

Supplementary Materials

Supplementary Table 1. Definitions used to identify comorbid conditions and comedications in the French healthcare databases.

Supplementary Table 2. Age- and sex-adjusted association between baseline characteristics and the choice of NOAC therapy compared to VKA therapy in OAC new users.

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Supplementary Table 1. Definitions used to identify comorbid conditions and comedications in the SNIIRAM-PMSI databases.

Covariates*	Hospital discharge diagnoses†	LTD diagnoses†	Specific procedures or drug reimbursements
AF definition (Patterns of use of DOAC therapy in new users with AF)			
Nonvalvular atrial fibrillation	I48	I48	Radiofrequency ablation, cardioversion
Lower limb orthopaedic procedures			Lower limb orthopaedic surgery or procedures
History of valvular heart disease/Prosthetic heart valve	I05-I09, I33-I39/ Z95.2, Z95.3 ou Z95.4		Heart valve surgery
Deep vein thrombosis/pulmonary embolism	I26, I80 (except I80.0), I81, I82	I26, I80-I82	Lower limb venous ultrasonography, pulmonary/lower limb angiography, ventilation/perfusion scan
CHA₂DS₂-VASc and HAS-BLED scores			
Heart failure	I50 or I11.0, I13.0, I13.2, I13.9, K76.1, J81 related to I50	I50	Specific medications approved for heart failure including beta-blockers (bisoprolol, carvedilol, metoprolol), eplerenone, bumetanide, furosemide when licensed for heart failure only
Antihypertensive drugs			Diuretics, beta blockers, calcium channel blockers, agents acting on the renin-angiotensin system and other antiadrenergic agents
Diabetes	E10-E14	E10-E14	Insulins and blood glucose lowering drugs
History of ATE (ischemic stroke, arterial systemic embolism or transient ischemic attack)	I63 (except I63.6), G46 related to I63 or I69.3; I74, G45 (except G45.4)	I63, I74, G45	
Peripheral vascular disease	I20, I21, I22, I23, I24, I25, I70, I71, I72, I73, E10.5, E11.5, E12.5, E13.5, E14.5	I70-I73 , I20-I25	
Abnormal renal function	N18, I12.0, I13.1, I13.2, E10.2, E11.2, E13.2, E14.2, N08.3	N18, I12	
Abnormal liver function	R18, I85, K70, K71.3, K71.4, K71.5, K71.7, K72.1, K73, K74, K76.1, B18, C22, C78.7	K70, K73, K74, B18, C22	Antiviral agents for systemic use HCV (ribavirin, [peg]interferon alpha and DAA), and against HCB ([peg]interferon alpha and NnRTIs).
Major bleeding	I60-I62, S06.3-S06.6, I85, K25-K29, K62.5, K92, D62, N02, R31, R58, H11.3, H35.6, H43.1, H45.0, H92.2, J94.2, K66.1, M25.0, N92, N93.8, N93.9, N95.0, R04.0		
Predisposition for bleeding	Anemias : D50, D51, D52, D53, D55, D56, D57, D58, D59, D60, D62, D63, D64 or coagulation defects, purpura and other hemorrhagic: D65, D66, D67, D68, D69		
Alcohol abuse	F10, K70, T51, K6, G31.2, G62.1, G72.1, I42.6, K29.2, Z71.4, Z72.1, Z50.2.		disulfiram, acamprosate, nalmefene and products with naltrexone licensed in adult patients with alcohol dependence
Drug-drug interaction			Platelet aggregation inhibitors (including low-dose acetylsalicylic acid), heparins, NSAIDs
Other comorbidities			
Ischemic heart disease (including myocardial infarction)	I20-I25	I20-I25	Nitrovasodilator agents
Frailty	G81-G83	G81-G83	Home hospital bed, wheelchair, high level of nursing home stay
Dementia or Parkinson's disease	F00-F03, G30, G20	F00-F03, G30, G20	Anticholinesterases or NMDA receptor antagonists: anticholinergic and dopaminergic agents
Psychiatric disorders	F20-29, F30-39	F20-29, F30-39	Antidepressants, antipsychotics, conventional mood stabilizers
Smoking	F17, Z71.6, Z72.0; J43-J44	J43-J44	Nicotine replacement therapy
Recently hospitalized for coagulopathy, purpura and other haemorrhagic conditions	D65-D69		
Liver fibrosis and cirrhosis	K70.0, K70.2, K70.3, K70.4, K71.7, K72, K74		

Recent gastrointestinal ulceration or intracranial haemorrhage	K25, K26, K27, K28, K29.0, I60, I61, I62, S06.4, S06.5, S06.6		
Recently or currently treated cancer	C00-D09, D37-D48, Z510, Z511	C00-D09, D37-D48	Radiotherapy procedures
Baseline comedications			
Antiarrhythmics and cardiac glycosides			Antiarrhythmics: class I and III, verapamil, digitalis glycosides
Lipid-lowering agents			HMG CoA reductase inhibitors, fibrates, ezetimibe
Antiplatelet drugs			Platelet aggregation inhibitors including low-dose acetylsalicylic acid
Oral corticosteroids			Mineralo- and gluco-corticoids
Antiulcer agents			Mainly proton pump inhibitors and H2-receptor antagonists

LTD: long-term diseases; ATE: arterial thromboembolic events (mainly stroke); DVT/PE: deep vein thrombosis/pulmonary embolism; NMDA: N-methyl-D-aspartate; HIV: human immunodeficiency virus; PI: Protease inhibitor; NNRTIs: Non-nucleoside reverse transcriptase inhibitors; NnRTI: Nucleoside and nucleotide reverse transcriptase inhibitors; DAA: direct-acting antiviral; HMG CoA: 3-hydroxy-3-methyl-glutaryl-CoA; NSAIDs: Non-steroidal anti-inflammatory drugs.

* Comorbidities were identified using ICD-10 diagnosis codes for hospital discharge/LTD, or specific procedures, or drug reimbursements. Concomitant medications were identified as those dispensed at least once during the 4-month period preceding the index date. Influenza vaccination was determined during the first 'flu vaccination campaign preceding the index date.

†ICD-10 codes

Supplementary Table 2. Age- and sex-adjusted association between baseline characteristics and the choice of NOAC therapy compared to VKA therapy in OAC new users.

Baseline characteristics	Dabigatran vs VKA			Rivaroxaban vs VKA			Apixaban vs VKA					
	RR*	95% CI	p-value†	RR*	95% CI	p-value†	RR*	95% CI	p-value†			
Female sex	1.11	1.05	1.17	***	1.03	1.00	1.07	*	1.07	1.04	1.09	***
Age (years)												
18-54 (Ref)	1.00	1.00	1.00		1.00	1.00	1.00		1.00	1.00	1.00	
55-64	0.87	0.78	0.98	*	0.92	0.87	0.97	**	0.97	0.92	1.02	
65-74	0.86	0.77	0.95	**	0.89	0.84	0.94	***	0.98	0.93	1.03	
75-79	0.73	0.65	0.81	***	0.77	0.73	0.82	***	0.91	0.87	0.96	***
80-84	0.58	0.52	0.65	***	0.65	0.61	0.68	***	0.83	0.79	0.87	***
85-89	0.44	0.39	0.49	***	0.50	0.48	0.54	***	0.74	0.70	0.77	***
>=90	0.28	0.25	0.32	***	0.37	0.35	0.40	***	0.61	0.57	0.65	***
Deprivation index												
quintile 1 (least deprived) (Ref)	1.00	1.00	1.00		1.00	1.00	1.00		1.00	1.00	1.00	
quintile 2	0.97	0.91	1.05		0.94	0.92	0.97	***	0.97	0.95	1.00	*
quintile 3	0.99	0.93	1.07		0.90	0.87	0.92	***	0.94	0.92	0.97	***
quintile 4	0.96	0.89	1.03		0.85	0.83	0.87	***	0.90	0.88	0.93	***
quintile 5 (most deprived)	1.00	0.94	1.07		0.85	0.83	0.87	***	0.91	0.89	0.93	***
Overseas departments	1.60	1.41	1.82	***	0.83	0.77	0.89	***	0.77	0.72	0.83	***
First prescriber's specialty												
Hospital practitioner (Ref)	1.00	1.00	1.00		1.00	1.00	1.00		1.00	1.00	1.00	
General practitioner	1.37	1.29	1.46	***	1.16	1.10	1.23	***	1.00	0.96	1.04	
Private cardiologist	2.92	2.76	3.08	***	1.80	1.70	1.90	***	1.65	1.59	1.71	***
Private orthopedic surgeon	1.96	1.20	3.21	**	1.48	1.20	1.81	***	1.32	1.07	1.61	**
Other private specialist	1.07	0.93	1.24		1.12	1.04	1.21	**	1.03	0.97	1.10	
From CHA₂DS₂-VASc score												
Heart Failure	0.52	0.49	0.54	***	0.70	0.68	0.71	***	0.77	0.75	0.78	***
Antihypertensive drugs	0.60	0.57	0.63	***	0.74	0.72	0.76	***	0.80	0.78	0.82	***
Diabetes	0.67	0.63	0.71	***	0.76	0.74	0.77	***	0.80	0.79	0.82	***
ATE	0.85	0.79	0.92	***	0.71	0.68	0.74	***	0.90	0.88	0.92	***

Vascular diseases	0.47	0.42	0.53	***	0.63	0.61	0.66	***	0.71	0.67	0.74	***
From HAS-BLED score												
Abnormal renal function	0.17	0.15	0.19	***	0.31	0.30	0.33	***	0.40	0.38	0.42	***
Abnormal liver function	0.46	0.39	0.54	***	0.58	0.54	0.62	***	0.60	0.57	0.64	***
Bleeding predisposition	0.53	0.47	0.59	***	0.63	0.60	0.65	***	0.70	0.67	0.72	***
Major bleeding	0.23	0.20	0.26	***	0.36	0.33	0.39	***	0.41	0.38	0.45	***
Alcohol abuse	0.55	0.48	0.62	***	0.69	0.65	0.72	***	0.68	0.65	0.72	***
Drug-drug interactions	0.22	0.20	0.24	***	0.36	0.34	0.37	***	0.40	0.37	0.43	***
Parenteral anticoagulants	0.04	0.03	0.06	***	0.07	0.06	0.07	***	0.07	0.06	0.07	***
Antiplatelets drugs	0.34	0.31	0.37	***	0.49	0.47	0.51	***	0.56	0.53	0.60	***
NSAIDs	1.80	1.43	2.28	***	1.24	1.12	1.38	***	1.18	1.06	1.32	**
Other comorbidities												
Valvular heart diseases	0,25	0,20	0,31	***	0,40	0,36	0,45	***	0,47	0,41	0,54	***
Ischemic heart diseases	0.51	0.46	0.56	***	0.65	0.63	0.67	***	0.74	0.71	0.77	***
Frailty (proxies)	0.48	0.45	0.51	***	0.58	0.55	0.61	***	0.64	0.62	0.66	***
Dementia or Parkinson's disease	0.66	0.60	0.72	***	0.82	0.78	0.85	***	0.77	0.75	0.80	***
Psychiatric disorders	0.74	0.70	0.78	***	0.86	0.84	0.88	***	0.86	0.84	0.88	***
Smoking	0.56	0.52	0.60	***	0.71	0.69	0.74	***	0.74	0.71	0.76	***
Comedications												
Antiarrhythmics or cardiac glycosides	1.42	1.35	1.50	***	1.22	1.19	1.25	***	1.18	1.16	1.20	***
Lipid-lowering agents	0.76	0.71	0.81	***	0.81	0.79	0.84	***	0.90	0.87	0.92	***
Oral corticosteroids	0.85	0.80	0.91	***	0.94	0.91	0.97	***	0.94	0.91	0.96	***
Antiulcer agents	0.61	0.56	0.66	***	0.73	0.71	0.75	***	0.78	0.75	0.81	***
Polymedication (≥5 ATC classes)	0.37	0.35	0.40	***	0.55	0.54	0.57	***	0.60	0.59	0.62	***
Polymedication (≥10 ATC classes)	0.33	0.30	0.36	***	0.49	0.46	0.52	***	0.54	0.51	0.57	***

NOAC: Non vitamin K antagonist oral anticoagulant; VKA: vitamin K antagonist; OAC: oral anticoagulant; RR: Relative risk; IC: Confidence interval; ATE: arterial thromboembolic events (ischaemic stroke, arterial systemic embolism or transient ischaemic attack); NSAIDs: non-steroidal anti-inflammatory drugs

* RR determined using negative binomial regression analysis adjusting for age and sex(except for age and sex covariates, adjusted for sex and for age only, respectively).

† p-values : *** $p < 0,001$; ** $p < 0,01$; * $p < 0,05$

Reading example: Age and sex being equal, frailty reduced the probability for a prescription of dabigatran (instead of VKA) by 52% (1 minus the estimated RR of 0.48). For rivaroxaban and apixaban, this reduction was 42% and 36%, respectively.

Supplementary Table 3. Comparison of selected baseline characteristics of DOAC new users with AF at risk of stroke according to level of HAS-BLED score and type of DOAC dose.

N (%)	Patients with CHA2DS2-VASc ≥ 2 (N=116,391)				Patients aged ≥ 75 years old and history of ATE (N=9,503)			
	HAS-BLED ≥ 3 (N=30 273)		HAS-BLED <3 (N=86 118)		HAS-BLED ≥ 3 (N=7,143)		HAS-BLED <3 (N=2,360)	
	Reduced doses* (N=16,090)	Standard doses* (N=14,183)	Reduced doses* (N=33,845)	Standard doses* (N=52,273)	Reduced doses* (N=4,178)	Standard doses* (N=2,965)	Reduced doses* (N=1,379)	Standard doses* (N=981)
Age (years), mean	81.8	74.8	81.3	70.9	84.8	81.1	81.3	70.9
Age ≥ 80 years	10,786 (67.0)	3,982 (28.1)	22,962 (67.8)	9,984 (19.1)	3,496 (83.7)	1,720 (58.0)	1,188 (86.1)	567 (57.8)
First prescriber's specialty								
Hospital practitioner or private cardiologist	12,315 (76.6)	11,364 (80.1)	25,221 (74.5)	41,728 (79.8)	3216 (77.0)	2965 (80.2)	1013 (73.5)	798 (81.3)
General practitioner	3321 (20.6)	2426 (17.1)	7836 (23.2)	9302 (17.8)	860 (20.6)	503 (17.0)	322 (23.4)	157 (16.0)
Frailty (proxies)	6,689 (41.6)	4,600 (32.4)	6,932 (20.5)	4,779 (9.1)	2,599 (62.2)	1,642 (55.4)	589 (42.7)	316 (32.2)
Dementia or Parkinson's disease	2121 (13.2)	935 (6.6)	3169 (9.4)	1555 (3.0)	789 (18.9)	355 (12.0)	259 (18.8)	111 (11.3)
Any valvular diseases†	2,640 (16.4)	1,809 (12.8)	2,740 (8.1)	3,342 (6.4)	566 (13.5)	330 (11.1)	144 (10.4)	95 (9.7)
Prosthetic heart valve†	544 (3.4)	384 (2.7)	425 (1.3)	474 (0.9)	94 (2.2)	52 (1.8)	19 (1.4)	14 (1.4)
Ischaemic heart disease	7,232 (44.9)	5,274 (37.2)	6,827 (20.2)	9,142 (17.5)	1,338 (32.0)	758 (25.6)	336 (24.4)	185 (18.9)
Antiplatelet agents at initiation	6,035 (37.5)	4,891 (34.5)	620 (1.8)	1,264 (2.4)	874 (20.9)	510 (17.2)	11 (0.8)	7 (0.7)
Lipid-lowering agents	9252 (57.5)	9213 (65.0)	12836 (37.9)	21820 (41.7)	2606 (62.4)	2132 (71.9)	697 (50.5)	611 (62.3)
Polymedication (≥ 10 ATC classes)	3,627 (22.5)	2,946 (20.8)	2,150 (6.4)	2,798 (5.4)	788 (18.9)	473 (16.0)	104 (7.5)	67 (6.8)

* Reduced-dose DOAC: dabigatran 150mg, Rivaroxaban 20 and apixaban 5mg; reduced-dose DOAC: dabigatran 75mg and 110mg, rivaroxaban 10mg and 15mg and apixaban 2.5mg

† Covariates defined by hospitalization data only