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Therapeutic Monitoring of Direct Oral Anticoagulants—Back to the Future?

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This Commentary relates to the article by Bernier et al on pages 472–477.

Since the initial reassuring results of the RE-LY trial,[1] clinical use of direct oral anticoagulants (DOACs) has increased exponentially, and today they play a central role not only in the prevention of cardioembolic thrombotic events with subsequent predominant neurological injury in patients with atrial fibrillation but also many other indications, such as prevention and treatment of deep vein thrombosis, pulmonary embolism, or acute coronary syndrome.[2,3] This success story is based on the following 3 key aspects: (1) data from a remarkable and still growing number of large randomized controlled clinical trials providing overwhelming evidence that DOACs generally are at least equivalent to, with a tendency for an improved risk–benefit ratio, vitamin K antagonists (VKAs) in many clinical indications for anticoagulation; (2) a growing body of personal experience from treating physicians, overall generally validating the aforementioned positive trial findings in clinical practice; and (3), possibly most important, among the specific benefits accounting for wide clinical acceptance of DOACs not only for treating physicians but particularly patients, is the merit that until now no need for laboratory monitoring and regular adaption of medication have been defined.

On the downside, like in other anticoagulants, bleeding events remain prevalent as a major complication of DOAC therapy,[4] questioning patients and physicians whether and to what extent and dosage oral anticoagulation should be prescribed in high-risk constellations for bleeding, renal insufficiency, or elderly patients even in otherwise broadly accepted indications.

In this issue of JCVP, Bernier et al[5] question the "noninferior but easier to use than VKA" concept, generally strived for by all major trials at least targeting atrial fibrillation. The authors prospectively measured the plasma levels of dabigatran and rivaroxaban by high-pressure liquid chromatography—tandem mass 11 spectrometry (HPLC-MS/MS)—revealing that patients after bleeding events were more prone to have particularly high DOAC concentrations, whereas patients with thrombosis were more likely to have specifically low DOAC concentrations. The main risks associated with hemorrhages were abnormal DOAC concentrations beyond the 95th percentile, a high HAS–BLED score, the patient's age, and the creatinine blood level while the main risk associated with thrombosis was solely a DOAC concentration below the fifth percentile. This study thus demonstrates that both major anticoagulation side effects, bleeding as well as thrombotic complications, are clearly correlated with out of range plasma DOAC levels in a clinical scenario.

At first sight, this finding might not seem to be particularly surprising because pathophysiological considerations would suggest the same, and several large randomized controlled clinical trials have shown that DOAC treatment without testing of plasma levels is generally safe and efficient. Therefore, routine *regular repetitive* testing of DOAC plasma concentrations and possible dose adaption in analogy to the way physicians are familiar with for decades from treating patients with vitamin K antagonists might probably

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neither be particularly innovative nor of great clinical use. However, closely looking further for the practical meaning of the current findings, the story has potentially other exciting implications for daily clinical practice.

First, testing of DOAC plasma concentrations might render decision making of DOAC dosage selection at therapy initiation much easier for the clinician. Although there is overwhelming evidence from recent trials that adequately high dosing is crucial for clinical efficacy of anticoagulation treatment, at the same time there is a known tendency for drug underdosing in daily clinical practice, typically in those patients who are at a specifically high risk for thrombotic complications, such as in renal insufficiency or elderly patients.[6,7] Here, measuring individual actual plasma concentrations could greatly facilitate choosing the right dose from the very start of treatment. Second, pharmacological interactions between DOACs and other drugs have been described.[8] Here again, measurement of DOAC plasma concentration could reassure physicians to be in the therapeutic range and help prevent high-risk constellations for either thrombotic or bleeding events. And third, because bleeding as well as thrombotic complications are not uncommon in patients with indication for anticoagulation, testing for ideal drug levels after such events might enable physicians to take the right consequences, which might be resuming previous medication without changes, chose to switch to another dose or drug agent, or favor completely different therapeutic options, such as propose interventional left atrial appendage closure for protection of stroke in atrial fibrillation.

There are also several additional potential interesting future implications for measurement of DOAC plasma concentrations. Just to give one example, combined anticoagulation with antiplatelet therapy has been proposed and tested in several clinical indications often with predominantly positive[9] but sometimes also negative net effects.[10] Respective findings might be re-thought and therapeutic recommendations adapted taking into account measurements of DOAC plasma concentration. Most important, conversely to what we all are familiar with from clinical practice in VKA therapy for many years, potential usefulness of testing for DOAC plasma concentrations might be apparent even if not performed repetitively—eg, every other week—but only once or if indicated as suggested above, to confirm or contradict the chosen DOAC agent and dose for specific indications and clinical scenarios. Here, the most important next step would be development of a standardized, easy-to-use laboratory method to reliably measure plasma DOAC levels. There is reason enough by now.

REFERENCES

1. Connolly SJ, Ezekowitz MD, Yusuf S, et al; RE-LY Steering Committee and Investigators. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med.* 2009;361:1139–1151.
2. Kuno T, Ueyama H, Takagi H, et al. Meta-analysis of antithrombotic therapy in patients with atrial fibrillation undergoing percutaneous coronary intervention. *Am J Cardiol.* 2020;125:521–527.
3. Mekaj YH, Mekaj AY, Duci SB, et al. New oral anticoagulants: their advantages and disadvantages compared with vitamin K antagonists in the prevention and treatment of patients with thromboembolic events. *Ther Clin Risk Manag.* 2015;11:967–977.
4. Udayachalerm S, Rattanasiri S, Angkananard T, et al. The reversal of bleeding caused by new oral anticoagulants (NOACs): a systematic review and meta-analysis. *Clin Appl Thromb Hemost.* 2018;24:117S–126S.
5. Bernier M, Lancrerot SL, Parassol N, et al. Therapeutic drug monitoring of direct oral anticoagulants may increase their benefit/risk ratio. *J Cardiovasc Pharmacol.* 2020 [epub ahead of print].
6. López-López JA, Sterne JAC, Thom HHZ, et al. Oral anticoagulants for prevention of stroke in atrial fibrillation: systematic review, network meta-analysis, and cost effectiveness analysis. *BMJ.* 2017;359:j5058.
7. Miyazaki M, Matsuo K, Uchiyama M, et al. Inappropriate direct oral anticoagulant dosing in atrial fibrillation patients is associated with prescriptions for outpatients rather than inpatients: a single-center retrospective cohort study. *J Pharm Health Care Sci.* 2020;6:2.
8. Lim G. Interaction between NOACs and other drugs increases bleeding risk. *Nat Rev Cardiol.* 2017;14:696–697.
9. Lopes RD, Heizer G, Aronson R, et al; AUGUSTUS Investigators. Antithrombotic therapy after acute coronary syndrome or PCI in atrial fibrillation. *N Engl J Med.* 2019;380:1509–1524.
10. Dangas GD, Tijssen JGP, Wöhrle J, et al; GALILEO Investigators. A controlled trial of rivaroxaban after transcatheter aortic-valve replacement. *N Engl J Med.* 2020;382:120–129.