Document Control

Title

Guideline for the emergency reversal of apixaban, dabigatran and rivaroxaban

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Lead Director
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Superseded Documents
Guideline for patients receiving dabigatran requiring emergency reversal for surgery or treatment of haemorrhage

Issue Date	Review Date	Review Cycle
Oct 2021	Aug 2024	Three years

Consulted with the following stakeholders:

- Anaesthetists
- Anticoagulation pharmacists
- Emergency medicine
- Haematology

Approval and Review Process

- Medicines Management Group
- ED Governance Group
- Medicine Divisional Governance

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CONTENTS

1. Purpose

1.1. The purpose of this document is to detail the process for using idarucizumab (Praxbind®) and Andexanet alfa (*Ondexxya*®)

1.2. The policy applies to all appropriate Trust staff

1.3. Implementation of this policy will ensure that:

- Idarucizumab and Andexanet alfa are used safely and appropriately

2. Definitions

DOAC

2.1. Direct oral anticoagulant

Idarucizumab (Praxbind®)

2.2. Licensed reversal agent for dabigatran

Andexanet alfa

2.3. Licensed reversal agent for rivaroxaban and apixaban

3. Responsibilities

3.1. It is the responsibility of all staff using Idarucizumab and Andexanet alfa to ensure that guidance is followed and exceptions are documented.

3.2. The decision to use Idarucizumab or Andexanet alfa should be made by a consultant. Where this is not possible a middle grade doctor or suitably specialist NMP may make the decision.

Role of Medicines management Group

3.3. The Medical director is responsible for:

- Overall responsibility for the implementation of this guidance

Role of Anticoagulant Working Group

3.4. The Anticoagulant Working Group is responsible for:

- Acting as an oversight for use of Idarucizumab and Andexanet alfa
- Ensuring that use is appropriate

4. Dabigatran

4.1. Dabigatran is a direct factor thrombin inhibitor

4.2. The effect of dabigatran on routine coagulation screening tests is dependent on factors specific to the laboratory performing the test. **Appendix 1** shows the effect of all the direct oral anticoagulants on clotting screens

4.3. The aPTT is the most useful test for assessing the anticoagulant effect of dabigatran. A normal aPTT is likely to exclude a therapeutic level of anticoagulation with dabigatran.

4.4. A standard thrombin time is likely to be very sensitive to dabigatran, but is not recommended for assessment of level of anticoagulation.

Emergency surgery

4.5. Dabigatran is usually stopped in advance of surgery and delaying surgery until no longer anticoagulated is preferential – see trust guideline on anticoagulants and surgery.

4.6. If the procedure cannot be delayed for the time required, the increased risk of bleeding should be assessed against the urgency of the intervention

4.7. **Emergency surgery –** see **Appendix 2** flowchart below

Reversal or overdose

4.8. **Praxbind (idarucizumab) is a specific reversal agent for dabigatran in adults when rapid reversal is required**

4.9. The dose is 5g (2x2.5g vials) given as two consecutive infusions over 5 to 10 minutes each or as a bolus injection. Please see MEDUSA monograph for full details. A second dose may be given if required

4.10. It is kept in the emergency department and should be used only where absolutely necessary as judged by the above specified people. **Appendix 3** flowchart is provided to guide decision making but does not replace clinical judgement

4.11. The vials should be kept in the fridge protected from light and used within an hour of opening.

5. Apixaban and rivaroxaban

5.1. Apixaban and rivaroxaban are direct inhibitors of activated factor X (factor Xa)

5.2. The effect of Apixaban and rivaroxaban on routine coagulation screening tests is dependent on factors specific to the laboratory performing the test. **Appendix 1** shows the effect of all the direct oral anticoagulants on clotting screens

Andexanet Alfa for reversal of Apixaban and Rivaroxaban

5.3. Andexanet alfa has limited clinical evidence and no direct trial comparison against existing treatments like prothrombin complex concentrate. Indirect comparison data is also uncertain. Because of this, the drug has received very limited NICE approval in haemorrhage **Appendix 4**

5.4. Andexanet alfa is recommended as an option for reversing anticoagulation from apixaban or rivaroxaban in adults with life-threatening or uncontrolled bleeding, only if:

- the bleed is in the gastrointestinal tract, and
- the company provides andexanet alfa according to the commercial arrangement.

5.5. Andexanet alfa is recommended only in research for reversing anticoagulation from apixaban or rivaroxaban in adults with life-threatening or uncontrolled bleeding in the skull (intracranial haemorrhage; ICH), in the form of an ongoing randomised trial mandated by the regulator.

5.6. Please see **Appendix 4** for dosing regimens. Infusion and reconstitution guidance can be found on the MEDUSA monograph

5.7. Andexanet alfa has a risk factor of 6 and an overall risk rating of **RED** due to:

- Therapeutic risk
- Complex method
- Reconstitution of powder in a vial
- Use of a part vial or ampoule, or use of more than one vial or ampoule
- Use of a pump or syringe driver
- Use of non-standard giving set/device

Please undertake administration carefully and refer to the MEDUSA monograph for more information. Pharmacy can be contacted for advice if needed via 2392 or bleep 500 out of hours.

5.8. Treatment monitoring after administration of andexanet alfa should not be based on anti-FXa activity assays. In these assays, the FXa inhibitor dissociates from andexanet alfa, resulting in the detection of falsely elevated anti-FXa activity levels, and consequently a substantial underestimation of the reversal activity of andexanet alfa.

5.9. Monitor treatment using clinical parameters indicative of appropriate response (i.e. achievement of haemostasis), lack of efficacy (i.e. re-bleeding), and adverse events (i.e. thromboembolic events).

Emergency surgery

5.10. Andexanet alfa is not licenced for use or NICE approved for reversal of anticoagulation prior to surgery

5.11. Off-label use of andexanet alfa to reverse FXa anticoagulation prior to surgery with intended heparin anticoagulation has been reported to cause unresponsiveness to heparin and healthcare professionals are advised to avoid such use.

6. Monitoring Compliance with and the Effectiveness of the Guideline

Standards/ Key Performance Indicators

6.1. Key performance indicators comprise:

- Annual audit of idarucizumab and Andexanet alfa usage

Process for Implementation and Monitoring Compliance and Effectiveness

6.2. Training to be done through ED training days.

6.3. Monitoring process

- Compliance will be monitored by the anticoagulation working group
- This will be reported to the medicines management group

7. References

- Idarucizumab (Praxbind®) Summary of Product Characteristics
- Andexanet alfa (*Ondexxya*®)Summary of Product Characteristics
- Andexanet alfa for reversing anticoagulation from apixaban or rivaroxaban - TA697
- Reversal of the anticoagulant effect of dabigatran: idarucizumab - ESNM73

8. Associated Documentation

- Oral Anticoagulation Policy
- Peri-operative management of anticoagulation Policy
- Medusa injectable medicines guide
- Hatton-Wyatt, E. Pruchniewicz, J. (2016) Peri-operative management of patients on warfarin and the new oral anticoagulants. Update in Anaesthesia. 31, 14-23

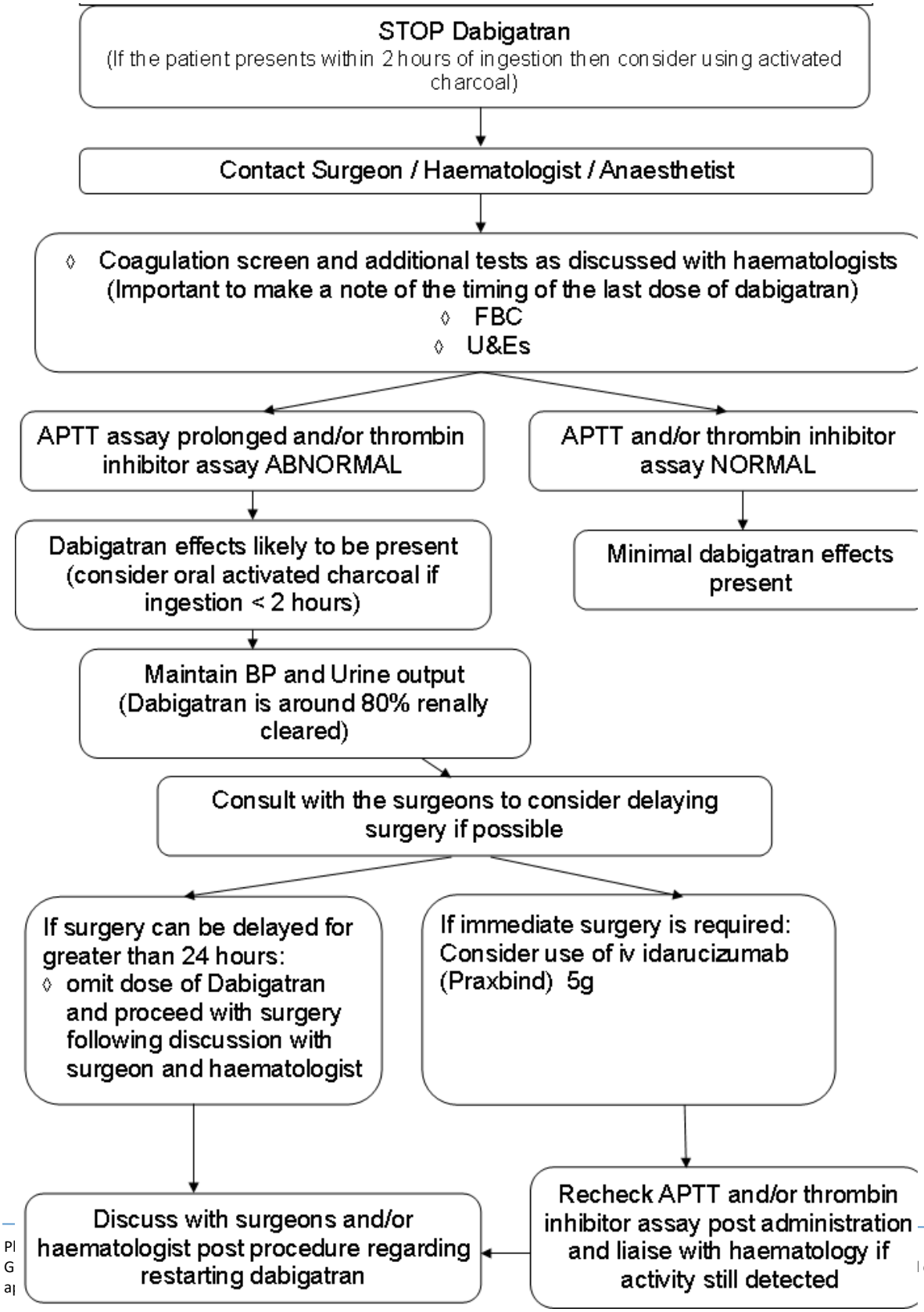
Appendix 1 – Information on Drug Effects

Apixaban, dabigatran, rivaroxaban and edoxaban are direct oral anticoagulants that are alternatives to coumarins (e.g. warfarin) in selected groups of patients for certain indications. All these drugs accumulate in renal impairment. A standard clotting screen has not been validated for assessing the degree of anticoagulation in a patient taking these agents and should not be used for this purpose. Consult haematology for advice.

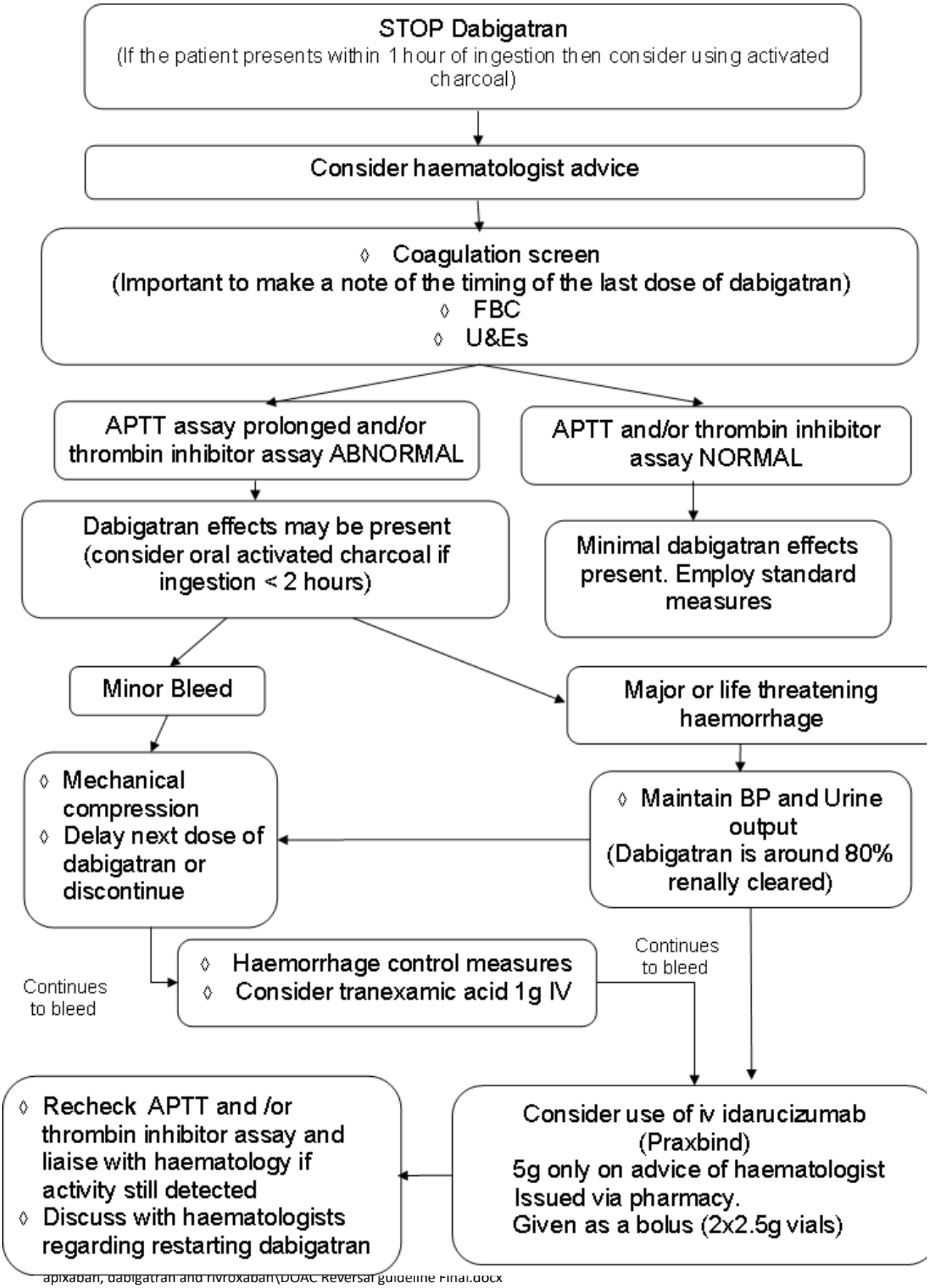
The table below gives information on the drugs' effects on coagulation screens:

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

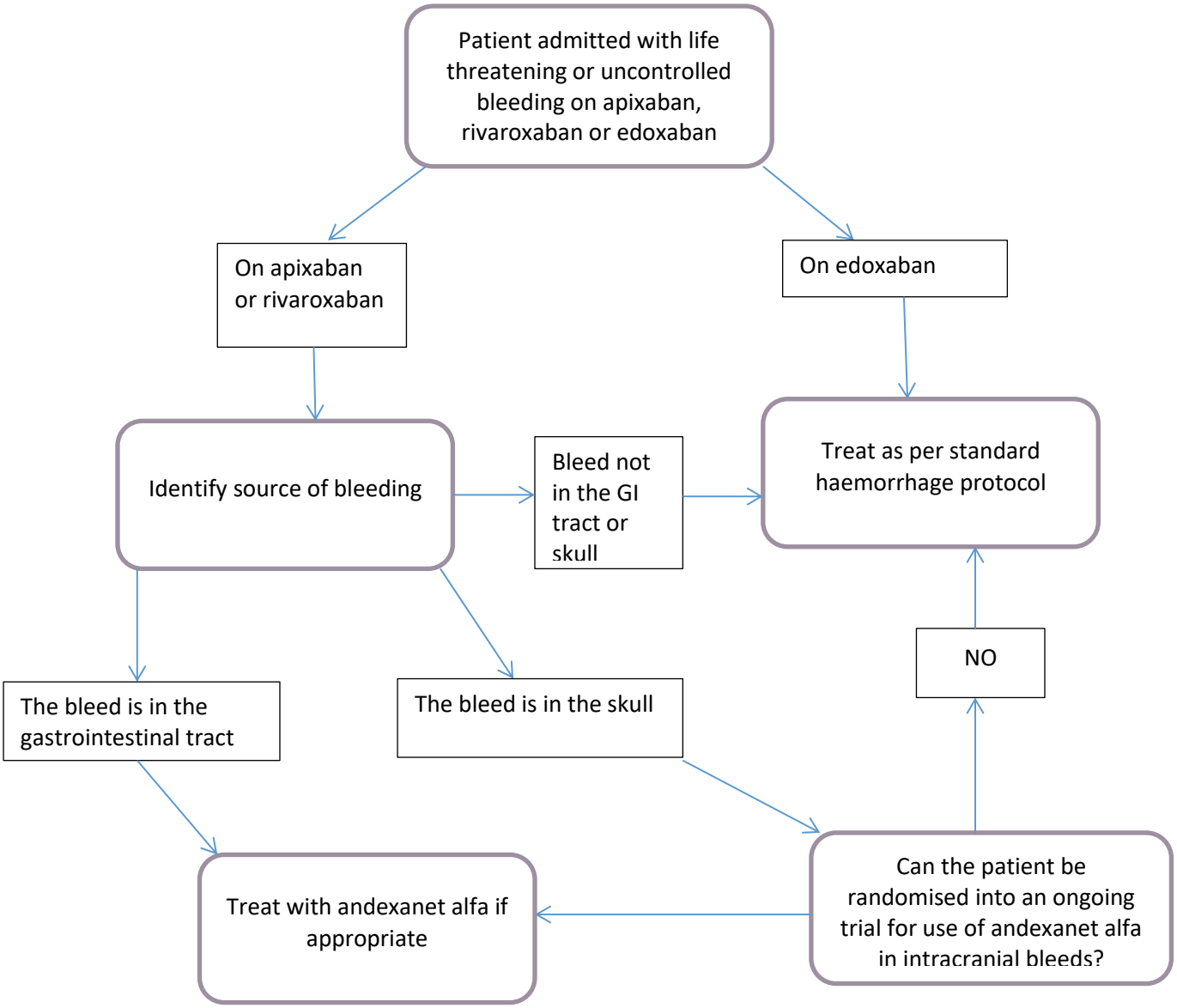
Appendix 2 – Patient receiving Dabigatran therapy – emergency surgery protocol



Appendix 3 Patient receiving Dabigatran therapy – haemorrhage protocol



Appendix 4 – andexanet alfa use guide



FXa inhibitor	Last dose	Timing of last dose before Andexanet alfa initiation	
		< 8 hours or unknown	≥ 8 hours
Apixaban	≤ 5mg	Low dose	Low dose
	> 5mg or unknown	High dose	
Rivaroxaban	≤ 10mg	Low dose	
	>10mg or unknown	High dose	

Dosing regimens	Initial intravenous bolus	Continuous intravenous infusion	Number of 200mg vials needed
Low dose	400mg at target rate of 30mg/min	4mg/min for 120min (480mg)	5
High dose	800mg at target rate of 30mg/min	8mg/min for 120min (960mg)	9