SUPPLEMENTAL MATERIAL

Supplemental Methods

Details/definitions of switching treatment, discontinuation and drug coverage:

- A switch was defined as a dispensation of another anticoagulant molecule recorded after initiation of the studied anticoagulant treatment. Date of switch (and end of follow-up) was the date of the first dispensation of the other anticoagulant molecule.
- A patient was considered to have discontinued if >30 days had elapsed after the coverage by the last dispensation of anticoagulant treatment without refilling it. If hospitalization occurred within this period, the length of the hospital stay was deducted from the number of days without refilling of the treatment. For patients treated with VKAs, international normalized ratio (INR) testing realized during a private hospitalization was counted as a VKA dispensation. INR testing was used as a proxy of a VKA prescription only to extend VKAs treatment exposure, but it was not used as an index date. Date of discontinuation was the last day covered by the last dispensation of studied NOACs treatment.
- NOACs drug coverage was derived based on the recommended dose. The median number of coverage days was calculated in the VKAs patient population after data extraction, for patients with at least two dispensations of VKAs treatment (with the same CIP code) between 2014 and 2016.

Additional adjustment analyses performed:

Three additional comparative methods were performed:

- Using a modified adjustment approach: comparison of outcomes adjusted for confounding factors, using a stepwise selection of variables. First, all known and identified confounding factors were included in a univariate model (Fine and Gray or Cox model) to determine the p-value between the covariate ant the outcome, and to check the proportionality assumption. All confounding factors with p-value <20% were included in the "full model", except of the covariate was collinear with other confounding factors. The full model was a multivariate model including all confounding factors significant at the 20% level in the univariate model, and the following factors, which were forced: exposure, age at index date, gender, type of prescriber and comorbidity scores. Then, a manual backward method was used, i.e. step-by-step removal of non-statistically significant covariates (for categorical variable, p-value associated with the inclusion of all modality of variable in the model) at the 5% level (from the largest to the smallest p-value). The confounding factors were free-access-to-care status (where 100% of healthcare expenses are covered for people whose financial resources are below a threshold), comorbid conditions in the 24 months before index date, and drugs dispensed within 3 months before index date. The choice was made to keep all variables not respecting the proportionality assumption without modification in the model, checking that the inclusion in the model of interaction between time function (log) and the variable did not alter the relation between exposure and outcome.

- Using a PS adjusted approach: comparison of outcomes adjusted on propensity scores. Risk of effectiveness, safety, and mortality have been studied using the same method as for the main analysis (cox or Fine and Gray models). The log-linearity assumption was checked for the PS and if the assumption was violated, a model with the PS categorized in deciles was used. If the proportionality assumption was violated for the PS, the PS was still kept in the model without any modification, after verifying that the inclusion of interaction between time and PS did not sharply modified the relation between exposure and outcome.

- Using a High-Dimensional Propensity Scores (HdPS) matching approach. Comparison of outcomes was performed using hdPS, to try to improve the propensity score's performance by including

an important number of confounders within the score model. These confounders were identified in claims data thanks to an algorithm developed by Schneeweiss et al. So, in addition to the socio-demographic covariables, hdPS permits to take account of the health history of patient in the year prior to exposure through the following dimensions:

- Outpatient drug dispensation,
- Outpatient act (CCAM codes),
- Outpatient biology,
- Outpatient visits and consultations,
- Physician claims codes for inpatient and outpatient diagnostic codes,
- Hospitalization discharge data for inpatient diagnostic codes,
- Hospitalization discharge data for inpatient procedure codes.

Supplemental tables

Table I. Diagnoses used for identification of stroke and systemic thromboembolic events (effectiveness outcome) or major bleeding (safety outcome).

ICD-10 description	ICD-10 codes for hospitalizations
Ischemic stroke or not specified	
Cerebral infarction (except cerebral infarction due to cerebral venous thrombosis, non-pyogenic)	I63 (except I636)
Stroke, not specified as hemorrhage or infarction	I64
Hemorrhagic stroke	
Subarachnoid hemorrhage	I60
Intracerebral hemorrhage	I61
Other non-traumatic intracranial hemorrhage	I62
Systemic thromboembolic events	
Arterial embolism and thrombosis	I74
Intracranial bleeding	
Intracranial hemorrhage	I60, I61, I62
Epidural hemorrhage	S064
Traumatic subdural hemorrhage	S065
Traumatic subarachnoid hemorrhage	S066
Gastric duodenal and rectal bleeding	
Esophageal varices with bleeding	I850
Gastro-esophageal laceration-hemorrhage syndrome	K226
Gastric ulcer/duodenal ulcer/peptic ulcer/gastrojejunal ulcer with hemorrhage	K250, K252, K254, K256, K260, K262, K264, K266, K270, K272, K274, K276, K280, K282, K284, K286
Acute hemorrhagic gastritis	K290
Hemorrhage of anus and rectum	K625
Hematemesis	K920
Melena	K921
Gastrointestinal hemorrhage, unspecified	K922
Acute posthemorrhagic anemia	D62

ICD-10 description	ICD-10 codes for hospitalizations
Intraocular bleeding	
Retinal hemorrhage	H356
Vitreous hemorrhage	H431
Vitreous hemorrhage in diseases classified elsewhere	H450
Otorrhagia	H922
Pericardic	
Hemopericardium, not elsewhere classified	I312
Respiratory bleeding	
Hemothorax	J942
Hemorrhage from respiratory passages	R04
Haemoperitoneum	K661
Intra articular bleeding	
Hemarthrosis	M250
Uterine and vaginal bleeding	
Recurrent and persistent hematuria	N02
Other specified abnormal uterine and vaginal bleeding	N938
Abnormal uterine and vaginal bleeding, unspecified	N939
Postmenopausal bleeding	N950
Unspecified hematuria	R31
Other bleeding	
Hemorrhage, not elsewhere classified	R58
Traumatic secondary and recurrent hemorrhage	T792

Table II: Description of 1:n matching (n variable, and n≤3) on propensity score for apixaban versus VKAs, apixaban versus rivaroxaban, and apixaban versus dabigatran OAC-naive cohorts.

	Apixaban and VKAs n (%)	**Apixaban and rivaroxaban** n (%)	**Apixaban and dabigatran** n (%)
Total matched patients treated with apixaban	68,208 (77.9)	81,759 (93.4)	21,245 (24.3)
Matched patients treated with apixaban			
Matching 1:n with n=			
1	39,563 (58.0)	63,680 (77.9)	21,245 (100.0)
2	17,940 (26.3)	17,867 (21.9)	0 (0.0)
3	10,705 (15.7)	212 (0.3)	0 (0.0)
Total matched patients treated with:	**VKAs** 107,558 (95.5)	**Rivaroxaban** 100,050 (99.987)	**Dabigatran** 21,245 (100.0)

OAC, oral anticoagulant; VKA, vitamin K antagonist.

Table III: Confounding factors for apixaban and VKAs, apixaban and rivaroxaban, and apixaban and dabigatran matched cohorts with weighting

	apixaban and VKA		apixaban and rivaroxaban		apixaban and dabigatran	
	Apixaban n=68,208	**VKAs n=68,208***	**Apixaban n=81,759**	**Rivaroxaban n=81,759****	**Apixaban n=21,245**	**Dabigatran n=21,245**
Gender, %						
Male	49.7	49.9	52.5	52.6	53.9	54.1
Age at index date (in years), Mean	76.4	76.3	73.9	73.8	72.7	72.7
Covered by CMUC, %	2.4	2.4	2.4	2.4	2.9	2.9
Type of prescriber of the index medication, %						
General practitioners	21.9	22.6	18.8	18.8	22.2	22.5
Office-based cardiologists	21.8	21.7	34.5	34.5	33.3	32.8
Other office-based specialties	2.6	2.5	2.4	2.4	2.1	2.1
Hospital-based physicians	52.6	52.0	43.4	43.4	41.5	41.6
Unknown	1.1	1.1	1.0	1.0	0.9	1.0
Comorbidities, %						
Coronary artery disease	10.2	10.5	7.8	7.8	6.0	6.1
Obesity	10.6	10.6	9.1	9.0	9.1	9.1
Anemia	7.0	7.5	5.0	5.1	4.2	4.2
Malnutrition	10.0	10.5	7.2	7.3	5.6	5.7
CHA_2DS_2-VASc score, %						
0	3.8	3.8	6.6	7.0	8.6	8.9
1	8.8	9.0	12.9	13.4	14.5	14.2
2	16.6	16.6	20.2	20.8	20.6	21.0
3	24.3	24.0	24.7	24.6	23.4	23.5
4	20.9	20.8	17.7	17.4	16.2	16.0
≥5	25.6	25.8	17.9	16.8	16.7	16.4
Modified HAS-BLED score, %						
0	2.7	2.8	3.8	3.9	4.9	4.9
1	17.3	17.3	21.8	22.0	23.7	23.9
2	37.8	37.5	41.2	40.9	39.4	39.7
3	29.9	29.6	25.3	25.2	23.8	23.4
≥4	12.3	12.8	8.0	8.1	8.1	8.1
Charlson score, %						
0	1.1	1.1	1.9	2.0	2.8	2.8
1-2	10.2	10.4	16.6	16.8	19.3	19.4
3-4	34.6	34.3	39.8	39.5	40.1	40.0
≥5	54.2	54.2	41.7	41.6	37.8	37.8
Co-dispensed drugs within the three months before index date, %						
Heparin group						
1 and +	2.9	3.0	2.6	2.5	2.5	2.4
Platelet aggregation inhibitors						
0	55.5	55.2	57.9	58.0	61.1	61.0
1-2	19.4	19.5	17.5	17.4	16.5	16.4
3 and +	25.1	25.2	24.6	24.6	22.4	22.6
Other antithrombotic agents						
1 and +	0.8	0.8	0.7	0.7	0.9	0.9

	apixaban and VKA		apixaban and rivaroxaban		apixaban and dabigatran	
	Apixaban n=68,208	**VKAs n=68,208***	**Apixaban n=81,759**	**Rivaroxaban n=81,759** **	**Apixaban n=21,245**	**Dabigatran n=21,245**
NSAIDs						
1 and +	12.8	12.9	14.7	14.7	15.9	16.1
Strong inhibitors of both CYP3A4 and P-gp						
1 and +	0.6	0.6	0.5	0.5	0.5	0.5
HIV protease inhibitors						
1 and +	0.0	0.0	0.0	0.0	0.0	0.0
Anticonvulsant strong inducer of hepatic enzymes						
1 and +	0.6	0.6	0.5	0.5	0.5	0.5
Co-dispensing or co-prescription of 2 platelet aggregation inhibitors, %	2.7	2.7	2.0	2.0	1.6	1.7

* From 107,558 VKAs patients recomputed due to matching 1:n, 39,563 Apixaban patients matched 1:1, 17,940 Apixaban patients matched 1:2 and 10,705 Apixaban patients matched 1:3

** From 100,050 Rivaroxaban patients recomputed due to matching 1:n, 63,680 Apixaban patients matched 1:1, 17,867 Apixaban patients matched 1:2 and 212 Apixaban patients matched 1:3

CHA_2DS_2-VASc, congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke, transient ischemic attack or thromboembolism, vascular disease, age 65–74 years, sex category; CUMC, Couverture maladie universelle Protection Complémentaire; CYP, cytochrome P450; HIV, human immunodeficiency virus; P-gp, P-glycoprotein; VKA, vitamin K antagonist.

Supplemental figures

Figure I: Balance of covariates before and after matching using absolute weighted standardized difference for a) apixaban and VKAs, b) apixaban and rivaroxaban, and c) apixaban and dabigatran cohorts

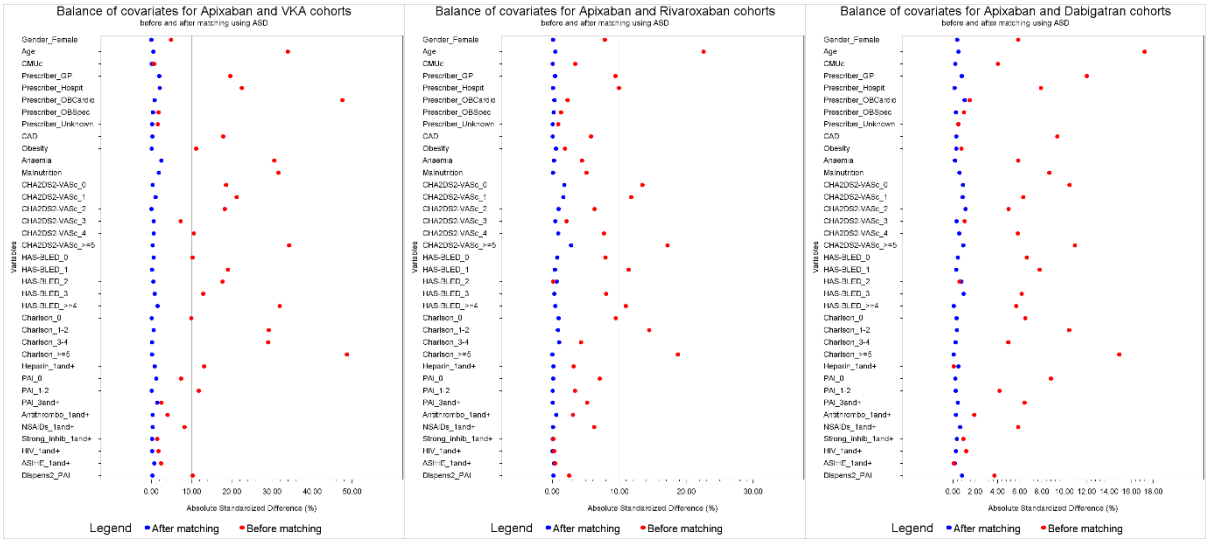
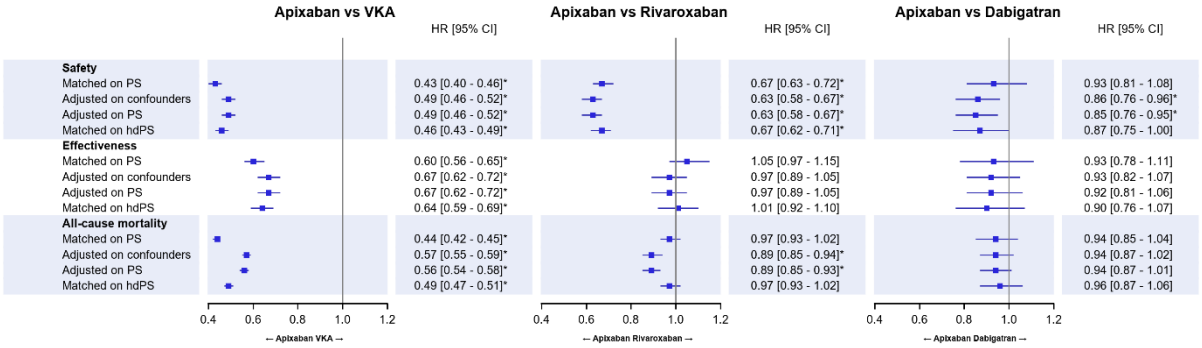


Figure II. Forest plots of the results of the main (PS-matched) and additional (adjusted on confounders, adjusted on PS, and matched on HdPS) analyses

To support the robustness of the main comparative analysis (i.e. PS-matching approach), three **additional comparative methods** were performed:

- Using a modified adjustment approach: comparisons of outcomes adjusted for confounding factors, using a stepwise selection of variables.
- Using a PS adjusted approach: comparison of outcomes adjusted on propensity scores.
- Using an High-Dimensional Propensity Scores (HdPS) matching approach: comparisons of outcomes were performed using HDPS.

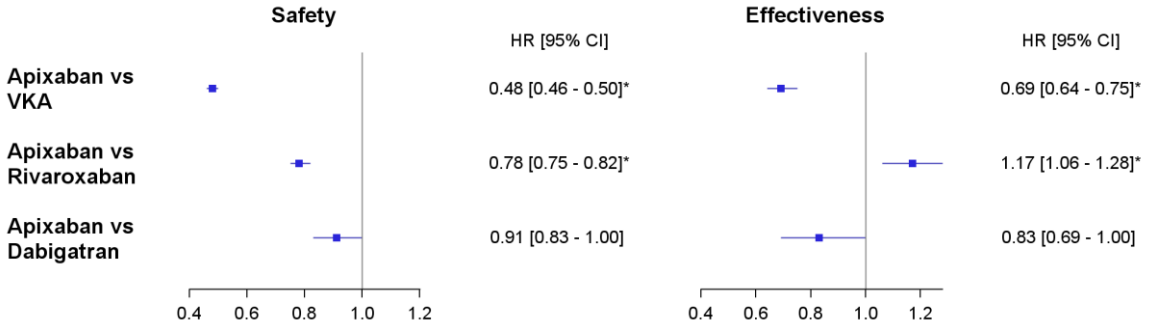


Safety: major bleeding events leading to hospitalization, and identified from main hospital discharge diagnoses; effectiveness: stroke and STE identified from main hospital discharge diagnoses
For the comparison between apixaban and VKAs, Fine and Gray models were used as the mortality was high in the VKAs cohort (>10%). For the other comparisons, Cox models were used.
In case of violation of the proportionality assumption, the direction of the association was not modified after inclusion of the interaction between time function and exposure.

Figure III. Forest plot presenting the results of the sensitivity analysis (comparisons matched on propensity scores with modified definitions of the outcomes)

To support the validity of the definitions used to identify outcomes, sensitivity analysis was conducted with modified outcomes definitions:

- Expanding the safety outcome definition to associated diagnoses of hospital stays and blood transfusions.
- Removing 'hemorrhagic stroke' from the definition of effectiveness events (i.e. restricted to 'ischemic stroke or not specified" and "systemic thromboembolism events').



Safety: both main and associated diagnoses of hospital stays for major bleeding events and transfusion (from medical procedures codes); effectiveness: main diagnoses of hospital stays for stroke and STE (not considering the diagnoses of hemorrhagic stroke).
In case of violation of the proportionality assumption, the direction of the association was not modified after inclusion of the interaction between time function and exposure.

We have not specifically computed the risks related to the different sites of hemorrhagic stroke (ICH vs SAH vs SDH) as some numbers were very low, as shown by the table below, and as the validity of detailed diagnoses is questionable (for instance, in some elderly patients, no radiologic investigation was performed when the overall health status was poor).

	Apixaban	**VKA**	**Rivaroxaban**	**Dabigatran**
ICH	140	595	244	22
SAH	43	144	48	7
SDH	115	398	115	21