Managing patients on dabigatran (Pradaxa®)

Guideline

Insert number

1. Purpose

This guideline is intended to assist clinicians with the management of patients who are admitted to hospital already taking dabigatran. It is not intended as a guideline for the initiation of treatment with dabigatran as it is not approved for inclusion on the List of Approved Medicines (LAM). Haematology consultation is advisable in most clinical situations.

Dabigatran is associated with a bleeding risk and significant haemorrhage and death has been reported. Post marketing cohort studies have not shown any increase in bleeding risk over warfarin. There is a wide variation in plasma levels of dabigatran between individuals. The clinical consequences of this variation are unknown at present.

2. 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 not mandatory, but sound reasoning must exist for departing from the recommended principles within a guideline.

3. Supporting documents

- Queensland Health List of Approved Medicines
- Statewide Heparin Intravenous Infusion Order and Administration – Adult form
- Guidelines for Anticoagulation Using Warfarin
- Guideline for managing patients on a factor Xa inhibitor –Apixaban (Eliquis®) or Rivaroxaban (Xarelto®)

4. Guideline

4.1 Indications

Dabigatran is an oral direct thrombin inhibitor. It is available as 75 mg, 110 mg and 150 mg capsules. It is not currently listed on the Queensland Health List of Approved Medicines (LAM)*. Supply of the medication will require completion of an Individual Patient Approval (IPA).

Table 1 Approved indications for dabigatran*

TGA approved indications	PBS listed
Prevention of venous thromboembolic (VTE) events in adult patients who have undergone elective total hip knee replacement	Yes (except 150 mg)
Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation and at least one additional risk factor for stroke	Yes (except 75mg)
Treatment of acute VTE and prevention of subsequent VTE	No

TGA = Therapeutic Goods Administration PBS = Pharmaceutical Benefits Scheme
* Confirm current approvals at List of approved medicines (LAM) | Queensland Health, Therapeutic Goods Administration (TGA) | Australian Government Department of Health and Pharmaceutical Benefits Scheme (PBS) | Home

Several factors are known to increase the risk of bleeding with dabigatran. These are outlined in the table below. See section 4.3 for more information on drug interactions.

Table 2 Factors known to increase risk of bleeding (see 4.3 for more information)

Characteristic	Risk factor
Age	75 years or over
Factors increasing dabigatran plasma levels	Moderate renal impairment (CrCl 30-50mL/min) Opening / crushing or chewing the capsule Selected P-glycoprotein-inhibitor co-medications
Pharmacodynamic interactions	Aspirin (Acetylsalicylic acid, ASA) NSAID's Clopidogrel
Disease / procedures with special haemorrhagic risks*	Congenital or acquired coagulation disorders Thrombocytopenia or functional platelet defects Active ulcerative gastrointestinal disease Recent gastrointestinal bleed Recent biopsy or major trauma Recent intracranial haemorrhage Brain, spinal or ophthalmic surgery Bacterial endocarditis

* Prescribers should note that these are contraindications

Dabigatran is primarily renally excreted and is **contraindicated if creatinine clearance (CrCl) is less than 30mL/min.** Doses of dabigatran should be reduced if the CrCl is between 30-50mL/min or the patient is older than 75 years of age. The manufacturers also specify that dabigatran is contraindicated if liver enzymes are greater than two times the upper limit of normal (ULN) or if hepatic disease may affect survival.

Note: Calculation of CrCl should be determined using ideal body weight with the Cockcroft-Gault equation as it is more accurate than eGFR for patients who are elderly or who have low body weight (see online calculators available locally, on QHEPS, in AMH or eTG).

4.2 Monitoring / Pathology testing

Routine monitoring is not required with therapeutic dabigatran use. However, in certain situations, such as in the event of a bleed, in emergency situations or a suspected overdose and in the perioperative setting, monitoring should be considered. The time between last intake of dabigatran and blood collection must be determined as this influences dabigatran levels and thus the results of the coagulation assay.

4.2.1 Recommended assays

A dilute thrombin clotting time assay such as the Hemoclot® Thrombin Inhibitor (HTI) assay is the recommended assay to determine dabigatran drug levels. This is currently not routinely available in Queensland Health facilities. Advice should be sought from local laboratories on availability of this test.

Thrombin time (TT) is very sensitive to dabigatran, and a normal TT excludes the presence of significant dabigatran levels but is not useful for monitoring or dose adjustment.

Availability of these two tests should be discussed with local laboratories.

Activated partial thromboplastin time (APTT) is moderately sensitive to dabigatran; it becomes increasingly insensitive with higher levels. In patients receiving dabigatran 150mg twice daily, a peak APTT approximately two times the baseline value is seen while a trough APTT of one and a

half times the baseline value is seen. Trough APTT values greater than 80 seconds are associated with increased bleeding risk. In patients undergoing hip surgery, greater test variability is seen, thus APPT levels measured in the first two to three days following surgery should be interpreted with caution.

4.2.2 Assays not recommended

Monitoring with International Normalised Ratio (INR) is not recommended as dabigatran has little effect on the prothrombin time.

4.3 Drug interactions

Thrombolytic agents or antiplatelet agents (e.g. streptokinase, urokinase, alteplase, tenecteplase, aspirin, clopidogrel, prasugrel, ticagrelor, and dipyridamole): Concomitant administration of these agents with dabigatran is a relative contraindication as dual therapy is associated with higher risks of bleeding and anaemia, especially if other risk factors (see section 4.1) are present.

Other Anticoagulants: Concomitant administration is not recommended with rivaroxaban, apixaban warfarin, heparin, low molecular weight heparin and heparin derivatives.

Non-steroidal anti-inflammatory drugs (NSAIDs): Monitor for risks of bleeding if dabigatran used with NSAIDs.

Selective serotonin reuptake inhibitors (SSRI's) and Serotonin and noradrenaline reuptake inhibitors (SNRI's): Duloxetine and venlafaxine are likely to increase risk of serious bleeding due to their effect on platelet aggregation (desvenlafaxine may behave similarly).

Substrates of P-glycoprotein: The prodrug dabigatran etexilate is a substrate for the P-glycoprotein efflux transporter. P-glycoprotein (P-gp) is an efflux transporter pump present in many organs. It plays an important role in drug transport. As an efflux transporter it limits the bioavailability of orally administered drugs by pumping them back into the intestinal lumen for excretion. An inhibitor of P-gp will increase the bioavailability of a P-gp substrate, whereas induction of P-gp will reduce the bioavailability of a substrate drug.

P-glycoprotein Inhibitors

Avoid use in combination with the following inhibitors which may increase the levels of dabigatran.

- azole antifungals (e.g. ketoconazole, itraconazole)
- non-dihydropyridine calcium channel blockers (e.g. verapamil, diltiazem)
- immunosuppressants (e.g. cyclosporin tacrolimus)
- macrolides (e.g. clarithromycin, erythromycin)
- protease inhibitors (e.g. ritonavir, darunavir, saquinavir)
- others (e.g. amiodarone, quinidine, ticagrelor)

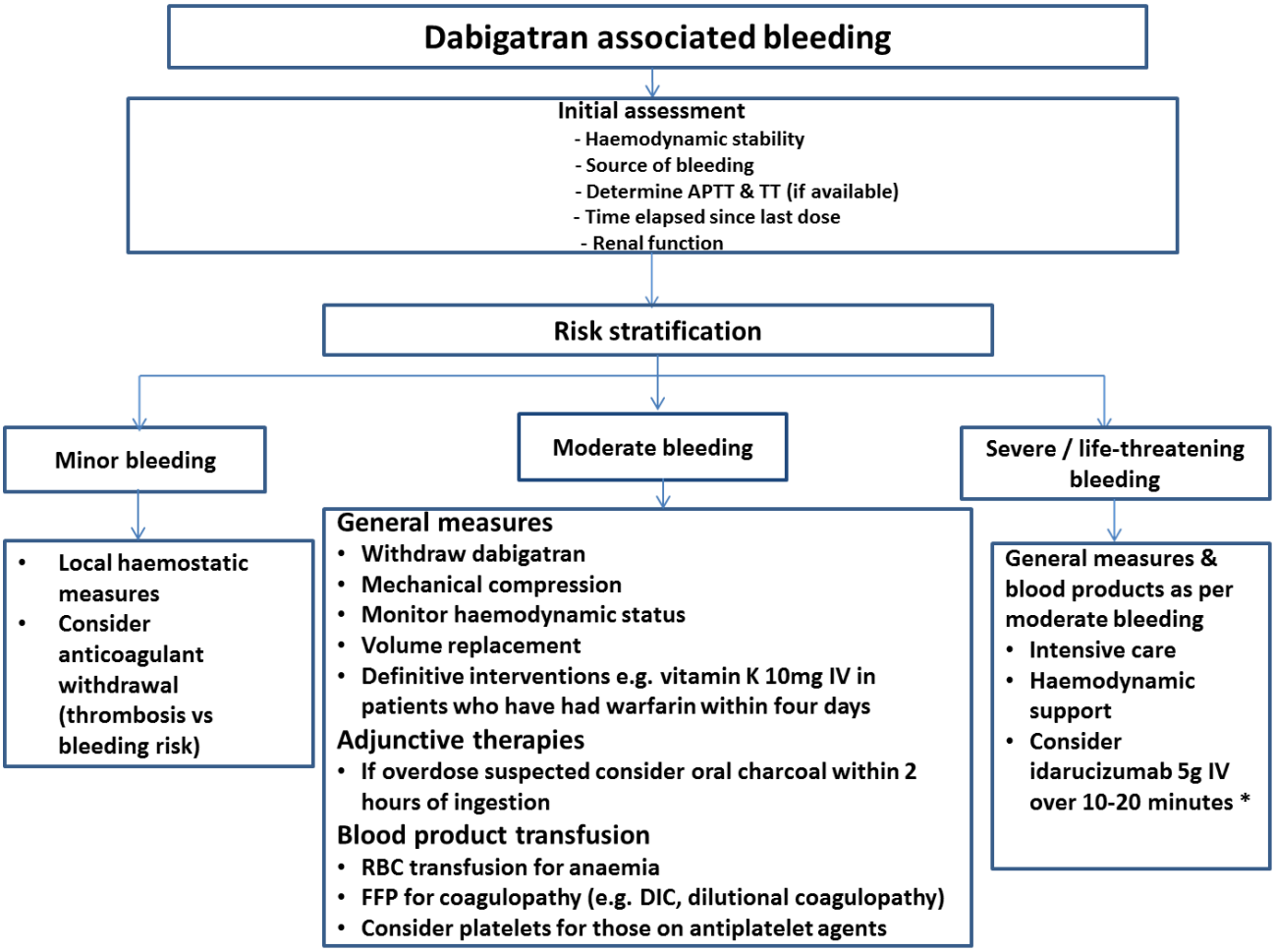
P-glycoprotein Inducers

Avoid concomitant use of dabigatran with the following inducers of the P-glycoprotein efflux transporter which may reduce levels of dabigatran.

- phenytoin
- carbamazepine
- rifampicin
- St John's Wort

4.4 Pharmacological management of bleeding due to dabigatran

Idarucizumab is a monoclonal antibody targeted against dabigatran. Idarucizumab potently and specifically inhibits dabigatran anticoagulant activity in human plasma in vitro and in rats in vivo. This agent, idarucizumab, is included on the LAM with the restriction, *Specialist Staff or rural senior medical officers for management of serious bleeding in patients anticoagulated with dabigatran or for reversal of dabigatran when emergency invasive procedures are required that cannot await restoration of normal haemostasis expected on withholding dabigatran*. For dabigatran associated bleeding the protocol below should be followed:



* For administration of idarucizumab see 4.4.1

Figure 1 Management of dabigatran associated bleeding

Moderate bleeding: non-trivial bleeding with a reduction in haemoglobin of less than 20g/L, or requiring transfusion of less than two units of red blood cells
Severe/ life-threatening bleeding: bleeding with a reduction in haemoglobin of greater than or equal to 20 g/L, or requiring transfusion of greater than or equal to two units of red blood cells, or involving a critical site.

4.4.1 Preparation and administration of idarucizumab (PRAXBIND®)

Refer to local guidelines if available.

Before an individual patient can be treated with idarucizumab:

- A coagulation screen (TT if available or APTT), to confirm the presence of dabigatran, is recommended.
- Contact pharmacy department to determine if an SAS category A form will need to be completed by the prescriber.

Dose

- The dose of idarucizumab is 5g irrespective of the dose of dabigatran or the time since last administration.
- The effect of idarucizumab is immediate and lasts for 24 hours
- Limited data support the use of an additional 5g IV dose if coagulation parameters re-elevate in the presence of clinically relevant bleeding, or if another emergency procedure is needed
- Dabigatran can be reinitiated 24 hours after administration of idarucizumab if full anticoagulation is not contraindicated and clinically normal haemostasis achieved

- No dose adjustment is required for renal impairment
- The safety and efficacy of idarucizumab in paediatric patients has not been established – contact a paediatric haematologist for advice
- Use with caution in hereditary fructose intolerance. Idarucizumab contains sorbitol which may cause serious adverse reactions, including fatalities, with parenteral administration. Consider daily metabolic load of sorbitol/fructose from all sources including idarucizumab and other drugs.

Preparation

- Idarucizumab is stored in the fridge
- Idarucizumab is supplied as **two** vials of **ready to use** solution. Each vial contains 2.5g in 50mL i.e. **two** vials equal **one** dose of idarucizumab.
- Further dilution of the solution is not required
- Once idarucizumab has been withdrawn from the vial, administration must occur within one hour.

Administration

- The infusion must be given in a clean line
- If a pre-existing intravenous infusion line is used, the full line must be flushed with **sodium chloride 0.9% before** and **after** the idarucizumab infusion.
- **Do not** administer idarucizumab with any other drugs or blood products.
- The complete dose of 5g should be given as two consecutive intravenous infusions over five to ten minutes each (i.e. total infusion time 10-20 minutes).
- Alternatively, each vial of idarucizumab can be drawn up in two 30mL syringes and each syringe given as a bolus dose over 5 minutes.
- Immediately flush entire line with 0.9% sodium chloride once infusion is complete

Monitoring

- No specific monitoring for idarucizumab is required
- Common adverse drug reactions include: hypokalaemia, delirium, pneumonia and fever
- Serious adverse drug reactions include: hypersensitivity reactions and thromboembolic disorders

4.5 Peri-operative management of patients on dabigatran

4.5.1 Elective or semi-acute surgery

- Assess the risk of bleeding against the risk of thrombosis as dabigatran may not need to be discontinued for minor procedures.
- If dabigatran needs to be withheld, plan ahead as the reversal agent is only indicated for emergency invasive procedures.
- Consider bridging anticoagulant therapy if there is a high risk of thrombosis (see section 4.6).

As dabigatran is primarily renally excreted, renal function will determine the withholding time prior to surgery and this should be checked five to seven days prior to surgery. The patient should be advised when to withhold dabigatran pre-operatively. In situations where complete haemostasis is required, APTT and TT (if available) should be checked pre-operatively.

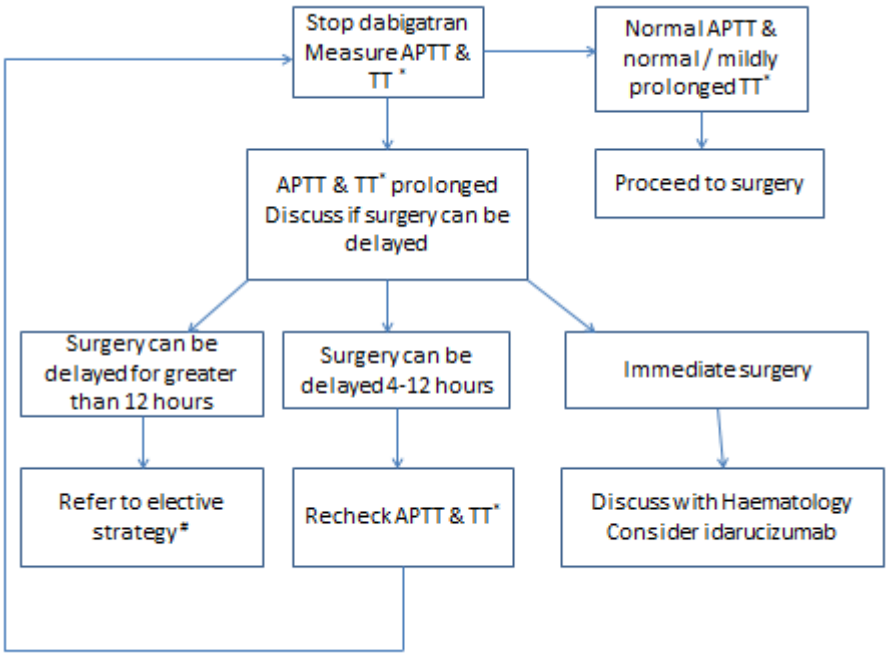
Table 3 Perioperative interruption of dabigatran: suggested approach

Renal function (CrCl mL/min)	Dabigatran half-life (range)	Low bleeding risk surgery	High bleeding risk surgery*
Normal to mild impairment (50mL/min or above)	15 (12-34) hours	Last dose 24 hours before surgery	Last dose 48-72 hours before surgery
Moderate impairment (30-49mL/min)	18 (13-23) hours	Last dose 48-72 hours before surgery	Last dose 96 hours before surgery
Severe impairment (less than 30mL/min)	27 (22-35) hours	Last dose 96 hours before surgery Do not restart	Last dose 96 hours before surgery Do not restart

* Types of surgery associated with high risk of bleeding include cardiac surgery, neurosurgery, abdominal surgery, surgery involving a major organ, or in major surgery where complete haemostasis may be required. Other procedures such as spinal anaesthesia may require complete haemostasis. Other risk factors for bleeding include advancing age, co-morbidities (e.g. major cardiac, respiratory or liver disease) and concomitant use of antiplatelet therapy.

4.5.2 Urgent surgery

- Stop dabigatran.
- Check full blood count, electrolytes (including calcium), renal function and coagulation screen (APTT, TT (if available) and fibrinogen assay); indicate time of last dabigatran dose on request form. Coagulation test results can then be used to determine how to proceed.
- In life-threatening situations, it may be necessary to consider idarucizumab before the results are known
- Refer to 4.4.1 for information regarding the preparation and administration of idarucizumab



* If available
# Refer to 4.5.1

Figure 2 Suggested management of patients on dabigatran requiring urgent surgery

4.5.3 Recommendations regarding neuraxial analgesia

- Epidural and spinal anaesthesia are contraindicated if the TT (or APTT if unavailable) is abnormal (as dabigatran has not been fully eliminated from the system).
- Dabigatran should not be recommenced in patients who have an epidural or spinal catheter in place.
- Dabigatran should not be restarted within six hours of removal of spinal or epidural catheter; a longer delay should be considered if there are multiple punctures or traumatic insertion of spinal or epidural catheter.

4.5.4 Restarting dabigatran after surgery

- Determine whether any interacting drugs have been started postoperatively (see Table 2).
- Following minor surgery where bleeding risk is low, dabigatran can be restarted, at the pre-admission dose, 24 hours after surgery
- For major surgery, dabigatran should not be restarted for at least 48 hours and preferably 72 hours.
- For patients at high risk of thrombosis, a reduced dose of dabigatran (75mg daily) or a prophylactic dose of UFH or LMWH (enoxaparin 40mg daily or dalteparin 5000 units daily) can be considered until full anticoagulation is appropriate.

4.6 Switching to or from other anticoagulants

4.6.1 Conversion with parenteral anticoagulants

Check renal function prior to restarting dabigatran. Do not restart dabigatran in severe renal impairment i.e. CrCl less than 30mL/min. If moderate renal impairment exists (30-50mL/min), dose adjustment is required. The recommended doses of dabigatran in moderate renal impairment are:

For AF or treatment of acute VTE - 110mg twice daily*

For Prophylaxis of VTE - 150mg daily*

*As dabigatran is non-LAM an IPA will need to be completed to enable the reduced dose of dabigatran to be prescribed.

Table 4 Conversion with parenteral anticoagulants

Drug conversion	Timing of dabigatran dose
From LMWH to dabigatran	When next LMWH dose due
From UFH continuous infusion to dabigatran	Immediately when infusion ceased
From dabigatran to parenteral anticoagulant	If CrCl is 30mL/min or greater, 12-24 hours after last dose If CrCl is less than 30mL/min, 48 hours after last dose – UFH only as LMWH not recommended

4.6.2 Conversion with warfarin

- When converting from **warfarin to dabigatran**, cease warfarin and start dabigatran when the INR is less than two
- For conversion from **dabigatran to warfarin**, adjust the starting time of warfarin based on renal function (see Table 5) and start dosing as per the Queensland Health Guidelines for Anticoagulation Using Warfarin - Adult.
- Whilst on therapy with both warfarin and dabigatran, blood samples for INR should be collected just before the dose of dabigatran.
- If patient has previously been on warfarin restart on usual dose.

Table 5 Recommendation when to stop dabigatran when swapping to warfarin

Calculated Creatinine Clearance	Time from warfarin initiation to stopping dabigatran
Greater than 50mL/min	3 days after starting warfarin
31 to 50mL/min	2 days after starting warfarin
Less than 30mL/min	Consult Haematology

Note: Dabigatran is contraindicated if CrCl is less than 30mL/min. Do not restart.

4.7 Venous Thromboembolism (VTE) prophylaxis

Do not commence pharmacological VTE prophylaxis (e.g. heparin, enoxaparin, dalteparin) if patient is taking dabigatran. If dabigatran is ceased, and VTE prophylaxis is indicated, start pharmacological prophylaxis with an alternative agent when APTT is within normal range

4.8 Acute coronary syndrome (ACS)

Patients that present with NSTEACS whilst on dabigatran should be managed as per local guidelines and discussed with the treating cardiologist regarding anticoagulation strategy i.e. continuing OAC verses withholding and bridging with a parenteral anticoagulant (e.g. LMWH or UFH). Management of anticoagulant and antiplatelet therapy in patients post coronary stenting is complex and requires assessing the patients bleeding risk and embolic risk as well as stent thrombosis risk. Currently there is limited trial evidence available; however several dedicated trials are in progress. Management should be performed on a case by case basis in conjunction with local guidelines and discussion with the treating cardiologist and physician.

In general the available evidence to date suggests:

- There is sufficient evidence that continuation of the oral anticoagulant (OAC) used for chronic therapy, rather than switching or 'bridging' to other anticoagulants, confers a lower risk for severe bleeding
- Triple therapy with OAC, aspirin and clopidogrel is associated with a significant bleeding risk. The duration of triple therapy should be as short as possible (usually 1-6 months). This should be followed by OAC and antiplatelet monotherapy (preferably clopidogrel).
- In select cases OAC or clopidogrel alone is reasonable following coronary stenting (e.g. elective stenting, high bleeding risk)
- Where a NOAC is used in combination with clopidogrel and / or low dose aspirin, the lowest tested dose for stroke prevention in AF should be considered (i.e. dabigatran 110mg twice daily, rivaroxaban 15mg daily or apixaban 2.5mg twice daily). Avoid ticagrelor or prasugrel due to excess bleeding risk.
- After 12 months, continuing OAC therapy alone may be reasonable although continuing long term antiplatelet monotherapy may be recommended in some patients (e.g. diffuse coronary disease or complex stenting).
- A proton pump inhibitor should be considered in all patients, particularly where aspirin is used

Where local guidelines are not available, consensus recommendations on the management of AF patients with ACS developed in Europe in 2014 are available at http://eurheartj.oxfordjournals.org/content/ehj/35/45/3155.full.pdf.

5. Definition

Term	Definition
TGA	Therapeutic Goods Administration
PBS	Pharmaceutical Benefits Scheme
LAM	Queensland Health List of Approved Medicines
IPA	Individual Patient Approval
CrCl	Creatinine clearance which is an indicator for renal function
ULN	Upper limit of normal
HTI	Hemoclot® Thrombin Inhibitor
INR	International normalised ratio
APTT	Activated partial prothrombin time
TT	Thrombin time
SAS	Special Access Scheme
ACS	Acute coronary syndrome
RBC	Red blood cells
FFP	Fresh frozen plasma
DIC	Disseminating intravascular coagulopathy
NSAIDs	Non-steroidal anti-inflammatory drugs
LMWH	Low molecular weight heparin
UFH	Unfractionated heparin
ACS	Acute coronary syndrome
(N)OAC	(New)Oral anticoagulant
VTE	Venous thromboembolism
STEMI	ST elevation myocardial infarction
NSTEACS	Non-ST elevation acute coronary syndrome

Version Control

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Disclaimer

This guideline has been prepared to promote and facilitate standardisation and consistency of practice, using a multidisciplinary approach.

Information in this guideline is current at time of publication.

The Department of Health, Queensland Government does not accept liability to any person for loss or damage incurred as a result of reliance upon the material contained in this guideline.

Clinical material offered in this guideline does not replace or remove clinical judgement or the professional care and duty necessary for each specific patient case.

Clinical care carried out in accordance with this guideline should be provided within the context of locally available resources and expertise.

This Guideline does not address all elements of standard practice and assumes that individual clinicians have the responsibility to:

- Discuss care with consumers in an environment that is culturally appropriate and which enables respectful confidential discussion. This includes the use of interpreter services where necessary.
- Advise consumers of their choice and ensure informed consent is obtained.
- Provide care within scope of practice, meet all legislative requirements and maintain standards of professional conduct.
- Apply standard precautions and additional precautions as necessary, when delivering care.
- Document all care in accordance with mandatory and local requirements.

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