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ORIGINAL RESEARCH ARTICLE

Frailty as a Marker for the Plasma Concentrations of Direct Oral Anticoagulants in Older Patients: Results of an Exploratory Study

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Abstract

Background Frailty makes older adults vulnerable to adverse health outcomes and can modify pharmacokinetics and drug exposure.

Objective We aimed to explore the relationship between different frailty assessments and trough plasma concentrations of direct oral anticoagulants in older patients.

Methods The frailty status of adults aged ≥ 70 years receiving regular direct oral anticoagulant medication was assessed by four different instruments: Fried physical phenotype, Rockwood frailty index, Short Physical Performance Battery, and FRAIL scale. The two performance measures "slow gait speed" and "weak grip strength" were used to build a separate score depending on the number of positive criteria (none, one, two). For each participant, a single steady-state direct oral anticoagulant trough plasma concentration was collected, dose-normalized, and its relationship to the various frailty assessments analyzed.

Results Forty-two participants completed the study, with most using apixaban ($n = 22$). Dose-normalized apixaban trough concentrations were 2.48-fold higher in frail participants (Fried phenotype) than in robust participants ($p = 0.009$) and correlated positively with Fried physical phenotype ($r_s = 0.535$, $p = 0.010$) and negatively with Short Physical Performance Battery ($r_s = -0.434$, $p = 0.044$). Compared with participants who met none of the criteria "slow gait speed" and "weak grip strength", apixaban trough concentrations were approximately 1.9-fold higher in participants who were positive for one ($p = 0.018$) or two ($p = 0.013$) of these measures.

Conclusions In this exploratory study, higher levels of frailty on performance-based frailty assessments were associated with higher apixaban exposure in older adults.

Clinical Trial Registration German Clinical Trials Register DRKS00016741; registered 20 February, 2019.

Key Points

In this exploratory study, dose-normalized apixaban plasma trough concentrations were higher in frail than in robust older adults.

Apixaban exposure correlated with frailty assessments that included performance tests such as the Fried phenotype and the Short Physical Performance Battery.

In participants who met at least one of the two performance criteria "slow gait speed" and "weak grip strength", apixaban trough concentrations were higher than in older adults who met neither of these criteria.

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1 Introduction

Frailty is a highly relevant geriatric syndrome that makes older adults more vulnerable to adverse health outcomes when exposed to one or multiple stressors [1]. Frailty is a predictor of mortality and disability in the activities of daily living (ADLs) [2]. Community-dwelling frail older persons are more likely to be hospitalized and to experience falls and fractures compared with robust individuals [3].

Frailty has also been associated with pharmacokinetic changes [4]. Levels of inflammatory markers such as interleukin-6 are increased in frail patients [5], which may reduce the expression of cytochrome P450 (CYP) enzymes such as CYP3A4, CYP2C9, and CYP2C19 and lower the metabolism of drugs that are substrates of these enzymes [6]. In addition, concomitant sarcopenia could affect the

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pharmacokinetics of specific drugs through changes in body composition [4].

A recent pilot study found that elimination half-lives of direct oral anticoagulants (DOACs) were prolonged in older clinically frail patients treated for acute hip fracture at an orthogeriatric unit [7]. The estimated elimination half-lives showed no correlation with the participants' glomerular filtration rates. Therefore, alterations in other elimination pathways must be responsible for the observed pharmacokinetic characteristics in this population [7].

In recent years, the percentage of DOAC prescriptions for anticoagulation therapy in patients with atrial fibrillation has grown rapidly [8]. The prevalence of atrial fibrillation increases with age, reaching a peak of 15.1% in the 85- to 89-year-old age group [9]. Therefore, it seems particularly relevant to ensure safe and adequate DOAC dosing in older patients and to identify clinical parameters that could cause or predict a significant modification of DOAC pharmacokinetics and that might require dose adjustments. Elevated DOAC plasma concentrations are associated with an increased risk of bleeding [10]. Therapeutic drug monitoring of DOAC plasma concentrations is possible, but is not part of routine medical care [11]. A promising alternative strategy to personalize anticoagulation with DOACs could be to identify meaningful clinical variables that correlate with DOAC drug concentrations in older patients. Although frailty is not yet typically documented in most medical settings, some healthcare systems have started to routinely assess frailty as a specific clinical parameter. For instance, the National Health Service England now requires that all general practitioners within its system screen for frailty in their patients aged ≥ 65 years [12].

The aim of this study was to explore the relationship between different frailty assessments and DOAC trough concentrations in older adults. Because in clinical practice, instead of a complex and laborious assessment of frailty, the measurement of a single marker would be most practical to estimate frailty, the relationship between single performance measures (e.g., gait speed, grip strength) and DOAC trough concentrations was also investigated.

2 Methods

2.1 Study Design

This was an exploratory, cross-sectional, single-center study performed at the Center for Geriatric Medicine, Heidelberg University, Heidelberg, Germany. The participants were categorized based on their frailty status. Additionally, a single DOAC trough sample was collected at steady-state. The frailty assessments and trough sampling were conducted preferably within 24 hours and not more than 7 days apart.

The study was approved by the responsible Ethics Committee of the Medical Faculty of Heidelberg University (S-866/2018) and registered with the German Clinical Trials Register (DRKS00016741) before the inclusion of the first participant. All study procedures were carried out in accordance with the current version of the Declaration of Helsinki.

2.2 Study Population

Patients were eligible for inclusion if they were aged ≥ 70 years, had been regularly using one of the four approved DOACs apixaban, edoxaban, rivaroxaban, or dabigatran for at least 7 days, were mentally and physically able to participate in the study, and provided written informed consent. Exclusion criteria were an insufficient knowledge of the German language and the inability to give informed consent. To allow for a balanced recruitment, we aimed to include 10–20 participants per DOAC and frailty category (robust, pre-frail, or frail) according to the Fried physical phenotype of frailty [2].

2.3 Baseline Characteristics

The participants' sociodemographic data, comorbidities, their results on the Mini-Mental State Examination [13], and their present and recently discontinued comedication were recorded from their medical records and/or assessed during an interview. Detailed information regarding the participants' DOAC treatment was collected: type of DOAC, dose, dosing frequency, dosing times, start of DOAC treatment, start of treatment with the current dose and dosing times, adherence to regular intake during a time equaling five half-lives of the respective DOAC (i.e., during the past 3 days for apixaban, edoxaban, and rivaroxaban, and 3–6 days for dabigatran depending on the participant's estimated creatinine clearance), treatment indication, and, if applicable, correct mode of intake (taking rivaroxaban 20-mg and 15-mg doses with a meal and dabigatran capsules without opening them).

2.4 Frailty Assessments

In the absence of a gold standard for the evaluation of a patient's frailty status, we used four different frailty assessments:

Physical Phenotype of Frailty Fried and co-workers identified a physical phenotype of frailty based on five criteria: unintentional weight loss, self-reported exhaustion, low physical activity, slow walking speed, and weakness (grip strength) [2]. Individuals who meet none of the criteria are

classified as robust, those who meet one to two as pre-frail, and those who meet three or more criteria are classified as frail [2].

We used a German translation of the frailty phenotype [14] and the same cut-off values as defined by Fried and co-workers [2]. Usual gait speed was measured over a distance of 15 ft (4.57 m) from a static start. Walking aids were permitted if necessary to perform the task. To reflect the original frailty phenotype, the first of two walks was used to evaluate the frailty criterion. Maximum grip strength in the self-reported dominant hand was measured using an analog hand-held Jamar dynamometer (Sammons Preston Rolyan, Bolingbrook, IL, USA), scoring the average of three consecutive trials. In the case of unclear dexterity or injury of the dominant hand, grip strength was evaluated in both hands and the results of the stronger hand were used for analyses. To explore the relevance of selected performance parameters in this study, the two criteria "gait speed" and "grip strength" were used to build a separate score based on the number (none, one, or two) of criteria met.

Short Physical Performance Battery The Short Physical Performance Battery (SPPB) is a set of three performance-based measures of lower extremity function: standing balance (side-by-side, semi-tandem, and tandem stands), gait speed, and five times chair rise test [15]. The SPPB was included among the frailty assessments because the European Medicines Agency recommended this instrument for the evaluation of physical frailty in clinical trial populations [16]. In the present study, the SPPB was performed as previously described [15], scoring the faster of two 8-ft (2.44-m) walks.

FRAIL scale The FRAIL scale is a five-item patient-reported questionnaire, evaluating the criteria fatigue, resistance, ambulation, illnesses, and weight loss [17]. Four out of the five questions reflect components of the physical phenotype of frailty, while the item "illnesses" is part of the frailty index [17]. A validated German translation of the FRAIL scale was used in the present study [18].

Frailty index The frailty index assesses frailty in relation to the accumulation of deficits, such as symptoms, diseases, or disabilities [19]. In the present study, we adapted a 40-item frailty index published by Searle and co-workers [20]. ADLs were assessed by self-report with the Barthel Index [21] and instrumental ADLs (IADLs) by self-report with the Lawton and Brody Scale [22]. For both ADLs and IADLs, depending on another person's help to complete the task was scored as a deficit. Self-reported comorbidities were drawn from the category "illnesses" of the FRAIL scale [17]. For the variables "weight loss," "grip strength," and "gait speed at usual pace" we referred to the respective criteria and cut-off values of the physical phenotype of frailty [2]. Peak flow was measured using a Mini-Wright meter (Clement Clarke International, Essex, UK) following a standardized protocol, scoring the highest of three attempts [23]. The participants' body mass index was assessed during the study.

Because of safety concerns, we refrained from including the fast-paced walk. In the absence of information on the exact mode of shoulder strength assessment for the original data set, we excluded this variable. Therefore, the final frailty index comprised 38 items.

2.5 Plasma Sample Collection and Laboratory Evaluations

The participants and, if applicable, their nurses (inpatients) were given detailed instructions regarding the timing of the last dose before blood sampling and asked to withhold the upcoming dose until sampling was completed. Directly before blood sampling, information with respect to the participants' DOAC treatment (Sect. 2.3) was reassessed with the participants, and, if applicable, their medical charts and nurses, to verify that all necessary prerequisites for correct steady-state trough sampling were met. Changes in the participants' comedication were documented. Samples were collected into lithium heparin tubes, centrifuged at room temperature for 10 min at 2500*g* within 30 min of collection, and the plasma was frozen at < -20 °C. DOAC concentrations in plasma were analyzed with ultra-performance liquid chromatography coupled to tandem mass spectrometry, using a validated assay with a lower limit of quantification of 1 ng/mL for all four DOACs [24]. During blood sampling, a second lithium heparin tube was collected to measure the participants' creatinine concentration (Laboratory Dr. Limbach, Heidelberg, Germany) and to estimate their current creatinine clearance using the Cockcroft and Gault formula [25] on the basis of the participants' current ($\leq$ 24 h) body weight.

2.6 Statistical Analysis

Only participants who completed the study were included in the statistical analysis. Their data are presented as mean with standard deviation (continuous variables) and absolute numbers and percentages (categorical variables). Correlations between the different frailty assessments were analyzed using Spearman's correlation.

For further analyses, DOAC trough concentrations were dose-normalized, assuming dose-proportional DOAC pharmacokinetics [26–29]. Apixaban trough

concentrations were divided by the respective single dose. To ensure high bioavailability, we required that the rivaroxaban 15-mg and 20-mg doses were taken with a meal, allowing us to assume dose-proportional pharmacokinetics for the entire dose range of 2.5-mg to 20-mg doses [27]. Accordingly, rivaroxaban trough concentrations were dose-normalized by dividing them by the respective daily dose [27]. Unless stated otherwise, all reported DOAC trough concentrations are dose-normalized.

Correlations of DOAC trough concentrations with the frailty assessments and patient characteristics were analyzed using Spearman's correlation. For further analyses, DOAC trough concentrations were log-transformed. Analysis of variance with Tukey's test for post-hoc analysis (apixaban) was used to assess differences in trough concentrations between different frailty groups. To explore the relationship between apixaban trough concentrations and both chronological and biological age, i.e., frailty, we used stepwise linear regression with score on the physical phenotype of frailty and age as independent variables.

To compare apixaban trough concentrations with previous pharmacokinetic data in older adults [30–32], we classified the participants as accurately or inaccurately dosed according to the dosing recommendations for anticoagulation therapy in atrial fibrillation [30] regardless of the actual indication for apixaban treatment. Differences in mean dose-normalized apixaban trough concentrations between accurately and inaccurately dosed participants were assessed using a two-tailed unpaired t-test.

We screened the participants' comedication for potential pharmacokinetic drug-DOAC interactions using an electronic database (AiD*Klinik*®). IBM SPSS Statistics version 27 (IBM Deutschland GmbH, Ehningen, Germany) was used for all statistical analyses. Two-sided p-values ≤ 0.05 were considered statistically significant.

3 Results

3.1 Study Population

Recruitment took place from February 2019 to February 2020. Forty-four participants were included and 42 completed the study. As a consequence of the coronavirus disease 2019 pandemic, recruitment was stopped prematurely. The majority ($n = 39$) of the participants in the final study population were inpatients or outpatients of the geriatric rehabilitation unit at Agaplesion Bethanien Hospital, Heidelberg, Germany. Apixaban was the most commonly used DOAC ($n = 22$). The characteristics of the apixaban subpopulation are shown in Table 1. Based on the physical phenotype of frailty, three participants were classified as robust, 11 as pre-frail, and eight as frail. Six participants did not meet any of the frailty criteria "gait speed" and "grip strength," five met only one criterion, and 11 met both criteria. The rivaroxaban group included 14 participants, yet, with a rather homogeneous distribution of frailty status, and no participant in this sample was classified as robust according to the physical phenotype of frailty and 11 out of the 14 participants met both frailty criteria "gait speed" and "grip strength" (Table S1 of the Electronic Supplementary Material [ESM]). The Spearman correlations of dose-normalized trough concentrations with patient characteristics, frailty assessments, and functional parameters in this pre-frail and frail rivaroxaban subsample are shown in Table S2 of the ESM. Because of the small numbers in the edoxaban ($n = 4$) and dabigatran ($n = 2$) groups, we did not perform specific analyses of these subsamples.

3.2 Apixaban

In the subsample, the participants' score on the Fried phenotype significantly correlated with the respective scores of the SPPB ($r_s = -0.747$, $p < 0.001$), the FRAIL scale ($r_s = 0.640$, $p = 0.001$), and the frailty index ($r_s = 0.798$, $p < 0.001$) [Figs. S1–S3 of the ESM].

Twenty participants received apixaban for anticoagulation in atrial fibrillation, one for both atrial fibrillation and the treatment of pulmonary embolism, and one participant for the prophylaxis of recurrent deep vein thrombosis (Table 1). When the dose adjustment criteria for apixaban dosing in atrial fibrillation [30] were applied to the entire study sample, two participants in the 5-mg twice-daily (BID) group were incorrectly dosed high and nine participants in the 2.5-mg BID group were incorrectly dosed low. Trough samples were drawn on average (± standard deviation) 2.8 (± 9.0) minutes before the end of the 12-hour dosing interval. There was no difference in mean apixaban trough concentrations between accurately ($n = 11$) and inaccurately dosed ($n = 11$) participants ($p = 0.573$). Table 2 lists the mean (non-dose-normalized) apixaban trough concentrations in the 5-mg BID and 2.5-mg BID dosing groups.

Dose-normalized trough concentrations were 2.48-fold higher in frail participants compared with robust participants ($p = 0.009$) (Table 3). In addition, in participants who met either one ($p = 0.018$) or two ($p = 0.013$) of the frailty criteria "gait speed" and "grip strength," trough concentrations were approximately 1.9-fold higher than in participants who met neither of these criteria (Table 3, Fig. 1).

Apixaban trough concentrations were significantly correlated with age, but not with creatinine clearance or body weight (Table 4). They were also positively correlated with

Table 1 Characteristics of apixaban study patients

Characteristic	Apixaban ($n = 22$)
Age, years: mean (± SD; range)	81.7 (± 6.6; 71–97)
Female, *n* (%)	15 (68.2)
Creatinine clearance (CG), mL/min: mean (± SD; range)	47.1 (± 15.8; 14.8–73.2)
Weight, kg: mean (± SD; range)	68.1 (± 16.0; 43.4–100.3)
Indication for DOAC, *n* (%)	
Atrial fibrillation (nonvalvular)	20 (90.9)
Atrial fibrillation + treatment of PE	1 (4.5)
Prophylaxis of recurrent DVT/PE	1 (4.5)
Ambiguous	0 (0)
Dose in mg, *n* (%)	
5 BID	9 (40.9)
2.5 BID	13 (59.1)
Fried category, *n* (%)	
Robust	3 (13.6)
Pre-frail	11 (50.0)
Frail	8 (36.4)
Number of Fried criteria met, *n* (%)	
0	3 (13.6)
1	5 (22.7)
2	6 (27.3)
3	6 (27.3)
4	2 (9.1)
5	0 (0)
Short Physical Performance Battery score, *n* (%)	
10–12	5 (22.7)
8–9	5 (22.7)
0–7	12 (54.5)
FRAIL scale score, *n* (%)	
0	5 (22.7)
1–2	7 (31.8)
≥ 3	10 (45.5)
Frailty index: mean (± SD; range)	0.37 (± 0.16; 0-0.65)
Number of Fried criteria "gait speed" + "grip strength" met, *n* (%)	
0	6 (27.3)
1	5 (22.7)
2	11 (50.0)
Gait speed, m/s: mean (± SD; range)	0.80 (± 0.37; 0.16–1.68)
Grip strength (female), kg: mean (± SD; range)	15.9 (± 4.5; 10.0–22.7)
Grip strength (male), kg: mean (± SD; range)	27.4 (± 13.8; 17.3–57.7)

BID twice daily, *CG* Cockcroft and Gault formula, *DVT* deep vein thrombosis, *PE* pulmonary embolism, *SD* standard deviation

the number of positive criteria for the physical phenotype of frailty and negatively correlated with the score on the SPPB and gait speed (faster of two walks) (Table 4, Fig. 1). The number of positive Fried criteria ($p = 0.008$) but not age ($p = 0.123$) was identified as a significant predictor variable in a stepwise linear regression model to explain apixaban trough concentrations. Figure 1 depicts individual apixaban trough concentrations relative to the number of positive Fried criteria, the SPPB, and the number of performance criteria met (slow gait speed, weak grip strength). Figures S4–S7 of the ESM show individual apixaban trough concentrations relative to the number of positive Fried criteria in four different subgroups of the study sample (5 mg BID, 2.5 mg BID, accurately dosed participants, and inaccurately dosed 2.5 mg BID). Tables S3 and S4 of the ESM show the distribution of the different frailty categories in the

Table 2 Apixaban trough concentrations (non-dose-normalized) in the 5-mg BID and 2.5-mg BID dosage groups

Apixaban	5 mg BID Complete subsample ($n = 9$)	5 mg BID Accurate dose ($n = 7$)	2.5 mg BID Complete subsample ($n = 13$)	2.5 mg BID Accurate dose ($n = 4$)	2.5 mg BID Inaccurate dose ($n = 9$)
Trough, ng/mL					
Mean (± SD)	178.8 (± 70.0)	177.1 (± 67.0)	102.1 (± 54.2)	132.3 (± 83.8)	88.7 (± 33.4)
Median	193.0	193.0	100.0	104.0	76.6
Range	78.4–263.0	78.4–260.0	55.4–255.0	66.1–255.0	55.4–155.0

BID twice daily, *SD* standard deviation

Accurate dose = accurate dose according to the recommendations for the dosing in atrial fibrillation [30]; inaccurate dose = inaccurate dose according to the recommendations for the dosing in atrial fibrillation [30]

Table 3 Dose-normalized apixaban trough concentrations and frailty status: analysis of variance and post-hoc analysis results

Characteristic	Apixaban trough dose-normalized[a] (ng/mL), mean (± SD)	Model *p*-value	*p*-values for post-hoc analysis		
Fried category			Robust	Pre-frail	Frail
Robust	19.9 (± 3.8)	0.012	–	0.057	0.009
Pre-frail	36.3 (± 9.6)		–	–	0.348
Frail	49.3 (± 25.0)		–	–	–
Number of Fried criteria "gait speed" + "grip strength" met			0	1	2
0	23.5 (± 5.6)	0.008	-	0.018	0.013
1	44.0 (± 5.8)		-	–	0.918
2	44.7 (± 22.6)		-	–	–

SD standard deviation

[a]Mean non-dose-normalized apixaban concentrations in the different frailty groups are shown in Table S5 of the ESM

various apixaban dosage groups and Table S5 of the ESM lists the mean non-dose-normalized apixaban trough concentrations relative to the different frailty categories.

Apixaban trough concentrations showed a weak positive non-significant correlation with the frailty index and the score on the FRAIL scale (Table 4, Figs. S8–S9 of the ESM). Two participants were treated with a potentially pharmacokinetically interacting comedication (one amiodarone, one carbamazepine). However, both participants had apixaban trough concentrations within the expected range [30]. In addition, the significant differences between robust and frail participants ($p = 0.017$) and those who met one ($p = 0.018$) or two ($p = 0.017$) of the frailty criteria "gait speed" and "grip strength" compared to those who met neither of these criteria remained intact when both participants were excluded from the analyses.

4 Discussion

DOAC concentrations are related to effect. Higher concentrations have been associated with bleeding events [33], while lower concentrations appear to predispose to the occurrence of strokes [34], albeit a therapeutic range for DOAC concentrations remains to be defined [35]. A number of factors can contribute to impaired drug clearance such as renal and liver impairment, sarcopenia, and hypoalbuminemia, many of which are present in frail patients [36]. In an earlier study in older patients with hip fracture, many of which appeared to be frail, elevated DOAC concentrations have been observed [7]. However, no standardized instruments to measure frailty were used in this study [7]. We therefore evaluated the relationship between different validated frailty assessments and DOAC trough concentrations.

In our exploratory study, apixaban trough concentrations were twice as high in frail compared with robust participants. Frailty assessments that focus on performance-based measures (Fried criteria, SPPB) correlated significantly with apixaban trough concentrations, with a higher degree of frailty indicating higher plasma concentrations. Moreover, a score combining the two performance-based frailty criteria "gait speed" and "grip strength" revealed significantly higher plasma concentrations in participants who met at least one of the two criteria compared with those who met none. Frailty that was defined by instruments that included no (FRAIL scale) or only a limited number of

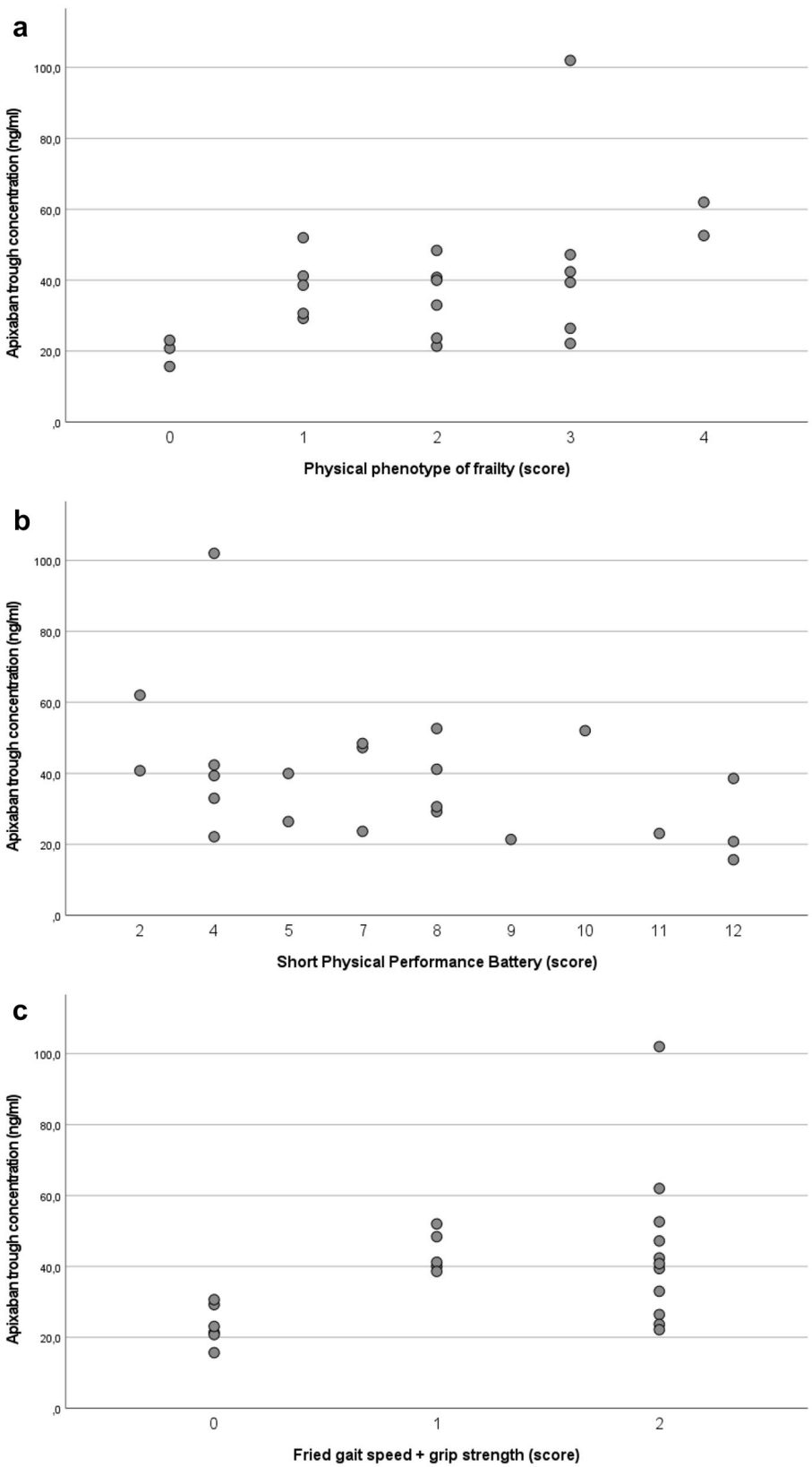

Fig. 1 Dose-normalized apixaban trough concentrations relevant to **a** the score on the physical phenotype of frailty, **b** the score on the Short Physical Performance Battery, and (**c**) the number of Fried criteria "gait speed" and "grip strength" met

Table 4 Spearman correlation of dose-normalized apixaban trough concentrations with patient characteristics, frailty assessments, and functional parameters

Characteristic	Apixaban trough ($n = 22$) r_s (p-value)
Age	0.536 (0.010)
Creatinine clearance (Cockcroft and Gault formula)	0.020 (0.930)
Weight	0.088 (0.696)
Number of Fried criteria met	0.535 (0.010)
Short Physical Performance Battery score	− 0.434 (0.044)
FRAIL scale score	0.182 (0.418)
Frailty index	0.274 (0.218)
Number of Fried criteria "gait speed" + "grip strength" met	0.498 (0.018)
Gait speed (fastest of two 15-ft walks)	− 0.433 (0.044)
Gait speed (first of two 15-ft walks)	− 0.382 (0.079)
Mean grip strength (female)	− 0.267 (0.337)
Mean grip strength (male)	− 0.429 (0.337)
Peak flow	0.049 (0.830)

performance-based measures (frailty index) showed only a weak positive correlation with apixaban trough concentrations, and no statistical significance was reached for these correlations.

Both low gait speed and weak grip strength are regarded as established clinical parameters in geriatric medicine as they are highly predictive for adverse health outcomes in older patients [37, 38]. In addition, gait speed and grip strength are included in the modern diagnosis of sarcopenia [39]. According to the European consensus criteria, the diagnosis of sarcopenia is probable when low muscle strength is measured, while sarcopenia is considered as confirmed if also low muscle quantity or quality are present [39]. Low appendicular lean mass, indicating low skeletal muscle quantity, has been recently identified as an independent risk factor for supratherapeutic DOAC (apixaban and rivaroxaban) trough and peak concentrations in older adults [40]. Moreover, older patients with supratherapeutic DOAC trough concentrations had significantly lower handgrip strength compared with patients whose trough concentrations were within the therapeutic range [40]. The authors concluded that the altered body composition with a lower fraction of skeletal muscle changed the volume of distribution of the hydrophilic DOACs resulting in higher plasma concentrations [40].

Although these recent findings support the results of our exploratory study, sarcopenia-related changes in body composition and drug distribution might only be one of several factors contributing to higher apixaban trough concentrations in frail older persons. As the concept of frailty may be regarded as an equivalent of a person's biological age, age-related changes in pharmacokinetics are expected to be particularly pronounced in frail older adults [4], although the available evidence for this is sparse [41]. Indicators of physical frailty, such as the Fried phenotype, low gait speed, and reduced grip strength can be regarded as surrogates for the generalized decline of physiological resources in frailty. Liver size, hepatic blood flow, and possibly hepatocellular oxygen supply show an age-related decrease, which may result in a reduction of phase I hepatic clearance of certain drugs [4, 42]. About 25% of an oral apixaban dose is metabolized, primarily via CYP3A [43]. It has been speculated that CYP3A-mediated metabolism may decrease in older adults, though the respective evidence has been inconclusive [42]. Metabolic clearance of midazolam, a CYP3A marker substrate, is lower in older palliative care patients than in younger healthy adults [44]. Specific information on CYP3A-mediated metabolism in frail older persons is limited [41]. Frailty is associated with an increase in inflammatory parameters [45], which might reduce hepatic phase I metabolism [42]. Yet, in one clinical study using the erythromycin breath test to assess CYP3A activity, the results did not differ between frail — characterized by the Fried phenotype — and robust participants [46]. However, erythromycin is also a substrate of P-glycoprotein and as such not an ideal CYP3A probe drug [42].

Out of the three physiological variables that influence apixaban dosing — age, weight, and renal function — only age was significantly correlated with apixaban trough concentrations in our study population. Data on apixaban pharmacokinetics in old age are limited. A population pharmacokinetic model using data from 11 studies with apixaban for the treatment of venous thromboembolism calculated only a small influence of age on apixaban concentrations and predicted a 5% higher exposure in an 80-year-old male patient compared with a 60-year-old reference patient [47]. However, the studies that served as a basis for the model included only a limited number of older patients aged ≥ 75 years and their frailty status is unknown [47]. A single-dose study found that apixaban exposure was 32% higher in older adults aged ≥ 65 years than in younger adults aged 18–40 years, with renal impairment most likely contributing to the increased exposure in the older age group [48]. Because all study participants were < 80 years of age, were described as healthy, and had not used any prescription or over-the-counter medication within the last week before sampling [48], these data are unlikely to be representative for the general older population and particularly not for patients with frailty.

In a study evaluating "real-world" older patients, three of four participants aged ≥ 80 years with atrial fibrillation who received a reduced apixaban dose of 2.5 mg BID, although they did not qualify for it according to the approval, had trough and peak apixaban concentrations within the ranges

for the 5-mg BID dose that was actually indicated [32]. The mean apixaban trough concentration in inaccurately reduced 2.5-mg BID dose participants in our study was comparable to these data, while mean trough concentrations for the accurately dosed 5-mg and 2.5-mg BID groups tended to be higher than previously described in "real-world" patients [31, 32] (**Table 2**). In line with previous findings in older adults [49], the mean and median apixaban trough concentrations still tended to be lower in inaccurately compared with accurately reduced participants in our study. The underlying physiological mechanisms leading to higher apixaban exposure in older adults have not been precisely elucidated yet. It appears, however, plausible that the age-related changes are rather linked to an older person's functional status (biological age, i.e., frailty) than to his or her chronological age. This may account for our observation that stepwise linear regression identified the individual Fried phenotype score as a better predictor of apixaban trough concentrations than chronological age.

Renal function is known to contribute to apixaban clearance [47]. However, apixaban trough concentrations did not show a significant correlation with the participants' creatinine clearance in our study sample. A poor and non-significant correlation of apixaban trough concentrations with creatinine clearance in real-world patients has been previously reported [31]. Renal excretion of apixaban only contributes about 27% to its overall clearance, and apixaban exposure increases by 16% in individuals with mild renal impairment (creatinine clearance 65 mL/min) and by 29% in individuals with moderate renal impairment (creatinine clearance 40 mL/min) compared with adults with normal renal function [50]. With a mean creatinine clearance of 47 mL/min and a standard deviation of 15.8 mL/min, interpatient differences in renal function might not have been pronounced enough to detect a correlation with apixaban trough concentrations in our study population.

A number of studies have aimed at evaluating the clinical outcomes of DOAC treatment in frail older adults [51–54]. However, so far, no study has evaluated the risk-benefit profile of different DOAC dosing strategies in older adults with frailty, for instance by investigating the clinical outcomes of accurately and inaccurately dosed apixaban treatment in this patient group. Moreover, although the relationship between apixaban plasma concentrations and anti-Factor Xa activity does not seem to be influenced by age [55], it is unclear whether this would also apply to frail older adults. Future research should target the question whether treatment outcomes might be improved by tailoring apixaban dosing to the degree of physical frailty of the older patient or whether treatment in this population should be guided by concentration measurements.

Besides the small sample size, there are other limitations of our study that need to be addressed. We only included a very limited number of robust older patients. The majority of our participants were geriatric rehabilitation patients and their physical performance might have been affected by subacute medical conditions. We cannot rule out that subacute medical conditions or recent recovery from acute illness may have had a residual effect on apixaban concentrations. In addition, we relied on estimated creatinine clearance instead of measured creatinine clearance. We also assumed dose linearity of both apixaban and rivaroxaban pharmacokinetics based on data from non-geriatric populations. Moreover, we only collected plasma concentrations at a single sampling timepoint, while the most meaningful pharmacokinetic parameter to predict favorable and unfavorable clinical outcomes of DOAC treatment remains to be identified [56].

5 Conclusions

In this exploratory study, the physical phenotype of frailty, the SPPB, and the performance measures gait speed and grip strength were identified as indicators of apixaban trough concentrations. The predictive quality of performance-based frailty measures for apixaban pharmacokinetics as well as clinical outcomes of apixaban treatment need to be addressed in future studies that include larger samples of robust and frail study participants, and these studies should evaluate whether exposure differences will require dose adjustment for frail people.

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Declarations

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Ethics Approval The study was approved by the Ethics Committee of the Medical Faculty of Heidelberg University (S-866/2018).

Consent to Participate Written informed consent was obtained from each participant included in the study.

Consent for Publication Not applicable.

Availability of Data and Material The authors confirm that all relevant data are included in the article and/or its supplementary information files.

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Authors' Contributions Conceptualization: AE, JM, DC, AB, GM, WEH, JMB; data curation: AE, JM, KIF, JB; formal analysis: AE, JM, PB, DC, FS, GM, WEH, JMB; funding acquisition: WEH, JMB; investigation: AE, JM, KIF; project administration: AE, JMB; resources: JB, WEH, JMB; supervision: GM, JMB; visualization: AE, GM, WEH; writing, original draft: AE; writing, review and editing: AE, JM, PB, KIF, JB, DC, FS, AB, GM, WEH, JMB. All authors read and approved the final version of the manuscript.

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