

Comparison of the Short-Term Risk of Bleeding and Arterial Thromboembolic Events in Nonvalvular Atrial Fibrillation Patients Newly Treated With Dabigatran or Rivaroxaban Versus Vitamin K Antagonists

A French Nationwide Propensity-Matched Cohort Study

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Background—The safety and effectiveness of non-vitamin K antagonist (VKA) oral anticoagulants, dabigatran or rivaroxaban, were compared with VKA in anticoagulant-naïve patients with nonvalvular atrial fibrillation during the early phase of anticoagulant therapy.

Methods and Results—With the use of the French medico-administrative databases (SNIIRAM and PMSI), this nationwide cohort study included patients with nonvalvular atrial fibrillation who initiated dabigatran or rivaroxaban between July and November 2012 or VKA between July and November 2011. Patients presenting a contraindication to oral anticoagulants were excluded. Dabigatran and rivaroxaban new users were matched to VKA new users by the use of 1:2 matching on the propensity score. Patients were followed for up to 90 days until outcome, death, loss to follow-up, or December 31 of the inclusion year. Hazard ratios of hospitalizations for bleeding and arterial thromboembolic events were estimated in an intent-to-treat analysis using Cox regression models. The population was composed of 19713 VKA, 8443 dabigatran, and 4651 rivaroxaban new users. All dabigatran- and rivaroxaban-treated patients were matched to 16014 and 9301 VKA-treated patients, respectively. Among dabigatran-, rivaroxaban-, and their VKA-matched-treated patients, 55 and 122 and 31 and 68 bleeding events and 33 and 58 and 12 and 28 arterial thromboembolic events were observed during follow-up, respectively. After matching, no statistically significant difference in bleeding (hazard ratio, 0.88; 95% confidence interval, 0.64–1.21) or thromboembolic (hazard ratio, 1.10; 95% confidence interval, 0.72–1.69) risk was observed between dabigatran and VKA new users. Bleeding (hazard ratio, 0.98; 95% confidence interval, 0.64–1.51) and ischemic (hazard ratio, 0.93; 95% confidence interval, 0.47–1.85) risks were comparable between rivaroxaban and VKA new users.

Conclusions—In this propensity-matched cohort study, our findings suggest that physicians should exercise caution when initiating either non-VKA oral anticoagulants or VKA in patients with nonvalvular atrial fibrillation. (*Circulation*. 2015;132:1252-1260. DOI: 10.1161/CIRCULATIONAHA.115.015710.)

Key Words: atrial fibrillation ■ anticoagulants ■ comparative effectiveness research ■ databases, factual ■ France ■ hemorrhage ■ pharmacoepidemiology ■ stroke

Long-term prophylaxis with oral anticoagulants (OACs) is now widely recommended by international guidelines to prevent stroke in all patients with atrial fibrillation (AF) without contraindications presenting an independent risk factor for stroke.¹⁻³

However, there are several important considerations in the management of patients taking OACs, starting with the initiation of therapy. The initial phase of anticoagulant therapy, especially in patients with newly diagnosed AF, is of concern: early bleeding and thromboembolic risks have been observed to be significantly higher during the first 90 days of therapy in AF patients initiating warfarin.⁴⁻⁶

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Recently, non-vitamin K antagonist (VKA) oral anti-coagulants (NOACs), such as the direct thrombin inhibitor dabigatran and the factor Xa inhibitor rivaroxaban, have been introduced as alternatives to VKAs.^{7,8}

Unlike VKAs, NOACs have 2 fixed-dose regimens: dabigatran and rivaroxaban are usually given at 150 mg twice daily and 20 mg daily, respectively, except in patients with a high bleeding risk for whom the recommended doses are dabigatran 110 mg twice daily in Europe and rivaroxaban 15 mg daily (10 mg daily in Japan in elderly patients or patients with renal dysfunction).⁹⁻¹¹ Large randomized trials have demonstrated the relative safety and efficacy of these agents versus warfarin, but in selected patients with nonvalvular AF (nv-AF)¹²⁻¹⁴ and subsequent observational data have provided conflicting results.¹⁵⁻¹⁹ Few of these studies specifically focused on the early phase of therapy,^{15,20} and most of them were based on Medicare and Danish data. Large postmarketing studies using other databases are needed to better understand the short-term comparative effectiveness and safety of each specific agent and the dosage of NOACs versus VKAs.

At the initiative of the French medicines agency, we therefore conducted an observational study using the French nationwide medico-administrative databases to assess the bleeding and arterial thrombotic risks of dabigatran and rivaroxaban, each compared with VKA, during the early phase of therapy.²¹ In this article, we focused on newly treated patients with nv-AF.

Methods

Study Design and Data Source

We performed a retrospective propensity-matched cohort study using 2 French nationwide datasets linked by a unique patient identifier:

1. The French National Health Insurance information system (SNIIRAM), which collects all individualized and anonymous healthcare claims reimbursed by the French National Health Insurance covering the entire French population: this database also contains patient data such as age, sex, vital status, and eligibility for 100% health insurance coverage for serious and costly long-term diseases (LTDs) encoded in the *International Classification of Diseases, 10th Revision* (ICD-10), and healthcare professional characteristics, as well, but does not include outpatient medical indications;
2. The French Hospital Discharge database (PMSI), which contains discharge diagnoses (ICD-10 codes) and medical procedures for all patients admitted to hospital in France.

This linkage has previously been used to conduct large-scale epidemiological or postauthorization studies.^{22,23}

Study Population

This study was based on the French National Health Insurance general scheme, covering ≈50 million people. To be eligible for inclusion, patients had to have evidence of continuous general scheme enrolment for a 5-year preindex period.

The index date was the date of first reimbursement for an OAC. New users, defined as patients with no reimbursement for any OAC during the previous 24 months, were assigned to 1 of the 3 treatment groups according to their index OAC: dabigatran or rivaroxaban with both inclusion periods defined between July 20, 2012 (NOAC French market entry date) and November 30, 2012; or VKA with patients included during the same period of 2011. NOAC doses were classified as low (dabigatran 75 mg and 110 mg or rivaroxaban 10 mg and 15 mg) or high (dabigatran 150 mg or rivaroxaban 20 mg).

Patients <18 years of age, or who were reimbursed for both dabigatran and rivaroxaban or VKA and NOAC on the index date, or who died on the index date, were excluded. Patients presenting a contraindication to treatment (history of valvular heart disease, ongoing cancer treatment, dialysis for end-stage renal disease, hematologic disease or certain immune system disorders considered to be at higher risk of major bleeding (ie, LTD or discharge diagnoses ICD-10 codes D50-D89), hepatic cirrhosis or fibrosis or liver failure, acute bleeding peptic ulcer) were also excluded. Finally, patients undergoing lower limb orthopedic procedures during the 6-week preindex period were excluded, because they were assumed to be treated for primary prevention of venous thromboembolic events (Table I in the online-only Data Supplement).

From the resulting cohort, we identified: (1) patients with nv-AF by using LTD or discharge diagnoses with ICD-10 code I48 or specific procedures during the 4-year preindex period; (2) patients with deep vein thrombosis/pulmonary embolism by using discharge diagnoses (I26, I80 except I80.0, I81, I82) or specific procedures during the 6-week preindex period; (3) outpatients assumed to have nv-AF among the remaining patients with an algorithm by using proxies discriminating AF from deep vein thrombosis/pulmonary embolism with a 95% specificity (age, sex, use of β-blockers, antiarrhythmics, antiplatelets, antihypertensives, Holter/echocardiography procedures, specialty of the first anticoagulant prescriber, and d-dimer assessment; see online-only Data Supplement).²⁴

Outcomes

The primary end points were (1) hospitalization for bleeding, including intracranial (hospital discharge ICD-10 codes I60, I61, I62, S06.3, S06.4, S06.5, S06.6), gastrointestinal (I85.0, K25.0, K25.2, K25.4, K25.6, K26.0, K26.2, K26.4, K26.6, K27.0, K272, K27.4, K27.6, K28.0, K282, K28.4, K28.6, K29.0, K62.5, K92.0, K92.1, K92.2) and other bleeding (D62, N02, R31, R58, H11.3, H35.6, H43.1, H45.0, H92.2, J94.2, K66.1, M25.0, N92.0, N92.1, N92.4, N93.8, N93.9, N95.0, R04.0, R04.1, R04.2, R04.8, R04.9) and (2) a composite outcome combining hospitalization for bleeding and all-cause mortality.

The secondary end points were (1) hospitalization for ischemic stroke (I63 except for I63.6) or systemic embolism (I74) and (2) a composite outcome combining hospitalization for ischemic stroke or systemic embolism and all-cause mortality. Only principal discharge diagnoses were used to define end points.

Follow-Up

Patients were followed for up to 90 days from the day after the index date until predefined outcome, loss to follow-up (>2 consecutive months with no reimbursement), death from any cause, end of the year of inclusion, or end of the 90-day follow-up, whichever came first.

Baseline Covariates

The following sociodemographic covariates were used: sex, age at initiation of treatment, and the deprivation index of the patient's municipality of residence (divided into quintiles with a sixth group created for patients residing in overseas departments).²⁵ Baseline covariates also included the specialty of the first OAC prescriber and comorbidities or comedications deemed to be risk factors for bleeding or arterial thromboembolic events.

Comorbidities (heart failure, diabetes mellitus, coronary heart disease, dementia, history of stroke or systemic embolism, peripheral vascular disease, chronic kidney disease, history of transient ischemic attack, history of hospitalization for bleeding) were identified by hospital discharge/LTD diagnoses and specific procedures or drug reimbursements (Table I in the online-only Data Supplement). Comedications (antihypertensives, antiarrhythmics, nonsteroidal anti-inflammatory drugs, antiplatelets, lipid-lowering and antiulcer agents, cardiac glycosides, oral corticosteroids, benzodiazepine drugs) were defined as medications dispensed at least once during the 4-month preindex period.

Because smoking status and alcohol abuse were not directly available from the databases, we used reimbursement of nicotine replacement therapy and hospital discharge diagnoses related to tobacco use (ICD-10 F17, Z71.6, and Z72.0) or alcohol abuse (F10, K70, T51

E24.4, G31.2, G62.1, G72.1, I42.6, K29.2, K86.0, Z50.2, Z71.4, and Z72.1). Clinical scores predicting the risk of stroke (CHA₂DS₂-VASc) or bleeding (HAS-BLED) in nv-AF patients adapted to medicoadministrative data were calculated.

Statistical Analyses

All analyses were performed separately according to type (dabigatran/rivaroxaban) and dose (low/high) of NOACs by using an intent-to-treat approach. A propensity score (PS) matching analysis was performed to create similar treatment groups with respect to observed characteristics. This PS was determined by using a logistic regression model including the covariates listed above as potential confounders, with age as a categorical variable, with the exception of smoking and alcohol abuse, because only a small proportion of tobacco and alcohol users was identified. The CHA₂DS₂-VASc and HAS-BLED scores were not included in the PS because most of their clinical characteristics were already taken into account. One NOAC-treated patient was matched to 2 VKA-treated patients on the logit of the estimated PS without replacement.²⁶ We used nearest-neighbor matching within a caliper width equal to 0.2 of the standard deviation of the logit of the PS.²⁷

Before matching, categorical and continuous baseline covariates were compared between NOAC-exposed and VKA-exposed patients using the χ^2 test and the Wilcoxon test, respectively, and absolute standardized differences, as well. After matching, weighted standardized differences adapted to incomplete many-to-one matching were calculated to assess the balance between NOAC-exposed and their matched VKA-exposed patients.²⁸ Crude incidence rates were calculated, and Cox models with robust sandwich estimates were used to account for the clustering within matched sets.²⁹ Hazard ratios and their 95% confidence intervals were reported.

Two sensitivity analyses were performed to assess the robustness of the findings based on the primary analyses: exclusion of traumatic bleeding events (S06.3, S06.4, S06.5, S06.6), and restriction of the study population to hospitalized or LTD nv-AF patients. Two subgroup analyses according to age (<75; ≥75) and level of the HAS-BLED score (<3; ≥3) were also performed for the bleeding events in nv-AF patients.

All statistical analyses were performed by using SAS Enterprise Guide 4.3 software (SAS Institute, Inc, Cary, NC).

Results

Characteristics of the Cohort

Out of a total of 65 743 VKA new users, 15 400 (23.4%) were excluded because of contraindications and 1 771 (2.7%) were excluded because of a lower limb orthopedic procedure. Among the NOAC new users, 3 185 (16.8%) of the 18 974 dabigatran patients and 3 050 (15.4%) of the 19 815 rivaroxaban patients were excluded because of contraindications and 4 149 (21.9%) and 7 548 (38.1%), respectively, were excluded because of a lower limb orthopedic procedure. The most frequent contraindication was the exclusion criterion hematologic disease or certain immune system disorders, particularly nutritional anemia. Among the 71 589 eligible patients, 32 807 (45.8%) were identified as having nv-AF (26.9% by ICD-10 I48 or specific procedures and 18.9% by using the algorithm). This population was composed of 19 713 VKA (fluidione: 83.7%, warfarin:

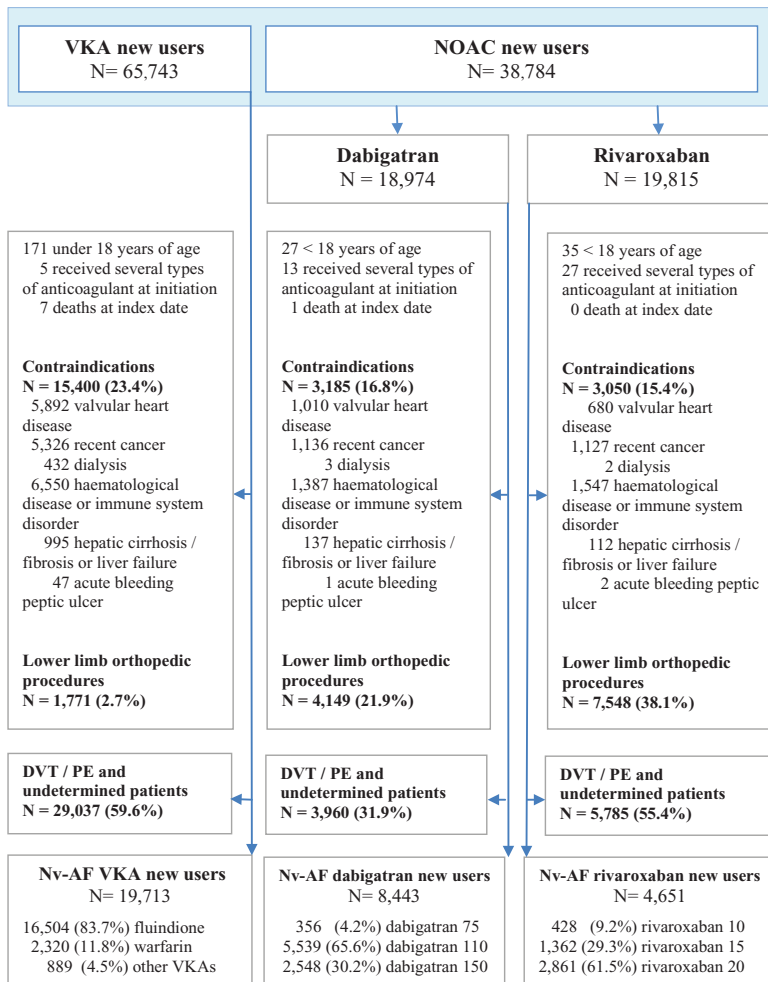


Figure 1. Study population flow chart. All figures are numbers or percentages of patients. DVT indicates deep vein thrombosis; NOAC, non-vitamin K antagonist oral anticoagulants; PE, pulmonary embolism; and VKA, vitamin K antagonist;

Table 1. Dabigatran- and VKA-Matched-Treated Patients: Baseline Characteristics According to Treatment Group After Propensity Score Matching

	Dabigatran All Doses n=8443	VKA D-All Doses Matched n=16 014	Stand Diff†	Dabigatran 75–110 mg n=5895	VKA D75–110 Matched n=11 571	Stand Diff†	Dabigatran 150 mg n=2548	VKA D150 Matched n=5096	Stand Diff†
Characteristics	n (%)*	n (%)*		n (%)*	n (%)*		n (%)*	n (%)*	
Female	3903 (46)	7430 (46)	0.011	3048 (52)	5912 (51)	0.011	855 (34)	1711 (34)	0.000
Age, mean (SD)	74.0 (11.3)	73.9 (11.2)	0.008	77.4 (10.1)	76.9 (10.0)	0.035	66.1 (10.0)	66.5 (10.3)	0.040
18–49 y	271 (3)	508 (3)	0.004	97 (2)	191 (2)	0.002	174 (7)	353 (7)	0.004
50–64 y	1294 (15)	2499 (16)	0.000	521 (9)	1090 (9)	0.014	773 (30)	1506 (30)	0.017
65–74 y	2305 (27)	4322 (27)	0.011	1214 (21)	2417 (21)	0.002	1091 (43)	2229 (44)	0.019
75–79 y	1562 (19)	2990 (19)	0.001	1174 (20)	2347 (20)	0.002	388 (15)	763 (15)	0.007
≥80 y	3011 (36)	5695 (36)	0.009	2889 (49)	5526 (48)	0.008	122 (5)	245 (5)	0.001
Deprivation index									
Quintile 1	1617 (19)	2966 (19)	0.002	1197 (20)	2322 (20)	0.010	420 (16)	824 (16)	0.008
Quintile 2	1553 (18)	2979 (19)	0.004	1013 (17)	2064 (18)	0.011	540 (21)	1045 (21)	0.017
Quintile 3	1654 (20)	3120 (19)	0.001	1142 (19)	2239 (19)	0.002	512 (20)	1042 (20)	0.009
Quintile 4	1752 (21)	3344 (21)	0.003	1240 (21)	2403 (21)	0.010	512 (20)	1049 (21)	0.012
Quintile 5	1767 (21)	3413 (21)	0.001	1232 (21)	2410 (21)	0.007	535 (21)	1078 (21)	0.004
Overseas dpts	100 (1)	192 (1)	0.004	71 (1)	133 (1)	0.007	29 (1)	58 (1)	0.000
First prescriber’s specialty									
Hospital practitioner	2806 (33)	5619 (35)	0.002	1919 (33)	3884 (34)	0.008	887 (35)	1771 (35)	0.001
General practitioner	1865 (22)	3786 (24)	0.008	1410 (24)	2743 (24)	0.014	455 (18)	942 (18)	0.016
Private cardiologist	3613 (43)	6296 (39)	0.009	2459 (42)	4718 (41)	0.002	1154 (45)	2294 (45)	0.006
Other specialties	159 (2)	313 (2)	0.000	107 (2)	226 (2)	0.008	52 (2)	89 (2)	0.022
HAS-BLED, mean (SD)	2.3 (1.0)	2.3 (1.0)	0.009	2.4 (0.9)	2.4 (0.9)	0.015	2.0 (1.0)	2.0 (1.0)	0.000
CHA ₂ DS ₂ -VAsC, mean (SD)	3.2 (1.6)	3.2 (1.6)	0.011	3.6 (1.5)	3.6 (1.5)	0.015	2.4 (1.5)	2.4 (1.5)	0.016
Comorbidities									
Heart failure	1901 (23)	3681 (23)	0.002	1407 (24)	2739 (24)	0.008	494 (19)	941 (18)	0.024
Diabetes mellitus	1626 (19)	3172 (20)	0.001	1158 (20)	2294 (20)	0.001	468 (18)	931 (18)	0.003
CKD	198 (2)	366 (2)	0.012	170 (3)	310 (3)	0.015	28 (1)	51 (1)	0.010
Dementia	326 (4)	592 (4)	0.013	303 (5)	584 (5)	0.001	23 (1)	54 (1)	0.016
History of stroke	603 (7)	1190 (7)	0.002	453 (8)	870 (8)	0.012	150 (6)	295 (6)	0.004
History of TIA	210 (2)	417 (3)	0.000	151 (3)	305 (3)	0.003	59 (2)	100 (2)	0.024
CHD	1766 (21)	3442 (21)	0.001	1391 (24)	2786 (24)	0.011	375 (15)	771 (15)	0.012
PVD	521 (6)	1034 (6)	0.001	408 (7)	813 (7)	0.001	113 (4)	227 (4)	0.001
History of bleeding	224 (3)	408 (3)	0.003	172 (3)	346 (3)	0.011	52 (2)	89 (2)	0.022
Alcohol abuse‡	136 (2)	300 (2)	0.015	85 (1)	168 (1)	0.001	51 (2)	140 (3)	0.049
Smoking‡	301 (4)	570 (4)	0.006	173 (3)	312 (3)	0.016	128 (5)	268 (5)	0.011
Comedications									
Antihypertensives	6758 (80)	12 905 (81)	0.001	4883 (83)	9590 (83)	0.001	1875 (74)	3809 (75)	0.026
Cardiac glycosides	994 (12)	2000 (12)	0.004	739 (13)	1429 (12)	0.012	255 (10)	488 (10)	0.015
Antiarrhythmics	5905 (70)	11 141 (70)	0.007	4025 (68)	7915 (68)	0.005	1880 (74)	3786 (74)	0.012
Lipid-lowering agents	3959 (47)	7570 (47)	0.001	2850 (48)	5524 (48)	0.013	1109 (44)	2223 (44)	0.002
Oral corticosteroids	1108 (13)	1995 (12)	0.004	768 (13)	1469 (13)	0.005	340 (13)	687 (13)	0.004
Antiulcer agents	3458 (41)	6513 (41)	0.005	2557 (43)	5012 (43)	0.003	901 (35)	1743 (34)	0.024
Benzodiazepines	2471 (29)	4752 (30)	0.003	1883 (32)	3640 (31)	0.012	588 (23)	1161 (23)	0.007
Antiplatelets	4499 (53)	8423 (53)	0.000	3350 (57)	6497 (56)	0.004	1149 (45)	2286 (45)	0.005
NSAIDs	1636 (19)	2976 (19)	0.001	1072 (18)	2053 (18)	0.005	564 (22)	1119 (22)	0.004

CHD indicates coronary heart disease; CKD, chronic kidney disease; D, dabigatran; Dpts, departments; NOAC, non-vitamin K antagonist oral anticoagulants; NSAIDs, nonsteroidal anti-inflammatory drugs; PVD, peripheral vascular disease; R, rivaroxaban; SD, standard deviation; Stand Diff, absolute weighted standardized differences; TIA, transient ischemic attack; and VKA, vitamin K antagonist.

*Dichotomous variables are expressed as n (%); continuous variables are expressed as mean (standard deviation).

†Absolute weighted standardized differences comparing baseline characteristics between NOAC- (all NOAC patients were matched) and VKA-matched-treated patients.

‡Smoking or alcoholism data: reimbursements for nicotine replacement therapy and hospital discharge diagnoses related to tobacco use or alcohol abuse.

Table 2. Rivaroxaban- and VKA-Matched-Treated Patients: Baseline Characteristics According to Treatment Group After Propensity Score Matching

Characteristics	Rivaroxaban All Doses n=4651			Rivaroxaban 10–15 mg n=1790			Rivaroxaban 20 mg n=2861		
	VKA R-All Doses Matched n=9301	n (%)*	Stand Diff†	VKA R10–15 Matched n=3580	n (%)*	Stand Diff†	VKA R20 Matched n=5722	n (%)*	Stand Diff†
Female		2108 (45)	0.003	978 (55)	1950 (54)	0.003	1130 (39)	2265 (40)	0.002
Age, mean (SD)		73.6 (11.4)	0.024	79.1 (10.1)	78.5 (9.8)	0.060	70.2 (10.8)	70.5 (10.9)	0.030
18–49 y		160 (3)	0.008	32 (2)	71 (2)	0.014	128 (4)	262 (5)	0.005
50–64 y		747 (16)	0.005	125 (7)	233 (7)	0.019	622 (22)	1209 (21)	0.015
65–74 y		1275 (27)	0.013	260 (15)	536 (15)	0.013	1015 (35)	2037 (36)	0.003
75–79 y		891 (19)	0.013	355 (20)	707 (20)	0.002	536 (19)	1088 (19)	0.007
≥80 y		1578 (34)	0.009	1018 (57)	2033 (57)	0.002	560 (20)	1126 (20)	0.003
Deprivation index									
Quintile 1		934 (20)	0.009	378 (21)	773 (22)	0.012	556 (19)	1130 (20)	0.008
Quintile 2		965 (21)	0.002	350 (20)	697 (19)	0.002	615 (21)	1222 (21)	0.003
Quintile 3		956 (21)	0.002	364 (20)	712 (20)	0.011	592 (21)	1174 (21)	0.004
Quintile 4		847 (18)	0.002	324 (18)	654 (18)	0.004	523 (18)	1037 (18)	0.004
Quintile 5		908 (20)	0.009	358 (20)	708 (20)	0.006	550 (19)	1111 (19)	0.005
Overseas dpts		41 (1)	0.008	16 (1)	36 (1)	0.012	25 (1)	48 (1)	0.004
First prescriber's specialty									
Hospital practitioner		1004 (22)	0.003	389 (22)	796 (22)	0.012	615 (21)	1258 (22)	0.012
General practitioner		992 (21)	0.009	463 (26)	912 (25)	0.009	529 (18)	1048 (18)	0.005
Private cardiologist		2576 (55)	0.005	905 (51)	1818 (51)	0.004	1671 (58)	3347 (58)	0.002
Other specialties		79 (2)	0.000	33 (2)	54 (2)	0.026	46 (2)	69 (1)	0.034
HAS-BLED, mean (SD)		2.3 (1.0)	0.052	2.5 (0.9)	2.5 (0.9)	0.015	2.2 (1.0)	2.1 (1.0)	0.033
CHA ₂ DS ₂ -VASc, mean (SD)		3.1 (1.5)	0.045	3.7 (1.4)	3.6 (1.4)	0.038	2.8 (1.5)	2.7 (1.5)	0.014
Comorbidities									
Heart failure		982 (21)	0.028	469 (26)	917 (26)	0.013	513 (18)	1013 (18)	0.006
Diabetes mellitus		875 (19)	0.024	319 (18)	593 (17)	0.033	556 (19)	1055 (18)	0.025
CKD		117 (3)	0.002	75 (4)	163 (5)	0.018	42 (1)	72 (1)	0.018
Dementia		138 (3)	0.012	93 (5)	172 (5)	0.018	45 (2)	72 (1)	0.027
History of stroke		219 (5)	0.015	97 (5)	182 (5)	0.015	122 (4)	234 (4)	0.009
History of TIA		100 (2)	0.008	49 (3)	73 (2)	0.046	51 (2)	90 (2)	0.016
CHD		963 (21)	0.005	430 (24)	840 (23)	0.013	533 (19)	1011 (18)	0.025
PVD		282 (6)	0.019	137 (8)	254 (7)	0.021	145 (5)	272 (5)	0.015
History of bleeding		110 (2)	0.009	55 (3)	99 (3)	0.018	55 (2)	101 (2)	0.012
Alcohol abuse‡		50 (1)	0.031	19 (1)	33 (1)	0.014	31 (1)	101 (2)	0.058
Smoking‡		125 (3)	0.018	42 (2)	72 (2)	0.023	83 (3)	193 (3)	0.027
Comedications									
Antihypertensives		3624 (78)	0.007	1486 (83)	2987 (83)	0.011	2138 (75)	4340 (76)	0.026
Cardiac glycosides		604 (13)	0.006	251 (14)	447 (12)	0.045	353 (12)	682 (12)	0.013
Antiarrhythmics		3393 (73)	0.022	1235 (69)	2511 (70)	0.025	2158 (75)	4413 (77)	0.040
Lipid-lowering agents		2204 (47)	0.011	811 (45)	1657 (46)	0.020	1393 (49)	2720 (48)	0.023
Oral corticosteroids		534 (11)	0.018	211 (12)	418 (12)	0.003	323 (11)	615 (11)	0.017
Antiulcer agents		1756 (38)	0.002	730 (41)	1409 (39)	0.029	1026 (36)	2052 (36)	0.000
Benzodiazepines		1343 (29)	0.027	597 (33)	1199 (33)	0.003	746 (26)	1485 (26)	0.003
Antiplatelets		2604 (56)	0.024	1086 (61)	2154 (60)	0.010	1518 (53)	2969 (52)	0.023
NSAID		867 (19)	0.027	297 (17)	583 (16)	0.008	570 (20)	1107 (19)	0.015

CHD indicates coronary heart disease; CKD, chronic kidney disease; D, dabigatran; Dpts, departments; NOAC, non-vitamin K antagonist oral anticoagulants; NSAIDs, nonsteroidal anti-inflammatory drugs; PVD, peripheral vascular disease; R, rivaroxaban; SD, standard deviation; Stand Diff, absolute weighted standardized differences; TIA, transient ischemic attack; and VKA, vitamin K antagonist.

*Dichotomous variables are expressed as n (%); continuous variables are expressed as mean (standard deviation).

†Absolute weighted standardized differences comparing baseline characteristics between NOAC- (all NOAC patients were matched) and VKA-matched-treated patients.

‡Smoking or alcoholism data: reimbursements for nicotine replacement therapy and hospital discharge diagnoses related to tobacco use or alcohol abuse.

Table 3. Events, Person-Years at Risk, and Crude Event Rates Among NOAC New Users and Matched VKA New Users

	Dabigatran All Doses	VKA D-All Doses Matched	Dabigatran 75–110	VKA D75–110 Matched	Dabigatran 150	VKA D75–110 Matched	Rivaroxaban All Doses	VKA R-All Doses Matched	Rivaroxaban 10–15	VKA R10–15 Matched	Rivaroxaban 20	VKA R20 Matched
Bleeding events	55/1684/3.3	122/3292/3.7	43/1195/3.6	101/2368/4.3	12/489/2.5	30/1054/2.8	31/848/3.7	68/1913/3.6	16/328/4.9	36/734/4.9	15/520/2.9	40/1178/3.4
Bleeding events or death	158/1684/9.4	341/3292/10.4	137/1195/11.5	295/2368/12.5	21/489/4.3	56/1054/5.3	75/848/8.8	161/1913/8.4	43/328/13.1	89/734/12.1	32/520/6.2	80/1178/6.8
Ischemic stroke or SE	33/1687/2	58/3300/1.8	28/1198/2.3	37/2376/1.6	5/490/1	14/1056/1.3	12/851/1.4	28/1918/1.5	6/329/1.8	13/736/1.8	6/521/1.2	15/1182/1.3
Ischemic stroke or SE or death	136/1687/8.1	280/3300/8.5	121/1198/10.1	243/2376/10.2	15/490/3.1	43/1056/4.1	60/851/7.1	125/1918/6.5	37/329/11.2	66/736/9	23/521/4.4	56/1182/4.7

Values are events/ person-years at risk/crude event rate/100 person-years. D, dabigatran; NOAC, non-vitamin K antagonist oral anticoagulants; R, rivaroxaban; SE, systemic embolism; and VKA, vitamin K antagonist.

11.8%), 8443 dabigatran (low doses: 69.8%), and 4651 rivaroxaban (low doses: 38.5%) new users (Figure 1).

Baseline patient characteristics, before matching, are shown in Tables II and III in the online-only Data Supplement. Dabigatran and rivaroxaban were more frequently initiated than VKA by cardiologists in private practice. Dabigatran and rivaroxaban users had a lower mean CHA₂DS₂-VASc score and fewer comorbidities than VKA users. The mean HAS-BLED score was comparable between NOAC and VKA users. Patients treated with dabigatran 150 mg or rivaroxaban 20 mg were more frequently males, younger, with lower mean HAS-BLED and CHA₂DS₂-VASc scores, and much fewer comorbidities than VKA users. Patients initiating low-dose dabigatran or rivaroxaban were more frequently females and older than VKA users. The proportion of antiplatelet users was higher among patients initiating low-dose dabigatran or rivaroxaban.

In the overall study population, the median duration from the start of treatment (from the day after the index date) to the end of follow-up was 87 days (interquartile range, 56–90 days) for the dabigatran/matched VKA cohort and 80 days (interquartile range, 53–90 days) for the rivaroxaban/matched VKA cohort.

Evaluation of Propensity Score Matching

All 8443 dabigatran-treated patients and 4651 rivaroxaban-treated patients were matched with at least 1 VKA user, and 89.7% and 100.0% of these patients were matched with 2 VKA users, respectively. For each NOAC dose category, 100% of the patients were matched with 2 VKA users, except for the low-dose dabigatran category, in which 96.3% of patients were matched with 2 VKA users.

Before matching, across all variables included in the PS, the absolute standardized differences ranged from 0.000 to 0.861 for dabigatran and from 0.001 to 0.518 for rivaroxaban. After matching, all standardized differences were <0.030 and 0.050, respectively, indicating a good balance between treatment groups (Tables 1 and 2).

Association With Primary End Points

Table 3 presents the number of bleeding and arterial thromboembolic events, person-years at risk, and crude event rates for each of the combinations of NOAC dose group and their matched VKA-treated patients.

No significant difference in bleeding risk was observed between VKA- and dabigatran- or rivaroxaban-treated patients (HR, 0.88; 95% confidence interval, 0.64–1.21 and HR, 0.98; 95% confidence interval, 0.64–1.51, respectively).

The bleeding risk was not significantly different in patients exposed to either low or high doses of each NOAC in comparison with patients exposed to VKA (Figure 2).

The incidence of the composite outcome comprising hospitalization for bleeding and death was comparable between VKA and NOAC new users for all NOAC types and doses (Figure 2).

The results of sensitivity analyses confirmed those obtained with the primary analyses for both dabigatran and rivaroxaban. No significant difference between NOAC and VKA was observed in the subgroup analyses (Figure 2).

Association With Secondary End Points

No significant difference was observed between VKA- and dabigatran- or rivaroxaban-treated patients (HR, 1.10; 95% confidence interval, 0.72–1.69 and HR, 0.93; 95% confidence interval, 0.47–1.85, respectively) in terms of arterial thromboembolic events. Analyses according to NOAC doses did not show any increased risk of stroke or systemic embolism. No significant difference in the incidence of the composite outcome comprising stroke, systemic embolism and death was observed according to the various NOAC types and doses (Table 3; Figure 3).

Discussion

In this large-scale, nationwide cohort study, no significant differences were observed between NOAC (dabigatran or rivaroxaban) and VKA in terms of hospitalizations for bleeding or for arterial thromboembolic events during the early phase of anticoagulant therapy among new users with nv-AF. To our knowledge, this is the first study to assess the short-term benefit/risk balance of both dabigatran and rivaroxaban versus VKA using French medico-administrative databases, because previous studies were conducted on Danish and US Medicare data.^{15–20} This study also provides insight into French prescribing patterns of dabigatran and rivaroxaban immediately following their approval for stroke prevention in nv-AF. Significant channeling of the new drugs, ie, NOAC over VKA toward a younger and healthier population, was observed, and the channeling of low doses of each NOAC (dabigatran 75/110 mg or rivaroxaban 10/15 mg) over high doses toward older patients with higher bleeding and stroke risks, as well.

The results of this study are consistent with the overall findings of the randomized clinical trials and most of the subsequent observational studies that did not find any evidence for increased stroke or bleeding risks with NOAC in comparison with warfarin in the short to medium term.^{7,8,15–17,20}

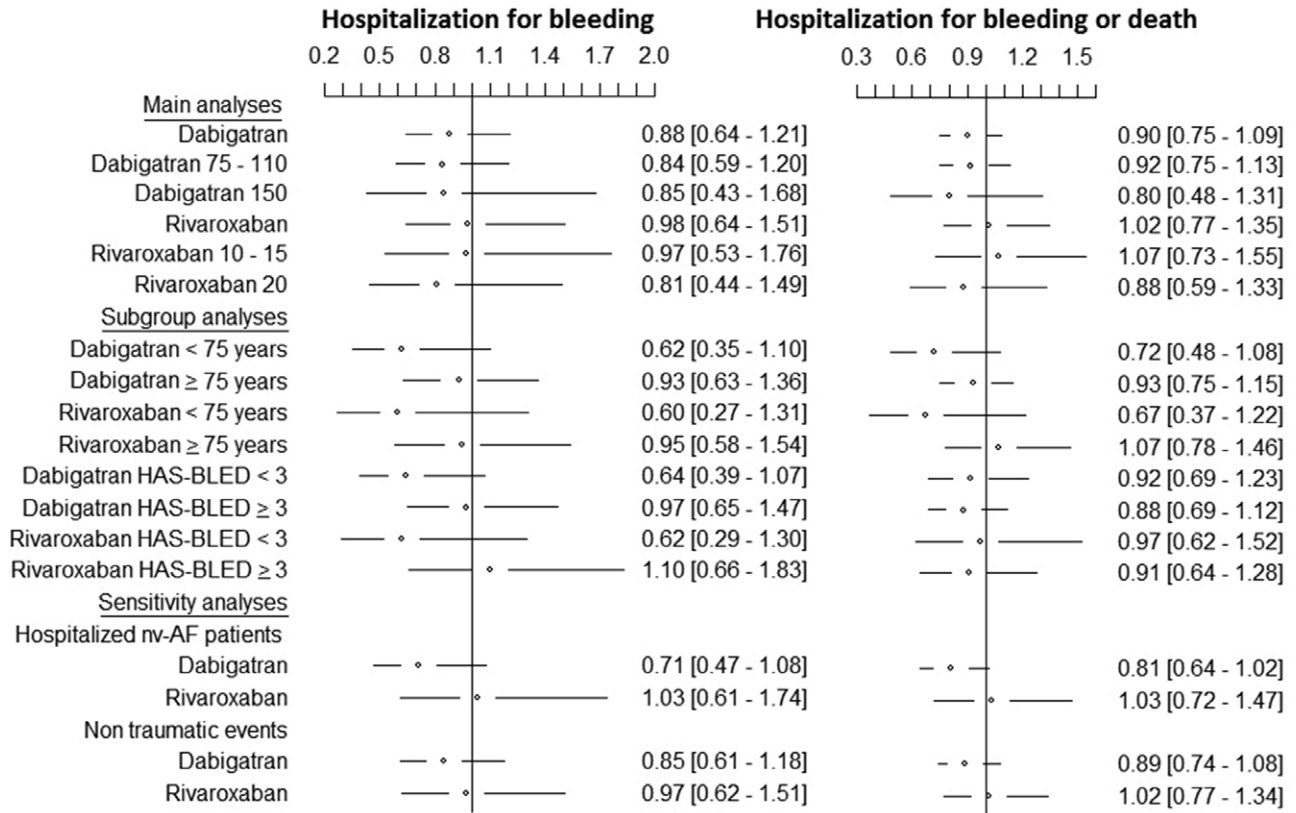


Figure 2. Hazard ratios for hospitalized bleeding events according to type and dose of NOAC. All figures are hazard ratios and their 95% confidence interval. NOAC indicates non-vitamin K antagonist oral anticoagulants; and nv-AF, nonvalvular atrial fibrillation.

Few observational studies on NOAC have been published to date, and this study is one of the first large incident cohorts to assess rivaroxaban effectiveness and bleeding risks relative to VKA.¹⁷ The observed prescribing trends are in line with those described in the available observational studies.¹⁵⁻¹⁷ French prescribing practices appear to be strongly guided by bleeding risk, as suggested by the high proportion of patients who were prescribed low doses, especially dabigatran 75 mg and rivaroxaban 10 mg. These doses have not been approved in the European Union on the basis of clinical judgment, which raises the question of their effectiveness in patients at high risk of stroke.^{9,10} It should be noted that more than one-third of dabigatran- or rivaroxaban-treated patients were aged 80 and over, a population that was underrepresented in pivotal clinical trials.^{7,8}

Nevertheless, as in the study by Sørensen et al,¹⁵ our design focused on the early phase of OAC therapy, bearing in mind that early events can have a major impact on the overall success

of treatment, starting with treatment persistence. Although our overall results are reassuring in relation to the initiation of NOACs in nv-AF patients in France with no marked excess thromboembolic or bleeding risk, they also suggest that particular caution is required when initiating NOACs. Indeed, the initiation of VKAs has been shown to be hazardous owing to the increased risks of bleeding and stroke, which may partly explain the reported underuse of anticoagulant therapy in nv-AF.^{4-6,20} But, on the basis of this study comparing NOAC with VKA, NOACs cannot be considered to be safer than VKA during the early phase of treatment. On the contrary, the clinical implications of our results are that physicians must be just as cautious when initiating NOACs as when initiating VKAs, particularly in view of the absence of an antidote and objective monitoring of the extent of anticoagulation. However, one should keep in mind when initiating OAC therapy that good anticoagulation control is difficult to achieve and maintain with VKA: the quality of anticoagulation in warfarin-treated

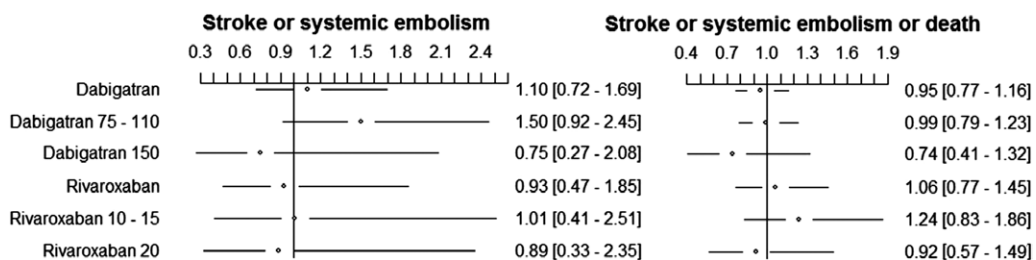


Figure 3. Hazard ratios for stroke or systemic embolism according to type and dose of NOAC. All figures are hazard ratios and their 95% confidence interval. NOAC indicates non-vitamin K antagonist oral anticoagulants.

patients with AF has been reported to be suboptimal by many authors in the real-world setting,^{30–32} with the corresponding significantly increased risk of adverse clinical outcomes.^{33,34}

Because of the observational design and the 2 existing dosage regimens of NOAC, residual confounding by indication is a particular concern in this study.³⁵ Various techniques were used to mitigate this bias. First, we excluded patients with no nv-AF or with contraindications to avoid artificially biasing the treatment effect by ineligible populations or inappropriate treatment indications. Exclusion of these patients could partly explain the apparent discrepancy between our results and those of a recent study based on Medicare data, in which no exclusions were reported.¹⁸ Second, VKA-treated patients were selected in 2011, a period during which NOACs could not be prescribed in France for stroke prevention in nv-AF. Third, analyses were restricted to low and high doses with consistent results.³⁶ Finally, the use of PS matching provides one of the best conditions for nondifferential comparison between NOAC and VKA.^{26–29} Moreover, variables of the PS would be expected to be strong confounders. However, PS matching did not control for unobserved factors. Because this study was based on administrative data, confounders such as lifestyle or alcohol consumption and differences between severity levels of certain diseases such as renal impairment were not taken into account. Residual confounding therefore cannot be excluded.

Identifying AF on the basis of administrative data is challenging and a source of selection bias. We therefore used a highly specific algorithm to more accurately identify treated AF outpatients.²⁴ The results are consistent with those obtained on patients identified only by I48 ICD-10 code or specific procedures.

Outcome misclassification, although nondifferential, also constitutes a limitation, because the external validity of the ischemic stroke and bleeding diagnosis codes have not been previously assessed in the French PMSI database. However, only primary hospital discharge diagnoses were used to define outcomes. Furthermore, this database is used to calculate payments for acute inpatient care with internal and external quality control processes.

Intention-to-treat analysis was performed because of the short-term follow-up and the use of medico-administrative databases. The accuracy of this approach to estimate the treatment assignment effect could be open to criticism, because exposure to treatment was based on pharmacy claims, which do not indicate how the patient actually takes the medications.

With a maximum 3-month follow-up period, our study only captured early events. The outcomes studied are rare events, and the small number of events in this study may not have allowed identification of small-to-moderate differences between groups. Because the study was conducted at the time of the introduction of NOACs for nv-AF patients in France, time-varying characteristics of both patients and prescribers cannot be ruled out. Finally, a much longer follow-up would be necessary to assess the long-term benefit-risk balance of NOACs versus VKAs, especially for arterial thromboembolic events.

In conclusion, in this study based on medico-administrative data, no statistically significant difference was observed between NOACs, dabigatran or rivaroxaban, and VKAs in terms of the risk of bleeding or arterial thromboembolic events during the early phase of anticoagulant therapy in

nv-AF patients. The same level of clinical caution is therefore required when initiating either NOACs or VKAs. Similar analyses should be extended to other NOACs such as apixaban, and observational studies should now focus on NOAC head-to-head comparison in a noninferiority design.

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Disclosures

None.

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CLINICAL PERSPECTIVES

The non-vitamin K antagonists (VKA) oral anticoagulants (NOACs), such as the direct thrombin inhibitor dabigatran and the factor Xa inhibitor rivaroxaban, have provided patients who have atrial fibrillation with a convenient, fixed-dose alternative to VKAs. Although NOACs might have some advantages over VKAs, some concerns have emerged about their safety. Few real-world data has been reported so far, and few studies have specifically focused on the early phase of therapy. However, early bleeding and thromboembolic risks have been observed to be significantly higher during the first 90 days of therapy in patients who have atrial fibrillation initiating warfarin. We therefore conducted a large postmarketing study using the French medicoadministrative databases to better investigate the short-term comparative effectiveness and safety of each specific agent of NOAC versus VKA. In this nationwide propensity-matched cohort study (8443 dabigatran- and 4651 rivaroxaban-treated patients matched with at least 1 VKA user), no significant difference between NOAC (dabigatran or rivaroxaban) and VKA was found in terms of hospitalizations for bleeding or for arterial thromboembolic events during the early phase of therapy among new users with nonvalvular atrial fibrillation. Physicians must therefore be as cautious when initiating NOACs as when initiating VKAs, particularly in view of the absence of a NOAC antidote and objective monitoring of the extent of anticoagulation. These results are consistent with those from the few observational studies published to date and offer clinicians a more comprehensive picture of the NOAC benefit-risk balance during the early phase of treatment.

Comparison of the Short-Term Risk of Bleeding and Arterial Thromboembolic Events in Nonvalvular Atrial Fibrillation Patients Newly Treated With Dabigatran or Rivaroxaban Versus Vitamin K Antagonists: A French Nationwide Propensity-Matched Cohort Study

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SUPPLEMENTAL MATERIAL

Supplementary Table 1. ICD-10 codes/procedures used to identify comorbid conditions in the SNIIRAM-PMSI databases.

	Hospital discharge diagnoses*	LTD*	Specific procedures or drug reimbursements
Exclusion criteria			
History of valvular heart disease	I05-I09, I33-I39		Heart valve surgery
Cancer under treatment	C00-D09, D37-D48, Z510, Z511	C00-D09, D37-D48	Cancer radiotherapy
Hematological disease or certain immune system disorders	D50-D89	D50-D89	
Hepatic cirrhosis or fibrosis or liver failure	R18, I85, K70, K71, K72, K74	R18, I85, K70, K71, K72, K74	
Acute peptic ulcer bleeding	K25.0, K25.2, K26.0, K26.2, K27.0, K27.2		
Dialysis for end-stage renal disease			Specific diagnosis-related groups
NOAC indications			
Lower limb orthopedic procedures			Lower limb orthopedic surgery or procedures
Nonvalvular atrial fibrillation	I48	I48	Radiofrequency ablation, cardioversion
Deep-vein thrombosis/pulmonary embolism	I26, I80 (except I80.0), I81, I82		Lower limb venous ultrasonography, pulmonary/lower limb angiography, ventilation/perfusion scan
Baseline covariates			
Heart failure	I50 or I11.0, I13.0, I13.2, I13.9, K76.1, J81 related to I50	I50	Specific beta-blockers approved for heart failure (bisoprolol, carvedilol, metoprolol, nebivolol)
Diabetes	E10-E14	E10-E14	Antidiabetic drugs
Coronary heart disease	I20-I25	I20-I25	Nitrovasodilator
Dementia	F00-F03, G30	F00-F03, G30	Anticholinesterase inhibitors or NMDA receptor antagonist
History of stroke or systemic embolism	I63 (except I63.6) or G46 related to I63 or I69.3; I74	I63, I74	
Peripheral vascular disease	I70-I73	I70-I73	
Chronic kidney disease	N18, I12, I13.1, I13.2	N18	
History of transient ischemic attack	G45 (except G45.4)		
History of hospitalization for bleeding	ICD-10 codes used to identify outcomes		

Abbreviation: LTD, long-term diseases; NOAC

*ICD-10 codes

Supplementary Table 2. Dabigatran- and VKA matched-treated patients: baseline characteristics according to treatment group before propensity score matching.

Characteristics	VKA N=19,713	Dabigatran all doses N=8,443			Dabigatran 75–110 mg N=5,895			Dabigatran 150 mg N=2,548		
	N(%)*	N(%)*	p [†]	Stand Diff [‡]	N(%)*	p [†]	Stand Diff [‡]	N(%)*	p [†]	Stand Diff [‡]
Female	9,422 (48)	3,903 (46)	0.0157	0.031	3,048 (52)	<0.0001	0.078	855 (34)	<0.0001	0.293
Age, mean (SD)	74.1 (11.3)	74.0 (11.3)	0.2154	0.008	77.4 (10.1)	<0.0001	0.310	66.1 (10.0)	<0.0001	0.748
18-49 years	621 (3)	271 (3)	0.7938	0.003	97 (2)	<0.0001	0.098	174 (7)	<0.0001	0.170
50-64 years	3,215 (16)	1,294 (15)	0.0394	0.027	521 (9)	<0.0001	0.227	773 (30)	<0.0001	0.336
65-74 years	4,953 (25)	2,305 (27)	0.0001	0.049	1,214 (21)	<0.0001	0.108	1,091 (43)	<0.0001	0.380
75-79 years	3,647 (19)	1,562 (19)	0.9999	0.000	1,174 (20)	0.0148	0.036	388 (15)	<0.0001	0.087
≥80 years	7,277 (37)	3,011 (36)	0.0456	0.026	2,889 (49)	<0.0001	0.246	122 (5)	<0.0001	0.861
Deprivation index										
Quintile 1	3,419 (17)	1,617 (19)	0.0003	0.047	1,197 (20)	<0.0001	0.076	420 (16)	0.2793	0.023
Quintile 2	3,788 (19)	1,553 (18)	0.1070	0.021	1,013 (17)	0.0005	0.053	540 (21)	0.0176	0.049
Quintile 3	3,822 (19)	1,654 (20)	0.6948	0.005	1,142 (19)	0.9784	0.000	512 (20)	0.3970	0.018
Quintile 4	4,053 (21)	1,752 (21)	0.7168	0.005	1,240 (21)	0.4297	0.012	512 (20)	0.5836	0.012
Quintile 5	4,359 (22)	1,767 (21)	0.0274	0.029	1,232 (21)	0.0479	0.030	535 (21)	0.2008	0.027
Overseas dpts	272 (1)	100 (1)	0.1883	0.017	71 (1)	0.3040	0.016	29 (1)	0.3203	0.022
First prescriber's specialty										
Hospital practitioner	7,470 (38)	2,806 (33)	<0.0001	0.097	1,919 (33)	<0.0001	0.112	887 (35)	0.0025	0.064
General practitioner	5,275 (27)	1,865 (22)	<0.0001	0.109	1,410 (24)	<0.0001	0.065	455 (18)	<0.0001	0.215
Private cardiologist	6,585 (33)	3,613 (43)	<0.0001	0.194	2,459 (42)	<0.0001	0.172	1,154 (45)	<0.0001	0.245
Other specialties	383 (2)	159 (2)	0.7385	0.004	107 (2)	0.5298	0.009	52 (2)	0.7368	0.007
HAS-BLED, mean (SD)	2.3 (1.0)	2.3 (1.0)	0.1827	0.019	2.4 (0.9)	<0.0001	0.133	2.0 (1.0)	<0.0001	0.351
CHA ₂ DS ₂ -VAsc, mean (SD)	3.4 (1.6)	3.2 (1.6)	<0.0001	0.084	3.6 (1.5)	<0.0001	0.140	2.4 (1.5)	<0.0001	0.606
Comorbidities										
Heart failure	4,953 (25)	1,901 (23)	<0.0001	0.061	1,407 (24)	0.0499	0.029	494 (19)	<0.0001	0.138
Diabetes	4,253 (22)	1,626 (19)	<0.0001	0.057	1,158 (20)	0.0014	0.048	468 (18)	0.0002	0.080
CKD	903 (5)	198 (2)	<0.0001	0.122	170 (3)	<0.0001	0.090	28 (1)	<0.0001	0.211
Dementia	783 (4)	326 (4)	0.6614	0.006	303 (5)	<0.0001	0.056	23 (1)	<0.0001	0.200

History of stroke	1,717 (9)	603 (7)	<0.0001	0.058	453 (8)	0.0131	0.037	150 (6)	<0.0001	0.109
History of TIA	576 (3)	210 (2)	0.0425	0.027	151 (3)	0.1438	0.022	59 (2)	0.0836	0.038
CHD	4,675 (24)	1,766 (21)	<0.0001	0.067	1,391 (24)	0.8504	0.003	375 (15)	<0.0001	0.230
PVD	1,561 (8)	521 (6)	<0.0001	0.068	408 (7)	0.0117	0.038	113 (4)	<0.0001	0.145
History of bleeding	491 (2)	224 (3)	0.4275	0.010	172 (3)	0.0701	0.026	52 (2)	0.1659	0.030
Alcohol abuse [§]	412 (2)	136 (2)	0.0077	0.036	85 (1)	0.0016	0.049	51 (2)	0.7685	0.006
Smoking [§]	750 (4)	301 (4)	0.3313	0.013	173 (3)	0.0017	0.048	128 (5)	0.0029	0.059
Comedications										
Antihypertensives	16,159 (82)	6,758 (80)	0.0001	0.049	4,883 (83)	0.1294	0.023	1,875 (74)	<0.0001	0.203
Cardiac glycosides	2,915 (15)	994 (12)	<0.0001	0.089	739 (13)	<0.0001	0.066	255 (10)	<0.0001	0.145
Antiarrhythmics	13,258 (67)	5,905 (70)	<0.0001	0.058	4,025 (68)	0.1412	0.022	1,880 (74)	<0.0001	0.144
Lipid-lowering agents	9,635 (49)	3,959 (47)	0.0023	0.040	2,850 (48)	0.4748	0.011	1,109 (44)	<0.0001	0.107
Oral corticosteroids	2,333 (12)	1,108 (13)	0.0025	0.039	768 (13)	0.0137	0.036	340 (13)	0.0274	0.045
Antiulcer agents	8,198 (42)	3,458 (41)	0.3256	0.013	2,557 (43)	0.0146	0.036	901 (35)	<0.0001	0.128
Benzodiazepines	6,191 (31.)	2,471 (29)	0.0004	0.047	1,883 (32)	0.4365	0.012	588 (23)	<0.0001	0.188
Antiplatelets	10,336 (52)	4,499 (53)	0.1883	0.017	3,350 (57)	<0.0001	0.088	1,149 (45)	<0.0001	0.147
NSAID	3,425 (17)	1,636 (19)	<0.0001	0.052	1,072 (18)	0.1513	0.021	564 (22)	<0.0001	0.120

Supplementary Table 3. Rivaroxaban- and VKA matched-treated patients: baseline characteristics according to treatment group before propensity score matching.

Characteristics	VKA	Rivaroxaban all doses			Rivaroxaban 10-15 mg			Rivaroxaban 20 mg		
	N=19,713	N=4,651			N=1,790			N=2,861		
	N(%)*	N(%)*	p^{\dagger}	Stand Diff [‡]	N(%)*	p^{\dagger}	Stand Diff [‡]	N(%)*	p^{\dagger}	Stand Diff [‡]
Female	9,422 (48)	2,108 (45)	0.0024	0.050	978 (55)	<0.0001	0.137	1,130 (39)	<0.0001	0.168
Age, mean (SD)	74.1 (11.3)	73.6 (11.4)	0.0026	0.039	79.1 (10.1)	<0.0001	0.464	70.2 (10.8)	<0.0001	0.347
18-49 years	621 (3)	160 (3)	0.3127	0.016	32 (2)	0.0013	0.088	128 (4)	0.0002	0.069
50-64 years	3,215 (16)	747 (16)	0.6802	0.007	125 (7)	<0.0001	0.294	622 (22)	<0.0001	0.139
65-74 years	4,953 (25)	1,275 (27)	0.0013	0.052	260 (15)	<0.0001	0.268	1,015 (35)	<0.0001	0.227
75-79 years	3,647 (19)	891 (19)	0.3008	0.017	355 (20)	0.1657	0.034	536 (19)	0.7632	0.006
≥80 years	7,277 (37)	1,578 (34)	0.0001	0.062	1,018 (57)	<0.0001	0.408	560 (20)	<0.0001	0.393
Deprivation index										
Quintile 1	3,419 (17)	934 (20)	<0.0001	0.070	378 (21)	<0.0001	0.096	556 (19)	0.0061	0.054
Quintile 2	3,788 (19)	965 (21)	0.0177	0.038	350 (20)	0.7289	0.009	615 (21)	0.0040	0.057
Quintile 3	3,822 (19)	956 (21)	0.0715	0.029	364 (20)	0.3326	0.024	592 (21)	0.1003	0.033
Quintile 4	4,053 (21)	847 (18)	0.0003	0.059	324 (18)	0.0133	0.062	523 (18)	0.0046	0.058
Quintile 5	4,359 (22)	908 (20)	0.0001	0.064	358 (20)	0.0387	0.052	550 (19)	0.0005	0.071
Overseas dpts	272 (1)	41 (1)	0.0066	0.047	16 (1)	0.0868	0.046	25 (1)	0.0264	0.048
First prescriber's specialty										
Hospital practitioner	7,470 (38)	1,004 (22)	<0.0001	0.363	389 (22)	<0.0001	0.359	615 (21)	<0.0001	0.365
General practitioner	5,275 (27)	992 (21)	<0.0001	0.127	463 (26)	0.4134	0.020	529 (18)	<0.0001	0.199
Private cardiologist	6,585 (33)	2,576 (55)	<0.0001	0.454	905 (51)	<0.0001	0.353	1,671 (58)	<0.0001	0.518
Other specialties	383 (2)	79 (2)	0.2718	0.018	33 (2)	0.7702	0.007	46 (2)	0.2200	0.025
HAS-BLED, mean (SD)	2.3 (1.0)	2.3 (1.0)	0.1270	0.030	2.5 (0.9)	<0.0001	0.195	2.2 (1.0)	<0.0001	0.164
CHA ₂ DS ₂ -VASc, mean (SD)	3.4 (1.6)	3.1 (1.5)	<0.0001	0.149	3.7 (1.4)	<0.0001	0.222	2.8 (1.5)	<0.0001	0.379
Comorbidities										
Heart failure	4,953 (25)	982 (21)	<0.0001	0.095	469 (26)	0.3157	0.025	513 (18)	<0.0001	0.176
Diabetes	4,253 (22)	875 (19)	<0.0001	0.069	319 (18)	0.0002	0.094	556 (19)	0.0090	0.053
CKD	903 (5)	117 (3)	<0.0001	0.112	75 (4)	0.4474	0.019	42 (1)	<0.0001	0.183

Dementia	783 (4)	138 (3)	0.0012	0.055	93 (5)	0.0122	0.059	45 (1)	<0.0001	0.147
History of stroke	1,717 (9)	219 (5)	<0.0001	0.160	97 (5)	<0.0001	0.129	122 (4)	<0.0001	0.181
History of TIA	576 (3)	100 (2)	0.0039	0.049	49 (3)	0.6564	0.011	51 (2)	0.0005	0.075
CHD	4,675 (24)	963 (21)	<0.0001	0.072	430 (24)	0.7701	0.007	533 (19)	<0.0001	0.125
PVD	1,561 (8)	282 (6)	<0.0001	0.073	137 (8)	0.6906	0.010	145 (5)	<0.0001	0.116
History of bleeding	491 (2)	110 (2)	0.6192	0.008	55 (3)	0.1340	0.035	55 (2)	0.0644	0.039
Alcohol abuse [§]	412 (2)	50 (1)	<0.0001	0.081	19 (1)	0.0029	0.083	31 (1)	0.0003	0.081
Smoking [§]	750 (4)	125 (3)	0.0002	0.063	42 (2)	0.0017	0.085	83 (3)	0.0166	0.050
Comedications										
Antihypertensives	16,159 (82)	3,624 (78)	<0.0001	0.101	1,486 (83)	0.2697	0.028	2,138 (75)	<0.0001	0.177
Cardiac glycosides	2,915 (15)	604 (13)	0.0017	0.052	251 (14)	0.3819	0.022	353 (12)	0.0005	0.072
Antiarrhythmics	13,258 (67)	3,393 (73)	<0.0001	0.125	1,235 (69)	0.1328	0.037	2,158 (75)	<0.0001	0.181
Lipid-lowering agents	9,635 (49)	2,204 (47)	0.0677	0.030	811 (45)	0.0038	0.072	1,393 (49)	0.8516	0.004
Oral corticosteroids	2,333 (12)	534 (11)	0.5010	0.011	211 (12)	0.9529	0.001	323 (11)	0.3978	0.017
Antiulcer agents	8,198 (42)	1,756 (38)	<0.0001	0.078	730 (41)	0.5083	0.016	1,026 (36)	<0.0001	0.118
Benzodiazepines	6,191 (31)	1,343 (29)	0.0008	0.055	597 (33)	0.0898	0.042	746 (26)	<0.0001	0.118
Antiplatelets	10,336 (52)	2,604 (56)	<0.0001	0.071	1,086 (61)	<0.0001	0.167	1,518 (53)	0.5309	0.013
NSAID	3,425 (17)	867 (19)	0.0414	0.033	297 (17)	0.4023	0.021	570 (20)	0.0008	0.065

Abbreviations: D, dabigatran; R, rivaroxaban; Stand Diff, absolute weighted standardized differences; Dpts, departments; CKD, Chronic kidney disease; TIA, Transient ischemic attack; CHD, Coronary heart disease; NSAID, non-steroidal anti-inflammatory drugs; PVD, Peripheral vascular disease.

*Dichotomous variables are expressed as N (%); continuous variables are expressed as mean (standard deviation).

As all NOAC patients were matched, their baseline characteristics are the same as those presented in Tables 2 and 3 of the manuscript.

†*p*-value of the test comparing baseline characteristics between NOAC- and VKA-treated patients.

‡ Absolute weighted standardized differences comparing baseline characteristics between NOAC- and VKA-treated patients.