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Title	**Reversal of anticoagulation and management of bleeding in adult patients on either warfarin, non-Vitamin K oral anticoagulants (NOACs) or heparin**
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Associated Trust Documents on the Intranet	CG 228 - Guidelines on the use of Octaplex (Prothrombin complex concentrate/PCC) for rapid reversal of Warfarin in cases of major haemorrhage or emergency surgery CG375 - Major Haemorrhage Protocol in Adults, Children and Neonates and Procedure for Obtaining Blood and Blood Products in an Emergency

CONTENTS

Reversal of anticoagulation and management of bleeding in adult patients on either warfarin, non-Vitamin K oral anticoagulants (NOACs) or heparin

Clinical Guidelines are to assist management but individual clinical judgement remains important and must be used in dealing with the problems specific to each patient.

1. Purpose and scope

These guidelines are for the use of all medical and nursing staff in the management of patients who are bleeding on anticoagulation or who require reversal of anticoagulation for emergency surgery.

This document will include information on warfarin (and other vitamin K antagonists), unfractionated heparin (UFH), low molecular weight heparin (LMWH) and the NOACs (dabigatran, rivaroxaban, apixaban and edoxaban).

2. General Principles of Management of Anticoagulant-Associated Bleeding

- 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), thrombin time (TT), fibrinogen concentration, renal and liver function tests
- Consider reversal agent
- Consider the half-life of the drug
- Correct haemodynamic compromise with intravenous fluids and transfusion (red cells etc as indicated)
- Apply mechanical pressure, if possible
- Use endoscopic, radiological or surgical measure

3. Management of patients on warfarin (or other vitamin K antagonists e.g. phenindione / acenocoumarol)

3.1. Major bleeding (i.e. life, limb or sight–threatening haemorrhage) on warfarin

Also refer to:

- Appendix 1: Flowchart for management of bleeding in patients on anticoagulation with Warfarin or other vitamin K antagonists (phenindione, acenocoumarol) – see page 17.
- Intranet for Guidelines on the use of Octaplex (Prothrombin complex concentrate/PCC) for rapid reversal of Warfarin in cases of major haemorrhage or emergency surgery.

- Stop warfarin
- Give phytomenadione (vitamin K) 5 - 10mg by slow IV injection
- Emergency anticoagulation reversal should be with prothrombin complex concentrate (PCC) – Octaplex – refer to Octaplex guidelines on intranet for indications, dose and administration.
- Octaplex is available from Blood Transfusion Lab.
- In cases of major or life-threatening haemorrhage, the use of Octaplex can be authorised by senior member of team (consultant) looking after the patient and it is not mandatory to discuss use with on-call consultant haematologist.
- Fresh frozen plasma (FFP) produces suboptimal reversal of anticoagulation and should not be used to reverse warfarin unless no PCC is available in the case of a severe bleed.
- Repeat FBC and coagulation screen immediately after infusion, at 6 hours and at regular intervals after until stable.

3.2. Non-major bleeding on warfarin

- **INR > 8.0 and minor bleeding**
  - Stop warfarin
  - Give phytomenadione (vitamin K) 1–3 mg by slow IV injection
  - Repeat dose of phytomenadione if INR still too high after 24 hours
  - Restart warfarin when INR <5.0
  - The cause of the elevated INR should be investigated.
  - Unexpected bleeding at therapeutic levels—always investigate possibility of underlying cause e.g. unsuspected renal or gastro-intestinal tract pathology.

- **INR 5.0–8.0 and minor bleeding**
  - Stop warfarin
  - Give phytomenadione (vitamin K) 1–3 mg by slow IV injection
  - Restart warfarin when INR <5.0
  - The cause of the elevated INR should be investigated.
  - Unexpected bleeding at therapeutic levels—always investigate possibility of underlying cause e.g. unsuspected renal or gastro-intestinal tract pathology.

3.3. High INR >5.0 and >8.0 in non-bleeding patients

- **INR > 8.0 and no bleeding**
  - Stop warfarin
  - Give phytomenadione (vitamin K) 1–5 mg orally
  - Repeat dose of vitamin K if INR still too high after 24 hours
  - Restart warfarin when INR <5.0
  - The cause of the elevated INR should be investigated

- **INR 5.0–8.0 and no bleeding**
  - Withhold 1 or 2 doses of warfarin and reduce subsequent maintenance dose
  - The cause of the elevated INR should be investigated

3.4. Reversal of warfarin for emergency surgery

This section should be read in conjunction with Guidelines on the use of Octaplex (Prothrombin complex concentrate/PCC) for rapid reversal of warfarin in cases of major haemorrhage or emergency surgery.

- Stop warfarin.
- Take blood samples for INR, FBC, cross-match & other tests if indicated.
- If surgery can be delayed for 6 -12 hours, give phytomenadione (vitamin K) 2.5 - 5 mg IV, depending on urgency and degree of reversal required. Repeat INR in 6 hrs to ensure correction (additional doses of vitamin K may be required if INR is still high).
- If surgery cannot be delayed (i.e. immediate or within 6 hours), give IV phytomenadione 5 -10mg and consider PCC (Octaplex 25-50 units/kg depending on initial INR) to reverse warfarin. Discuss with on-call consultant haematologist to authorise use of Octaplex, particularly if high-risk thrombotic cases.
- Repeat INR immediately after the PCC.
- When INR is satisfactory (INR <1.5) proceed with operation.
- Consider post-operative enoxaparin until therapeutic oral anticoagulation can be restarted, after assessment of thrombotic risk and bleeding risk.

4. Management of the bleeding patient on intravenous unfractionated heparin (IV UFH)

- Stop heparin pump
- As UFH at therapeutic intravenous (IV) doses has a half–life of 45 to 90 minutes, it is usually sufficient to stop the infusion
- Check APTT and APTT ratio (APTTR) and FBC
- UFH can be rapidly reversed with protamine sulphate. If bleeding is severe, reverse anticoagulation with iv protamine sulphate.
- Protamine sulphate dose may be calculated from the quantity of UFH administered in the 2 hours prior to reversal using the assumption that 1 mg protamine neutralizes 80–100 units of UFH, maximum dose 50mg.
    - e.g. bleeding during an IV infusion of UFH 1250 units/hour requires 25 mg protamine. Bleeding soon after a bolus dose of 5000 units requires 50 mg.
- Give protamine sulphate at a rate not exceeding 5mg/min to minimize the risk of adverse reactions and not more than 50mg at one time.
- The reversal effect of protamine can be monitored by the APTT.
- The maximum recommended dose of 50 mg protamine is sufficient to reverse UFH in most settings.
- Repeat treatment is rarely necessary. Contact on-call consultant haematologist if required.

- **<u>Side-effects of protamine sulphate:</u>**
- Protamine can cause severe allergic reactions including anaphylaxis, hypotension, bronchospasm and skin reactions in up to 10% of patients. Risk factors are previous exposure to protamine sulphate (including protamine-containing insulin preparations), rate of administration, vasectomy and fish allergy. Patients at risk may be pre-treated with corticosteroids and antihistamines.
- At higher doses, protamine may have significant anticoagulant and antiplatelet effects

5. Management of the bleeding patient on low molecular weight heparin (LMWH) e.g. tinzaparin, enoxaparin

- The half-life of the anticoagulant activity of LMWH lasts approximately 4 hours.
- LMWH activity may be monitored with the anti-Xa test.
- According to the drug's SPC
    - peak anti-Factor Xa activity for tinzaparin reaches a maximum at 4-6 hours
    - Half-life of enoxaparin is 4 to 5 hours. The amount of enoxaparin in the body drops to 50% after 8 hours and 33% or less after 12 hours.
- Although LMWH may also prolong the APTT, this test should not be used to assess the extent of drug effect.
- Protamine sulphate does not fully reverse the anti-Xa inhibition by LMWH (only reverses approximately 60% of LMWH).
- If bleeding is severe, stop LMWH and reverse anticoagulation with iv protamine sulphate as follows:
- Take blood for anti–Xa assay in citrate sample (request 'Heparin level' on ICE), coagulation screen and FBC on admission. N.B. the result of the anti–Xa assay will not be available the same day.
- The total dose of protamine sulphate will depend on the length of time since the injection and the nature of the bleed.
- If time since last dose of LMWH is < 8 hours previously:
    - 1mg protamine sulphate neutralises approximately 100 anti-Xa units LMWH (consult product literature of LMWH for details via www.medicines.org.uk and look in overdose section of SPC), maximum dose 50mg.
    - Give 25–50 mg protamine by intravenous injection at a rate not exceeding 5mg/minute (maximum dose 50mg). Give any remainder of the calculated protamine dose by slow intravenous infusion over 8–16 hours (Protamine sulphate should be given slower than 5 mg/min to minimize the risk of adverse reactions). Refer to the Medusa IVGUIDE for further information on administration.
    - If ineffective, consider further protamine sulphate 0.5 mg per 100 anti-Xa units of LMWH
- If time since last dose of LMWH is > 8 hours:
    - consider smaller doses of protamine sulphate (0.5mg per 100 anti-Xa units of LMWH).
- Repeat treatment is rarely necessary.

6. Management of the patient on non-Vitamin K oral anticoagulants (NOACs) - dabigatran, rivaroxaban, apixaban, edoxaban

The NOACs include the oral direct factor Xa inhibitors (apixaban, edoxaban and rivaroxaban) and the oral direct thrombin inhibitor (dabigatran).

All NOACs are partially eliminated via the kidney (27% of apixaban, 80% of dabigatran, 50% of edoxaban and 35% of rivaroxaban absorbed doses are excreted renally).

A specific reversal agent is available to reverse the anticoagulant effects of dabigatran only (known as idaracizumab or Praxbind®).

There are **no specific reversal agents** available for apixaban, edoxaban or rivaroxaban.

Measurement of anticoagulant effect

Routine monitoring of NOACs is not required, and there is no role for routine monitoring to assess efficacy of treatment. However, in specific situations some laboratory tests may help to assess for the presence of anticoagulation effect (overdose, acute bleeding, or in the event of urgent surgery).

It is important to take into account key information to guide the interpretation of results from coagulation tests in these patients, including the timing of the last dose of the specific anticoagulant and the patient's renal function.

- **Dabigatran** - presence of the drug is indicated by prolongation of the APTT and thrombin time (TT). Normal TT suggests the level of dabigatran is likely to be very low.
- **Rivaroxaban** - the Prothrombin time (PT) is prolonged with presence of the drug. Neither the PT or APTT can be used to monitor rivaroxaban anticoagulation. Normal PT makes therapeutic anticoagulation unlikely but cannot be fully excluded.
- **Apixaban** - the PT and APTT will be prolonged with presence of the drug. However, the PT and APTT cannot be used to predict apixaban effect as these can be normal despite presence of clinically significant drug level.
- **Edoxaban** - prolongs PT and APTT. However, the PT and APTT cannot be used to predict edoxaban effect as can be normal despite presence of clinically significant drug level.

6.1. Management of bleeding associated with NOACs

6.1.1. General measures:

- Stop the NOAC immediately and contact on-call consultant haematologist
- Document the timing and amount of the last NOAC dose and presence of pre-existing renal or hepatic impairment
- Renal function must be assessed as this will give an indication of how prolonged the anticoagulant effect will be.

    - Calculate creatinine clearance (CrCl) using the Cockcroft-Gault formula:

      $$\text{Estimated CrCl in ml/min} = \frac{(140 - \text{Age}) \times \text{Weight} \times \text{Constant}}{\text{Serum creatinine}}$$

      Age (in years).
      Weight* (in kilograms).
      Constant = 1.23 (Men); 1.04 (Women).
      Serum creatinine in micromole/litre (umol/l).

      *NB: Ideal Body Weight (IBW) should be used if the patient is clinically obese i.e. >20% over IBW.

- Assess the source of bleeding
- Request full blood count, PT, APTT, TT, fibrinogen, creatinine and liver function tests
- Correct haemodynamic compromise with intravenous fluids and transfusion support as indicated
- Apply mechanical pressure, if possible
- Use endoscopic, radiological or surgical measures
- Diuresis should be encouraged by oral or IV fluid replacement to increase excretion of the drug, but diuretic drugs should be avoided as these may reduce plasma volume and increase the concentration of the drug.

- Activated charcoal
    - Administration of activated charcoal should be considered in patients with moderate and severe bleeding who present within 2 hrs of the last oral dose of NOAC.

- Reversal agents
    - There are no specific reversal agents for the factor Xa inhibitors (apixaban, rivaroxaban, edoxaban).
    - Idarucizumab (Praxbind®) is a specific reversal agent for dabigatran and is indicated for rapid reversal of dabigatran for emergency surgery/ urgent procedures (within 8 hours) and in life-threatening or uncontrolled bleeding.
      The use of idarucizumab needs to be approved via the on-call consultant haematologist (see Appendix 3).

- Pro-haemostatic agents

- There is limited evidence on the use of pro-haemostatic agents e.g. prothrombin complex concentrate (PCC) in NOAC-related bleeding. Where available, it is only reasonable to consider the use of pro-haemostatic agents, in the circumstance of life-threatening bleeding unable to be managed with supportive measures and in consultation with a haematologist. The risk of thrombotic complications may be significant.
- PCC (Octaplex) – off licence use. Efficacy of PCC in patients who are actively bleeding has not been firmly established and one has to balance the potential pro-thrombotic effects against the potential anticoagulant benefits. Data regarding their efficacy in NOAC-associated bleeding are limited to healthy volunteers and animal models.

- Dialysis
  - Consider where available in patients receiving dabigatran with life-threatening bleeding, particularly if renal function is impaired.
  - There is no role for dialysis in the Factor Xa inhibitors (apixaban, edoxaban and rivaroxaban) due to the high plasma binding of most Factor Xa inhibitors and dialysis is not expected to significantly reduce their plasma levels.

Summary of treatment options in NOAC-associated bleeding

Definition of major/clinically significant bleeding - reduction in Hb ≥ 20g/L, transfusion of ≥2 units of red cells.

Definition of life-threatening/limb-threatening/sight-threatening bleeding – bleeding in critical area or organ (intraocular, intracranial, intraspinal, compartment syndrome, retroperitoneal or pericardial), hypotension not responding to resuscitation.

Refer to the appropriate guide below describing the treatment options and measures to take according to bleeding severity (mild bleeding, major or life-threatening bleeding) in patients taking a NOAC.

- **Appendix 2: Quick reference guide on the management of patients with bleeding related to factor Xa inhibitors (rivaroxaban, apixaban, or edoxaban)**

- **Appendix 3: Quick reference guide on the management of patients with bleeding related to direct thrombin inhibitor, dabigatran**

6.2. Patients on NOACs requiring emergency surgery or urgent invasive procedures

There are few data on the management of emergency surgery in patients receiving NOACs. The ability to make predictions regarding haemostasis at surgery in these patients is limited by uncertainty in the concentration of each drug that is associated with haemostatic safety. If an anticoagulant effect cannot be excluded neuroaxial anaesthesia must be avoided.

When possible, surgery should be delayed to allow the plasma level of the drug to fall (see table 1). The concentration of drug can be estimated from the dose of the drug, time of last dose and the patients' renal function.

Table 1: Usual time to discontinue NOACs before surgery or invasive procedures for which anticoagulation needs to be stopped.

Renal function (Creatinine Clearance, ml/min)	**Low bleeding risk procedure (hrs)**	**High bleeding risk procedure (hrs)**
Dabigatran		
≥ 80	24	48
≥ 50 to <80	24 – 48	48 – 72
≥ 30 to < 50	48 – 72	96
Rivaroxaban		
≥ 30	24	48
< 30	48	72
Apixaban		
≥ 30	24	48
< 30	48	72
Edoxaban		
≥ 30	24	48
< 30	48	72

Pro-haemostatic agents

There are few data that strongly support the use of PCC and activated PCC in the management of emergency surgery and so a pragmatic approach might be to proceed with surgery considering PCC only in the event of diffuse coagulopathic bleeding.

Tranexamic acid is likely to reduce bleeding and should be given.

6.2.1. Protocol for patient receiving dabigatran requiring emergency surgery

- Stop dabigatran
- Contact surgeon/haematologist/anaesthetist
- Send urgent samples for FBC, renal and liver function, PT, APTT and TT
- Document time of last dose of dabigatran
    - If APTT (and TT) are prolonged dabigatran anticoagulant effect is likely to be present.
    - The APTT cannot be used to determine the drug concentration as some patients with therapeutic concentrations will have a normal APTT.
    - Normal TT suggests the level of dabigatran is likely to be very low.
- Consider activated charcoal if ingestion is <2hrs and anaesthetist agrees
- Discuss with surgeon possibility of delaying surgery
- Risk of bleeding depends on:
    - Time since last dose
    - Type of surgery
    - Renal function
- If immediate surgery required (i.e. within 8 hours) with prolonged APTT and/or prolonged TT, consider reversal with idarucizumab (Praxbind®). Discuss with on-call consultant haematologist for approval.
    - See Appendix 4 for guidance on use of idarucizumab (Praxbind®).
- Management of bleeding
    - refer to Appendix 3: Quick reference guide on the management of patients with bleeding related to the direct thrombin inhibitor, dabigatran

6.2.2. Protocol for patient receiving rivaroxaban, apixaban or edoxaban requiring emergency surgery

- Stop rivaroxaban/apixaban/edoxaban
- Contact surgeon/haematologist/anaesthetist
- Send urgent samples for FBC, renal and liver function, PT, APTT and TT and anti-Xa assay, if available
- Document time of last dose of rivaroxaban/apixaban/edoxaban
- Interpretation of effects on coagulation screens:

A) <u>Rivaroxaban</u>
    - Rivaroxaban prolongs the PT more than the APTT
    - Neither the PT or APTT can be used to monitor rivaroxaban anticoagulation
    - Normal PT makes therapeutic anticoagulation unlikely but cannot be fully excluded

B) <u>Apixaban or edoxaban</u>
    - Both will prolong PT and APTT. However, these cannot be used to predict apixaban/edoxaban effect as can be completely normal despite presence of clinically significant drug level.
    - If PT and APTT are prolonged, anticoagulant effect is likely still present

- Consider activated charcoal if ingestion is <2hrs and anaesthetist agrees

- Discuss with surgeon possibility of delaying surgery
- Risk of bleeding depends on:
    - Time since last dose
    - Type of surgery
    - Renal function
- If immediate surgery required consider need for haemostatic agent perioperatively or postoperatively.
    - Give tranexamic acid 1g IV
    - Consider prothrombin complex concentrate, PCC (Octaplex) 25-50 units/kg (maximum dose 3000 units) - must be authorised by on-call haematologist. PCC can reverse the coagulation abnormalities but data on clinical efficacy is not available.
- Management of bleeding
    - refer to Appendix 2: Quick reference guide on the management of patients with bleeding related to factor Xa inhibitors (rivaroxaban, apixaban, or edoxaban)

6.3. Management of overdose of NOACs

For overdoses of NOACs, contact the UK National Poisons Information Service on 0344 892 0111 and on-call haematologist via switchboard.

If the patient has bleeding complications (related to overdose or otherwise) please see the corresponding flowchart in Appendix 2 or Appendix 3.

6.4. Long-term considerations for all NOACS

- Consider drug interactions (refer to manufacturers' SPCs via www.medicines.org.uk or contact Medicines Information on Ext 7114).
- Consider effects of concomitant use of NSAIDS, antiplatelets, co-existing bleeding disorder
- Consider safety for re-anticoagulation

7. Audit

Compliance with this guideline will be audited by exception reporting via incident reporting system.

8. References

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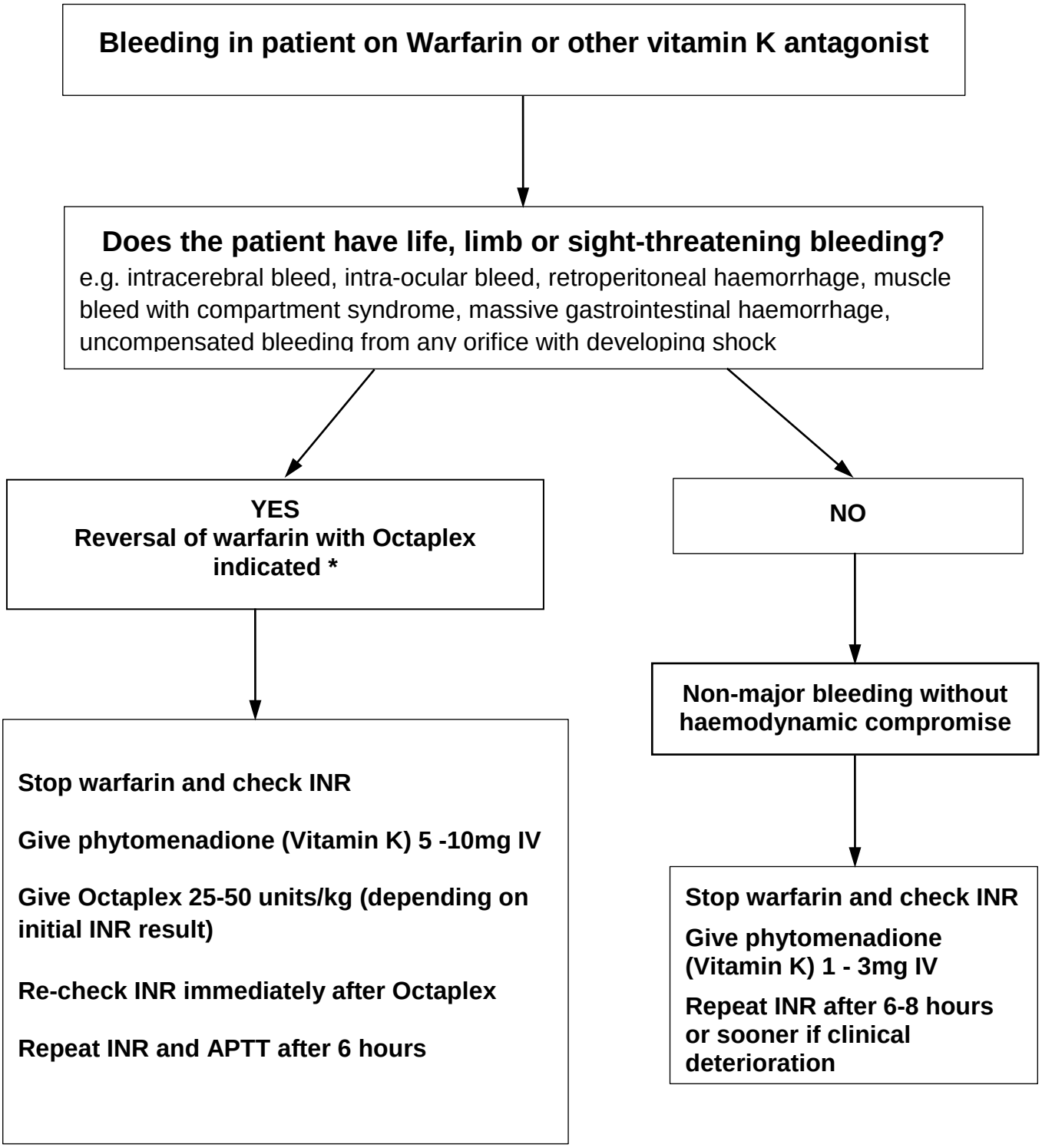
Summary of Product Characteristics. Lixiana®. Accessed March 2017 via http://www.emc.medicines.org.uk.

Summary of Product Characteristics. Praxbind®. Accessed March 2017 via http://www.emc.medicines.org.uk.

Appendix 1: Flowchart for management of bleeding in patients on anticoagulation with Warfarin or other vitamin K antagonists (phenindione, acenocoumarol)



*** Refer to Octaplex guidelines on intranet for full details of dose and administration**

The clinical decision to use Octaplex to reverse warfarin in cases of major haemorrhage should be approved by either the Consultant in charge of the patient or a Consultant Haematologist. If Octaplex is to be administered for an indication other than major haemorrhage on a vitamin K antagonist (e.g. for emergency surgery), then the patient must be discussed with the Consultant Haematologist on-call. PCC should not be used to enable elective or non-urgent surgery.

Appendix 2: Quick reference guide on management of patients with bleeding related to factor Xa inhibitors (rivaroxaban, apixaban, or edoxaban)

	Bleeding patient on APIXABAN, RIVAROXABAN or EDOXABAN		
General action	➢ **STOP ORAL ANTICOAGULANT** ➢ **Contact on-call haematologist** ➢ **Assess clinical bleeding and resuscitate patient as appropriate.** ➢ **Send urgent samples for FBC, G&S, renal and liver function, PT, APTT and TT, anti-Xa level. Calculate creatinine clearance using Cockcroft-Gault formula (see page 10).** ➢ **Document dose, dosing regimen and time of last intake of APIXABAN, RIVAROXABAN or EDOXABAN** ➢ **If ingestion is within 2 hours consider activated charcoal**		
Interpretation of coagulation tests	**1) <u>Rivaroxaban</u> - Prolongs the PT more than the APTT. - Normal PT makes therapeutic anticoagulation unlikely but cannot be fully excluded 2) <u>Apixaban or edoxaban</u> - Routine coagulation tests cannot be used to predict apixaban or edoxaban effect as can be normal despite presence of clinically significant drug level. - If PT and APTT are prolonged, anticoagulant effect is likely still present**		
Bleeding Severity	**Mild bleeding**	**Major/clinically significant bleeding**	**Life-threatening bleeding**
Action Specific to Bleeding Severity	**- Local haemostatic measures** **- Mechanical compression** **- Tranexamic acid- by mouth, 1-1.5g, 2-3 times daily or by slow IV injection 1g every 6-8hrs** **- Investigate cause for bleed** **- Delay / omit next dose of NOAC if felt appropriate (balance thrombotic and bleeding risks)** **- If bleeding continues move to guidance for major bleeding or life-threatening bleeding)**	**- Local haemostatic measures to control bleeding** **- Mechanical compression** **- Consider surgical / radiological / endoscopic intervention or wound packing** **- Optimise tissue oxygenation** **- Maintain adequate hydration and good urine output to aid drug clearance.** **-Tranexamic acid 1g IV stat** **-Transfusion support as indicated:** **Transfuse red cells to maintain Hb>80g/L** **Transfuse Platelets to maintain Plt >75x10^9/Lor 100x10^9/L if CNS bleed** **- Identify bleeding source** **- If ongoing bleeding resulting in clinical instability, move to guidance as described for life-threatening bleeding**	**- Follow measures as for major bleeding.** **- Consider prothrombin complex concentrate (Octaplex) 50 units/kg bolus (maximum dose 3000 units) – discuss with on-call haematologist.** **- Tranexamic acid 1g IV stat**

Appendix 3: Quick reference guide on the management of a patient with bleeding related to direct thrombin inhibitor, dabigatran.

	Bleeding patient on DABIGATRAN		
General action	➢ **STOP ORAL ANTICOAGULANT** ➢ **Contact on-call haematologist** ➢ **Assess clinical bleeding and resuscitate patient as appropriate.** ➢ **Send urgent samples for FBC, G&S, renal and liver function, PT, APTT and TT. Calculate creatinine clearance using Cockcroft-Gault formula (page 10).** ➢ **Document dose and time of last intake of DABIGATRAN** ➢ **If ingestion is within 2 hours consider activated charcoal**		
Interpretation of coagulation tests	**- If APTT and TT are normal, then DABIGATRAN is unlikely to be causing a significant anticoagulant effect. Normal TT suggests the level of dabigatran is likely to be very low.** **- If APTT and TT are prolonged then DABIGATRAN is producing anticoagulant effect.**		
Bleeding Severity	**Mild bleeding**	**Major/clinically significant bleeding**	**Life-threatening bleeding**
Action Specific to Bleeding Severity	**- Local haemostatic measures** **- Mechanical compression** **- Tranexamic acid - by mouth, 1-1.5g, 2-3 times daily or by slow IV injection 1g every 6-8hrs** **- Investigate cause for bleed** **- Delay / omit next dose of NOAC if felt appropriate (balance thrombotic and bleeding risks)** **- If bleeding continues move to guidance for major bleeding or life-threatening bleeding)**	**- Local haemostatic measures to control bleeding** **- Mechanical compression** **- Consider surgical / radiological / endoscopic intervention or wound packing - Optimise tissue oxygenation** **- Maintain adequate hydration and good urine output to aid drug clearance.** **-Tranexamic acid 1g IV stat** **-Transfusion support and activate 'Major Haemorrhage Protocol' as indicated** **Transfuse red cells to maintain Hb>80g/L, transfuse Platelets to maintain Plt >75x10^9/L or 100x10^9/L if CNS bleed** **- Identify bleeding source** **- Consider haemodialysis/ haemofiltration if rapidly available** **- If ongoing bleeding resulting in clinical instability, consider Idarucizumab as described for life-threatening bleeding**	**- Follow measures as for major bleeding.** **- Consider specific reversal agent idarucizumab (Praxbind®) – discuss with on-call consultant haematologist.** **Idarucizumab total dose of 5 g, administered as two 2.5g vials given as either two consecutive intravenous infusions of 2.5g (=50mL) over 5-10 minutes or two separate bolus intravenous injections of 2.5g (= 50mL) given as quickly as possible (no more than 15 minutes apart).** **See appendix 4 for further details on idarucizumab.** **- If idarucizumab is not available, consider PCC (Octaplex) – discuss with on-call consultant haematologist.**

Appendix 4: Guidelines on the use of idarucizumab (Praxbind®) for the management of bleeding in patients receiving dabigatran

Background

Idarucizumab is a specific reversal agent for dabigatran. It is a humanised Fab fragment that binds specifically to dabigatran, resulting in rapid clearance of dabigatran from the circulation and reversal of its anticoagulant effect.

Idarucizumab **will not** reverse the effect of any of the other NOAC drugs e.g. apixaban, rivaroxaban or edoxaban**.**

Indications:

Idarucizumab is a specific reversal agent for dabigatran and is indicated in adult patients when rapid reversal of its anticoagulant effect is required.

- For emergency surgery / urgent procedures (i.e. within 8 hours and for which normal haemostasis is required)
- In life-threatening or uncontrolled bleeding.

In mild or moderate bleeding e.g. patients presenting with a non-life threatening bleed or in need of non-urgent surgery or invasive procedure, discontinuation of dabigatran and administration of appropriate supportive care is usually sufficient.

Use must be authorised by consultant haematologist on-call. (Stock holding 4 vials (2 doses) and costs about £1000 per dose).

Action:

Idarucizumab completely reverses the anticoagulant effect of dabigatran within minutes. Achieving haemostasis however, may take several hours and will be dependent on identifying and treating the source of bleeding.

Dosage and administration

The recommended dose of idarucizumab is 5 g (2 x 2.5 g/ 50 mL).
Administer intravenously 2 x 2.5 g vials given as either two consecutive intravenous infusions of 2.5 g (= 50 mL in each vial) over 5-10 minutes or two separate bolus intravenous injections of 2.5 g (= 50 mL) given consecutively as quickly as possible (no more than 15 minutes apart).

Idarucizumab must not be mixed with other medicinal products. A pre-existing intravenous line may be used for administration of idarucizumab. The line must be flushed with sodium chloride 0.9 % solution for injection prior to and at the end of infusion. No other infusion should be administered in parallel via the same intravenous access.

Administration of a second 5 g dose of idarucizumab may be considered in the following situations (limited data to support) in consultation with on-call Haematologist:

- recurrence of clinically relevant bleeding together with prolonged clotting times (e.g. APTT or TT), or
- patients require a second emergency surgery/urgent procedure and have prolonged clotting times.

Dose adjustments

No dose adjustment is required for renal impairment, hepatic impairment or in elderly patients aged 65 years and above.

Monitoring

Send repeat APTT, PT, TT, fibrinogen at 15 minutes after administration.

Monitor for re-elevation of coagulation parameters; signs/symptoms of clinically relevant bleeding and thromboembolic events.

Contra indications and adverse reactions
There are no contra indications.
No adverse reactions have been identified in clinical studies.

Special warnings and precautions for use
- Known hypersensitivity to idarucizumab.
- Hereditary fructose intolerance - The recommended dose of idarucizumab contains 4 g sorbitol as an excipient. In patients with hereditary fructose intolerance the risk of treatment with idarucizumab must be weighed against the potential benefit of such an emergency treatment.
- Thromboembolic events - Reversing dabigatran therapy exposes patients to the thrombotic risk of their underlying disease.
- Urinary protein testing - idarucizumab causes transient proteinuria as a physiologic reaction to renal protein overflow after treatment. The transient proteinuria is not indicative of renal damage, which should be taken into account for urine testing.

Availability
Idarucizumab is kept in the Antidote tray in the A&E fridge and should only be used after discussion with the on-call Consultant Haematologist.

Restarting of Antithrombotic Therapy
Dabigatran treatment can be re-initiated 24 hours after administration of idarucizumab, if the patient is clinically stable and adequate haemostasis has been achieved.

For other antithrombotic therapy (e.g. low-molecular weight heparin) this can be started at any time, if the patient is clinically stable and adequate haemostasis has been achieved.

Absence of antithrombotic therapy exposes patients to the thrombotic risk of underlying disease or condition.