

# Guideline for the Management of Adult Patients with Heparin-Induced Thrombocytopenia / Thrombosis (HIT)

September 2022

(minor update December 2024)



**Queensland**  
Government

## Guideline for the management of adult patients with HIT - September 2022

Published by the State of Queensland (Queensland Health), September 2022

This document is licensed under a Creative Commons Attribution 3.0 Australia licence.



To view a copy of this licence, visit [creativecommons.org/licenses/by/3.0/au](https://creativecommons.org/licenses/by/3.0/au)

© State of Queensland (Queensland Health) 2022

You are free to copy, communicate and adapt the work, provided you attribute the State of Queensland (Queensland Health).

### For more information contact:

Medication Services Queensland, Queensland Health, GPO Box 48, Brisbane QLD 4001,

email [Medicationsafety@health.qld.gov.au](mailto:Medicationsafety@health.qld.gov.au)

An electronic version of this document is available at

<https://qheps.health.qld.gov.au/medicines/medication-safety/high-risk-med>

### Disclaimer:

The content presented in this publication is distributed by the Queensland Government as an information source only. The State of Queensland makes no statements, representations or warranties about the accuracy, completeness or reliability of any information contained in this publication. The State of Queensland disclaims all responsibility and all liability (including without limitation for liability in negligence) for all expenses, losses, damages and costs you might incur as a result of the information being inaccurate or incomplete in any way, and for any reason reliance was placed on such information.

# Contents

---

<b>List of Tables</b>	<b>4</b>
<b>List of Figures</b>	<b>4</b>
<b>Purpose</b>	<b>5</b>
<b>Scope</b>	<b>5</b>
<b>1 Summary of recommendations</b>	<b>6</b>
<b>2 Overview of HIT</b>	<b>7</b>
<b>3 Diagnosing HIT</b>	<b>8</b>
3.1 Calculating probability of HIT using 4Ts	8
3.2 Immunoassay for HIT antibodies	10
3.3 Functional assay for diagnosing HIT	10
<b>4 Management of HIT</b>	<b>11</b>
4.1 Treatment options for HIT	11
4.1.1 Rivaroxaban	14
4.1.2 Bivalirudin	15
4.1.3 Fondaparinux	17
4.1.4 Argatroban	18
4.1.5 Danaparoid	19
4.1.6 Warfarin	20
<b>5 Perioperative management of patients treated for HIT</b>	<b>20</b>
<b>6 Anticoagulation for intermittent haemodialysis in patients with a history of HIT</b>	<b>21</b>
<b>7 Post HIT care follow up</b>	<b>21</b>
7.1 VTE prophylaxis for patients with a history of HIT	22
7.2 Heparin re-challenge	23
<b>8 Supporting Documents</b>	<b>23</b>
<b>9 Approval</b>	<b>23</b>
<b>10 Version control</b>	<b>23</b>
<b>References</b>	<b>24</b>

# List of Tables

Table 1: Key recommendations for management of HIT .....	6
Table 2: Pre-test scoring system for HIT—The 4T's .....	9
Table 3: Availability of anticoagulants for treatment of HIT .....	12
Table 4: Clinical factors influencing anticoagulant choice for HIT treatment.....	13
Table 5: Dosing of Rivaroxaban for HIT treatment.....	15
Table 6: Initial dosing of Bivalirudin for HIT treatment.....	16
Table 7: Dose adjustment of ongoing Bivalirudin infusion for HIT treatment.....	16
Table 8: Dosing of Fondaparinux for HIT treatment.....	17
Table 9: Dosing of Argatroban for HIT treatment .....	18
Table 10: Initial dosing of Danaparoid for HIT treatment .....	19
Table 11: Maintenance dosing of Danaparoid for HIT Treatment .....	19
Table 12: Anticoagulation for intermittent haemodialysis in patients with a history of HIT ....	21
Table 13: Thromboprophylaxis options for patients with a history of HIT .....	22

# List of Figures

Figure 1: Pathway for diagnosing heparin-induced thrombocytopenia .....	8
---	---

# Purpose

This guideline provides recommendations regarding best practice for the management of anticoagulant medications for the treatment of adult patients who develop acute heparin-induced thrombocytopenia/thrombosis (HIT). Recommendations outlined are based on available evidence at the time of publication and expert consensus to promote safe use of anticoagulants across Queensland Health facilities.

Note: This guideline uses creatinine clearance (CrCl) as an estimate for measurement of kidney function to inform dosing and monitoring in line with the references quoted. All calculated measures of kidney function are estimates, each with their own limitations. Care should be taken if the measure of kidney function lies close to a threshold which prompts dose adjustment, if the patient is at extremes of age, bodyweight, or if the patient's body surface area is significantly different from 1.73m<sup>2</sup>.

# Scope

This guideline provides information for all Queensland Health employees (permanent, temporary, and casual) and all organisations and individuals acting as its agents (including visiting medical officers and other partners, contractors, consultants, and volunteers). Compliance with this guideline is recommended. Sound reasoning must exist for departing from the instructions within.

# 1 Summary of recommendations

**Table 1: Key recommendations for management of HIT**

	Recommendation	Quality of evidence	Strength of recommendation
1	A 4Ts score is recommended for all patients with suspected HIT prior to laboratory testing.	Moderate	Strong
2	For individuals with low probability of HIT (4Ts score of 3 or less):  Further laboratory testing with a screening immunoassay or confirmatory functional assay is not recommended.  However, if there are missing or unreliable clinical data, then laboratory testing should be performed.	Low	Weak
3	For individuals with intermediate or high probability of HIT (4Ts score of 4 or greater) and a positive immunoassay result:  Initial treatment should include discontinuing heparin and commencing a non-heparin alternative.	Low	Strong
4	In specific circumstances it may be suitable to confirm positive immunoassay results with functional testing, regardless of 4Ts score. [Note: This is not always practical due to limited availability of laboratories capable of performing functional testing.]		Good practice point
5	Heparin exposure must be ceased in patients with suspected or confirmed HIT. Continued use of heparin, even in low concentrations, has been associated with adverse outcomes in HIT patients.	Moderate	Strong
6	A non-heparin anticoagulant (rivaroxaban, bivalirudin, fondaparinux, argatroban or danaparoid) should be used to treat HIT.	Low to Moderate	Strong
7	A non-heparin anticoagulant should be given in therapeutic rather than prophylactic doses. If the patient is to be transitioned to warfarin from an alternate non-heparin anticoagulant, do not commence warfarin until the platelet count has normalised.	Low	Strong

Source: Adapted from (Joseph, et al., 2019)

## 2 Overview of HIT

Heparin-induced thrombocytopenia/thrombosis (HIT) is an antibody-mediated adverse drug reaction to heparin. Patients who develop HIT have platelet-activating antibodies (mainly IgG) that bind to platelet factor 4 (PF4) and heparin to form complexes leading to platelet activation and thrombin generation. Although antibody formation is common, only 0.2 to 3% of patients will develop HIT (Joseph, et al., 2019).

This antibody-mediated platelet activation and consequent thrombin generation, results in a fundamental paradox:

Despite thrombocytopenia induced by an anticoagulant, the major clinical effect in HIT is an increased risk of thrombosis (Greinacher, 2009)

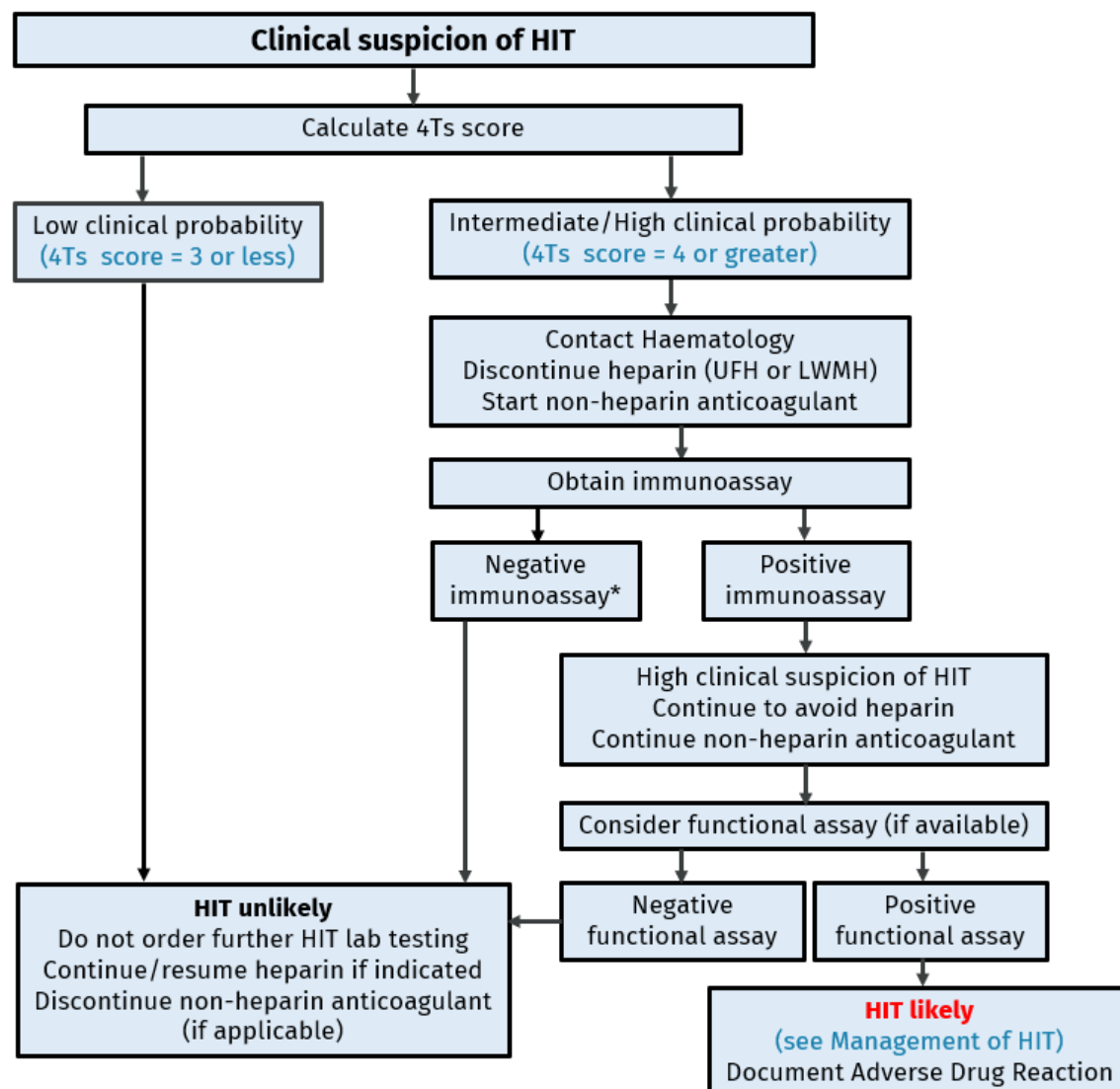
HIT usually develops after 5 to 10 days of exposure to heparin (therapeutic or prophylactic). However, it can arise much more rapidly if there has been previous heparin exposure in the last 100 days. It can occur with either unfractionated heparin (UFH) or a low molecular weight heparin (LMWH) but is more common with UFH.

HIT can have serious sequelae with an initial 6% daily risk of venous or arterial thromboembolism, as well as skin necrosis, amputation, and death. Therefore, prompt diagnosis and consultation with an appropriate specialist (haematologist, vascular physician, or clinical pharmacologist) for the introduction of an alternative non-heparin anticoagulant is crucial (Joseph, et al., 2019).

## 3 Diagnosing HIT

HIT is not easy to diagnose due to the limited predictive value of available screening methods. An accurate diagnosis of HIT must be based on a clinical review, detection of pathogenic HIT antibodies, and haematologist opinion (Joseph, et al., 2019).

**Figure 1: Pathway for diagnosing heparin-induced thrombocytopenia**



Source: Adapted from (Cuker, et al., 2018), (Joseph, et al., 2019)

\* A functional assay may be considered for patients with high probability of HIT and negative immunoassay.

### 3.1 Calculating probability of HIT using 4Ts

A pre-test probability tool should be used prior to contacting a haematologist regarding the need for a HIT screen. The most widely used tool for determining the pre-test probability of HIT is the 4Ts pre-test clinical score (Warkentin & Heddle, 2003) (Lo, et al., 2006). Table 2 shows a simplified version of the 4Ts pre-test tool. When using the 4Ts tool, points are

allocated according to clinical features within each of four categories up to a maximum score of eight. The resulting pre-test scores can be divided into the following probability groups: high (6 to 8 points), intermediate (4 to 5 points), and low (3 points or less) (Lo, et al., 2006).

**Table 2: Pre-test scoring system for HIT—The 4Ts**

Category	Clinical features		Points
<b>Thrombocytopenia</b>	Platelet count fall greater than 50% and platelet nadir greater than or equal to $20 \times 10^9/L$		2 points
	Platelet count fall 30 to 50% or platelet count fall greater than 50% and platelet nadir 10 to $19 \times 10^9/L$		1 point
	Platelet count fall less than 30% or platelet nadir less than $10 \times 10^9/L$		0 points
<b>Timing of onset of platelet count fall after heparin exposure</b>	Clear onset between days 5 to 10 or platelet count fall within one day (if prior heparin exposure in previous 30 days)		2 points
	Consistent with days 5 to 10 platelet count fall, but not clear (e.g. missing platelet counts); onset after day 10; or platelet count fall within one day (if prior heparin exposure in previous 30 to 100 days)		1 point
	Platelet count fall in less than or equal to 4 days without prior heparin exposure		0 points
<b>Thrombosis or other clinical sequelae</b>	Confirmed new thrombosis, skin necrosis at heparin injection sites, post heparin acute systemic reaction, anaphylactoid reaction, or adrenal haemorrhage		2 points
	Progressive or recurrent thrombosis; erythematous skin lesions at heparin injection sites, suspected thrombosis not yet proven		1 point
	None		0 points
<b>Other cause for thrombocytopenia</b>	No other cause for platelet count fall		2 points
	Possible other cause for platelet count fall (e.g. sepsis)		1 point
	Probable other cause for platelet count fall (e.g. disseminated intravascular coagulation, medication, within 72 hours of surgery)		0 points
<b>Interpretation</b>	0 to 3 points	<b>LOW PROBABILITY</b> (less than 1%)	
	4 to 5 points	<b>INTERMEDIATE PROBABILITY</b> (approximately 10%)	
	6 to 8 points	<b>HIGH PROBABILITY</b> (approximately 50%)	

Source: Adapted from (Joseph, et al., 2019) (Lo, et al., 2006) (UpToDate, 2022)

In patients with a low probability 4Ts score (less than 4) HIT is unlikely and further testing is not required; heparin can continue or be resumed. (Cuker, et al., 2018)

In patients with an intermediate probability 4Ts score (4 or 5 points) it is recommended that heparin is discontinued. If there is a high risk of bleeding, a prophylactic dose of non-heparin anticoagulant is suggested. If the risk of bleeding is not high, then therapeutic dose non-heparin anticoagulant can be used. (Cuker, et al., 2018)

In patients with a high probability 4Ts score (greater than 5), it is recommended that heparin is discontinued, and a non-heparin anticoagulant is initiated at therapeutic dose. (Cuker, et al., 2018)

## 3.2 Immunoassay for HIT antibodies

An immunoassay can be used to detect the presence of anti-PF4/heparin antibodies in patients with an intermediate or high probability 4Ts score for HIT. Choice of immunoassay will be dependent on local availability. The following is a list of immunoassay tests that may be used: ELISA (IgG), ELISA (poly-specific antibodies), IgG-specific chemiluminescent assay, particle gel immunoassay (PaGIA), or latex agglutination assay.

If the high sensitivity immunoassay is negative, HIT is unlikely, and heparin can be resumed.

If the immunoassay is positive, continue to avoid heparin, and continue using a non-heparin anticoagulant. Obtain haematology advice.

## 3.3 Functional assay for diagnosing HIT

A functional assay can be used to detect antibodies capable of binding and activating platelets. Some function assays that can be used include serotonin release assay (SRA), heparin-induced platelet activation test (HIPA), platelet aggregation test (PAT), and flow cytometry-based assays.

A negative functional assay indicates HIT is unlikely, and heparin can be resumed. There is limited availability in Queensland for functional assays for HIT. The need for further testing should be discussed with haematology.

A positive functional assay indicates HIT is likely. Management strategies are outlined below.

## 4 Management of HIT

If high clinical suspicion of HIT, the following actions must be taken IMMEDIATELY:

- Cease all heparin products including UFH, LMWH (e.g. enoxaparin or dalteparin), and heparin locks from central lines (if present)
- Initiate therapeutic anticoagulation with an anticoagulant that is not heparin-based (refer to section 4.1 Treatment options for HIT). **Do not use UFH or LMWH.** Anticoagulation should be used in all cases of HIT, even in the absence of thrombosis, as there is pro-thrombotic milieu that will continue until heparin antibodies have cleared completely.

Once diagnosis of HIT is confirmed, document the adverse drug reaction to heparin on the medication chart or electronic medicines management system (see section 7, Post HIT care follow up).

In patients with acute isolated HIT, bilateral lower extremity ultrasound should be performed to exclude asymptomatic proximal deep vein thrombosis. Additionally, in patients with an upper extremity central venous catheter, an upper extremity ultrasound should be performed of the limb with the catheter. If there is no evidence of thrombosis, anticoagulation is recommended until platelet count recovery (Cuker, et al., 2018), or up to 30 days. If there is a clot, then anticoagulant treatment should continue for 3 months. Repeat ultrasound at the end of therapy is advisable for future reference in case of recurring events but does not alter the duration of treatment.

### 4.1 Treatment options for HIT

Anticoagulant choice for treatment of HIT should be made in consultation with a haematologist, vascular physician, or clinical pharmacologist—see Table 3 for a comparison of anticoagulant options and Table 4 for clinical factors that may influence choice of anticoagulant.

**Table 3: Availability of anticoagulants for treatment of HIT**

	<b>PBS</b>	<b>LAM status relevant to treatment of acute HIT</b>
Rivaroxaban (Xarelto®) 10 mg	Not listed for treatment of HIT	Venous thromboembolism (VTE) prophylaxis for inpatients previously diagnosed with heparin-induced thrombocytopenia (HIT). *
Rivaroxaban (Xarelto®) 15 mg, 20 mg	Not listed for treatment of HIT	For use as an alternative anticoagulant therapy for management of heparin-induced thrombocytopenia (HIT) in patients with a calculated GFR greater than 15 mL/min. Note: patients must be under the care of a Consultant Physician with consideration for an additional Haematology consultation. *
Bivalirudin (Angiomax®)	Non-PBS	For use as an alternative anticoagulant therapy for management of heparin-induced thrombocytopenia (HIT) in patients where rivaroxaban or fondaparinux is inappropriate. Note: patients must be under the care of a Consultant Physician with consideration for an additional Haematology consultation. *
Fondaparinux (Arixtra®)	Non-PBS	For use as VTE prophylaxis in patients with a history of heparin-induced thrombocytopenia where rivaroxaban is inappropriate. * For use as an alternative anticoagulant therapy for management of heparin-induced thrombocytopenia (HIT) in patients with a calculated GFR greater than 30 mL/min where rivaroxaban is inappropriate. Note: patients must be under the care of a Consultant Physician with consideration for an additional Haematology consultation. *
Argatroban (Acova®)	SAS Category A	For use as an alternative anticoagulant therapy for management of heparin-induced thrombocytopenia (HIT) in patients where rivaroxaban or fondaparinux is inappropriate. Note: patients must be under the care of a Consultant Physician with consideration for an additional Haematology consultation. **
Danaparoid (Orgaran®)	Non-PBS	For use as VTE prophylaxis in patients with a history of heparin-induced thrombocytopenia where rivaroxaban is inappropriate. * For use as an alternative anticoagulant therapy for management of heparin-induced thrombocytopenia (HIT) in patients where rivaroxaban or fondaparinux is inappropriate. Note: patients must be under the care of a Consultant Physician with consideration for an additional Haematology consultation. * Anticoagulation for intermittent haemodialysis in patients with a history of heparin-induced thrombocytopenia (HIT). *

Information correct as at 21 September 2022. Refer to PBS Schedule (<http://www.pbs.gov.au/pbs/home>) and the Queensland Health List of Approved Medicines ([LAM](#)) for current restrictions.

\* When medicines are used in ways other than as specified in the TGA approved product information, documentation and evaluation should be undertaken with reference to QHMAC's advice in the LAM formulary notes; and the CATAG guiding principles for the quality use of off-label medicines ([www.catag.org.au](http://www.catag.org.au)).

\*\*Where a medicine is not TGA approved, patients should be made fully aware of the status of the medicine and appropriate consent obtained.

GFR = glomerula filtration rate; HIT = heparin-induced thrombocytopenia; LAM = Queensland Health List of Approved Medicines; PBS = Pharmaceutical Benefits Scheme; SAS = special access scheme

**Table 4: Clinical factors influencing anticoagulant choice for HIT treatment**

Clinical factor	Preferred anticoagulant	Qualifying remarks
Oral administration	Rivaroxaban	Rivaroxaban is absorbed orally and reaches maximum concentrations within 2 to 4 hours when taken with food.
Parenteral administration	Bivalirudin Fondaparinux Argatroban Danaparoid	If the patient is unable to take oral medication, a parenteral preparation is required.
Kidney impairment (less than 30 mL/min) [Note: refer to section 6 for anticoagulation during intermittent dialysis]	Bivalirudin Argatroban	Rivaroxaban contraindicated if estimated kidney function is less than 15 mL/min. Fondaparinux and danaparoid are contraindicated if estimated kidney function is less than 30 mL/min. Risk of calciphylaxis with warfarin, particularly for patients with end-stage kidney disease on dialysis. Bivalirudin and argatroban are options for patients with end-stage kidney disease (i.e. estimated kidney function less than 15 mL/min).
Liver disease and coagulopathy	Bivalirudin	Argatroban requires a dose reduction if liver dysfunction and should be avoided if Child-Pugh score greater than 6.
Monitoring requirements	Rivaroxaban Fondaparinux	Monitoring is not routinely required with rivaroxaban or fondaparinux unless signs of kidney impairment. Danaparoid requires monitoring of anti-Xa levels. Bivalirudin and argatroban require monitoring of APTT levels.

Source: Adapted from (MIMS Online, 2021)

## 4.1.1 Rivaroxaban

Rivaroxaban is the preferred anticoagulant in Queensland Health facilities for patients with acute HIT. It is a direct oral anticoagulant (DOAC) that acts as a direct and reversible factor Xa inhibitor. It is an attractive option for acute HIT treatment based on several key advantages including in vitro confirmation that it does not have an immunologic interaction with HIT antibodies (Krauel, Hackbarth, Furl, & Greinacher, 2012). Compared to warfarin it also has a rapid onset of action, reaching maximum concentrations 2 to 4 hours after oral administration and does not cause a reduction in protein C anticoagulant activity. Rivaroxaban should also be effective during longer-term anticoagulation after platelet recovery. Therefore, the transition from parenteral to oral warfarin anticoagulation therapy and associated costs can be avoided (Warkentin, Pai, & Linkins, 2017). Rivaroxaban advantages also include ease of administration and proven efficacy in long-term treatment of VTE (Linkins, et al., 2014). Routine monitoring of anticoagulant activity is not usually required as rivaroxaban has predictable linear kinetics and influences global clotting tests (Kreutz, 2012). Seek pharmacist and haematologist advice regarding recommended monitoring of rivaroxaban in the management of HIT and refer to [Statewide Anticoagulant Guideline](#).

Whilst HIT is not a registered indication for the use of rivaroxaban in Australia, the 15 mg and 20 mg tablets are listed on the Queensland Health List of Approved Medicines (LAM) for this indication (see [Table 3](#)).

In certain circumstances use of rivaroxaban may not be suitable. Examples include:

- inability to take oral medication
- severe kidney impairment (less than 15mL/min)
- severe liver impairment (Child-Pugh C)
- significant drug interactions (refer to product information)
- if there is a requirement to use an alternative agent with a shorter half-life (e.g. concern about bleeding or recent surgery).

Rivaroxaban should not be used in conjunction with other anticoagulants (e.g. dabigatran, apixaban or warfarin). The manufacturer contraindicates treatment with medications that are strong inhibitors of both CYP3A4 and P-glycoprotein (e.g. azole antifungals such as itraconazole or HIV protease inhibitors such as ritonavir) because they may increase plasma levels of rivaroxaban and therefore increase the risk of bleeding. Concomitant use of a strong inducer of CYP3A4 (e.g. rifampicin, phenytoin, carbamazepine) may result in lower plasma levels of rivaroxaban and possibly reduced efficacy. Refer to full TGA approved product information for further details. Also refer to the [Statewide Anticoagulant Guideline](#), which is available at: <https://qheps.health.qld.gov.au/medicines/medication-safety/high-risk-med>

Rivaroxaban is not recommended for patients requiring renal replacement therapy or those with severe kidney impairment (i.e. less than 15 mL/min)—use an alternative anticoagulant instead (see [Table 4](#)).

**Table 5: Dosing of Rivaroxaban for HIT treatment**

Thrombotic status	Dose
No thrombosis	15 mg twice daily until platelet count returns to normal then, 20 mg once daily up to day 30, then cease.
Thrombosis	15 mg twice daily until day 21 (irrespective of platelet count) then, 20 mg once daily for 3 to 6 months individualised as advised by haematologist, vascular physician, or clinical pharmacologist.

Source: Adapted from (Linkins, et al., 2014), (Buller, et al., 2012), (Patel, et al., 2011)

Patients with confirmed deep vein thrombosis (DVT) or pulmonary embolism (PE) are eligible to receive PBS-subsidised rivaroxaban in the community upon discharge.

For patients without a confirmed thrombus, rivaroxaban treatment for HIT is considered 'off-label' and patients will need to obtain hospital-subsidised stock on discharge. Patients should not be discharged without a clear plan specifying duration of treatment.

After initial anticoagulant therapy and when platelet count has returned to normal, warfarin may be a suitable oral anticoagulant for maintenance therapy in patients with HIT if rivaroxaban cannot be used (e.g. due to abnormal kidney or liver function). The use of alternative non-heparin parenteral anticoagulants for patients with acute HIT will depend on factors such as their local availability, dosing, monitoring requirements, and elimination half-lives.

### 4.1.2 Bivalirudin

Bivalirudin is a parenteral direct thrombin inhibitor. It reversibly inhibits both free and fibrin-bound thrombin, preventing conversion of fibrinogen to fibrin, and therefore preventing thrombus formation. Thrombin-induced platelet aggregation is also inhibited. (MIMS Online, 2021)

Initial dosing of bivalirudin is based on actual bodyweight and kidney function (see Table 6). Loading doses are generally not required. Seek advice for patients with bodyweight greater than 150 kg and start dosing with maximum bodyweight 150 kg.

Bivalirudin requires reconstitution then a further dilution prior to administration. Reconstitute a single vial of 250 mg powder with 5 mL water for injection to give a concentration of 50 mg/mL, gentle swirl until dissolved and solution is clear to opalescent and colourless to slightly yellow. Dilute reconstituted solution with 45 mL of a compatible fluid (0.9% sodium chloride or 5% glucose) to make a final concentration of 5 mg/mL in total volume 50 mL.

**Table 6: Initial dosing of Bivalirudin for HIT treatment**

Estimated kidney function	Bivalirudin starting dose (Maximum 22.5 mg/hr)
Greater than 60 mL/min	0.15 mg/kg/hr
30 to 60 mL/min	0.08 mg/kg/hr
Less than 30 mL/min and not on kidney replacement therapy	0.05 mg/kg/hr
Continuous kidney replacement therapy	0.05 mg/kg/hr
Intermittent kidney replacement therapy or peritoneal dialysis	0.02 mg/kg/hr

Source: Adapted from (Burcham, et al., 2013), (Kliser, Burch, Klem, & Hassell, 2008)

Measure a baseline APTT prior to commencing bivalirudin infusion. If baseline APTT is elevated, consult haematologist for advice. Monitor APTT every 3 hours until 2 consecutive results within target range, then check next morning\* (i.e. within 24 hours)—see Table 7 for dose adjustment nomogram. Bivalirudin undergoes both enzymatic and kidney excretion with an elimination half-life 25 minutes (57 minutes if estimated kidney function is less than 30 mL/min) (MIMS Online, 2021)—monitor kidney function.

**Table 7: Dose adjustment of ongoing Bivalirudin infusion for HIT treatment**

<b>If APTT level not in target range within 24 hours, SEEK ADVICE</b>			
<b>Queensland Health APTT</b> (sec) [Notify prescriber if 2 consecutive results are less than 45]	<b>Withhold infusion</b> (min)	<b>Infusion rate change</b> (mg/kg/hr)	<b>Repeat APTT assay</b> (hours)
Less than 45	0	<b>Increase</b> by 0.01 mg/kg/hr	3 hours
45 to 59	0	<b>Increase</b> by 0.005 mg/kg/hr	3 hours
60 to 80	<b>Target APTT range</b>	<b>NO change</b>	3 hours until 2 consecutive APTT results within range, then check next morning* (i.e. within 24 hours)
81 to 95	0	<b>Decrease</b> by 0.005 mg/kg/hr	3 hours
96 to 110	120	<b>Decrease</b> by 0.01 mg/kg/hr	3 hours
Greater than 110	Until APTT in Target range	<b>Decrease</b> by 0.01 mg/kg/hr	3 hours

Source: (Burcham, et al., 2013)

\* Note: More frequent testing 4 to 6 hourly may be required in some high-risk patient groups (e.g. ICU, kidney impairment)

### 4.1.3 Fondaparinux

Fondaparinux is a parenteral factor Xa inhibitor. It has weight-based dosing and is administered by subcutaneous injection (see Table 8). Monitoring of drug levels is not usually required however kidney function should be monitored as fondaparinux is excreted by the kidneys with an elimination half-life 17 to 20 hours (Linkins, et al., 2012). As such, it is not recommended for patients with severe kidney impairment (i.e. less than 30 mL/min)—use an alternative anticoagulant instead (see [Table 4](#)).

If used in patients with moderate kidney impairment (30 to 49 mL/min) seek specialist advice before initiating treatment (Joseph, et al., 2019), and consider monitoring. Monitor taking 2-hour post dose peak anti-Xa level and adjust dose using anti-Xa assay (specify fondaparinux on pathology request form) aiming for target range 1 to 1.5 units/mL (adapted from (Staley, Simmons, Feldman, Williams, & Pham, 2019)).

**Table 8: Dosing of Fondaparinux for HIT treatment**

Bodyweight	Fondaparinux dose
Less than 50 kg	5 mg subcut once daily
50 to 100 kg	7.5 mg subcut once daily
Greater than 100 kg	10 mg subcut daily

Source: (Joseph, et al., 2019)

#### 4.1.3.1 Anti-Xa monitoring instructions for fondaparinux

1. Note target peak anti-Xa level (2 hours post dose) is 1 to 1.5 units/mL.
2. Use blue top (citrate) blood collection tubes.
3. Take blood sample after the third or fourth dose aligning with local phlebotomy times and ensuring collection of blood sample two (2) hours after a subcutaneous dose for a peak fondaparinux level.
4. Ensure levels are arranged for collection during normal haematology laboratory hours (i.e. collect blood sample at 10:00 for fondaparinux given once daily at 08:00).
5. Seek advice on dose adjustment from consultant, haematologist, or clinical pharmacist.

## 4.1.4 Argatroban

Argatroban is a parenteral direct thrombin inhibitor. Although not currently registered in Australia it is LAM listed for HIT treatment in patients with end stage kidney failure (see [Table 3](#)) and is available on Special Access Scheme (SAS) category A.

Argatroban undergoes hepatobiliary excretion with an elimination half-life ranging 40 to 50 minutes (Linkins, et al., 2012) and should be avoided if patient has moderate to severe liver impairment (i.e. Child-Pugh score greater than 6—Child Class B or C)—use an alternative anticoagulant instead (see Table 4). Seek advice for patients with mild liver impairment—a dose reduction may be considered.

Measure a baseline APTT prior to commencing argatroban infusion (Table 9). If baseline APTT is elevated, consult haematologist for advice. Monitor APTT every 2 hours until 2 consecutive results within target range, then check APTT next morning (i.e. within 24 hours).

**Table 9: Dosing of Argatroban for HIT treatment**

Dilution	Continuous IV infusion	Monitoring
Dilute 250 mg in 250 mL 0.9% sodium chloride resulting in a 1 mg/mL final concentration	120 microg/kg/hr IV (maximum 600 microg/kg/hr) Bolus dose is <b>NOT</b> required	Monitor APTT and adjust aiming for APTT 1.5 to 3 times patient baseline.  Monitor every 2 hours until two consecutive results, then monitor daily.

Source: (Grouzi, 2014)

## 4.1.5 Danaparoid

Danaparoid is a parenteral anticoagulant that is a more selective factor Xa inhibitor than LMWH and is a suitable option for HIT treatment. It is predominantly used for patients on intermittent haemodialysis (see section 6) or when APTT cannot be used for monitoring. Dosing is three-pronged with an initial weight-based IV bolus (see Table 10) followed by accelerated IV infusion, then a maintenance dose dependent on kidney function (see Table 11). Danaparoid is excreted by the kidneys with an elimination half-life of 24 hours (Linkins, et al., 2012). Monitor daily anti-Xa levels (specify danaparoid on pathology request form) and adjust dose aiming for a level of 0.5 to 0.8 units/mL (Joseph, et al., 2019).

**Table 10: Initial dosing of Danaparoid for HIT treatment**

Danaparoid IV bolus		Danaparoid accelerated Initial IV infusion
Bodyweight	Bolus dose	
Less than 60 kg	1500 units IV	400 units/hr for 4 hours then 300 units/hr for 4 hours
60 to 75 kg	2250 units IV	
76 to 90 kg	3000 units IV	
Greater than 90 kg	3750 units IV	

Source: (Joseph, et al., 2019)

**Table 11: Maintenance dosing of Danaparoid for HIT Treatment**

Estimated kidney function	Danaparoid maintenance dose
Greater than 60 mL/min	200 units/hr
30 to 60 mL/min	150 units/hr
Less than 30 mL/min	Not recommended

Source: Adapted from (Joseph, et al., 2019)

### 4.1.6 Warfarin

Warfarin is not recommended for initial treatment of HIT because it can paradoxically worsen the thrombosis. If used, it can result in venous limb gangrene and skin necrosis (Ahmed, Majeed, & Powell, 2007). If the patient is taking warfarin when diagnosed with HIT, cease warfarin, and administer vitamin K to reverse the anticoagulant effects (see Reversal of warfarin section in the [Statewide Anticoagulant Guideline](#)). Warfarin should not be administered until platelet counts have normalised (Linkins, et al., 2012). It may then be used in situations requiring long term anticoagulation where a DOAC is not a suitable option.

## 5 Perioperative management of patients treated for HIT

Patients on anticoagulants should be monitored for bleeding and non-essential invasive procedures should be avoided.

For urgent surgical procedures in patients being treated for active HIT, seek urgent advice from a haematology consultant.

For non-urgent surgical procedures in patients being treated for active HIT, delay surgery until HIT has resolved as risk of thrombosis is very high in the first 30 days. Seek specialist advice on the perioperative management of anticoagulation and VTE prophylaxis with a non-heparin anticoagulant.

Management of patients with previous HIT requiring cardiac surgery should be discussed with the cardiac surgeon, cardiac anaesthetist, intensive care physician, clinical immunologist, and haematologist.

## 6 Anticoagulation for intermittent haemodialysis in patients with a history of HIT

Anticoagulant therapy is required for patients who are undergoing intermittent haemodialysis—see Table 12 for options in patients with a history of HIT. Danaparoid is the anticoagulant of choice.

**Table 12: Anticoagulation for intermittent haemodialysis in patients with a history of HIT**

Anticoagulant	Dose	Monitoring
Danaparoid	Greater than 55 kg: 3750 units bolus at commencement of haemodialysis.  If no clotting is noted, the dose can be decreased to 3000 units on the third and subsequent dialysis sessions.	Anti-Xa level prior third treatment.  Target anti-Xa level is less than 0.20 units/L.
Argatroban	250 microg/kg bolus at commencement of haemodialysis followed by a continuous infusion of 2 microg/kg/min for duration of dialysis.  Reduce dose if significant liver impairment.	Monitoring not required, and short half-life means likely cleared 40 mins after completion of dialysis.

Source: Danaparoid dosing (Davenport, 2009); Argatroban dosing (Murray, et al., 2004)

Citrate locks (e.g. Taurolock®) or danaparoid 375 units diluted with 0.9% sodium chloride are suitable heparin alternatives for locking temporary dialysis central venous catheter lumens.

## 7 Post HIT care follow up

A high clinical suspicion or confirmed case of HIT should be documented in the Allergy and Adverse Drug Reaction (ADR) section of the medication chart or within the relevant sections of electronic medication management systems. While the documentation may note the specific agent involved, it should also include all heparin products as causative agents for HIT.

Discuss with the patient options for Medic Alert such as necklace or bracelet and, provide details on the ordering process. Ensure clinical handover includes details of episode of HIT.

A patient with a history of HIT should not be re-exposed to heparin unless there is a strong clinical need such as cardiac bypass.

## 7.1 VTE prophylaxis for patients with a history of HIT

If thromboprophylaxis is required for a patient with a history of HIT, a non-heparin alternative agent should be considered (see Table 13). Rivaroxaban is the preferred anticoagulant in Queensland Health facilities for these patients.

**Table 13: Thromboprophylaxis options for patients with a history of HIT**

Anticoagulant	Estimated kidney function	Standard VTE prophylaxis dosing	Considerations/Limitations
Rivaroxaban	15 mL/min or greater	10 mg ONCE daily orally	Absorbed orally and reaches maximum concentrations within 2 to 4 hours when taken with food.
	Less than 15mL/min	Not recommended	Therapeutic drug monitoring is not routinely required. Rivaroxaban is contraindicated if estimated kidney function is less than 15 mL/min.
Fondaparinux	Greater than 50 mL/min	2.5 mg ONCE daily subcutaneously	May be considered if parenteral administration is required. Therapeutic drug monitoring is not routinely required.
	30 to 50 mL/min	1.5 mg ONCE daily subcutaneously	Kidney function should be monitored. Monitoring for potential drug accumulation may be required if thromboprophylaxis is prolonged.
	Less than 30 mL/min	Not recommended	Fondaparinux is contraindicated if estimated kidney function is less than 30 mL/min.
Danaparoid	30 mL/min or greater	750 anti-Xa units TWICE daily subcutaneously	May be considered if parenteral administration is required. Therapeutic drug monitoring is not routinely required.
	Less than 30 mL/min	Seek specialist advice. If necessary, use with caution and reduce dosing frequency to 750 anti-Xa units ONCE daily subcutaneously	Kidney function should be monitored. Danaparoid is excreted by the kidneys with an elimination half-life of 24 hours. Use with caution if kidney impairment. Monitoring for potential drug accumulation may be required if thromboprophylaxis is prolonged. Danaparoid is contraindicated if estimated kidney function is less than 30 mL/min. However, for patients undergoing intermittent haemodialysis danaparoid is the anticoagulant of choice.

Source: Adapted from (MIMS Online, 2021), (UK Renal Pharmacy Group, 2020), (UK Renal Pharmacy Group, 2018), (Matthew & Russ, 2007)

## 7.2 Heparin re-challenge

If a heparin re-challenge is required for a clinical indication or due to the high cost or lack of availability of alternative anticoagulants, it should only be considered in consultation with a haematologist. Although there is no consensus regarding timing of re-exposure to heparin for acute HIT, a waiting period of at least 100 days after the last detection of HIT antibodies is recommended.

## 8 Supporting Documents

Queensland Health Anticoagulant Guideline. Available at:

<https://qheps.health.qld.gov.au/medicines/medication-safety/high-risk-med>

## 9 Approval

Approving Officer: Justin Lee, Director, Medication Services Queensland, 2022

## 10 Version control

Version	Amendments	Author/s	Approved
Version 1.0	Endorsed by QHMAC to support the non-TGA registered indication for use of rivaroxaban to treat HIT	Peter Wood	2018
Version 2.0	Review coordinated with over-arching Statewide Anticoagulant Guideline Inclusion of anticoagulation for intermittent haemodialysis	Sarah Mathers	Sept 2022
Version 2.0.1	Amend bivalirudin nomogram to two consecutive APTT results for dose stabilisation and clarify subsequent monitoring frequency	Sarah Mathers	Dec 2024

# References

- Ahmed, I., Majeed, A., & Powell, R. (2007). Heparin-induced thrombocytopenia: diagnosis and management update. *Postgraduate Medical Journal*, 83(983), 575-582.
- Buller, H., Prins, M., Lensin, A., Decousus, H., Jacobson, B., Minar, E., & al, e. (2012). Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. *New England Journal of Medicine*, 366, 1287-1297.
- Burcham, P., Abel, E., Gerlach, A., Murphy, C., Belcher, M., & Blais, D. (2013). Development and implementation of a nurse-driven, sliding-scale nomogram for bivalirudin in the management of heparin-induced thrombocytopenia. *American Journal of Health-System Pharmacy*, 70(11), 980-987. doi:10.2146/ajhp120246
- Cuker, A., Arepally, G., Chong, B., Cines, D., Greinacher, A., Gruel, Y., . . . Santesso, N. (2018). American Society of Hematology 2018 guidelines for management of venous thromboembolism: heparin-induced thrombocytopenia. 2(22), 3360-3392. doi:10.1182/bloodadvances.2018024489
- Davenport, A. (2009). Antibodies to heparin-platelet factor 4 complex: pathogenesis, epidemiology, and management of heparin-induced thrombocytopenia in haemodialysis. *American Journal of Kidney Disease*, 54(2), 361-374.
- Greinacher, A. (2009). Heparin-induced thrombocytopenia. *Journal of Thrombosis and Haemostasis*, 7(Suppl. 1), 9-12.
- Grouzi, E. (2014). Update on argatroban for the prophylaxis and treatment of heparin-induced thrombocytopenia type II. *Journal of Blood Medicine*, 5, 131-141.
- Hale, T. (2020). Medications and Mothers' Milk. Retrieved from HalesMeds.com: <https://www.halesmeds.com/>
- Joseph, J., Rabbolini, D., Enjeti, A., Favaloro, E., Kopp, M.-C., McRae, S., . . . Chong, B. (2019). Diagnosis and management of heparin-induced thrombocytopenia: a consensus statement from the Thrombosis and Haemostasis Society of Australia and New Zealand HIT Writing Group. *Medical Journal of Australia*, 210(11), 509-516. doi:10.5694/mja2.50213
- Kearon, C., Akl, E., Ornelas, J., Blaivas, A., Jimenez, D., Bounameaux, H., . . . Moores, L. (2016, February). Antithrombotic Therapy for VTE Disease: CHEST Guideline and Expert Panel Report. *Chest*, 149(2), 315-352. doi:10.1016/j.chest.2015.11.026
- Kliser, T., Burch, J., Klem, P., & Hassell, K. (2008). Safety, efficacy, and dosing requirements of bivalirudin in patients with heparin-induced thrombocytopenia. *Pharmacotherapy*, 28(9), 1115-24. doi:10.1592/phco.28.9.1115

- Krauel, K., Hackbarth, C., Füll, B., & Greinacher, A. (2012). Heparin-induced thrombocytopenia: in vitro studies on the interaction of dabigatran, rivaroxaban, and low-sulfated heparin with platelet factor 4 and anti-PF4/heparin antibodies. *Blood*, 119(5), 1248-1255.
- Kreutz, R. (2012). Pharmacodynamic and pharmacokinetic basics of rivaroxaban. *Fundamental and Clinical Pharmacology*, 26, 27-32.
- Linkins, L., Dans, A., Moores, L., Bona, R., Davidson, B., Schulman, S., & Crowther, M. (2012). Treatment and prevention of heparin-induced thrombocytopenia: Antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*, 141, e495S-530S. doi:10.1378/chest.11-2303
- Linkins, L., Warkentin, T., Pai, M., Shivakumar, S., Manji, R., Wells, P., & Crowther, M. (2014). Design of the rivaroxaban for heparin-induced thrombocytopenia study. *Journal of Thrombosis and Thrombolysis*.
- Lo, G., Juhl, D., Warkentin, T., Sigouin, C., Eichler, P., & Greinacher, A. (2006). Evaluation of a pretest clinical score (4 T's) for the diagnosis of heparin-induced thrombocytopenia in two clinical settings. *Journal of Thrombosis and Haemostasis*, 4, 759-765.
- MIMS Online. (2021, September).
- Murray, P., Reddy, B., Grossman, E., Hammes, M., Trevino, S., Ferrell, J., & al, e. (2004). A prospective comparison of three argatroban treatment regimens during hemodialysis in end-stage renal disease. *Kidney Int*, 66, 2446-2453.
- Patel, M., Mahaffey, K., Garg, J., Pan, G., Singer, D., & Hacke, W. e. (2011). Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. 365, 883-891.
- Rossi, S. (2021, January). Australian Medicines Handbook Pty Ltd. (S. Rossi, Ed.) Adelaide, South Australia, Australia. Retrieved from Australian Medicines Handbook: <https://amhonline.amh.net.au/chapters/blood-electrolytes/anticoagulants?menu=vertical>
- Staley, E., Simmons, S., Feldman, A., Williams, L., & Pham, H. (2019). Monitoring fondaparinux in the setting of antithrombin deficiency. *Laboratory Medicine*, 50, 208-211. doi: 10.1093/labmed/lmy054
- UK Renal Pharmacy Group. (2018, February 21). Danaparoid sodium. Retrieved August 24, 2022, from The Renal Drug Database: <https://renaldrugdatabase.com/monographs/danaparoid-sodium>
- UK Renal Pharmacy Group. (2020, May 04). Fondaparinux Sodium. Retrieved August 24, 2022, from The Renal Drug Database: <https://renaldrugdatabase.com/monographs/fondaparinux-sodium>
- UpToDate. (2022).
- Warkentin, T., & Hedde, N. (2003). Laboratory diagnosis of immune heparin-induced thrombocytopenia. *Current Hematology Reports*, 2, 148-157.

Warkentin, T., Pai, M., & Linkins, L. (2017). Direct oral anticoagulants for treatment of HIT: update of Hamilton experience and literature review. *Blood*, 130(9), 1104-1113. doi:10.1182/blood-2017-04-778993