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This Medicines Information Leaflet is produced locally to optimise the use of medicines by encouraging prescribing that is safe, clinically appropriate and cost-effective to the NHS.

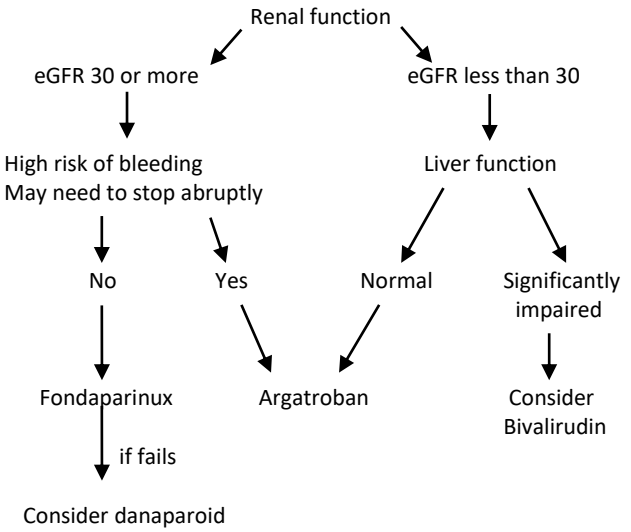
Alternative anticoagulants for use in heparin–induced thrombocytopenia in adults

Heparin-induced thrombocytopenia (HIT) is an immune-mediated complication of therapy with heparins (including low molecular weight heparins (LMWH)). It is the most important and most frequent drug-induced, immune mediated type of thrombocytopenia. It is associated with significant morbidity and mortality if unrecognized. LMWH is not a suitable alternative if HIT develops during treatment with unfractionated heparin (UFH) as there is cross-reactivity in vivo in 50% of cases. This document is intended as guidance on the use of the recommended medicines in treating HIT and is not intended as a substitute for expert advice. If a patient has a history of HIT and a specific indication for heparin then their management should be discussed with the haemostasis consultants (via bleep 5529).

Choice and duration of anticoagulation

Fondaparinux is recommended as the first line option since it is cost-effective, practically easy to administer and there is widespread familiarity with this agent. Argatroban is preferred in patients with renal impairment (eGFR less than 30 ml/min/1.73m^2), those at high risk of bleeding or where treatment may need to stop abruptly. For patients with both renal and liver impairment, use of bivalirudin could be considered. Danaparoid may be used if there is a poor response to fondaparinux.

Figure 1: Summary on choice of anticoagulant



Patients should be therapeutically anticoagulated for 3 months if HIT is associated with a thrombotic complication. In HIT without thrombosis patients should be anticoagulated for 4 weeks. When a patient is stable and their platelet count has recovered, it is reasonable to switch to an appropriate oral anticoagulant for the remaining duration of treatment.

1. Fondaparinux

Fondaparinux is a synthetic factor Xa inhibitor. A 2015 study of 133 patients on fondaparinux by Kang et al., concluded fondaparinux seems to be an effective and safe alternative anticoagulant for the management of HIT. The dosing of patients was variable but it was concluded that a prophylactic dose of 2.5mg subcutaneously once daily seems to be effective if no indication for full anticoagulation exists (which is not thought to be the case with danaparoid (see below)). In HIT with thrombosis, a weight-based treatment dose should be given; 5mg (if less than 50kg), 7.5mg (if 50-100kg) or 10mg (if greater than 100kg) subcutaneously once daily.

2. Argatroban

Argatroban, a synthetic L-arginine derivative, is a direct thrombin inhibitor that binds reversibly to thrombin.

Before using argatroban

A baseline APTT value should be obtained

Monitoring and rate adjustments

Argatroban is monitored using the activated partial thromboplastin time (APTT). The target range for steady state APTT is 1.5 – 3 times the initial baseline value, but not exceeding 100 seconds.

Dose Guidelines

The standard initial dosage in routine adult patients without hepatic impairment is 2micrograms/kg/minute, administered as a continuous infusion. For instructions on administration see argatroban Medusa monograph). The tables 1 and 4 are to be used as guides for inital dosing. IV prescription sets are available on ePR and Careview to support prescribers.

Table 1: *Standard* initial infusion rates for argatroban (1mg/ml)

Body weight (kg)	Initial infusion rate (mL/hour)
50	6
60	7
70	8
80	10
90	11
100	12
110	13
120	14
130	16
140	17

The first APTT measurement should be taken 2 hours after initiation of therapy and adjusted according to tables 2 and 3.

Table 2: Rate adjustments for argatroban therapy based on APTT for ***standard*** rate infusion (1mg/ml)

APTT(s)	Infusion rate change	Next APTT
Less than 1.5 times baseline	Increase by 0.5 micrograms/kg/min **(see table 3)**	2 hours
1.5 – 3 times baseline (max. 100s)	No change	2 hours. After 2 consecutive APTT within target range – check daily
More than 3 times baseline (or greater than 100s)	Stop infusion and recheck APTT at 2 hours. If within target range, resume at half previous infusion rate	2 hours

Table 3: Suggested change in argatroban infusion rate where APTT is less than 1.5 times baseline (1mg/ml)

Body weight (kg)	Adult patients: increase by 0.5microgram/kg/min
50	Increase by 1.5ml/hour
60	Increase by 1.8ml/hour
70	Increase by 2.1ml/hour
80	Increase by 2.4ml/hour
90	Increase by 2.7ml/hour
100	Increase by 3.0ml/hour
110	Increase by 3.3ml/hour
120	Increase by 3.6ml/hour
130	Increase by 3.9ml/hour
140	Increase by 4.2ml/hour

The maximum recommended dose is 10micrograms/kg/min. When interpreting APTT values, always check that the previous infusion rate was set correctly.

Use in renal impairment

The standard dose recommendations for use in adult patients are applicable to patients with renal impairment

Use in hepatic impairment, the critically ill and post-cardiac surgery

For patients who are critically ill, post cardiac surgery, or in patients with moderate hepatic impairment (Child-Pugh Class B), a reduced initial infusion rate of 0.5micrograms/kg/minute (as a continuous infusion) is recommended as per table 4. Argatroban is contra-indicated in patients with severe hepatic impairment (Child-Pugh Class C). The first APTT measurement should be taken 4 hours after initiation of therapy and adjusted according to tables 5 and 6.

Table 4: *Reduced* initial infusion rates for argatroban (1mg/ml)

Body weight (kg)	Initial infusion rate (mL/hour)
50	1.5
60	1.8
70	2.1
80	2.4
90	2.7
100	3.0
110	3.3
120	3.6
130	3.9
140	4.2

Table 5: Rate adjustments for argatroban therapy based on APTT for ***reduced*** rate infusion (1mg/ml)

APTT(s)	Infusion rate change	Next APTT
Less than 1.5 times baseline	Increase by 0.1 micrograms/kg/min **(see table 6)**	4 hours
1.5 – 3 times baseline (max. 100s)	No change	4 hours. After 2 consecutive APTT within target range – check daily
More than 3 times baseline (or greater than 100s)	Stop infusion and recheck APTT at 2 hours. If within target range, resume at half previous infusion rate	4 hours

Table 6: Suggested change to argatroban infusion rate where APTT is less than 1.5 times baseline in **patients with hepatic impairment, the critically ill or post-cardiac surgery** (1mg/ml)

Body weight (kg)	Adult patients: increase by 0.1micrograms/kg/min
50	Increase by 0.3ml/hour
60	Increase by 0.4ml/hour
70	Increase by 0.4ml/hour
80	Increase by 0.5ml/hour
90	Increase by 0.5ml/hour
100	Increase by 0.6ml/hour
110	Increase by 0.7ml/hour
120	Increase by 0.7ml/hour
130	Increase by 0.8ml/hour
140	Increase by 0.8ml/hour

Transition from argatroban to warfarin

Transition to warfarin should be delayed until restoration of platelets to at least 100 x 10^9/l. Argatroban affects the INR and this needs to be considered when transitioning to warfarin. **A minimum overlap of 5 days is recommended.**

If the argatroban dose is less than or equal to 2 mcg/kg/min:

1. Stop argatroban when INR on combined argatroban and warfarin is greater than 4
2. Repeat INR in 4–6 hours
3. If INR is less than 2, restart argatroban
4. Repeat procedure daily until INR greater than or equal to 2 is achieved

If the argatroban dose is greater than 2 mcg/kg/min:

1. Reduce argatroban dose to 2 mcg/kg/min
2. Repeat INR in 4–6 hours
3. Stop argatroban when INR on combined argatroban and warfarin is greater than 4
4. Repeat INR in 4–6 hours
5. If INR is less than 2, restart argatroban
6. Repeat procedure daily until INR equal to or greater than 2 is achieved

An alternative option is to convert from argatroban to fondaparinux (if not contraindicated due to renal function), which has minimal effect on the INR, before transitioning to warfarin. Please note this may not be suitable for patients felt to be at increased bleeding risk due to prolonged half-life of fondaparinux.

3. Bivalirudin

There are limited data available on the use of bivalirudin in HIT. Clearance of bivalirudin by mechanisms that are independent of organ function offers potential advantages in patients with both renal and hepatic dysfunction. Bivalirudin is a bivalent direct thrombin inhibitor. It has a short half-life of 25 minutes, approximately 80% of administered bivalirudin is proteolytically cleaved by thrombin, with the remaining 20% eliminated by renal mechanisms.

Dose Guidelines

Bivalirudin is given to achieve an APTT 1.5 to 2.5 times baseline. No initial bolus is needed. A recent study (Kiser et al.) suggested the following initial infusions rates (renal dysfunction is defined as eGFR less than 30ml/min):

- Patients **without** evidence of hepatic or renal dysfunction - 0.15–0.2 mg/kg/hour
- Patients with hepatic dysfunction alone- 0.14mg/kg/hour
- Patients with **renal dysfunction** or **combined hepatic and renal dysfunction** - 0.03–0.05 mg/kg/hour
- Patients receiving continuous renal replacement therapy - 0.03–0.04 mg/kg/hour.

Table 7: Rate adjustments for bivalirudin therapy based on APTT

APTT(s)	Infusion rate change	Next APTT
Less than 1.5 times baseline	Increase rate by 20%	2 hours
1.5 – 2.5 times baseline	No change	2 hours. After 2 consecutive APTT within target range – check every 12 hours
More than 2.5-3 times baseline	Decrease rate by 20%	2 hours
More than 3 times baseline	Hold for 1 hour, then restart at 50% lower rate	2 hours

4. Danaparoid

Danaparoid is a non-heparin mixture of low molecular weight sulphated glycosaminoglycuronans derived from porcine mucosa. It exerts its antithrombotic effect principally through antithrombin-mediated inhibition of factor Xa and, to a much lesser extent, thrombin. It may have a unique ability to inhibit platelet factor 4:heparin complexes (Krauel et al.) and should be considered in

patients who have a poor response to fondaparinux and direct thrombin inhibitors. It is primarily excreted renally. The elimination half-life, based on anti Xa activity, ranges from 17 to 28 hours.

Dose Guidelines

Loading Dose: To establish rapid, therapeutic-dose anti-coagulation with danaparoid, a weight-adjusted initial bolus dose is recommended (table 8).

Table 8: Suggested loading doses for danaparoid

Body weight (kg)	Initial IV bolus dose (units)
Less than 55	1250
55-90	2500
Greater than 90	3750

Maintenance dose: Initially 400 units per hour for 2 hours, then 300 units per hour for 2 hours, then 200 units per hour to continue (adjusted according to anti Xa levels if necessary.)

NB. The first syringe will run out after approximately 19 hours. Please bear this in mind when prescribing, and ensure that sufficient danaparoid has been prescribed and ordered from pharmacy to cover out-of-hours periods.

Use in Renal Impairment

Danaparoid is renally excreted and there is no specific antidote. It is contraindicated in severe renal impairment and whilst it can be used with caution in moderate renal impairment we would prefer to use argatroban in this group of patients.

Monitoring and Rate Adjustments

Routine monitoring of the anticoagulant effect of danaparoid is not normally required. If monitoring is deemed appropriate (weight less than 55kg or greater than 90kg), then anti-factor Xa levels (danaparoid standard curve) should be measured. Monitoring should start soon after completion of the accelerated infusion protocol (target range 0.5 – 0.8 anti-Xa units/mL). When sending blood samples to the laboratory for assay, it is imperative that it is stated on the form that the patient is being treated with danaparoid. **When interpreting anti-Xa values, always check that the previous infusion rate was set correctly.** Once stable anticoagulation within the desired therapeutic range has been achieved, subsequent doses can be given by twice daily subcutaneous injection, if desired. Because bioavailability is high, the total daily dose is the same. For example, an infusion rate of 125 units per hour (total daily dose 3000 units (125 units x 24 hours)) would equate to a subcutaneous regimen of 1500 units twice daily.

For guidance on administration of the medicines above, please refer to the to the Medusa monograph.

5. Use of DOACS

There is some data for the efficacy of DOACS (rivaroxaban/ apixaban) in the management of HIT with or without thrombosis. It is reasonable to consider using treatment dose DOACs in clinically stable patients with a CrCL over 30ml/min and platelets over 50 x 10^9/l. Please discuss with haemostasis consultant/ registrar on bleep 5529 or via switchboard out of hours. Note that the use of DOACs for HIT without thrombosis is off-label.

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Updated by:

Dr Claire Davies, Consultant Haematologist and Mary Collins (Anticoagulation Pharmacist).

With Advice from:

Dr Nicola Curry, Consultant Haematologist; Dr Susie Shapiro, Consultant Haematologist and Vicki Price, Lead Anticoagulation Pharmacist.

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