Guidelines for testing and perioperative management of dabigatran and rivaroxaban: for possible use in local management protocols

These guidelines have been produced by PHARMAC in conjunction with bpac^{nz}, with the assistance of practising specialists. 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.

Also see: Guidelines for management of bleeding with dabigatran or rivaroxaban: for possible use in local management protocols

Testing for dabigatran or rivaroxaban anticoagulant effect

Routine testing for anticoagulant effect is not required during treatment with dabigatran or rivaroxaban. However, testing may be required in:

- Patients with moderate or severe **renal dysfunction**.
- The **perioperative setting**.
- The event of **bleeding**.
- Concurrent use of potentially **interacting medicines**, i.e. strong inducers or inhibitors of CYP3A4 or P-glycoprotein.
- The event of an **overdose**.
- Prior to administering **idarucizumab** (Praxbind – a reversal agent for dabigatran) and 30 minutes after treatment.

Different tests are indicated to investigate the coagulation effect in patients taking dabigatran or rivaroxaban. The time of the last dose of anticoagulant must be specified when requesting all tests and consultation with a haematologist is recommended when interpreting results.

Tests that can specifically quantify the anticoagulant effect of either dabigatran or rivaroxaban exist, but are not universally available and their sensitivity may differ depending on which reagents are used;[1] advice should be sought from local laboratories as to the availability of these tests, otherwise use the recommended testing below.

N.B. The international normalised ratio (INR) is an unreliable measure of coagulation in patients taking dabigatran or rivaroxaban and should not be used for this purpose.[2, 3]

Anticoagulant clearance is determined by renal function

The renal function of the patient strongly influences the half life of dabigatran and to a lesser extent rivaroxaban, therefore a recent creatinine clearance (CrCl – calculated using the Cockcroft-Gault equation) is helpful to guide management decisions. More than 90% of the anticoagulant effect of either medicine can be expected to have cleared after four half lives.[4]

Characteristics of dabigatran and rivaroxaban[1, 2]

	Dabigatran	Rivaroxaban
Half life	12 hours in normal renal function. Half-life extended in older people and people with renal dysfunction, e.g. 19 hours in moderate chronic kidney disease (CKD) and 28 hours in severe CKD	5–9 hours in normal renal function. Half-life slightly extended in older people and people with CKD, e.g. ten hours in severe CKD
Renal excretion	80%	36%
Plasma binding	35%	92–95%

Assessing the anticoagulant effect of dabigatran

There are two tests that are recommended to assess the anticoagulant effect of dabigatran, however, these tests are non-specific and a prolonged result may also be due to other factors such as the presence of other anticoagulants (e.g. heparin) or congenital or acquired fibrinogen deficiencies (e.g. due to liver disease or cancer).

To assess the anticoagulant effect of dabigatran, request:

Activated partial thromboplastin time (aPTT)

- Moderately sensitive, i.e. a normal result does not exclude the presence of dabigatran, therefore it is used in conjunction with the thrombin time (see below).
- The expected result is approximately twice baseline in a patient taking dabigatran 150 mg, twice daily, but may vary by test brand.
- If the aPTT is > 2.5 times baseline, the patient may be over anticoagulated.[6]
- A result > 80 seconds when the next dose is due (the trough) indicates an elevated bleeding risk.

Thrombin time (TT)

- Very sensitive with a linear dose-response relationship; therefore a normal result excludes the presence of dabigatran, but an elevated result may be caused by clinically insignificant quantities of dabigatran.[1]
- Significantly elevated at therapeutic doses.

Always indicate the time of last dabigatran dose when requesting tests – consult a haematologist to help interpret the test results

Interpretation of anticoagulant testing in patients taking dabigatran

aPTT and TT normal	aPTT normal or slightly prolonged and TT abnormal	aPTT prolonged and TT abnormal
⬇	⬇	⬇
Dabigatran not present	Dabigatran present: most likely at low concentration (could be at therapeutic range)	Dabigatran present and/or other haemostatic defect

Additional tests able to quantify dabigatran levels

The availability of the following tests may vary throughout New Zealand.

Dilute thrombin time (dTT)

- Very sensitive and able to measure levels of dabigatran due to a linear dose-response relationship.[7]

Haemoclot® thrombin inhibitor assay

- Sensitive and able to measure levels of dabigatran due to a linear dose-response relationship.[7]
- A clotting time > 65 seconds at the trough in a patient taking dabigatran, 150 mg, twice daily, is associated with an increased risk of bleeding.

N.B. The ecarin clotting time (ECT) and ecarin chromogenic assay (ECA) are both sensitive to dabigatran and able to quantify dabigatran levels,[7] however, these tests are not widely available in New Zealand.

Assessing the anticoagulant effect of rivaroxaban

There are a number of limitations when testing the anticoagulant effect of rivaroxaban relating to availability of tests and variability caused by different reagents (see below). The timing of the last dose of rivaroxaban together with an estimate of the patient's renal function may therefore provide more useful information as this allows the clearance of the medicine to be estimated. If a recent CrCl is not available this should be requested.

To assess the anticoagulant effect of rivaroxaban, request:

- **The chromogenic anti-Xa assay** is preferred:
  - Calibrated against rivaroxaban it can quantify the concentration of rivaroxaban, but when calibrated against low-molecular weight heparin it can only detect the presence of rivaroxaban.[1]
- **Prothrombin time** (PT) is a potential alternative if the anti-Xa assay is not available.[7] *Caution: not all PT reagents are sensitive to rivaroxaban (discuss with local laboratory if more information is required):*
  - A prolonged PT is consistent with a therapeutic concentration (or higher) of rivaroxaban, however, a normal PT, i.e. 12–15 seconds, may not exclude rivaroxaban at therapeutic levels as the sensitivity is determined by the reagents used.[1, 8, 9]

N.B. The TT and aPTT are not useful as they are insensitive to rivaroxaban and cannot exclude clinically significant levels of the medicine.[1, 7]

Additional tests that may guide treatment in a patient taking dabigatran or rivaroxaban

A platelet count is useful to determine whether replacement treatment is required:

- A transfusion of platelet concentrate is indicated if the platelet count is less than 70–80 $\times 10^9$/L.
- If the patient is taking an anti-platelet medicine, one to two bags of platelet concentrate is recommended.

A fibrinogen assay may be used to monitor patients for disseminated intravascular coagulation and to determine whether replacement treatment is required:

- Testing is indicated before and 30 minutes after the administration of idarucizumab.
- If the patient's fibrinogen concentration is less than 1.5 g/L, one bag of cryoprecipitate per 30 kg of bodyweight will increase their fibrinogen by approximately 1 g/L .

Perioperative management of dabigatran and rivaroxaban

The type of procedure, a recent CrCl and the timing of the last dose of anticoagulant are important when considering the risk of bleeding in patients taking dabigatran or rivaroxaban.

Risk of bleeding associated with invasive procedures [8]

Minimal risk of bleeding	Low risk of bleeding	High risk of bleeding
• Minor dermatological procedures, e.g. removal of basal or squamous carcinomas or premalignant lesions • Minor dental procedures, e.g. dental extractions, restorations, prosthetics or endodontics • Cataract procedures	• Abdominal hernia repair or hysterectomy • Arthroscopy • Bronchoscopy, including biopsy • Coronary angiography • Cutaneous or lymph node biopsy • Epidural injections with INR < 1.2 • Gastrointestinal endoscopy, including biopsy • Haemorrhoid removal • Laparoscopic cholecystectomy • Pacemaker or cardioverter defibrillator implantation* • Surgery of the hand, foot or shoulder	• Any major operation lasting more than 45 minutes • Bowel resection • Cancer surgery • Cardiac surgery • Intracranial or spinal surgery • Colonic polyp resection† • Gastrointestinal surgery • Major surgery with extensive tissue damage • Major orthopaedic surgery • Nephrectomy or kidney biopsy • Reconstructive plastic surgery • Surgery in highly vascular areas such as the kidneys, liver or spleen • Urological surgery

* Low risk of bleeding, however, withholding DOAC is currently recommended

† Polyps less than 1 cm may be considered as low bleeding risk

Semi-acute or elective surgery

- For minor procedures, dabigatran and rivaroxaban may not need to be discontinued.
- Balance the risk of bleeding against the risk of thrombosis when considering if anticoagulation should be discontinued prior to surgery.
- The timing of discontinuation for dabigatran and rivaroxaban prior to surgery is dependent on the clearance of the anticoagulant which can be determined from a recent CrCl, although less so for rivaroxaban as it is primarily metabolised in the liver.
- There is no reversal agent available for rivaroxaban* therefore surgery requires advance planning.
- Patients should be given clear written instructions about when to stop anticoagulant treatment prior to surgery.
- Bridging anticoagulant treatment, i.e. using low molecular weight heparin after dabigatran or rivaroxaban is stopped, is not necessary.

* Andexanet alfa (Andexxa –coagulation factor Xa [recombinant] inactivated-zhzo) has been approved in the United States to reverse uncontrolled or life-threatening bleeding in patients treated with rivaroxaban or apixaban, but is not available in New Zealand.[10]

Recommended timing of last dose of dabigatran prior to surgery [8]

Renal function (CrCl)	Low bleeding risk procedure*	High bleeding risk procedure
≥ 80 mL/min	24 hours before surgery	48 hours before surgery
50–79 mL/min	24–48 hours before surgery	48–72 hours before surgery
30–49 mL/min	48–72 hours before surgery	96 hours before surgery
< 30 mL/min	Dabigatran is contraindicated. Specialist advice recommended. Surgery should be avoided until at least five days after the last dose of dabigatran.	

* Dabigatran may not need to be discontinued for minor procedures

Recommended timing of last dose of rivaroxaban prior to surgery[8]

Renal function (CrCl)	Low bleeding risk procedure*	High bleeding risk procedure
>50 mL/min	24 hours before surgery	48–72 hours before surgery
30–50 mL/min	48 hours before surgery	72 hours before surgery
< 30 mL/min	Specialist advice recommended	

* Rivaroxaban may not need to be discontinued for minor procedures

Urgent surgery

- Stop dabigatran or rivaroxaban.
- Request full blood count, electrolytes (including calcium), renal function and coagulation screen including fibrinogen assay; add aPTT and TT for patients taking dabigatran and anti-Xa (where available) or PT for patients taking rivaroxaban.
- Consider delaying surgery, if appropriate, until coagulation screen is normal or until sufficient time has elapsed for medicine clearance
- Where urgent surgery cannot be delayed, e.g. to control life-threatening bleeding, consult with the Haematology Service for bleeding control measures prior to and during surgery:
  - For patients taking dabigatran consider **idarucizumab**.
  - For patients taking rivaroxaban consider **prothrombin complex** (Prothrombinex-VF) 50 IU/kg or **recombinant factor VIIa** (Novoseven)* (see: "Guidelines for management of bleeding with dabigatran or rivaroxaban").

* The effect of factor VIIa in patients taking rivaroxaban is uncertain[9]

Use of idarucizumab in other clinical situations

Currently idarucizumab is indicated for the reversal of life-threatening or uncontrolled bleeding or when emergency surgery or urgent procedures are required. Clinical experience suggests that there are other situations where the rapid reversal of dabigatran may also be beneficial such as:

- Prior to thrombolysis in patients with acute coronary syndrome or thrombotic stroke.
- Patients with fractured neck of femur where a delay in surgical repair is associated with a poorer outcome.

The decision to use idarucizumab would take into account the individual clinical circumstance and usually follow a discussion with a haematologist and the relevant specialist (e.g. neurologist, cardiologist, orthopaedic surgeon).

Re-starting oral anticoagulation following surgery

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

Following elective surgery, where the wound is stable, haemostasis is satisfactory and the patient does not have a high risk of thrombosis:

- Dabigatran is restarted with a single capsule (75 mg, 110 or 150 mg – depending on the indication) one to four hours after surgery with the usual daily dose commenced the following day.
- Rivaroxaban is restarted at the patient's usual dose the day after surgery.
- If the patient has a particularly high risk of thrombosis, anticoagulation may need to be restarted earlier.
- Following a procedure with a high risk of bleeding, dabigatran or rivaroxaban should be delayed until 48–72 hours after surgery.[8]

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