Guidelines for management of bleeding with dabigatran or 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 testing and perioperative management of dabigatran and rivaroxaban

Characteristics of dabigatran and rivaroxaban[1, 2]

Dabigatran	Rivaroxaban
Direct oral anticoagulant (DOAC); direct thrombin inhibitor	Direct oral anticoagulant (DOAC); factor Xa inhibitor
Idarucizumab (Praxbind) is a reversal agent for dabigatran; it is available in most hospitals for patients with life-threatening or uncontrolled bleeding	There is currently no specific reversal agent for rivaroxaban in New Zealand
Half-life of 12–14 hours in people with 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	Half-life of 5–9 hours in people with normal renal function; half-life slightly extended in older people and people with CKD, e.g. ten hours in severe CKD
Undergoes 80% renal excretion	Undergoes 36% renal excretion
Plasma protein binding is 35%	Plasma protein binding is 92–95%

The management priority in patients with dabigatran or rivaroxaban-associated bleeding is to control the bleeding and provide general haemodynamic support.

Bleeding is managed differently depending on whether it is associated with dabigatran or rivaroxaban.

N.B. Bleeding is often internal and may not be externally visible, e.g. gastrointestinal bleeding.

Dabigatran-associated bleeding

Dabigatran-associated bleeding

- Assess the severity of the bleeding
- Initiate standard resuscitation procedures
- Check **full blood count**, **renal function** and **electrolytes** (including calcium)
- Stop dabigatran (or delay if bleeding mild) and consider discontinuing other medicines with an anticoagulant effect, e.g. antiplatelet medicines
- If idarucizumab may be required, check coagulation screen including **fibrinogen assay**, **activated partial thromboplastin time (aPTT)** and **thrombin time (TT)** and, if available, **dilute thrombin time (dTT)** or **Haemoclot® thrombin inhibitor assay** to determine if dabigatran is present. Indicate the time of the last dabigatran dose when requesting tests.

Mild bleeding:

- Local haemostatic measures, where possible:
  - Mechanical compression
  - **Tranexamic acid**, topically or orally, 15 mg/kg, three to four times daily – the usual adult dose is 1 g, i.e. two 500 mg tablets, per dose
- Delaying the next dose of dabigatran may be sufficient when bleeding is mild or discontinue treatment as clinically appropriate

Moderate bleeding:

Consult haematology service.

- Local measures, where possible:
  - Mechanical compression
  - Consider wound packing or surgical intervention
- **Fluid replacement**, as dabigatran is largely renally excreted
- Blood product transfusion:
  - **Consider platelets** if levels less than 70–80 × 10^9/L or if patient is taking an antiplatelet medicine
- Administer an anti-fibrinolytic medicine:
  - **Tranexamic acid** IV (15–30 mg/kg) +/- continuous infusion (1mg/kg/hour)
- **Oral charcoal** (50 g) may be considered if dabigatran was taken within the last two hours; care should be taken to avoid aspiration if the patient is unconscious.[3, 4]

Severe* to life-threatening† bleeding:

Implement measures for moderate bleeding and reverse the anticoagulant effect by administering **idarucizumab** in the following situations:

- Symptomatic intracranial bleeding
- Bleeding into critical organs, e.g. intraocular, intraspinal, pericardium or compartment syndrome
- Uncontrolled bleeding with haemodynamic instability, e.g. severe gastrointestinal bleeding
- Bleeding requiring urgent surgery

Haemodialysis should be considered in patients with severe renal failure as dabigatran may take several days to clear in these patients. Idarucizumab has a relatively short half-life and haemodialysis may be preferable to multiple doses of idarucizumab.

* Reduction in Hb ≥ 20 g/L, transfusion of ≥ 2 units of red blood cells, or symptomatic bleeding in a critical area or organ, e.g. intraocular, intracranial, intraspinal, intramuscular with compartment syndrome, retroperitoneal, intra-articular or pericardial bleeding

† Reduction in Hb ≥ 50 g/L, transfusion of ≥ 4 units of red blood cells, hypotension requiring inotropic medicines or bleeding requiring surgical intervention

Reversal of dabigatran

Idarucizumab is a monoclonal antibody fragment that completely reverses the effect of dabigatran within minutes;[4] the effect is specific to dabigatran and it will not reverse other anticoagulants. Idarucizumab is indicated for the reversal of life-threatening or uncontrolled bleeding or when emergency surgery or urgent procedures are required.[6] There are no contraindications other than hypersensitivity to idarucizumab or its excipients.[5] Caution is required in patients with hereditary fructose intolerance due to the presence of sorbitol.[5]

- Idarucizumab is indicated when rapid reversal of dabigatran is required for patients who need urgent surgery or where there is uncontrolled or life-threatening bleeding.
- Idarucizumab may also be considered in other clinical situations, e.g. prior to thrombolysis in patients with acute coronary syndrome or thrombotic stroke.
- Idarucizumab is unlikely to provide clinically significant benefit if the last dose of dabigatran was taken more than 24 hours ago, unless there is severe renal impairment, e.g. CrCl < 30 mL/min.

Test results determine if dabigatran is present

Testing is required to determine if dabigatran is present prior to the administration of idarucizumab.

Request: **Activated partial thromboplastin time** (aPTT) and **Thrombin time** (TT)

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

Administer idarucizumab:

- Prior to administration request full blood count (if not already done) and record vital signs.
- The dose of idarucizumab is 5 g, given as two 2.5 g/50 mL IV infusions, five to ten minutes apart, or as a bolus of two consecutive IV injections; a further 5 g may be given approximately 24 hours later, if advised by a haematologist, e.g. if clinically relevant bleeding re-occurs and the patient has prolonged clotting time or they require a second emergency procedure.[6]
- No dose adjustments are required for patients with renal or hepatic impairment or for older patients.[5]
- Idarucizumab should not be mixed with other medicines; an established IV line can be used after if it has been flushed with 0.9% NaCl.[5]
- Request aPTT, TT and fibrinogen 30 minutes after administration.

Monitor following administration:

- Consider if a prophylactic antithrombotic, e.g. low-molecular weight heparin, is needed to reduce the risk of a thrombosis. This may be given any time after idarucizumab.[5]
- Medicine interactions with idarucizumab have not been studied, however, they are clinically unlikely.[7]
- Headache is the most common adverse effect associated with idarucizumab, others include hypokalaemia, delirium, constipation, pyrexia, pneumonia.[8]
- Dabigatran can be re-started 24 hours after administration of idarucizumab if the patient is stable and haemostasis has been achieved.[5]

Rivaroxaban-associated bleeding

Rivaroxaban-associated bleeding

- Assess severity of bleeding
- Initiate standard resuscitation procedures
- Check **full blood count**, **renal function** and **electrolytes** (including calcium)
- Request a **chromogenic anti-Xa assay** or if not available **prothrombin time (PT)**; indicate the time of the last dose of rivaroxaban when requesting tests
- Stop rivaroxaban (or delay if bleeding mild) and consider discontinuing other medicines with an anticoagulant effect, e.g. antiplatelet medicines
- There is currently no reversal agent for rivaroxaban available in New Zealand*

* 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.[9]

Mild bleeding:

- Local haemostatic measures, where possible:
  - Mechanical compression
  - **Tranexamic acid**, topically or orally, 15 mg/kg, three to four times daily – the usual adult dose is 1 g, i.e. two 500 mg tablets, per dose
- Delaying the next dose of rivaroxaban may be sufficient when bleeding is mild or discontinue treatment as clinically appropriate

Moderate to severe bleeding*:

Consult haematology service

- Local measures, where possible:
  - Mechanical compression
  - Consider wound packing or surgical intervention
- **Fluid replacement**
- Blood product transfusion:
  - Consider **platelets** if levels less than 70–80 × 10^9/L or if patient is taking an antiplatelet medicine
- Administer an anti-fibrinolytic medicine:
  - **Tranexamic acid** IV (15–30 mg/kg) +/- continuous infusion (1mg/kg/hr)
- Consider **prothrombin complex** (Prothrombinex-VF, BERIPLEX NZ) 50 IU/kg; repeat if necessary under the guidance of a haematologist.†

* Reduction in Hb ≥ 20 g/L, transfusion of ≥ 2 units of red blood cells, or symptomatic bleeding in a critical area or organ, e.g. intraocular, intracranial, intraspinal, intramuscular with compartment syndrome, retroperitoneal, intra-articular or pericardial bleeding

† There is limited data available on the effectiveness of prothrombin complex in patients taking rivaroxaban

Life-threatening bleeding*:

Implement measures for moderate to severe bleeding and attempt to counteract the anticoagulant effect by administering:

- **Recombinant factor VIIa**† (Novoseven – 100 microgram/kg by IV bolus); repeat if necessary under the guidance of a haematologist

N.B. dialysis is not effective for the removal of rivaroxaban as it is highly protein bound.

* Symptomatic intracranial bleeding, reduction in Hb ≥ 50 g/L, transfusion of ≥ 4 units of red blood cells, hypotension requiring inotropic medicines or bleeding requiring surgical intervention

† The effect of recombinant factor VIIa in patients taking rivaroxaban is currently uncertain[10]

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