APPENDIX 7

PROTECTING ANTICOAGULATED PATIENTS FROM BLEEDING

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Before commencing any anticoagulant, evaluation of the relative risk of bleeding vs thromboembolism is required. If there is clinical suspicion of active major bleeding, anticoagulation should be withheld while urgent confirmatory tests are performed.

HEPARIN

Monitoring heparin therapy.

Patients receiving *low molecular weight heparin* (eg dalteparin) therapy do not routinely require monitoring. However, monitoring using the anti Xa heparin assay should be carried out in:

- **patients with a creatinine clearance below 30 ml/min**
- patients weighing >100kg
- women who are pregnant on therapeutic doses

Initially, weekly measurement is advised. The anti Xa assay (measured 4 hrs after injection) should be **0.5 units/mL** for prophylaxis, or 0.5-1.0 units/mL for treatment of acute venous thromboembolism.

Where therapeutic anticoagulation is required in the presence of a high bleeding risk, recent major surgery or severe renal impairment, *unfractionated heparin* (UFH) should be used as its half life is 1½ hours when given by IV infusion and it can be rapidly reversed with protamine sulphate.

Monitoring is essential in patients receiving continuous IV infusion of *unfractionated heparin*. A scheme for instigating and monitoring use of unfractionated heparin is as follows:

1. Measure APTT ratio at start of therapy. Give a 5000 unit loading dose as a bolus injection IV.
2. In patients at risk of bleeding consider omitting bolus dose.
3. Draw 25,000units of unfractionated heparin made up to 50mL with 0.9% sodium chloride (resulting concentration of 500units/mL) into a 50mL syringe. Start IV infusion, at 2mL/hr.
4. The target therapeutic range for APTT ratio is 1.5-3.5. Check APTT ratio 6 hours after infusion started (and after any dose change) and adjust as follows:

APTT ratio	**ACTION**
>6	stop for 1 hr; reduce by 1mL/hr (500units/hr)
5.3-5.9	reduce by 0.6mL/hr (300units/hr)
4.7-5.2	reduce by 0.4mL/hr (200units/hr)
4.1-4.6	reduce by 0.2mL/hr (100units/hr)
3.6-4.1	reduce by 0.1mL/hr (50units/hr)
1.5-3.5	NO CHANGE
1.2-1.4	increase by 0.4mL/hr (200units/hr)
<1.2	increase by 0.8mL/hr (400units/hr)

5. Repeat APTT ratio daily while on unfractionated heparin. Check platelet count at start of therapy and after 5 days. Where therapeutic subcutaneous *unfractionated heparin* (**eg. 24 hour dose of 18 units/kg/hour given in two divided doses as 12,500units sc bd**) is used, it should be monitored 6 hrs after injection and then daily with the APPT ratio; discuss these patients with haematology (**bleep 6068 or via switchboard out of hours**).

Bleeding in a patient on heparin. Older patients on heparin for >4 days are most at risk but bleeding can occur in anyone, from any source. Bleeding can be silent into a "third space", eg the retroperitoneum. A falling haematocrit, back pain or even severe anxiety in the patient, can give a clue. Arterial puncture sites should be carefully compressed and observed. Any painful swelling should be regarded as haematoma.

Action – if the patient is on continuous IV infusion of unfractionated heparin (UFH) via a pump, the UFH should be STOPPED (heparin activity will be lost from the plasma

within 2 to 4 hrs). For rapid reversal, 25-50mg protamine sulphate should be given by slow IV injection, no more than 50mg to be given in any one dose.
Protamine may cause hypotension, bradycardia and anaphylaxis so should be given when anaesthetic support is present. Protamine is less effective against LMWH but can still provide some reversal of anticoagulation given at the same dose. It may need to be repeated if bleeding persists as it has a shorter half-life than LMWH. Administration of plasma products will *not* reverse heparin anticoagulation. The risk of thrombosis during the period of heparin withdrawal and control of bleeding does not outweigh the risk of continued bleeding – if bleeding persists seek Haematology advice.

Heparin Induced Thrombocytopenia (HIT). Up to 1 in 10 patients on IV or SC heparin may have a fall in platelet count which is usually transient and resolves spontaneously in 24-48 hours without thrombotic complication. Rarely a heparin interaction with an antibody in the plasma causes platelet activation and **thrombocytopenia**. This can lead to an explosive thrombotic disease called HIT. It is crucial to recognise this syndrome and immediately stop heparin by ALL routes and ALL doses including that in IV fluids and cannulae eg flushes. Alternative anti-thrombotic agents such as **argatroban** or danaparoid should be used in this situation. Seek *urgent* advice from the Haematology Department on-call registrar (**bleep 6068 or via switchboard out of hours**).

Invasive procedures in patients on heparin. Intravenous UFH should be stopped at least 2 hours before undertaking an invasive procedure. In a patient on prophylaxis with LMWH, or on subcutaneous UFH, the time should be extended to 12 hours. In patients on therapeutic doses of LMWH, the time should be extended to 18-24 hours.

WARFARIN - Tackling excessive warfarin-induced anticoagulation
INR >**5.0** with no bleeding. Withdraw warfarin for 1–2 days and review.
If INR >8.0 with no bleeding, give 0.5–1.0 mg Vitamin K orally and repeat INR in 24-48 hours. Omit warfarin until INR <4.0. **The cause of the elevated INR should be investigated**.

Minor haemorrhage, e.g. haematuria, epistaxis. Reduce dose or, if INR >4.5, withhold warfarin for one or more days. If INR>8.0 give Vitamin K (phytomenadione) 0.5 to 2.0 mg orally (the IV preparation of Konakion can be given by mouth). Repeat INR in 24-48 hours. Vitamin K administration is, however, not appropriate for minor bleeds in a patient with an artificial heart valve as it may induce warfarin resistance; here temporary cessation of warfarin may need cover with heparin. Seek advice from a cardiologist or haematologist. **Refer for the investigation of the bleeding source**.

Major life-threatening haemorrhage. Obtain venous access and take blood for full blood count, clotting screen and cross-matching. Stop warfarin and immediately give Vitamin K 5.0mg by slow IV injection. Prothrombin Complex Concentrate (PCC), held in the Haemophilia centre, should be given. **Contact the on-call haematology registrar (bleep 6068 or via switchboard out of hours)**
Recommended doses of PCC: INR ≤4.0: 20units/kg;
INR >4.0: 30units/kg
The single dose should not exceed **3000**units. FFP (15mL/kg) should only be infused if PCC is unavailable. Do not re-start warfarin until bleeding is controlled.
Repeat INR after 6 hours and after 24 hours; discuss with Haematology if bleeding persists. Further administration of Vitamin K may be necessary after 24 hours.

ANTICOAGULANT AGENTS
Fondaparinux
Protamine has no effect on the anticoagulant effect of fondaparinux.
Recombinant factor VIIa (*NovoSeven*) has been used with some success.
Contact the on-call haematology registrar (bleep 6068 or via switchboard out of hours).

Novel Oral Anticoagulants (NOACs):
Rivaroxaban, dabigatran and apixaban

The NOAC bleeding pathway should be followed

No reversal agent is available for the novel oral anticoagulants.
The drugs should be stopped and the haematologist alerted.
It is important to document the time of last dose.
Check FBC, coagulation screen, renal function and arrange a group and save.
Mild bleeding may only require withholding one or two doses of the drug.
Tranexamic acid 1g po/iv should be considered.
Major bleeding: in addition to the above measures, this requires haemorrhage control (surgical or radiological), transfusion of packed red cells (aim Hb >80 g/L), platelets (aim for PLT > 60 x 10^9/l or CNS bleed aim PLT > 100 x 10^9/l). Consider tranexamic acid 1g po/iv. Consider PCC 25-50 units/Kg). Dabigatran is potentially dialysable and this should be considered.
Urgent Haematology advice should be sought.

IM injections should be avoided in patients taking anticoagulants