

Guidelines for testing and perioperative management of dabigatran - for possible inclusion into local management protocols

The following guidelines have been prepared by PHARMAC with the assistance of practicing specialists in response to requests for information. They are provided to assist clinical services to develop their own guidelines in accordance with local procedures and should not be adopted without appropriate review.

Testing for dabigatran anticoagulant effect

Routine testing is not required during treatment with dabigatran. However, testing may be required in:

- patients with moderate or severe reduction of renal function;
- the perioperative setting; or
- in the event of bleeding.

Tests that can measure the anticoagulant effect of dabigatran exist but are not yet well understood. Note that INR (international normalised ratio) is relatively insensitive to dabigatran with only supra-therapeutic concentrations of dabigatran resulting in an INR of approximately 2.0.^a Advice should also be sought from local laboratories on the sensitivity of the coagulation tests used as these may differ and will affect test results.^b

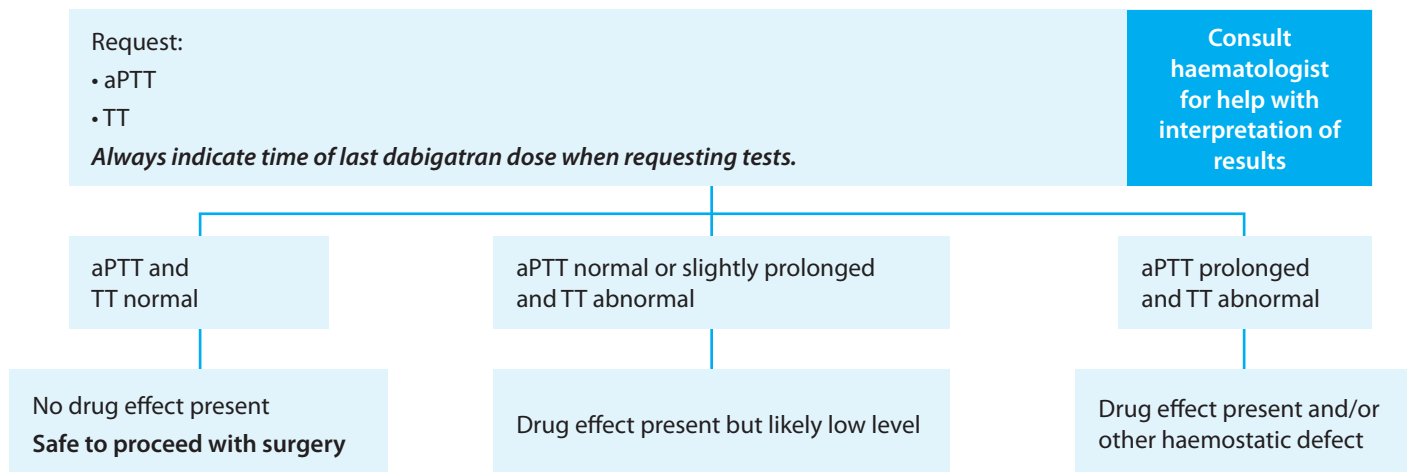
The recommended tests for assessing the effect of dabigatran are:^{a,c}

• Activated partial thromboplastin time (aPTT)

- Moderately sensitive but has reduced responsiveness at higher doses.
- Result approximately twice baseline value at dabigatran treatment doses of 150 mg bid but varies for different test brands.
- Result of >80 seconds at trough (when the next dose is due) is associated with a higher bleeding risk.

• Thrombin time (TT)

- Very sensitive with linear dose-response relationship.
- Significantly raised at therapeutic doses.



Other tests which can be done to guide the treatment of a patient on dabigatran include:

• Fibrinogen assay

- May be useful to monitor for disseminated intravascular coagulation (DIC) and determining whether replacement treatment is required.
- Note that reagents vary in responsiveness to dabigatran for fibrinogen assays and some brands may give misleading results.^b
- If fibrinogen concentration is below ~1.5 g/L (note this is dependent on assay reagents), a dose of 1 bag of Cryoprecipitate per 30 kg body weight will increase fibrinogen by approximately 1 g/L.

• Platelet count

- Useful to determine whether replacement is required.
- Transfusion of Platelet Concentrate is indicated where the platelet count is below 70-80 X 10⁹ /L.
- If the patient has been treated with an anti-platelet agent, a dose of 1 to 2 bags of Platelet Concentrate is appropriate for adults.

• Ecarin clotting time (ECT) (if available)

- Sensitive with a linear dose-response relationship.
- Result increased 2-4 times at dabigatran doses of 150 mg bid.

• Haemoclot® thrombin inhibitor assay (if available)

- Sensitive with a linear dose-response relationship.
- Clotting time from 30 to 75 seconds at dabigatran dose of 220 mg/day.

Perioperative management of dabigatran

Semi-acute or elective surgery

- Assess the risk of bleeding against the risk of thrombosis when considering discontinuing anticoagulation.
- For minor procedures, dabigatran may not need to be discontinued.
- **If dabigatran does need to be stopped, it is important to plan ahead as there is no treatment available to immediately reverse dabigatran.**
- Dabigatran is primarily renally excreted; therefore, the timing of discontinuation is dependent on the patient's renal function. Renal function should be checked at the pre-admission clinic and the patient should be given clear instructions about when to stop dabigatran treatment.

Renal function (CrCl, mL/min)	Half-life of dabigatran (hours) ^d	Timing of discontinuation after last dose of dabigatran before surgery	
		Standard risk of bleeding	High risk of bleeding ^e
> 80	13 (11-22)	24 hours	2-4 days
> 50 to ≤ 80	15 (12-34)	24 hours	2-4 days
> 30 to ≤ 50	18 (13-23)	At least 2 days (48 hours)	4 days
≤ 30 ^f	27 (22-35)	2-5 days	> 5 days

- If there is a risk of thrombosis, consider bridging anticoagulant therapy.

Urgent surgery

- Stop dabigatran.
- Check full blood count, electrolytes (including calcium), renal function and coagulation screen including aPTT, TT and fibrinogen assay. Indicate time of last dabigatran dose when requesting test.
- Consider delaying surgery if appropriate until coagulation screen (aPTT, TT and fibrinogen assay) is normal or until sufficient time has elapsed for drug clearance.
- Where urgent life-saving surgery cannot be delayed, consult with Haematology Service over measures (for e.g. recombinant factor VIIa) to control bleeding prior to and during the surgery.

Re-starting dabigatran after surgery

The appropriate time to re-start dabigatran after surgery will be determined by the nature of the surgery, the urgency for restarting thromboprophylaxis and the haemostatic state of the patient. Discussion with a Haematologist is appropriate to determine individual case management.

In elective situations where the wound is stable and haemostasis is satisfactory, it is suggested that dabigatran is re-started with a single capsule (75 mg, 110 mg or 150 mg depending on the indication) 1–4 hours after surgery with the usual daily dose commenced the following day.

A delay in restarting dabigatran will be appropriate if the wound is not stable and clinically significant wound losses are still present. Short term use of an alternative reversible anticoagulant (bridging anticoagulation) may be appropriate where thromboprophylaxis is required but the risks from wound bleeding are increased. The risk for thrombosis should be assessed.

^a van Ryn et al. Thromb Haemost 2010 Jun; 103(6): 1116-27.

^b Lindahl et al. Thromb Haemost 2011 Feb; 105(2): 371-8.

^c Dabigatran Medsafe datasheet 11 February 2011.

^d Stangier et al. Clin Pharmacokinet 2010; 49: 259-268, geometric mean (range).

^e Types of surgery associated with a high risk of bleeding (or in major surgery where complete haemostasis may be required) including but not limited to cardiac surgery, neurosurgery, abdominal surgery, or surgeries involving a major organ. Other procedures such as spinal anaesthesia may also require complete haemostatic function. Other important determinants of bleeding risk include advancing age, co-morbidities (eg, major cardiac, respiratory, or liver disease) and concomitant use of anti-platelet therapy.

^f Dabigatran is contraindicated for use in patients with CrCl ≤30 ml/min. CrCl = creatinine clearance.

Acknowledgement:

We would like to thank the following clinicians for their advice and input into these guidelines: Dr John Carter (Haematologist, CCDHB), Dr Paul Harper (Haematologist, MidCentral DHB), Dr Laura Young and Dr Paul Ockelford (Haematologists, ADHB), Dr Mark Smith (Haematologist, CDHB), Dr Julie-Anne Bell (Haematologist, Waikato DHB), Dr Jim Faed (Haematologist, Southern DHB and Transfusion Medicine Specialist, NZ Blood Service) and Mr Allan Panting (Orthopaedic Surgeon, Nelson Marlborough DHB).