NOACS/DOACS*: COAGULATION TESTS

Thrombosis Canada
Thrombose Canada

OBJECTIVES:

- To describe the effect of the newer direct oral anticoagulants (DOACs) on routine laboratory coagulation tests: prothrombin time (PT), international normalized ratio (INR), activated partial thromboplastin time (aPTT), and thrombin clotting time (TCT).
- To describe tests used to accurately quantify DOAC levels.
- To discuss how clinicians should use and interpret coagulation tests in patients taking a DOAC who are bleeding or require elective surgery or an invasive procedure.

BACKGROUND:

Four DOACs, a direct thrombin inhibitor (dabigatran) and three direct factor Xa inhibitors (apixaban, edoxaban, and rivaroxaban) are approved for clinical use in Canada for various indications, based on findings from large randomized trials.

LABORATORY COAGULATION TEST INTERPRETATION IN PATIENTS RECEIVING DOACS:

The effects of DOACs on routine laboratory coagulation tests are summarized in **Table 1.**

TABLE 1. EFFECT OF NEW/NOVEL ORAL ANTICOAGULANTS ON LABORATORY COAGULATION TESTS

Laboratory Test	Dabigatran	Apixaban, Edoxaban, or Rivaroxaban
Prothrombin time (PT) and International Normalized Ratio (INR)[¶]	Variable effect (usually INR<2.0 at peak blood levels)[†]	Rivaroxaban and edoxaban can increase PT/INR; apixaban has a minimal effect[†]
Activated partial thromboplastin time (aPTT)[¶]	Non-linear increase[†]	Rivaroxaban and edoxaban can increase aPTT; apixaban has a minimal effect[†]
Thrombin clotting time (TCT) (Not widely available)	Increases TCT[‡]; if normal, no detectable anticoagulant effect	No effect
Anti-factor Xa level (Not widely available)	No effect	Can be used to accurately quantify the anticoagulant effect. Specific apixaban, edoxaban, or rivaroxaban calibrators are required

*NOACs/DOACs = Non-vitamin K antagonist Oral AntiCoagulants, also known as Direct Oral AntiCoagulants

Laboratory Test	Dabigatran	Apixaban, Edoxaban, or Rivaroxaban
Other specialized tests: • Dilute thrombin time (Hemoclot®) • Ecarin clotting time (ECT) (Not widely available)	Hemoclot® and ECT can be used to accurately quantify dabigatran levels	No effect

¶ Results may vary according to the PT or aPTT reagent used. A dose-response curve of PT and aPTT using dabigatran, apixaban, edoxaban, and rivaroxaban calibrators may assist in the local interpretation of these assays.

† Drug overdose or bioaccumulation may increase these coagulation tests.

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

EFFECT OF DABIGATRAN ON COAGULATION TESTS:

There is currently no readily available, routine laboratory test that can reliably monitor the anticoagulant effect of dabigatran in a manner similar to how the INR is used to monitor warfarin therapy or how the aPTT is used for intravenous (IV) unfractionated heparin (UFH) therapy; therefore, these laboratory tests should NOT be used to monitor the anticoagulant effect of dabigatran.

- Dabigatran is a direct thrombin inhibitor. It has a peak effect 1-3 hours after oral intake and, if testing is done within this time period, it often leads 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), the aPTT may be elevated to ~50-80 seconds or higher (normal: 22-35 seconds) and the TCT will usually be markedly elevated above the laboratory reference range. After this peak effect period, the effect of dabigatran on the PT/INR and aPTT diminishes, although there will be a prolonged effect on the TCT, which is the most sensitive test to detect the anticoagulant effect of dabigatran.
- The relationship between dabigatran anticoagulant effect and any of the routine laboratory tests of coagulation is variable, depending on the reagent sensitivity.
- A commercially calibrated dilute TCT (Hemoclot®) can be used to quantify the anticoagulant effect of dabigatran and may be considered for patients. However, this test is not widely available and there are not yet established therapeutic reference intervals for interpreting test results.

WHAT DO NORMAL COAGULATION TESTS MEAN IN DABIGATRAN-TREATED PATIENTS?

- In some dabigatran-treated patients, a normal aPTT indicates that plasma levels of the drug are sufficiently low to allow surgery or thrombolytic therapy in acute ischemic stroke; however, **a normal aPTT does not exclude a clinically important anticoagulant effect.**
- A normal TCT indicates no detectable residual anticoagulant effect and is the most sensitive way to completely exclude any residual anticoagulant effect; however, the TCT may be elevated in the

presence of clinically insignificant levels of dabigatran, sometimes for a prolonged period of time. Moreover, the TCT is not a widely available test.

EFFECT OF APIXABAN, EDOXABAN, AND RIVAROXABAN ON COAGULATION TESTS:

There is currently no readily available, routine laboratory test that can reliably monitor the anticoagulant effect of apixaban, edoxaban, and rivaroxaban in a manner similar to how the INR is used to monitor warfarin therapy or how the aPTT is used for IV UFH therapy; therefore, these laboratory tests should NOT be used to monitor the anticoagulant effect of apixaban, edoxaban, or rivaroxaban.

- Apixaban, edoxaban, and rivaroxaban are factor Xa inhibitors. Edoxaban and rivaroxaban may affect the PT/INR and aPTT but have no effect on the TCT. However, the effect on the PT/INR is variable, depending on the sensitivity of the PT or aPTT reagent used. Apixaban has a minimal effect on PT/INR and aPTT.
- Apixaban achieves peak plasma concentration approximately 3 hours after ingestion. Even if testing is done at this time, the effect of apixaban on PT/INR and aPTT is much less pronounced than for edoxaban and rivaroxaban and these tests are not useful to assess if apixaban is present in clinically important or greater quantities. TCT is not affected.
- Edoxaban has a peak effect approximately 1-2 hours after ingestion. It prolongs PT/INR and aPTT in a dose dependent manner but both assays are insufficiently sensitive at low therapeutic levels and reagent-dependent. Therefore, a normal PT/INR or aPTT does not exclude the presence of "on therapy" or greater edoxaban concentrations. TCT is not affected.
- Rivaroxaban has a peak effect 1-3 hours after oral intake and, if testing is done within this time, it often leads to an elevated PT/INR and aPTT. For example, soon after oral intake, the INR may be elevated to ~1.7-2.5 and the aPTT may be slightly elevated (35-40 seconds). After this peak effect, the effect of rivaroxaban on PT/INR and aPTT diminishes but there may be a residual effect on these tests. A normal PT/INR or aPTT does not exclude the presence of "on therapy" or greater rivaroxaban concentrations. TCT is not affected.
- Specific anti-Xa assays with drug-specific calibrators (different than those used to assess LMWH activity) can be used to quantify the anticoagulant effect of apixaban, edoxaban, and rivaroxaban. However, these tests are not widely available and there are no established therapeutic reference intervals for interpreting test results. Furthermore, the anti-Xa assays specific for low-molecular-weight heparins (LMWHs) or UFH should NOT be used to monitor the anticoagulant effect of apixaban, edoxaban, or rivaroxaban.

WHAT DO NORMAL COAGULATION TESTS MEAN IN APIXABAN, EDOXABAN, OR RIVAROXABAN-TREATED PATIENTS?

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

LABORATORY TESTING IN PATIENTS RECEIVING A DOAC WHO ARE BLEEDING:

Laboratory testing may help in the management of patients who are bleeding, especially if it is life-threatening. The timing of the last dose of the anticoagulant and assessment of renal function should be obtained to help interpret laboratory results. Patients with moderate or severe bleeding should urgently have the following laboratory tests: CBC, PT/INR, aPTT, creatinine.

Dabigatran-treated patients who are bleeding:

- In bleeding patients with a highly elevated aPTT (e.g. greater than 80 sec) and/or an unmeasurable TCT (i.e. value greater than the critical limit of the laboratory's reference range), a significant anticoagulant effect of dabigatran is likely.
- If the aPTT is normal in a dabigatran-treated patient, the residual anticoagulant effect is generally low enough that usual treatment for a bleed unrelated to anticoagulation is sufficient.
- **See the Clinical Guide: NOACs/DOACs: Management of Bleeding**

Apixaban, edoxaban, and rivaroxaban-treated patients who are bleeding:

- Since no common coagulation assay can reliably predict the drug levels of apixaban, edoxaban, or rivaroxaban, a normal PT/INR or aPTT should not be used to suggest the absence of a significant residual anticoagulant effect.
- **See the Clinical Guide: NOACs/DOACs: Management of Bleeding**

LABORATORY TESTING IN PATIENTS WHO REQUIRE AN ELECTIVE SURGERY/INVASIVE PROCEDURE:

As discussed in the **Clinical Guide: NOACs/DOACs: Peri-operative Management**, 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/procedures, dabigatran should be stopped prior to surgery based on a calculated creatinine clearance and the bleeding risk associated with the procedure. **See the Clinical Guide: NOACs/DOACs: Perioperative Management.** No coagulation testing prior to surgery is recommended.

Apixaban, edoxaban, and rivaroxaban-treated patients:

- For most elective surgery/procedures, apixaban, edoxaban, or rivaroxaban, should be stopped prior to surgery based on a calculated creatinine clearance and the bleeding risk associated with the procedure. See the Clinical Guide: **NOACs/DOACs: Perioperative Management**. No coagulation testing prior to surgery is recommended.

PEDIATRICS:

There are no management studies evaluating the use of DOACs in children; therefore, DOACs are not recommended in children until dosing, safety and efficacy are confirmed.

OTHER CONSIDERATIONS:

- For each of the DOACs, serum creatinine and estimated creatinine clearance (e.g. using the Cockroft-Gault equation) should be done at baseline, at least yearly, and in clinical situations

when renal function may deteriorate because these drugs are at least partially renally cleared and will accumulate in renal insufficiency.
- If specific assays for quantifying DOAC activity are available in your center and you feel there is a benefit in determining this activity in a specific patient, discussion with the coagulation laboratory director is recommended in order to evaluate the relevance of the indication and guidance as to the interpretation of the results.

OTHER RELEVANT THROMBOSIS CANADA CLINICAL GUIDES:

- Apixaban (Eliquis®)
- Dabigatran (Pradaxa®)
- Edoxaban (Lixiana®)
- NOACs/DOACs: Comparison and Frequently Asked Questions
- NOACs/DOACs: Management of Bleeding
- NOACs/DOACs: Perioperative Management
- Rivaroxaban (Xarelto®)

REFERENCES:

Baglin T. The role of the laboratory in treatment with new oral anticoagulants. J Thromb Haemost 2013;11(Suppl 1):122-128.

Cuker A et al. Laboratory measurement of the anticoagulant activity of the non-vitamin K oral anticoagulants. J Am Coll Cardiol 2014;64(11):1128-1139.

Gosselin R et al. Comparison of the effect of the anti-Xa direct oral anticoagulants apixaban, edoxaban, and rivaroxaban on coagulation assays. Int J Lab Hematol 2016;38(5):505-513.

Samuelson BT et al. Laboratory assessment of the anticoagulant activity of direct oral anticoagulants: a systematic review. Chest 2017;151(1):127-138.

Date of Version: 2018Nov16