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Supplement: Appropriateness of DOACs in older hospitalized subjects with atrial fibrillation

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Supplementary table 1. General characteristics of the total cohort with or without atrial fibrillation.

		Total cohort
N		2054
Age, years		82.8 (7.9)
Sex, female		985 (48%)
Admitting ward, nephrology vs geriatry		560 (27%)
Arterial hypertension		1613 (79%)
Diabetes mellitus		705 (34%)
Congestive heart failure		669 (33%)
Atrial fibrillation		609 (30%)
Pulmonary embolism		23 (1%)
COPD		571 (28%)
CAD		345 (17%)
Cerebrovascular disease		282 (14%)
Cancer		530 (26%)
Osteoporosis		318 (15%)
Anaemia		1295 (68%)
Recent bleeding		144 (7%)
eGFR, ml/min/m^2		43.8 (30.6-58.8)
eGFR, ml/min/m^2		
	≥ 60	481 (23%)
	45-59.9	503 (24%)
	30-44.9	575 (28%)
	15-29.9	452 (22%)
	<15	43 (2%)
Number of medications		7 (5-9)
Polypharmacy (>5 drugs)		1401 (68%)
DOAC therapy		253 (12%)
DOAC type		
	Dabigatran	46 (18%)
	Rivaroxaban	84 (33%)
	Apixaban	95 (38%)

	Edoxaban	28 (11%)
DOAC indication		
	AF	204 (81%)
	PE	7 (3%)
	DVT	3 (1%)
	Unknown	39 (15%)
Vitamin K antagonists		203 (9.9%)
LMWH		248 (12.1%)
No VKA or DOAC		
No anticoagulation		
Antiplatelet therapy		248 (12.1%)
CHA2DS2-VASc		
	continuous	-
	>0/1 in M/F	-
HAS-BLED		
	continuous	-
	≥3	-

Continuous variables reported as mean (standard deviation) or median (25-75 centile). Categorical variables reported as absolute numbers and percentage.
Abbreviations: AF, atrial fibrillation; CAD, coronary artery disease; PE, pulmonary embolism; DVT, deep vein thrombosis; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; LMWH, low molecular weight heparin; VKA, vitamin K antagonist; DOAC, direct oral anticoagulant

Supplementary Table 2. DOAC type, dosages and indications in the total cohort with or without atrial fibrillation.

DOAC type	DOAC Indication	Atrial fibrillation
Dabigatran - N 46 (18%)	AF 36	Dabigatran - N 36 (6%)
150 mg bid – N 10	PE 2	*150 mg bid – N 9*
110 mg bid – N 35	DVT 1	*110 mg bid – N 27*
75 mg bid – N 1	Unknown 7	
Rivaroxaban - N 84 (33%)	AF 68	Rivaroxaban - N 68 (11%)
20 mg od – N 48	PE 3	*20 mg od – N 36*
15 mg od – N 30	DVT 0	*15 mg od – N 32*
10 mg od – N 6	Unknown 13	
Apixaban - N 95 (38%)	AF 77	Apixaban - N 77 (13%)
5 mg bid – N 28	PE 3	*5 mg bid – N 22*
2.5 mg bid – N 67	DVT 1	*2.5 mg bid – N 55*
	Unknown 14	
Edoxaban – N 28 (11%)	AF 23	Edoxaban – N 23 (4%)
60 mg od – N 12	PE 0	*60 mg od – N 9*
30 mg od – N 14	DVT 1	*30 mg od – N 14*
15 mg od – N 2	Unknown 4	

Abbreviations: AF, atrial fibrillation; PE, pulmonary embolism; DVT, deep vein thrombosis

Supplementary table 3. List of pharmacokinetic drug-drug interactions with direct oral anticoagulants (DOACs).

Interacting Drug	*Mechanism*	*N*
Apixaban		*14*
Ketoconazole	CYP 3A4 and P-gp strong inhibitors	
Itraconazole	CYP 3A4 and P-gp strong inhibitors	
Voriconazole	CYP 3A4 and P-gp strong inhibitors	
Posaconazole	CYP 3A4 and P-gp strong inhibitors	
Ritonavir	CYP 3A4 and P-gp strong inhibitors	
Crizotinib	Strong p-gp inhibition, moderate CYP 3A4 inhibition	
Imatinib	Strong p-gp inhibition, moderate CYP 3A4 inhibition	
Abiraterone	Strong P-gp inhibition, moderate CYP 3A4 inhibition	
Enzalutamide	Strong CYP 3A4 induction, strong P-gp inhibition	
Sunitinib	Strong P-gp inhibition, CYP 3A4 competition	
Vandetanib	Strong P-gp inhibition, CYP 3A4 competition	
Amiodarone	CYP 3A4 and P-gp moderate inhibitors	7
Clarithromycin	CYP 3A4 and P-gp moderate inhibitors	3
Diltiazem	CYP 3A4 and P-gp moderate inhibitors	
Quinidine	CYP 3A4 and P-gp moderate inhibitors	
Verapamil	CYP 3A4 and P-gp moderate inhibitors	3
Erythromycin	CYP 3A4 and P-gp moderate inhibitors	
Fluconazole	CYP 3A4 and P-gp moderate inhibitors	
Cyclosporine	CYP 3A4 and P-gp weak inhibitors	
Naproxene	P-gp inhibition	
Dronedarone	CYP 3A4 and P-gp moderate inhibitors	
Rifampicin	CYP 3A4 and P-gp strong inducers	
Phenytoin	CYP 3A4 and P-gp strong inducers	
Carbamazepine	CYP 3A4 and P-gp inducers	
Phenobarbital	CYP 3A4 strong inducer	
Vinblastine	Strong P-gp induction and CYP 3A4 competition	
Doxorubicin	Strong P-gp induction and CYP 3A4 competition/inhibition	
Valproic acid	CYP 3A4/P-gp strong induction/inhibition	1
Edoxaban		*2*
Cyclosporine	Strong to moderate P-gp inhibition, moderate CYP 3A4 inhibition	
Erythromycin	CYP 3A4 and P-gp moderate inhibitors	
Dronedarone	CYP 3A4 and P-gp moderate inhibitors	
Ketoconazole	CYP 3A4 and P-gp moderate inhibitors	
Amiodarone	CYP 3A4 and P-gp moderate inhibitors	1
Quinidine	CYP 3A4 and P-gp moderate inhibitors	
Verapamil	CYP 3A4 and P-gp moderate inhibitors	
Digoxin	P-gb substrate competition	1
Ritonavir	CYP 3A4 and P-gp strong inhibitors	
Itraconazole	CYP 3A4 strong inhibition and BCRP P-gp strong competition	
Crizotinib	Strong p-gp inhibition, moderate CYP 3A4 inhibition	
Imatinib	Strong p-gp inhibition, moderate CYP 3A4 inhibition	
Abiraterone	Strong P-gp inhibition, moderate CYP 3A4 inhibition	
Enzalutamide	Strong CYP 3A4 induction, strong P-gp inhibition	
Sunitinib	Strong P-gp inhibition, CYP 3A4 competition	
Vandetanib	Strong P-gp inhibition, CYP 3A4 competition	
Tacrolimus	Strong to moderate P-gp inhibition, moderate CYP 3A4 inhibition	
Rifampicin	CYP 3A4 and P-gp strong inducers	
Phenytoin	CYP 3A4 and P-gp strong inducers	
Carbamazepine	CYP 3A4 and P-gp inducers	
Phenobarbital	CYP 3A4 strong inducer	
Vinblastine	Strong P-gp induction and CYP 3A4 competition	
Doxorubicin	Strong P-gp induction and CYP 3A4 competition/inhibition	
Valproic acid	CYP 3A4/P-gp strong induction/inhibition	
Rivaroxaban		*6*
Ketoconazole	CYP 3A4 and P-gp strong inhibitors	
Itraconazole	CYP 3A4 and P-gp strong inhibitors	

Voriconazole	CYP 3A4 and P-gp strong inhibitors	
Posaconazole	CYP 3A4 and P-gp strong inhibitors	
Ritonavir	CYP 3A4 and P-gp strong inhibitors	
Clarithromycin	CYP 3A4 and P-gp moderate inhibitors	
Erythromycin	CYP 3A4 and P-gp moderate inhibitors	
Fluconazole	CYP 3A4 moderate inhibitor	
Verapamil	CYP 3A4 and P-gp moderate inhibitors	1
Amiodarone	CYP 3A4 and P-gp moderate inhibitors	4
Dronedarone	CYP 3A4 and P-gp moderate inhibitors	
Crizotinib	Strong p-gp inhibition, moderate CYP 3A4 inhibition	
Imatinib	Strong p-gp inhibition, moderate CYP 3A4 inhibition	
Abiraterone	Strong P-gp inhibition, moderate CYP 3A4 inhibition	
Enzalutamide	Strong CYP 3A4 induction, strong P-gp inhibition	
Sunitinib	Strong P-gp inhibition, CYP 3A4 competition	
Vandetanib	Strong P-gp inhibition, CYP 3A4 competition	
Tacrolimus	Strong to moderate P-gp inhibition, moderate CYP 3A4 inhibition	
Rifampicin	CYP 3A4 and P-gp strong inducers	
Phenytoin	CYP 3A4 and P-gp strong inducers	
Carbamazepine	CYP 3A4 and P-gp inducers	
Phenobarbital	CYP 3A4 strong inducer	
Vinblastine	Strong P-gp induction and CYP 3A4 competition	
Doxorubicin	Strong P-gp induction and CYP 3A4 competition/inhibition	
Valproic acid	CYP 3A4/P-gp strong induction/inhibition	1
Dabigatran		*15*
Ketoconazole	CYP 3A4 and P-gp strong inhibitors	
Itraconazole	CYP 3A4 and P-gp strong inhibitors	
Dronedarone	CYP 3A4 and P-gp moderate inhibitors	
Glecaprevir/pibrentasvir	P-gp inhibition and competition	
Verapamil	CYP 3A4 and P-gp moderate inhibitors	2
Clarithromycin	Strong CYP 3A4 and moderate P-gp inhibitors	
Quinidine	CYP 3A4 and P-gp moderate inhibitors	
Ticagrelor	Moderate P-gp inhibitor	
Amiodarone	CYP 3A4 and P-gp moderate inhibitors	1
Cyclosporine	CYP 3A4 and P-gp weak inhibitors	
Tacrolimus	Strong P-gp inhibition	
Ritonavir	CYP 3A4, BCRP and P-gp strong inhibitors	
Crizotinib	Strong p-gp inhibition, moderate CYP 3A4 inhibition	
Imatinib	Strong p-gp inhibition, moderate CYP 3A4 inhibition	
Abiraterone	Strong P-gp inhibition, moderate CYP 3A4 inhibition	
Enzalutamide	Strong CYP 3A4 induction, strong P-gp inhibition	
Sunitinib	Strong P-gp inhibition, CYP 3A4 competition	
Vandetanib	Strong P-gp inhibition, CYP 3A4 competition	
Pantoprazole	P-gp and CYP 2C9 inhibition	10
Rifampicin	CYP 3A4, BCRP and P-gp strong inducers	
Phenytoin	CYP 3A4 and P-gp strong inducers	
Carbamazepine	CYP 3A4 and P-gp inducers	
Phenobarbital	CYP 3A4 strong inducer	
Vinblastine	Strong P-gp induction and CYP 3A4 competition	
Doxorubicin	Strong P-gp induction and CYP 3A4 competition/inhibition	
Valproic acid	CYP 3A4/P-gp strong induction/inhibition	2

Abbreviations: CYP, cytochrome P450; P-gp, glycoprotein P; BRCP, breast cancer resistance protein.

Supplementary Figure 1. Relation between eGFR (estimated by CKD-EPI equation) and the odds ratio of smPC violation (any, overdosed or underdosed) and of being discharge without anticoagulant therapy, according to the best fitting models (restricted cubic splines). Odds ratios with 95% confidence intervals are reported comparing each eGFR value to the median eGFR.