Does One Dose Really Fit All? On the Monitoring of Direct Oral Anticoagulants: A Review of the Literature

Thomas Moner-Banet[1] Lorenzo Alberio[2] Pierre-Alexandre Bart[3]

[1] Department of Internal Medicine, Riviera-Chablais Hospital, Rennaz, Switzerland
[2] Division of Haematology and Central Haematology Laboratory, CHUV Lausanne University Hospital, University of Lausanne (UNIL), Lausanne, Switzerland
[3] Department of Internal Medicine, CHUV Lausanne University Hospital, University of Lausanne (UNIL), Lausanne, Switzerland

Address for correspondence Lorenzo Alberio, MD, Division of Haematology and Central Haematology Laboratory, Centre Hospitalier Universitaire Vaudois (CHUV), Rue du Bugnon 46, 1005 Lausanne, Switzerland (e-mail: lorenzo.alberio@chuv.ch).

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Abstract

Background There is an increasing amount of literature on direct oral anticoagulant (DOAC) laboratory monitoring. The aims of the present review were to evaluate published data on monitoring DOACs, to provide clinical guidance on how to interpret results, and to summarize why, when, and how to monitor DOACs.

Methods The publications screened for this review were obtained through a PubMed search for articles published in English or French before April 2019 that had the following as their main themes: DOAC monitoring, DOAC exposure–effect relationship, DOAC drug interactions, and pharmacokinetics and pharmacodynamics of DOACs.

Results DOACs show important inter- and intrapersonal concentration variability and a significant exposure–effect relationship. Concentrations out of the expected range have been shown to lead to an increased adverse event rate and a lower efficacy. No definitive therapeutic range exists for DOACs except for dabigatran for which trough levels of 40 to 200 ng/mL seem to be the consensus. Indications to monitor include suspected drug accumulation in special patient populations, suspected drug failure, and acute situations such as hemorrhagic or thrombotic events.

Conclusion There is a likely benefit to monitor DOACs in order to improve their safety and efficacy but randomized controlled trials are required to determine the therapeutic range of these drugs and evaluate whether DOAC monitoring can improve outcomes in a clinical setting.

Keywords
- direct oral anticoagulant
- monitoring
- dose tailoring
- plasma level

Introduction

Since the 20th century, oral anticoagulation has been performed using vitamin K antagonists (VKAs), which require regular laboratory monitoring due to their unpredictable pharmacokinetics and pharmacodynamics. This sparked an interest for better molecules that would be simpler to use and less variable in their efficacy. A few years ago, the direct oral anticoagulants (DOACs) hit the market. Their key features are the simplified posology (marketed as "one dose fits all") and the lack of a need for monitoring. Their place in the therapeutic arsenal is in rapid expansion as an increasing number of studies are conducted on different patient populations.

Since their approval, DOACs have been subject to controversy regarding whether or not they should be monitored; this debate continues to this day. Since "one dose" DOACs have shown similar, if not better, efficacy and safety as VKAs,

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little research has been performed to study the possible benefits of individual dose tailoring for these drugs. However, DOACs have been shown to display considerable variation in their plasma levels and out-of-target concentrations could lead to an increased risk of adverse events such as bleeding or thromboembolism.

Currently, it is still unclear whether DOACs should be monitored. Therefore, we propose in this article a review of the literature on this topic, showing if, when, and how DOACs should be monitored.

Research Strategy

The publications screened for this review were obtained through a PubMed search for articles published in English or in French before April 2019 that had the following as their main themes: DOAC monitoring, DOAC exposure–effect relationship, DOAC drug interactions, and pharmacokinetics and pharmacodynamics of DOACs.

The following keywords were used either alone or in combinations: "direct oral anticoagulant," "DOAC," "novel oral anticoagulant," "NACO," "Dabigatran," "Rivaroxaban," "Apixaban," "Edoxaban," "monitoring," "concentration," "plasma level," "laboratory," "safety," "bleeding," "ischemic event," "stroke," "thromboembolism," "therapeutic range," "interaction," and "dose tailoring."

The articles were compiled, reviewed, and selected if they presented either a review of the literature, a meta-analysis, or original clinical data on DOAC monitoring. Then their bibliographies were reviewed and articles were selected among them following the same principles.

Official product information and European Medicines Agency and U.S. Food and Drug Administration (FDA) documentation for mentioned DOACs were also reviewed.

Why Should We Monitor DOACs?

DOACs meet most of the usual criteria for requiring some form of dose tailoring or therapeutic drug monitoring.[1] They notably show important intra- and interpersonal variability in concentrations and new data suggest that out-of-target concentrations are linked to more frequent adverse events. DOAC characteristics are summarized in ►Table 1.

The absence of initial routine monitoring guidelines from licensing authorities seems in part to be the result of direct comparison to VKA instead of safety and efficacy optimization. The consensus being that monitoring would be superfluous since "one dose" DOACs have shown noninferior, if not better, efficacy and safety as VKAs.[2–5]

In the next sections, we will review the available data on concentration variability and exposure–effect relationship for each DOAC.

Dabigatran

The RE-LY trial,[2] a study that compared two dabigatran doses with warfarin in atrial fibrillation (AF), was further analyzed by Reilly et al.[6] They evaluated the rate of bleeding events in relation to dabigatran trough levels. They found that the trough levels of dabigatran were subject to important variations with a fivefold increase between the 10th and 90th percentiles.

Age and creatinine clearance were the principal modifiers. The variable bioavailability of dabigatran (3–7%) could also be implicated, as suggested by Powell.[7] Genetic single nucleotide polymorphism (SNP) variants might also increase variability, as discussed further in this article.[8]

Reilly et al. showed a 55% trough level increase in patients with major bleeding events. The rate of ischemic events was increased among patients with low trough concentrations. The authors concluded that there was no optimal dose that would work for all patients and that a subset of patients could benefit from individualized dose tailoring by monitoring of dabigatran trough concentrations.

Boehringer Ingelheim, the manufacturer of dabigatran, was accused of withholding information regarding the potential benefits of monitoring dabigatran. A *British Medical Journal* (BMJ) investigation revealed that during U.S. litigation the company was forced to release internal correspondence and documentation.[9] The BMJ reported that in these documents an optimal benefit–risk ratio within 40 to 215 ng/mL for dabigatran trough concentrations was indicated. Moreover, in these internal communications concerns were voiced about not being able to defend the "no monitoring" attitude to health authorities after Reilly et al.'s study.

A Boehringer Ingelheim internal simulation study of the RE-LY data with dose tailoring showed a better safety profile if patients treated by dabigatran 150 mg with trough levels of >90 ng/mL after 1 week had a dose switch to 110 or 75 mg/day.[10] This dose titration showed comparable ischemic event rates versus no titration (risk ratio [RR] = 1.06, confidence interval [CI] 90%: 0.76–1.5), but the risk of major bleeding was significantly reduced (RR = 0.8, CI 90%: 0.66–0.97). These data were not shared with regulation authorities. As early as 2015, Safouris et al. studied the idea of an algorithm to adjust dabigatran doses first in regard to the patient characteristics and then depending on a plasma concentration measurement made in certain situations.[11] They suggested that doses should be adjusted if trough concentrations were out of the 48 to 200 ng/mL range.

Pradaxa FDA approval papers directly mention the relationship between trough levels and bleeding risk using data from the RE-LY trial.[12] Even with these data, the FDA did not, at the time, require any form of routine monitoring as their conclusions were that the 110 and 150 mg doses were respectively better and equivalent to warfarin in terms of bleeding risk.[2,12] Product information of dabigatran presents thresholds for increased bleeding risk (trough levels >200 ng/mL in therapeutic indications, or >2 times the upper limit of normal activated partial thromboplastin time).[13]

A study by Šinigoj et al. ($n = 44$) showed that bleeding patients had significantly higher dabigatran trough levels (93 ± 36 vs. 72 ± 62 ng/mL, $p = 0.02$); however, they found no association between peak levels and bleeding risk.[14] Albaladejo et al. in a study including patients hospitalized for bleeding events while taking DOACs found that the median concentration of dabigatran was 162 ng/mL (range: 3–3,500 ng/mL; median

Table 1 Summary of DOAC characteristics

DOAC		Dabigatran (Pradaxa)	Rivaroxaban (Xarelto)	Apixaban (Eliquis)	Edoxaban (Lixiana)
References		12,13,96,108,109	22–24,105,110,111	41,42,112,113	48,114–117
Target		Factor IIa	Factor Xa	Factor Xa	Factor Xa
Approved indications		VTE treatment Stroke prevention in AF (with restrictions)	VTE prevention in orthopaedics VTE treatment Stroke prevention in AF	VTE prevention in orthopaedics VTE treatment Stroke prevention in AF	VTE treatment Stroke prevention in AF
Posology	VTE prophylaxis	–	10 mg qd	2.5 mg bid	–
	VTE treatment	150 mg bid	15 mg bid for 3 wk then 20 mg qd	10 mg bid for 7 d then 5 mg bid	60 mg qd
	Stroke prevention	150 mg bid	20 mg qd	5 mg bid	60 mg qd
Posology adaptation		110 mg bid if GFR 30–49 mL/min or >80 y old	15 mg od if GFR < 49 mL/min	2.5 mg bid if 2/3: • > 80 years old • < 60 kg • Cr >133 µmol/L	30 mg od if GFR 15–49 mL/min or <60 kg or P-gp inhibitor
Not indicated		GFR < 30 mL/min Child A–C cirrhosis	GFR < 15 mL/min Child C cirrhosis Should be used with caution if GFR < 30 mL/min	GFR < 15 mL/min Child C cirrhosis	GFR < 15 mL/min Child C cirrhosis
Bioavailability		3–7%	80–100%	50%	62%
Protein fixation		35%	95%	87%	40–60%
Time to peak		0.5–2 h	2–4 h	3–4 h	0.5–3 h
Metabolism		UGT (20%)	CYP 3A4/3A5/2J2	CYP 3A4/3A5	CYP 3A4 (minimal)
Elimination		80% renal, active form 20% renal and biliary, metabolites	36% renal, active form 32% renal metabolites 32% biliary metabolites	30% renal, active form 45% biliary, active form 25% renal and biliary metabolites	50% renal, active form 40% biliary, active form 10% renal and biliary metabolites
Half-life		12–14 h	5–13 h	8–15 h	10–14 h

Abbreviations: AF, atrial fibrillation; bid, twice daily; DOAC, direct oral anticoagulant; GFR, glomerular filtration rate; od, once a day; PE, pulmonary embolism; qd, every day; VTE, venous thromboembolism.

time of measurement: 8.5 hours (0.8–29 hours) after the last dose, $n = 123$), which is a value in the peak range measured at almost trough time.[15] Volbers et al. found in a study measuring dabigatran levels in acute cerebrovascular events ($n = 19$) that patients with intracranial hemorrhage had significantly higher plasma concentrations in comparison to patients with an acute ischemic event ($p < 0.05$).[16] The BISTRO II ($n = 351$) randomized trial, which compared enoxaparin to dabigatran for orthopaedic prophylaxis showed a correlation between dabigatran peak concentrations and deep venous thrombosis and bleeding events using a logistic regression analysis. They did not analyze trough levels.[17] Testa et al. ($n = 565$) associated patients with low dabigatran trough levels and high CHA2DS2-VASc scores with thromboembolic events.[18] Chin et al. in a simulation study using data from the RE-LY trial and Reilly et al.'s follow-up study estimated that a trough concentration of 30 to 130 ng/mL was optimal and proposed the thrombin time (TT) as a screening assay (trough TT target of 130–300 seconds, with a normal range in their laboratory of 18–28 seconds).[19] Recently Chaussade et al. associated trough levels of >243.9 ng/mL to higher bleeding rates in a prospective study realized in a geriatric setting. This cutoff had a sensitivity of 54% and a specificity of 98% ($n = 68$). They found that patients who bled during the 1-year follow-up had higher dabigatran trough and peak levels ($p = 0.01$ for both).[20]

Another substudy of the RE-LY trial showed that some SNPs had an impact on bleeding risk. One of which had 32% prevalence in the white European ancestry population and significantly reduced dabigatran exposure and bleeding risk; the authors suggested genetic screening before treatment in such patients.[8] Another approach could be to use laboratory monitoring with dose-tailoring strategies in these patients.

Overall, these studies demonstrate that out-of-expected range concentrations of dabigatran can lead to a higher adverse event rate and that there is potential for some form of therapeutic drug monitoring to improve outcomes for patients.

Rivaroxaban

Despite its rather constant bioavailability, rivaroxaban also exhibits multiple-fold plasma trough and peak level variations.[21–24] Gulilat et al. even reported 60-fold variations in random plasma levels ($n = 94$).[25] Genetic variants have

been identified that could explain part of this important variability.[26]

The dose-exposure effect of rivaroxaban is well known, with higher doses leading to significantly more bleeding.[27] The FDA approval papers for Xarelto mention an increased bleeding risk as the area under the curve (AUC) increases, a twofold increase resulting in 50% more major bleeds.[23]

A Japanese study by Nakano et al. analyzing prothrombin time (PT) measurements made with the HemosIL Recombi-PlasTin assay (normal range: 8–12 seconds) found an increased risk of bleeding in patients with peak PT >20 seconds (62.5 vs. 22.7%, $p = 0.022$). In this study, the trough PT was not associated with bleeding events (likely due to the lack of sensitivity of PT).[28] Woodruff et al. compared PT levels measured within 24 hours of taking rivaroxaban in a retrospective study ($n = 199$) and were able to conclude that patients with PT >30 seconds (twice the upper limit of the normal PT of the assay used in the study) had a threefold higher bleeding risk compared with those with PT <30 seconds ($p = 0.006$).[29] In a recent study involving 94 patients, Sakaguchi et al. showed that the rivaroxaban peak concentration was an independent predictive bleeding risk factor ($p = 0.012$). Trough levels were not associated with bleeding in this study.[30] In a prospective study ($n = 156$), Wada et al. showed that the rivaroxaban peak concentration was an independent predictive variable for the risk of bleeding ($p < 0.01$). In the same study, higher trough levels showed a nonsignificant trend toward higher bleeding risk.[31] Albaladejo et al. in a study including patients taking rivaroxaban hospitalized for bleeding events ($n = 285$) found that the median concentration of rivaroxaban was 124 ng/mL (range: 0–1,245; median time of measurement: 14 hours [0.2–62 hours] after the last dose), which is a high value for such timing.[15] Krause et al. were able to show in a prospective study involving 212 young venous thromboembolism patients that a weight-adjusted dose (mg/kg) was correlated with bleeding rates ($p < 0.01$) and found that bleeders showed a trend toward higher trough levels ($p = 0.08$).[32]

A study performed by Seiffge et al. on stroke patients ($n = 241$) did not find a difference between the plasma levels of ischemic and hemorrhagic stroke patients at the time of the event.[33] This may be due to the fact that they included patients who had peak concentrations as well as patients who had trough concentrations. Similarly, in a small study ($n = 23$), Zalewski et al. found no relation between trough levels and bleeding rates.[34]

Much circumstantial data on the rivaroxaban exposure–effect relationship come from case reports.[35,36] However, case reports have also shown that despite overdoses of rivaroxaban and apixaban (showing very high anti-Xa activity), sometimes no bleeding occurred.[37,38] An observational study reporting rivaroxaban and apixaban overdoses described a 7% bleeding rate; although anti-Xa values were not measured, these data support the fact that a high plasma level does not necessarily lead to a bleeding episode.[39] This may suggest that the anticoagulant effect of a given rivaroxaban concentration varies as a function of the individual prothrombotic state and that acutely elevated rivaroxaban trough levels are less predictive of bleeding than long-lasting overexposure.

These studies seem to show that rivaroxaban concentrations can affect outcomes such as bleeding or thrombosis and that interindividual variation is to be expected regarding the efficacy of the drug. However, evidence is less clear than for dabigatran and data on possible therapeutic ranges are still lacking. Peak levels seemed to be more correlated to adverse events than trough levels, which could be due to the low sample size and small effect size of variations in trough levels in the mentioned studies.

Apixaban

Apixaban trough levels vary significantly, as for dabigatran and rivaroxaban.[40] Early pharmacokinetics studies showed a variance of around 30% for the AUC of apixaban concentration, which is less variable than other DOACs.[41] Eliquis product information shows a four- to sixfold variation in trough levels across most dosages but mentions that no clinically relevant information for a single patient can be extrapolated from these data alone.[42] Gulilat et al. reported a 50-fold variation in random plasma levels.[25] Ueshima et al. found in a genomic study involving Japanese patients that there were genotypes that could affect significantly apixaban plasma levels.[43]

Apixaban FDA approval papers show that increased AUCs at a steady state lead to higher bleeding rates ($p = 0.02$). A twofold increase in AUC meant that the risk of major bleeding over 1 year increased from 1.79 to 3.11% (70% increase).[44] In a prospective study involving 169 patients taking apixaban, Wada et al. showed that both trough and peak levels were independent predictors of bleeding risk ($p < 0.01$).[31] Bhagirath et al. using data from the AVERROES trial found a significant correlation between apixaban trough levels and minor bleeding ($p < 0.01$) and that patients in the lowest trough level decile had an increased stroke risk ($p = 0.013$).[45] In a study of patients taking DOACs hospitalized for bleeding events ($n = 34$), Albaladejo et al. found that the median concentration of apixaban was 111 ng/mL (range: 18–537; median time of measurement 11 hours [2.6–87 hours] after the last dose), which is a highly elevated value at almost trough time.[15] However, in a simulation study using data from clinical trials and analyzing the exposure–response relation for apixaban, Byon et al. found no significant relation between trough levels and bleeding events.[46]

Overall, the data for apixaban also seem to suggest that a significant exposure–effect relationship exists and that dose tailoring could help improve outcomes.

Edoxaban

Edoxaban is also known for multiple-fold inter- and intrapersonal variability.[47]

Edoxaban FDA approval papers specifically mention relationship between trough levels, renal function, and bleeding risk, a twofold increase in trough levels meaning a doubling of bleeding rates.[48]

Weitz et al. in a phase II study ($n = 1146$) that compared edoxaban to warfarin in AF were able to show that increased exposure was correlated with bleeding rates, with trough levels being the most predictive parameter ($p = 0.01$ for major bleeds, as calculated by Giugliano).[49,50] Salazar et al. showed in an exposure–outcome modeling analysis of phase I and II trials of edoxaban that plasma levels seemed to be correlated to bleeding, trough levels being again the most predictive factor ($p < 0.001$).[51] Ruff et al. in a subanalysis of the ENGAGE trial, comparing edoxaban to warfarin, showed that there was a similar safety with dose-tailored edoxaban and classic warfarin therapy. The dose tailoring was done on clinical factors alone. In this study higher trough concentrations led to more bleeding events and lower trough concentrations were linked to increased thromboembolic events.[52] Yin et al. also analyzed data from the ENGAGE trial and found that a higher percentage of inhibition of endogenous factor Xa (FXa) activity (obtained using a Russell's viper venom test) was correlated with both major bleeding and thromboembolic and stroke events when levels of inhibition were high and low, respectively ($p < 0.001$). They also identified a threshold at which the inhibition of FXa activity was capped (440 ng/mL).[53] Chao et al. compared Asians to non-Asians in regard to the safety profile of edoxaban in the ENGAGE trial and found that there was a better safety profile for Asians, which they explained with lower mean trough levels.[54]

In summary, the exposure–effect relationship for edoxaban seems well defined with trough levels being the most predictive parameter but precise therapeutic intervals are still lacking.

Is There a Known Therapeutic Range for DOACs?

Although many studies have measured peak and trough levels while on treatment, a therapeutic range cannot be extrapolated from that data alone. We summarized observed plasma concentration data for multiples indications for each DOAC in ►Table 2.

Data suggest that there could be an optimal risk–benefit range in which DOAC concentrations can be stabilized. However, no study has validated a therapeutic interval for any DOAC as of yet and the precise levels for each DOAC at which the risk of thromboembolism or bleeding increases are not yet known. ►Fig. 1 summarizes cut-off values and suggested therapeutic ranges, if they exist. It is worth noting that the quality of the data used to create these ranges is low and that care should be taken when interpreting results.

Methods of Monitoring

Standard DOAC monitoring is not easy considering that clinicians are not as familiar with it as with VKA and international normalized ratio. Most easily accessible laboratory assays are unspecific and/or unable to cover the whole range of concentrations that would be needed for efficient monitoring and more specialized assays (anti-IIa and anti-Xa assays) are only available in some laboratories today.

►Table 3 summarizes current monitoring guidelines for DOACs and gives recommendations for interpretation of standard coagulation tests.

Indications for Monitoring

While the lack of data for the clinical outcomes of monitoring is an obstacle to clear indications, guidelines for laboratory and clinical monitoring in specific situations are appearing.[55,56] In the next section we address which patient populations should be considered for monitoring.

Off-Label Doses

Studies have shown that approximately 25% of patients on DOACs are inappropriately dosed.[57,58] This is likely due to factors outside approved dosing criteria, making clinicians cautious to prescribe the full dosage and perhaps a bias in the perception of bleeding risk, which is overestimated by clinicians.[59,60] Underdosing was shown to increase thromboembolic event and stroke rates.[61] Similarly, inappropriately highly dosed patients had a higher bleeding rate.[62]

While some instances of these inappropriately dosed patients are likely due to lack of awareness of the recommendations for DOAC prescription, patients with unique characteristics for whom the risk–benefit ratio of various doses is uncertain are potential targets for DOAC monitoring to confirm the maintained efficacy of an off-label dose.

Renal Insufficiency

All DOACs are at least partially eliminated by the kidneys, and the low glomerular filtration rate (GFR) has been associated with higher AUCs and higher bleeding rates across most dosages for most DOACs, thus justifying the use of adjusted doses in patients with <50 mL/min GFR.[63] Patients with chronic kidney disease (CKD), notably due to uremic toxins, are at a higher risk of bleeding and of thromboembolic events.[64] This increases the risk of adverse events when out-of-target range excursions of plasma concentrations of DOAC occur, possibly justifying a closer monitoring of their plasma levels to ensure optimal safety.

DOACs showed a similar, if not better, efficacy and safety profile in renal failure patients when compared with VKA.[65–67] Rivaroxaban also showed lower rates of stroke and systemic embolism without a change in bleeding rates in patients with at least one episode of >20% decrease in renal function during follow-up in a re-analysis of the ROCKET-AF trial which compared it to warfarin.[68]

Despite initial and once per year renal function work-up, renal function can often deteriorate acutely and lead to retention of DOACs, especially in elderly patients. This is confirmed by a recent study that associated variation of renal function over time and major bleeding events in DOAC-treated AF patients.[69] Therefore, patients with suspected or confirmed acute impaired renal function should be considered for DOAC laboratory monitoring.

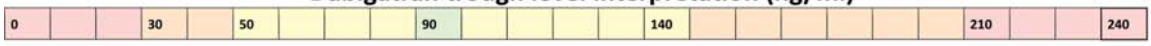
Table 2 Observed peak and trough concentrations for different indications and DOACs

DOAC	Population	Peak levels	Ref.	Trough levels	Ref.
Dabigatran 150 mg bid	Stroke prevention in patients with AF	175 (74, 383)[a] 184 (64, 443)[b] 159 (±83)[c]	6 104 14	91 (40, 215)[a] 90 (31, 225)[b] 69 (±40)[c]	6 104 14
Dabigatran 110 mg bid	Stroke prevention in patients with AF and GFR 30–49 mL/min or >80 y old	187 (±122)[c]	14	90 (±71)[c]	14
Dabigatran 150 mg bid	Treatment of DVT/PE	175 (117, 275)[d]	118	60 (39, 95)[d]	118
Rivaroxaban 20 mg qd	Treatment of DVT/PE	270 (189, 419)[e] 215 (22, 535)[a]	22 105	26 (6, 87)[e] 32 (6, 239)[a]	22 105
Rivaroxaban 20 mg qd	Stroke prevention in patients with AF	249 (184, 343)[e]	22	44 (12, 137)[e]	22
Rivaroxaban 15 mg qd	Stroke prevention in patients with AF and GFR 30–49 mL/min	229 (178, 313)[a]	22	57 (18, 136)[a]	22
Rivaroxaban 10 mg qd	VTE prevention after orthopaedic surgery	125 (91, 196)[b] 101 (7, 273)[a] 149 (108, 209)[b]	22 105 21	9 (1, 38)[b] 14 (4, 51)[a] 17 (8, 50)[b]	22 105 21
Apixaban 10 mg bid	Treatment of DVT/PE for the first 7 d	251 (111, 572)[b]	42	120 (41, 335)[b]	42
Apixaban 5 mg bid	Treatment of DVT/PE after 7 d	132 (59, 302)[b]	42	63 (22, 177)[b]	42
Apixaban 5 mg bid	Stroke prevention in patients with AF	171 (91, 321)[b]	42	103 (41, 230)[b]	42
Apixaban 2.5 mg bid	VTE prevention in elective orthopaedic surgery	77 (41, 146)[b]	42	51 (23, 109)[b]	42
Apixaban 2.5 mg bid	Stroke prevention in patients with AF if 2/3: • 80 years old • < 60 kg • Creatinine > 133 µmol/L	123 (69, 221)[b]	42	79 (34, 162)[b]	42
Apixaban 2.5 mg bid	Prevention of DVT/PE after 6 mo of therapeutic treatment	67 (30, 153)[b]	42	32 (11, 90)[b]	42
Edoxaban 60 mg qd	Treatment of DVT/PE	234 (149, 317)[d]	107	19 (10, 39)[d]	107
Edoxaban 60 mg qd	Stroke prevention in patients with AF	170 (120, 245)[f] 301 (60, 569)[g]	49 47	36 (19, 62)[d] 39 (13, 110)[g]	52 47
Edoxaban 30 mg qd	Treatment of DVT/PE in patients with >1/3: • GFR 30–49 mL/min • ≤ 60 kg • p-gp inhibitor	164 (99, 225)[d]	107	16 (8, 32)[d]	107
Edoxaban 30 mg qd	Stroke prevention in patients with AF with >1/3: • GFR 30–49 mL/min • ≤ 60 kg • p-gp inhibitor	85 (55, 115)[f] 169 (10, 400)[g]	49 47	27 (15, 45)[d] 38 (7, 147)[g]	52 47

Abbreviations: AF, atrial fibrillation; bid, twice daily; DOAC, direct oral anticoagulant; DVT, deep venous thrombosis; GFR, glomerular filtration rate; qd, every day; VTE, venous thromboembolism.
[a]Mean (10th, 90th percentiles).
[b]Median (5th, 95th percentiles).
[c]Mean (SD).
[d]Median (IQR).
[e]Mean (5th, 95th percentiles).
[f]Median (1.5 × IQR), obtained from box plots.
[g]Mean (min, max).

*In **green**: estimated median concentration target. In **yellow**: estimated target range. In **orange**: increased risk of adverse event. In **red**: highly increased risk of adverse event*

Dabigatran trough level interpretation (ng/ml)



28 ng/ml: 50% increased stroke and thrombo-embolic event (Reilly et al.)[6]
48 ng/ml: proposed dose adjustment threshold by Safouris et al.[11]
90 ng/ml: threshold at which the 110 mg bid dosage was proposed in a Boehringer Ingelheim simulation study[10] and median concentration in pharmacokinetic studies for the 150 bid dosage[104]
140 ng/ml: threshold at which the 75 mg bid dosage was proposed in a Boehringer Ingelheim simulation study[10]
200 ng/ml: proposed dose adjustment threshold by Safouris et al.[11]
210 ng/ml: doubled bleeding risk if above this level when compared to median of 88 ng/ml(Reilly et al.)[6]
225 ng/ml: 90th percentile of trough concentrations[104]
244 ng/ml: This cut-off had a sensitivity of 54% and a specificity of 98% for predicting bleeding (Chaussade et al.)[20]

Rivaroxaban trough level interpretation (ng/ml)

10 ng/ml: mean 5th percentile of concentrations in pharmacokinetic studies[22,105]
35 ng/ml: mean concentration in pharmacokinetic studies[22,105]
110 ng/ml: mean 95th percentile of concentrations in pharmacokinetic studies[22,105]
124 ng/ml: median concentration in rivaroxaban taking patients admitted for bleeding[15]
150 ng/ml: rough conversion to ng/ml of PT 20-30s using PT-concentration graphs from,[23] associated in multiple studies with higher rates of bleeding[28-30]

Apixaban trough level interpretation (ng/ml)

17 ng/ml: significantly increased risk of stroke (Bhagirath et al.)[45]
60-100 ng/ml: median concentration in pharmacokinetic studies[42]
130 ng/ml: significantly increased bleeding risk (Wada et al.),[31] concentrations were extrapolated from anti-Xa activity using data from Beyer et al.[106]
200 ng/ml: mean 95th percentile of concentrations in pharmacokinetic studies[42]
230 ng/ml: 20% increased bleeding risk compared to expected median trough concentration (Bhagirath et al.)[45]

Edoxaban trough level interpretation (ng/ml)

10 ng/ml: 5th percentile of through concentrations[48]
27 ng/ml: median concentration in pharmacokinetic studies,[52,107] 2% major bleeding risk over one year (data from a subset of patients with normal clearance of ENGAGE AF)[48]
55 ng/ml: 4% major bleeding risk over one year[48]
65 ng/ml: 90th percentile of concentrations[47]
130 ng/ml: doubling of major bleeding risk for a through edoxaban level after one month of therapy compared to a 6% bleeding risk for the median concentration in pharmacokinetic studies (27 ng/ml), extrapolated from a graph by Ruff et all. data from ENGAGE-AF with a mean follow up of 2.8 years.[52]

Fig. 1 Proposed DOACs through level interpretation. In *green*: estimated median concentration target. In *yellow*: estimated target range. In *orange*: increased risk of adverse event. In *red*: highly increased risk of adverse event. DOAC, direct oral anticoagulant.

Table 3 DOAC monitoring methods (based on various studies[119–122])

Coagulation test	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
PT	Less sensitive than APTT. Not usable	Normal PT likely excludes excess plasma concentrations but does not exclude concentrations within the therapeutic range. Variable between laboratories	Not sensitive enough to be used	Normal PT likely excludes excess plasma concentrations but does not exclude concentrations within the therapeutic range. Variable between laboratories
INR	International sensitivity ratio not available for dabigatran. Not usable	International sensitivity ratio not available for rivaroxaban. Not usable	International sensitivity ratio not available for apixaban. Not usable	International sensitivity ratio not available for edoxaban. Not usable
APTT	Normal APTT likely excludes excess plasma concentrations but does not exclude concentrations within the therapeutic range. Variable between laboratories	Less sensitive and more variable than PT	Less sensitive than PT. Not usable	Less sensitive than PT. Not usable
TT	Normal TT excludes clinically relevant dabigatran presence. Too sensitive for quantitative measurement			
Anti-Xa (calibrated)		Sensitive, linear across clinical ranges. Quantitative assay	Sensitive, linear across clinical ranges. Quantitative assay	Sensitive, linear across clinical range. Quantitative assay
Anti-IIa (calibrated)	Sensitive, linear across clinical ranges. Quantitative assay			
Recommendation	TT to exclude drug presence. Calibrated Anti-IIa for quantitative measurement	PT to exclude excess drug concentration. Calibrated Anti-Xa for quantitative measurement	Calibrated anti-Xa for quantitative measurement	PT to exclude excess drug concentration. Calibrated anti-Xa for quantitative measurement
		A normal PT cannot exclude the presence of anti-Xa DOACs		

Abbreviations: APTT, activated partial thromboplastin time; DOAC, direct oral anticoagulant; INR, international normalized ratio; PT, prothrombin time; TT, thrombin time.

Overall, while patients with CKD could benefit from plasma level monitoring, studies still need to be conducted to attest the usefulness of such monitoring.

Elderly Patients

Old age was associated with more adverse events in DOAC trials. However, DOACs still mostly presented a similar or better safety profile in the elderly when compared with warfarin.[70–72] Lower rates of bleeding were observed in >75-year-old patients taking reduced dose edoxaban in the ENGAGE trial, showing the impact of dose reduction.[70] Dabigatran 150 twice daily (bid) and rivaroxaban 20 mg once daily were shown to increase risk of major bleeding when compared with warfarin in the elderly but older elderly patients (>75 years old) were those who benefited the most from the treatment (lowest number needed to treat).[73] Of note, the deterioration of renal function is highly correlated with age and could explain by itself the higher rates of bleeding in elderly patients.

A study performed by Bando et al. showed that there was no increased adverse event rates when compared with younger patients with adequate dose reduction of rivaroxaban in elderly patients with AF.[74] Nissan et al. showed that above-expected range trough and peak plasma levels of apixaban are more frequent in elderly patients, even on the right dosage.[75] In a study performed by Khan et al. on over 75-year-old AF patients taking DOACs, those with major bleeding also presented an acute deterioration of renal function. This underlines the importance of GFR monitoring in the elderly taking DOACs.[76] Finally, hypoalbuminemia, a frequent condition in the elderly, has also been associated with higher rates of bleeding in rivaroxaban-taking patients.[29]

Elderly patients are a fragile population in which bleeding events could be more frequent for those taking DOACs. Severity and consequences of bleeding events are likely to

be worse in older patients due to frailty and comorbidities. DOAC concentration fluctuations out of the target range are likely to be more frequent due to GFR variation, hypoalbuminemia, and polymedication. This perhaps warrants some form of monitoring in this population to ensure an optimal safety profile. However, studies are needed to verify the usefulness of this approach and determine if old age is an independent risk factor for adverse events in the elderly taking DOACs.

Thromboembolic and Bleeding Events

A thrombotic or hemorrhagic event under well-conducted DOAC treatment should always raise the question of out-of-target drug levels versus real treatment failure (i.e., side effect occurring despite an adequate drug level). Monitoring should be performed in such circumstances in the emergency department especially now that antidotes are on the market. Plasma levels can help determine when these expensive drugs are really needed and help follow the reversal of the anticoagulation when they are given. A threshold of >50 ng/mL is usually used to consider an antidote administration in severely bleeding patients.[77,78]

Dosing Errors

Dosing errors (overdoses most often) are good indications for DOAC monitoring. Although not all overdoses lead to bleeding and the necessity of reversing anticoagulation as mentioned before,[37,38] knowing the drug levels can be very useful in the clinical setting.

Surgical Procedures and Emergency Invasive Procedures

DOACs should not be routinely interrupted before minor surgical procedures.[79] They should be stopped at least 2 to 3 days before any surgical procedure with a high bleeding risk or even sooner should renal function be altered and resumed 48 hours later. For low bleeding risk procedures, DOACs should be stopped 1 to 2 days before or sooner depending on renal function, DOACs should then be resumed after 24 hours.[80–82] Therefore, for the majority of elective patients, DOAC monitoring is not needed. However, in CKD patients and in patients taking interacting drugs, monitoring cold be useful.[83]

In cases where the appropriate stopping period cannot be easily assessed or followed, such as emergency procedures, drug monitoring can give critical information to the clinician. Guidelines exist regarding the thresholds that should be used[84] but little data support these values and a lot of debates exist regarding whether monitoring should be used while we lack precise cut-offs. A summary of existing thresholds can be found in ►Table 4. These values might be too conservative as they represent more or less the usual trough levels in healthy patients and very little data are available on the individual anticoagulant potential of a given concentration.[85] When possible, surgery should be delayed until DOAC activity in plasma is below these thresholds, otherwise reversal should be considered when the procedure cannot be delayed and plasma concentrations of DOACs are significantly higher than >30 ng/mL.[77,78]

When thrombolytic treatment for stroke is needed, DOAC levels should be monitored to ensure the safety of the procedure. Certain thresholds have been defined to consider a patient safe for thrombolysis; these can be found in ►Table 4.

DOAC monitoring in the perioperative setting probably has a place since it can greatly influence the clinician's decisions; however, more studies are required to clearly identify safe thresholds for various procedures and when reversal is needed.

Liver Insufficiency

Patients with liver insufficiency have often been excluded from phase III DOAC trials and therefore little data on how this affects drug levels have been produced. DOACs are all partly eliminated by the liver and therefore caution should be exerted in such cases. Therefore, DOACs are currently contraindicated in severe cirrhosis, especially if there is associated coagulopathy. The AUC of rivaroxaban doubles in patients with Child-B cirrhosis[86]; a doubling in AUC has been shown to increase by 50% the risk of major bleeding in patients taking rivaroxaban.[23] A meta-analysis on the subject of DOACs in cirrhosis patients showed that DOACs have a similar safety profile as VKA and low-molecular-weight heparin.[87]

Bleeding and thromboembolic events are more frequent in cirrhosis.[88] In addition to DOAC accumulation due to liver failure, hypoalbuminemia, a common factor in cirrhosis, is associated with higher bleeding rates in rivaroxaban.[29] Therefore, specific care should be taken in cirrhotic patients receiving DOACs, especially since hepatic vein thrombosis is starting to be treated with DOACs off label.[89]

Monitoring DOAC concentrations in this patient population could lead to better safety and efficacy but studies are needed to confirm the usefulness of it.

Drug Interactions

DOACs are subject to many clinically important interactions (see ►Table 5) with significant variations in their concentrations. Most of these drugs are not formally contraindicated and caution measures, such as monitoring DOAC levels, could be taken when it is necessary to treat the patient with both drugs.

A study performed by Chang et al. ($n = 91{,}330$) assessed the bleeding risk of patients treated by DOACs (dabigatran, rivaroxaban, and apixaban) and concomitant drugs. They showed that drugs with interaction risks are frequently prescribed with DOACs. Amiodarone and fluconazole were associated with a significantly higher bleeding rate. They paradoxically found that atorvastatin reduced the bleeding rate, which they associated with the lower incidence of hemorrhagic transformation of ischemic strokes. They did not find an increased bleeding risk in patients treated with digoxin, verapamil, cyclosporine, and macrolides.[90]

Table 4 Recommended thresholds for interventions and thrombolysis

Any DOAC	Erdoes et al. (2018)[123]	International consensus statement on the perioperative management of direct oral anticoagulants in cardiac surgery	<30 ng/mL is safe for high-risk cardiac operations <50 ng/mL is the recommended threshold if the operation is urgent and has low bleeding risk	The authors suggest monitoring of DOACs in cardiac surgery with impaired renal or hepatic function or if bridging to heparins is needed
Dabigatran	Pernod et al. (2013)[84]	Recommendations of a French working group on perioperative hemostasis	<30 ng/mL to operate without increased bleeding risk 30–200 ng/mL: delay intervention if possible by 12 h then re-measure 200–400 ng/mL: delay intervention if possible by 12–24 h then re-measure >400 ng/mL: high risk of hemorrhage, overdose	The 30 ng/mL threshold comes from the expected plasma concentrations with the stopping time of 24–72 h in the elective surgery protocol of the RELY trial. The other thresholds are expert opinions
	Steiner et al. (2013)[124]	Recommendations for the emergency management of DOAC-related complications	<50 ng/mL to consider thrombolysis in ischemic stroke <50 ng/mL to consider intervention in SAH patients	Level of evidence IV: expert opinion for both thresholds
	Albaladejo et al. (2018)[78]	Management of bleeding and emergency invasive procedures in patients on dabigatran: updated guidelines from the French Working Group on Perioperative Haemostasis (GIHP), September 2016	<30 ng/mL is safe to operate in very high hemorrhagic risk patients (neurosurgery, liver surgery) <30 ng/mL for perimedullar anesthesia or deep nerve block <50 ng/mL is safe to operate in high hemorrhage risk patients where hemostasis is controllable and low risk patients	Steps to be taken when the thresholds are not met depending on the urgency of the procedure are detailed in the article. They mainly include reversal through antidotes and waiting
Rivaroxaban	Pernod et al. (2013)[84]	Recommendations of the French Working Group on Perioperative Haemostasis	<30 ng/mL to operate without increased bleeding risk 30–200 ng/mL: delay intervention if possible by 12 h then re-measure 200–400 ng/mL: delay intervention if possible by 12–24 h then re-measure >400 ng/mL: high risk of hemorrhage, overdose	The 30 ng/mL threshold comes from the expected plasma concentrations with the stopping time of 48 h in the elective surgery protocol of the ROCKET-AF trial. The other thresholds are expert opinions
	Steiner et al. (2013)[124]	Recommendations for the emergency management of DOAC-related complications	<100 ng/mL to consider thrombolysis in ischemic stroke <100 ng/mL to consider intervention in SAH patients	Level of evidence IV: expert opinion for both thresholds
	Douketis et al. (2017)[82]	The Perioperative Anticoagulant Use for Surgery Evaluation (PAUSE) study for patients on a direct oral anticoagulant who need an elective surgery or procedure: design and rationale	<50 ng/mL as a safe threshold for invasive procedures	Decided based on pharmacokinetic studies by expert consensus
Apixaban	Steiner et al. (2013)[124]	Recommendations for the emergency management of DOAC-related complications	<10 ng/mL to consider thrombolysis in ischemic stroke <10 ng/mL to consider intervention in SAH patients	Level of evidence IV: expert opinion for both thresholds. This is possibly a typographical error since 10-fold higher thresholds are mentioned in the same paper for rivaroxaban while both DOACs do not exhibit such a difference in expected concentrations
	Douketis et al. (2017)[82]	The Perioperative Anticoagulant Use for Surgery Evaluation (PAUSE) study for patients on a direct oral anticoagulant who need an elective surgery or procedure: design and rationale	<50 ng/mL as a safe threshold for invasive procedures	Decided based on pharmacokinetic studies by expert consensus

Abbreviations: DOAC, direct oral anticoagulant; SAH, subarachnoid hemorrhage.

Extreme-Weight Patients

Extreme-weight patients (<50 kg and >120 kg) can be exposed to higher and lower concentrations respectively and sometimes out-of-target drug levels.[91] Some studies have shown variability in DOAC AUC with extreme weight but the effect was not deemed clinically significant.[92,93] Safety and efficacy were shown to be similar to those of VKA in this population.[94] However, it is worth mentioning that a meta-analysis of phase III trial data for DOACs showed a similar safety profile in extreme-weight patients but these studies did not include many patients weighing over 100 kg, which may be too low to show an effect.[95] A recent in vivo study on obese patients showed that rivaroxaban concentrations

Table 5 DOAC interactions that affect plasma levels

DOAC	Ref.	Drugs at risk of interaction[a]	Increases significantly plasma levels	Lowers significantly plasma levels
Dabigatran	13,96	Potent P-gp inhibitors/inducers P-gp/CYP3A4 dual inhibitors/inducers	*Ketoconazole* and *Itraconazole*[b] *Dronedarone*[b] *Ciclosporin*[b] **Tacrolimus** *Ritonavir* and *protease inhibitors*[b] Verapamil[d] Amiodarone[d] *Quinidine*[b] Macrolides Ticagrelor Posaconazole	**Rifampicin**[c] **St John's Wort**[c] **Carbamazepine**[c] **Phenytoin**[c] Magnesium and aluminum based antacids[d]
Rivaroxaban	22,105,110,125	Potent P-gp/CYP 3A4 dual inhibitors/inducers	**Ketoconazole**, **posaconazole**, and **itraconazole**[e] **Ritonavir** and **protease inhibitors**[e] Macrolides[f] Diltiazem[f] Verapamil[f]	**Rifampicin**[c] **St John's-Woth**[c] **Carbamazepine**[c] **Phenytoin**[c]
Apixaban	42,112	Potent P-gp/CYP 3A4 dual inhibitors/inducers	**Ketoconazole**, **posaconazole**, and **itraconazole**[e] **Ritonavir and protease inhibitors**[e] Macrolides[f] Diltiazem[f]	**Rifampicin**[c] **St John's-Woth**[c] **Carbamazepine**[c] **Phenytoin**[c]
Edoxaban	114,115,126	Potent P-gp inhibitors	Ketoconazole[g] Erythromycin[g] Ciclosporin[g] Protease inhibitors Verapamil[g] Dronedarone[g] Quinidine[g]	**Rifampicin**

Abbreviation: DOAC, direct oral anticoagulant.
Note: In *italics*: contraindicated; in **bold:** not recommended or to be avoided.
[a]Cytostatic agents and other anticancer drugs could also be at risk of interaction and caution should be exerted in these cases since pharmacokinetic as well as pharmacodynamic interactions have been suggested.[127]
[b]Increased risk of hemorrhage, contraindicated.
[c]Concomitant use should be avoided, risk of important lowering of efficacy.
[d]Should be taken at least 2 hours after Pradaxa, clinicians should be cautious.
[e]To be avoided, increased hemorrhagic risk, if unavoidable surveillance is warranted.
[f]ROCKET-AF data showed no increased risk of hemorrhage if GFR >30 mL/min.[110]
[g]Lead to higher concentrations and higher bleeding risk, dose adaptation to 30 mg once daily is needed.

above 80 ng/mL efficiently inhibited thrombin generation, an effect that disappeared at concentrations below 50 ng/mL.[85] For dabigatran, product information mentions an increase in plasma levels with low body weight (<50 kg).[96] It has been suggested that in the very obese with supratherapeutic creatinine clearance, dabigatran concentrations could be subtherapeutic.[97]

As few trials have studied the safety of usual DOAC doses in extreme-weight patients, it is safe to monitor such patients until further evidence is provided.[98–100]

High Bleeding Risk Patients

In patients whose clinical scores such as the "HAS-BLED score" show important hemorrhagic risk and who are still being treated with DOAC, it could be safe to monitor drug levels. It should be safe to ensure that patients with clinical conditions that could favor bleeding do not have high DOAC through plasma levels.

Adherence Monitoring

Doubts on patient compliance could be in part alleviated by drug-level monitoring. Hu et al. found in a study dedicated to compliance assessment in dabigatran therapy for AF that 10.7% of patients were noncompliant and that dabigatran monitoring was a way of identifying such patients.[101] A study conducted by Keita et al. showed that only 50 to 67.5% of patients taking DOACs had a high adherence rate as defined by the MMAS-8 adherence score.[102]

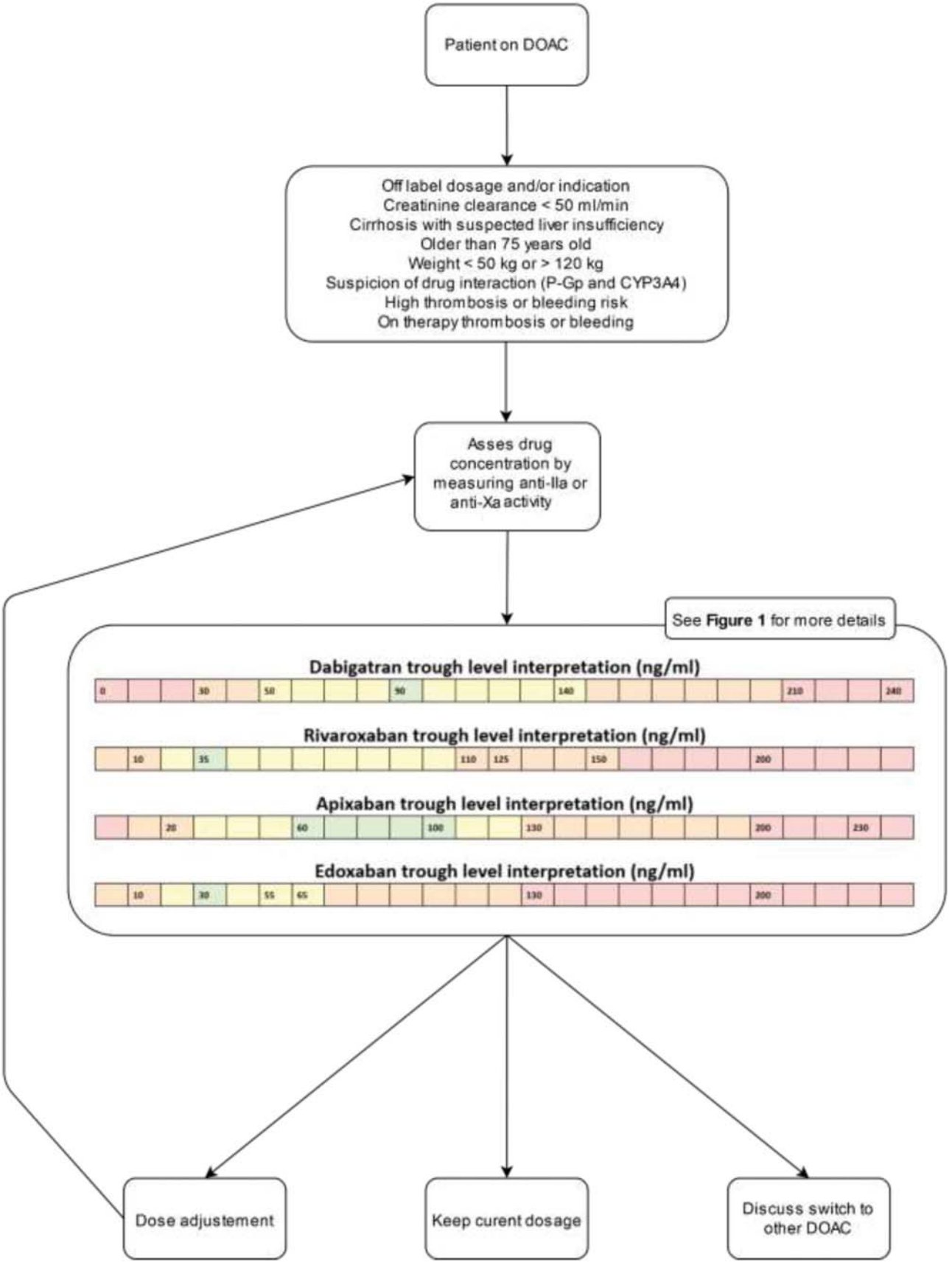


Fig. 2 Proposed DOAC monitoring algorithm. In *green*: estimated median concentration target. In *yellow*: estimated target range. In *orange*: increased risk of adverse event. In *red*: highly increased risk of adverse event (see ►**Fig. 1** for references). DOAC, direct oral anticoagulant.

A barrier to DOAC adherence monitoring is that their concentration at trough is not dependent on adherence; trough levels reached after the first pill are the same after the next. Therefore, DOAC monitoring cannot verify compliance on the long term; it can just confirm that the last dose has been taken. Peak levels are too variable to be used in this way and the peak time is too narrow for clinical use. D-dimers could be used for adherence monitoring as they are lowered by efficient anticoagulation.[103]

A Practical Approach to DOAC Monitoring: A Case Study

We present here a case vignette describing the practical approach to DOAC monitoring and results' interpretation using the algorithm depicted in ►Fig. 2.

An 86-year-old female patient known for diabetes and AF treated by metformin and apixaban 5 mg bid presents to the emergency department (ED) in the afternoon, shortly after a fall from her height in the street without witness. She cannot tell whether she hit her head or had loss of consciousness and has no specific complaints besides a slight headache. The review of systems is without particularity. She recalls having taken apixaban 5 mg in the morning. The clinical exam reveals hypovolemia with signs of dehydration and a frontal hematoma without neurological focal signs. Her blood panels show an acute renal insufficiency with a creatinine clearance of 35 mL/min/1.783 m^2 and an inflammatory syndrome. While the patient was being watched in the ED, she developed an altered mental state with disorientation. A cerebral CT-scan showed an acute right-sided subdural hematoma.

As discussed above, bleeds (even if provoked) while on anticoagulant therapy should prompt monitoring of the DOAC plasma levels. A quantitative measurement at admission will help in guiding the reversal strategy. In this case, an initial apixaban concentration >600 ng/mL justified the administration of high-dose (i.e., 50 IU/kg body weight) 4-factor prothrombin concentrate in addition to tranexamic acid. At follow-up, after correction of the hypovolemia and improvement of the renal function, the patient's apixaban trough level was measured at 170 ng/mL, a value which is at the higher side of the observed concentration range and associated with higher bleeding rates (see ►Figs. 1 and 2).[31–42] Despite no formal indication, the patient's dose was lowered to 2.5 ng/mL and a later trough level was found to be 100 ng/mL, which allowed for continuation of the latter dosage.

Conclusion

Many questions still exist regarding whether DOACs should be monitored. However, an increasing amount of evidence is showing that high or low plasma levels can lead to increased adverse events. Therefore, improving the efficacy and safety of DOACs could be possible through plasma level monitoring. Precise therapeutic intervals are still lacking as well as threshold for increased adverse event risk and more studies are required to identify populations in which monitoring would be useful.

Randomized controlled clinical trials investigating the effect of DOAC plasma level monitoring and dose tailoring are the next step to determine the therapeutic range of these drugs and to evaluate whether DOAC monitoring can be used effectively to improve their usage.

For the time being, we can only consider the observed trough level ranges as an approximation of drug targets and monitor populations which are likely to benefit most from this testing, for instance, to exclude drug accumulation, when drug failure is suspected, or in acute situations such as hemorrhagic or thrombotic events.

Conflict of Interest

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