Risk of bleeding and arterial thromboembolism in patients with non-valvular atrial fibrillation either maintained on a vitamin K antagonist or switched to a non-vitamin K-antagonist oral anticoagulant: a retrospective, matched-cohort study

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Summary

Background Patients with non-valvular atrial fibrillation who are receiving or have been previously exposed to a vitamin K antagonist could be switched to a non-vitamin K-antagonist oral anticoagulant (NOAC) but little information is available about the risk of bleeding and arterial thromboembolism after such a switch. We aimed to compare the risk of bleeding between individuals who switched and those who remained on a vitamin K antagonist (non-switchers) in real-world conditions.

Methods We did a matched-cohort study with information from French health-care databases. We extracted data for adults (aged ≥18 years) with non-valvular atrial fibrillation who received their first prescription for a vitamin K antagonist (fluindione, warfarin, or acenocoumarol) between Jan 1, 2011, and Nov 30, 2012, and who were either switched to a NOAC (dabigatran or rivaroxaban) or maintained on the vitamin K antagonist. Each switcher was matched with up to two non-switchers on the basis of eight variables, including sex, age, and international normalised ratio number. The primary endpoint was incidence of bleeding (intracranial haemorrhage, gastrointestinal haemorrhage, or other) in switchers versus non-switchers, and switchers stratified by type of NOAC versus non-switchers, noted from databases of hospital admissions. Each patient was followed up to 1 year; the study closed on Oct 1, 2013.

Findings Of 17 410 participants, 6705 switched to a NOAC (switchers) and 10 705 remained on vitamin K-antagonist therapy (non-switchers). Median age of participants was 75 years (IQR 67–82), 8339 (48%) were women, and the median duration of vitamin K-antagonist exposure before a switch was 8·1 months (IQR 3·9–14·0). After a median follow-up of 10·0 months (IQR 9·8–10·0), we noted no difference between groups for bleeding events (99 [1%] in switchers *vs* 193 [2%] in non-switchers, p=0·54). In adjusted multivariate analyses, the risk of bleeding in switchers was not different from that in non-switchers (hazard ratio [HR] 0·87; 95% CI 0·67–1·13, p=0·30). Additionally, no differences were noted when the risk of bleeding was compared between switchers from a vitamin K antagonist to dabigatran (HR 0·78, 95% CI 0·54–1·09, p=0·15), switchers from a vitamin K antagonist to rivaroxaban (HR 1·04, 95% CI 0·68–1·58, p=0·86), and non-switchers.

Interpretation In this matched-cohort study, our findings suggest that patients with non-valvular atrial fibrillation who switch their oral anticoagulant treatment from a vitamin K antagonist to a non-vitamin K antagonist are not at increased risk of bleeding. Future studies with longer follow-up might be needed.

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Introduction

Non-vitamin K-antagonist oral anticoagulants (NOACs), including dabigatran[1] and rivaroxaban,[2] provide an alternative to vitamin K antagonists for the prevention of arterial thromboembolism (ischaemic stroke or systemic embolism)[1,2] in patients with non-valvular atrial fibrillation. Because of increasing life expectancy,[3] a growing epidemic of atrial fibrillation is expected.[4] In 2010, the worldwide number of individuals with this disease was estimated at 33·5 million.[4] In 2003, an estimated 46–53% of individuals with atrial fibrillation were receiving a vitamin K antagonist.[5,6] Patients might be switched to a NOAC for several reasons, including if they cannot take or be stabilised on vitamin K antagonists. With the assumption that only half of those with atrial fibrillation were on a vitamin K antagonist in 2010—probably an underestimate—theoretically at least 17 million people could be switched from a vitamin K antagonist to a NOAC.

Subgroup analyses of the RE-LY[7] and ROCKET-AF[8] randomised trials have showed that patients switching from a vitamin K antagonist to dabigatran or rivaroxaban had similar benefits as those starting a NOAC without previous vitamin K-antagonist treatment. So far, we have identified three observational cohort studies[9–11] comparing risk of bleeding[9,10] and of myocardial infarction[11] between

switchers to dabigatran and non-switchers, which all used health-care data from Danish registries. Two studies reported contradictory results: Sørensen and colleagues[9] showed that the risk of bleeding was three times higher in individuals who switched from warfarin to dabigatran 110 mg compared with those who stayed on warfarin, but no raised risk in switchers to dabigatran 150 mg. By contrast, Larsen and colleagues[10] reported a non-significant bleeding risk in switchers to dabigatran at both doses. In the third study,[11] Larsen and colleagues showed a non-significant increased risk of myocardial infarction in switchers to dabigatran, compared with non-switchers.

Little information exists about the effect of switching from a vitamin K antagonist to dabigatran or rivaroxaban on health outcomes. Therefore, we aimed to examine the risk of bleeding between individuals who switched from a vitamin K antagonist to a NOAC (switchers) and those who remained on a vitamin K antagonist (non-switchers), in those needing anticoagulation for non-valvular atrial fibrillation (appendix p 3) in real-world conditions.

See Online for appendix

We also assessed the risk of arterial thromboembolism (ischaemic stroke or systemic embolism and myocardial infarction) and composite events (including haemorrhage, ischaemic stroke or systemic embolism, myocardial infarction, and death).

Methods

Study design and participants

We did a nationwide, retrospective, matched-cohort study in France using information from a comprehensive French national health-insurance database (Système National d'Information Inter-Régimes de l'Assurance Maladie [SNIIRAM]; appendix p 2).[12–16] This database contains anonymised individual data about all reimbursements for patient-health expenditure, including drugs and outpatient medical and nursing care, which have been prescribed or done by health-care professionals. The SNIIRAM database does not provide any direct information about the medical indication for each reimbursement but does contain the patient's status with respect to full reimbursement of care related to a severe and costly long-term condition listed in the International Classification of Diseases, 10th edition (ICD-10).[17] SNIIRAM also includes important status information but not cause of death.

We cross-referenced information from the SNIIRAM database to the French hospital discharge database (Programme de Médicalisation des Systèmes d'Information [PMSI]) that provides medical information about all patients admitted to hospital in France, including discharge diagnoses coded in ICD-10, medical procedures, and French diagnosis-related groups.[18]

We included patients who were aged 18 years or more; had their first prescription of a vitamin K antagonist between Jan 1, 2011, and Nov 30, 2012, without having had a vitamin K antagonist reimbursed in the 12 months before Jan 1, 2011; and were starting vitamin K antagonists for non-valvular atrial fibrillation. In France, three vitamin K antagonists are available—fluindione, warfarin, and acenocoumarol.[19] We excluded patients who had switched from one type of vitamin K antagonist to another, and those who had dementia. So that all individuals on a vitamin K antagonist could theoretically have been switched to a NOAC, we also excluded patients with contraindications for NOACs—ie, surgery for valvular heart disease, recent cancer, dialysis for kidney failure, current or recent gastroduodenal ulceration, hepatic impairment or liver disease, and any lesion or condition with a substantial risk of severe bleeding such as anaemia.

For each individual who switched from a vitamin K antagonist to a NOAC, we randomly selected up to two non-switchers (1:2) matched for the following variables: age (matched within 2 years), sex, history of ischaemic stroke or systemic embolism, history of ischaemic heart disease, vitamin K antagonist type (fluindione, warfarin, or acenocoumarol), date of vitamin K-antagonist initiation (within 7 days), duration of vitamin K-antagonist use before the index date (ie, the date of switching for the switchers), and international normalised ratio (INR) number measured between 45–15 days before the index date (appendix pp 4, 12). For non-switchers, the index date was similar to that of their matched pairs (within 7 days), which was established after matching for the date of vitamin K-antagonist initiation and accounting for a similar duration of vitamin K-antagonist therapy as their matched pairs (appendix pp 4, 13). So that the switcher and non-switcher groups were similar in terms of the probability to switch at index date, we decided to match them for the number of INR measurements instead of actual INR values because this information was not available in SNIIRAM. Indeed, infrequent INR measurements could be a marker of INR stability.[20] In eligible individuals, only individuals with non-valvular atrial fibrillation diagnosis constituted the analytical sample (appendix p 3). Switchers were further stratified according to the type (dabigatran or rivaroxaban) and dose (dabigatran 75–110 mg, dabigatran 150 mg, rivaroxaban 10–15 mg, or rivaroxaban 20 mg) of NOAC that they switched to. The comparator group was non-switchers after the index date. We used the index date to define the beginning of follow-up. Individuals remained in the study until they died, had an event of interest, switched to a NOAC for the non-switched group or to a vitamin K antagonist for the switched group, had 1 year of follow-up, or study closure on Oct 1, 2013. For patients who stopped their treatment before the end of the study, observation continued to the last reimbursement date plus 90 days. The study was approved by the French Data Protection Agency.

Outcomes

We designated events occurring after the index date as outcomes. They were identified from the PMSI database

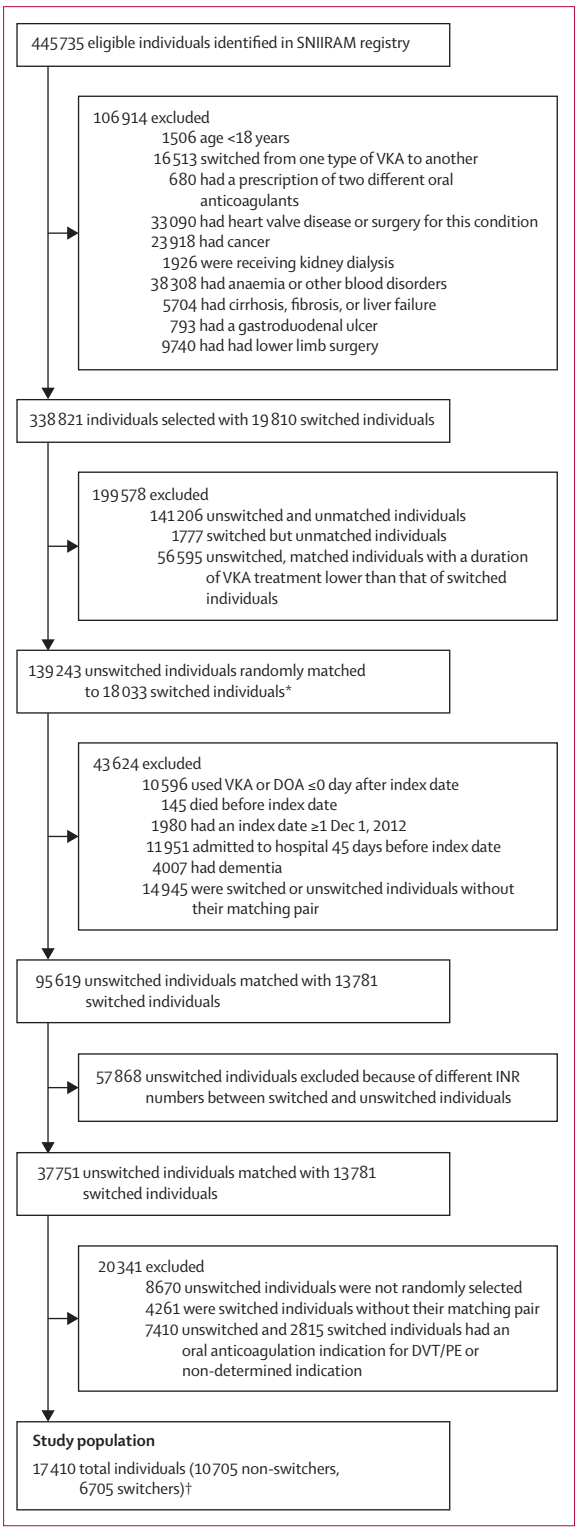

Figure: **Study profile**
SNIIRAM=Système National d'Information Inter-Régimes de l'Assurance Maladie. VKA=vitamin K antagonist. DOA=direct oral anticoagulant. INR=international normalised ratio. DVT=deep vein thrombosis. PE=pulmonary embolism. *Matching ratio varied between 1:2 and 1:20. †Matching ratio varied between 1:1 (40%) and 1:2 (60%).

that contains data about discharges. If deaths occurred from any cause, the information was extracted from the SNIIRAM database.

The primary outcome was bleeding events (ICD-10 codes for intracranial haemorrhage: I60, I61, I62, S06.3, S06.4, S06.5, S06.6; gastrointestinal haemorrhage: K25.0, K25.2, K25.4, K25.6, K26.0, K26.2, K26.4, K26.6, K27.0, K27.2, K27.4, K27.6, K28.0, K28.2, K28.4, K28.6, K29.0, K92.0, K92.1, K92.2, I85.0, K62.5; and other: N02, R31, D62, R58, J94.2, R04.0, R04.1, R04.2, R04.8, R04.9, K66.1, M25.0, N92.0, N92.1, N92.4, N93.8, N93.9, N92.0, N95.0, H11.3, H35.6, H43.1, H45.0, H92.2, I32.2).

Secondary outcomes were ischaemic stroke (ICD-10 code: I63 [cerebral infarction except I63.6]) or systemic embolism (ICD-10 code: I74), first or recurrent myocardial infarction (ICD-10 codes: I21 and I25), and

	Non-switchers (n=10 705)	Switchers (n=6705)	p value
Matching variables (vitamin K antagonist start date)			
Age (years)	75 (67–82)	75 (67–82)	0·86*
Sex			
Male	5574 (52%)	3497 (52%)	..
Female	5131 (48%)	3208 (48%)	..
Type of vitamin K antagonist			
Acenocoumarol	212 (2%)	169 (3%)	0·025†
Fluindione	9688 (90%)	5·998 (89%)	..
Warfarin	805 (8%)	538 (8%)	..
History of ischaemic stroke or systemic embolism	410 (4%)	280 (4%)	0·25†
History of ischaemic heart disease	1276 (12%)	808 (12%)	0·80†
INR measured over 45–15 days before the index date			
0	1258 (12%)	884 (13%)	0·83‡
1	3539 (33%)	2097 (31%)	..
2	2527 (24%)	1580 (24%)	..
3–5	3088 (29%)	1939 (29%)	..
>5	293 (3%)	205 (3%)	..
Duration of vitamin K antagonist therapy before index date (months)	9·15 (6·0)	9·19 (6·0)	0·68*
Covariates (index date)			
Social deprivation index (quintiles)*			
1 (lowest)	1634 (15%)	1225 (18%)	<0·0001†
2	1827 (17%)	1197 (18%)	..
3	1937 (18%)	1254 (19%)	..
4	2111 (20%)	1179 (18%)	..
5 (highest)	2254 (21%)	1198 (18%)	..
Missing data	942 (9%)	652 (10%)	..
Comorbidities			
Transient ischaemic attacks	128 (1%)	80 (1%)	0·99†
Heart failure	4987 (47%)	3086 (46%)	0·8†
Diabetes	2141 (20%)	1134 (17%)	<0·0001†
Hypertension	9211 (86%)	5646 (84%)	0·0008†
Chronic renal impairment	319 (3%)	125 (2%)	<0·0001†
Chronic hepatitis	14 (<1%)	6 (<1%)	0·43†
Peripheral arterial disease	304 (3%)	157 (2%)	0·046†

(Table 1 continues on next page)

	Non-switchers (n=10 705)	Switchers (n=6705)	p value
(Continued from previous page)			
History of hospital admission for bleeding	163 (2%)	119 (2%)	0·20†
Intracranial	16 (<1%)	26 (<1%)	0·002†
Gastrointestinal	86 (<1%)	43 (<1%)	0·23†
Other	63 (<1%)	51 (<1%)	0·17†
Alcohol-related conditions	152 (1%)	72 (1%)	0·049†
Smoking-related conditions	252 (2%)	153 (2%)	0·76†
Modified CHA_2DS_2-VASc score	4 (3–4)	3 (2–4)	0·077*
Modified HAS-BLED score	2 (2–3)	2 (2–3)	0·019*
Concomitant medications			
Antiplatelet agents	2380 (22%)	1636 (24%)	0·001†
Non-steroidal anti-inflammatory drugs	690 (6%)	538 (8%)	<0·0001†
Antiarrhythmic agents	6636 (62%)	4716 (70%)	<0·0001†
Digitalis glycosides	1504 (14%)	963 (14%)	0·56†
Nitrate derivatives	588 (5%)	365 (5%)	0·89†
Lipid-lowering agents	5036 (47%)	3135 (47%)	0·71†
Oral corticosteroids	939 (9%)	702 (10%)	0·0002†
Gastroprotective agents	3910 (37%)	2427 (36%)	0·66†
Benzodiazepines	3005 (28%)	1988 (30%)	0·025†
Antihypertensive agents	9386 (88%)	5803 (87%)	0·030†

Data are median (IQR) or n (%). *Wilcoxon-Mann-Whitney test. †χ^2 test. ‡Cochran–Mantel–Haenszel test. INR=international normalised ratio.

Table 1: **Demographic and clinical characteristics of the study population**

	Total (n=17 410)	Non-switch (n=10 705)	Switch (n=6705)	p value
Follow-up time (months)	10·0 (9·8–10·0)	10·0 (10·0–10·0)	10·0 (7·4–10·0)	0·0004*
No event	10·0 (10·0–10·0)	10·0 (10·0–10·0)	10·0 (9·6–10·0)	<0·0001*
With event	3·9 (2·0–6·3)	4·3 (2·3–6·5)	3·2 (1·1–5·7)	<0·0001*
Endpoints				
Bleeding	292 (2%)	193 (2%)	99 (1%)	0·54†
Intracranial	62 (<1%)	46 (<1%)	16 (<1%)	0·10†
Gastrointestinal	111 (<1%)	66 (<1%)	45 (<1%)	0·26†
Other	123 (<1%)	82 (<1%)	41 (<1%)	0·61†
Ischaemic stroke plus systemic embolism	140 (<1%)	92 (<1%)	48 (<1%)	0·77†
Ischaemic stroke	82 (<1%)	51 (<1%)	31 (<1%)	0·65†
Systemic embolism	58 (<1%)	41 (<1%)	17 (<1%)	0·33†
First and recurrent myocardial infarction	167 (1%)	102 (1%)	65 (1%)	0·38†
Death	452 (3%)	308 (3%)	144 (2%)	0·11†
Any event (composite event)	976 (6%)	650 (6%)	326 (5%)	0·13†

Data are median (IQR) or n (%). *Wilcoxon-Mann-Whitney test. †Log-rank test.

Table 2: **Number of events with a median follow-up of 10 months (IQR 9·8–10·0) in the study population**

composite outcomes that combined both primary and secondary endpoints and death.

Statistical analysis

We used χ^2 tests and *t*-tests to assess the similarity of switchers and non-switchers according to the matching variables. Additionally, we calculated the standardised difference between these groups as the difference in means or proportions divided by the pooled SD. We defined an imbalance between the groups as an absolute value greater than 0·10.[21,22]

We analysed univariate association between exposure and covariates with χ^2 and Fisher's exact tests for classified variables, a Cochran–Mantel–Haenszel trend test for ordered variables, and a *t*-test and analysis of variance for continuous variables. Additionally, we used a log-rank test to examine differences between switchers and non-switchers in the occurrence of events. For the multivariate analysis, we used a conditional Cox model[23] to estimate hazard ratios (HRs) and their 95% CIs of bleeding, ischaemic stroke or systemic embolism, myocardial infarction, and of composite events, at a median follow-up of 10 months (IQR 9·8–10·0). The proportional hazards assumption was met (ie, the p values for switching status × follow-up time interaction terms for bleeding, ischaemic stroke or systemic embolism, and myocardial infarction were not significant).

The following covariates were used in the adjusted models: the social deprivation index, comorbidities, and concomitant drugs. The social deprivation index is a measure of the level of deprivation in an area based on the median household income, the percentage of high-school graduates in the population aged 15 years and older, the percentage of manual workers in the active population, and unemployment. This index is divided into quintiles: the lower quintile (Q1) represents the least deprivation and the highest one (Q5) the most deprivation.[24]

We accounted for the following comorbidities in the year before the index date: transient ischaemic attack, heart failure, diabetes, high blood pressure, chronic kidney disease, chronic hepatitis, peripheral arterial disease, hospital admissions for haemorrhage, alcohol and smoking-related disorders, and consultation. The CHA_2DS_2-VASc score (described in full in appendix p 5)[25] was used to assessed the risk for ischaemic stroke or systemic embolism in patients with atrial fibrillation and HAS-BLED score (appendix p 6)[26] assessed the risk of bleeding in patients receiving oral anticoagulation in atrial-fibrillation care. We calculated the scores with information from the medico-administrative databases. We defined concomitant drugs as those dispensed at least once in the 4 months before the index date (ie, antiplatelet agents, non-steroidal anti-inflammatory drugs, antiarrhythmic agents, digitalis glycosides, nitrate derivatives, lipid-lowering agents, oral corticosteroids, gastroprotective agents, benzodiazepines, and antihypertensive agents).

We analysed four models, all by use of a conditional Cox model. Model 1 contained no covariate. Model 2 was adjusted for covariates which we selected using a backward deletion method with an α-to-remove of 0·15.[27]

Model 3 was further adjusted for all covariates, and model 4 was further adjusted for all matching variables and covariates. Furthermore, we did a sensitivity analysis to assess the robustness of the results from the main analyses of bleeding risk by running all models without CHA_2DS_2-VASc and HAS-BLED scores. Some items included in these scores were also used as covariates. This analysis checked whether the presence of both scores and covariates affected the risk estimate through multicolinearity.

We tested interactions between switching status and outcomes according to sex, age (<75 and ≥75 years), type of vitamin K antagonist, HAS-BLED score (<3 and ≥3), and INR number (≤1 and >1); we did not test according to the CHA_2DS_2-VASc score here because our primary outcome was risk of bleeding. We noted no evidence of interactions (all p values for interaction varied between 0·06 and 0·99 depending on the covariates, definition of switching status, and outcome); therefore, all analyses were done without stratification.

We used SAS software, version 9.3 for all statistical analyses.

Role of the funding source

There was no funding source for this study. KB and MZ had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between Jan 1, 2011, and Nov 30, 2012, 17 410 (39%) of 445 735 individuals who started a vitamin K antagonist for the first time were eligible for our study. 6705 (39%) of these switched to a NOAC and 10 705 (61%) were non-switchers (figure). If we did not find at least one matched control for a switcher, they were excluded. Switchers and non-switchers were similar for matching baseline characteristics (table 1, appendix p 7).

The median follow-up time was slightly but significantly shorter in switchers than in non-switchers (table 2). We noted no significant difference between switchers and non-switchers for the primary outcome of bleeding events (99 [1%] in 6705 switchers *vs* 193 [2%] in 10 705 non-switchers, p=0·54). We also noted no difference between switchers and non-switchers for any event, ischaemic stroke or systemic embolism, first or recurrent myocardial infarction, or death (table 2).

In multivariate analyses, different strategies of adjustment for selected covariates (models 1–4) generated similar HRs for bleeding. Results from models 1 and 2 for risk of bleeding are presented in table 3; results from models 3 and 4 are in the appendix (p 8). Without (model 1) and with adjustment for covariates (model 2), the bleeding risk in switchers was similar to that in non-switchers, even when results were stratified by NOAC type and dose. Sensitivity analyses showed that HRs remained stable when the models were run without CHA2DS2-VASc or HAS-BLED scores (appendix p 9).

For ischaemic stroke or systemic embolism and first or recurrent myocardial infarction, results from model 1 are presented in table 4. Results were consistent with the other models (appendix p 10). Similar to our results for risk of bleeding we noted no significant difference in the occurrence of ischaemic stroke or systemic embolism between switchers and non-switchers, even when results were stratified by NOAC type and dose according to all models.

The risk of first or recurrent myocardial infarction was similar in switchers and non-switchers (table 4). Notably,

	n (events)/ N total	Crude incidence rate per 100 person-years	Model 1*			Model 2†		
			HR	95% CI	p value	HR	95% CI	p value
Switching status								
No switch	193/10 705	2·42	1·00	..	..	1·00	..	..
Switch	99/6705	2·15	0·90	0·70–1·16	0·42	0·87‡	0·67–1·13	0·30
Type of treatment after index date								
Vitamin K antagonist	193/10 705	2·42	1·00	..	..	1·00	..	..
Dabigatran	57/4370	1·92	0·79	0·57–1·09	0·16	0·78‡	0·54–1·09	0·15
Rivaroxaban	42/2335	2·58	1·11	0·74–1·66	0·60	1·04‡	0·68–1·58	0·86
Type and dose of treatment after index date								
Vitamin K antagonist	193/10 705	2·42	1·00	..	..	1·00	..	..
Dabigatran 75–110 mg	47/3356	2·07	0·85	0·59–1·22	0·37	0·84‡	0·57–1·22	0·36
Dabigatran 150 mg	10/1014	1·41	0·59	0·28–1·26	0·17	0·57‡	0·26–1·23	0·15
Rivaroxaban 10–15 mg	14/731	2·84	0·93	0·48–1·80	0·82	0·90‡	0·45–1·79	0·77
Rivaroxaban 20 mg	28/1604	2·47	1·24	0·75–2·07	0·40	1·14‡	0·68–1·93	0·62

HR=hazard ratio. *Conditional Cox model. †Conditional Cox model adjusted for age and selected covariates by use of the backward-elimination method. ‡Selected covariates were age, hypertension, chronic renal impairment, history of arterial disease, HAS-BLED score, and concomitant antiplatelet agent and corticosteroids.

Table 3: **Bleeding risk with a median follow-up of 10 months (IQR 9·8–10·0) in the study population**

the HR was 1·31 (95% CI 0·88–1·93; p=0·19) for switchers to dabigatran compared with non-switchers but 0·76 (0·41–1·39; p=0·37) for switchers to rivaroxaban compared with non-switchers.

Additionally, we did not show any difference (with model 2) between switchers and non-switchers in the occurrence of composite events (table 5; results from models 3 and 4 are in the appendix p 11).

During follow-up, 1946 (11%) of 17 410 participants changed their treatment: 979 (9%) of 10 705 non-switchers changed from a vitamin K antagonist to a NOAC and 967 (14%) of 6705 switchers changed from a NOAC to vitamin K antagonist. The median duration of follow-up before changing treatment was 4 months (IQR 2–6). When we adjusted analyses for switching during the follow-up, HRs for switchers during follow-up versus non-switchers during follow-up were similar to those in the main analyses: bleeding risk (HR 0·83, 95% CI 0·63–1·08, p=0·16); ischaemic stroke or systemic embolism (0·97, 0·66–1·40, p=0·85); first or recurrent

	Ischaemic stroke or systemic embolism*					First or recurrent myocardial infarction*				
	n (events)/ N total	Crude incidence rate per 100 person-years	HR	95% CI	p value	N (events)/ N total	Crude incidence rate per 100 person-years	HR	95% CI	p value
Switching status										
No switch	92/10705	1·15	1·00	..	..	102/10705	1·27	1·00	..	..
Switch	48/6705	1·04	0·97	0·66–1·40	0·85	65/6705	1·41	1·10	0·80–1·53	0·55
Type of treatment after index date										
Vitamin K antagonist	92/10705	1·15	1·00	..	..	102/10705	1·27	1·00	..	..
Dabigatran	32/4370	1·08	1·10	0·70–1·73	0·70	48/4370	1·62	1·31	0·88–1·93	0·19
Rivaroxaban	16/2335	0·98	0·75	0·39–1·45	0·39	17/2335	1·04	0·76	0·41–1·39	0·37
Type and dose of treatment after index date										
Vitamin K antagonist	92/10705	1·15	1·00	..	..	102/10705	1·27	1·00	..	..
Dabigatran 75–110 mg	30/3356	1·32	1·13	0·71–1·81	0·62	35/3356	1·55	1·33	0·84–2·11	0·23
Dabigatran 150 mg	2/1014	0·28	0·80	0·16–4·12	0·79	13/1014	1·84	1·24	0·59–2·61	0·56
Rivaroxaban 10–15 mg	9/731	1·83	1·41	0·55–3·61	0·47	6/731	1·21	1·24	0·41–3·75	0·70
Rivaroxaban 20 mg	7/1604	0·62	0·41	0·15–1·12	0·08	11/1604	0·97	0·62	0·29–1·30	0·20

HR=hazard ratio. *Model 1 was a conditional Cox model. Because of the low number of events according to type of treatment after the index date, we only present results from model 1.

Table 4: **Risk of arterial thromboembolism with a median follow-up of 10 months (IQR 9·8–10·0) in the study population**

	n (events)/ N total	Crude incidence rate per 100 person-years	Model 1*			Model 2†		
			HR	95% CI	p value	HR	95% CI	p value
Switching status								
No switch	650/10705	8·21	1·00	..	..	1·00	..	..
Switch	326/6705	7·15	0·90	0·79–1·04	0·16	0·89‡	0·77–1·03	0·11
Type of treatment after index date								
Vitamin K antagonist	650/10705	8·21	1·00	..	..	1·00	..	..
Dabigatran	212/4370	7·20	0·91	0·77–1·09	0·30	0·90‡	0·76–1·08	0·27
Rivaroxaban	114/2335	7·07	0·89	0·70–1·13	0·33	0·86‡	0·67–1·10	0·24
Type and dose of treatment after index date								
Vitamin K antagonist	650/10705	8·21	1·00	..	..	1·00	..	..
Dabigatran 75–110 mg	184/3356	8·21	0·98	0·81–1·18	0·84	0·96‡	0·79–1·16	0·66
Dabigatran 150 mg	28/1014	3·98	0·63	0·40–0·98	0·04	0·67‡	0·42–1·06	0·08
Rivaroxaban 10–15 mg	50/731	10·27	1·04	0·72–1·50	0·83	1·03‡	0·70–1·49	0·90
Rivaroxaban 20 mg	64/1604	5·68	0·79	0·57–1·09	0·15	0·76‡	0·55–1·05	0·10

Composite events were bleeding, ischaemic stroke or systemic embolism, myocardial infarction, and death. HR=hazard ratio. *Conditional Cox model. †Conditional Cox model adjusted for age and selected covariates with the backward-elimination method. ‡Selected covariates were age, diabetes, hypertension, HAS-BLED score, concomitant antiplatelet, lipid-lowering, and gastroprotective agents, digitalis glycosides, and oral corticosteroids.

Table 5: **Risk of composite events with a median follow-up of 10 months (IQR 9·8–10·0) in the study population**

	Source	Study design	Exposure	N individuals (NOAC/ vitamin K antagonist)	Age, years (NOAC/ vitamin K antagonist)	Crude incidence rates per 100 person-years (NOAC/vitamin K antagonist)	Follow-up, months	HR	95% CI
Risk of major bleeding									
Ezekowitz, 2010[7]	RE-LY study	Randomised trial	Dabigatran 110 mg *vs* warfarin	3011/2929	71·4 for all	2·7/3·6	24	0·74	0·60–0·90
Sørensen, 2013[9]	Danish national health-care databases	Cohort study	Dabigatran 110 mg *vs* warfarin	782/45 403	79·6 (8·3)/73·5 (10·0)	5·2/1·5	4	3·30	2·40–4·53
Larsen, 2014[10]	Danish national health-care databases	Matched-cohort study	Dabigatran 110 mg *vs* warfarin	2038/8504	82 (77–86)/74 (67–81)	3·5/2·6	13	1·17	0·89–1·53
Bouillon, 2015 (present study)	French national health-insurance databases	Matched-cohort study	Dabigatran 75–110 mg *vs* vitamin K antagonist	3356/10 705	76·5 (9·5)/74·0 (10·0)	2·1/2·4	9	0·85*	0·59–1·22*
Ezekowitz, 2010[7]	RE-LY study	Randomised trial	Dabigatran 150 mg *vs* warfarin	3049/2929	71·4 for all	3·3/3·6	24	0·92	0·76–1·12
Sørensen, 2013[9]	Danish national health-care databases	Cohort study	Dabigatran 150 mg *vs* warfarin	349/45 403	67·9 (8·2)/73·5 (10·0)	1·4/1·5	4	1·11	0·46–2·67
Larsen, 2014[10]	Danish national health-care databases	Matched-cohort study	Dabigatran 150 mg *vs* warfarin	2038/8504	69 (64–73)/74 (67–81)	2·1/2·6	13	0·86	0·64–1·15
Bouillon, 2015 (present study)	French national health-insurance databases	Matched-cohort study	Dabigatran 150 mg *vs* vitamin K antagonist	1014/10 705	67·4 (8·5)/74·0 (10·0)	1·4/2·4	9	0·59*	0·28–1·26*
Mahaffey, 2013[8]	ROCKET-AF study	Randomised trial	Rivaroxaban 20 mg *vs* warfarin	3948/3938	71·9 (9·1)/71·8 (9·3)	3·9/3·3	1–30	1·19	0·99–1·43
Bouillon, 2015 (present study)	French national health-insurance databases	Matched-cohort study	Rivaroxaban 10, 15, and 20 mg *vs* vitamin K antagonist	2335/10 705	73·1 (10·2)/74·0 (10·0)	2·6/2·4	9	1·11*	0·74–1·66*
Risk of ischaemic stroke or systemic embolism									
Ezekowitz, 2010[7]	RE-LY study	Randomised trial	Dabigatran 110 mg *vs* warfarin	3011/2929	71·4 for all	1·5/1·7	24	0·87	0·66–1·15
Sørensen, 2013[9]	Danish national health-care databases	Cohort study	Dabigatran 110 mg *vs* warfarin	782/45 403	79·6 (8·3)/73·5 (10·0)	0·6/0·2	4	3·52	1·40–8·84
Bouillon, 2015 (present study)	French national health-insurance databases	Matched-cohort study	Dabigatran 75–110 mg *vs* vitamin K antagonist	3356/10 705	76·5 (9·5)/74·0 (10·0)	1·3/1·2	9	1·13*	0·71–1·81*
Ezekowitz, 2010[7]	RE-LY study	Randomised trial	Dabigatran 150 mg *vs* warfarin	3049/2929	71·4 for all	1·2/1·7	24	0·66	0·49–0·89
Sørensen, 2013[9]	Danish national health-care databases	Cohort study	Dabigatran 150 mg *vs* warfarin	349/45 403	67·9 (8·2)/73·5 (10·0)	0·9/0·2	4	5·79	1·81–18·56
Bouillon, 2015 (present study)	French national health-insurance databases	Matched-cohort study	Dabigatran 150 mg *vs* vitamin K antagonist	1014/10 705	67·4 (8·5)/74·0 (10·0)	0·3/1·2	9	0·80*	0·16–4·12*
Mahaffey, 2013[8]	ROCKET-AF study	Randomised trial	Rivaroxaban 20 mg *vs* warfarin	3948/3938	71·9 (9·1)/71·8 (9·3)	2·0/2·1	1–30	0·94	0·75–1·18
Bouillon, 2015 (present study)	French national health-insurance databases	Matched-cohort study	Rivaroxaban 10, 15, and 20 mg *vs* vitamin K antagonist	2335/10 705	73·1 (10·2)/74·0 (10·0)	1·0/1·2	9	0·75*	0·39–1·45*
Myocardial infarction									
Ezekowitz, 2010[7]	RE-LY study	Randomised trial	Dabigatran 110 mg *vs* warfarin	3011/2929	71·4 for all	0·7/0·5	24	1·27	0·80–2·02
Larsen, 2014[11]	Danish national health-care databases	Cohort study	Dabigatran 110 mg *vs* warfarin	1554/49 868	82 (77–86)/75 (68–81)	1·3/0·7	16	1·45	0·98–2·15
Bouillon, 2015 (present study)	French national health-insurance databases	Matched-cohort study	Dabigatran 75–110 mg *vs* vitamin K antagonist	3356/10 705	76·5 (9·5)/74·0 (10·0)	1·6/1·3	9	1·33*	0·84–2·11*
Ezekowitz, 2010[7]	RE-LY study	Randomised trial	Dabigatran 150 mg *vs* warfarin	3049/2929	71·4 for all	0·8/0·5	24	1·43	0·91–2·24
Larsen, 2014[11]	Danish databases	Cohort study	Dabigatran 150 mg *vs* warfarin	1825/49 868	69 (64–74)/75 (68–81)	0·8/0·7	16	1·30	0·84–2·01
Bouillon, 2015 (present study)	French national health-insurance databases	Matched-cohort study	Dabigatran 150 mg *vs* vitamin K antagonist	1014/10 705	67·4 (8·5)/74·0 (10·0)	1·8/1·3	9	1·24*	0·59–2·61*
Mahaffey, 2013[8]	ROCKET-AF study	Randomised trial	Rivaroxaban 20 mg *vs* warfarin	3948/3938	71·9 (9·1)/71·8 (9·3)	1·0/1·4	1–30	0·76	0·56–1·02
Bouillon, 2015 (present study)	French national health-insurance databases	Matched-cohort study	Rivaroxaban 10, 15, and 20 mg *vs* vitamin K antagonist	2335/10 705	73·1 (10·2)/74·0 (10·0)	1·0/1·3	9	0·76*	0·41–1·39*

Data are mean (SD) or median (IQR). NOAC=non-vitamin K-antagonist oral anticoagulants. HR=hazard ratio. *Results are from model 1.

Table 6: **Studies of safety profile of vitamin K-antagonist oral anticoagulants assessed according to switching status**

myocardial infarction (1·10, 0·80–1·53, p=0·55); and composite events (0·85, 0·73–0·99, p=0·03). Although the difference between switchers and non-switchers was significant for composite events in this analysis, the HR was similar to that of the main analysis (0·85 *vs* 0·89).

We put our results into perspective by comparing them to the results of published studies (table 6).[7–11]

Discussion

Our results suggest that after a median follow-up of 10 months, the risk of bleeding events in participants who switched from vitamin K antagonist to a NOAC was not higher than it was in those who continued to take a vitamin K antagonist (panel). Even after the switch group was divided into two subgroups according to NOAC type, no significant differences were noted, either between those who switched from a vitamin K antagonist to dabigatran or those who switched to rivaroxaban. Moreover, no significant increase in the risk of ischaemic stroke or systemic embolism, first or recurrent myocardial infarction, or composite events was noted when we compared individuals who switched from a vitamin K antagonist to dabigatran, or individuals who switched to rivaroxaban with those who did not switch.

Because dabigatran and rivaroxaban have been recently licensed (in October, 2010, in the USA) for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation, only a few cohort studies have been done in real-life conditions to examine the effectiveness and safety of NOACs in individuals previously exposed to vitamin K antagonists, and most of these studies have focused on dabigatran. We identified three observational studies,[9–11] all based on Danish health-care registries, and our findings were generally consistent with those in the scientific literature[7,8] in that we noted no evidence of a raised risk of bleeding[7,8,10] and ischaemic stroke or systemic embolism[7,8] in switchers to dabigatran or rivaroxaban. We did note a non-significant increased risk of myocardial infarction in switchers to dabigatran in other published trials.[7,8,11] However, results from one study[9] are discordant—Sørensen and colleagues[9] reported a three-times higher risk of bleeding in switchers to dabigatran 110 mg, and higher risks of ischaemic stroke or systemic embolism in switchers to dabigatran 110 mg (3·5-times higher) and to dabigatran 150 mg (5·8-times higher). These results were inconsistent with those reported by Larsen and colleagues,[10] although both teams used the same registries. The investigators attributed this discrepancy to differences in follow-up times and when the studies were done—Sørensen and colleagues[9] used Danish data from a few months after the introduction of dabigatran with 4 months of follow-up, whereas the follow-up time in Larsen's study[10] was longer (mean 13 months). The crude incidence rates per 100 person-years of all the events examined in our study were similar to those in other studies (table 6). For example, major bleeding events ranged from 2·7 to 5·2[7,9,10] for dabigatran 110 mg, 1·4 to 3·3[7,9,10] for dabigatran 150 mg, and was 3·9[8] for rivaroxaban 20 mg.

Because we did our study with information from health-care databases, our findings were moderately immune from information bias. Indeed, the prescription data are accurate and exhaustive because information about prescribed and reimbursed drugs is automatically and immediately captured in pharmacies where the drugs are delivered (SNIIRAM database). Data for hospital admissions (PMSI database) are also accurate and precise because they are used to allocate money to both public and private hospitals; therefore, the quality of diagnosis codes from these data is regularly checked against patients' medical records. Additionally, although SNIIRAM and PMSI are independent databases, we believe that diagnostic bias did not differ between switched and non-switched individuals. In our study, we could not specifically calculate the sensitivity and specificity of the diagnoses used to define endpoints and comorbidities. However, a previous study[28] that assessed the validity of the PMSI database against three French registries (Lille, Strasbourg, and Toulouse) included in the WHO MONICA project[29] showed a positive predictive value of 79% and a sensitivity of 76% for acute myocardial infarction. Although such information was not available at the time of the study for bleeding and ischaemic stroke or systemic embolism, these values might be close to those for myocardial infarction because crude incidence rates and risk estimates calculated in our study were very close to those from other studies.[7–10] Results from other variables defined with health-care data, such as non-valvular atrial fibrillation, comorbidities, hospital admissions related to alcohol and tobacco use, and CHA_2DS_2-VASc and HAS-BLED scores, are unclear. However, these variables were significantly associated with an event during follow-up—eg, as expected, the CHA_2DS_2-VASc score was strongly associated with ischaemic stroke and systemic embolism, and the HAS-BLED score was associated with bleeding events. Generally, our results for comorbidities and concomitant drugs, and median CHA_2DS_2-VASc and HAS-BLED scores were similar to those reported in a drug use study[30] and we—as they did—noted that switchers had fewer comorbidities and took more concomitant drugs than did non-switchers.

However, our study might have been affected by other biases, especially selection and prescription biases. Our study population was probably younger (median age 75 years) and had less comorbidity than the source population. However, because we rigorously applied the same selection criteria for both switchers and non-switchers, these differences should not have compromised any comparisons. The main bias of our study was prescription bias because we do not know why a patient was switched from a vitamin K antagonist to a NOAC. If the reason for switching does not depend on

clinical or laboratory data (eg, the patient was switched to a NOAC to avoid monthly blood tests for INR), the resulting bias should have few repercussions on the results. By contrast, if the switch depended on variables such as difficulty in stabilisation of the INR, any identified difference in risk between switchers and non-switchers is more difficult to interpret because whether this difference is due to the NOAC or the setting that led to the change in treatment (advanced age, many comorbidities, unstable INR) is unclear. In our study, we accounted for this bias by matching individuals in the two groups on the basis of criteria that might incite a change in treatment, to attribute the events to the effect of the drugs. By rendering switched and non-switched groups similar according to several baseline characteristics, we excluded a large number of participants from the study. This exclusion is one of the drawbacks of our study shared with other matched-cohort studies.[31,32]

Finally, to account for confounding biases such as comorbidities and concomitant drugs, we used several models with various adjustment strategies. Estimated HRs are slightly affected by these strategies; however, our results, based on observational data, do not provide information about causality because we cannot rule out the confounding effect of unmeasured or unknown factors. Although we made the switched and non-switched groups as similar as possible (with eight matching variables), our results might have been affected by further residual confounding. During follow-up, 11% of participants changed their treatment (9% of non-switchers switched to a NOAC, and 14% of switchers went onto a vitamin K antagonist). This change in treatment could have affected the risk estimations. We attempted to account for such changes by doing further analyses adjusted for switching during the follow-up and noted a very slight, non-significant change in the relation between exposure and studied outcomes.

Although we have not shown an increased risk of bleeding, ischaemic stroke, systemic embolism, or myocardial infarction in switchers from vitamin K antagonists to NOACs compared with non-switchers, any health risks related to the use of NOACs should continue to be monitored for several reasons. First, our results are based on a short follow-up time and some diseases might take longer to manifest, especially ischaemic stroke or systemic embolism, and myocardial infarction. Second, we studied the risk of events immediately after NOAC licensing. NOAC prescribing behaviour and use could change over time—eg, more patients might be switched from a well tolerated vitamin K antagonist to a NOAC, which is not recommended. Third, the power of this study was possibly insufficient to show a very small raised risk.

A key strength of our study was our use of an exhaustive, well characterised, national health-care database,[12–16] which enabled us to constitute a large study population of switched and non-switched groups matched for eight criteria. This method rendered switched and non-switched groups similar so risk ratio estimates were not confounded by these criteria. The main limitation of this method is overmatching;[33] however, we do not believe that our results were significantly affected by this limitation because the matching factors are associated with both exposure to a vitamin K antagonist and studied outcomes, and the matching factors are not affected by either exposure or outcome. Furthermore, unexposed (non-switchers) and exposed (switchers) individuals were probably unrelated because they were selected from a large database.

Millions of individuals with atrial fibrillation or venous thromboembolism in the world who are receiving vitamin K-antagonist therapy could be switched to a NOAC, and therefore the effectiveness and safety of NOACs in this population should be assessed in real-life conditions. In our large, observational, post-marketing study, we noted no evidence of increased risk of severe bleeding, ischaemic stroke or systemic embolism, first or recurrent myocardial infarction, or composite events in individuals who switched from a vitamin K antagonist to a NOAC compared with those who were maintained on a vitamin K antagonist.

Panel: Research in context

Systematic review

We searched Web of Science for English-language articles published between Jan 1, 2011, and Jan 18, 2015 with the search terms "atrial fibrillation", "dabigatran", "rivaroxaban", "apixaban", "risk", "safety", "efficacy", and "adverse event". We identified 1471 articles, and selected studies that included comparisons of the risk of bleeding and arterial thromboembolism between non-vitamin K-antagonist oral anticoagulants (NOACs) and vitamin K antagonists, especially in patients with non-valvular atrial fibrillation previously exposed to a vitamin K antagonist. We did not quantitatively assess the quality of identified studies.

Interpretation

To our knowledge, our matched-cohort study is the first to examine in real-life conditions both effectiveness and safety outcomes of patients receiving vitamin K-antagonist therapy who switch to a NOAC. We found no evidence to support an increased risk of severe bleeding, ischaemic stroke or systemic embolism, first or recurrent myocardial infarction, or composite events (including all these outcomes and death) in individuals who switched from a vitamin K antagonist to a NOAC, compared with those who continued on a vitamin K antagonist. These results are consistent with those from a few existing studies.[7,8,10,11] Our findings offer clinicians a more comprehensive picture of the risks and benefits associated with NOACs in patients who are used to taking vitamin K antagonists.

Contributors

KB and MZ wrote the first and successive drafts of the paper. KB and MB did the statistical analysis. KB, MZ, GM, P-OB, and PR collaborated on building the protocol and definitions of the diseases and concomitant drugs. All authors contributed to the interpretation of results and revision of the paper, and approved the final version of the paper. KB and MZ are guarantors.

Declaration of interests

We declare no competing interests.

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Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Bouillon K, Bertrand M, Maura G, Blotière P-O, Ricordeau P, Zureik M. Risk of bleeding and arterial thromboembolism in patients with non-valvular atrial fibrillation either maintained on a vitamin K antagonist or switched to a non-vitamin K-antagonist oral anticoagulant: a retrospective, matched-cohort study. *Lancet Haematol* 2015; **2:** e150–59.

Webappendix

Table of contents

SNIIRAM health insurance database

Health insurance is divided into three main schemes: 1) general scheme covering employees in the industry, business and service sectors, as well as some categories of workers considered as employees; 2) agricultural scheme covering farmers and farm employees; 3) social scheme for independent professionals covering craftspeople, retailers, manufacturers and independent professions. In this study, only individuals benefiting from the general scheme have been included as important information such as LTD scheme and vital status are not exhaustive for other schemes. Health insurance general scheme is the supportive health insurer of four out of five people in France. It finances 75% of national health expenditure.[1]

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Definition of non-valvular atrial fibrillation

Confirmed non-valvular atrial fibrillation

Atrial fibrillation is considered as ‘confirmed’ when the study participant has one of the following criteria:

- hospitalization for atrial fibrillation (ICD-10 code: I48) at least once during the year before starting of the VKA therapy;
- full reimbursement for atrial fibrillation care considered as a severe and costly long-term disease (LTD), ICD-10 code: I48) obtained during the year before or 30 days after the start of the VKA therapy;
- treatment for electrical cardioversion or catheter or surgical ablation during the year before the start of the VKA therapy.

Probable non-valvular atrial fibrillation

Atrial fibrillation is considered as ‘probable’ when the study participant got an ECG-Holter or took an antiarrhythmic drug six weeks before or two weeks after starting VKA therapy.

Matching procedure

We performed the matching procedures following three steps: first, for each switcher, we randomly selected up to 20 non-switchers matched on age, sex, history of ischemic stroke/systemic embolism, history of ischemic heart disease, VKA type, and date of VKA initiation; second, an index date is calculated for non-switchers from the VKA initiation date adding the duration of VKA treatment of their corresponding matched switcher. Then, we excluded all non-switchers whose duration of VKA treatment (difference between the date of the last reimbursement plus 30 days and the date of the first reimbursement) was inferior to the duration of VKA treatment of the corresponding switchers; third, the INR number over a month 15 days before the index date has been estimated and the second matching on this criterion is undertaken with matching ratio 1:2.

Tables

Table 1. Items included in the modified CHA2DS2-VASc score

Letter	Original items (Lip et al, Chest 2010)	Modified items	Score
C	Left ventricular dysfunction or congestive heart failure	Yes (only congestive heart failure has been considered)	1
H	Hypertension	No	1
A2	Age ≥ 75 years	No	2
D	Diabetes	No	1
S2	Stroke /TIA/ systemic embolism	No	2
v	Vascular disease (previous history of MI, peripheral arterial disease or aortic plaque)	Yes (only previous history of MI, peripheral arterial disease have been considered)	1
A	Age 65-74 years	No	1
Sc	Gender (female)	No	1

All conditions were defined during the period one year before index date.
The CHA2DS2-VASc score varies from 0 to 9.

Table 2. Items included in the modified HAS-BLED score

Letter	Original items (Pisters et al, Chest 2010)	Modified items	Score
H	Hypertension	No	1
A	Impaired renal and/or hepatic function	No	1 or 2
S.	Previous history of stroke	No	1
B.	Previous history of bleeding or predisposition to bleeding	No	1
L	Labile INR	Yes (see table below)	1
E	Age> 65 years (Elderly)	No	1
D	Drugs/alcohol concomitantly	Yes for alcohol consumption. We considered that it is the case when an individual has been hospitalized for all causes related to alcohol.	1 or 2

All conditions were defined during the period one year before index date.
The HAS-BLED score varies from 0 to 9.

We arbitrarily defined "labile INR" as follows:

Month of treatment	Expected INR frequency in one month	Labile if
1st	8 (twice a week)	≥ 10
2nd	4 (once a week)	≥ 6
3rd	2 (once every 2 weeks)	≥ 4
4th	2 (once every 2 weeks)	≥ 4
5th	2 (once every 2 weeks)	≥ 4
6th	2 (once every 2 weeks)	≥ 4
7th	1	≥ 2
8th	1	≥ 2
9th	1	≥ 2

The period during which the number of INR was estimated was defined in Figure 1 in Webappendix.

Table 3. Description of matching variables according to switching status in the study population (N=17,410)

	Total N=17,410 N (%) / mean (SD)	Non-switchers N=10,705 N (%) / mean (SD)	Switchers N=6,705 N (%) / mean (SD)	Standardized difference*
Age (years)	74.0 (10.0)	74.0 (10.0)	73.9 (10.1)	0.00214
Women	8,339 (47.9)	5,131 (47.9)	3,208 (47.8)	-0.00172
Type of VKA				0.04177
Acenocoumarol	381 (2.2)	212 (2.0)	169 (2.5)	
Fluindione	15,686 (90.1)	9,688 (90.5)	5,998 (89.5)	
Warfarin	1,343 (7.7)	805 (7.5)	538 (8)	
Ischemic stroke or systemic embolism	690 (4.0)	410 (3.8)	280 (4.2)	0.01765
Ischemic heart disease	2,084 (12.0)	1,276 (11.9)	808 (12.1)	0.00403
INR over 30 days in 15 days before the index date				-0.00243
0	2,142 (12.3)	1,258 (11.8)	884 (13.2)	
1	5,636 (32.4)	3,539 (33.1)	2,097 (31.3)	
2	4,107 (23.6)	2,527 (23.6)	1,580 (23.6)	
3 to 5	5,027 (28.9)	3,088 (28.8)	1,939 (28.9)	
> 5	498 (2.9)	293 (2.7)	205 (3.1)	
Duration of VKA therapy before switch (months)	9.17 (6.0)	9.15 (6.0)	9.19 (6.0)	0.00794

SD: standard deviation; VKA: vitamin K antagonist

*Standardized difference = difference in means or proportions divided by pooled standard deviation.

Table 4. Bleeding risk with a median follow-up of 10.0 months (IQR 9.8-10.0) in the study population (N=17,410)

	N(events)/ Ntotal N=17,410	Crude incidence rate per 100 PY	Model 1*			Model 2†			Model 3§			Model 4‖		
			HR	[95% CI]	P-value	HR	[95% CI]	P-value	HR	[95% CI]	P-value	HR	[95% CI]	P-value
Switching status														
No switch	193/10705	2.42	1			1			1			1		
Switch	99/6705	2.15	0.90	0.70-1.16	0.42	0.87‡	0.67-1.13	0.30	0.85	0.65-1.12	0.25	1.01	0.65-1.55	0.98
Type of treatment after index date														
VKA	193/10705	2.42	1			1			1			1		
Dabigatran	57/4370	1.92	0.79	0.57-1.09	0.16	0.78‡	0.54-1.09	0.15	0.75	0.52-1.07	0.11	0.88	0.54-1.44	0.61
Rivaroxaban	42/2335	2.58	1.11	0.74-1.66	0.60	1.04‡	0.68-1.58	0.86	1.04	0.67-1.61	0.86	1.23	0.71-2.13	0.46
Type and dose of treatment after index date														
VKA	193/10705	2.42	1			1			1			1		
Dabigatran 75-110	47/3356	2.07	0.85	0.59-1.22	0.37	0.84‡	0.57-1.22	0.36	0.81	0.54-1.21	0.30	0.94	0.57-1.57	0.82
Dabigatran 150	10/1014	1.41	0.59	0.28-1.26	0.17	0.57‡	0.26-1.23	0.15	0.54	0.25-1.21	0.14	0.67	0.27-1.65	0.38
Rivaroxaban 10-15	14/731	2.84	0.93	0.48-1.80	0.82	0.90‡	0.45-1.79	0.77	0.85	0.41-1.77	0.67	0.98	0.45-2.14	0.95
Rivaroxaban 20	28/1604	2.47	1.24	0.75-2.07	0.40	1.14‡	0.68-1.93	0.62	1.17	0.68-2.01	0.58	1.40	0.72-2.70	0.32

IQR: interquartile range; PY: person-years; HR: hazard ratio; CI: confidence interval; VKA: vitamin K antagonist

*Conditional Cox model

†Conditional Cox model adjusting for age and selected covariates using the 'backward elimination' method

‡Selected covariates: age, hypertension, chronic renal impairment, history of arterial disease, HAS-BLED score, concomitant antiplatelet agent and corticosteroid

§Conditional Cox model adjusted for age and all covariates

‖Conditional Cox model adjusted all matching variables and covariates

Comment: matching variables and covariates used in these analyses are listed in the method section of the manuscript

Table 5. Bleeding risk with a median follow-up of 10.0 months (IQR 9.8-10.0) without adjustment for CHA2DS2-VASc and HAS-BLED scores in the study population (N=17,410)

	N(events)/ Ntotal N=17,410	Crude incidence rate per 100 PY	Model 1*			Model 2†			Model 3§			Model 4‖		
			HR	[95% CI]	P-value	HR	[95% CI]	P-value	HR	[95% CI]	P-value	HR	[95% CI]	P-value
Switching status														
No switch	193/10705	2.42	1			1			1			1		
Switch	99/6705	2.15	0.91	0.71-1.17	0.47	0.85‡	0.65-1.11	0.24	0.84	0.64-1.11	0.22	1.04	0.68-1.59	0.87
Type of treatment after index date														
VKA	193/10705	2.42	1			1			1			1		
Dabigatran	57/4370	1.92	0.80	0.58-1.11	0.18	0.75‡	0.53-1.05	0.10	0.74	0.52-1.06	0.10	0.91	0.56-1.48	0.71
Rivaroxaban	42/2335	2.58	1.12	0.75-1.68	0.58	1.04‡	0.69-1.59	0.85	1.02	0.66-1.58	0.92	1.26	0.73-2.16	0.41
Type and dose of treatment after index date														
VKA	193/10705	2.42	1			1			1			1		
Dabigatran 75-110	47/3356	2.07	0.85	0.59-1.22	0.38	0.79‡	0.54-1.17	0.24	0.79	0.53-1.18	0.25	0.96	0.58-1.60	0.88
Dabigatran 150	10/1014	1.41	0.62	0.29-1.32	0.21	0.58‡	0.27-1.27	0.17	0.58	0.26-1.27	0.17	0.75	0.31-1.81	0.52
Rivaroxaban 10-15	14/731	2.84	0.93	0.48-1.80	0.82	0.85‡	0.42-1.72	0.65	0.84	0.40-1.72	0.63	0.99	0.46-2.15	0.98
Rivaroxaban 20	28/1604	2.47	1.26	0.76-2.10	0.38	1.17‡	0.69-1.99	0.55	1.15	0.67-1.97	0.62	1.44	0.75-2.77	0.27

IQR: interquartile range; PY: person-years; HR: hazard ratio; CI: confidence interval; VKA: vitamin K antagonist

*Conditional Cox model

†Conditional Cox model adjusting for age and selected covariates using the 'backward elimination' method

‡Selected covariates: age, chronic renal impairment, history of arterial disease, history of bleeding, concomitant lipid-lowering drug, non-steroidal anti-inflammatory drug and corticosteroid

§Conditional Cox model adjusted for age and all covariates

‖Conditional Cox model adjusted all matching variables and covariates

Comment: matching variables and covariates used in these analyses are listed in the method section of the manuscript

Table 6. Risk of ischemic stroke/systemic embolism and first/recurrent myocardial infarction with a median follow-up of 10.0 months (IQR 9.8-10.0) in the study population (N=17,410)

	N(events)/ Ntotal N=17,410	Crude incidence rate per 100 PY	Model 1*			Model 2†			Model 3I			Model 4#		
			HR	[95% CI]	P-value	HR	[95% CI]	P-value	HR	[95% CI]	P-value	HR	[95% CI]	P-value
Ischemic stroke/systemic embolism														
Switching status														
No switch	92/10705	1.15	1			1	Ref	-	1			1		
Switch	48/6705	1.04	0.97	0.66-1.40	0.85	1.09‡	0.70-1.70	0.71	1.22	0.74-2.00	0.44	1.02	0.55-1.90	0.94
Type of treatment after index date														
VKA	92/10705	1.15	1			1	Ref	-	1			1		
Dabigatran	32/4370	1.08	1.10	0.70-1.73	0.70	1.49§	0.87-2.56	0.15	1.67	0.90-3.10	0.11	1.36	0.68-2.73	0.39
Rivaroxaban	16/2335	0.98	0.75	0.39-1.45	0.39	0.66§	0.30-1.45	0.30	0.70	0.31-1.62	0.41	0.52	0.19-1.39	0.19
First/recurrent myocardial infarction														
Switching status														
No switch	102/10705	1.27	1			1	Ref	-	1			1		
Switch	65/6705	1.41	1.10	0.80-1.53	0.55	1.03**	0.71-1.48	0.89	0.99	0.68-1.46	0.97	0.93	0.55-1.59	0.80
Type of treatment after index date														
VKA	102/10705	1.27	1			1	Ref	-	1			1		
Dabigatran	48/4370	1.62	1.31	0.88-1.93	0.19	1.21††	0.79-1.84	0.38	1.16	0.74-1.84	0.51	1.09	0.61-1.94	0.78
Rivaroxaban	17/2335	1.04	0.76	0.41-1.39	0.37	0.67††	0.35-1.28	0.22	0.68	0.34-1.39	0.29	0.64	0.28-1.43	0.27

IQR: interquartile range; PY: person-years; HR: hazard ratio; CI: confidence interval; VKA: vitamin K antagonist

*Conditional Cox model

†Conditional Cox model adjusting for age and selected covariates using the 'backward elimination' method

‡Selected covariates: age, heart failure, diabetes, chronic renal impairment, hypertension, history of arterial disease, HAS-BLED score, concomitant antiarrhythmic agent

§Selected covariates: age, heart failure, diabetes, chronic renal impairment, history of arterial disease, HAS-BLED score, concomitant antiarrhythmic agent

ICConditional Cox model adjusted for age and all covariates

#Conditional Cox model adjusted all matching variables and covariates

**Selected covariates: age, heart failure, diabetes, hypertension, chronic renal impairment, history of bleeding, alcohol-related hospitalisation, CHA2DS2-VASc and HAS-BLED scores, concomitant non-steroidal anti-inflammatory agent

††Selected covariates: age, hypertension, chronic renal impairment, history of bleeding, alcohol-related hospitalisation, HAS-BLED score, concomitant non-steroidal anti-inflammatory agent

Comment 1: matching variables and covariates used in these analyses are listed in the method section of the manuscript

Comment 2: due to a low number of events, we did not presented results according to dose of non-vitamin K antagonist oral anticoagulants

Table 7. Risk of composite events (bleeding, ischemic stroke/systemic embolism, myocardial infarction, and death) with a median follow-up of 10.0 months (IQR 9.8-10.0) in the study population (N=17,410)

	N(events)/ Ntotal N=17,410	Crude incidence rate per 100 PY	Model 1*			Model 2†			Model 3§			Model 4‖		
			HR	[95% CI]	P-value	HR	[95% CI]	P-value	HR	[95% CI]	P-value	HR	[95% CI]	P-value
Switching status														
No switch	650/10705	8.21	1			1			1			1		
Switch	326/6705	7.15	0.90	0.79-1.04	0.16	0.89‡	0.77-1.03	0.11	0.89	0.77-1.04	0.13	0.89	0.72-1.09	0.25
Type of treatment after index date														
VKA	650/10705	8.21	1			1			1			1		
Dabigatran	212/4370	7.20	0.91	0.77-1.09	0.30	0.90‡	0.76-1.08	0.27	0.91	0.76-1.09	0.30	0.90	0.72-1.14	0.38
Rivaroxaban	114/2335	7.07	0.89	0.70-1.13	0.33	0.86‡	0.67-1.10	0.24	0.86	0.67-1.11	0.24	0.85	0.64-1.14	0.29
Type and dose of treatment after index date														
VKA	650/10705	8.21	1			1			1			1		
Dabigatran 75-110	184/3356	8.21	0.98	0.81-1.18	0.84	0.96‡	0.79-1.16	0.66	0.97	0.79-1.18	0.74	0.95	0.75-1.21	0.70
Dabigatran 150	28/1014	3.98	0.63	0.40-0.98	0.04	0.67‡	0.42-1.06	0.08	0.66	0.41-1.05	0.08	0.65	0.40-1.06	0.09
Rivaroxaban 10-15	50/731	10.27	1.04	0.72-1.50	0.83	1.03‡	0.70-1.49	0.90	1.03	0.70-1.50	0.88	1.01	0.68-1.52	0.95
Rivaroxaban 20	64/1604	5.68	0.79	0.57-1.09	0.15	0.76‡	0.55-1.05	0.10	0.75	0.54-1.05	0.09	0.74	0.51-1.07	0.11

IQR: interquartile range; PY: person-years; HR: hazard ratio; CI: confidence interval; VKA: vitamin K antagonist

*Conditional Cox model

†Conditional Cox model adjusting for age and selected covariates using the 'backward elimination' method

‡Selected covariates: age, diabetes, hypertension, HAS-BLED score, concomitant antiplatelet, lipid lowering and gastro-protective agents, digitalis glycosides, and oral corticosteroids

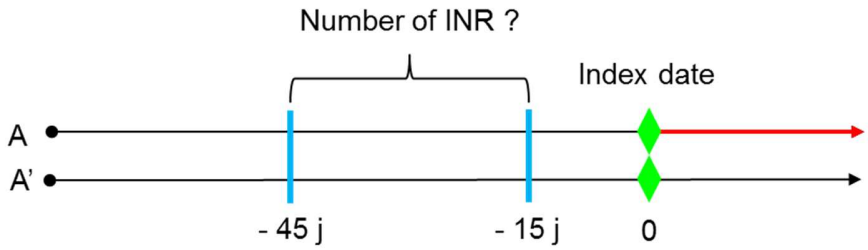
§Conditional Cox model adjusted for age and all covariates

‖Conditional Cox model adjusted all matching variables and covariates

Comment: matching variables and covariates used in these analyses are listed in the method section of the manuscript

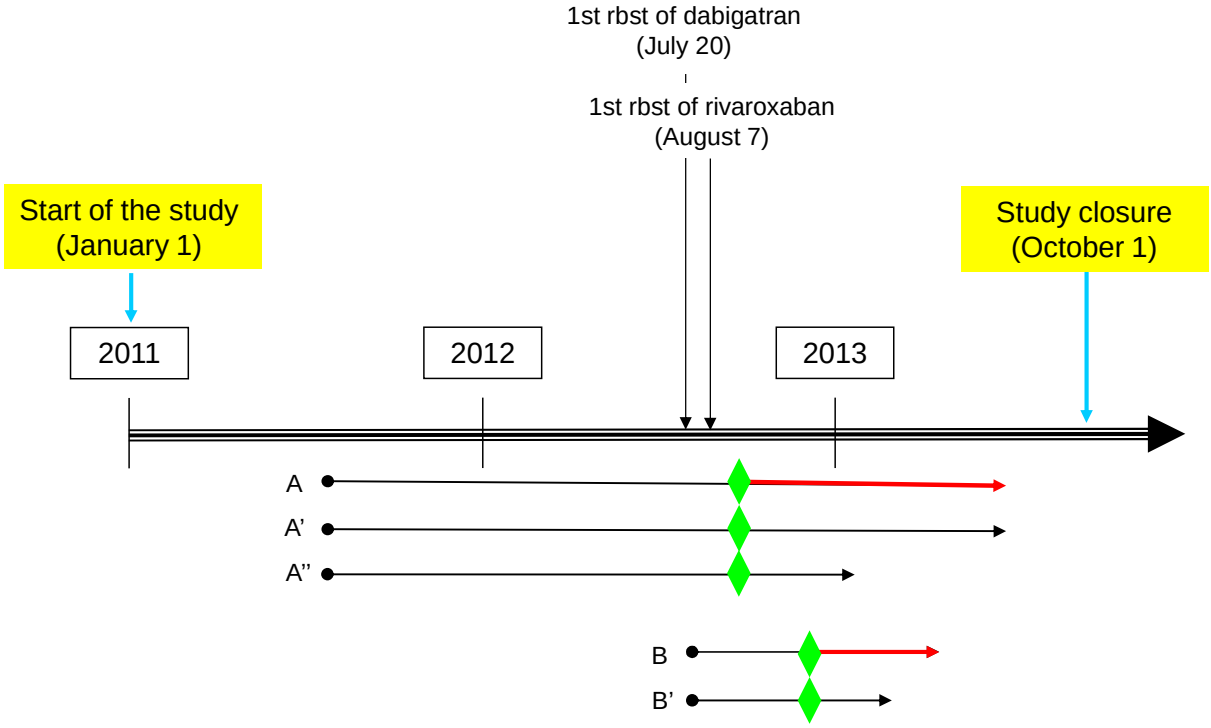
Figures

Figure 1. Definition of the number of INR



Comment: matching on the number of INR over 30 days and 15 days before the index date allows to take into account the fact that NOAC may be preferentially prescribed to individuals most at risk of bleeding. We did not consider the INR number during the 15 days before the index date, since it was assumed that switchers probably would have had at least one within these days and 15 days would be more than enough to switch (the half-life of VKA does not exceed 2 days).

Figure 2. Study design



Individuals A/A'A'' (matched ratio 1:2) and B/B' (matched ratio 1:1) are matched.
A and B are switchers; A', A'', and B' are non-switchers.
Black horizontal line represents VKA exposure; red horizontal line represents NOAC exposure.
Green diamond represents index date.
Rbst : reimbursement.