

Clinical Guideline: Management of bleeding related to apixaban, rivaroxaban and dabigatran

This document is now under review and should be considered with approved product information and other information resources, November 2019.

August 2016



Disclaimer

This guideline provides advice of a general nature. This statewide guideline has been prepared to promote and facilitate standardisation and consistency of practice, using a multidisciplinary approach. The guideline is based on a review of published evidence and expert opinion.

Information in this statewide guideline is current at the time of publication.

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Health practitioners in the South Australian public health sector are expected to review specific details of each patient and professionally assess the applicability of the relevant guideline to that clinical situation.

If for good clinical reasons, a decision is made to depart from the guideline, the responsible clinician must document in the patient's medical record, the decision made, by whom and detailed reasons for the departure from the guideline.

This statewide guideline does not address all the elements of clinical practice and assumes that the individual clinicians are responsible for:

- > discussing 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
- > advising consumers of their choice and ensure informed consent is obtained
- > providing care within scope of practice, meeting all legislative requirements and maintaining standards of professional conduct, and
- > documenting all care in accordance with mandatory and local requirements.

Document title:	Clinical Guideline: Management of bleeding related to apixaban, rivaroxaban and dabigatran
First developed:	January 2015
Subsequent updates:	July 2015
Version Number:	2.0
Last reviewed:	August 2016
ISBN number:	N/A
Replaces document:	Dabigatran Clinical Guidelines, Updated February 2014
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Introduction

This guideline outlines the actions that should be taken when a patient presents with bleeding associated with the new oral anticoagulants (NOAC), apixaban, rivaroxaban or dabigatran.

Supportive measures and standard resuscitation procedures should be implemented and in the case of clinically significant bleeding specialist advice sought.

Two flow diagrams describe the treatment options available: Refer to pages 6 and 7 of this document.

Background

NOAC are indicated for the prevention of systemic embolism in selected patients with non-valvular atrial fibrillation (AF) and for the prevention and /or treatment of venous thromboembolism (VTE). Bleeding is the most common side effect of the oral anticoagulants apixaban, rivaroxaban and dabigatran and it may be serious or life threatening.

Currently there are no antidotes available to reverse bleeding associated with these medicines. NOAC have different mechanisms of action to warfarin and hence bleeding is managed differently.

Definitions and Abbreviations

Abbreviations:

AF	Atrial fibrillation
aPTT	Activated partial thromboplastin time
FBC	Full blood count
Hb	Haemoglobin
FEIBA®	Factor VIII inhibitor bypass activity
NOAC	New (or Novel) anticoagulant medications
PT	Prothrombin time
TT	Thrombin time = thrombin clotting time
Prothrombinex®-VF	Prothrombinex®-VF contains the concentrated human coagulation factors II, IX and X and low levels of the factors V and VII.
VTE	Venous thromboembolism

Definitions:

1. Clinically significant bleeding means:

There has been a reduction in Hb ≥ 20 g / L and /or transfusion of ≥ 2 units of red cells.

2. Life threatening bleeding means:

There is bleeding in a critical area or organ (intraocular, intracranial, intraspinal, compartment syndrome, retroperitoneal or pericardial), hypotension not responding to resuscitation.

Standards

The information in this guideline aligns with the Australian Commission on Safety and Quality in Health Care - National Safety and Quality Health Service Standards:

- > Standard 4: Medication Safety
- > Standard 7: Blood and Blood Products

Principles of the standards

The National Safety and Quality Health Service Standards propose evidence based improvement strategies to deal with gaps between current and best practice outcomes that affect a large number of patients.

- > **Standard 4: Medication Safety** – describes the systems and strategies to ensure clinicians safely prescribe, dispense and administer appropriate medicines to informed patients. The clinical workforce is supported for the prescribing, dispensing, administering, storing, manufacturing, compounding and monitoring of medicines.
- > **Standard 7: Blood and Blood Products** – describes the systems and strategies for the safe, effective and appropriate management of blood and blood products so the patients receiving blood are safe. Health service organisations must have systems in place for the safe and appropriate prescribing and clinical use of blood and blood products.

Quality, safety and risk management

Unwanted bleeding is the most common side effect of the oral anticoagulants apixaban, rivaroxaban and dabigatran and it may be serious or life threatening.

Compliance with adverse drug reaction reporting procedures is required. For further information:

- > Therapeutic Goods Association - [Advisory Committee on the Safety of Medicines \(ACSOM\)](#)
- > SA Health Preventing Adverse Drug Events [Policy Directive](#) and [Guideline](#).

Protocol

Two flow diagrams describe the treatment options available for mild, clinically significant or life threatening bleeding caused by or associated with new (or novel) anticoagulant medications (NOAC), which are grouped according to their mechanisms of action.

Refer to:

- > Fig. 1: Summary of the approach to management of a patient presenting with bleeding related to factor Xa inhibitors, **rivaroxaban** (Xarelto®) or **apixaban** (Eliquis®) - page 6.
- > Fig. 2: Summary of the approach to management of a patient presenting with bleeding related to direct thrombin inhibitor, **dabigatran** (Pradaxa®) – page 7.

Fig. 1: Summary of the approach to management of a patient presenting with bleeding related to (factor Xa inhibitors) RIVAROXABAN (Xarelto®) or APIXABAN (Eliquis®)

1. *It is essential to know the drug, the dose and the time the last dose was taken.*
2. *Creatinine clearance must be calculated.*

Bleeding patient on rivaroxaban or apixaban

- > Initiate standard resuscitation procedures as required.
- > Take blood for coagulation screen for urgent FBC, creatinine, aPTT, PT and rivaroxaban or apixaban level (2 x citrate tubes, indicate time and strength of last dose of rivaroxaban or apixaban).

Expected overall coagulation test patterns and their interpretation:

1. **Rivaroxaban**
 - > If PT is normal then rivaroxaban is unlikely to be causing a significant anticoagulant effect.
 - > Both PT and aPTT are prolonged by rivaroxaban and the response is dose dependent. PT is more sensitive than aPTT to rivaroxaban and this should be taken into consideration. If PT is prolonged (> aPTT) then rivaroxaban is causing an anticoagulant effect.
2. **Apixaban**
 - > Routine coagulation tests cannot be used for predicting the apixaban effect as these tests can be completely normal despite the presence of clinically significant drug level.

STOP RIVAROXABAN / APIXABAN THERAPY

Mild Bleeding

- > Local haemostatic measures
- > Delay next dose of rivaroxaban / apixaban or discontinue if felt appropriate by prescribing physician.

Clinically Significant Bleeding

- > **Consult on-call haematologist or critical bleeding consultant if ongoing bleeding**
- > Consider oral charcoal administration if rivaroxaban / apixaban ingestion < 4 hours prior.
- > Local haemostatic measures. Mechanical compression. Consider seeking an opinion regarding surgical intervention.
- > Maintain adequate hydration to aid drug clearance.
- > Transfusion support. Packed cell transfusion as indicated by Hb and ongoing bleeding.
- > Consider platelet transfusion if platelets < 50 x 10⁹/L or if taking antiplatelet therapy, (to correct possible contributing factors).
- > Pro-haemostatic agents. If ongoing bleeding resulting in clinical instability despite above measures, consider pro-haemostatic measures as described for life threatening bleeding

Life Threatening Bleeding

- > **Consult on-call haematologist or critical bleeding consultant**
- > Consult intensive care unit or if necessary other appropriate facility.
- > Institute measures as for clinically significant bleeding.
- > Prothrombinex-VF 50 units/kg (off licence use).
- > Tranexamic acid 15-30 mg/kg IV +/- infusion for gastrointestinal bleeds.
- > Pro-haemostatic agents are unlikely to improve outcome in patients with normal PT in case of rivaroxaban.

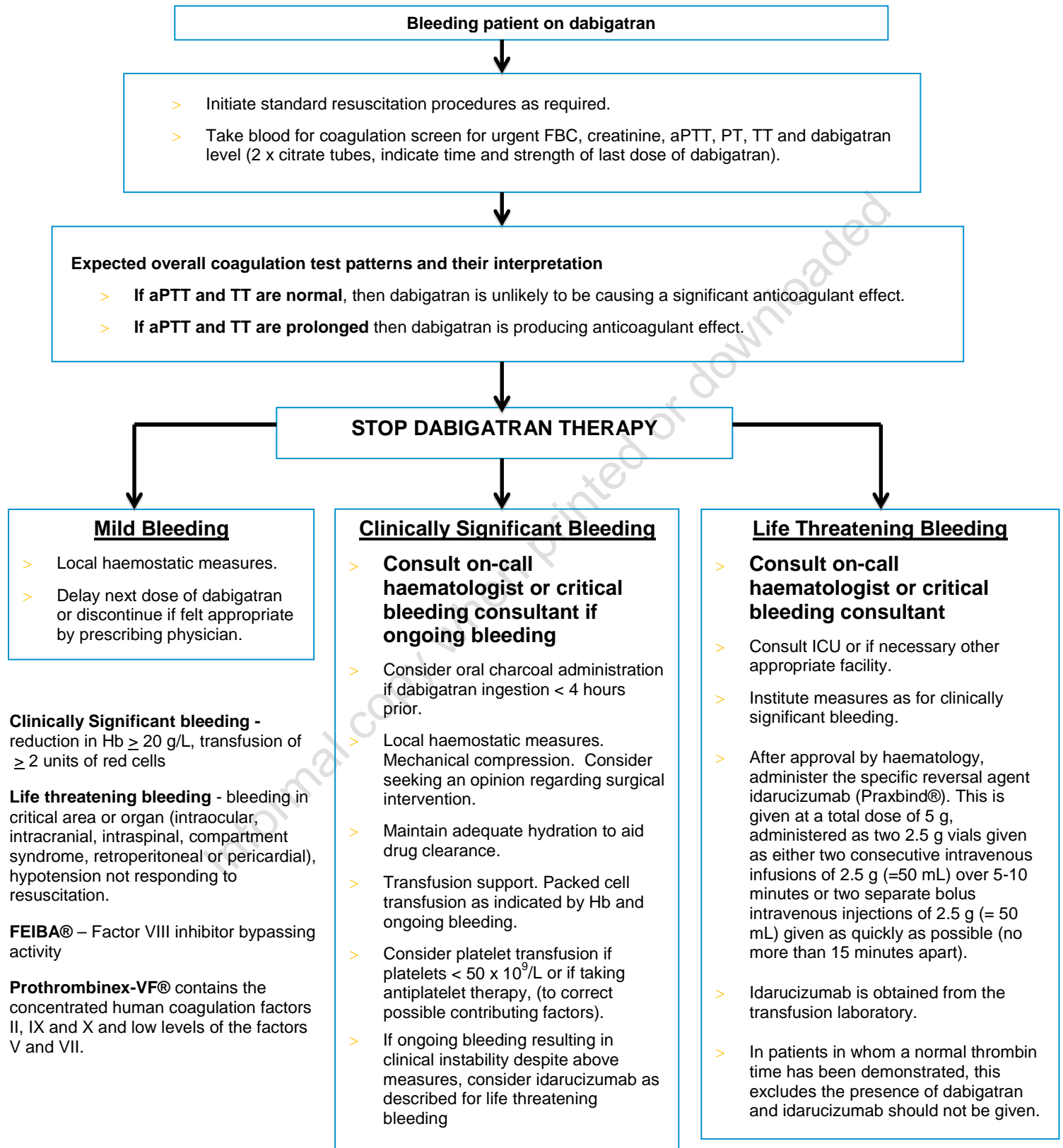
Clinically Significant bleeding - reduction in Hb > 20 g/L, transfusion of > 2 units of red cells.

Life threatening bleeding - bleeding in critical area or organ (intraocular, intracranial, intraspinal, compartment syndrome, retroperitoneal or pericardial), hypotension not responding to resuscitation.

Prothrombinex-VF® contains the concentrated human coagulation factors II, IX and X and low levels of the factors V and VII.

Fig. 2: Summary of the approach to management of a patient presenting with bleeding related to thrombin inhibitor, DABIGATRAN (Pradaxa®)

1. It is essential to know the dose and the time the last dose of dabigatran was taken.
2. Creatinine clearance must be calculated.



Acknowledgement

SA Health sincerely thanks all staff involved in the preparation and review of this guideline, in particular:

- > Dr Simon McRae, Director, Haemophilia Treatment Centre, Royal Adelaide Hospital
- > Dr Safoorah Sagheer, Haemostasis and Thrombosis Fellow, SA Pathology
- > Naomi Burgess, Director, Medicines and Technology Policy and Programs, SA Health
- > Elizabeth Campbell, Project Pharmacist, Medicines and Technology Policy and Programs, SA Health

References

1. Tran et al. New oral anticoagulants: a practical guide on prescription, laboratory testing and peri-procedural/bleeding management. *Internal Medicine Journal* 44 (2014);525-536. Available from: http://asth.org.au/downloads/NOAC_imj_12448.pdf
2. Australian Commission on Safety and Quality in Health Care - [National Safety and Quality Health Service Standards](#)
3. Therapeutic Goods Association. [Advisory Committee on the Safety of Medicines \(ACSOM\)](#)

Related documents

1. Clinical Guideline: Safe Prescribing of New Oral Anticoagulants: apixaban, rivaroxaban and dabigatran
2. [Preventing Adverse Drug Events Directive](#)
3. [Preventing Adverse Drug Events Guideline](#)
4. Recognising and Responding to Clinical Deterioration Policy
5. Recognising and Responding to Clinical Deterioration Guideline
6. [BloodSafe e-learning](#)

Appendix

1. Guideline for the administration of idarucizumab for the reversal of dabigatran

Guideline for the administration of Idarucizumab for the reversal of Dabigatran

Background: Idarucizumab is a humanised Fab fragment that binds specifically to dabigatran, resulting in rapid clearance of dabigatran from the circulation and reversal of its anticoagulant effect. Idarucizumab **does not** reverse the effect of other anticoagulants.

Indications: Use of idarucizumab has been approved for the following indications **only**;

1. Patients receiving dabigatran with overt, uncontrollable, or life-threatening bleeding that in which it is felt that reversal of anticoagulant effect will improve clinical outcome.
OR
2. Patients receiving dabigatran who require emergency surgery or other invasive procedures that cannot be delayed for at least 8 hrs and for which normal haemostasis is required.

Initial assessment of patient in whom idarucizumab may be required

1. *Confirm that patient is taking dabigatran*

In patients with life-threatening bleeding this can be done by history alone, and laboratory confirmation of presence of drug is not required. In patients in whom immediate reversal is not required, urgent blood should be taken for measurement of aPTT and where available thrombin time (TT) and dabigatran level. These results may influence the decision to administer idarucizumab in the non-urgent setting.

2. *Contact haematology on-call for advice and approval of administration*

Haematology approval is required prior to administration of drug. For patients located at the RAH, NAHLN or country locations the critical bleed haematologist should be contacted via the RAH switchboard or via transfusion on 8222 5430. At FMC and the QEH the on-call haematologist should be contacted.

3. *Additional supportive measures*

Additional supportive measures such as mechanical compression, surgical haemostasis and transfusion support should be given. Other specific pro-haemostatic agents such as prothrombinex are not required if idarucizumab is to be administered.

Dose of idarucizumab

The total dose of idarucizumab is 5 g (= 100 mL).

Each vial of idarucizumab contains 2.5 g in 50 mL.

Administration of idarucizumab

The 5 g dose is given as follows:

- two consecutive intravenous infusions of 2.5 g (=50 mL) over 5 -10 minutes each;
OR
- two separate bolus intravenous injections of 2.5 g (= 50 mL) given as quickly as possible (no more than 15 minutes apart).

Post administration considerations

1. A minority of patients will demonstrate a rebound in anticoagulant effect at 12-24 hours following reversal of dabigatran by idarucizumab. This is more likely in individuals with high initial drug levels (>500 nanogram/mL). In patients with recurrent bleeding or in who there is concern regarding post-procedural bleeding, in who the presence of drug is confirmed by elevated coagulation parameters (aPTT, TT, dabigatran level), a second dose of 5 g may be required.
2. The decision to restart anticoagulant therapy of any form should only be considered once haemostasis is secure, and should be made at a consultant level. Some active idarucizumab may remain circulating for up to 24 hours after infusion and may impact the expected efficacy of re-instituted anticoagulation with dabigatran within that time period. Idarucizumab does not impact of the effect of other anticoagulant drugs.

Additional notes

The use of idarucizumab is not yet TGA approved and is currently only available as part of a special access scheme. All adverse events require reporting and should be communicated to the initial approving haematologist.

The recommended dose of idarucizumab contains 4 g sorbitol as an excipient. Therefore, in patients with hereditary fructose intolerance, the risk of treatment with idarucizumab must be weighed against the potential benefit of such an emergency treatment.

References

1. Pollack CV, et al. Idarucizumab for dabigatran reversal. *N Engl J Med* 2015;373:511-520
2. Falavero, EJ and Lippi, G. Laboratory testing in the era of direct or non-vitamin K antagonist oral anticoagulants: a practical guide to measuring their activity and avoiding diagnostic errors. *Semin Thromb Hemost* 2015: 41:208-227.
3. Schiele F, et al. A specific antidote for dabigatran: functional and structural characterization. *Blood* 2013; 121(18):3554-3562.

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