Click on the appropriate link below:

- START HERE - GENERAL NON-PHARMACOLOGICAL MEASURES
- HEAD INJURY IN PATIENTS TAKING ORAL ANTICOAGULANTS
- BLEEDING WITH IV UNFRACTIONATED HEPARIN (PUMP-HEP)
- BLEEDING WITH LOW MOLECULAR WEIGHT HEPARIN
- BLEEDING WITH FONDAPARINUX SODIUM
- BLEEDING WITH DANAPAROID SODIUM
- ACTIONS TO BE TAKEN FOR HIGH INR – NO BLEEDING
- ACTIONS TO BE TAKEN FOR HIGH INR – MINOR BLEEDING
- MANAGEMENT OF BLEEDING WITH WARFARIN OR OTHER VKA
- USAGE/DOSAGE OF BERIPLEX/ PCC IN COUMARIN PATIENTS
- PCC OR BERIPLEX ADMINISTRATION TABLE
- BLEEDING WITH THROMBOLYTIC THERAPY
- BLEEDING WITH DABIGATRAN EXETILATE
- ASSESSMENT OF BLEEDING – RIVAROXABAN, APIXABAN OR EDOXABAN
- MANAGEMENT OF BLEEDING - RIVAROXABAN, APIXABAN OR EDOXABAN
- BLEEDING WITH NSAID’S OR ANTI PLATELET THERAPY
- BLEEDING WITH FIBRINOLYTIC DRUGS
- FURTHER SUPPORTING INFORMATION
GENERAL NON-PHARMACOLOGICAL MEASURES

1. Stop the Anti-Thrombotic Drug
2. Document the timing and amount of last drug taken
3. Document any pre-existing renal or hepatic impairment
4. Estimate the half life of the drug
5. Assess the source of bleeding
6. Request FBC, Full coagulation screen, Creatinine
7. If available request laboratory specific assay
8. Correct haemodynamic compromise with IV fluids and red cell transfusion
9. Apply mechanical pressure to active bleeding sites
NOW CLICK HERE TO RETURN TO LIST FOR SPECIFIC PHARMACEUTICAL ACTIONS TO MANAGE ANTICOAGULATION RELATED BLEEDING
HEAD INJURY IN PATIENTS ON ORAL ANTICOAGULATION
BLEEDING WITH IV UNFRACTIONATED HEPARIN (PUMP-HEP)

Following significant head injury with clear CT scan the INR should be maintained as close to 2.0 as possible for 4 weeks

REMEMBER! Delayed intracranial bleeding can occur in patients on Warfarin even if CT head is normal - advise patient/family on signs and symptoms

Does Patient have a supra-therapeutic INR?

Reverse INR with PCC immediately (prior to CT head)

Reverse anticoagulation with PCC immediately (prior to CT head and INR result)

Clear Head Injury and suspicion of haematoma?

Patient on ORAL ANTICOAGULANTS?
STOP heparin pump

Check APTT ratio and a FBC
(if APTT ratio >3.0 INR may be unreliable)

Consider reversal by administration of protamine sulphate injection by slow intravenous injection (max rate 5 mg/min) over a period of >5 minutes

Calculate Protamine dose based on the quantity of UFH administered in the previous 2 hours (1 mg protamine sulphate neutralizes 80–100 units of UFH)

Reversal effect can be monitored by APTT
BLEEDING ON LOW MOLECULAR WEIGHT HEPARIN, E.G. DALTEPARIN OR ENOXAPARAPIN

Patient on LMWH?
(Bleeding is rare even if Anti-Xa level high)

Check FBC, coagulation screen and request freeze 'plasma'

If within 8h of LMWH administration consider reversal with protamine sulphate over a period of >5 mins (1mg per 100 anti-Xa units)

If ineffective, consider further protamine sulphate 0.5 mg per 100 anti-Xa units

Consider rFVIIa if there is continued life-threatening bleeding despite protamine sulphate and the time frame suggests LMWH may be contributing to bleeding. (2C)
**BLEEDING ON FONDAPARINUX SODIUM**

**Patient on FONDAPARINUX?**

(Doses above the recommended regimen may increase risk of bleeding)

There is **no antidote** to Fondaparinux - manage through cessation of drug and haemostatic measures. Consider rFVIIa if there is continued life-threatening bleeding

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**BLEEDING ON DANAPAROID SODIUM**

**Patient on DANAPAROID?**

(half-life of Anti-Xa activity of approx 24hours, can be monitored by anti-Xa assay)

There is **no antidote** to Danaparoid - manage through cessation of drug and haemostatic measures. Consider plasmapheresis if there is continued life-threatening bleeding
**ACTIONS TO BE TAKEN FOR HIGH INR (WITH NO BLEEDING)**

**INR >8.0**
- Stop VKA
- Give Vitamin K *orally* using the IV preparation
- Recheck INR at 24 hours
- Repeat Vit K administration *orally* if INR remains high
- Restart Warfarin when INR <5.0

**INR 5.0-8.0**
- Stop VKA for 1-2 doses
- Restart when INR <5.0 with reduced maintenance dose
- INR should correct to <5.0 in 24-72 hours
- The cause of elevated INR should be investigated

**IF THERE IS UNEXPECTED BLEEDING AT THERAPEUTIC INR LEVELS—ALWAYS INVESTIGATE POSSIBILITY OF UNDERLYING CAUSE E.G. UNSUSPECTED RENAL OR GASTRO-INTESTINAL TRACT PATHOLOGY**
ACTIONS TO BE TAKEN FOR HIGH INR (MINOR BLEEDING ONLY)

**INR >8.0**
- Stop VKA
- Give Vitamin K **Intravenously** using the IV preparation
- Recheck INR at 24 hours
- Repeat Vit K administration intravenously if INR remains high
- Restart Warfarin when INR <5.0

**INR 5.0-8.0**
- Stop VKA
- Give Vitamin K **Intravenously** using the IV preparation
- Restart when INR <5.0 with reduced maintenance dose

**IF THERE IS UNEXPECTED BLEEDING AT THERAPEUTIC INR LEVELS—ALWAYS INVESTIGATE POSSIBILITY OF UNDERLYING CAUSE E.G. UNSUSPECTED RENAL OR GASTRO-INTESTINAL TRACT PATHOLOGY**
MANAGEMENT OF BLEEDING WITH WARFARIN OR OTHER VITAMIN K ANTAGONIST ORAL ANTICOAGULANTS

ASSESS BLEEDING

Major or Minor?

Major eg gastro-intestinal, CNS haemorrhage, Intra-ocular, any bleed requiring invasive procedure

Vitamin K 5 mg slowly over 5 minutes
Hospitalise urgent FBC, INR, Group and antibody screen
Administer Prothrombin complex concentrate IV
25-50 units per Kg, dependant on INR (from Haematology Laboratory)

Minor eg bruising, brief epistaxis, transient haematuria

Check INR at 4-24hours

Immediate check PT and APTT

Inadequate correction

Adequate correction
INR <1.5

Repeat PT and APTT in 4-6 hours to prolonged coagulation tests

Consider other factors contributing eg.DIC, Congenital coagulation factor deficiency  Liver disease, Inadequate replacement, Lupus inhibitor

As needs seek haematological advice
THE USE AND DOSAGE OF BERIPLEX® P/N PROTHROMBIN COMPLEX CONCENTRATE (FACTORS II, VII, IX AND X) IN MAJOR BLEEDING IN COUMARIN ANTICOAGULATED PATIENTS

Standard Operating Procedure

- Request from Haematology Laboratory
- Dose as 25-50 units of FIX per Kg, titrated against INR
- Each bottle of Beriplex® P/N 500 contains 500 units FIX in 20mls.
- Reconstitute as per manufacturer’s instruction eg 500 units in 20ml water for injection warmed to maximum 37oC.
- **Maximum single dose 5000 UNITS FIX (200mls).**
- Administer infusion: first 1ml over 1 minute in case of reaction, then 8ml/min (max equivalent to approx 210 units/min)
- Patients may have reactions, commonly chills, as with other blood products.
- Administer vitamin K 5mg IV, as the PCC only has a half-life of some 6 hours, compared to 30-40 hours for warfarin.
- See nomograms for guide for given Kg body weight range and INR

<table>
<thead>
<tr>
<th>Initial INR</th>
<th>2.0 – 3.9</th>
<th>4.0 – 6.0</th>
<th>&gt;6.0</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Approximate dose units (Factor IX)/kg body weight</strong></td>
<td>25</td>
<td>35</td>
<td>50</td>
</tr>
<tr>
<td><strong>Approximate dose ml/kg body weight</strong></td>
<td>1</td>
<td>1.4</td>
<td>2</td>
</tr>
<tr>
<td><strong>Maximum Single Dose for patients weighing 100kg or over</strong></td>
<td>2500 units</td>
<td>3500 units</td>
<td>5000 units</td>
</tr>
</tbody>
</table>

NB Check INR immediately after infusion to demonstrate correction, as per protocol

Repeated dosing with prothrombin complex concentrate (Beriplex® P/N) for patients requiring urgent reversal of Vitamin K antagonist treatment is not supported by clinical data and therefore not recommended.
**APPROXIMATE DOSE OF BERIPLEX® P/N PROTHROMBIN COMPLEX CONCENTRATE PER KG WEIGHT AT DIFFERENT INITIAL INR LEVELS:**

<table>
<thead>
<tr>
<th>Initial INR</th>
<th>2.0 – 3.9</th>
<th>4.0 – 6.0</th>
<th>&gt;6.0</th>
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<tr>
<td>Approximate dose units (Factor IX)/kg body weight</td>
<td>25</td>
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<td>50</td>
</tr>
<tr>
<td>Approximate dose ml/kg body weight</td>
<td>1</td>
<td>1.4</td>
<td>2</td>
</tr>
<tr>
<td>Kg body weight range and estimated dose units rounded to nearest 500 for INR reading</td>
<td>2.0 – 3.9</td>
<td>4.0 – 6.0</td>
<td>&gt;6.0</td>
</tr>
<tr>
<td>41-50 kg</td>
<td>1000 units</td>
<td>1500 units</td>
<td>2000 units</td>
</tr>
<tr>
<td>51-60 kg</td>
<td>1500 units</td>
<td>2000 units</td>
<td>2500 units</td>
</tr>
<tr>
<td>61-70 kg</td>
<td>1500 units</td>
<td>2500 units</td>
<td>3000 units</td>
</tr>
<tr>
<td>71-80 kg</td>
<td>2000 units</td>
<td>2500 units</td>
<td>3500 units</td>
</tr>
<tr>
<td>81-90 kg</td>
<td>2000 units</td>
<td>3000 units</td>
<td>4000 units</td>
</tr>
<tr>
<td>91-100 kg or above 100 kg</td>
<td>2500 units</td>
<td>3500 units</td>
<td>5000 units</td>
</tr>
</tbody>
</table>

**NB Check INR immediately after infusion to demonstrate correction, as per protocol**

Repeated dosing with prothrombin complex concentrate (Beriplex® P/N) for patients requiring urgent reversal of Vitamin K antagonist treatment is not supported by clinical data and therefore not recommended.
**BLEEDING WITH THROMBOLYTIC THERAPY**

Patient bleeding POST-THROMBOLYSIS?

Check FBC and Coagulation screen

Consider tranexamic acid 10mg/kg IV and/or cryoprecipitate (which is rich in fibrinogen)

Seek advice if needed from on call CoE consultant (in cases of stroke)

**BLEEDING WITH DABIGATRAN EXETILATE**

Patient on DABIGATRAN?

In life threatening bleed administer Idarucizumab (Praxbind ®) Available in the emergency drug fridge and given as a 5g IV Bolus (2x2.5g vials)

In non life-threatening bleed apply standard haemostatic measures, add oral activated charcoal if drug taken within last 2 hours
ASSESSMENT OF BLEEDING WITH RIVAROXABAN, APIXABAN OR EDOXABAN (ANTI-XA THERAPIES)

Patient on ANTI-XA THERAPY?

There is no specific antidote to these drugs

Determine time since last dose

Initiate resuscitation with IV fluids, blood transfusion and other general haemostatic supportive measures as necessary

Check FBC, U&E’s and a coagulation screen (If within the normal reference ranges, then there is likely to be only a low level of the anticoagulant present)

If platelets <50 consider platelet transfusion

In patients with ongoing life-threatening bleeding, not controlled by the above measures, administer prothrombin complex concentrate (PCC) at 25units/kg
MANAGEMENT OF BLEEDING WITH THE ANTI-XA ANTICOAGULANTS

DETERMINE TIME OF LAST DOSE AND ASSESS BLEEDING

Major or Minor Bleeding?

Major - e.g. gastro-intestinal, CNS haemorrhage, Intra-ocular, any bleed requiring invasive procedure

Major - e.g. bruising, brief epistaxis, transient haematuria

Hospitalise. If within 2 hrs of therapy consider oral charcoal. Resuscitate and urgent blood tests

Review patient and medications consider test FBC and electrolytes

FBC

Coagulation screen (PT, Thrombin Time & APTT)

Group and screen biochemistry

If platelets < 60 consider transfuse 1 adult dose platelets

Abnormal Drug present

If < normal reference ranges = likely low level anticoagulant

Review progress

Ongoing life-threatening bleeding, not controlled by the above measures.

Consider Tranexamic Acid (1g i.v.) Administer Prothrombin complex concentrate IV 25 units per Kg, (from Haematology Laboratory)
NON-STEROIDAL ANALGESICS OR ANTI-PLATELET THERAPY (ASPIRIN AND THE P2Y12 INHIBITORS [CLOPIDOGREL AND PRASUGREL] AND GPIIA/IIIB INHIBITORS (E.g. ABCIXIMAB):

- Patient on ANTI PLATELET THERAPY?
- Check FBC and Coagulation screen
- Initiate resuscitation with IV fluids, blood transfusion and other general haemostatic supportive measures as necessary
- Reverse any co-prescribed anticoagulation
- Consider transfusion of platelets (2-3 adult doses) in critical bleeding or prior to emergency surgery (and in thromobcytopaneia caused by Abciximab)

SUPPORTING NOTES

- Platelets are of uncertain limited use in the immediate phase of bleeding with clopidogrel, as this is a pro-drug, the metabolite circulating for approximately 18 hours.
- NB There are no specific reversal agents for the P2Y12 antagonists
FIBRINOLYTIC DRUGS

The fibrinolytic drugs which are currently licensed in the UK are: alteplase, tenecteplase, reteplase, urokinase and streptokinase. All five agents function indirectly by promoting generation of plasmin, which then mediates clot lysis. Specific information is available from relevant Trust guidance. General recommendations for the management of bleeding are below:

Patient on FIBRINOLYTIC DRUG?

Major bleeding (ie intercerebral) within 48 hours of administration of a fibrinolytic drug?

Stop infusion and any other anti-thrombotic drugs

Administer FFP 12ml/kg

Administer IV tranexamic acid 1g tds

If there is a depletion of fibrinogen administer cryoprecipitate or fibrinogen concentrate

Further intervention should be guided by results of coagulation
**FURTHER SUPPORTING INFORMATION:**

### Protamine Sulphate

Protamine sulphate 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 sulphate may have significant anticoagulant and antiplatelet effects.

### Bleeding on vitamin K antagonist anticoagulants eg warfarin

Presents commonly with bruising, mucocutaneous bleeding, or haematuria. This is uncommon with INR’s <5.0. Per annum the general risk is of haemorrhage is of the order of 0.25% death, 2% for hospitalisation and 5-7% for minor bleeding.

Active intervention may be appropriate for those patients with major bleeding or those with minor bleeding and classified as being at high risk for haemorrhage. Asymptomatic standard risk patients do not require INR reversal at INR <7.0 but correction should be considered in *high risk* patients whose risk of bleeding is approximately 15 fold higher.

In haemorrhagic cases, withholding warfarin and normalisation of the INR for brief periods is associated with a low risk (0.7-1%) of thrombo-embolism.

### High risk for bleeding is determined by

1. Age over 70 years, Anaemia, renal failure, diabetes mellitus, previous MI
2. Previous GI bleed, previous CVE
3. Anticoagulation in the first 100 days

Fresh frozen plasma (FFP) only increases factor levels to at best 20-30% and will not normalise the INR, whereas this may be achieved with the more potent prothrombin complex concentrates, containing factors II, V, VII and IX. Intravenous vitamin K may reduce the INR within four hours, whereas the oral preparation is less predictable.
Bleeding classification

Examples of "major" bleeding:

1. Intracranial (CT or MRI documented)
2. Retroperitoneal (CT or MRI documented)
3. Intra-ocular (excludes conjunctival)
4. Spontaneous muscle haematoma associated with compartment syndrome
5. Pericardial
6. Non-traumatic intra-articular
7. Any invasive procedure to stop bleeding
8. Active bleeding plus either BP ≤ 90 mmHg systolic, oliguria, or ≥ 2 g/dl fall in haemoglobin

Examples of "minor" bleeding:
Any other bleeding that would not influence your decision to anticoagulate a patient

Vitamin K administration

Colloidal Vitamin K (10 mg/ml, Konakion MM, Roche).

\textit{IV may rarely cause anaphylaxis}

Withhold in patients with history of previous severe allergic reaction

Otherwise administration should be:

- draw up vitamin K dose in a 1ml insulin syringe
- inject dose into a 50ml infusion bag of 5% glucose
- administer as slow iv infusion over 5-10 mins (~1mg/min)

For oral administration of vitamin K

Use the colloidal Vitamin K preparation for injection (10 mg/ml) i.e. Konakion MM (Roche).

- draw up vitamin K dose in a 1ml insulin syringe
- inject dose into a 10ml gradated syringe
- then make ~10% dilution with water for injection
- ie 0.1ml vitamin K (1mg) to 1ml water for injection
- “squirt” diluted solution into mouth and instruct patient to swallow
Management of Variable INRs

Due to hepatic enzyme polymorphisms, some patients may have “unstable” INR’s, not attributable to any of the usual known causes for instability. This results in frequent testing with dose adjustments and in some cases, bleeding or thrombotic episodes. Control may possibly be improved by a broader therapeutic target range (eg 2.0-4.0), or a trial may be considered of supplemental daily low-dose oral vitamin K (100 to 200 mcg, Solgar Vitamins Ltd), with close monitoring of the INR and warfarin dose adjustment to counter an initial lowering of the INR in response to vitamin K.

Warfarin drug interactions

Almost any drug can interact with oral anticoagulants, in particular:

- Alcohol, steroids and hormones, analgesics, antibiotics, antidepressants, antiepileptics, antifungals, antiplatelet drugs, barbiturates, hormone antagonists, lipid lowering drugs, thyroxine, ulcer drugs, vitamins e.g. Vitamin K.
- When prescribing, a non-interacting drug is preferable, otherwise:
  - If a new warfarin potentiating drug lasts <7 days either:
    Make no change, minor dose reduction, or miss one complete warfarin dose
  - If a new warfarin potentiating drug lasts >7 days then:
    Check INR 3-7 days after start of drug. Adjust dose on basis of result.