

**Date:** June 17, 2014

**To:** All Zones: Physicians, Pharmacy Services, and Laboratory Staff

**From:** AHS Laboratory Services

**Re:** Thrombin Time for Assessment of Dabigatran (Pradaxa®) Clearance.

---

## PLEASE POST OR DISTRIBUTE AS WIDELY AS APPROPRIATE

---

### Key Messages:

1. The Thrombin Time (TT) assay is available across Alberta as a routine test. Access to STAT testing is more limited. However, STAT testing will become available at additional sites across the province in the near future. Local clinicians will be notified as the test becomes available at each site. See Table
2. The TT is the most sensitive test available for assessing dabigatran (Pradaxa®) **CLEARANCE** from the circulation. Where such testing is needed the TT is recommended instead of, or in addition to, the aPTT. Of note, TT will not measure the amount of dabigatran or assess FEIBA effectiveness.
3. The concentration below which dabigatran loses its anticoagulant effect is uncertain. However, on the basis of indirect evidence, expert opinion is that dabigatran levels <30 ng/ml can be considered negligible.
4. To add an additional margin of error for assay imprecision, laboratories will append a comment to each result specifying the TT (in sec) that corresponds to 20 ng/ml of dabigatran.
5. Because of variations in methodology, the TT threshold specified will vary between sites, and may also vary over time with changes in lot (batch) of reagent. Clinicians are urged to **READ THE APPENDED COMMENT** with each result.
6. A simultaneous INR, aPTT and fibrinogen level may be of value for follow-up. Decreased fibrinogen levels may also affect the TT.

### Background:

Dabigatran (Pradaxa) was licensed for the treatment of Non-Valvular Atrial Fibrillation in October 2010. Though routine monitoring of this agent is not necessary, testing for drug clearance may be needed in select circumstances.

Manufacturer data [1] as well as independent inter-laboratory comparison studies [2] initially suggested that the aPTT is an adequate test for assessment of dabigatran clearance. However, these results were either obtained *in vitro* or from otherwise healthy individuals. In contrast, post-marketing studies indicate that real patients may demonstrate greater variability in results with some showing a normal aPTT even in the presence of clinically significant dabigatran concentrations [3,4].

The TT has previously been shown to be extremely sensitive to dabigatran [1, 4] and remains prolonged even at very minimal concentrations. The concentration threshold at which this drug's anticoagulant effect becomes insignificant is not known precisely. Some experts suggest that a level <30 ng/ml is safe for surgical intervention [5]. In consultation with expert groups within Alberta including the Laboratory Services Provincial Hematology Network, the Provincial Venous

Thromboembolism-Anticoagulation Management Steering Committee, and the Cardiovascular Health & Stroke Strategic Clinical Network there was general agreement that 20 ng/ml was a reasonable threshold to adopt.

### Thrombin Time (TT) Interpretation:

The TT is a simple coagulation test in which patient plasma is mixed with active Thrombin and the time until clot formation is measured in seconds. The TT is very sensitive to the presence of any Thrombin inhibitors in the plasma. This includes oral Thrombin inhibitors such as dabigatran, as well as parenteral Thrombin inhibitors such as heparin (both unfractionated and LMWH), argatroban, lepirudin and bivalirudin. In fact, the TT is so sensitive to all of these agents that the results are often above the analytic range of the test (reported as >XXX sec) at therapeutic levels. Therefore the TT is most useful for assessment of drug **CLEARANCE**. It has less value in the context of overdose assessment where aPTT and PT-INR may be of more use.

Another cause for a prolonged TT that may be encountered is a low fibrinogen level which can occur with massive hemorrhage, disseminated intravascular coagulation or post-thrombolytic therapy. In this context measurement of a fibrinogen level would be particularly useful. Uncommon causes of TT prolongation include dysfibrinogenemia, some paraproteins, and high levels of Fibrinogen Degradation Products (FDPs).

In addition to being very sensitive to Direct Thrombin Inhibitors (such as dabigatran) the test is also more specific than the PT or the aPTT. The TT is NOT affected by variations in clotting factor levels (except fibrinogen), the Lupus Anticoagulant, and Vitamin K antagonism/deficiency. The TT is also NOT affected by the other novel oral anticoagulants which belong to the class of drugs known as Direct Xa Inhibitors, including Rivaroxaban (Xarelto®) and Apixaban (Eliquis®). Furthermore, treatment with Prothrombin Complex Concentrates, whether activated (eg. FEIBA) or inactivated (eg. Octaplex or Beriplex) does not affect the TT. While these agents (especially FEIBA) are sometimes used off-label to manage life-threatening dabigatran associated bleeding they are not true reversal agents and therefore do not have any affect on circulating dabigatran levels or the TT.

### References:

1. van Ryn J, Stangier J, Haertter S, Liesenfeld KH, Wienen W, Feuring M, Clemens A. Dabigatran etexilate-- a novel, reversible, oral direct thrombin inhibitor: interpretation of coagulation assays and reversal of anticoagulant activity. *Thromb Haemost* 2010, 103: 1116-1127.
2. Kitchen,S. UK NEQAS for Blood Coagulation: New Oral Anticoagulant Survey Results. April 2012 Supplementary Exercise. Sheffield, UK.
3. Antovic JP, Skeppholm M, Eintrei J, Boija EE, Soderblom L, Norberg EM, Onelov L, Ronquist-Nii Y, Pohanka A, Beck O, Hjemdahl P, Malmstrom RE. Evaluation of coagulation assays versus LC-MS/MS for determinations of dabigatran concentrations in plasma. *Eur J Clin Pharmacol* 2013, 69: 1875-1881.
4. Stang L, Nahiriak S, Butcher K, Szkotak A. Dabigatran Assessment in Patients with Acute Complications using Routine Coagulation Assays. *Blood Coagul Fibrinolysis* 2014, X: XX-XX (In Press).
5. Gilles Pernod, Pierre Albaladejo. Prise en charge d'un patient traité par dabigatran ou rivaroxaban au long cours, présentant une hémorragie ou nécessitant une chirurgie urgente [French]. Groupe d'interet en Hemostase Peri-operatoire. Version 2.0 , 20\_02\_2013.

### Inquiries and feedback may be directed to:

Dr. Artur Szkotak, Hematopathologist, University of Alberta Hospital, 780-407-7104

**This bulletin has been reviewed and approved by:**

Dr. Carolyn O'Hara, Deputy Zone Clinical Department Head, Diagnostic Health – Laboratory & Pathology,  
North Zone at 780-407-3477 or Carolyn.OHara@albertahealthservices.ca

<b>Zone/Site</b>	<b>Instrument</b>	<b>Target Implementation Date</b>
<b>Edmonton Zone</b> <ul style="list-style-type: none"> <li>University (UAH)</li> <li>Royal Alex (RAH)</li> </ul>	Stago Evolution	June 23, 2014
<ul style="list-style-type: none"> <li>Grey Nuns (GN)</li> <li>Miscercordia (MIS)</li> <li>Sturgeon</li> </ul>	Stago Compact	June 23, 2014
<b>Calgary Zone</b> <ul style="list-style-type: none"> <li>Calgary Lab Services (CLS)</li> </ul>	ACL Top	July 2, 2014
<ul style="list-style-type: none"> <li>Canmore</li> </ul>	CA560	July/Aug 2014
<ul style="list-style-type: none"> <li>High River</li> </ul>	ACL500	July/Aug 2014
<b>South Zone</b> <ul style="list-style-type: none"> <li>Chinook Regional Hospital</li> </ul>	CA1500	July 2, 2014
<ul style="list-style-type: none"> <li>Medicine Hat</li> </ul>	CA1500/560	July/Aug 2014
<b>Central Zone</b> <ul style="list-style-type: none"> <li>Red Deer</li> </ul>	ACL TOP	July 2014
<ul style="list-style-type: none"> <li>Camrose</li> </ul>	ACL1000	July/Aug 2014
<ul style="list-style-type: none"> <li>Drumheller</li> </ul>	CA560	July/Aug 2014
<ul style="list-style-type: none"> <li>Wainwright</li> </ul>	ACL1000	July/Aug 2014
<ul style="list-style-type: none"> <li>Wetaskiwin</li> </ul>	CA560	July/Aug 2014
<b>North Zone</b> <ul style="list-style-type: none"> <li>Cold Lake</li> </ul>	ACL Elite	July/Aug 2014
<ul style="list-style-type: none"> <li>Grande Prairie</li> </ul>	CA1500	July 2 2014
<ul style="list-style-type: none"> <li>Hinton</li> </ul>	ACL1000	July/Aug 2014
<ul style="list-style-type: none"> <li>Peace River</li> </ul>	CA560	July/Aug 2014
<ul style="list-style-type: none"> <li>Westlock</li> </ul>	ACL Elite Pro	July/Aug 2014
<b>North Zone Dynalife</b> <ul style="list-style-type: none"> <li>Fort McMurray</li> <li>High Level</li> </ul>	ACL Elite Pro	July/Aug 2014