OPEN

# Periprocedural Management of Direct Oral Anticoagulants Should Be Guided by Accurate Laboratory Tests

**Accepted for publication:** May 19, 2016.

***To the Editor:***

We read with interest the recent discussion[1,2] about the 2015 American Society of Regional Anesthesia and Pain Medicine guidelines concerning interventional spine and pain procedures in patients on direct oral anticoagulants (DOACs).[3] We agree that the interruption of DOACs should not be based only on their respective half-life but also on the residual drug concentration. Indeed, a recent multicenter study showed a high interindividual variability of DOACs' plasma concentration. Furthermore, a poor correlation between renal function and plasma concentration of rivaroxaban, apixaban, and dabigatran was found, except for dabigatran measurements at trough.[4] Douketis et al stated recently that stopping dabigatran 48 hours before the procedure in patients with creatinine clearance greater than 50 mL/min may not be long enough to achieve normal coagulation tests in greater than 95% of patients. Indeed, in the prospective study of Douketis et al,[5] the mass spectrometry (LC-MS/MS) measured a dabigatran level greater than 20 ng/mL in approximately 16% of patients undergoing high bleeding risk procedures.

However, some issues need to be addressed regarding the laboratory assays. Contrary to the statement of Benzon et al,[1] it should be mentioned that specific tests to measure DOACs are more widely available than in the past years, and some of them are already CE marked and easily available in the European Union (ie, The Hemoclot Thrombin Inhibitor [HTI] and the STA-Ecarin Chromogenic Assay II [ECA-II]). The US Food and Drug Administration is now considering an expansion of the availability of these tests in laboratories in the United States. Regarding the interpretation of the laboratory tests made by Douketis et al in their study, we have the following comments.

First, the activated partial thromboplastin time can be normal in the presence of therapeutic concentrations of dabigatran and is therefore not recommended for the detection of low dabigatran plasma concentration. In addition, activated partial thromboplastin time is not specific to dabigatran and the sensitivity depends on the reagent and the coagulometer.[6]

Second, the thrombin time (TT) shows the highest sensitivity toward dabigatran. In the study of Douketis et al,[5] TT was higher than the upper limit of the reference range in 43% of patients undergoing a high bleeding risk surgery. This percentage could be different in other laboratories, as TT is not standardized and is affected by many variables (ie, type of thrombin or the clot detection method).[6] Therefore, it is not possible to draw conclusions from multicenter studies in which centers use different procedures for TT. Thus, a normal TT can only reasonably exclude the presence of clinically relevant concentrations of dabigatran.

Third, concerning the LC-MS/MS, the authors should have mentioned if their measurements include acyl-glucuronides, which can account for 20% of total dabigatran. Nevertheless, this proportion seems to be smaller for low dabigatran concentrations.[6]

Finally, the conventional HTI (a diluted TT) is affected by a limit of quantitation between 30 and 50 ng/mL,[6] and not 20 ng/mL as reported by the authors.[5] This limit of quantitation was not able to measure accurately DOAC concentrations encountered in the perioperative setting. Therefore, it is recommended to adapt the calibration and use an appropriate method for the measurements of low DOAC concentrations (ie, using the HTI LOW or the ECA-II for dabigatran) as they were found more accurate than the standard method (HTI).[6]

These laboratory assays are helping physicians to adapt the period of interruption of DOACs to achieve residual plasma concentrations allowing high bleeding procedures. For example, Spyropoulos et al[7] increased the period of arrest for dabigatran before a high bleeding procedure in patients with creatinine clearance greater than 50 mL/min, from 48 hours in the first prospective study to 72 hours. Thus, despite their attractive pharmacokinetic properties, the high interindividual variability of plasma concentrations observed with DOACs supports further studies with accurate laboratory tests to validate a unique periprocedural management.

**Sarah Lessire, MD**
Université catholique de Louvain
CHU UCL Namur
Department of Anesthesiology
Namur Thrombosis and Hemostasis Center (NTHC), Namur Research Institute for Life Sciences (NARILIS)
Yvoir, Belgium

**Jonathan Douxfils, PharmD, PhD**
Université de Namur
Department of Pharmacy
Namur Thrombosis and Hemostasis Center (NTHC), NARILIS
Namur, Belgium

**Anne-Sophie Dincq, MD**
Université catholique de Louvain
CHU UCL Namur
Department of Anesthesiology
Namur Thrombosis and Hemostasis Center (NTHC), NARILIS
Yvoir, Belgium

**François Mullier, PharmD, PhD**
Université catholique de Louvain
CHU UCL Namur, Haematology Laboratory, Namur Thrombosis and Hemostasis Center (NTHC), NARILIS
Yvoir, Belgium

*The authors declare no conflict of interest.*



## REFERENCES

1. Benzon HT, Lindholm P, Huntoon MA. Direct oral anticoagulants: correlation of laboratory monitoring with safe interventional pain procedures. *Reg Anesth Pain Med*. 2016;41:123–124.
2. Douketis JD, Syed S, Schulman S. Periprocedural management of direct oral anticoagulants: comment on the 2015 American Society of Regional Anesthesia and Pain Medicine guidelines. *Reg Anesth Pain Med*. 2016;41: 127–129.
3. Narouze S, Benzon HT, Provenzano DA, et al. Interventional spine and pain procedures in patients on antiplatelet and anticoagulant medications: guidelines from the American

Society of Regional Anesthesia and Pain Medicine, the European Society of Regional Anaesthesia and Pain Therapy, the American Academy of Pain Medicine, the International Neuromodulation Society, the North American Neuromodulation Society, and the World Institute of Pain. *Reg Anesth Pain Med*. 2015;40:182–212.

4. Testa S, Tripodi A, Legnani C, et al. Plasma levels of direct oral anticoagulants in real life patients with atrial fibrillation: results observed in four anticoagulation clinics. *Thromb Res*. 2016; 137:178–183.
5. Douketis JD, Wang G, Chan N, et al. Effect of standardized perioperative dabigatran interruption on the residual anticoagulation effect at the time of surgery or procedure. *J Thromb Haemost*. 2016;14:89–97.
6. Douxfils J, Pochet L, Lessire S, Vancraeynest C, Dogné JM, Mullier F. Mass spectrometry in the therapeutic drug monitoring of direct oral anticoagulants. Useful or useless? [published online ahead of print March 3, 2016] *TrAC Trends Anal Chem*.
7. Spyropoulos AC, Al-Badri A, Sherwood MW, Douketis JD. Periprocedural management of patients receiving a vitamin K antagonist or a direct oral anticoagulant requiring an elective procedure or surgery. *J Thromb Haemost*. 2016; 14:1–11.

## Reply to Dr Lessire et al

**Accepted for publication:** July 27, 2016.

***To the Editor:***

We thank Lessire and associates for their interest[1] in our work.[2] We agree with their first point that a normal activated partial thromboplastin time (aPTT) may not exclude a clinically important effect of dabigatran.[3] The aPTT assay we used (Siemens Dade Actin FS, Malvern, Pennsylvania) is considered a more sensitive assay but there is a need for additional study comparing the sensitivity of different aPTT assays to measure dabigatran's anticoagulant effect and we are in the process of doing this. Their second point seems to infer that clinicians should rely on a normal thrombin clotting time to exclude a residual anticoagulant effect of dabigatran. However, the thrombin clotting time can be abnormal in patients who likely have a small, clinically unimportant residual anticoagulant effect of dabigatran. We are concerned that measuring such a test may, if abnormal, lead to unnecessary postponement of a surgery/procedure or, perhaps, inappropriate use of idarucizumab to reverse this presumed anticoagulant effect.[4] As regard their final 2 points, we agree with the need to use an appropriately calibrated dilute thrombin time assay to measure dabigatran's anticoagulant effect and also agree with their point regarding the interpretation of dabigatran plasma levels when measured using mass spectrometry/high-performance liquid chromatography.

Taken together, the comments by Lessire and associates highlight the urgent need for further real-world clinical research to (a) determine and standardize which tests (and which assay types) are best able to reliably measure the residual anticoagulant effect of dabigatran (and other direct oral anticoagulants) after treatment interruption in patients who require a surgery/procedure, and (b) to determine what residual anticoagulant levels are clinically important—that is, the level that confers an increased risk for bleeding in a variety of perioperative settings.[5]

**James Douketis, MD**
**Sam Schulman, MD, PhD**
Department of Medicine
McMaster University
Hamilton, Ontario, Canada

**Summer Syed, MD, MSc**
Department of Anesthesiology
McMaster University
Hamilton, Ontario, Canada

*The authors declare no conflict of interest.*

### REFERENCES

1. Lessire S, Douxfils J, Dincq AS, Mullier F. Periprocedural management of direct oral anticoagulants should be guided by accurate laboratory tests. *Reg Anesth Pain Med*. 2016;41: 787–788.
2. Douketis JD, Syed S, Schulman S. Periprocedural management of direct oral anticoagulants: comment on the 2015 American Society of Regional Anesthesia and Pain Medicine guidelines. *Reg Anesth Pain Med*. 2016;41:127–129.
3. Douxfils J, Mani H, Minet V, et al. Non-VKA oral anticoagulants: accurate measurement of plasma drug concentrations. *Biomed Res Int*. 2015;2015:345138.
4. Levy JH, Ageno W, Chan NC, et al. When and how to use antidotes for the reversal of direct oral anticoagulants: guidance from the SSC of the ISTH. *J Thromb Haemost*. 2016;14:623–627.
5. Spyropoulos AC, Al-Badri A, Sherwood MW, Douketis JD. Periprocedural management of patients receiving a vitamin K antagonist or a direct oral anticoagulant requiring an elective procedure or surgery. *J Thromb Haemost*. 2016; 14:875–885.

## Use Your EYES

**Accepted for publication:** June 23, 2016.

***To the Editor:***

We read with great interest the article entitled "Primary failure of thoracic epidural analgesia in training centers: the invisible elephant?" by Tran et al,[1] focusing on the primary failure of thoracic epidurals in teaching centers mainly due to insufficient training, reduced exposure during residency, and lack of supervisors' experience.

Mastering techniques in our practice is a common goal and should be scored before actually performing any procedure on a patient. Technology and medical industries made huge steps forward developing sophisticated models, manikins, and simulators for every medical scenario,[2] helping trainees and residents the world over increase and master their skills. Despite the undiscussed usefulness of those simulators, a thing to focus on is the practical aspect: they are expensive and not portable, so it is difficult to achieve the 1:1 ratio of the simulators and trainees.

In teaching epidural, we developed a lightweight, small, Easy Yellow ligament Epidural Simulator (EYES). It has the following 2 characteristics:

1. replicable
2. simulates the loss of resistance (LOR).

This simulator is made up of 2 layers of a particular gummy-like sponge (from the package of the Echelon Flex 45; Ethicon Endo-Surgery LLC, Somerville, New Jersey) and a layer of wadding in between (Fig. 1; left). This sponge has almost no leakage of fluid when a forced injection is performed, up to more than 20 psi, tested with the B-Smart Injection Pressure Monitor (B. Braun, Melsungen, Germany) (Fig. 1; upper right). This EYES was tested by skilled physicians in epidurals and they judged the simulator to closely resemble the LOR in a clinical scenario.

Residents and trainees can perform punctures without costs, trying every type of syringe and technique with either air or saline. They can also see how deep the tip of the needle went through the EYES when the LOR is felt, comparing the different techniques and sensations (Fig. 1; lower right).

Our trainees and residents now first experience the LOR technique on this simulator and then perform an ultrasound scan of the spine[3] before performing their first epidural on a patient. This method of training has improved residents' confidence and allowed teachers to better evaluate their skills before letting them perform a real