NOACS/DOACS*: COAGULATION TESTS

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OBJECTIVES:

- To describe the effect of the newer direct oral anticoagulants (DOACs) on laboratory coagulation tests which are widely available: prothrombin time (PT), international normalized ratio (INR), activated partial thromboplastin time (aPTT), and thrombin clotting time (TCT).
- 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 (dabigatran, rivaroxaban, apixaban, and edoxaban) are approved for clinical use in Canada based on findings from large randomized trials.

LABORATORY COAGULATION TEST INTERPRETATION WITH DOACS:

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

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

Laboratory Test¶	Dabigatran	Rivaroxaban, Apixaban or Edoxaban
Prothrombin time (PT) and International normalized ratio (INR)	Variable effect (usually INR<2.0 at peak blood levels)†	Rivaroxaban can increase PT/INR; apixaban has a minimal effect†
Activated partial thromboplastin time (aPTT)	Non-linear increase†	Dose-dependent effect†
Thrombin clotting time (TCT)	Increases TCT‡ If normal, no detectable anticoagulant effect	No effect
Anti-factor Xa level	No effect	Can be used to measure anticoagulant effect. Specific rivaroxaban, apixaban and edoxaban calibrators are required. These assays are not widely available.
Other specialized tests: Dilute thrombin time (Hemoclot®) Ecarin clotting time (ECT)	Hemoclot® and ECT are more reliable than INR, aPTT, TCT in quantifying	No effect

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

Laboratory Test¶	Dabigatran	Rivaroxaban, Apixaban or Edoxaban
	dabigatran levels but are not widely available.	

¶ Results are variable according to the coagulation reagent used. A dose-response curve of PT or aPTT using dabigatran, rivaroxaban, apixaban and edoxaban 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) serum levels may lead to elevated TCT

EFFECT OF DABIGATRAN ON COAGULATION TESTS:

There is currently no readily available, common 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 IV heparin 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 standard laboratory tests of coagulation is highly variable.
- A commercially calibrated dilute TCT (Hemoclot®) is more reliable than other coagulation assays to measure the anticoagulant effect of dabigatran and may be considered for patients. However, this test is not widely available and there are not yet established standards 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 and may do so for a prolonged period of time.

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EFFECT OF RIVAROXABAN, APIXABAN AND EDOXABAN ON COAGULATION TESTS:

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

- Rivaroxaban, apixaban and edoxaban are Factor Xa inhibitors. Rivaroxaban may affect the PT/INR and aPTT but has no effect on the TCT. However, the effect on the PT/INR is variable, depending on the sensitivity of the PT reagent used. Apixaban has a minimal effect on PT/INR and aPTT.
- 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), but the TCT will not be affected. After this peak effect, the effect of rivaroxaban on PT/INR and aPTT diminishes but there may be a residual effect on these tests.
- The effect of apixaban on PT/INR and aPTT is much less pronounced than for rivaroxaban.
- Specific anti-Xa assays with drug-specific calibrators (different than those used to assess LMWH activity) can be used to measure the anticoagulant effect of rivaroxaban, apixaban and edoxaban. However, these tests are not widely available and there are no established standards for interpreting test results. Furthermore, the anti-Xa assays specific for Low-molecular-weight heparins (LMWHs) or Unfractionated heparin (UFH) should NOT be used to monitor the anticoagulant effect of rivaroxaban or apixaban.

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

- In rivaroxaban-, apixaban-, and edoxaban-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

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Rivaroxaban-treated and apixaban-treated patients who are bleeding:

- Since no common coagulation assay can reliably predict the drug levels of either rivaroxaban or apixaban, 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: Peri-Operative Management. No coagulation testing prior to surgery is recommended.

Rivaroxaban-treated, apixaban-treated and edoxaban-treated patients:

- For most elective surgery/procedures, rivaroxaban, apixaban or edoxaban 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: Peri-Operative Management**. No coagulation testing prior to surgery is recommended.

PEDIATRICS:

There are no 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 measuring 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 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

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- NOACs/DOACs: Peri-Operative Management
- Pediatrics: New Anticoagulants
- Rivaroxaban (Xarelto®)

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