SK Clinical Guideline 2

Dabigatran ("Pradax") and Bleeding Patients

A Consensus-Based Guidance Document

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* This guidance document was created by the Provincial Transfusion Medicine Service, with input from key medical specialists in Saskatoon, Regina as well as across the country - after consideration of the best-available evidence. Note that existing medical evidence is limited and thus this issue will require continued review as more data becomes available and as more clinical experience using dabigatran accumulates.

1.0 Introduction

Dabigatran is an oral direct thrombin inhibitor approved for use in patients with non-valvular atrial fibrillation and VTE prophylaxis following hip or knee replacement surgery. Direct thrombin inhibitors (DTIs) exert their anticoagulant effect by directly attaching to and inhibiting both free and fibrin-bound thrombin.

2.0 Purpose

The purpose of this document is to provide guidance in the management of patients who experience bleeding complications while on dabigatran. It is not intended to guide the selection of alternate oral anticoagulants.

3.0 Bleeding Risks

- In studies of atrial fibrillation, the overall bleeding risk associated with dabigatran was similar to warfarin, including the elevated bleeding risk associated with increased patient age.
- There was a significantly higher incidence of gastrointestinal bleeding and a significantly lower incidence of intracranial hemorrhage in the patients taking dabigatran (compared to warfarin).
- The main concern regarding bleeding on dabigatran is that there is no specific antidote for reversal of the anticoagulant effect.

4.0 Pharmacokinetics

- Dabigatran is rapidly absorbed with peak dabigatran levels achieved within 2 - 4 hours.
- Bioavailability is low – approximately 6%
- The half-life of dabigatran is 12-17 hours, and steady-state concentrations are reached within two to five days after multiple doses.
- Dabigatran is renally eliminated so clearance is significantly influenced by renal function, and any deterioration in renal function will prolong the half-life.

5.0 Laboratory Testing and Dabigatran

5.1 **Indications for laboratory testing:**

Currently, routine therapeutic monitoring is not indicated.

5.2 **Situations where laboratory testing may be useful to assess for residual drug effect:**

- The bleeding patient
- Preoperative setting
- Patient who may have been exposed to trauma

5.3 **Laboratory assays:**

Laboratory assays may be broadly categorized into generally available tests and specialized laboratory assays.

5.3.1 Generally available tests:

These include a prothrombin time (PT/INR), activated partial thromboplastin time (aPTT), thrombin time (TT). Dabigatran prolongs these assays; however, the degree of prolongation does NOT reliably predict plasma dabigatran levels nor does it provide an accurate assessment of risk of surgical hemorrhage in patients on dabigatran. The information provided by these assays is limited to whether there is residual dabigatran effect or not.

Note: A normal PT or aPTT does not exclude the presence of residual dabigatran. The thrombin time is typically very sensitive and, again, only provides information on presence or absence of residual drug.

5.3.2 Specialized laboratory assays:

These include ecarin clotting time (ECT) and dilute thrombin time (dTT). When appropriately calibrated, the ECT and dTT generally provide reliable information on plasma dabigatran levels. However, these assays are not widely available. In addition there is currently no information on plasma dabigatran levels and risk of hemorrhage and/or the safety of surgical or other invasive interventions.

6.0 Consensus-Based Protocol for Bleeding Management

Notes:

- There are no known specific agents to reverse the drug.
- Plasma will not reverse the drug as dabigatran will inhibit thrombin in transfused plasma.
- The only known way to remove the drug is dialysis, but this has limited efficacy and may not be practical in an actively bleeding anticoagulated patient.
- There is very little data to help guide us in managing bleeding complications on the drug:
- There is no readily available laboratory test to quantify the degree of anticoagulation:
- Standard coagulation tests (PTT, PT/INR) do not accurately reflect drug levels.
- Thrombin Time (TT) is the most sensitive to the drug.
- Fibrinogen activity testing may not be reliable on dabigatran.

6.1 For minor bleeding:

- Evaluate drug adherence and timing of last dose, current renal function (i.e., estimated creatinine clearance), whether anatomical defects may explain hemorrhage.
- Review results of locally-available coagulation tests:
  - If aPTT and TT are normal (or aPTT alone in the absence of TT availability), no drug is present. Re-evaluate for other cause of bleeding.
- Use local measures to control the bleeding. (i.e. mechanical compression, tranexamic acid 10 mg/kg iv or 25 mg/kg po, etc.)
- Keep well-hydrated to promote diuresis. Dabigatran is 80% renally-cleared.
- Replace fluids and use blood products if needed.
- Use clinical judgment to hold or continue dabigatran. Stopping the drug will decrease the continued bleeding risk. But the risk of stroke and the severity of the bleeding should be weighed.

  Consider additional factors, such as duration of the drug effects (1 -2 days in patients with normal renal function, but can be > 5 days in patients with impaired renal function) and the onset of action when restarting (peak activity within 2 – 4 hours).
- Contact regional/ provincial Transfusion Medicine Medical Director for further consultation.

6.2 For severe or life-threatening bleeding:

- Stop dabigatran.
- Assess adherence and timing of last dose. If last dose within the previous 2 hours consider administration of activated charcoal.
- Lab testing:
  - CBC, aPTT, INR, TT (if available), fibrinogen (if available), creatinine (kidney function), electrolytes (including calcium, which is necessary for adequate hemostasis).
    - If aPTT and TT are normal (or aPTT alone in the absence of TT availability), no drug is present.
    - If aPTT is normal and TT is prolonged, there is likely drug present, but the patient is unlikely to be therapeutically anticoagulated. Re-evaluate for other cause of bleeding.
    - If aPTT and TT are prolonged, then anticoagulant effect is present. Determine drug half-life based on time from last dose and creatinine clearance.
  - Repeat testing every 4 – 6 hours until bleeding has stopped.
- Control the bleeding site and provide supportive care of patient.
- Use local measures (i.e. compression, wound packing, topical/oral/IV tranexamic acid).
- Contact surgery or interventional radiology for possible embolization.
- Consider dialysis; may be able to remove 30-60% of the drug. (Best with a charcoal filter.)

- Perform blood transfusion as necessary and when appropriate products are available, use the following transfusion considerations:
  - Red blood cells (RBCs): Transfuse RBCs per institutional guidelines or to keep Hgb > 90 g/L.
  - Plasma: After the 4th unit of RBCs alone, start giving RBCs and plasma on a 1:1 ratio (to avoid dilutional coagulopathy).
  - Platelets: give 1 adult dose after 8 units RBCs/4 units plasma.
  - Cryoprecipitate: Consider 8 units of cryo if ongoing bleeding after 8 RBCs/4 plasma/1 platelet dose.

  Please note that neither plasma nor cryoprecipitate is expected to reverse the anti-coagulant effect of dabigatran.

- Contact regional/provincial transfusion medicine medical directors for further consultation.

6.3 Exceptional Measures

- Special hemostatic blood products - either the *activated* prothrombin complex concentrate called "FEIBA" (preferred) or *activated* Factor VII ("NiaStase;" preferred if FEIBA is not available) should be considered if bleeding is life threatening and all other measures to control bleeding have failed.
  - These agents do not actually reverse the drug; they overcome its effects. Thus, the correct dose is unknown.
  - There is insufficient data in the medical literature to support the immediate, upfront use of such agents
  - Thrombosis is a potential side effect of all agents, but much more so with Factor VIIa.
  - Prothrombin complex concentrates (PCCs, "Beriplex,"/"Octaplex") are less likely to reverse dabigatran however, are also less likely to cause thrombotic side effects.

- Contact regional/provincial Transfusion Medicine Medical Director for further consultation.
  - Saskatoon & Northern SK: Transfusion Medicine Medical Director - Saskatoon Health Region, (306) 655-1000
  - Regina & Southern SK: Physician on call for hematology/blood transfusion - Regina Qu'Appelle Health Region Blood Transfusion Service, (306) 766-4444

7.0 Selected References

- Connolly SJ, et al. Dabigatran versus Warfarin in Patients with Atrial Fibrillation. NEJM. Sep 17, 2009. (RE-LY)
- Eikelboom JW, et al. Risk of Bleeding With 2 Doses of Dabigatran Compared With Warfarin in Older and Younger Patients With Atrial Fibrillation: An Analysis of the Randomized Evaluation of Long-Term Anticoagulant Therapy (RE-LY) Trial. Circulation. 2011; 123: 2363-2372.
- Kaatz S, et al. Guidance on the emergent reversal of oral thrombin and factor Xa inhibitors. Am J Hematol 2012. Published online in Wiley Online Library (DOI: 10.1002/ajh.23202).
- RxFiles Trial Summary (Review) Nov 2010. www.rxfiles.ca
- FDA Website. "Pradaxa (dabigatran etexilate mesylate): Drug Safety Communication - Safety Review of Post-Market Reports of Serious Bleeding Events." Dec 7, 2011. www.fda.gov

Find the most up-to-date version of the Saskatchewan Transfusion Resource Manual and related documents at www.health.gov.sk.ca/transfusion-medicine .

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Patient with Bleeding on Dabigatran Therapy

- Initiate standard resuscitation measures, as indicated.
- Check labs: CBC, Coag's (including TT, where available), Renal function, Lytes (including Ca^{++}).
- Stop Dabigatran, determine time of last dose. Consider oral charcoal if 2 hours from last dose.
- Consult Transfusion Medicine Medical Director(s) as needed.

Mild Bleeding
(clinically determined or EBL<750mL or <15%)

- Delay or discontinue dabigatran as appropriate
- Local hemostatic measures (mechanical compression, tranexamic acid 10 mg/kg iv or 25 mg/kg po)
- Keep well-hydrated

Moderate Bleeding
(clinically determined or EBL 750mL – 2000 mL or 15-40%)

Mild Bleed measures PLUS:

- Local hemostatic measures (surgical interventions)
- Fluid replacement
- Transfusion as needed

Life-Threatening Bleeding
(clinically determined or EBL>2000mL or >40%

Moderate Bleed measures PLUS:

- Consider hemodialysis
- Consider FEIBA, Factor VIIa
- Consult TM Medical Director

Provincial Transfusion Medicine Medical Directors:

Saskatoon & Northern SK: Saskatoon Health Region - (306) 655-1000 (ask for transfusion medicine medical director)

Regina & Southern SK: Regina Qu'Appelle Health Region Blood Transfusion Service – (306) 766-4444 (ask for physician on call for hematology/ blood transfusion)

*Adaptable only under the authority of the Provincial Transfusion Medicine Medical Directors.