

SUPPLEMENTAL MATERIALS

Figure S1 The plot depicts the relation between standardized values and original trough values, by DOAC drug (Apixaban or Dabigatran administered BID, and Edoxaban or Rivaroxaban administered OID). For instance, a standardized trough value of 0 corresponds to about 50 ng/mL for Edoxaban or Rivaroxaban, and to about 100 ng/mL for Apixaban or Dabigatran.

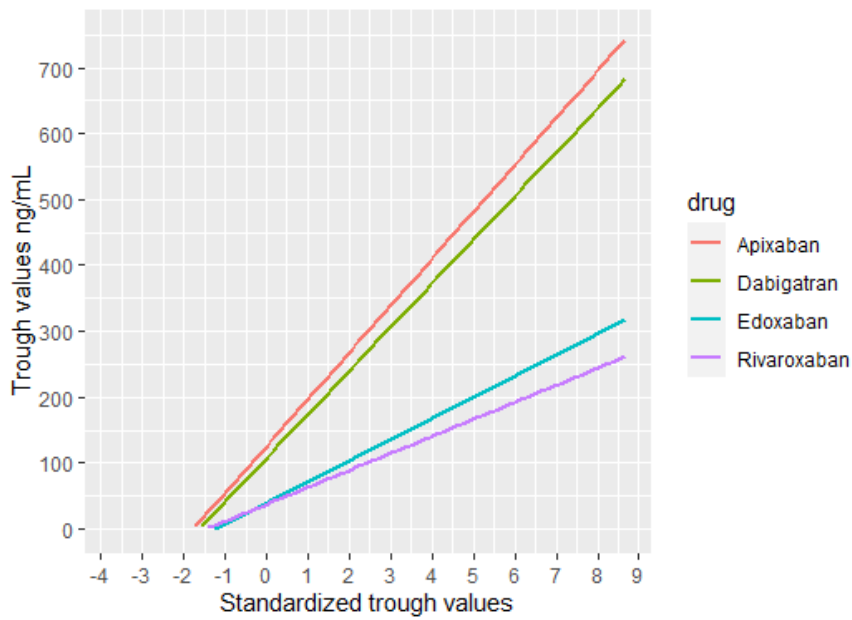


Table S1 Results of DOAC measurements, mean \pm SD and range (min-max)

	C-trough level N=1657		C-peak level N=1303	
	N (%)	ng/mL	N (%)	ng/mL
Apixaban	521 (31.4)	123 \pm 69 (8-468)	412 (31.6)	247 \pm 97 (16-784)
Dabigatran	221 (13.3)	106 \pm 64 (9-367)	190 (14.6)	217 \pm 102 (32-499)
Edoxaban	583 (35.3)	40 \pm 33 (7-284)	469 (36.0)	220 \pm 100 (6-497)
Rivaroxaban	332 (20.0)	37 \pm 30 (6-331)	232 (17.8)	215 \pm 99 (9-498)

DOAC: direct oral anticoagulants; SD = Standard Deviation

Table S2 Deaths (n=46)

	N (%)
Thrombotic complications	6 (13.0)
Hemorrhagic complication	3 (6.5)
Cancer	9 (19.6)
Sepsis	5 (10.9)
SARS-CoV-2	5 (10.9)
Heart failure	5 (10.9)
Respiratory failure	3 (6.5)
Polytrauma	1 (2.2)
Acute renal insufficiency	1 (2.2)
Sudden death	1 (2.2)
Senile cachexia	2 (4.3)
Not specified but not OAT related	1 (2.2)
Unknown	4 (8.7)

AMI: acute myocardial infarction; OAT: oral anticoagulant therapy

Table S3 Hazard ratios of the primary thrombotic outcome endpoint, adjusted for potential confounders, in patients below and above the first quintile of absolute DOAC plasma concentration. Patients were classified as being below the first quintile if their absolute DOAC plasma concentration was below the first quintile of the distribution of values measured in other patients taking the same dose of corresponding DOAC.

Characteristic	First Model (C-trough), n=1657		Second model (C-peak), n=1298	
	HR	95% CI	HR	95% CI
1 st quintile vs others, C-trough	1.47	0.26 – 8.15	-	-
1 st quintile vs others, C-peak	-	-	7.39	1.62 – 33.8
CHA ₂ DS ₂ VASc score	1.90	0.97-3.70	2.09	1.07 – 4.07
BMI, Kg/m ²	0.92	0.80-1.07	0.95	0.83 - 1.08
Glomerular filtration rate, ml/min	1.02	1.00-1.05	1.02	1.00 - 1.05
Low-dose vs Standard dose DOAC	3.87	0.77-19.5	3.25	0.63-16.9
Antiplatelet treatment (yes vs. no)	0.28	0.03-2.45	0.24	0.03-2.08

Both models were estimated using the Fine & Gray competitive risk regression model. The AIC was 117.8 and 106.7 for the models using C-trough and C-peak, respectively.

BMI: Body-Mass Index; CI: confidence interval; DOAC: Direct oral anticoagulant; HR: hazard ratio

1st quintile at C-trough - Apixaban 2.5 mg/BID: ≤ 65 ng/ml; Apixaban 5 mg/BID: ≤ 75 ng/ml; Edoxaban 30 mg: ≤ 21 ng/ml; Edoxaban 60 mg: ≤ 20 ng/ml; Rivaroxaban 20 mg: ≤ 19 ng/ml; Dabigatran 110 mg/BID: ≤ 63 ng/ml; Dabigatran 150 mg/BID: ≤ 53 ng/ml.

1st quintile at C-peak - Apixaban 2.5 mg/BID: ≤ 148 ng/ml; Apixaban 5 mg/BID: ≤ 174 P pron ng/ml; Edoxaban 30 mg: ≤ 131 ng/ml; Edoxaban 60 mg: ≤ 157 ng/ml; Rivaroxaban 20 mg: ≤ 127 ng/ml; Dabigatran 110 mg/BID: ≤ 131 ng/ml; Dabigatran 150 mg/BID: ≤ 119 ng/ml.

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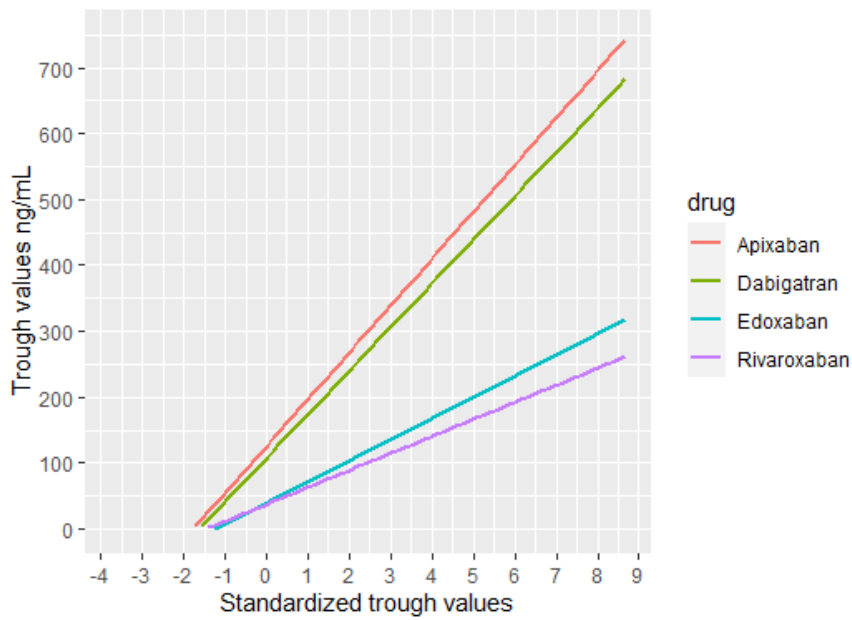


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