Ballarat Health Services

DRUG GUIDELINE

HEPARIN

HIGH RISK MEDICATION

SCOPE (Area): **FOR USE IN:** All acute wards
EXCLUSIONS: Paediatrics (seek Paediatrician advice)
SCOPE (Staff): Medical, Nursing and Pharmacy

Note: Heparin is also known as heparin sodium and unfractionated heparin.

BRAND NAMES

Heparin Sodium Injection (DBL).
Heparin Sodium Injection (Pfizer).
Heparin pre-mixed bags (Baxter).

PHARMACOLOGY AND PHARMACOKINETICS

Unfractionated heparin (UFH) is a mixture of sulfated glycosaminoglycans, some of which possess anticoagulant properties. It is rapidly removed from the body with a half-life of 30 to 60 minutes, however the half-life may increase with increasing dosage or in renal impairment. Due to this short half-life it must be given by continuous intravenous infusion with monitoring of APTT and appropriate dosage adjustments for conditions requiring full anticoagulation. Its short half-life and ability to be monitored and adjusted gives it an advantage over low molecular weight heparin (LMWH) in particular patients.

INDICATIONS

- **For conditions for which full anticoagulation is required and the ability to rapidly reverse, withdraw or closely monitor the anticoagulation is desirable (via intravenous infusion).**
  - Conditions include (but are not limited to) deep vein thrombosis, pulmonary embolus, mechanical heart valves (whilst waiting for long term anticoagulation to become therapeutic), acute coronary syndromes etc.
  - Patients for which rapid withdrawal, reversal or close monitoring may be useful include (but are not limited to) the morbidly obese, those with severe renal impairment, or those in whom bleeding is more likely but anticoagulation must be maintained (e.g. perioperatively).
- **For the prevention of venous thromboembolism (via subcutaneous injection).**
- **Atrial fibrillation (AF) of less than 48 hours duration undergoing cardioversion.**
- **For maintaining patency of perm catheters in haemodialysis patients (see CPP0065 – not covered in this guideline).**
- **For anticoagulation of extracorporeal circuits during haemodialysis or haemofiltration treatment (ICU and Dialysis only – not covered in this guideline).**

CONTRAINDICATIONS

This list is not exhaustive. Some patients may still require anticoagulation even with some of the conditions below. The risks and benefits of therapy must always be weighed up.

- **History of Heparin-induced thrombocytopenia (HIT) - consult with Intensive Care or Haematology – may require alternative anticoagulant.**
- **Ongoing full anticoagulation with another agent.**
- **Severe thrombocytopenia (platelets less than 50 x 10^9/L).**
- **Active bleeding or disease states with an increased risk of bleeding.**
- **History of haemorrhagic stroke.**
- **Recent large thromboembolic stroke.**
- **Severe hepatic disease or impairment (with elevated INR), including oesophageal varices.**
- **Subacute or acute bacterial endocarditis.**

PRECAUTIONS

- **Thrombocytopenia** – use with care (see 'Heparin-induced thrombocytopenia' below).
- **Severe uncontrolled hypertension (BP greater than 200/120)** – use with great care.
- **Intrathecal or epidural analgesia or anaesthesia, or lumbar puncture** – seek specialist advice, at risk of epidural haematoma which can cause paralysis.

PREGNANCY AND BREASTFEEDING

Unfractionated heparin is considered safe to use during pregnancy and breastfeeding.

However, the use of anticoagulants during pregnancy may be associated with an increased risk of placental haemorrhage and subsequent pre-term birth or foetal loss. Prolonged use or high doses of heparin has been associated with maternal osteopenia. Consult with a haematologist for further advice regarding use during pregnancy. Seek specialist advice before prescribing, information may update regularly.

DRUG INTERACTIONS

- Administration with other drugs that affect the clotting process may increase the risk of bleeding (Note: combined use with antiplatelets and 'crossover' with warfarin is, however, often indicated). See below for more information re enoxaparin, warfarin and DOACs.
- Heparin can cause hyperkalemia, combination with other drugs that increase potassium can increase this risk, monitor potassium.

DOSAGE AND ADMINISTRATION

Important Safety Information regarding Heparin

- Heparin is a high risk medication. Intravenous infusion must only be administered from premixed bags
- Heparin 25,000 unit in 5 mL ampoules will ONLY be kept in Theatre in the 'cell saver kit'. They must be separated from similar looking ampoules, including other strengths of heparin. Concentrated ampoules will NOT be supplied to other areas of the hospital.
- Intravenous infusion should only be prescribed on the Heparin Intravenous Infusion Chart (MR/700.3). The "how to" guide for medical and nursing staff is available on the second page
- Unsafe abbreviations must be avoided- always prescribe in full as "units"
- Intravenous administration of Heparin requires an Independent Double Check. See CPP 0287 Medication Administration

Before commencing treatment:

- ***Check INR, APTT, full blood count, liver function tests.***
    - ***Seek specialist advice (ICU/Haematology) if thrombocytopenia or impaired coagulation or impaired liver function present.***
- ***Check for contraindications.***
    - ***Ask the patient SPECIFICALLY whether they have had an adverse reaction to Heparins, including Heparin-induced thrombocytopenia, and check available records for such reactions. Record answers on the Heparin Intravenous Infusion Chart (MR/700.3) – if Yes to HIT provide detailed information in the medical record and seek Specialist advice.***
- ***Confirm that enoxaparin or any of the direct oral anticoagulants (DOACs) such as rivaroxaban, dabigatran or apixaban have NOT been administered within the last 12 hours - seek senior medical advice if they have been administered. If ceasing warfarin ensure that INR is less than 2.***

For PROPHYLAXIS of venous thromboembolism (see Thromboprophylaxis CPG0022):

Heparin 5,000 units in 0.2 mL subcut, two to three times a day.

Patients with AF (less than 48 hours duration) undergoing Cardioversion: See Appendix 1

For conditions requiring FULL ANTICOAGULATION administer via continuous intravenous infusion – see next page.

Administration of heparin via intravenous infusion:

1. Weigh patient and record on 'Heparin Intravenous Infusion Chart' (MR/700.3). Actual body weight should be used to calculate loading and initial rate.

2. Does the patient require a loading dose?

- **Loading doses enable more rapid achievement of therapeutic anticoagulation - omit in patients with ischaemic stroke, switching from other full anticoagulation or postoperative.**

3. Calculate loading dose (if required) and initial rate of infusion according to the following tables:

INTRAVENOUS LOADING DOSE			
NB: omit in patients with ischaemic stroke, switching from other full anticoagulation or postoperative			
Use heparin 5,000 units in 5 mL ampoules. For slow IV push over 3-5 minutes.			
Actual Body Weight	**DVT, PE (not thrombolysed), other serious thrombotic conditions**	**In place of warfarin maintenance, acute coronary syndromes, STEMI treated with tenecteplase**	**PE post thrombolysis**
40-50 kg	3,500 units	2,500 units	**No bolus**
51-60 kg	4,500 units	3,500 units	
61-70 kg	5,000 units	4,000 units	
71-80 kg	6,000 units	4,000 units	
81-90 kg	7,000 units	4,000 units	
>90 kg	7,500 units	4,000 units	

INITIAL RATE OF INTRAVENOUS INFUSION						
Use heparin 25,000 units in 250 mL pre-mixed bag (100 units/mL)						
Actual Body Weight	**DVT, PE (not thrombolysed), other serious thrombotic conditions**		**In place of warfarin maintenance, acute coronary syndromes, STEMI treated with tenecteplase**		**PE post thrombolysis (4 hourly APTT for first 24 hours)**	
40-50 kg	800 units/hour	8 mL/hour	550 units/hour	5.5 mL/hour	800 units/hour	8 mL/hour
51-60 kg	1,000 units/hour	10 mL/hour	650 units/hour	6.5 mL/hour	1,000 units/hour	10 mL/hour
61-70 kg	1,200 units/hour	12 mL/hour	800 units/hour	8 mL/hour	1,200 units/hour	12 mL/hour
71-80 kg	1,350 units/hour	13.5 mL/hour	900 units/hour	9 mL/hour	1,350 units/hour	13.5 mL/hour
81-90 kg	1,550 units/hour	15.5 mL/hour	1,000 units/hour	10 mL/hour	1,550 units/hour	15.5 mL/hour
>90 kg	1,700 units/hour	17 mL/hour	1,000 units/hour	10 mL/hour	1,700 units/hour	17 mL/hour

4. Prescribe loading dose (if required) and initial infusion rate on 'Heparin Intravenous Infusion Chart' (MR/700.3).

- **Be sure to write 'units' in full.**
- **Record the indication for anticoagulation and target APTT (60 to 80 seconds for most indications) in the relevant section at the top of the chart.**
- **Record the baseline APTT and baseline platelet count in the section marked 'Heparin monitoring'.**
- **Record when the next APTT is due (6 hours from infusion commencement) in the 'Heparin monitoring' section. Ensure the person responsible for sampling blood for the next APTT is aware of the infusion and monitoring requirements.**
- **Ensure APTT orders are marked 'Urgent – on Heparin'.**

5. After each APTT measurement:

- **Medical staff must order the necessary boluses, pauses to infusion and/or adjustments to rate (according to the table below) in the 'Heparin monitoring' and 'Heparin ordering' sections of the Heparin Intravenous Infusion Chart (MR/700.3).**
- **Medical staff must immediately inform nursing staff of the outcome (e.g. increase or decrease rate, no change etc).**
- **Medical staff must record the time of next APTT according to the table below, in the 'Heparin monitoring' section. Inform the person responsible for taking and interpreting the measurement that this is to occur.**

NOMOGRAM FOR HEPARIN INFUSION DOSE ADJUSTMENT

APTT (seconds)	Bolus (units)	Pause infusion	Dose change Units/ hour	Dose change (mL/hr of 25,000 units/250mL)	Recheck APTT**
< 50	5,000 units*	0	↑ 150 units/hour	↑ 1.5 mL/hour	6 hours
50-59	0	0	↑ 100 units/hour	↑1 mL/hour	6 hours
60-80#	**0**	**0**	**0 (Target)**	**0 (Target)**	**Next morning**
81-89	0	0	↓ 50 units/hour	↓ 0.5 mL/hour	Next morning
90-109	0	30 minutes	↓ 100 units/hour	↓ 1 mL/hour	6 hours
110-130	0	30 minutes	↓ 150 units/hour	↓ 1.5 mL/hour	6 hours
>130 (Order repeat urgent APTT)	0	120 minutes or until APTT <120	↓ 200 units/hour	↓ 2 mL/hour	Immediately, then in 6 hours

** Omit in patients with ischaemic stroke, switching from other full anticoagulation or postoperative.*
 # Post STEMI thrombolysis a lower target range of 50-70 is appropriate. Seek specialist advice.
*** Post PE thrombolysis check APTT every 4 hours for first 24 hours*

Haemorrhage or allergy:

Monitor patient for any signs of haemorrhage (bruising, collapse, hypotension, tachycardia, sweating, abdominal pain/distension, back pain, lower limb paraesthesia/weakness, pleural effusion, unexplained drop in haemoglobin) or systemic allergic reactions. If either occurs **CEASE** infusion and obtain urgent Medical review.

Heparin reversal:

The anticoagulant effects of heparin can be reversed for patients with, or at risk of severe haemorrhage with the administration of protamine. For minor bleeding withdrawal of heparin is usually sufficient. See the Protamine Guideline (DRG0030) for further information.

Switching from LMWH to heparin and vice versa:

	Changing to → / Changing from ↓	Treatment	
		Heparin IV	Dalteparin or enoxaparin subcutaneous
Treatment	Heparin IV		Start when heparin infusion is ceased*
	Dalteparin or enoxaparin subcutaneous	Start when next dose is due (minimum 10 hours) without bolus	
Prophylaxis	Heparin Subcutaneous	As soon as diagnosis made	As soon as diagnosis is made
	Dalteparin or enoxaparin subcutaneous	As soon as diagnosis is made	Seek Consultant advice[#]

* Dose adjustment may be needed if APTT is above therapeutic range. Seek consultant advice

[#] Dose adjustment may be needed depending on when last dose of prophylactic LMWH was administered

Heparin Infusion Cessation:

When a heparin infusion in ceased this must be verbally handed over to nursing staff, and where possible documented in the progress notes. On MR/700.3 Heparin Intravenous Infusion the remaining lines should be crossed out and endorsed "ceased" with the doctor's signature, time and date.

General Administration Information

- **Infusion preparation:**
  Pre-mixed bag of heparin 25,000 units in 250 mL sodium chloride 0.9%. No other drugs are to be added to this bag.
  Infusion stable for 24 hours once infusion commenced – change IV bag at 24 hour mark if bag is not finished.
- **Infusion pump:** *Alaris PC with LVP and Guardrails*
- **Routes of administration:**
  IV injection: Yes
  IV intermittent infusion: No
  IV continuous infusion: Yes
  IM injection: No
  Subcut injection: Yes (for prophylaxis of venous thromboembolism)
- **Compatible/incompatible IV drugs/fluids:**
  Consult the Australian Injectable Drugs Handbook ('Yellow book') in your ward area. **Assume all unlisted drugs and IV fluids are incompatible – contact Pharmacy for further advice.**

MONITORING (INCLUDING BLOOD TESTS)

For ALL patients:

- Baseline INR, APTT, full blood count, liver function tests.
- Platelets should be monitored every two or three days between days 4 and 14 of therapy (sooner if the patient has been recently exposed to heparins), and weekly thereafter or until heparin is ceased to monitor for Heparin-induced thrombocytopenia (see below).
- Electrolytes, urea and creatinine should be monitored routinely.

For patients receiving an intravenous infusion:

- APTT requires regular monitoring to enable appropriate adjustment of dose. Specimens sent to the laboratory must be marked 'URGENT – ON HEPARIN'.
- Heparin requirements may be large in the acute stage of a large thromboembolus. These requirements may change suddenly during treatment.

NURSING PRACTICE POINTS

- **The initial heparin infusion is to commence <u>immediately</u> after the loading dose is given. If other bolus doses are required due to a low APTT, they are to be given at the same time the infusion rate is adjusted.**
- Use the heparin 5,000 units in 5 mL ampoule for the IV loading bolus dose and the 25,000 units in 250 mL pre-mixed bag for the maintenance IV infusion. Heparin 5000 units in 0.2 mL is for subcut administration.
- To bolus during a continuous heparin infusion press "Channel Select" on the LVP. Press the "BOLUS" button on the Alaris PC. A default dose of 5000 units (the standard and maximum dose) will appear. On the rare occasion a lesser dose is ordered, change the dose by pushing the dose button and typing in the dose. Press "Rapid Bolus" and the pump will automatically select 999 mL/hr (time of 1-3 minutes depending on the dose). Press the start button and the pump will deliver the bolus over the selected time and then immediately revert back to the continuous infusion rate that was running previously. Then update the continuous rate if it has changed.
- An unexpectedly high APTT may be due to blood being drawn from the limb into which the heparin infusion is running. Always draw blood from another limb.
- When ordering APTT tests for a patient on a heparin ensure the form is marked 'URGENT – ON HEPARIN'.
- The heparin infusion line should be clearly labeled. Care should be taken not to confuse other lines when disconnecting and reconnecting a patient.
- Heparin has a very short half life. Interruptions to therapy must be avoided to prevent a loss of anticoagulant effect
- The initial bolus and rate of infusion and any subsequent changes must be recorded and double signed in the 'Heparin administration' section of the Heparin Intravenous Infusion Chart (MR/700.3).

ADVERSE EFFECTS

Bleeding, bruising, hyperkalaemia, thrombocytopenia (transient or severe HIT – see below), transient elevation of liver aminotransferases, skin necrosis (usually at injection site), osteoporosis and alopecia with long-term use, allergic reactions including urticaria and anaphylaxis.

Heparin-induced thrombocytopenia (HIT)

Heparin-induced thrombocytopenia is a rare complication of heparin therapy (including LMWH). It is an immune-mediated process and can be pro-thrombotic and life-threatening. Regular monitoring of the platelet count is mandatory during treatment with heparins or LMWH.

It ***usually*** occurs between four and 14 days following the commencement of heparin or LMWH therapy. It may occur later in some patients, or sooner in those with exposure to heparins in the previous three months, even in low doses. Delayed onset HIT has also occurred several weeks after stopping heparin.

A minor transient decrease in the platelet count is not uncommon soon after commencing heparins. Provided the platelet count does not decrease to less than half the baseline level OR below 100 x 10^9/L heparin therapy can be continued with regular monitoring.

Should the platelet count decrease to either less than half the baseline level OR to below 100 x 10^9/L a diagnosis of Heparin-induced thrombocytopenia MUST be considered. Any indication of thrombosis in a patient on heparin must also raise the suspicion of HIT. In either of these situations immediately;

- cease heparin, and
- obtain specialist advice from a haematologist or ICU consultant.

Further testing and an alternative anticoagulant are likely to be required. For alternative treatment options please consult a haematologist or refer to the Therapeutic Guidelines: https://tgldcdp.tg.org.au.acs.hcn.com.au .

If HIT is known or suspected the patient's case should be reported to the Therapeutic Goods Administration (TGA) via https://aems.tga.gov.au/.

DRUG PRESENTATIONS, LOCATION AND STORAGE

Heparin sodium 25,000 units in 250 mL IV bags.
Heparin sodium 5,000 units in 5 mL ampoules.
Heparin sodium 5,000 units in 0.2 mL ampoules.
Heparin sodium 1,000 units in 1 mL ampoules.
Heparin sodium 5,000 units in 1 mL ampoules.
Heparin sodium 25,000 units in 5 mL ampoules.
Imprest locations: Most heparins are in many ward areas. The exception is heparin sodium 25,000 units in 5 mL vials for Theatre 'cell saver' kit only.
Store below 25°C.

Appendix 1: Intravenous Heparin stat dose for patients with AF (less than 48 hours duration ONLY) undergoing Cardioversion:

- Patients with AF (less than 48 hours duration ONLY, no recent TIA/stroke, no rheumatic heart disease, no mechanical valve) undergoing Direct Current Cardioversion (DCR) must be anticoagulated irrespective of long term stroke risk with a Direct Oral Anticoagulant (DOAC), unless other contraindications apply (Refer to DRG0054 Direct Oral Anticoagulant Drugs for more information, including regarding dosing in renal impairment and drug interactions).
- If not already fully anticoagulated, a DOAC should be administered 2 hours prior to DCR. For patients requiring DCR before 2 hours has elapsed post first DOAC dose, a stat dose of intravenous heparin should be administered as well as the DOAC. Note: DOACs take 2-4 hours to reach peak effect, and the heparin half-life is only 30-60 minutes.
- Post cardioversion, all patients require anticoagulation to continue for one month. If sinus rhythm is not achieved and maintained, anticoagulation should continue long term if aged 65 or greater, or if a CHA2DS2VA greater than 1.
- For patients receiving pharmacological cardioversion, consider DOAC/heparin.

HEPARIN IV STAT DOSE Use heparin 5,000 units in 5 mL injection Administer by IV injection over 3-5 minutes	
Weight*	**Dosage in patients with AF (less than 48 hours duration ONLY) undergoing DCR**
40-50 kg	3,500 units
51-60 kg	4,500 units
61-70 kg	5,000 units
71-80 kg	6,000 units
81-90 kg	7,000 units
>90 kg	7,500 units

*Actual body weight

Choice of DOAC

The Cardiovascular Guidelines has the following information on the use of DOACs in AF:

"Comparison between the different DOACs is difficult because apixaban, dabigatran and rivaroxaban have all been trialled against warfarin but not against each other. In the clinical trials, all the DOACs had significantly lower rates of intracranial bleeding and haemorrhagic stroke than warfarin. The rates of major bleeding with dabigatran and rivaroxaban were similar to warfarin, and the rate with apixaban was significantly lower than warfarin."

BHS ED preferred DOAC selection and dosing in AF (Consult Cardiologist On Call for patients on dual antiplatelet therapy)			
Drug	**Standard dosing**	Reduce dosing	Renal Contraindication[#]
Apixaban (first line)	**5 mg PO bd**	2.5 mg PO bd If 2 or more of: • age greater than 80 • weight less than 60 kg • SeCr greater than 133 micromol/L	CrCL less than 25 mL/min
For patients where compliance is a concern			
Rivaroxaban (second line)	**20 mg PO daily**	15 mg PO daily if • CrCL 30-49 mL/min OR • Combination with dual antiplatelet therapy	CrCL less than 30 mL/min
Notes: both apixaban and rivaroxaban are CYP3A4 substrates and contraindicated with strong CYP3A4 inhibitors - see https://amhonline.amh.net.au.acs.hcn.com.au/interactions/factor-xa-inhibitors-inter and change the interacting drug when starting apixaban or rivaroxaban wherever possible. Use of DOACs with BMI greater than 40 is uncertain[#].			

[#]consider warfarin