoxaban or Rivaroxaban, contact the on call Haematologist via switchboard, or the UK National Poisons Information Service on 0344 892 0111, for advice.

NB: Further information about Prothrombin complex concentrate can be found in the guideline for 'Management of patients receiving a vitamin K antagonist who are over-anticoagulated, bleeding, or in need of an urgent invasive procedure' (http://nuhnet/nuh_documents/Guidelines/Cancer%20and%20Associated%20Specialties/Clinical%20Haematology/2401.pdf), although please note that the dose using in the context of DOACs differs to that used in the context of vitamin K antagonists.

Lab measurement of factor Xa inhibitors
The factor Xa inhibitors do not routinely require monitoring of therapeutic response (unlike vitamin K antagonists, eg Warfarin). However there may be occasions where monitoring the effect of these agents is beneficial, eg if a patient has an episode of bleeding or requires an emergency procedure.

A standard clotting screen should not be used to measure the effect of the factor Xa inhibitors, as the results cannot reliably demonstrate efficacy of these agents, nor reliably demonstrate that there is no residual anticoagulant effect (ie normal prothrombin time may not exclude clinically relevant drug levels).

The below table demonstrates the anticipated impact on coagulation test parameters:

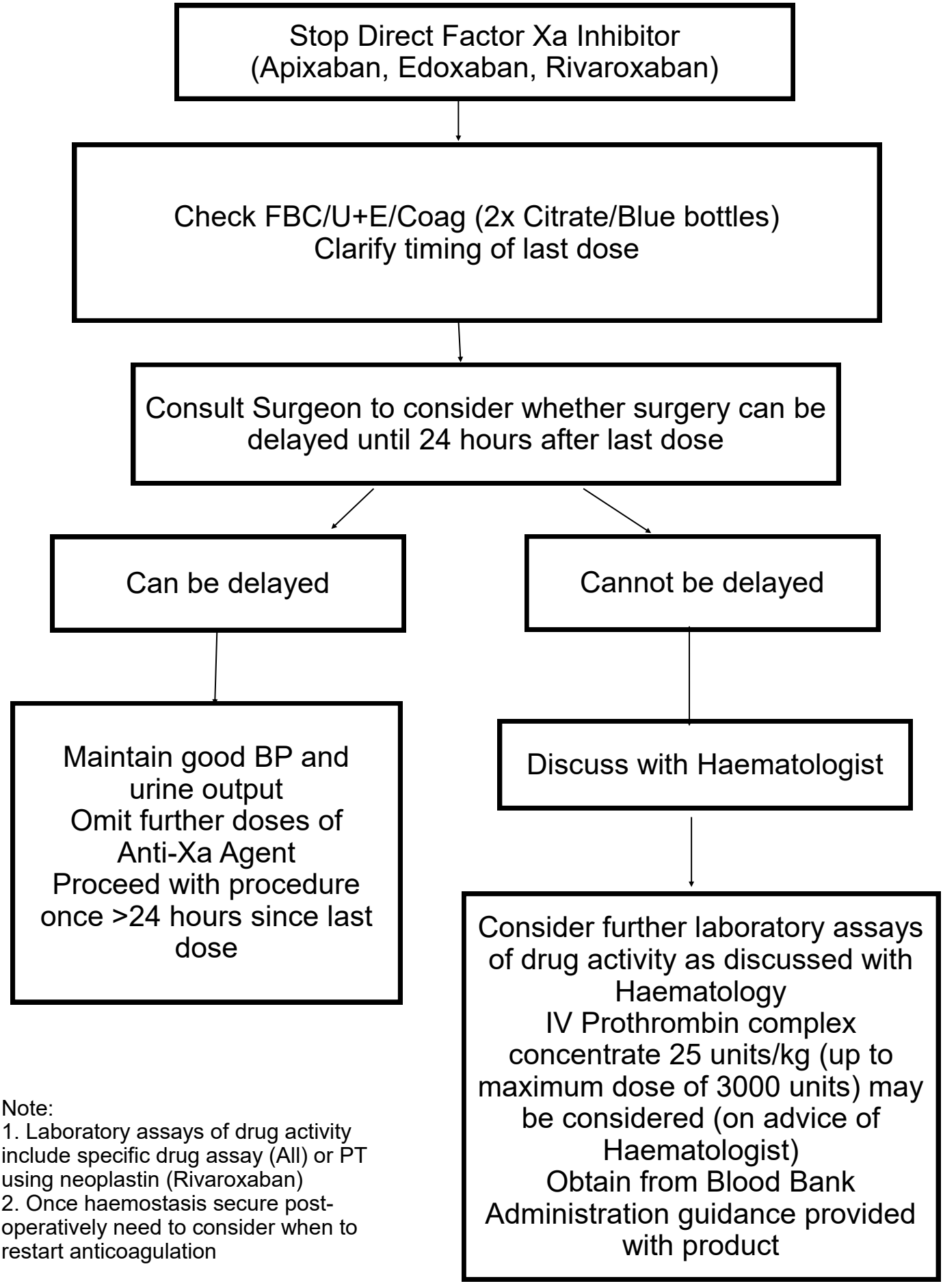
Parameter	**Apixaban (Eliquis®)**	**Edoxaban (Lixiana®)**	**Rivaroxaban (Xarelto®)**	**Dabigatran (Pradaxa®)**
Mechanism of action	Direct factor Xa inhibitor	Direct factor Xa inhibitor	Direct factor Xa inhibitor	Direct thrombin inhibitor
PT	Prolonged	Prolonged	Prolonged (in linear fashion if neoplastin used as reagent)	No effect
APTT	Prolonged	Prolonged	Prolonged (1.5-1.8 times control)	Prolonged (1.4-1.8 times control) greatly prolonged if supratherapeutic levels
TT	No effect	No effect	No effect	Prolonged
Drug Activity	Use anti Xa assay	Use anti Xa assay	Use anti Xa assay	Use Haemoclot thrombin inhibitor assay or ECT
Platelet count	No effect	No effect	No effect	No effect
D-dimer	Suppressed levels	Suppressed levels	Suppressed levels	Suppressed levels
Fibrinogen	No effect	No effect	No effect	Can give falsely low results

A specific drug (anti Xa) assay is the best way to assess the anticoagulant effect of all of the factor Xa inhibitors, although it is important to bear in mind that interpretation of the results is not straightforward, and it remains unclear at what drug level there is no longer a clinically relevant impact on risk of bleeding.

NB: It is possible to exclude clinically relevant levels of Rivaroxaban by checking the prothrombin time using Neoplastin.

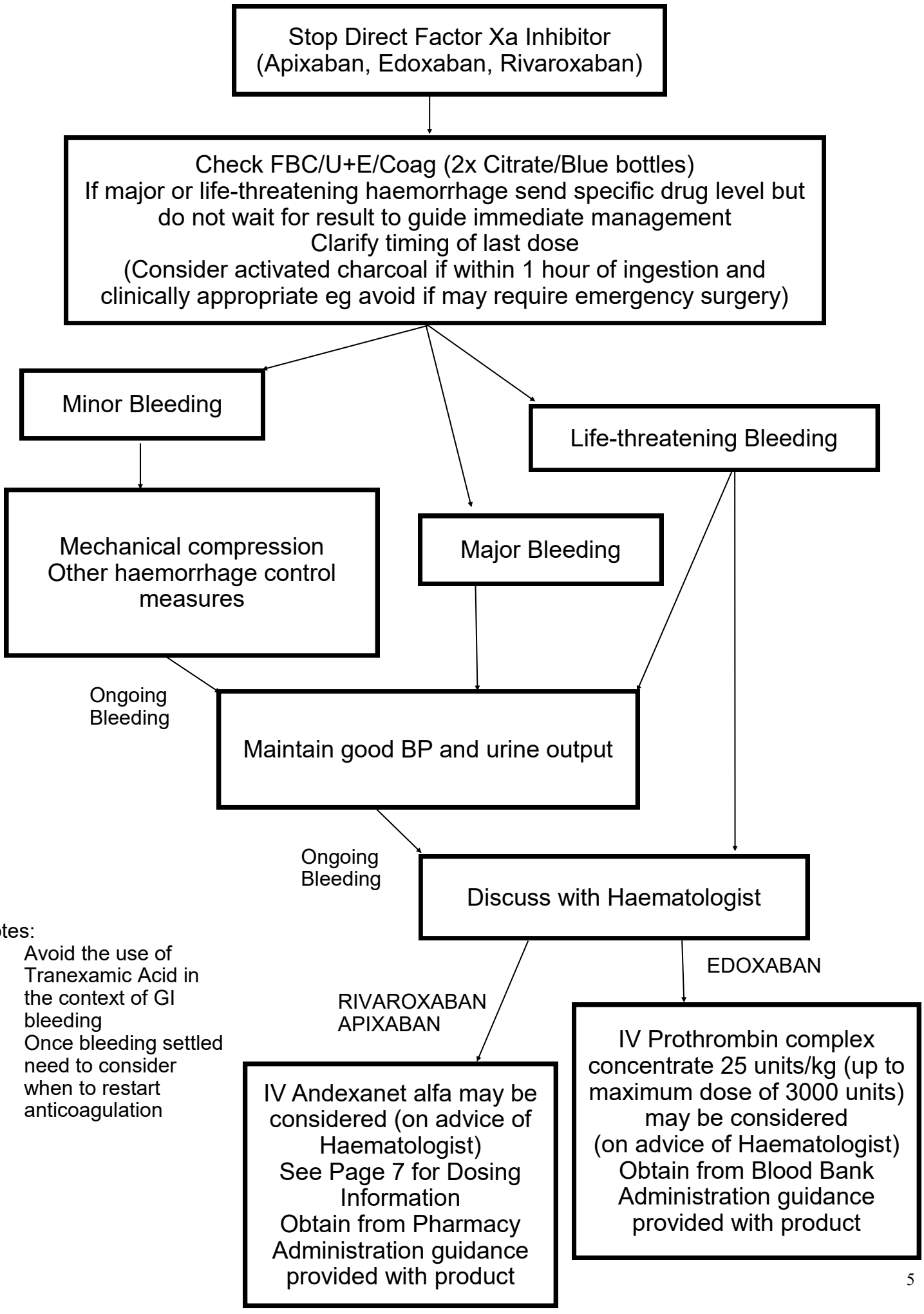
In the event that measurement of factor Xa inhibitors may be helpful for clinical management, please discuss with on call Haematologist .

PROTOCOL 1: EMERGENCY SURGERY



Note:
1. Laboratory assays of drug activity include specific drug assay (AII) or PT using neoplastin (Rivaroxaban)
2. Once haemostasis secure post-operatively need to consider when to restart anticoagulation

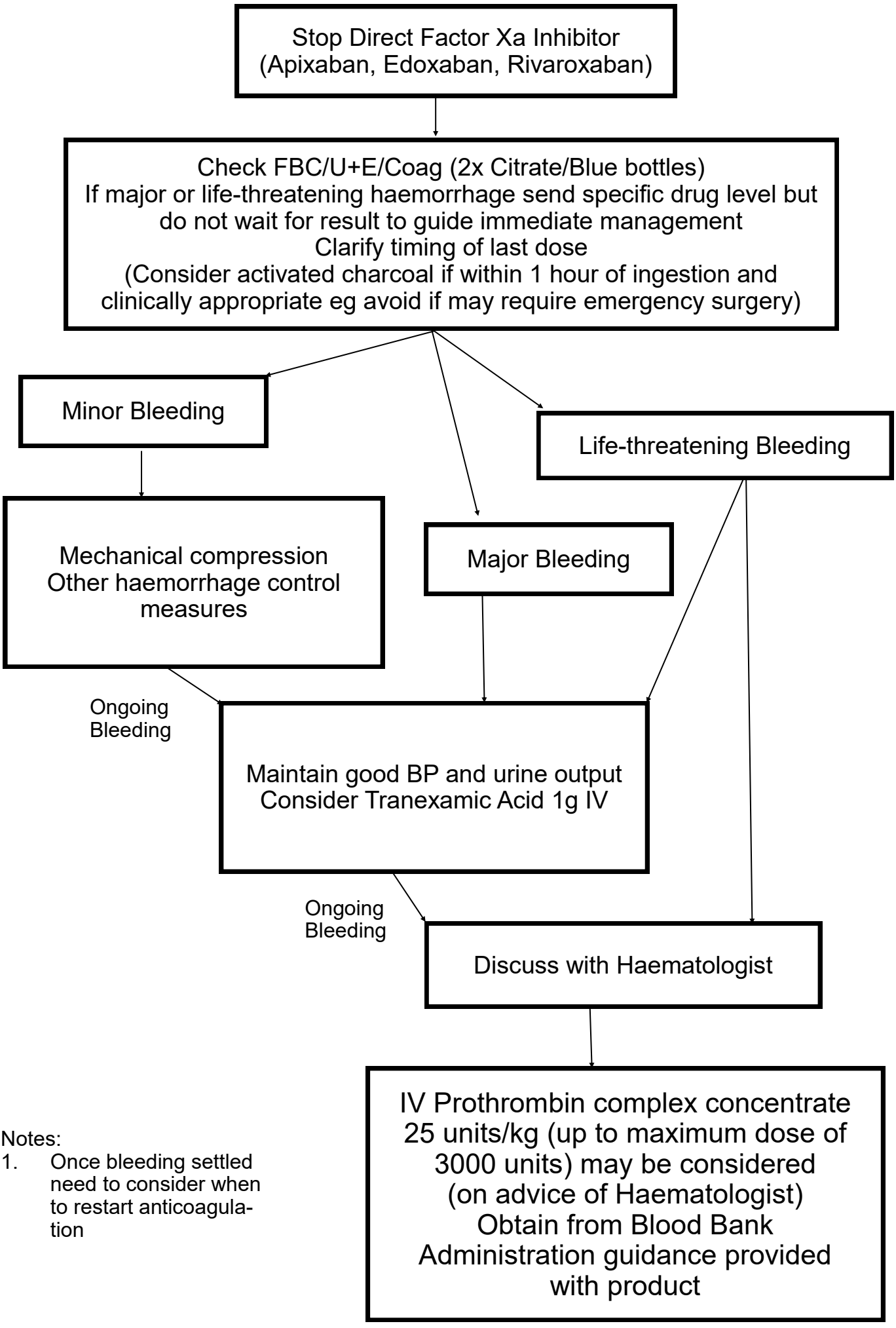
PROTOCOL 2: GI BLEEDING



Notes:

1. Avoid the use of Tranexamic Acid in the context of GI bleeding
2. Once bleeding settled need to consider when to restart anticoagulation

PROTOCOL 3: BLEEDING (EXCLUDING GI BLEEDING)



Notes:

1. Once bleeding settled need to consider when to restart anticoagulation

Dosing Information for Andexanet Alfa

Andexanet alfa is administered as an intravenous bolus at a target rate of approximately 30 mg/min over 15 minutes (low dose) or 30 minutes (high dose), followed by administration of a continuous infusion of 4 mg/min (low dose) or 8 mg/min (high dose) for 120 minutes (see table 1).

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

Reversal of Apixaban

The recommended dose regimen is based on the dose of Apixaban the patient is taking at the time of anticoagulation reversal, as well as on the time since the patient's last dose of Apixaban (see table 2).

Table 2: Summary of dosing for reversal of Apixaban

	Last dose	Timing of last dose before initiation of Andexanet alfa	
		< 8 hours or Unknown	≥ 8 hours
Apixaban	≤ 5 mg	Low dose	Low dose
	> 5 mg/ Unknown	High dose	

Reversal of Rivaroxaban

The recommended dose regimen is based on the dose of Rivaroxaban the patient is taking at the time of anticoagulation reversal, as well as on the time since the patient's last dose of Rivaroxaban (see table 3).

Table 3: Summary of dosing for reversal of Rivaroxaban

	Last dose	Timing of last dose before initiation of Andexanet alfa	
		< 8 hours or Unknown	≥ 8 hours
Rivaroxaban	≤ 10 mg	Low dose	Low dose
	> 10 mg/ Unknown	High dose	

No dose adjustment is required for elderly patients (aged 65 years and older), patients with renal impairment, or patients with hepatic impairment.

Infusion-related reactions are common

In case of mild or moderate infusion reactions, careful observation may be sufficient. For moderate symptoms, consideration may be given to a brief interruption or slowing of the infusion with resumption of the infusion after symptoms subside.

NB: Andexanet alfa can be obtained from Pharmacy, and administration guidance is provided with the product.

Equality Impact Assessment Report

1. **Name of Policy or Service**
   Response to external best practice policy

2. **Responsible Manager**
   Owen Bennett (Clinical Quality, Risk and Safety Manager)

3. **Name of person Completing EIA**
   Julian Holmes

4. **Date EIA Completed**
   22/09/2022

5. **Description and Aims of Policy/Service**
   Guideline for management of patients receiving factor Xa inhibitors Apixaban (Eliquis®), E doxaban (Lixiana®), or Rivaroxaban (Xarelto®) who are bleeding or require emergency surgery

6. **Brief Summary of Research and Relevant Data**
   NICE guideline, BCSH guideline, SPC

7. **Methods and Outcome of Consultation**
   N/A

8. **Results of Initial Screening or Full Equality Impact Assessment:**
9. **Decisions and/or Recommendations (including supporting rationale)**

Equality Group	Assessment of Impact
Age	No Impact Identified
Gender	No Impact Identified
Race	No Impact Identified
Sexual Orientation	No Impact Identified
Religion or belief	Some Jehovah witnesses may not accept Prothrombin complex concentrate
Disability	No Impact Identified
Dignity and Human Rights	No Impact Identified
Working Patterns	No Impact Identified
Social Deprivation	No Impact Identified

From the information contained in the procedure, and following the initial screening, it is my decision that a full assessment is not required at the present time.

10. **Equality Action Plan (if required)**
    N/A

11. **Monitoring and Review Arrangements**
    Review December 2024