

Date: March 13, 2012

To: Edmonton Zone – All Medical Staff

From: The Divisions of Adult Clinical Hematology and Hematopathology

RE: **New oral anticoagulants – Direct Thrombin Inhibitors & Direct Factor Xa inhibitors**

Dear Colleagues:

New oral anticoagulants are now licensed and available in our community for a number of indications. Currently, the most widely used of these is the direct thrombin inhibitor Dabigatran (Pradax). Unlike Warfarin this drug is not affected by food, has fewer drug interactions, and does not require routine coagulation monitoring. However, this drug still carries an age and dose-related **risk of hemorrhage**, which, unlike Warfarin, **cannot be reversed**. Cases of major bleeding in patients on Dabigatran in the Edmonton and Central zones have occurred and are increasing in frequency. (At the time of this communication, no cases of Factor Xa inhibitor associated hemorrhage have been identified.) The purpose of this communication is to inform clinicians of this problem and suggest management in case of bleeding:

Laboratory assessment:

- There is currently no single laboratory test routinely available that provides specific evaluation of the anticoagulation effect of Dabigatran or other novel anticoagulants.
- Dabigatran is mostly excreted via the kidneys with a half-life of approximately 12 hours in those with normal renal function, but prolonged in those with abnormal renal function. Creatinine/GFR measurement is essential in bleeding patients.
- A normal INR and PTT should exclude the presence of significant levels of Dabigatran or other novel anticoagulants in most, but not all, patients.
- **The most sensitive test for the presence of Dabigatran is the Thrombin Time** – a normal result excludes the presence of this drug, but not the other new oral anticoagulants. The most sensitive test for the presence of Direct Factor Xa inhibitors is the PT/INR.
- There are currently no locally available tests that accurately quantifies Dabigatran anticoagulant activity or that of the other novel anticoagulants.

Management of hemorrhage in patients:

- **Discontinue the medication.**
- **Consultation with Transfusion Medicine or Clinical Hematology is strongly recommended.**
- Consider use of oral activated charcoal.
- Investigate the source of bleeding.
- Order: CBC, PT/INR, PTT, Fibrinogen, Thrombin Time, Creatinine and Cross Match.
- Provide supportive care.

Detailed additional information on both Direct Thrombin and Factor Xa inhibitors is provided in the **Appendix** posted on the AHS website at: <http://www.albertahealthservices.ca/3290.asp>

Appendix

New oral anticoagulants, Dabigatran Etexilate (Direct Thrombin Inhibitor) and Rivaroxaban (Direct Factor Xa Inhibitor) are now licensed and available in our community for Deep Vein Thrombosis (DVT) prophylaxis in hip and knee arthroplasty. Dabigatran Etexilate is also now licensed for stroke prophylaxis in the setting of nonvalvular atrial fibrillation. Other new oral agents (Apixaban, Edoxaban) are undergoing clinical trial at present. These agents have an advantage over the traditional oral anticoagulant, Warfarin (Coumadin) in that they are not affected by food, have fewer drug interactions, and do not require routine coagulation monitoring. However, like traditional anticoagulants, they carry an age and dose-related **risk of hemorrhage**.

Dabigatran is contraindicated in patients with a Glomerular Filtration Rate (GFR) <30ml/min/1.73m². Further, advancing age is a risk factor for major bleeding with Dabigatran, reinforcing the recommendation to use the lower dose in the elderly patient with atrial fibrillation (AF). The annual major bleeding risk reported in the RELY study of stroke prevention in atrial fibrillation was comparable between Warfarin (3.36%/year) and Dabigatran 150 mg bid (3.11%/year) but lower for Dabigatran 110 mg bid (2.71%/year). The incidence of intracranial hemorrhage was significantly lower for both doses of Dabigatran [0.30%/year with 150 mg bid and 0.23%/year with 110 mg bid] than with Warfarin [0.74%/year]. Although anticoagulant monitoring is not necessary with Dabigatran, occasional monitoring with serum creatinine and GFR is prudent; every 6-12 months in individuals with normal renal function or more frequently with GFR in the range of 30-60ml/min/1.73m². Similarly occasional monitoring of liver function in patients on Rivaroxaban as well as the more traditional anticoagulant Coumadin would be sensible.

There have been cases of major bleeding in patients on Dabigatran in the Edmonton and Central zones that prompted this communication. Not all of these patients would have met the criteria to have been enrolled in the RELY trial. Some of these patients had low GFRs that were due to Acute or Chronic Renal Failure that have failure to clear the direct thrombin inhibitor.

1. **There currently is no single laboratory test routinely available that provides specific evaluation of anticoagulation effect of Dabigatran or Rivaroxaban. Specific assays are not currently available in Alberta Health Services.** The following laboratory tests can provide qualitative assessment:

1. **PT/INR**

The INR is relatively insensitive to Dabigatran and may be normal or only minimally increased, in patients on therapeutic doses of Dabigatran. It is likely to be increased at supra-therapeutic levels of Dabigatran.

Rivaroxaban increases the INR at therapeutic levels BUT the target INR level in these individuals is unknown, may vary depending on lab and is NOT equivalent to target levels on Warfarin. It is also important to note that point of care testing (fingerstick INRs) are not recommended if evaluating transition from Coumadin to Dabigatran as the point of care INRs are significantly higher than those obtained by venipuncture.

2. **activated Partial Thromboplastin Time (aPTT)**

Using the instrument / reagent combinations present in the Edmonton zone, it has been demonstrated that **our PTT is relatively sensitive to Dabigatran**. Most individuals on Dabigatran will have a PTT prolongation but this is usually lower than that seen in individuals on Unfractionated Heparin (UFH) and may be only marginally above the normal reference range. Most individuals with low (trough) levels of Dabigatran are expected to give PTT prolongations of a few seconds, but the occasional patient may not. Thus, a normal PTT result will exclude the presence of significant circulating Dabigatran in most patients.

Rivaroxaban is expected to cause mild PTT prolongations in most patients with therapeutic or supratherapeutic levels.

3. **Fibrinogen level**

There is no effect on Fibrinogen levels, as measured in the Edmonton Zone, from any of these agents at therapeutic or even moderately supra-therapeutic levels. However, in cases of markedly supra-therapeutic levels it is theoretically possible that the Fibrinogen level may be factitiously decreased. Of greater clinical relevance is that low Fibrinogen levels (eg. due to bleeding) will also prolong the Thrombin Time.

4. **Thrombin Time**

This assay is very sensitive to the effects of Dabigatran. Even sub-therapeutic Dabigatran dosing will result in Thrombin Time prolongation beyond the analytical range (greater than 120 seconds). For this reason it cannot be used to adjust Dabigatran dosing to therapeutic levels. However, a **normal** Thrombin Time excludes the presence of Dabigatran. Thrombin Time is the only test not affected by transfusion therapy and can be used to reliably assess for Dabigatran clearance.

Note: a prolonged Thrombin Time can also be caused by Heparin or low Fibrinogen levels.

Rivaroxaban, being a Direct Factor Xa inhibitor, does NOT prolong the Thrombin Time at all. Thrombin Time is not routinely available in many laboratories and is currently only available at the University of Alberta Hospital site.

In cases of uncertainty the following tests should be ordered:

Anticoagulant	Test
Direct Thrombin Inhibitor (i.e. Dabigatran)	aPTT Thrombin time Thrombin Time post-hepzyme Fibrinogen level
Direct Factor Xa Inhibitor (i.e. Rivaroxaban)	PT/INR

- **If are aware of or suspect Rivaroxaban or Direct Xa Inhibitor** - the presence of a normal INR indicates a lack of significant anti-Xa effect.
- **If suspect Dabigatran or Direct Thrombin Inhibitor** - The presence of a normal Thrombin Time excludes Dabigatran. The presence of a normal PTT may indicate the lack of significant Dabigatran in most patients. A normal Fibrinogen level with a significantly prolonged Thrombin Time suggests the presence of Dabigatran.
 - However, if the patient could have received Heparin, or there may be contaminating Heparin from a line draw, the demonstration of persistently prolonged Thrombin Time after “hepzyme” confirms the presence of Dabigatran.

Note: other Direct Thrombin Inhibitors such as Lepirudin or Argatroban will produce indistinguishable lab results from Dabigatran but these are given by continuous Intravenous (IV) infusion, and have a short half life and thus are only present in hospitalized patients.

2. In the acutely bleeding patient known or suspected to be on Dabigatran or Rivaroxaban:

There is no evidence based reversal strategy to guide management, nor is there an antidote (unlike Warfarin) to reverse the anticoagulant effect in acutely bleeding patients. However, the following steps may be appropriate:

Consultation with Transfusion Medicine or Clinical Hematology is strongly recommended.

- Discontinue the medication.
- If the medication was taken within the prior 2-4 hours, consider the use of oral activated charcoal.
- Investigate the source of bleeding and initiate mechanical compression, radiologic intervention or surgical / interventional hemostasis if appropriate as soon as possible.
- Immediately draw laboratory investigations – CBC, PT/INR, PTT, Fibrinogen and Thrombin Time, Creatinine and Cross Match.
- Consider the use of anti-fibrinolytics ie. Tranexamic acid 10 mg/kg IV or 25 mg/kg po to the nearest 500 mg.
- Reverse other anticoagulants and stop anti-platelet agents if present.
- Since renal impairment is associated with accumulation of Dabigatran and may be associated with a bleeding tendency in its own right, it is sensible to maintain aggressive diuresis to maximize drug excretion. Dabigatran is dialyzable, although incompletely, so consider dialysis early in the bleeding patient on Dabigatran with renal impairment. Due to high plasma protein binding, Rivaroxaban is not expected to be dialyzable.
- Blood transfusion support as necessary.
 - Provide red cell and platelet support as indicated by clinical and laboratory parameters. In particular, consider platelet transfusion in the bleeding patient who has received anti-platelet medication even though the platelet count may be normal.
 - Since these medications are inhibitors, routine transfusion of plasma has not been successful for reversal.
 - There are case reports that describe the effective use of factor concentrates such as FEIBA, recombinant Factor VIIa (rFVIIa) or prothrombin complex concentrates (PCC; octaplex or Beriplex) - these agents may be considered depending on availability of product and severity of bleeding. However, there is reasonable evidence that neither PCC nor rFVIIa are effective at reversing the anticoagulant effect of Dabigatran. There is slightly more evidence of efficacy in humans of the use of PCC when dealing with bleeding associated with Rivaroxaban, possibly by overwhelming the inhibitor with Factor X. Availability of these products is variable across the zone – consultation with Transfusion Medicine on call early on in the identification of patients who may require reversal is strongly recommended.

References:

1. Connolly SJ, Ezekowitz MD, Yusuf S et al. Dabigatran versus Warfarin in patients with atrial fibrillation. *N Engl J Med* 2009; 361(9):1139-51.
2. Van Ryn J, Stanieg J, Haertter S et al. Dabigatran etexilate – a novel reversible oral direct thrombin inhibitor: interpretation of coagulation assays and reversal of anticoagulant activity. *Thromb Haemost.* 2010; 103:1116-1127.
3. Eerenberg ES, Kamphuisen PW, Sijpkens MK et al. Reversal of Rivaroxaban and Dabigatran by Prothrombin Complex Concentrate: a randomized placebo-controlled, crossover study in healthy subjects. *Circulation* epub Sept 6, 2011
4. Eikelboom JW, Wallentin L, Connolly SJ 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 (RELY) trial. *Circ* 2011;123:2363-2372.
5. Favalaro E.J. et al. *Pathology.* 2011; 43: 682-692.