

Electronic Supplementary Material

Drugs & Aging

Frailty as a marker for the plasma concentrations of direct oral anticoagulants in older patients – Results of an exploratory study

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Table S1 Characteristics of rivaroxaban study patients

Characteristic	Rivaroxaban (n = 14)
Age, years: Mean (\pm SD; range)	84.4 (\pm 7.3; 70-95)
Female, n (%)	7 (50)
Creatinine clearance (CG), ml/min: Mean (\pm SD; range)	56.6 (\pm 17.1; 19.5-86.0)
Weight, kg: Mean (\pm SD; range)	81.6 (\pm 18.6; 47.0-120.2)
Indication for DOAC, n (%)	
Atrial fibrillation (nonvalvular)	7 (50.0)
Atrial fibrillation + treatment of PE	0 (0)
Atrial fibrillation + NSTEMI	1 (7.1)
Prophylaxis of recurrent DVT/PE	4 (28.6)
Peripheral artery disease	1 (7.1)
Ambiguous	1 (7.1)
Dose in mg, n (%)	
20 QD	3 (21.4)
15 QD	8 (57.1)
10 QD	1 (7.1)
2.5 BID	2 (14.3)
Fried category, n (%)	
Robust	0 (0)
Pre-frail	8 (57.1)
Frail	6 (42.9)
Number of Fried criteria met, n (%)	
0	0 (0)
1	2 (14.3)
2	6 (42.9)
3	4 (28.6)
4	2 (14.3)
5	0 (0)
Short Physical Performance Battery score, n (%)	
10-12	2 (14.3)
8-9	1 (7.1)
0-7	11 (78.6)
FRAIL scale score, n (%)	
0	2 (14.3)
1-2	5 (35.7)
\geq 3	7 (50.0)
Frailty index: Mean (\pm SD; range)	0.43 (\pm 0.15; 0.18-0.71)
Number of Fried criteria "gait speed" + "grip strength" met, n (%)	
0	0 (0)
1	3 (21.4)
2	11 (78.6)
Gait speed, m/s: Mean (\pm SD; range)	0.65 (\pm 0.21; 0.35-1.14)
Grip strength (female), kg: Mean (\pm SD; range)	14.5 (\pm 4.4; 7.3-20.3)
Grip strength (male), kg: Mean (\pm SD; range)	24.5 (\pm 5.1; 16.7-29.7)

BID, twice a day; CG, Cockcroft and Gault formula; DVT, deep vein thrombosis; NSTEMI, non-ST elevation myocardial infarction; PE, pulmonary embolism; QD, once a day; SD, standard deviation

Table S2 Spearman correlation of dose-normalized rivaroxaban trough concentrations with patient characteristics, frailty assessments, and functional parameters

Characteristic	Rivaroxaban trough (n = 14) r_s (p-value)	Rivaroxaban trough in QD dosed participants (n = 12) r_s (p-value)
Age	0.406 (0.150)	0.587 (0.045)
Creatinine clearance (Cockcroft and Gault formula)	-0.433 (0.122)	-0.469 (0.124)
Weight	0.053 (0.858)	-0.032 (0.923)
Number of Fried criteria met	0.032 (0.912)	0.074 (0.819)
Short Physical Performance Battery score	-0.050 (0.866)	-0.036 (0.911)
FRAIL scale score	-0.142 (0.628)	-0.104 (0.747)
Frailty index	-0.121 (0.680)	-0.126 (0.697)
Number of Fried criteria "gait speed" + "grip strength" met	0.065 (0.826)	0.194 (0.545)
Gait speed (fastest of two 15-foot walks)	-0.371 (0.191)	-0.448 (0.145)
Gait speed (first of two 15-foot walks)	-0.442 (0.114)	-0.517 (0.085)
Mean grip strength (female)	0.179 (0.702)	0.143 (0.787)
Mean grip strength (male)	-0.054 (0.908)	-0.314 (0.544)
Peak flow	-0.756 (0.002)	-0.737 (0.006)

QD, once a day

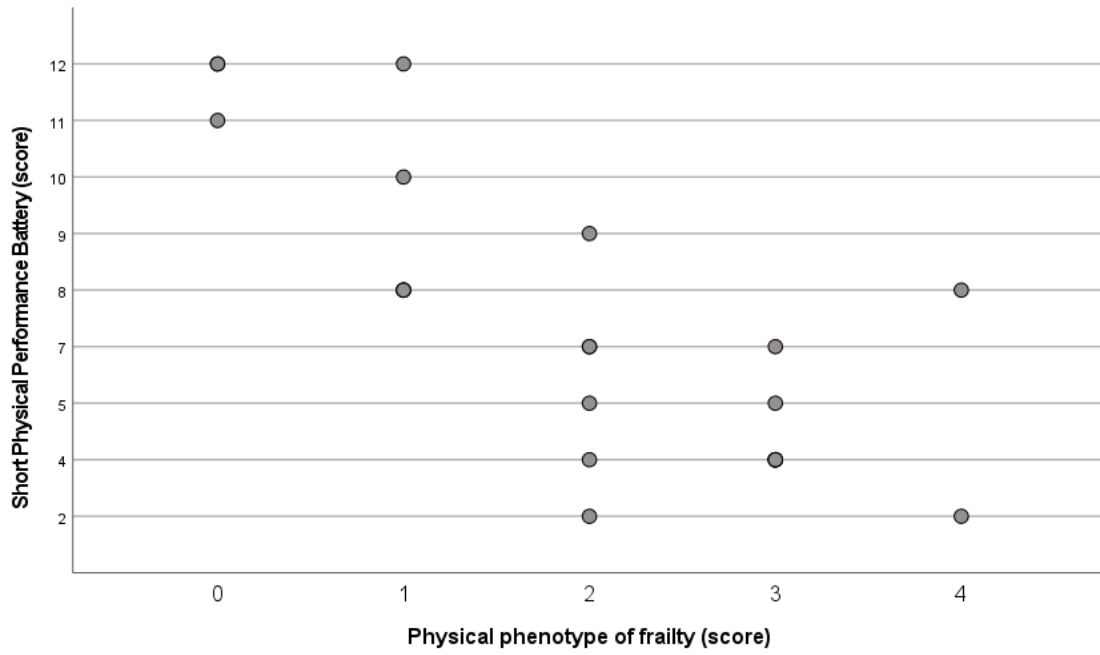


Fig. S1 Relationship between the score on the physical phenotype of frailty [1] and the score on the Short Physical Performance Battery [2] in the apixaban subsample (n = 22)

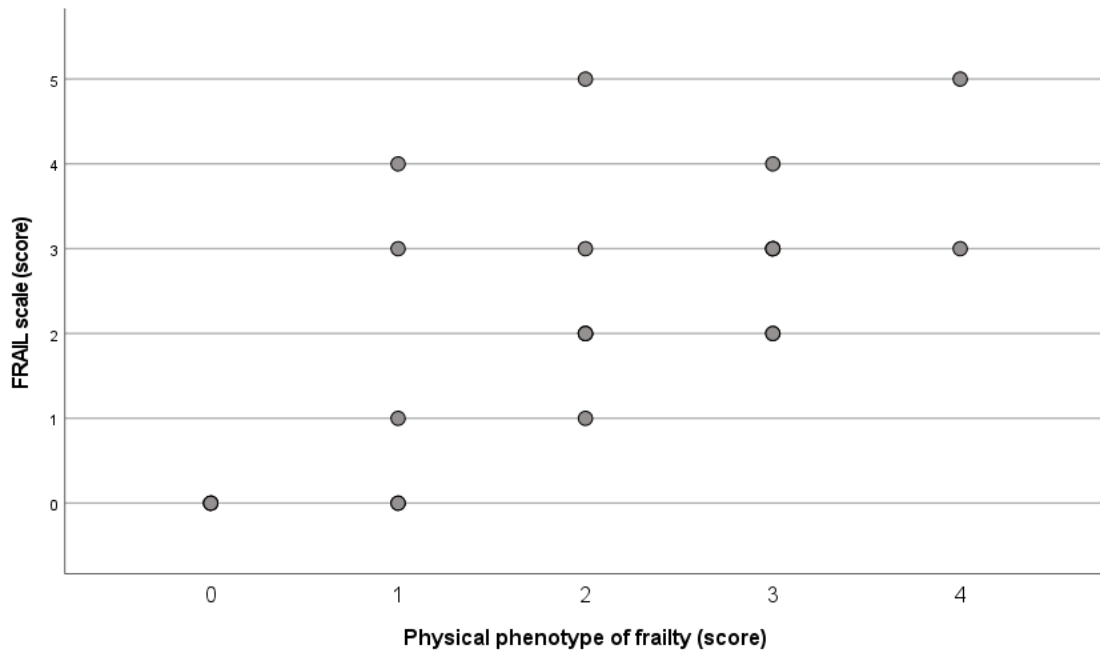


Fig. S2 Relationship between the score on the physical phenotype of frailty [1] and the score on the FRAIL scale [3] in the apixaban subsample (n = 22)

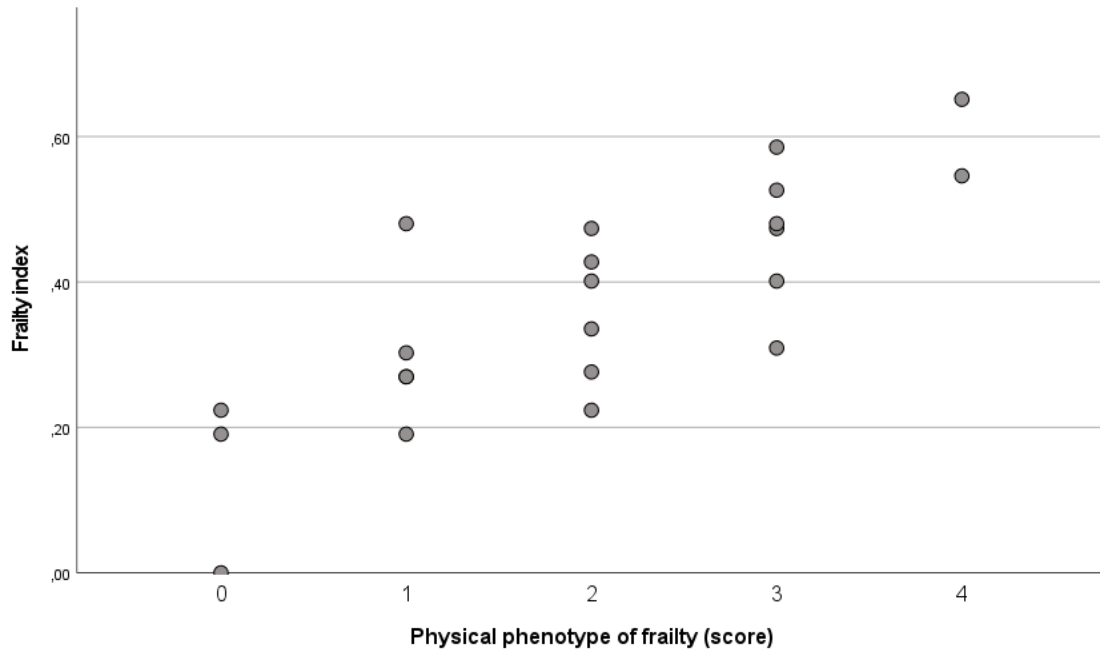


Fig. S3 Relationship between the score on the physical phenotype of frailty [1] and the frailty index [4] in the apixaban subsample (n = 22)

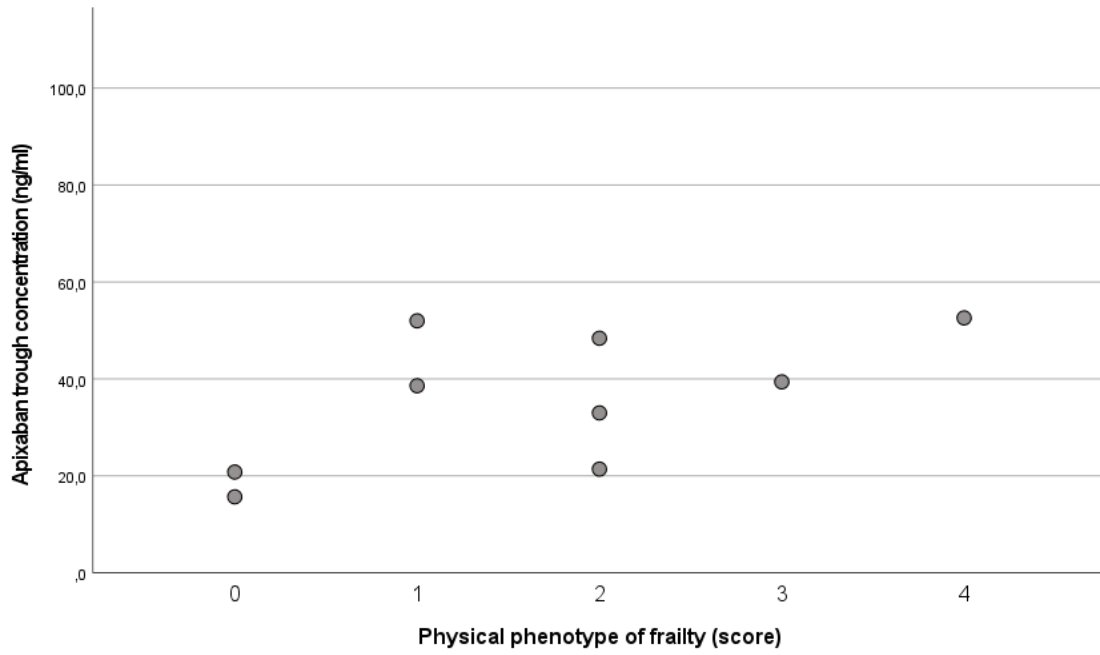


Fig. S4 Relationship between apixaban trough concentrations (dose-normalized) and score on the physical phenotype of frailty [1] in the 5 mg BID subgroup (n = 9)

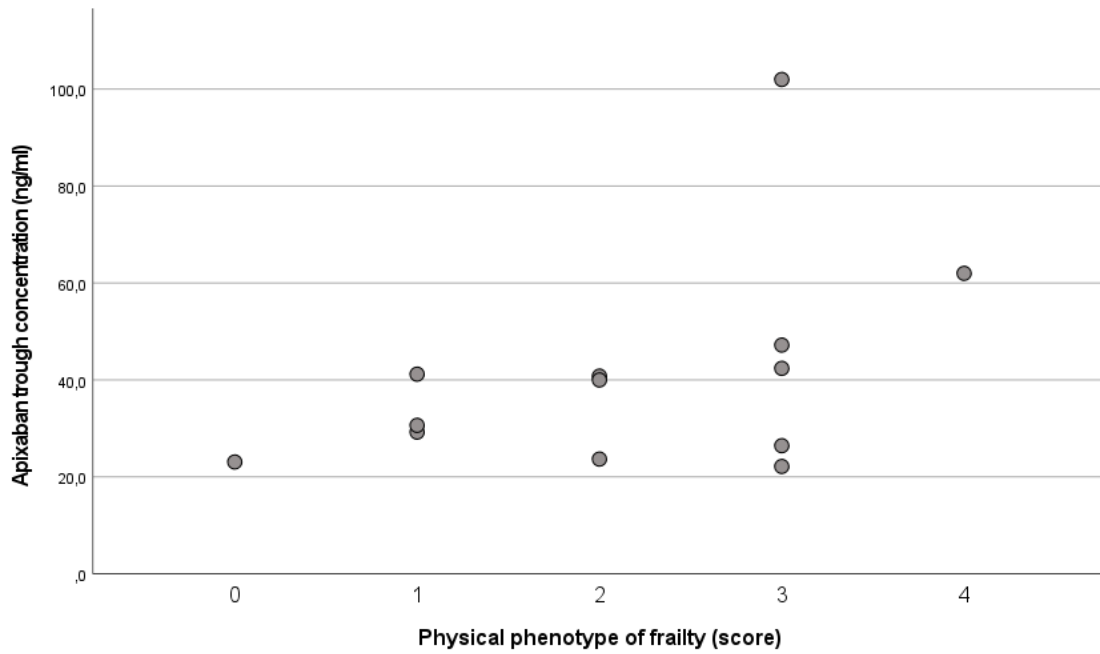


Fig. S5 Relationship between apixaban trough concentrations (dose-normalized) and score on the physical phenotype of frailty [1] in the 2.5 mg BID subgroup (n = 13)

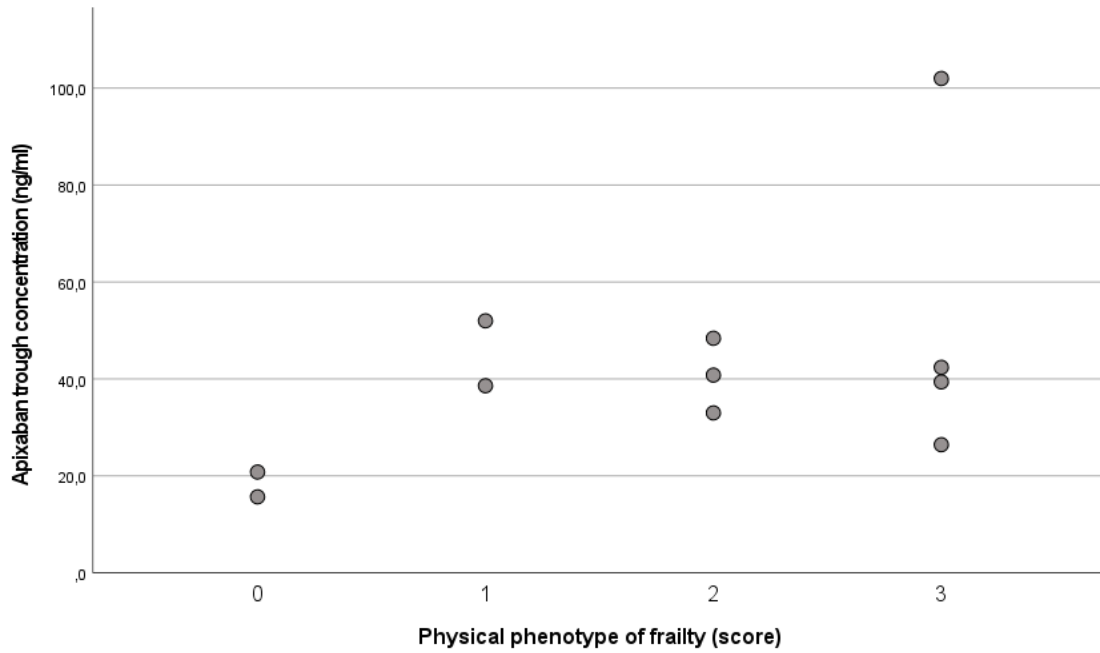


Fig. S6 Relationship between apixaban trough concentrations (dose-normalized) and score on the physical phenotype of frailty [1] in participants who are accurately dosed according to the dosing recommendations for anticoagulation therapy in atrial fibrillation [5] (n = 11)

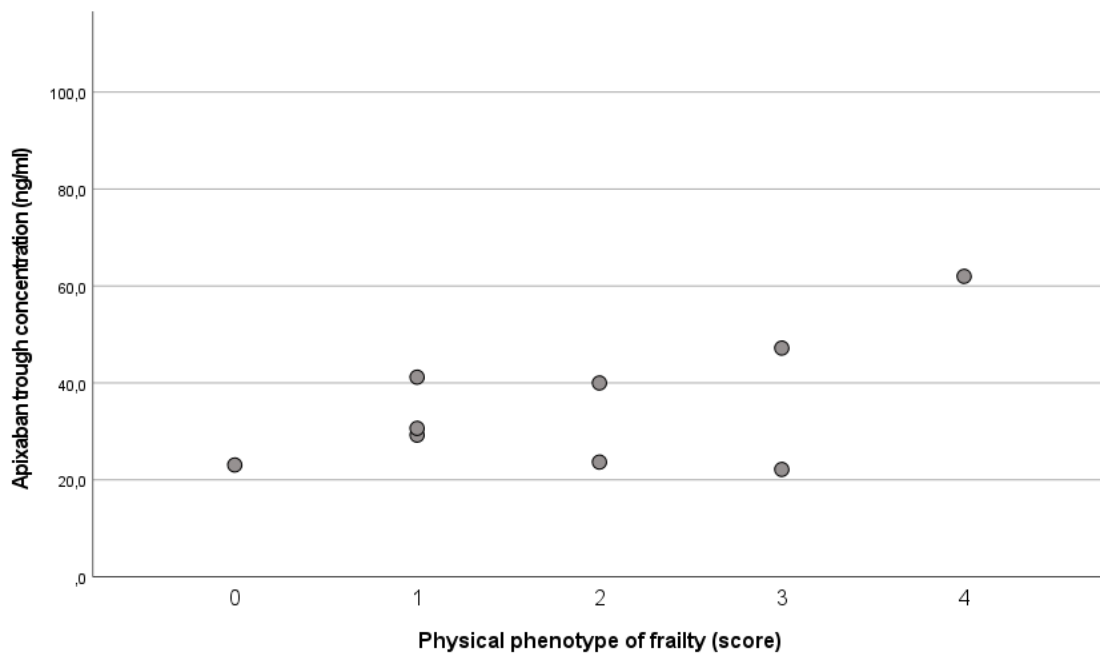


Fig. S7 Relationship between apixaban trough concentrations (dose-normalized) and score on the physical phenotype of frailty [1] in participants who are inaccurately dosed with 2.5 mg BID according to the dosing recommendations for anticoagulation therapy in atrial fibrillation [5] (n = 9)

Table S3 Frailty status of the participants in the different apixaban dosage groups

Frailty status	5 mg BID Accurate dose (n = 7)	2,5 mg BID Accurate dose (n = 4)	2,5 mg BID Inaccurate dose (n = 9)	5 mg BID Inaccurate dose (n = 2)
Robust	2	-	1	-
Pre-frail	4	1	5	1
Frail	1	3	3	1

BID, twice daily;

Accurate dose = Accurate dose according to the recommendations for the dosing in atrial fibrillation [5];

Inaccurate dose = Inaccurate dose according to the recommendations for the dosing in atrial fibrillation [5];

Table S4 Number of frailty criteria (weak grip strength, slow gait speed) met in the different apixaban dosage groups

Grip strength + gait speed (number of criteria met)	5 mg BID Accurate dose (n = 7)	2,5 mg BID Accurate dose (n = 4)	2,5 mg BID Inaccurate dose (n = 9)	5 mg BID Inaccurate dose (n = 2)
0	2	-	3	1
1	3	-	2	-
2	2	4	4	1

BID, twice daily;

Accurate dose = Accurate dose according to the recommendations for the dosing in atrial fibrillation [5];

Inaccurate dose = Inaccurate dose according to the recommendations for the dosing in atrial fibrillation [5];

Table S5 Mean and median non-dose-normalized apixaban trough concentrations relative to the different frailty categories

Frailty category	Non-dose-normalized apixaban trough concentration (ng/ml) Mean (\pm SD)	Non-dose-normalized apixaban trough concentration (ng/ml) Median (range)
Category according to the physical phenotype of frailty		
Robust (n = 3)	80.0 (\pm 23.2)	78.4 (57.7-104.0)
Pre-frail (n = 11)	134.6 (\pm 69.6)	103.0 (59.2-260.0)
Frail (n = 8)	151.9 (\pm 80.1)	136.5 (55.4-263.0)
Number of Fried criteria "gait speed" + "grip strength" met		
0 (n = 6)	82.8 (\pm 19.1)	77.5 (57.7-107.0)
1 (n = 5)	179.6 (\pm 75.4)	193.0 (100.0-260.0)
2 (n = 11)	140.2 (\pm 73.9)	118.0 (55.4-263.0)

SD, standard deviation

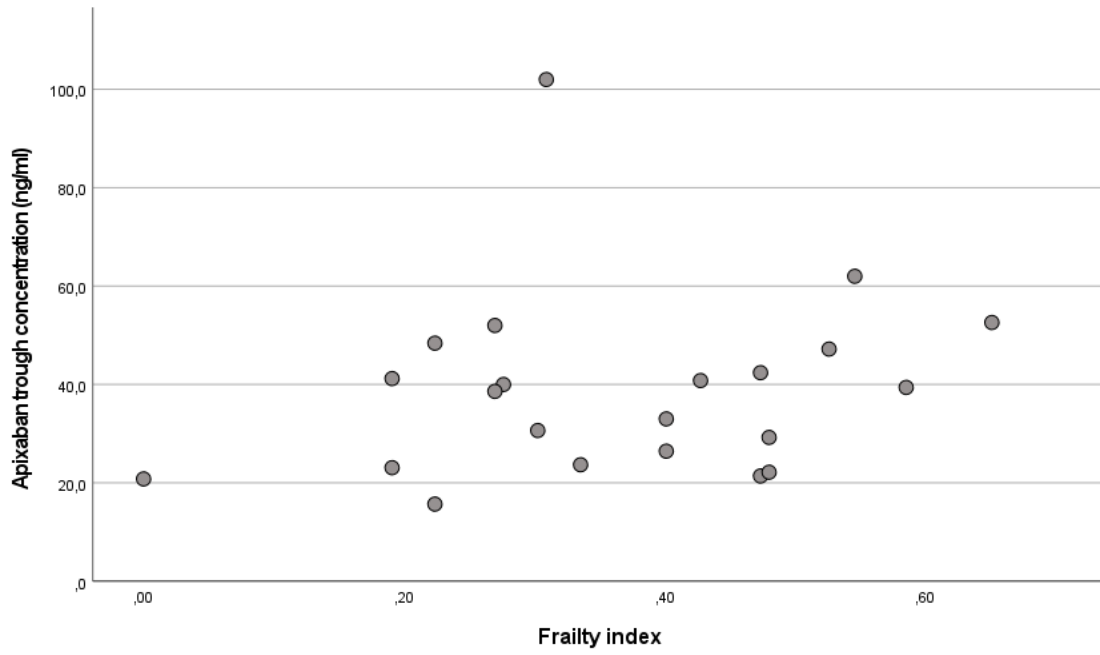


Fig. S8 Dose-normalized apixaban trough concentrations relevant to the frailty index

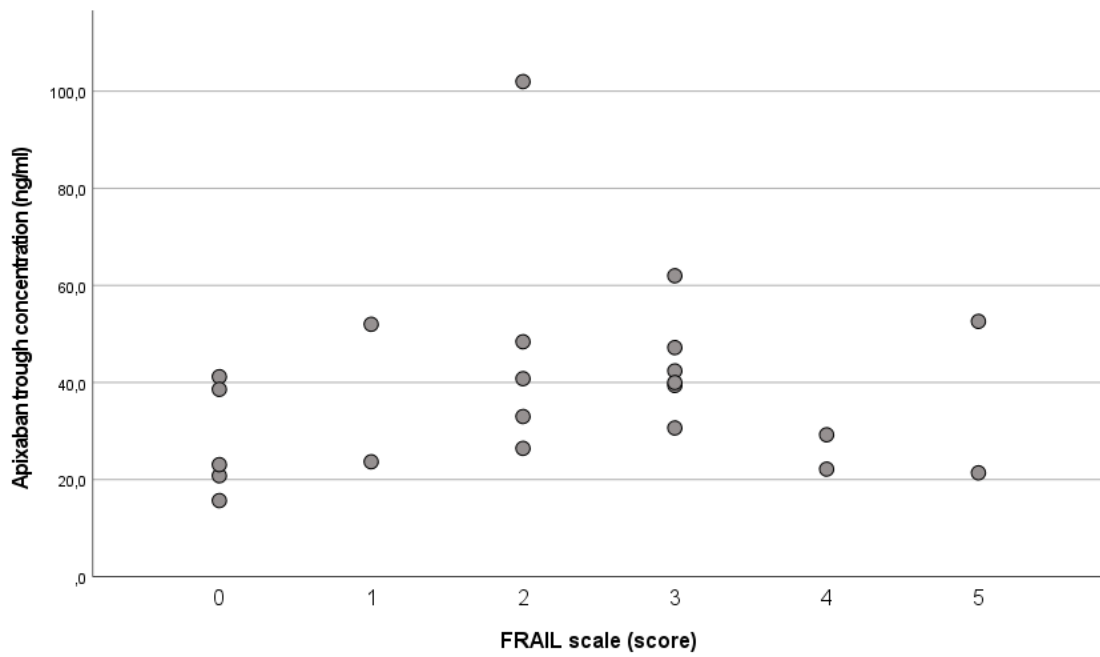


Fig. S9 Dose-normalized apixaban trough concentrations relevant to the score on the FRAIL scale

References

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