

INTERACTIONS BETWEEN DIRECT ORAL ANTICOAGULANTS AND ANTIEPILEPTIC DRUGS (INTER-DOAC): A PROSPECTIVE OBSERVATIONAL STUDY

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Background and aims. Potential drug-drug interactions (D-DI) limit concomitant use of antiepileptic drugs (AED) and direct oral anticoagulants (DOAC). Indeed, the European Society of Cardiology guidelines on the use of oral anticoagulants in patients with atrial fibrillation (AF) specifically recommend caution for most AED/DOAC combinations. However, knowledge about pharmacokinetic and pharmacodynamic DDI of AED and DOAC is limited and frequently restricted to in vitro findings. Moreover, plasma levels of direct anticoagulants are not routinely monitored with a lack of standardization in laboratory measurements and reference values. The availability of accurate DOAC plasma levels could lead to an improvement in clinical decisions and appropriate management in both emergency and routine situations. Through this study, we want to extend our knowledge about DOAC-AED DDI in vivo.

Methods. In this observational, prospective study, approved by the Italian Ethic Committee (CET03/2023 of 27 July 2023), we enrolled outpatients with non-valvular AF or pulmonary embolism (PE) and an indication for AED attending the Respiratory, Cardiology and Neurology Units in Pisa, Italy. Anthropometric parameters, comorbidities, repeated plasma DOAC and AED levels and clinical events (arterial/venous thrombosis, seizure, major or non-major clinically relevant bleeding, death) were recorded. For each DOAC plasma level we calculated the z-score based on data from 967 patients at the local laboratory, upon verification of their normal distribution. In the absence of universally accepted reference values, we defined the therapeutic range (TR) for DOAC as that corresponding to a z-score between -1.64 and 1.64. For AED, the TR was calculated based on the range provided by the local laboratory.

Results. Baseline characteristics of the study population (n=23), pharmaceutical molecules, DOAC and AED blood level within or outside the TR, events and follow-up time are listed in the table. A total of 136 blood tests were performed from September 2023 to March 2026. Each patient was followed up by the relevant specialist clinically. In 66 out of 68 (97%) trough samples and 7 out of 9 (78%) peak samples, respectively, plasma levels of DOAC were within the TR. In 24 out of 63 (38%) samples in patients with an indication for AED as antiepileptic therapy or mood stabilization, AED levels were within the TR. During follow-up (mean 294 days) we recorded a recurrent thromboembolic event, 2 non-major clinically relevant bleedings, a major bleeding and 2 episodes of seizure (in the same patient). Four patients died during the follow-up period, one of whom as a consequence of intracranial bleeding, one for neoplastic cachexia, one for respiratory failure in severe pulmonary emphysema and one for natural causes associated with advanced age. With the limit of the small sample size, we found no significant correlation between z-scores calculated for each DOAC or AED plasma levels and clinical events.

Conclusions. This study suggests that co-administration of AED and DOAC both in AF and PE patients results in DOAC acceptable blood values in a relevant percentage of cases; recurrences of venous thromboembolism or major bleeding appear to be manageable over a two and a half-year follow-up.

PATIENT ID	SEX	AGE [years]	DOAC	INDICATION	AED	INDICATION	DOAC TROUGH SAMPLES IN TR	DOAC PEAK SAMPLES IN TR	AED SAMPLES IN TR	EVENTS	FOLLOW-UP [days]
1	F	58	dabigatran	PE	valproic acid	mood disorders	4	1	5	0	903
2	M	78	rivaroxaban	PE + AF	valproic acid	mood disorders	4	1	-	recurrent TE/death	525
3	F	90	dabigatran	PE	valproic acid	mood disorders	2	-	-	death	726
4	F	77	apixaban	PE	levetiracetam	epilepsy	1	-	1	death	12
5	M	83	edoxaban	PE	lacosamide	epilepsy	6	-	3	0	408
6	F	74	rivaroxaban	PE	valproic acid	mood disorders	6	-	-	0	642
7	F	61	edoxaban	PE	valproic acid	mood disorders	2	-	-	nonmajor bleeding	0
8	M	65	edoxaban	PE	fenobarbital	epilepsy	5	-	4	nonmajor bleeding	630
9	F	80	apixaban	PE	levetiracetam	epilepsy	7	-	2	0	257
10	F	58	rivaroxaban	PE	levetiracetam	epilepsy	2	-	1	0	195
11	M	33	apixaban	PE	valproic acid	mood disorders	5	1	1	0	339
12	F	64	apixaban	PE	oxcarbazepine	mood disorders	1	-	-	0	66
13	F	41	edoxaban	PE	levetiracetam	epilepsy	2	2	2	0	280
14	F	50	apixaban	PE	valproic acid	mood disorders	2	1	2	0	364
15	F	84	edoxaban	AF	fenobarbital	epilepsy	3	-	-	0	205
16	M	66	dabigatran	PE	lacosamide	epilepsy	1	-	-	seizure	236
17	F	70	apixaban	AF	lamotrigine	epilepsy	3	-	-	0	326
18	F	77	edoxaban	PE	levetiracetam	epilepsy	3	1	1	0	275
19	F	85	edoxaban	PE	valproic acid	mood disorders	2	-	-	major bleeding/death	173
20	F	59	edoxaban	PE	valproic acid	mood disorders	1	-	-	0	11
21	F	75	rivaroxaban	PE	valproic acid	mood disorders	1	-	1	0	84
22	M	78	apixaban	AF	valproic acid	mood disorders	2	-	-	0	63
23	M	69	dabigatran	PE	valproic acid	mood disorders	1	-	1	0	50

Table 1 Demographic characteristics, pharmaceutical molecules, indication for DOAC and AED, DOAC and AED level blood samples within or outside the TR, events and follow-up time (DOAC: Direct Oral Anticoagulant; AED: Antiepileptic drug; TR: Therapeutic Range; F: Female; M: Male; PE: Pulmonary Embolism; AF: Atrial Fibrillation)