Direct oral anticoagulants: does one dose fit all? Why, when and how testing

Armando Tripodi[1,2]

[1]IRCCS Ca' Granda Ospedale Maggiore Policlinico Foundation, Angelo Bianchi Bonomi Hemophilia and Thrombosis Center, Milan; [2]Fondazione Luigi Villa, Milan, Italy

ABSTRACT

Direct oral anticoagulants (DOAC) are commonly prescribed using fixed-dose regimens, based on the assumption of predictable pharmacokinetics and a favorable balance between efficacy and safety. As a result, laboratory assessment is often considered unnecessary in patients receiving DOAC. However, increasing evidence from clinical trials and real-world studies challenges this "one-dose-fits-all" paradigm, demonstrating marked interindividual variability in drug exposure. Importantly, extreme plasma concentrations have been associated with an increased risk of thrombotic events or bleeding complications. This article revisits the role of the clinical laboratory in the management of patients treated with DOAC, clearly distinguishing routine dose adjustment from targeted measurement in selected clinical scenarios. It discusses situations in which laboratory testing may meaningfully support clinical decision-making, as well as practical considerations regarding DOAC measurement and their interference with commonly used hemostatic assays. Overall, a more nuanced, patient-centered use of laboratory testing may improve the safety and effectiveness of DOAC therapy.

Key words: anticoagulation, thrombosis, hemorrhage, monitoring, measuring

Introduction

Direct oral anticoagulants (DOAC) are widely used across the world and have replaced vitamin K antagonists (VKA) in many, but not all clinical indications.[1] The story of DOAC began many years ago with ximelagatran, a direct thrombin inhibitor that represents the predecessor of dabigatran. The program on ximelagatran clinical development was presented to the Cardiovascular and Renal drug Advisory Committee (CRAC) of the Food and Drug Administration in September 2004. The committee analyzed data, produced on ximelagatran, for the long-term secondary prevention of venous thromboembolism (VTE) after standard treatment of acute VTE, long-term prevention of stroke and other thromboembolic complications in patients with atrial fibrillation, and short-term prevention of VTE in patients undergoing knee replacement surgery.[2] Ximelagatran liver toxicity led CRAC to conclude that the benefit risk ratio of ximelagatran was unfavorable for the proposed indications.[2] In 2006 ximelagatran was withdrawn from the market[3] and was substituted with dabigatran. Since than other DOAC have been developed and included in the therapeutic armamentarium for the treatment/prevention of thrombosis in patients with cardiovascular diseases. Among the main advantages of DOAC over VKA one can list the prompt onset or offset of their action and their favorable pharmacokinetics, making the dose reached in blood after administration much more predictable than VKA. The latter property has been exploited in clinical trials in which DOAC have been given at fixed dose without adjustment by laboratory testing. These trials showed good efficacy/safety when compared with the gold standard VKA. Hence, DOAC were registered to be given at fixed dose based only on patients' characteristics and the value of the clinical laboratory, once considered as the cornerstone of the treatment with VKA, started to be debated in many instances (probably) for purely marketing reasons. This article overviews the situations when the laboratory may help clinicians to make a better management of patients on DOAC.

Corresponding author: Armando Tripodi, Angelo Bianchi Bonomi Hemophilia and Thrombosis Center, Via Pace 9, 20122 Milan, Italy. E-mail: armando.tripodi@unimi.it

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The role of the clinical laboratory

Clinicians may request the laboratory assistance to manage patients on anticoagulants for two main reasons. *"Monitoring"* that implies the measurement of the blood drug levels, which

is then used for dose-adjustment. This applies to VKA, unfractionated heparin and few other antithrombotic drugs. *"Measuring"* that implies the measurement of the drug levels, which are then used to make decision in special situations. Unfortunately, the distinction between *monitoring* and *measuring* has not been taken in due consideration and the fact that DOAC do not require dose-adjustment has been considered as evidence that the laboratory was no longer needed to manage patients on DOAC. The next paragraphs discuss the situations where the laboratory assistance is helpful.

Monitoring (dose-adjustment)

Although the concept of *"one-dose-fits-all"* that emerged from the clinical trials is widely adopted, hints from the literature and practice suggest that a subgroup of patients may benefit from dose-adjustment. For example, dabigatran plasma concentrations have been measured post-hoc for plasma samples collected during the RELY-trial and were then confronted with the frequency of stroke/major bleeding in patients with atrial fibrillation during the follow up. It emerged that the rate of bad outcomes was higher for those patients with extreme plasma concentrations.[4] Testa *et al*.[5] reported low drug levels and thrombotic complications in high-risk atrial fibrillation patients treated with DOAC. Siedler *et al*.[6] in their study of patients treated with DOAC for atrial fibrillation reported that the rate of recurrent stroke was higher in patients with low dabigatran or apixaban plasma concentrations than in those with higher levels. The MAS (measure and see) study[7,8] measured DOAC plasma concentrations one month after initiation of treatment. Patients were then followed up to 1.5 years to record thrombotic or bleeding complications. The rate of bleeding or thrombosis were higher for patients with extreme (low or high) DOAC plasma concentrations. Finally, Godino *et al*.[9] reported results from a case-control study that assessed DOAC levels among 1794 patients with atrial fibrillation, admitted to the emergency department for DOAC-related adverse events. Plasma DOAC levels, measured for patients presenting with stroke, transient ischemic attack, and systemic embolism or bleeding (cases), were compared with those presenting with the same events, due to other reasons (controls). The multivariate analysis showed that DOAC levels in the highest quartile were independently associated with bleeding events (OR 2.05, 95% CI, 1.49-2.82), $p<0.001$ and DOAC levels in the lowest quartile were independently associated with thromboembolic events (OR 2.04 (95% CI, 1.36-3.08), $p<0.001$. Although, the cross-sectional nature of exposure and outcome in some of the above studies does not allow to establish a causal relationship, their results suggest a link between DOAC level exposure and treatment complications.

All in all, the above observations tell us that for some patients with extreme plasma concentrations range and/or with one or more risk factors, such as old age, unexpected reduced creatine clearance, low/high body weight, better outcomes might be achieved by adjusting the dosage. The above observations point at the conclusion that the concept *"one-dose-fits-all"* is not valid for all patients according with the observation that there is a relatively large variability of DOAC plasma concentrations in patients who are taking the same dosage.[10]

Measuring (special situations)

There are situations when the measurement of DOAC levels may help making decisions on patients' management. Among them the most important are the following: i) to manage adverse events (thrombosis or bleeding) during treatment; ii) to detect over or under anticoagulation even without overt bleeding or thrombosis. iii) to manage suspicion of interference in patients taking other drugs; DOAC measurement before and after initiation of additional drugs may be useful to clear doubts of drug interference; iv) to assess the level of anticoagulation in patients who require (urgent) surgery or invasive procedure. Owing to the relatively short half-life, stopping DOAC two-three days before surgery, ensures that (hopefully) drugs are cleared from circulation if renal function (i.e., creatinine clearance) is normal. However, it should be realized that the above strategy does not ensure that DOAC are cleared from circulation. For example, there may be unexpected variation of the creatinine clearance, especially in the elderly, unpredictable variation of the metabolism or uncertain timing of the last dose intake. Measuring DOAC provides direct evidence of circulating drug; v) to make decision on thrombolytic therapy in patients on DOAC treatment for atrial fibrillation admitted to stroke units because of ischemic stroke. Knowledge of the residual circulating DOAC levels in these patients is essential to start thrombolytic treatment and avert bleeding; the combination of excessive residual drug and thrombolytic therapy may be devastating for these patients; vi) to manage antidotes administration. Idarucizumab or andexanet alpha have been licensed for use in patients on dabigatran or anti-FXa drugs, respectively, who present at emergency departments with potentially fatal bleeding. The protocol adopted for the registration trials of the above antidotes did not prescribe drug measurement before antidotes administration; post-hoc DOAC measurement at the end of the study revealed that about ¼ of the patients had concentrations of residual circulating drugs that were relatively low and (probably) did not justify antidotes administration.[11,12]

How to test

The basic tests of coagulation, prothrombin and activated partial thromboplastin times (PT, aPTT) and thrombin time (TT) are variably responsive to DOAC. For example, the PT is responsive to rivaroxaban, the aPTT to dabigatran, and TT is excessively responsive to dabigatran. Yet, PT/aPTT are global tests that, in addition to DOAC, are responsive to many coagulation factors. Hence, their prolongation over the upper limit of the normal range does not necessarily reflect the concentration of DOAC.[13] The measurement of DOAC concentrations can be accurately performed by dedicated coagulation tests, such as the dilute TT for dabigatran and the anti-FXa activity for the anti-FXa drugs. The above assays must be calibrated using commercially available certified standards for each drug.

Interference of DOAC with hemostatic parameters

DOAC interfere with the measurement of some of the most common hemostatic parameters. Among them, one may list the

following. Antithrombin can be overestimated depending on the drug used for treatment combined with method used for testing. For example, if the target enzyme when measuring antithrombin is thrombin and the drug used for treatment is dabigatran, thrombin in the assay will be inhibited by the combination of dabigatran and antithrombin. Hence, its activity is overestimated. Conversely, if the target enzyme is FXa and the drug on board is one of the anti-FXa, the activity of antithrombin is overestimated. All measurements that are based on aPTT are likely to be influenced by DOAC. Hence, fibrinogen Claus activity may be underestimated by dabigatran; activated protein C resistance may be overestimated by DOAC; protein C or protein S anticoagulant activities are overestimated by DOAC, whereas results obtained with chromogenic activity or antigen are not affected; results for the search of lupus anticoagulants (LA) may be of difficult interpretation for patients on DOAC and/or lead to frankly false-positive LA;[14] finally, measurement of FXIII activity may be underestimated by dabigatran.

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