

**USE AND INTERPRETATION OF LABORATORY COAGULATION
TESTS IN PATIENTS WHO ARE RECEIVING A NEW ORAL
ANTICOAGULANT (DABIGATRAN, RIVAROXABAN, APIXABAN)**



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TARGET AUDIENCE: All Canadian health care professionals: family physicians, internists, anesthesiologists, surgeons, interventional radiologists, nurse practitioners, pharmacists.

OBJECTIVES:

- To describe the effect of new oral anticoagulants (NOACs) on laboratory coagulations tests which are widely available and consist of: prothrombin time (PT), international normalized ratio (INR), activated partial thromboplastin time (aPTT) and thrombin clotting time (TCT).
- To inform clinicians about how to use and interpret coagulation tests in patients who are bleeding or require an elective surgery/procedure.

ABBREVIATIONS:

aPTT	activated partial thromboplastin time
CrCl	creatinine clearance
ECT	ecarin clotting time
FEIBA	factor eight inhibitor bypass activity
INR	international normalized ratio
LMWH	low-molecular-weight heparin
NOAC	new oral anticoagulant
PCC	prothrombin complex concentrate
PT	prothrombin time
rFVIIa	activated recombinant factor VII
TCT	thrombin clotting time

VTE	venous thromboembolism
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BACKGROUND:

Three NOACs (dabigatran, rivaroxaban, apixaban) are approved for clinical use in Canada based on findings from large, well-designed, randomized trials.

LABORATORY TEST INTERPRETATION AND PATIENT MANAGEMENT:

The effects of NOACs on laboratory coagulation tests are summarized in the **Table**.

Effect of Dabigatran on Coagulation Tests:

- Dabigatran can potentially affect the PT/INR, aPTT and TCT but these tests should not be used to monitor the anticoagulant effect of NOACs.
- Dabigatran has a peak effect 1-3 hours after oral intake and if testing is done within this time, it can lead to an elevated PT/INR, aPTT, and TCT. For example, soon after dabigatran intake, the INR may be slightly elevated to 1.5-1.8 (normal: 0.8-1.2), and the aPTT may be elevated to 50-80 seconds or higher (normal: 22-35 seconds). The TCT will be typically > 150 seconds (normal: 20-30 seconds).
- After this peak effect period, the effect of dabigatran on the PT/INR and aPTT diminishes but there may be some residual effect on the TCT, which is the most sensitive test to detect an anticoagulant effect of dabigatran.

What do Normal Coagulation Tests Mean in Dabigatran-Treated Patients?

- In dabigatran-treated patients, although normal aPTT may indicate that plasma levels of the drug are sufficiently low to allow surgery or thrombolytic therapy there remains uncertainty about this, in part due to variable sensitivity of different coagulation assays. Local validation of assay sensitivity is advisable before clinical decisions are based on assay results.
- A normal TCT indicates no detectable residual anticoagulant effect and is the best way to completely exclude a residual anticoagulant effect.

Effect of Rivaroxaban and Apixaban on Coagulation Tests:

- Rivaroxaban and apixaban are considered together since they are in the same drug class and have similar effects on coagulation tests; however, apixaban's effect on coagulation tests is less pronounced than rivaroxaban.
- These drugs can potentially affect the PT/INR and aPTT but have no discernable effect on the TCT. Of these tests, the effect is variable on the PT/INR and on the aPTT, depending on the sensitivity of assays used.
- Rivaroxaban and apixaban have a peak effect 1-3 hours after oral intake and if PT/INR and aPTT testing is done within this time period, this can lead to elevated PT/INR and aPTT. For example, soon after oral intake, INR may be elevated to 1.7-2.5, the aPTT may be slightly elevated (35-40 seconds), and the TCT will not be affected.
- After this peak effect, the effect of rivaroxaban and apixaban on PT/INR and aPTT diminishes but there may be a residual effect on these measures.

What do Normal Coagulation Tests Mean in Rivaroxaban-Treated and Apixaban-Treated Patients?

- In rivaroxaban- and apixaban-treated patients, a normal PT/INR and aPTT may be found at trough despite the presence of therapeutic levels of the drug. No routine coagulation test can reliably exclude a residual anticoagulant effect.

Need for Periodic Laboratory Testing in NOAC-Treated Patients?

Dabigatran-Treated Patients:

- Serum creatinine and estimated creatinine clearance (e.g. using Cockcroft-Gault equation) should be done approximately every 6-12 months in patients with moderately-impaired renal function.
- There is no laboratory test that can reliably monitor its anticoagulant effect in a manner similar to how the INR is used to monitor warfarin therapy or how the aPTT is used for heparin therapy.
- A dilute TCT (Hemoclot®) is more reliable than other coagulation assays to measure the anticoagulant effect of dabigatran and may be considered for patients who require urgent surgery or anticoagulant reversal; however, this test is not widely available and there are (as of yet) no established standards for interpreting test results.

Rivaroxaban-Treated and Apixaban-Treated Patients:

- Serum creatinine and estimated creatinine clearance (e.g. using Cockcroft-Gault equation) should be done approximately every 6-12 months in patients with moderately-impaired renal function.
- There is no conventional laboratory test that can reliably monitor the anticoagulant effect of rivaroxaban or apixaban.
- Although anti-factor Xa level testing might be used to measure the anticoagulant effect, this is not advisable because test interpretation is problematic. In other words, there is no 'therapeutic anti-factor Xa level' as for low-molecular-weight heparins (LMWHs) and the only clinical use of this test may be to determine if there is a residual (or excessive) anticoagulant effect.

CONCLUSIONS:

To date there are no studies that have managed NOAC-treated patients based on coagulation laboratory test results, and the guidance provided herein is based on studies assessing the effects of the NOACs in laboratory-based studies.

SPECIAL CONSIDERATIONS:

Laboratory Testing in Patients who are Bleeding:

Laboratory testing may help in the management of patients who are bleeding, especially if it is life-threatening. In gastrointestinal bleeding, the PT/INR and aPTT should be done irrespective of whether a patient is receiving an anticoagulant. The TCT should be done to screen for and evaluate dabigatran effects when the medication history is unknown or incomplete. The timing of the last dose of the anticoagulant should be obtained to help interpret laboratory results. Note that coagulation tests can be influenced by many other conditions, and their interpretation must take into consideration the clinical setting.

Dabigatran-Treated Patients:

- In dabigatran-treated patients who have a normal aPTT, the residual anticoagulant effect is likely to be very low such that treatment with general resuscitation measures (\pm packed red cell transfusion) is sufficient.
- In patients with an elevated aPTT and/or an unmeasurable TCT (i.e. > 150 seconds), a significant anticoagulant effect of dabigatran may be present. The use of coagulation factor concentrates such as prothrombin complex concentrates (PCC) has

been suggested as a nonspecific method of reversing dabigatran, especially in patients who have serious bleeding (see NOAC: Bleeding guide) but their clinical effectiveness in such circumstances has not been well-studied.

Rivaroxaban-Treated and Apixaban-Treated Patients:

- Since no assay can reliably predict low drug levels of either rivaroxaban or apixaban, a normal PT/INR, aPTT or TCT should not be used to suggest the absence of any significant residual anticoagulant effect.
- The use of coagulation factor concentrates (PCC, factor eight inhibitor bypass activity [FEIBA] or activated recombinant factor VII [rFVIIa]) has been suggested as a nonspecific method of reversing rivaroxaban or apixaban but their clinical effectiveness has not been well-studied.

Laboratory Testing in Patients who require an Elective Surgery/Procedure:

As discussed in the clinical guide NOAC: Peri-Operative Management, in patients who are receiving NOACs and require an elective surgery/procedure, there is no need for routine laboratory testing outside of what would be done prior to any surgery/procedure.

Dabigatran-Treated Patients:

- For most elective surgery/procedure, dabigatran should be stopped prior to surgery based on the latest calculated creatinine clearance value. No hemostasis monitoring prior to surgery is recommended (see NOAC: Peri-Operative Management guide).
- For patients undergoing surgery requiring anesthesia or surgery types associated with a high risk for bleeding (e.g. intracranial, cardiac), a normal TCT excludes the presence of any residual anticoagulant effect.

Rivaroxaban-Treated and Apixaban-Treated Patients:

- Since no assay can reliably predict low plasma drug levels of either rivaroxaban or apixaban, a normal PT/INR or aPTT should not be used to suggest the absence of any significant residual anticoagulant effect.

PEDIATRICS:

There are no studies evaluating the use of NOACs in children although studies are underway. NOACs in children are not recommended until dosing, safety and efficacy are confirmed (see Pediatrics guide). Pediatricians with expertise in thromboembolism should manage, where possible, pediatric patients with thromboembolism. When this is not possible, a

combination of a neonatologist/pediatrician and an adult hematologist, supported by consultation with an experienced pediatric hematologist, is recommended.

REFERENCES:

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Table. Effect of New Oral Anticoagulants on Laboratory Coagulation Tests

Laboratory Test¶	Dabigatran	Rivaroxaban or Apixaban
Prothrombin time (PT) and International normalized ratio (INR)	Dose-dependent effect† (usually INR<2.0 at peak blood levels)	Rivaroxaban can increase PT/INR, apixaban has a minimal effect
Activated partial thromboplastin time (aPTT)	Increases aPTT	Dose-dependent effect†
Thrombin clotting time (TCT)	Increases TCT‡ If normal, no detectable anticoagulant effect	No effect expected†
Anti-factor Xa level	No effect	Can be used to measure anticoagulant effect. Specific rivaroxaban and apixaban calibrators are required. These assays may not be available in emergency situations.

Other specialized tests:	Hemoclot® and ECT have been shown to be
Dilute thrombin time (Hemoclot®)	more reliable than routine coagulation tests
Ecarin clotting time (ECT)	to determine dabigatran levels. These assays
Anti-IIa testing (Hemochrom)	may not be available in emergency situations

† Drug overdose or bioaccumulation may increase these coagulation tests;

‡ TCT is very sensitive to presence of dabigatran and even low (potentially negligible) serum levels may lead to elevated TCT;

¶ Results are variable according to the coagulation reagent used, and a dose-response curve measured with dabigatran, rivaroxaban and apixaban calibrators may assist in the local interpretation of these assays.

Please note that the information contained herein is not to be interpreted as an alternative to medical advice from your doctor or other professional healthcare provider. If you have any specific questions about any medical matter, you should consult your doctor or other professional healthcare providers, and as such you should never delay seeking medical advice, disregard medical advice or discontinue medical treatment because of the information contained herein.