# Direct oral anticoagulants: When to consider laboratory testing?

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# Direct oral anticoagulants: When to consider laboratory testing?

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## Abstract

**Introduction**: Direct oral anticoagulants (DOACs) are increasingly prescribed for prevention of thromboembolic stroke, as well as for prevention and treatment of venous thromboembolism. Dose adjustment based on laboratory testing is not required; however, there are several potential situations that deserve insight into a DOAC plasma activity level.

**Methods**: Based on a series of real-life case descriptions, we discuss indications for dedicated DOAC testing, as well as the interpretation and consequences.

**Results**: Testing of DOACs in selected patients may help to better interpret acute situations such as bleeding or thrombosis while on anticoagulation, but also suspected drug failure, drug accumulation, or lack of adherence.

**Conclusion**: The 24/7 availability of target-specific tests with adequate calibration is recommended to support the clinician in the interpretation and where needed adjustment of the management of patients on DOACs. The relevance of laboratory-guided DOAC management, particularly in the elderly, merits further study.

KEYWORDS

anticoagulation, bleeding, direct oral anticoagulant, laboratory assay, thrombosis

## 1 | INTRODUCTION

Direct oral anticoagulants (DOACs) are rapidly becoming the most commonly prescribed oral anticoagulants for prevention of embolic stroke in patients with atrial fibrillation (AF) and for prevention and treatment of venous thromboembolism (VTE).[1] In contrast to the previous generation of oral anticoagulants, the vitamin K antagonists (VKA), DOACs are managed without frequent laboratory testing. DOACs are prescribed using clinical and selected laboratory criteria, typically involving renal function estimation (estimated clearance based on serum creatinine; estimated glomerular filtration rate (eGFR)) and ruling out significant liver disease. Upon selection of a specific DOAC for a given patient, current guidelines recommend repeated assessment of renal (and liver) functions for long-term follow-up, but the frequency of such assessments is uncertain in the absence of predictors of changes in renal (and liver) function over time.[2] Guidelines do not recommend any coagulation testing, which drastically deviates from the international normalized ratio (INR)-guided VKA management. Occasionally, the switch from VKA to DOAC triggers uncertainty among patients used to frequent INR assessment ("how is my INR" and "why is testing no longer required"?).

For the common indications, AF and VTE, each of 4 available DOACs can be selected and prescribed: the thrombin inhibitor dabigatran, and one of the factor Xa inhibitors, rivaroxaban, apixaban, or edoxaban. In addition to regular doses, all DOACs can be prescribed in doses adjusted based on clinical and/or laboratory criteria. There are many published reviews that outline indications based on trial outcomes,[3,4] differences among these agents (pharmacokinetics),[5] dose adjustments, and laboratory testing,[6-8] just to mention a few, and we do not intend to repeat such information in this article. Rather we like to focus on some of the unexplored areas, including potential indications for quantitative laboratory testing of DOACs, using a calibrated activity assay developed to detect clinically relevant activity of a given DOAC in blood, in situations of uncertainty in clinical management, as illustrated by the following case series.

  

## 2 | REAL-LIFE CASES

### 2.1 | A patient developing deep venous thrombosis (DVT) while on Xa inhibition

84-year-old lady, medical history: lacunar infarction, pulmonary embolism (PE) in conjunction with lung carcinoma (successfully treated with surgery), followed by uneventful cessation of anticoagulants. AF de novo for which rivaroxaban started 20 mg od, to be taken indefinitely; symptomatic anemia and epistaxis, pragmatic reduction in rivaroxaban dose to 15 mg od. She presented at the emergency department with a swollen leg, an ultrasound-confirmed DVT. Otherwise, there were no notable findings from history and physical examination. She said she had been compliant with the intake of DOAC. In the absence of an immediately available quantitative assay for rivaroxaban, the attending physician decided to continue with rivaroxaban at an increased dose, as used for treatment of acute DVT, that is, 15 mg bd, after obtaining a blood sample for additional testing. Afterward, it was found that the patient had an anti-Xa level of 333 μg/L (by calibrated chromogenic anti-Xa assay; time point between peak and trough), which was at the high end of the expected on-therapy range (5-95th percentile 184-343 μg/L for a peak level of a 20 mg od dose[9]). The eGFR was estimated with the Modification of Diet in Renal Disease (MDRD) formula: 59 mL/min; of note, MDRD is the assessment for renal function in our hospital. Thus, this patient experienced a recurrent DVT while on an adequate treatment with rivaroxaban raising questions about the efficacy of this agent in this patient. Theoretically, there can be different reasons for such treatment "failure". This patient experienced a recurrent episode of VTE, also in the absence of apparent malignancy; hence, she is considered to be "thrombophilic". Antiphospholipid antibodies should be considered in such case, and antiphospholipid syndrome (APS) can be a setting where recurrent thrombosis occurs in spite of adequate levels of anticoagulants. APS was ruled out in this patient by negative anticardiolipin antibody, negative anti-beta2 glycoprotein testing, and by aPTT-LA/mixing/confirmation assay; dRVVT testing was not possible because of rivaroxaban interference. There were no indications of new malignancy at the time (although later, a malignant polyp was removed by endoscopy). We therefore considered failure of this particular drug to prevent recurrent DVT and pragmatically switched therapy to VKA, assuming that INR-controlled anticoagulation in a target range 2-3 would in this case be more appropriate.

### 2.2 | A patient with changes in renal function while on DOAC

An 78-year-old woman with a history of chronic renal insufficiency due to diabetes type 2 and hypertension, both now properly managed by medication, peripheral artery disease, and microcytic anemia due to blood loss from gastritis; she developed AF for which apixaban 5 mg bd was started at an MDRD of 36 mL/min. In his discharge letter to the general practitioner (GP), the cardiologist wrote "I recommend control of liver and renal function after 1 year and in case the clearance becomes in the range of 15-30 mL/min, please adjust the dose to 2.5 mg bd". A few months later, she again developed microcytic anemia associated with upper gastrointestinal blood loss confirmed by gastroscopy (ulcer); at that moment, her eGFR had deteriorated to 21 mL/min; additional routine testing included PT 12.6, aPTT 26 (both within normal ranges), and anti-Xa activity of 832 μg/L (by calibrated chromogenic anti-Xa assay) at trough time, clearly elevated (on-therapy trough apixaban levels 41-230 μg/L[9]). After cessation for a few days, apixaban was resumed in an adjusted dose of 2.5 mg bd, on the advice of the cardiologist, but a trough anti-Xa level obtained a month later showed a persistently elevated level of 376 μg/L. As she experienced new episodes of gastrointestinal bleeding, anticoagulation had to be stopped completely, eventually.

### 2.3 | A patient with a rare complication of anticoagulation and incidental undetectable DOAC activity

A 58-year-old lady had a history of breast carcinoma (2008), cervix carcinoma (2015), treated with chemoradiation, and complicated by PE which was treated with low molecular weight heparin (LMWH), later switched to VKA; a few months later, during VKA, she had a recurrent DVT and VKA were again replaced by LMWH. During the previous episode of VKA, she observed hair loss, which resolved while on LMWH. With the cervix carcinoma in remission, she was started on a DOAC, apixaban 5 mg bd; unfortunately, hair loss recurred[10] and we switched to another class of DOAC, dabigatran 150 mg bd, which she has been using since without further hair loss complaints. On repeat visit, she complained about shortness of breath; a dabigatran peak blood sample yielded an undetectable activity of <30 μg/L by calibrated diluted thrombin time. While she denied incompliance, a repeat sample after new instructions about drug intake showed a detectable, albeit low, level of 58 μg/L 4 hours after dabigatran intake while a D-dimer level was normal (238 μg/L), providing circumstantial evidence of absence of pulmonary embolism as explanation for the shortness of breath. Based on these findings and considering that this was so far the best tolerated oral anticoagulant, we decided to continue this medication without further problems.

## 3 | CASE DISCUSSION

Laboratory testing of DOACs has been established in many countries to deal with a number of potential problems. While initially, the introduction of DOACs was encouraged with the suggestion that laboratory testing of DOAC activity levels would no longer be needed due to stable pharmacokinetics, the general notion is changing toward a situation in which for defined situations testing

is considered helpful. For all registered DOAC, "on-therapy" activity levels have been published (indicated for instance in reference 8), based on data from large clinical trials. In the DOAC literature, the term "therapeutic range" is avoided, because dose adjustment should not be made toward a certain laboratory assay target range; this is fundamentally different from the prescription of VKA, which are dose adjusted to fit a therapeutic range based on international normalized ratio (INR).

Frequently mentioned acute situations where knowledge of a DOAC activity level in blood may be helpful concern bleeding, thrombosis, urgent invasive procedures, and thrombolysis, while on DOAC therapy.[8,9,11] Other potential settings are extreme body weight, adherence to medication, suspected overdose, major decline in renal function, (contra), acute illness, and indications for antidote administration.[11]

In acute settings, the first step will generally be to use one or more of the routine screening assays PT, aPTT, and/or thrombin time (TT), based on the DOAC that is (thought to be) present in the given patient. These screening tests each have a certain sensitivity for a specific DOAC, depending on the reagents used (summarized in Ref. (8)). In many cases, there will be a need to obtain an activity level, and for that purpose, quantitative assays have been developed.[7-9] Two issues still require attention: First, these assays take more time and are not available 24/7 in every hospital; second, it is imperative to be aware of the approximate timing between drug intake and blood collection in order to interpret any level against published on-therapy ranges.

The above "real-life" cases illustrate some of these aspects.

The first patient is an illustration of someone who developed a DVT while on a DOAC at a suitable activity level. Would we not have measured anti-Xa activity, we would probably have suspected this older woman to be nonadherent to medication, a problem estimated to occur in up to 25% of patients on DOACs.[12,13] In this case, the reason for treatment "failure" remains unexplained (maybe persistent hypercoagulability that was not fully suppressed by this DOAC?). Pragmatically, the patient was switched to VKA, in retrospect, LMWH may have been considered, if we had postulated cancer (intestinal polyp)-associated thrombosis.

The second patient illustrates that, at least in our country with a strong tradition of anticoagulation management in specialized anticoagulation clinics ("trombosediensten"), prescribers such as this cardiologist may still be somewhat unexperienced in anticipating problems related to anticoagulation. In this elderly patient with a reduced renal function at onset, the advice to follow-up after 1 year turned out to be too optimistic. In general, there are no good predictors of decline in renal function in the population, which hinders determining the desired frequency of renal function assessment; in this patient, one could have argued that at least twice-yearly assessment would have been reasonable. In addition, awareness of rapid changes in renal function during intercurrent illness is essential, particularly in patients with established chronic kidney disease[14] and in the elderly where age and diabetes mellitus 2 are predictors of accelerated deterioration in renal function.[15] Guidelines do not yet inform on measures to be taken during acute changes in renal function due to for example dehydration during infection; consequently, there are only few recommendations how to handle DOAC treatment in such situations (other than by common sense).[5,16,17]

In this case, there was no acute illness; nevertheless, we observed an elevated apixaban level at a dose that was deemed appropriate for the estimated clearance at that moment. Although it is difficult to draw any conclusions based on cases, it should at least support the need for careful surveillance of all elderly persons on oral anticoagulation for the consequences of changes in health status related to renal and other functions.[16,17] This will require an infrastructure supporting prescriber, patient, and GP in making informed decisions on the use, adjustment, or cessation of any form of anticoagulant, in situations of illness or complications. Most likely, this should include recommendations on the use of quantitative laboratory assays to document DOAC levels to guide management. Moreover, additional studies in the elderly may be warranted to specifically address safety of DOAC treatment in this population, somewhat underrepresented in the large trials.[18]

The third patient is an exceptional case because a rare complication of hair loss, originally confined to users of VKA, but recently also reported for some DOACs,[10] that triggered changes in therapy to the eventual use of dabigatran. Routine DOAC testing in this patient would not have been required in the absence of a specific indication; however, the prescriber wanted to be assured that, after the drug selection process, at least this agent provided an adequate activity level. In fact, the first measurement provided an undetectable level; adherence was verified, and after new instructions, the patient indeed resumed DOAC intake as intended, illustrated by the measurable activity level in the second instance.

## 4 | EMBEDDING LABORATORY TESTING IN ROUTINE CARE

In a recent position paper, Tripodi et al[11] propose that (i) dedicated tests for DOACs should be set up in all clinically laboratories and made available to clinicians, (ii) regulatory authorities should urgently approve their use of patient management albeit in special conditions, and (iii) guidelines on how and when to test DOACs should be implemented in all hospitals. We fully support these proposals and would add that education in how to manage the patient on oral anticoagulants should be improved as well, as proposed by Heidbuchel et al[17] Within our hospital, we have instituted guideline-based protocols and all relevant screening and quantitative laboratory tests, but we are also aware of the need to teach our colleagues about the sensible use of these tools. Moreover, there is still a need for faster, whole blood assays to exclude the presence of clinically relevant DOAC levels. Faster whole blood tests such as ROTEM EXTEM clotting time (thromboelastography) had similar or even better sensitivity for ruling out clinically relevant levels of rivaroxaban compared to the frequently used aPTT (Cephascreen/Actin FSL) or PT (Neoplastin/

Innovin) reagents.[19] However, the cost-effectiveness of the use of such laboratory assays merits attention.

Past studies including HARM demonstrated the potential danger of anticoagulation showing increased rate of potentially avoidable hospital admissions of patients on anticoagulants (as well as platelet inhibitors).[20] In those days, VKA were the anticoagulants used. Now that DOACs replace VKA in many patients, some of the risks may change, but patients with bleeding complications are still admitted and it is imperative that proper actions are taken, including the proper use and interpretation of laboratory tests. Moreover, in all settings of perioperative management, decisions on whether or not to continue anticoagulation, or how long prior to surgery to stop anticoagulation are critically important. Guidelines do give information based on expected half-lives of DOAC; however, in some patients, like our case 2, a DOAC activity level may be much higher than anticipated and it is questionable whether this case is an exception or merely the tip of an iceberg. Do we really understand the pharmacokinetics of DOAC in elderly subjects outside studies and should we improve preoperative management, beyond verifying renal function?

At this stage, no conclusions can be drawn, but awareness about the pitfalls that may threaten the (elderly) patients on anticoagulants during episodes of illness and/or intervention[18,21] is of eminent importance.

## CONFLICT OF INTEREST

HtC is chairman of the board of the Dutch Federation of Anticoagulation Clinics and consultant to Stago.

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