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Letter to the Editors-in-Chief

Inappropriate low dosing of direct oral anticoagulants in older patients with non-valvular atrial fibrillation: Impact on plasma drug levels

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Dear Editor,

Direct oral anticoagulants (DOACs) are increasingly prescribed in older patients with non-valvular atrial fibrillation (NVAF). They provide higher convenience than vitamin K antagonists (VKA), with an improved efficacy and a reduced risk of intracranial bleeding [1]. Dose reduction criteria are clearly established for each DOAC, depending on renal function, weight, age or concomitant medications. However, many observational studies have reported that DOACs were frequently prescribed at an off-label dose, especially in older patients [2]. It is therefore possible that some patients do not receive the full benefit of their anticoagulant treatment.

Although DOACs do not require regular laboratory monitoring, their measurement may be helpful to improve efficacy and safety in older patients. Higher and variable DOAC concentrations have been described in the geriatric population, partly due to comorbidities or medications [3]. Moreover, a correlation between DOAC levels and clinical outcomes has been demonstrated [4]. Recent findings suggest that most elderly patients with lower-than-recommended DOAC doses have concentrations within the expected range [5,6]. Therefore, we aimed to evaluate the appropriateness of DOAC dosing in older patients with NVAF and to assess the relationship between clinical dosing and DOAC plasma levels.

We analyzed retrospectively DOAC measurements performed between 2012 and 2018 at the CHU UCL Namur, a tertiary care hospital. Patients aged ≥75 years, treated with apixaban, rivaroxaban or dabigatran etexilate for stroke prevention in NVAF were included. We excluded samples that were not taken at peak or trough and those for which information about weight or renal function was missing. Some patients had multiple peak and/or trough measurements. This work was approved by the local ethics committee (NUB: B039201524384).

Following data were extracted from electronic medical records: age, sex, weight, DOAC use (drug, dose, delay since the last intake), estimated creatinine clearance (CrCl) with the Cockcroft and Gault formula, CHARLSON comorbidity index, $CHADS_2$ and $HEMMORR^2HAGES$ scores, the concomitant use of drugs increasing the risk of bleeding, and P-glycoprotein/CYP3A4 inhibitors or inducers.

Blood was taken by antecubital venipuncture and collected into 0.109 M sodium citrate (9:1 v/v) tubes. Platelet-poor plasma (PPP) was obtained from the supernatant fraction after double centrifugation for 15 min at 1500*g* at room temperature. Apixaban and rivaroxaban plasma levels were estimated using calibrated chromogenic anti-Xa

Table 1
Population characteristics.

	All (n = 80)	Appropriate dose (n = 54)	Inappropriate low dose (n = 18)
Age (years; median [IQ])	79.5 [77–85]	79.5 [77–84.8]	79 [77.25–82.8]
Female (%)	55%	55.6%	44.4%
BMI (kg/m^2; median [IQ])	28.9 [22.8–33]	28.2 [22.8–33]	31 [26.6–34.7]
Creatinine (mg/dl; median [IQ])	1 [0.8–1.2]	1 [0.8–1.2]	1 [0.8–1.1]
CrCl (Cockcroft-Gault) (ml/min; median [IQ])	52.7 [41.4–69.6]	49.4 [41.3–69.1]	66.7 [61–86.8]
<50 ml/min	46%	52%	11%
<30 ml/min	6%	4%	6%
Charlson (median [IQ])	7 [6–8]	7 [6–8]	7 [4–8.8]
CHADS (median [IQ])	3 [2–4]	3 [2–4]	3 [2–3.8]
HEMORR^{2}HAGES (median [IQ])	2 [1.8–3]	2 [2–3]	2 [1–4]
Number of drugs (median [IQ])	10 [6–12]	10 [6–11.8]	9 [6–12]
NSAIDs (%)	2.5%	3.7%	0%
Antiplatelet therapy (%)	22.5%	16.7%	33.3%
Azole antifungals (%)	1.3%	1.9%	0%
Amiodarone (%)	38.8%	40.7%	27.8%
Diltiazem (%)	5.0%	7.4%	0%
Carbamazepine (%)	5.0%	3.7%	11.1%
Apixaban (n)	33	21	9
2.5 mg	17	9	7
5 mg	16	12	2
Dabigatran etexilate (n)	18	18	0
110 mg	9	9	0
150 mg	9	9	0
Rivaroxaban (n)	29	15	9
10 mg	2	0	2
15 mg	12	5	7
20 mg	15	10	0

IQ: interquartile, CrCl: creatinine clearance.

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assays: Biophen® Direct Factor Xa Inhibitors (Biophen® DiXaI, Hyphen BioMed, Neuville-Sur-Oise, France, lower limit of quantification (LLOQ) apixaban:12 ng/ml, rivaroxaban:24 ng/ml) or STA®-Liquid anti-Xa (Diagnostica Stago®, Asnière, France, LLOQ: apixaban:36 ng/ml, rivaroxaban:12 ng/ml). Dabigatran plasma levels were estimated with a diluted thrombin time (Hemoclot® Thrombin Inhibitor (HTI), Hyphen BioMed, LLOQ: 7 ng/ml) or an ecarin-based assay (STA®-ECA II, Diagnostica Stago, LLOQ: 46 ng/ml) [7].

DOAC measurements were subdivided in two groups: "appropriate dose" (AD) and "inappropriate low dose" (ILD). Due to the small number of "inappropriate high dose" (14 dosages; 8 patients), those were excluded from the analysis. We first assessed the appropriateness of DOAC dosing according to the European drug labeling (Supplementary Table 1) and studied the risk factor to have an inappropriate low dose prescribed using a logistic regression model. DOAC levels were compared to the expected on-therapy ranges at peak and trough, derived from pivotal trials (Supplementary Table 2). Proportions of measurements under, within or above the expected on–therapy range were

	Apixaban		Dabigatran		Rivaroxaban	
	Peak	Trough	Peak	Trough	Peak	Trough
AD	27	14	21	14	14	11
ILD	12	6	/	/	13	8

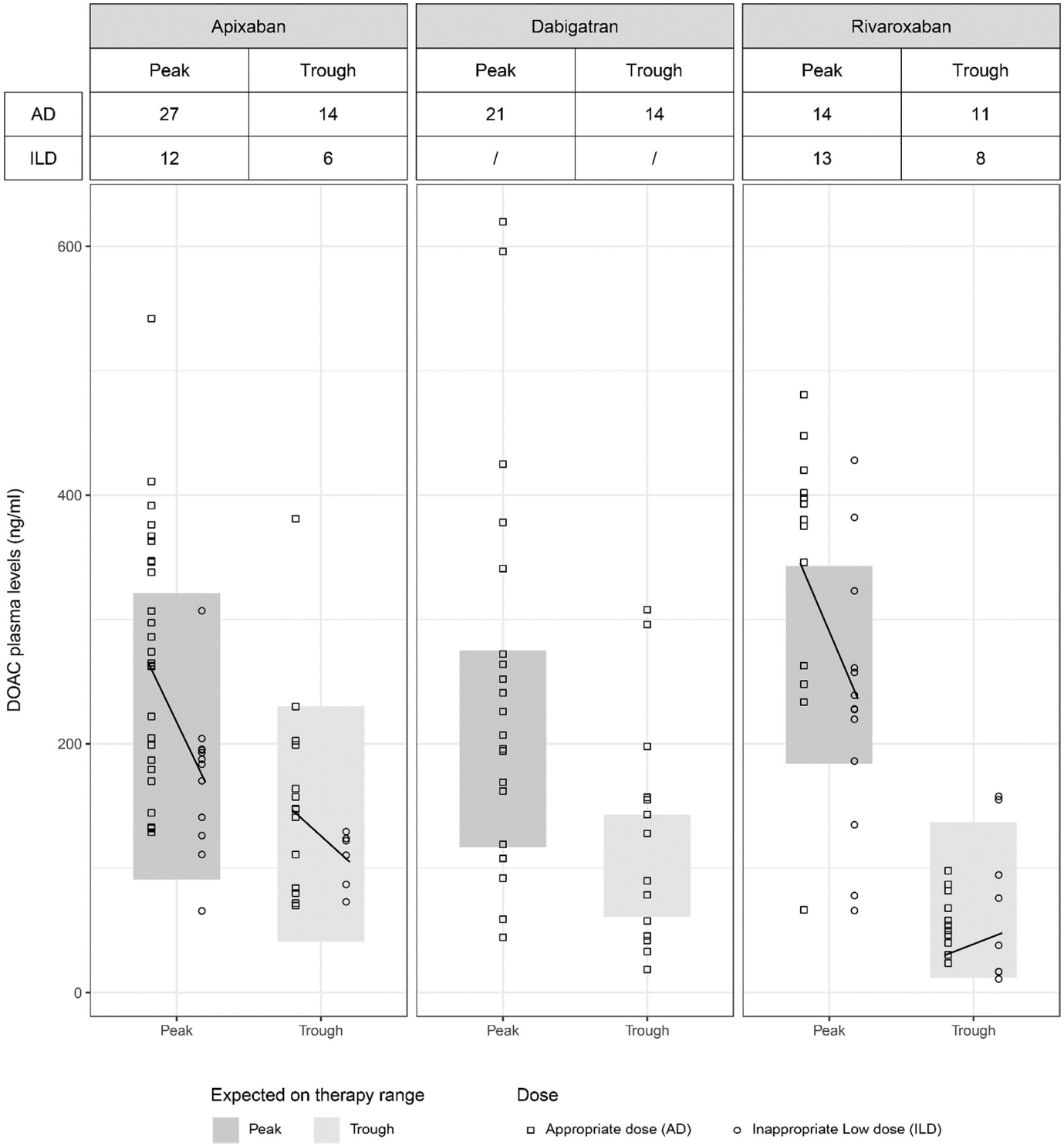

Fig. 1. Repartition of DOAC plasma concentrations at peak and trough for "appropriate dose" and "inappropriate dose".

described for both groups. Finally, we compared mean DOAC plasma concentrations between the two groups, at peak and trough, using a linear mixed model and considering the patients as a variable. The software used was *R* 3.6.3 with package Imer.

Baseline characteristics of the 80 included patients (median age 80 years) are summarized in Table 1. DOAC dosing was appropriate for 54 patients (68%): apixaban 64% (21/33); rivaroxaban 52% (15/29); dabigatran etexilate 100% (18/18). Out of the 26 patients with an inappropriate dosing, 18 (69%) were prescribed an inappropriate low dose. Two patients were taking apixaban 5 mg only once daily, a dose that was considered as inappropriate low. Patients were more likely to be prescribed an inappropriate low dose if they had a better creatinine clearance according to Cockcroft-Gault equation (OR 1.25 [95% CI, 1.03–1.54]). They also tended to have a higher body mass index (OR 1.4 [95% CI, 0.94–2.13]). A total of 152 DOAC measurements were performed (93 at peak, 59 at trough). Measured DOAC plasma levels varied from 44 to 620 ng/ml at peak, and from 11 to 667 ng/ml at trough.

At peak, in the AD group, 72% (10/14) and 7% (1/14) of rivaroxaban measurements were respectively above and under the expected range, while 21% (3/14) were within the range. In the ILD group, rivaroxaban peak levels were distributed as follows: 15% (2/13) above, 23% (3/13) under, and 62% (8/13) within the range (Fig. 1). In the apixaban's AD group, at peak, 67% (18/27) of measurements were within the expected range compared to 92% (11/12) in the ILD group. Nine measurements (33%) were above the range in the AD group, while one (8%) was under the range in the ILD group. At trough, most of rivaroxaban and apixaban's measurements were within the expected range in the AD group (11/11 and 13/14 respectively) as well as in the ILD group (5/8 and 6/6 respectively). In the ILD group, out of the 3 rivaroxaban measurements outside the range, 2 were higher than expected. Amiodarone was taken concomitantly for three of the four higher-than-expected rivaroxaban concentrations observed in the ILD group (2 peak and 2 trough).

Mean rivaroxaban and apixaban peak concentrations were significantly higher in the AD group (345 ng/ml and 266 ng/ml respectively) than in the ILD group (236 ng/ml and 169 ng/ml respectively) ($P = 0.0090$ and $P = 0.0092$). On the contrary, mean DOAC trough levels did not differ between groups (Fig. 1). These comparative analyses could not be performed for dabigatran since every prescription was considered appropriate. At peak 52% (11/21) of measurements were within the range, 24% (5/21) under and 24% above the range. At trough, 21% (3/14) of measurements were within the range, 36% (5/14) under and 43% (6/14) above the range.

In this retrospective analysis, we found that DOAC dosing was appropriate, according to drug labeling, for two third of our older patients. The prescription of an inappropriate low dose was the most common issue (69% of inappropriate doses), as recently described in a prospective multicenter study in Greece [8]. It seemed to be more frequent in patients with a higher BMI or good renal function. We can hypothesize that these patients mainly meet criteria for standard DOAC doses, with a higher risk of receiving a lower-than-recommended dose, as described previously in the FANTASIAA registry [9]. The underuse, or "softer" use, of anticoagulation may be explained by concerns on bleeding and falling. Half of our patients were treated with a reduced DOAC dose, more than observed in phase 3 clinical trials. For instance, in the ARISTOTLE study, 28% of apixaban patients aged 75 years and over received the reduced dose [10]. However, this difference is also partly due to the fact than less than half of real-life NVAF patients met the inclusion criteria of DOAC phase 3 trials [11].

The relationship between DOAC dosing and plasma levels has been studied in a few previous observational studies, with comparable results. Raccah et al. have shown that 24% of NVAF patients (median age 80 years) receiving an appropriate DOAC dose had drug levels above the expected range [12]. On the other hand, 21% of patients treated with an inappropriate low DOAC dose had plasma levels below the expected range. More specifically for the geriatric population, Nissan et al. have recently demonstrated that 40% of octogenarian patients receiving an appropriate full dose of apixaban had above-range plasma levels at peak and 30% at through, twice more than younger patients (<70 years) receiving the same dosing [5]. Conversely, most aged patients receiving an inappropriate low dose had apixaban concentrations in the expected range at peak and through (80% and 75% respectively).

The prescription of an inappropriate DOAC dose has been associated with an increased risk of hemorrhagic or thrombotic event among the general population [2]. In our aged population, we found higher-than-expected DOAC concentrations despite an appropriate prescription, and interestingly, mean rivaroxaban and apixaban peak levels observed in the "ILD" group (236 ng/ml and 169 ng/ml) were almost identical to median concentrations described in phase 3 trials (249 ng/ml and 171 ng/ml) [4]. However, it is uncertain how those ranges apply to the geriatric population. Further large prospective studies are needed to define DOAC levels associated with an increased risk of bleeding or thromboembolic events in older patients. A recent multicenter, double blind, placebo controlled Japanese study has demonstrated that an off-label low dose of edoxaban (15 mg) used in elderly patients with NVAF considered ineligible for standard anticoagulation was superior to placebo in preventing stroke or systemic embolism and did not result in a significantly higher incidence of major bleeding [13]. Further studies are therefore needed to know the clinical impact of off-label low doses compared to appropriate doses in geriatric patients.

We observed a high inter-individual variability in DOAC concentrations, particularly for dabigatran (from 44 to 620 ng/ml at peak and from 19 to 308 ng/ml at trough). A previous study conducted in 68 geriatric patients highlighted similar findings, with dabigatran levels ranging from 9 to 720 ng/ml at peak and from 2 to 594 ng/ml at trough [3]. It can be explained by the low bioavailability of dabigatran etexilate, the high dependency of renal function and comorbidities in a geriatric population. In total, 60% (21/35) of dabigatran measurements were outside the expected range despite an appropriate dose, with a similar proportion above and under the range. It is also partly due to the fact that the dabigatran on-therapy range was based on 25th–75th percentiles, instead of 5th -95th percentiles for apixaban and rivaroxaban.

Our study has several limitations. First it was a retrospective study, with a small size sample. Second, numerous DOAC measurements were asked in high-risk hospitalized patients. That could have influenced DOAC plasma concentrations. Third, the impact of co-medications on DOAC levels was not investigated. Fourth, 11% of DOAC measurements were not performed at steady-state. Finally, given the retrospective design of the study, we did not study the occurrence of thrombotic or hemorrhagic events.

In conclusion, a significant proportion of NVAF older patients received an inappropriate low DOAC dose based on drug labeling. However, for most of them, DOAC plasma levels were within the expected on-therapy range. These findings raise questions about the optimal DOAC on therapy range in real-life geriatric population. Further large prospective studies are needed to define DOAC levels associated with adverse events in older patients.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: François Mullier reports institutional fees from Stago, Werfen, Nodia, Roche Sysmex and Bayer. He also reports speaker fees from Boehringer Ingelheim, Bayer Healthcare, Bristol-Myers Squibb-Pfizer, Stago, Sysmex and Aspen all outside the submitted work.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.thromres.2021.02.034.

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