DOACs: Coagulation Tests

Thrombosis Canada
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* Direct Oral AntiCoagulants

Objectives:

- To describe the effect of 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, or TT).
- 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 with DOACs:

The effects of DOACs on routine laboratory coagulation tests are summarized in **Table 1.** Since the international normalized ratio (INR) and the international sensitivity index (ISI) used in the INR calculation are based on vitamin K antagonist sensitivity and not DOAC sensitivity, laboratories may consider reporting the PT (seconds) in addition to the INR.

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 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 shows dose dependent prolongation until approx 200 ng/mL†
Thrombin clotting time (TCT, or TT) (Not widely available)	Increases TCT‡. Normal TCT excludes the presence of dabigatran	No effect
Anti-factor Xa level (Drug specific levels not widely available)	No effect	Anti Xa assays can be used to accurately quantify the anticoagulant effect. Specific apixaban, edoxaban, or rivaroxaban calibrators are required
Other specialized tests: • Dilute thrombin time assay (dTT) • Ecarin chromogenic assay (ECA) and Ecarin clotting time (ECT) (not widely available) • Anti-Factor IIa assay (Chromogenic)	dTT, ECA/ECT, anti-Factor IIa can be used to accurately quantify dabigatran levels	No effect

¶ Results will vary according to the PT or aPTT reagent used and its sensitivity to the DOAC. 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 elevate the PT and aPTT.
‡ TCT is very sensitive to presence of dabigatran and even low (potentially negligible) plasma levels may lead to elevated TCT results.
* Reagent and dose dependent

Effect of Dabigatran on Coagulation Tests:

There is currently no routinely available laboratory test that can reliably assess the anticoagulant effect of dabigatran in a manner similar to how the INR is used to assess adequacy of warfarin therapy or how the aPTT is used to monitor 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 greater than twice the upper limit of the laboratory's reference range 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/TT, 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.
- Commercially available dilute thrombin time (dTT) assays, Ecarin-based assays or chromogenic anti-Factor IIa assays can be used to quantify the anticoagulant effect of dabigatran and may be

considered for patients. However, these assays are 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, the aPTT remains normal in the presence of dabigatran in the on-therapy range.
- A normal TCT excludes the presence of significant dabigatran concentrations and is the most sensitive way to completely exclude residual effect of dabigatran; however, the TCT may be elevated in the presence of clinically insignificant levels of dabigatran, sometimes for a prolonged period of time following last dose of dabigatran. Moreover, the TCT is not a widely available test.

Effect of Rivaroxaban, Apixaban and Edoxaban on Coagulation Tests:

There is currently no routinely available laboratory test that can reliably assess the anticoagulant effect of apixaban, edoxaban, and rivaroxaban in a manner similar to how the INR is used to assess the adequacy of warfarin therapy or how the aPTT is used to monitor 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. Apixaban has a minimal effect on PT/INR and aPTT and 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 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 the intensity of apixaban's anticoagulant effect. 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 edoxaban effect is 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 PT may be elevated to greater than twice the upper limit of the laboratory's reference range and the aPTT may be slightly elevated. After this peak effect, the effect of rivaroxaban on PT/INR and aPTT diminishes but there may be a residual effect on these tests even at trough levels (24 hours after last intake). A normal PT/INR or aPTT does not exclude the presence of on therapy or greater rivaroxaban concentrations. TCT is not affected.
- Anti-Xa assays with drug-specific calibrators (different than those used to assess low molecular weight heparin [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. Anti-Xa assays calibrated for LMWHs or UFH should NOT be used to assess for the anticoagulant effect of apixaban, edoxaban, or rivaroxaban, however LMWH anti Xa assays can identify patients with clinically important apixaban, edoxaban and rivaroxaban drug levels. In addition, antithrombin supplemented anti-factor Xa methods should not

be used as these methods tend to overestimate DOAC levels and are not validated by the manufacturers.

What do normal coagulation tests mean in apixaban-treated, edoxaban-treated and 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, it excludes above on-therapy levels of dabigatran but does not exclude on therapy levels. **See the Clinical Guide: 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: DOACs: Management of Bleeding**

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.
- While new assays are being offered, such as TEG and ROTEM and other point-of-care testing, the utility of these assays in the measurement of DOACs is limited and should be interpreted with caution.

Other Relevant Thrombosis Canada Clinical Guides:

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

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