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RESEARCH ARTICLE

Is there a Role for Measuring Direct Oral Anticoagulant Levels in Select Patients?

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ABSTRACT

Direct oral anticoagulants are recommended as first line therapy for patients with atrial fibrillation and venous thromboembolic disease. Measurement of drug levels or pharmacodynamic effect is not recommended during treatment. Dose adjustments are based on age, weight, kidney function and drug-drug interactions. These adjustments are generally based on an estimate of their effect on drug concentration. DOAC dosing recommendations differ across the world. These differences in prescribing recommendations result in different levels of DOAC exposure in patients with identical clinical characteristics. Additionally, data from clinical trials has shown that drug levels may vary significantly in individual patients with identical clinical characteristics despite taking the same prescribed dose. More concerning is that current prescribing recommendations provide cut points for dose adjustments, as an example age 80 or greater in the case of apixaban in atrial fibrillation, which may result in dramatically higher drug concentrations in patients with significantly higher bleeding risk.

Data from outcome trials in both atrial fibrillation and venous thromboembolism have provided mean-median drug concentrations for each of the DOACs. These trial results appear to demonstrate that once a threshold DOAC plasma concentration is reached, higher concentrations fail to provide significant added ischemic stroke reduction while at the same time add an increased risk of bleeding. Bleeding remains a significant problem with DOACs and is associated with an increase in short and long-term mortality, ischemic stroke, myocardial infarction, cost, and drug interruption and discontinuation.

Over the past years, our clinic has been assessing DOAC concentration in patients at risk for under or over exposure. Based on our experience, clinical characteristics alone appear to be insufficient, as a significant number of patients with characteristics suggesting high exposure would be under-dosed using a purely clinical approach and an even greater number, who are at elevated risk of bleeding would have had excessive levels, if prescribing were based strictly on the established dose reduction criteria. We propose, and provide our supporting clinical experience, that measuring DOAC levels in select patients will increase the margin of safety of these medications without compromising efficacy.

Introduction

Direct oral anticoagulants (DOACs) are generally recommended as first line therapy for prevention of thromboembolic events in patients with atrial fibrillation, pulmonary embolism (PE), and deep vein thrombosis (DVT). In contrast to warfarin, which requires routine monitoring of the INR, DOACs are currently prescribed without a recommendation to measure pharmacodynamic effects or drug levels. Dose adjustments of DOACs, which are specific for each DOAC, are recommended in individual patients, guided by clinical characteristics, including kidney function, age, weight, and concomitant medications.

DOAC dosing recommendations differ across the world. As an example, the recommended dabigatran dose in patients greater than 80 years of age is 110-mg twice a day in Europe[1] and the rest of the world, while it is 150-mg twice a day in the United States[2]. These differences in prescribing recommendations result in different levels of DOAC exposure in patients with identical clinical characteristics. Moreover, data from clinical trials has shown that drug levels may vary significantly in individual patients with identical clinical characteristics despite taking the same prescribed dose.[3,4] More concerning is that current prescribing recommendations provide cut points for dose adjustments, as an example age 80 or greater in the case of apixaban in atrial fibrillation, which may result in dramatically higher drug concentrations in patients with significantly higher bleeding risk.

Data from outcome trials in both atrial fibrillation and venous thromboembolism have provided mean-median drug concentrations for each of the DOACs. These trial results appear to demonstrate that once a threshold DOAC plasma concentration is reached, higher concentrations fail to provide significant added ischemic stroke reduction while at the same time add an increased risk of bleeding.[5] Over the past years, our clinic has been assessing DOAC concentration in patients at risk for under or over exposure. Clinical characteristics alone appear to be insufficient, as a significant number of patients with characteristics suggesting high exposure would be under-dosed using a purely clinical approach while an even greater number who are at elevated risk of bleeding would have had excessive levels, if prescribing were based strictly on the established dose reduction criteria. We propose, and provide our supporting clinical experience, that measuring DOAC levels in select patients will increase the margin of safety of these medications without compromising efficacy.

Current Treatment Approach

Current prescribing recommendations for apixaban in atrial fibrillation, the most commonly prescribed DOAC, are a dose reduction from 5 milligrams twice a day to 2.5 milligrams twice a day when at least 2 of the 3 dose reduction criteria are present: 1) age greater than or equal to 80 years, 2) weight less than or equal to 60 kilograms, and 3) creatinine greater than or equal to 1.5 milligrams per deciliter.[6]

Based on the prescribing recommendations, a 95-year-old (≥ 80) female with atrial fibrillation, weighing 62 kilograms (> 60), with a creatinine of 1.4 milligrams per deciliter (< 1.5) would be prescribed apixaban 5 milligrams twice a day, while an 80-year-old male (≥ 80) weighing 100 kilograms (> 60) with a creatinine of 1.5 milligrams per deciliter (≥ 1.5) would be prescribed apixaban 2.5 milligrams twice a day. It is obvious that even if both patients were given the **same** dose of apixaban, the 95-year-old female would have a significantly higher apixaban level, potentially by a factor of two. The fact that her recommended dose is twice that of his does not seem logical from a pharmacokinetic nor pharmacodynamic perspective. This is made even more concerning in that the very elderly female would be expected to have a significantly higher bleeding risk than the elderly male. Combining a dramatically higher drug concentration with a significantly higher bleeding risk would certainly not provide optimal risk and benefit.

Using the dose-adjustment strategy described above in patients with non-valvular atrial fibrillation, the ARISTOTLE outcomes trial, reported positive outcomes data with respect to both stroke and bleeding reduction with apixaban when compared with warfarin.[7] These findings are the foundation for the current prescribing recommendations. Of note, a subset of patients in ARISTOTLE had apixaban levels measured at both peak and trough. Median peak and trough apixaban were lower in those treated with 2.5-mg twice a day, a predominantly elderly high-risk cohort with respect to both stroke and bleeding, with median peak levels of 123 nanograms per milliliter, compared to 171 nanograms per milliliter in those treated with the 5-mg twice a day dosing (Table 1). Similarly, median trough levels were lower, 79 nanograms per milliliter in the 2.5-mg twice a day group, compared to 103 nanograms per milliliter in the 5-mg twice a day group (Table 1).[8]

Table 1. Apixaban steady state concentration (ng/mL)			
Dose (mg)	**Indication**	**PEAK***	**TROUGH***
2.5 BID	AF	123 (69, 221)	79 (34, 162)
5 BID	AF	171 (91, 321)	103 (41, 230)
2.5 BID	DVT PE	67 (30, 153)	32 (11, 190)
5 BID	DVT PE	132 (59, 302)	63 (22, 177)
EMEA Eliquis Product information[7] *Median (5th and 95th percentiles)			

Data from multiple clinical trials appears to demonstrate that once a threshold DOAC plasma concentration is reached, higher concentrations fail to provide significant added ischemic stroke reduction. Data from the dabigatran RELY (Figure 1) and the edoxaban ENGAGE-AF (Figure 2) atrial fibrillation outcomes trials clearly demonstrate this.[5] This lack of enhanced stroke protection at higher concentrations is in contrast to the increase in major bleeding events seen with higher plasma concentrations. There appears to be an inflection point at which the increased bleeding risk no longer justifies intensification of anticoagulation therapy. Moreover, increasing concentrations or anticoagulant effect results in a gradual, linear decrease in the risk of stroke or systemic embolic events, in contrast to the steeper increase in the risk of major bleeding. This is similar to what has been observed with warfarin and its pharmacodynamic effect. As the INR increases above 3, the reduction in stroke plateaus, while intracranial bleeding increases, particularly when the INR is above 4 or 4.5 (Figure 3)[5]. This is clinically relevant in that there is a wide range of drug concentrations across individual patients treated with each DOAC (Figures 1 and 2)[5].

Figure 1. Concentration dependent relationship for dabigatran on ischemic stroke and life-threatening bleeds.[5]

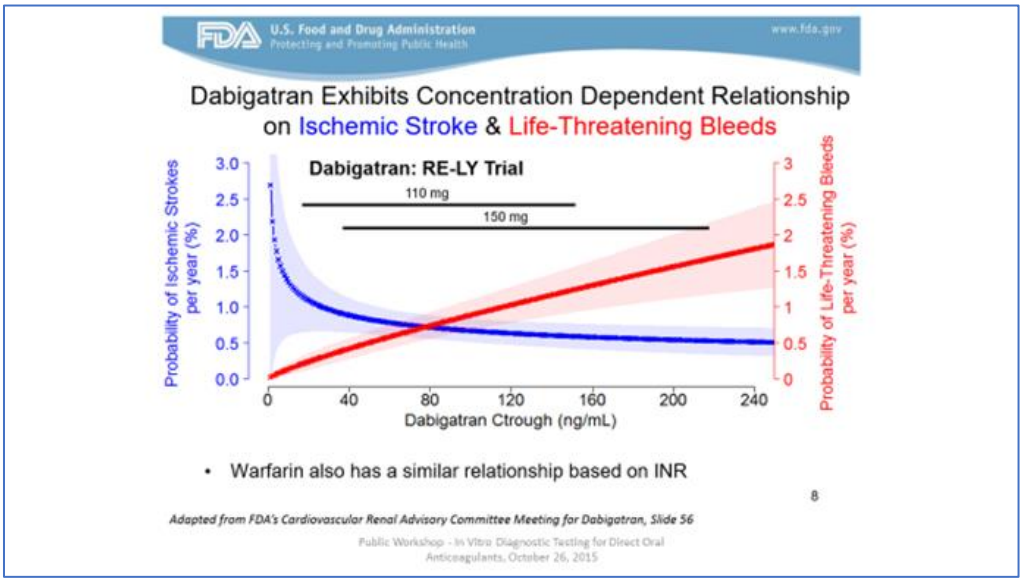


Figure 2. Concentration dependent relationship for edoxaban on ischemic stroke and life-threatening bleeds.[5]

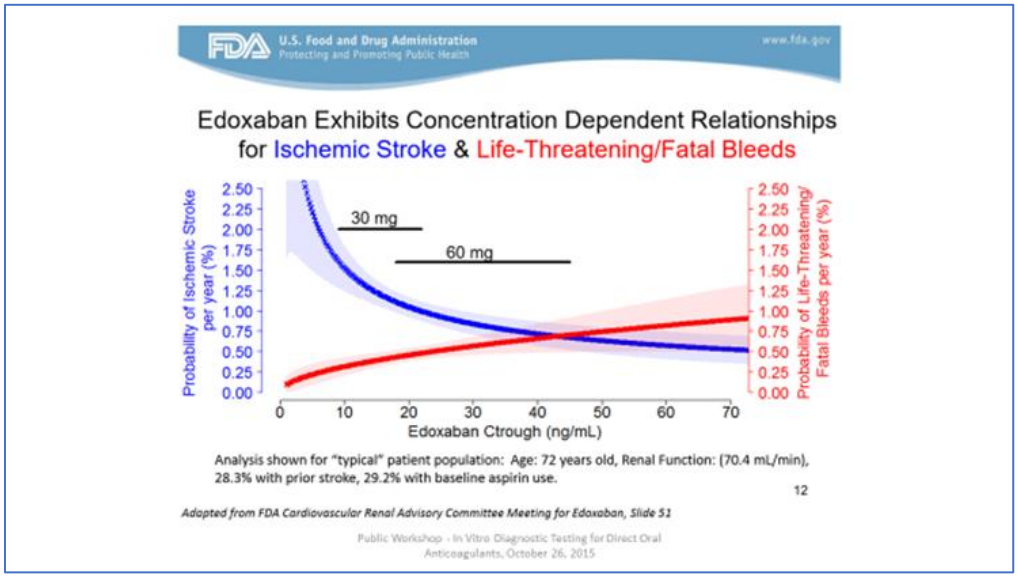
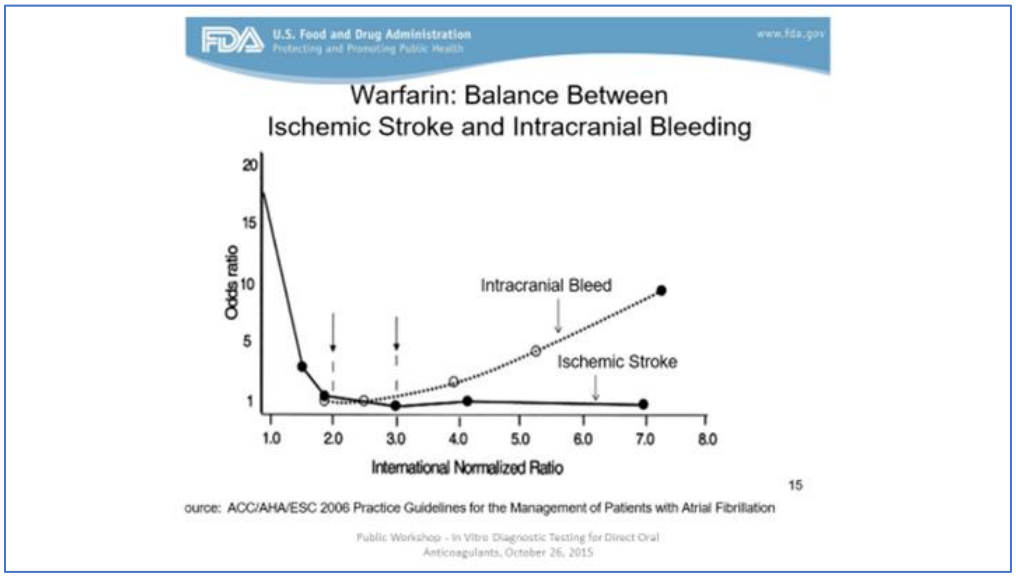


Figure 3. Pharmacodynamic dependent relationship for warfarin on ischemic stroke and life-threatening bleeds.[5]



Dose adjustment criteria for DOACs are mainly driven by estimating their impact on drug concentration. In healthy subjects, maximal apixaban plasma concentration (C_{max}) and the area under the curve inversely correlate with body weight, showing a 25–30% increase below 50 kilograms and an approximately 25–30% decrease with weights above 120 kg versus normal weight (65–85 kilograms).[9] Edoxaban C_{max} is increased approximately 40% in patients weighing < 60 kilograms,[9] which lead to a 50% dose reduction in the HOKUSAI-VTE and ENGAGE AF-TIMI 48 trials.[10,11] In HOKUSAI-VTE, 12% of the patients were underweight and the primary outcome, symptomatic VTE at 12 months, was comparable to the non-underweight population.[9] Half-dose edoxaban in the ENGAGE-AF trial resulted in approximately a 30% lower exposure to edoxaban, which probably explains the significant reduction of major bleeding compared to full-dose edoxaban-treated patients, while differences in efficacy were not observed with half-dose edoxaban.[9]

Despite the favorable bleeding profile of apixaban in ARISTOTLE, the rate of major hemorrhage among patients was substantial, 2.1% per year compared to warfarin's 3.1%.[12] Major bleeding is associated with an increase in both short and long-term mortality, ischemic stroke,

myocardial infarction, cost, and permanent drug discontinuation.[13] Patients with major bleeds while being treated with apixaban had a number of predisposing factors associated with increased drug concentration, including age greater than 75 years and impaired renal function.[12] Interestingly, an exploratory analysis demonstrated that the reduction in bleeding with apixaban appeared to be greater in patients with renal dysfunction and low body weight, a cohort that would likely have been treated with the reduced 2.5-mg twice-a-day apixaban dose.[12]

Non-major bleeding is also lower with apixaban compared to warfarin, but also remains a significant problem, occurring at a rate of 6.4 per 100 patient-years.[14] Non-major bleeding is clinically important, as it is a common complication that often results in adverse consequences, including death, hospitalization, and cessation of effective anticoagulation that can lead to worse subsequent clinical outcomes. These findings underscore the importance of preventing bleeding in anticoagulated patients by selecting the correct anticoagulant dose.

The Rationale for Change

In light of a guidance from the International Society on Thrombosis and Hemostasis in 2016 "suggesting" avoidance of DOACs in obese patients because of a concern for reduced plasma concentrations, or "underexposure", and their recommendation that if DOACs are used in obese patients, levels should be measured,[15] our anticoagulation clinic began to measure DOAC levels in obese patients using a commercially available liquid chromatography-mass spectrometry assay. In 28 obese patients, tested based on a concern for underexposure, 2 patients had levels **below** our expected "on-therapy" range, while 5 had levels **above** our expected "on-therapy" range. The 5 "over-exposed" patients had their dose reduced based on their laboratory results.[16]

A number of publications in the literature consider in-range DOAC levels to extend from the 5th to 95th or 10th to 90th percentiles.[17,18] As an example, for apixaban 5-mg twice a day, the in-range 5th to 95th percentile drug level at **peak** for atrial fibrillation extends from 91-321-ng/ml, a 3.5-fold difference, while trough levels would range from 41-230 ng/mL, a 5.6-fold difference (Table 1). What is obvious from this approach is that 5% of apixaban treated patients, 1 in 20, will have a **trough** level greater than 230 ng/mL which is 35% greater than the median **peak** level (171 ng/mL) for this dose and almost **double** the median peak level for the 2.5-mg dose (123 ng/mL), while a significantly greater percentage of patients would have a **trough** level greater than or equal to the **median peak** level of 171 nanograms per milliliter.

Taking this into account, a more pragmatic, pharmacologically-rational approach would take into account the following:

1) the half-life of **all** DOACs is about 12 hours;
2) the peak level for **all** DOACs is in the 3-4-hour range;
3) the drug level after approximately one half-life (e.g., 10-14 hours post dose) should be less than the mean-median peak level for the specific drug;
4) the drug level at peak should be at least half of the mean-median peak level for the specific drug;
5) the drug level after approximately one half-life (e.g., 10-14 hours post dose) should be at least one-quarter of the mean-median peak level for the specific drug.

Based on these considerations, our anticoagulation clinic considers "over-exposure" or supratherapeutic DOAC levels when:

1) the 10-14-hour (one half-life) level is greater than or equal to the mean-median peak level for the specific drug (e.g., a level at 12 hours of 130 ng/ml in a patient with atrial fibrillation treated with apixaban 2.5-mg twice a day would be considered excessive as the median **peak** level for this dose is 123 ng/ml, Table 1);
2) the 3-4-hour (peak) level is ≥ twice the mean-median peak level for the specific drug (e.g., a level at 3 hours of 400 ng/ml in a patient with atrial fibrillation treated with apixaban 5-mg twice a day would be considered excessive as the median peak level for this dose is 171 ng/ml, Table 1).

"Under-exposure" or subtherapeutic is considered when:

1) the 3-4-hour (peak) level is less than 50% of the mean-median peak level (e.g., a level at 3 hours of 60 ng/ml in a patient with a pulmonary embolus treated with rivaroxaban 20-mg daily would be considered low as the mean peak level is 215 ng/ml, Table 2);
2) the 10–14-hour (one half-life) level is less than one-quarter the mean peak level (e.g., a level at 12 hours of 50 ng/ml in a patient with a pulmonary embolus treated with rivaroxaban 20-mg daily would be considered low as the mean peak level is 215 ng/ml, Table 2).

Table 2. Rivaroxaban steady state concentration (ng/mL)			
Dose	**Indication**	**PEAK***	**TROUGH***
20 QD	DVT	215 (22, 535)	32 (6, 239)
EMEA Xarelto product information[19] *Mean (90% prediction interval)			

As a result of our unexpected finding in obese patients of a greater incidence of over- rather than under-exposure, along with the literature related to the increased bleeding risk without clinically meaningful additional stroke reduction at higher drug concentrations, our anticoagulation clinic modified its practice and started to measure DOAC levels in patients at risk of "over-exposure". These included patients with impaired renal function, the very elderly, very low weight, potential drug-drug interactions, and patients who approach but do not fulfill the dose reduction criteria (e.g., 79-year-old male weighing 80 kilograms with a creatinine of 1.6 mg/dL). Patients at risk for low levels and "under exposure" (drug-drug interactions, off-label low dose use) also had levels assessed. In 63 such patients, therapy was modified in 19 (30%), of which 13 were dose reductions, 4 dose increases, and in 2, a change to a different DOAC.[20]

A subsequent analysis of 41 very elderly male patients over the age of 80 found that only 24% of patients (10/41) who initiated therapy with their on-label dose had an appropriate level; while 34% (14/41) of patients who initiated therapy with their on-label dose had a level significantly above their "expected" level.[21] Of the 17 patients who initiated therapy with an off-label 2.5-mg twice a day dose, 13 (76%) had an "expected" level, while the remaining 4 (24%) had a level below their "expected" level (one of whom had a fluctuating creatinine which would have at times made 2.5-mg twice a day the on-label dose and at times the 5-mg twice a day the on-label dose). These findings were consistent across all age groups, including the very, very old (i.e., those over 90 years of age). A 91-year-old male weighing 145.6 pounds with a serum creatinine of 0.6 mg/dL treated with the on-label 5-mg twice a day dose had a trough apixaban level of 176.5 ng/mL, which is essentially the median peak level for the 5-mg twice a day dose (171 ng/mL) and significantly above the peak level for the 2.5-mg twice a day dose (123 ng/mL) (Table 1). Based on his elevated apixaban level, his dose was reduced to 2.5-mg twice a day.

Based on our clinic's experience, it appears that clinicians can identify patients who are at high risk of apixaban over-exposure. However, clinical characteristics alone appear to be insufficient, as a significant number of patients (almost 30%) with characteristics suggesting high exposure would be under-dosed using a purely clinical approach. Moreover, and more importantly, 70% of these patients who are at elevated risk of bleeding would have had excessive levels of apixaban if prescribing were based strictly on the established dose reduction criteria.

In contrast to atrial fibrillation, dose adjustment of apixaban[5] and rivaroxaban[22], the most prescribed DOACs, is not recommended for patients with DVT or PE. A dose reduction is recommended for edoxaban[23], from 60 mg to 30 mg once daily in patients with any one of the following: 1) creatinine clearance of 15 to 50 mL/min, 2) weight less than or equal to 60 kg, or 3) those taking certain concomitant P-gp inhibitor medications. Median and mean DOAC levels were lower in patients in the VTE clinical trials than in the atrial fibrillation trials. In the case of apixaban, the 5-mg twice a day dose in atrial fibrillation provides much higher drug levels at both peak, 171 as compared to 132 ng/mL for DVT, and trough 103 as compared to 63 ng/mL for atrial fibrillation and VTE, respectively (Table1). This is the result of a younger, lower weight population with better kidney function (Table 3). Thus, VTE patients who meet or approach the apixaban or rivaroxaban dose reduction criteria may have levels far in excess of what is needed to prevent recurrent events.

Table 3. Baseline characteristics of DOAC treated patients in atrial fibrillation and VTE outcomes trials

	Apixaban		Rivaroxaban			Dabigatran		Edoxaban		Meta-analysis
Diagnosis	AFIB	DVT-PE	AFIB	DVT	PE	AFIB	DVT-PE	AFIB	DVT-PE	AFIB
Trial	ARISTOTLE[6]	AMPLIFY[24]	ROCKET-AF[25]	EINSTEIN[26]	EINSTEIN[27]	RE-LY[28]	RECOVER[29]	ENGAGE AF-TIMI 48[11]	HOKUSAI-VTE[10]	ARISTOTLE, ROCKET, RE-LY, ENGAGE[30]
N	18,201	5,395	14,264	3,449	4,832	18,113	2,539	21,105	8,240	71,683
Age (yrs)	70	57	73	56	58	71	55	72	56	72
Male (%)	65	59	60	57	53	64	68	62	57	63
Weight (kg)	82	85	NR	NR	NR	83	86	NR	NR	NR
BMI (kg/m^2)	NR	NR	28	NR	NR	NR	28	NR	NR	NR
Creatinine Clearance (mean)	NR	NR	68	NR	NR	NR	106	NR	NR	NR
Population Stratified by Creatinine Clearance										
< 50 ml/min	17	6	21	7	8	20	6	19	7	19
50-79 ml/min	42	20	47	23	25	48	22	42	NR	45
≥ 80 ml/min	41	65	32	68	66	32	72	38	NR	36

Kg, Kilograms; BMI, Body mass Index; NR, not reported.

In fact, our clinic found this to be the case when apixaban levels were obtained in 15 male patients with VTE who clinically were at risk for over-exposure.[24] All 10 patients who were initially treated with apixaban 5-mg (2 of whom met the AF dose reduction criteria) had supratherapeutic apixaban levels on 5-mg twice a day. Of the 5 patients treated initially with apixaban 2.5-mg twice a day, 3 had adequate apixaban levels and would have had significantly elevated levels had they been treated with recommended dose of 5-mg twice a day, while the other 2 had trough levels that were on the lower side. In all 3 patients who met the apixaban AF dose reduction criteria, one of whom was treated initially with 2.5-mg, the 2.5-mg twice a day dose was the more appropriate dose.

A number of the DVT-PE patients had markedly elevated apixaban levels (e.g. trough > expected median peak), most notably one patient who met 2 of the 3 atrial fibrillation dose reduction criteria (age 91 and creatinine 1.5 mg/dL) and had a level at peak of 469.3 ng/mL, which is more than 3 times greater than the median VTE peak level (132 ng/ml) for 5-mg twice a day dosing and almost 4 times greater than the peak level for atrial fibrillation at the 2.5-mg twice a day dose (123 ng/mL).

There are additional clinical scenarios where assessment of DOAC levels could be of significant benefit. The first group consists of DOAC-treated patients who are receiving single or dual antiplatelet therapy with a combination of aspirin and/or a P2Y12 inhibitor (clopidogrel, prasugrel, and ticagrelor), especially those at increased risk of bleeding, the very elderly, and those with low weight, or renal dysfunction. Measurement of DOAC levels could be particularly important for those with a recent intracoronary stent or myocardial infarction who are at increased risk of catastrophic cardiac events, stent thrombosis, myocardial infarction, and death if there were a disruption in antiplatelet therapy because of bleeding. Moreover, these patients may require lower blood levels for prevention of thromboembolic events in the presence of antiplatelet therapy, as the combination of aspirin and clopidogrel[30] and aspirin[31] alone provide some, albeit lesser, thromboembolic protection in patients with atrial fibrillation.

Another cohort where knowledge of the drug level would be beneficial is patients whose creatinine clearance, creatinine, or weight, fluctuate above and below the cut-point for dose adjustment. As an example, the 80-year-old patient treated with apixaban whose serum creatinine fluctuates above

and below 1.5 mg/dL (e.g., from 1.4 to 1.6 to 1.4). It would seem to make pharmacologic and pharmacodynamic sense to know the apixaban level and select the dose based on the level rather than constantly check serum creatinine and change the dose up and down based on minor changes in creatinine or weight, or arbitrarily selecting a dose and risk under- or over-exposure.

Finally, those patients at extremes of the dose reduction criteria, including the very elderly (e.g., the 100-year-old), or the very low- (40-kg) or high-weight (200-kg) individual. For example, one of our clinicians (LB) recently saw a 101-year-old female who weighed 40-kilograms being treated for 6 months with apixaban 5-mg twice a day for a DVT, a dose which seems to be far in excess of what would be adequate.

Conclusion

In summary, the benefit-risk relationship of fixed-dose anticoagulant drugs could be improved with a strategy of DOAC level-based dose adjustment. Various factors can impact the thrombosis and bleeding balance of DOACs. Extremes of body mass, age, kidney function, and drug-drug interactions impact anticoagulant drugs in terms of dosing, safety, and efficacy, and should be carefully considered in the context of anticoagulant therapy.

Physicians should choose the most efficacious antithrombotic strategy for thromboembolism prevention, but also balance the risk of bleeding. Even minor bleeding has prognostic importance because it frequently leads to disruption of antithrombotic or anticoagulant therapy. Inconsistencies in dosing, including dose adjustment for VTE and dabigatran dosing in the elderly, highlight the knowledge gaps in DOAC prescribing recommendations. As opposed to prescribing based on empiric decisions and estimations of drug levels, it would seem prudent to switch to a strategy based on actual drug levels. This would generally require measuring levels once or twice after therapy initiation, as opposed to the chronic monitoring required for vitamin K antagonists.

Our approach has been to evaluate drug levels in the types of patients described above. Then, to use the peak and trough levels to decide whether to adjust the dose of the DOAC or switch to another DOAC or warfarin using the principles of under- and over-exposure outlined above.

We continue to accumulate data while treating these patients, and hope to continue to share our findings in the future. We recognize that even patients without the clinical characteristics associated with under- or over-exposure may have under- or over-exposure and thus may benefit from having a single level obtained after reaching steady state.

Conflicts of Interest Statement

The authors have no conflicts of interest to declare.

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