Supplemental Material

Effect of clarithromycin, a strong CYP3A and P-glycoprotein inhibitor, on the pharmacokinetics of edoxaban in healthy volunteers and the evaluation of the drug interaction with oral factor Xa inhibitors by a microdose cocktail approach

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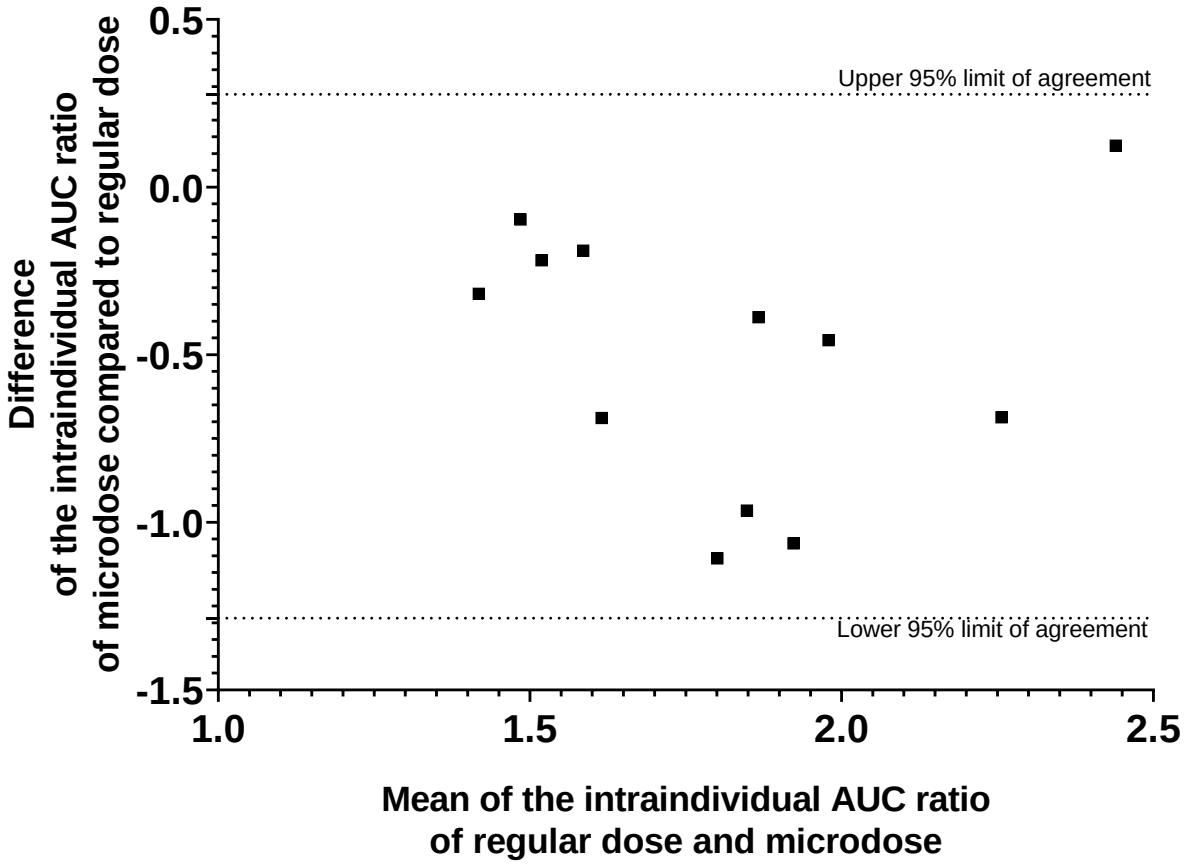
Supplemental Table S1: Pharmacokinetic parameters of factor Xa inhibitors and midazolam as marker for CYP3A activity

Drug (dose)	**Pharmacokinetic variable**		**Baseline**		**At clarithromycin steady-state**		**p-value of change**
			GM	*(95 % CI)*	*GM*	*(95 % CI)*	
Edoxaban (60 mg)	Cl / F	[L/h]	51	(44 – 60)	34	(30 – 38)	< 0.0001
	$t_{1/2}$	[min]	7.3	6.2-8.6	7.2	6.4-8.0	0.8
	T_{max}	[min]	76	46-95	100	59-125	0.3
	Vz	[L]	594	412-711	361	288-419	0.0006
µ-edoxaban (50 µg)	Cl / F	[L/h]	48	43-53	23	21-26	< 0.0001
	$t_{1/2}$	[min]	5.6	4.9-6.5	6.3	5.7-7.1	0.3
	T_{max}	[min]	70	45 - 85	103	44 - 132	0.4
	Vz	[L]	399	327-459	217	191-240	0.0002
µ-apixaban (25 µg)	Cl / F	[L/h]	4.9	4.1-5.9	3.5	3.0-4.2	< 0.0001
	$t_{1/2}$	[min]	7.1	6.4-7.9	8.1	7.4-8.9	0.14
	T_{max}	[min]	114	74-141	134	96-164	0.3
	Vz	[L]	52	43-59	43	35-50	0.06
µ-rivaroxaban (25 µg)	Cl / F	[L/h]	9.0	7.8-11.0	6.3	5.6-7.1	0.0003
	$t_{1/2}$	[min]	6.3	5.3-7.5	5.7	5.2-6.3	0.5
	T_{max}	[min]	55	47-62	55	38-63	0.5
	Vz	[L]	85	67-100	53	45-60	0.0042
µ-midazolam	AUC_{2-4}	[min*ng/mL]	6.4	5.1-7.9	40.3	35.9-45.1	< 0.0001

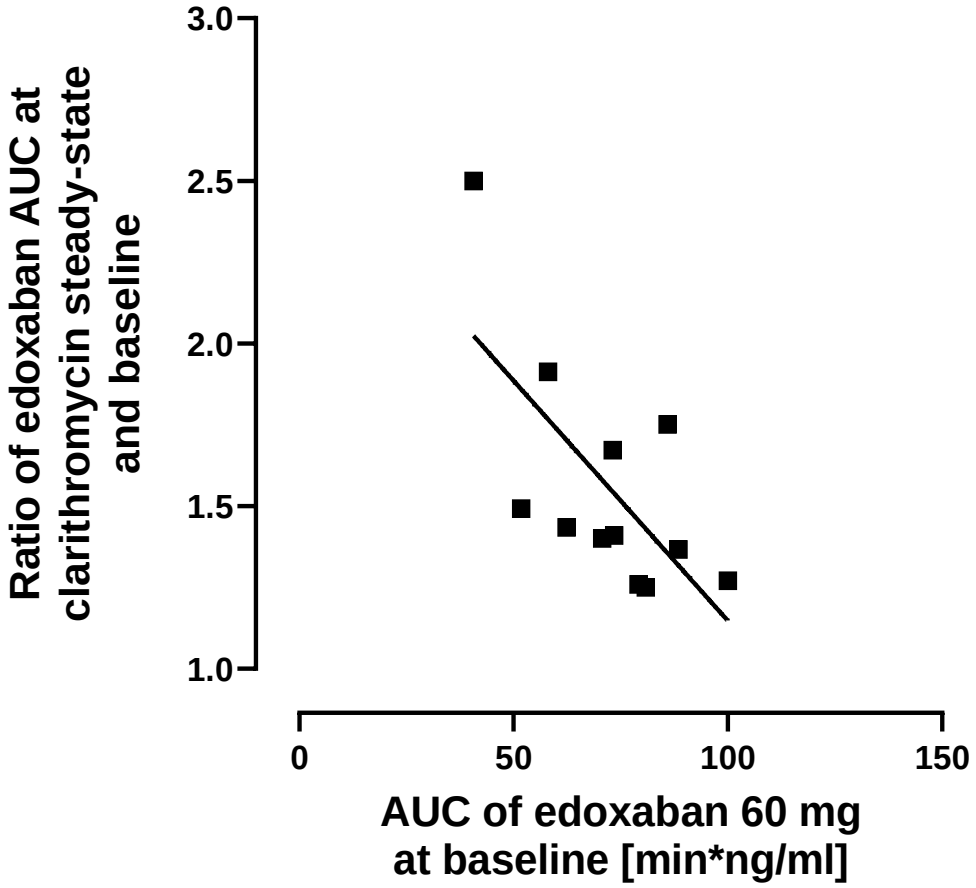
GM: geometric mean

Supplemental Table S2: Baseline characteristics of the 12 study participants

Laboratory parameter		**Mean**	**Standard deviation**	**Normal range**
Albumin	[g/L]	46.5	4.29	30 - 50
Alanine aminotransferase	[U/L]	17.67	11.9.	< 50
Alkaline phosphatase	[U/L]	56.58	16.3	40 - 130
Aspartate aminotransferase	[U/L]	21.58	5.42.	- < 46
γ-glutamyltranspeptidase	[U/L]	12.08	8.08	< 50
Bilirubin	[mg/dL]	0.675	0.32	< 0.3
Calcium	[mmol/L]	2.35	0.15	2,11 - 2,59
Chloride	[mmol/L]	104.8	1.27	98 - 111
Potassium	[mmol/L]	3.80	0.23	3,4 - 5,0
Sodium	[mmol/L]	140	1.66	135 - 146
Phosphate	[mmol/L]	1.05	0.17.	0,84 - 1,45
Total protein	[g/L]	70.4	3.86	60 - 80
Glucose	[mg/dL]	82.1	9.10	65 - 110
Urea	[mg/dL]	23.0	6.41	< 45
Creatine kinase	[U/L]	147	165	< 190
Creatinine	[mg/dL]	0.70	0.12	0,6 - 1,4
Estimated creatinine clearance	[mL/min]	129	28.9	> 60
Lipase	[U/L]	46.0	13.1	19 - 63
P-amylase	[U/L]	30.8	13.3	8 - 53
Erythrocytes	[/pL]	4.76	0.37	4,3 - 6,1
Hemoglobin	[g/dL]	13.6	1.23	13 – 17
Hematocrit	[L/L]	0.40	0.03	0,38 - 0,52
Leucocytes	[/nL]	7.06	1.96	4 - 10
Lymphocytes	[/nL]	1.70	0.40	1,0 - 4,8
Monocytes	[/nL]	0.40	0.10	0,2 - 0,8
Neutrophils	[/nL]	4.78	1.64	1,8 - 7,7
Basophils	[/nL]	0.03	0.01	< 0,2
Eosinophils	[/nL]	0.10	0.07	< 0,5
Platelets	[/nL]	266	45.4	150 - 440
Activated partial thromboplastin time	[s]	24.63	1.20	< 35
International normal ratio		1.02	0.05	< 1.2



Supplemental Figure S1 Bland-Altman plot for agreement between regular dose and microdose of edoxaban. The mean of intraindividual AUC ratios under clarithromycin (per volunteer/mean of AUC of edoxaban 60 mg and AUC of edoxaban 50 μg) were plotted against the difference of the intraindividual AUC ratio of the microdose compared to the regular dose.



Supplemental Figure S2 Regression of the individual baseline exposure of edoxaban 60 mg ($r^2 = 0.47$. $p = 0.03$). as a marker mainly influenced by P-glycoprotein activity with the ratio of the AUC increase at clarithromycin steady-state.

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