Head injury in patients on vitamin K antagonists e.g. Warfarin

- Patients on vitamin K antagonists eg warfarin with a strong suspicion of intracerebral haematoma after a clear head injury should have their INR reversed with PCC dose eg 25u/kg immediately and before the CT and INR results are available.
- Delayed intracranial bleeding can occur in patients on warfarin even when the initial CT scan is normal. In view of this, patients with a supra-therapeutic INR should have this corrected into the therapeutic range with oral vitamin K.
- It is suggested that the INR is maintained as close to 2.0 as possible for the 4 weeks after a significant head injury and a normal CT scan.

Bleeding

General non-pharmacological measures.

- Stop the antithrombotic drug
- Document the timing and amount of the last drug dose and presence of pre-existing renal or hepatic impairment
- Estimate the half-life and length of functional defect induced by the drug
- Assess the source of bleeding
- Request full blood count, prothrombin time, activated partial thromboplastin time, thrombin time, fibrinogen concentration, creatinine concentration
- If available, request a specific laboratory test to measure the antithrombotic effect of the drug
- Correct haemodynamic compromise with intravenous fluids and red cell transfusion
- Apply mechanical pressure, if possible use endoscopic, radiological or surgical measures

Additional specific pharmaceutical measures are as detailed in the following sections. Where bleeding is unexpected, or due to iatrogenic error, then an incident report should be submitted through the Trust’s Datix incident reporting system for future analysis and risk management.
Present 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.

**Bleeding with standard IV therapeutic unfractionated heparin (UFH), ie Pump-Hep**

- Stop heparin pump
- Check APTT ratio and a FBC (with APTT ratio >3.0 INR may be unreliable)
- UFH can be rapidly reversed with protamine sulphate, derived from fish sperm and forms a stable, inactive salt with heparin. Consider reversal by administration of protamine sulphate injection by slow intravenous injection (max rate 5 mg/min) over a period of >5 minutes, dosing as follows:

  The dose may be calculated from the quantity of UFH administered in the 2 h prior to reversal using the assumption that 1 mg protamine sulphate neutralizes 80–100 units of UFH.

  - For example, bleeding during an IV infusion of UFH 1250 units/h requires 25 mg protamine sulphate.
  - Bleeding soon after a bolus dose of 5000 units requires 50 mg.
  - The half-life of protamine is 7 min, which is shorter than UFH, thus, prolonged Protamine sulphate administration may be necessary if UFH has been administered subcutaneously, causing entry into the circulation to be delayed et al, 2008).

  The reversal effect of protamine can be monitored by the APTT.

- 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.
- Protamine sulphate should be given slowly over >5 min.
- Patients at risk may be pre-treated with corticosteroids and antihistamines.
- At higher doses, protamine sulphate may have significant anticoagulant and antiplatelet effects.
To antagonise an unfractionated heparin during extracorporeal circulation:

- Administer protamine sulphate 1.5 mg per 100 UNITS heparin (slow intravenous injection (max rate 5 mg/min) over a period of 10 minutes).

The requirement for further protamine sulphate may be monitored by APTT.

### Bleeding on Low molecular weight heparin, e.g. Dalteparin or Enoxaparin

Discontinue, consider reversal by administration of protamine. Low molecular weight heparin has a half-life of approximately 4 hours. Bleeding is rare even with high anti-Xa levels. Due to the relatively greater anti-Xa activity bleeding may occur even with a normal APTT ratio. Protamine sulphate does not fully reverse the anti-Xa inhibition.

Therapeutic heparin has usually decayed to prophylactic doses by 12hrs post injection so:

- Check FBC, coagulation screen and request freeze “plasma”.
- LMWH administration within 8 h of the time of requirement for correction of anticoagulation: give protamine sulphate (1 mg per 100 anti-Xa units of LMWH).
- If ineffective, consider further protamine sulphate 0.5 mg per 100 anti-Xa units (2C). Protamine sulphate should be given slower than 5 mg/min to minimise the risk of adverse reactions.
- LMWH administration greater than 8 h from the time of requirement for correction of anticoagulation: consider smaller doses of protamine (2C).
- Consider rFVIIa if there is continued life-threatening bleeding despite protamine sulphate and the time frame suggests there is residual effect from the LMWH contributing to bleeding. (2C).

### Bleeding on Fondaparinux Sodium

Fondaparinux is a synthetic and selective inhibitor of activated Factor X (Xa). Doses above the recommended regimen may lead to an increased risk of bleeding.

- There is no known antidote to Fondaparinux. Management of bleeding should be through cessation of treatment and general haemostatic measures
- Recombinant FVIIa should be considered for critical bleeding

### Bleeding on Danaparoid sodium

Danaparoid has a plasma half-life of anti-Xa activity of approximately 24 hours. Danaparoid may be monitored by anti-Xa assay using a danaparoid standard.

- There is no specific antidote for danaparoid. Management of bleeding should be through cessation of treatment and general haemostatic measures
- Plasmapheresis may be considered for critical bleeding.
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

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. Intra-venous vitamin K may reduce the INR within four hours, whereas the oral preparation is less predictable.

Actions to be taken for high INR

- INR > 8.0, no bleeding or minor bleeding
  - stop vitamin K antagonist (eg warfarin), restart when INR < 5.0;
  - if there are other risk factors for bleeding give phytomenadione (vitamin K1) 1-3 mg by slow intravenous injection or up to 5 mg by mouth (for partial reversal of anticoagulation give smaller oral doses of phytomenadione e.g. 1–2.5 mg using the intravenous preparation orally); Intra-venous vitamin K may reduce the INR within four hours, whereas the oral preparation is less predictable. If there are concerns the INR should be repeated at 4-6 hours

- INR 5.0–8.0, no bleeding or minor bleeding
  - stop vitamin K antagonist (eg warfarin) for 1–2 doses
  - restart when INR < 5.0 with the maintenance dose should be reduced
  - The INR should decline to <5.0 in 24-72 hours
  - 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
Management of bleeding with warfarin or other vitamin K antagonist oral anticoagulants

**ASSESS BLEEDING**

- **Major or Minor?**
  - **Major**
    - 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**
    - Minor eg bruising, brief epistaxis, transient haematuria
    - Check INR at 4-24 hours

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

- **Adequate correction**
  - INR <1.5
  - Consider other factors contributing eg.DIC, Congenital coagulation factor deficiency Liver disease, Inadequate replacement, Lupus inhibitor
  - As needs seek haematological advice

**Check INR at 4-24 hours**
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 37°C.
- **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>Approximate dose units (Factor IX)/kg body weight</td>
<td>25</td>
<td>35</td>
<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>Maximum Single Dose for patients weighing 100kg or over</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>
</tr>
</thead>
<tbody>
<tr>
<td>Approximate dose units (Factor IX)/kg body weight</td>
<td>25</td>
<td>35</td>
<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.
Vitamin K administration

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

*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.

Bleeding with thrombolytic therapy

Bleeding, by process of de-fibrination, is more common than with heparin (around 3%).

- Check a full coagulation screen (and FBC)
- Consider tranexamic acid 10 mg/kg IV and/or cryoprecipitate (rich in fibrinogen).
- Advice is as needs available from the on-call Consultant Haematologist, or specifically for stroke thrombolysis, the on-call Consultant Physician for Care of the Elderly.

Bleeding with Anti-Xa therapy (Rivaroxaban, Apixaban, Edoxaban)

Bleeding may be seen in around 3% of patients and given the short half-life of these drugs, minor bleeding can be managed by:

- Delay next drug administration or discontinue treatment as appropriate.
- **Currently there is no specific antidote for the Anti-Xa inhibitors**

Bleeding with Dabigatran Exetilate (Pradaxa®)

Bleeding may be seen in around 3% of patients. In cases of life-threatening bleeding associated with Dabigatran patients should be administered Idarucizumab (Praxbind®)

- Praxbind is available in 2x2.5g vial packs. Standard adult dose is 5g given by IV infusion or bolus (total volume 100mls)
- Praxbind is stored in the Emergency Department drug fridge at RCHT
- In non life-threatening Dabigatran-related bleeding, if a patient has taken a dose within in the last 2 hours consider oral activated charcoal to prevent further absorption of the drug
The assessment and hospital management of major bleeding due to use of Anti-Xa inhibitors (cerebral or gastro-intestinal)

- **There is no specific antidote for the Anti-Xa inhibitors**
- 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 (PT, Thrombin Time and APTT); If within the normal reference ranges, then there is likely to be only a low level of the anticoagulant present.
- If platelets <60 consider transfusion
- In situations with ongoing rivaroxaban-related life-threatening bleeding, not controlled by the above measures, administration of prothrombin complex concentrate (PCC) 25 units per kg may be considered.

**Overdose:**
- For Dabigatran or Rivaroxaban give oral activated charcoal if within 2 hours of ingestion.
- Rivaroxaban and apixaban are highly protein bound and are not dialysable
Management of bleeding with the **Anti-Xa Anticoagulants**: Determine interval since therapy

**ASSESS BLEEDING**

Major or Minor?

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

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

  - **FBC**
    - If platelets <60 consider transfuse 1 adult dose platelets

- Coagulation screen (PT, Thrombin Time & APTT)
  - Abnormal Drug present
    - Review progress

**Minor** - e.g. bruising, brief epistaxis, transient haematuria

- Review patient and medications consider test FBC and electrolytes

**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 (eg abciximab):

Check an FBC and as indicated a coagulation screen.
- Decisions to withhold anti-platelet drugs or to administer pro-haemostatic agents should be made after a careful multi-disciplinary assessment of the risks and benefits of intervention.
- Bleeding in patients during treatment with aspirin, P2Y12 antagonists or GPIIa/IIIb inhibitors should be managed in the first instance with general haemostatic measures. If necessary, drug cessation and reversal of the effect of coprescribed anticoagulants should also be considered.
- Platelet transfusion (2–3 adult doses) should be considered as an additional measure for critical bleeding or prevention of bleeding before emergency surgery.
- Platelet transfusion should be considered to prevent bleeding in severe thrombocytopenia (<10 x 10⁹/l) caused by abciximab

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.
- There are no specific reversal agents for the P2Y12 antagonists.

Fibrinolytic drugs
The fibrinolytic drugs 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:

For major bleeding (e.g. intracerebral) within 48 h of administration of a fibrinolytic drug:
- Stop infusion of fibrinolytic drugs and other antithrombotic drugs.
- Administer FFP 12 ml/kg.
- Administer intravenous tranexamic acid 1 g tds.
- If there is depletion of fibrinogen, administer cryoprecipitate or fibrinogen concentrate.

Further therapy should be guided by results of coagulation