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FORUM

The relationship between DOAC levels and clinical outcomes: The measures tell the tale

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Abstract

Direct oral anticoagulants (DOACs) are increasingly used for treatment and prevention of thromboembolic diseases, used in fixed dose regimens. Although their safety and efficacy profiles are considered optimal, clinical events still occur. Given that anticoagulation treatment is a delicate balance between clotting and bleeding, it is possible that an optimal target spot exists where the effect of anticoagulation achieves both the lowest possible risk of bleeding and thrombosis. Other currently available anticoagulants (ie, vitamin K antagonists and heparins) provide important clues for this. If such a target spot exists, tailored DOAC therapy may further benefit patients. This opinion article summarizes the current available evidence that suggests that such a tailored strategy could work. It also describes research suggestions for conducting studies in patient populations such as patients with extremes of body weight or impaired kidney function to evaluate whether tailored treatment with DOACs could lead to better patient outcomes.

KEYWORDS

direct oral anticoagulants, atrial fibrillation, venous thromboembolism, pharmacokinetics, pharmacodynamics, epidemiology

1 | INTRODUCTION

Since their introduction nearly a decade ago, the use of direct oral anticoagulants (DOACs) is rapidly increasing.[1] In large randomized clinical trials, DOACs were found to be noninferior to vitamin K antagonists (VKAs) for the prevention of arterial thromboembolism in patients with atrial fibrillation and for the management of venous thromboembolism.[2] Having fewer interactions with comedication and diet and a more stable pharmacokinetic profile than VKA, DOACs currently do not require routine laboratory monitoring. For these reasons, DOACs have replaced VKA in international guidelines as first choice of anticoagulant for management and prevention of thrombotic diseases.[3] Unfortunately, complications during management with DOACs still occur. In clinical trials, the risk for thromboembolic events in patients randomized to DOAC is 1% to 2% per year and although the risk of intracranial hemorrhage is lower with DOACs when compared with VKA, the overall major bleeding risk for DOAC use in observational studies remains 1% to 3% per year because of a large proportion of major extracranial bleeds.[3-6] This is reflected in the large number of emergency rooms visits for

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adverse drug events, which is higher for anticoagulants than for any other drug class.[7] In addition, the total number of oral anticoagulant users has increased in the past 5 years, which is related to the ageing population and changing guidelines.[8]

Because both bleeding complications and recurrent thromboembolic events still occur during management of DOACs, there is room for improvement in the management of these patients. In this Forum Article, we will argue that it may be worthwhile to study the relationship between DOAC concentrations and patient-important outcomes. First, we will discuss the balance between thrombosis and bleeding; second, the rationale for individual dosing of anticoagulants; and, last, we will appraise the current situation and discuss several research opportunities to further improve care in patients receiving anticoagulants.

2 | BALANCING THROMBOSIS AND BLEEDING

In the field of thrombosis and hemostasis, a pair of scales is typically used to illustrate the delicate balance between clotting and bleeding. In the normal situation, both bleeding and clotting are balanced by a continuous equilibrium between procoagulant and anticoagulant processes.[9] If under pathological circumstances, the scale is tipped toward the procoagulant side, thrombosis can occur. If this is the case, we aim to rebalance the scale with anticoagulant therapy to find a new equilibrium where the risk of bleeding and risk of recurrence are weighed. Ideally, the anticoagulants' effect reaches a so called "target" in the middle, where the effect of the anticoagulant achieves both the lowest possible risk of bleeding and thrombosis (Figure 1). The desired effect of anticoagulant therapy is similar to many other cardiovascular therapies (eg, treatments for hypertension, dyslipidemia, diabetes) for which a balance is maintained by measuring the effect of treatment (eg, blood pressure, cholesterol levels, blood glucose). Direct oral anticoagulants have a direct effect on the hemostatic system in a bidirectional manner as has been shown for dabigatran and edoxaban (ie, too much effect results in bleeding, too little effect in thromboembolism).[10,11] For rivaroxaban and apixaban, this is less well known because of an absence of studies that have been conducted on this issue, although preliminary (small-scale) studies suggest a similar bidirectional effect for rivaroxaban and apixaban as well.[12,13] Given that the pharmacodynamics of all DOACs are similar as they selectively and specifically inhibit coagulation serine proteases,[14] it is likely that an optimal dose-benefit relation exists for all DOACs. Here, two main questions need to be answered. First, do DOAC (level or activity) measurements correspond with the risk of clinical outcomes, and does a target spot (or therapeutic window) exist? Second, is this target range similar for specific patient populations, are perhaps different based on clinical characteristics, such as extremes of body weight and renal function?

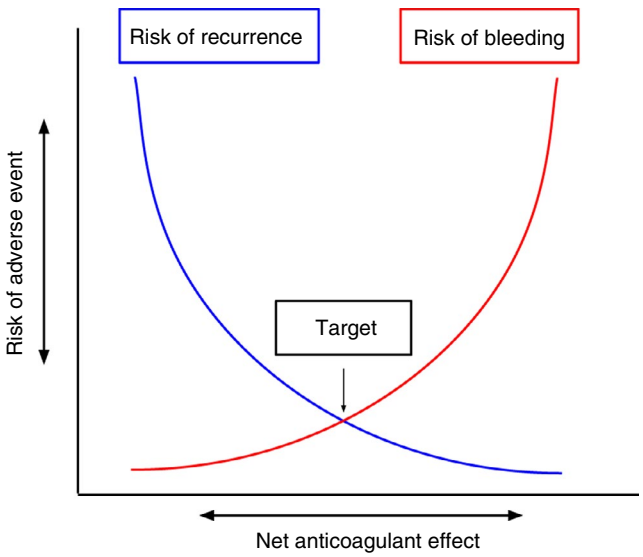

FIGURE 1 Simplified illustration of the theoretical optimal "target" between risk of adverse events and net anticoagulant effect

3 | CLUES FOR A "TARGET SPOT" IN OTHER ANTICOAGULANTS

The existence of an optimal individual dose for DOACs might be supported by the fact that various other (similar acting) anticoagulants have an individual "target spot" or therapeutic range. For VKAs, it is well established that adequate regulation of the international normalized ratio optimizes the risk-benefit ratio between bleeding and thromboembolic complications.[15,16] For heparins, anti-Xa level monitoring is suggested in patients with heparin resistance, a prolonged baseline activated partial thromboplastin time (APTT) or altered heparin responsiveness.[17] Unfractionated heparin is routinely monitored and adjusted based on the measured APTT, where an APTT of 1.5 to 2.5, that of baseline, is associated with the lowest bleeding and recurrence risk.[3,18,19] Low molecular weight heparin (LMWH) is dosed based on body weight and renal function.[20-23] Subsequently, measurement of anti-Xa levels are suggested to evaluate the safety of LMWH dosing in special patient populations (renal impairment, during pregnancy, critically ill patients).[3] These examples provide clues for the existence of a "target spot" with different classes of anticoagulants. It therefore may be worthwhile to at least investigate whether this optimal point between thrombosis and bleeding exists for DOACs as well.[24]

4 | DOACS, CURRENT SITUATION, AND EVIDENCE FOR INDIVIDUAL BASED DOSING

4.1 | Special situations or populations

Given the properties of DOACs (fixed-dose regimen) and the evidence on anticoagulants that have similar mechanisms of effect, it

seems reasonable to further investigate whether individually dosed regimens may improve patient important outcomes. This might especially be true for special patient populations or during specific situations.

4.1.1 | Extremes in body weight

Currently, DOACs do not require dose adjustments for extremes in body weight or body mass index (BMI). Because patients at extremes of body weight were underrepresented in DOAC clinical trials (<20% weighed > 90 to 100 kg and < 15% weighed < 50 kg),[4,5,25] and randomized trials of DOACs for these specific patient groups are currently unavailable, the current recommendation of DOAC use in patients weighing > 120 kg or with a BMI > 40 kg/m^2 is restricted to situations where VKAs cannot be used.[26,27] For patients weighing < 50 kg, no recommendations are available. Interestingly, available pharmacokinetic studies provide insights into the relationship between body weight and drug levels. For dabigatran, a subgroup analysis within the Randomized Evaluation of Long-Term Anticoagulation Therapy trial showed plasma trough concentrations 21% lower for high body weight (>100 kg) than for lower body weight (50-100 kg).[10] For apixaban, a pharmacokinetic study found 31% lower peak concentration in the high body weight (>120 kg and BMI > 30 kg/m^2) when compared with the reference group (65-85 kg).[28] On the other hand, a recent study used data from 913 patients using rivaroxaban, including patients at extremes of body weight (>120 kg and < 50 kg), to develop a pharmacokinetic model. In this study, renal function was the best predictor of rivaroxaban exposure and addition of body weight to the model did not show a significant reduction in drug exposure. The authors concluded that rivaroxaban can be used at extremes of body weight.[29] The clinical implications of these pharmacokinetic studies are unknown. Pharmacokinetic studies that include clinical endpoints are therefore much needed. Given the possible differences in drug exposure at the extremes of body weight, it seems worthwhile to study whether these patients could benefit from assessing drug-specific peak and through levels and dose adjustment, similar to weight-based dose adjustments for LMWH.

4.1.2 | Impaired kidney function

Because all DOACs are excreted by the kidneys to some extent, they require regular control of kidney function.[30] Because patients with a creatinine clearance (CrCl) less than 25 to 30 mL/min were excluded from the clinical trials,[4,5,25] data regarding the effectiveness and safety of DOACs in those with CrCl less than 25 mL/min are only available through nonrandomized small-scale studies of which statistical type I/type II errors could play a role.[31,32] Despite this knowledge gap, many DOACs are licensed and marketed for use up to a CrCl as low as 15 mL/min. Dose adjustments for patients with moderately impaired kidney function (CrCl 30-50 mL/min) are advised although the recommended adjustments in licensed doses of DOACs for different stages of renal impairment differ between European and North American guidelines.[33] Current knowledge of DOAC pharmacokinetics in patients with advanced renal failure is limited. A review of pharmacokinetic studies showed increased peak level exposure in patients with impaired kidney function (CrCl 15-30 mL/min) using DOACs.[34] These studies did not take clinical endpoints into account. For patients with advanced kidney failure, studying the benefits of tailored anticoagulant treatment might especially be interesting.

4.1.3 | Prior gastrointestinal surgery

Because of a change in absorptive surface after gastrointestinal surgery, drug absorption of DOACs is expected to be altered in these patients. Anticoagulant drug levels are therefore prone to large inter-individual variability. Available evidence for DOAC use in this patient population is very limited. Bariatric surgery or extensive bowel surgery may alter anticoagulant drug levels which can result in large inter-individual variability.[35,36]

4.1.4 | Specific situations

The measurement of drug levels may also be useful in a number of other specific clinical situations such as the initiation of interacting comedication or the development of a recurrent event thrombosis despite use of anticoagulant therapy.[37] Also, in case of suspected therapy nonadherence or restarting anticoagulation after a major bleeding, DOAC trough concentrations might be of interest. Defining target levels to ensure the optimal balance between risk of thrombosis and bleeding could also provide guidance in these clinical scenarios. In addition, in the acute onset of thrombotic disease, risk of progress of thrombosis is highest. Therefore, one may need to shift the balance of anticoagulant treatment more toward "bleeding" to obtain a stronger anticoagulant effect (eg, achieved with initial higher doses of DOAC as is currently common practice in venous thrombosis management). In a recent cohort study, DOAC level measurements in acute clinical situations (ie, acute ischemic stroke, bleeding, and perioperative evaluation) affected clinical management in 77% of 234 patients.[38]

4.2 | Inter-individual differences and evidence for individual based dosing

In most recent studies on DOAC testing, DOAC concentration ranges (on-therapy ranges) derived from the landmark randomized clinical trials are used as an indication for clinically relevant ranges.[39] However,, routine DOAC level assessments are not advised.[2] Yet, substantial inter-individual variation in plasma drug levels of DOACs has been described in both observational studies

as in clinical trials.[12,40,41] Given this variability, it is possible that specific patients groups are exposed to drug levels that are too high or too low. In another recent study on DOAC plasma levels among patients with nonvalvular atrial fibrillation using rivaroxaban or dabigatran, substantial between-individual variation (different levels among different persons) in plasma levels was found; however, within-individual DOAC levels (levels among the same individual at different time points) remained stable within or outside the on-therapy range.[42] These data suggest that performing a DOAC measurement at the start of therapy provides an accurate estimate of future measurements and that repeated (costly and time-consuming) measurements would not be necessary in a stable clinical situation. However, if the patient's clinical characteristics evolve (eg, change in kidney function, body weight, comedication, comorbidities), a repeated measurement might be indicated. A clinical consequence could be (both in special patient populations as in patients without additional risk factors) that if this initial measurement is out of range, a different dose or different anticoagulant could be considered. As mentioned, studies evaluating the clinical benefit of such a proposed a strategy are still to be performed.

Whether measurement of certain pharmacokinetic parameters of DOACs and subsequent adjusted dosing schemes are superior in terms of patient important outcomes and cost-effectiveness compared with the fixed-dose regimen needs to be evaluated in future large observational studies or trials. At this moment, such studies are scarce; however, several available studies provide clues that a dose-response relation between DOAC concentration and bleeding/thromboembolism exists. Data from the Randomized Evaluation of Long-Term Anticoagulation Therapy trial, in which warfarin was compared to dabigatran in patients with atrial fibrillation, showed with a multivariate logistic regression model that the risk of ischemic events was inversely related to trough dabigatran concentrations (c-statistic 0.66, 95% confidence interval 0.61-0.71). It also showed major bleeding risk increased with dabigatran exposure (c-statistic 0.72, 95% confidence interval 0.69-0.74). In other words, higher dabigatran levels were associated with a lower risk of thromboembolism, yet a higher risk of major bleeding.[10] In a post hoc analysis of the ENGAGE-AF trial [43] in which warfarin was compared with standard dose edoxaban (60 mg once daily) or low dose edoxaban (30 mg once daily) in patients with atrial fibrillation, low edoxaban plasma through concentrations were associated with higher risks of stroke and systemic embolism and high through values were associated with a higher risk of major bleeding.[11]

In a recent observational study in which DOAC concentrations were measured in 565 patients with atrial fibrillation from the START laboratory registry, thrombotic complications mainly occurred in patients with the lowest trough levels, in combination with a high CHA_2DS_2-VASc score.[12] In another study in which the quality of anticoagulants was evaluated in patients (n = 460 patients, 51% on DOAC) with an acute stroke, low DOAC plasma levels (<50 ng/mL) were an independent predictor of higher stroke severity and large vessel occlusion (odds ratio 3.84, 95% confidence interval 1.80-8.20) when compared with intermediate or high DOAC plasma levels. These studies do not however yet provide definitive evidence that monitoring anticoagulation levels will improve clinical outcomes, as they are limited in event rates and study design.

5 | WHAT THE FUTURE MIGHT BRING

As discussed in previous sections, several clues supporting the possibility of an optimal dose-benefit relation for DOACs are available. However, as only limited data are available, it is currently not known whether level-dosed DOAC strategies are superior to fixed-dosed DOAC strategies. These clues do, however, provide us with a number of research opportunities.

First, we need to know if patients on DOAC are willing to be monitored and tested on their DOAC level. Previous studies have shown that most patients on DOAC are satisfied with their current treatment and feel safe when using DOAC without regular thrombin inhibitor or anti-Xa measurements.[44,45] Because it is assumed that DOACs have a broad therapeutic window (ie, work the same for almost everybody; one size fits all approach) and that for efficacy and safety the actual DOAC plasma concentration is of less importance in a patient who takes this drug, gives credence to this patient strategy. Given that the overall bleeding and thromboembolism rates are similar as when using VKA, further supports that the fixed dose strategy is safe and effective for the majority of patients. Yet, according to a survey in patients who formerly used VKA and who were switched to DOAC up to 70% of them were willing to undergo some form of blood testing at least once a year if that could further increase the safety and efficacy of the DOAC they were using.[45]

Second, to find the optimal dose-effect for DOACs, we need to further optimize and standardize laboratory tests. These DOAC-specific drug level tests (ie, thrombin generation assays, ROTEM, and anti-Xa assays for the inhibitors and diluted thrombin time for dabigatran) are becoming increasingly available in hospitals.[39] Currently available tests are mostly performed in plasma or whole blood. New point-of-care tests that are being developed for DOAC level or activity measurements may be useful [46] but there are still many uncertainties about the associations of these tests with drug intake and if blood and urine levels correlate.

Third, we need to know if risk models for thromboembolism and major bleeding, such as HAS-BLED and CHA_2DS_2-VASc, can be further improved by adding anticoagulation levels to the prediction scores and by predicting the risk not only in a landmark analysis (ie, around the time of diagnosis of atrial fibrillation or venous thromboembolism) but also through time (ie, dynamic prediction). Studies that can investigate whether DOAC-specific measurements, either taken once, or over time correspond with risk of bleeding or thromboembolism could be performed by conducting large prospective studies or use available data from existing data (such as trials and registry data where patients on DOACs have been tested on DOAC plasma levels). In case there is an optimal target and subsequent dose for DOAC in patient populations or subgroups the final step would be to set up endpoint studies

to guide dose regimen selection/DOAC titration in clinical trials, for example in special patient populations mentioned previously.

6 | CONCLUSION

Even though fixed-dose DOAC regimens have been shown to have several clinical important advantages and noninferior efficacy when compared with VKA, patients who use DOACs still have a yearly risk of 1% to 3% to develop major bleeding. It is likely that patients could further benefit from tailored DOAC therapy in regard to clinical outcomes. This might in particular be the case for special populations (eg, extremely high or low body weight, impaired kidney function, prior intestinal surgery) and in specific clinical situations (eg, patients that restart anticoagulation after a major bleeding or patients that experience a thrombotic event while on DOAC therapy).

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CONFLICT OF INTEREST

None related to this work.

AUTHOR CONTRIBUTIONS

Myrthe M. A. Toorop, Willem M. Lijfering, and Luuk J. J. Scheres were the main investigators of the manuscript. Myrthe M. A. Toorop wrote the first draft of the manuscript and the final version. Willem M. Lijfering and Luuk J. J. Scheres were responsible for review of the manuscript.

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