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RESEARCH

Prevalence and bleeding risk associated with the concomitant use of direct oral anticoagulants and antiarrhythmic drugs in patients with atrial fibrillation, based on the French healthcare insurance database

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Abstract

Purpose Pharmacokinetic interactions exist between apixaban or rivaroxaban, and CYP3A4 and P-glycoprotein inhibitors such as amiodarone, verapamil and diltiazem. We aimed to estimate the prevalence of exposure to this drug-drug association (DDA) and to assess the bleeding risk associated in patients with atrial fibrillation (AF).

Methods We conducted a cohort study using a representative 1/97th sample of the French healthcare insurance database between 2014 and 2019. Patients with AF receiving apixaban or rivaroxaban were included and followed-up until hospitalization for bleeding, death, discontinuation of apixaban or rivaroxaban, exposure to strong CYP3A4 inhibitor, or until December 31st 2019, whichever came first. Primary outcome was hospitalization for bleeding registered as primary diagnosis. The association between the exposure to the DDA and hospitalization for bleeding was evaluated as a time-dependent variable in Cox model.

Results Between 2014 and 2019, the AF population under apixaban or rivaroxaban represented 10,392 patients. During the study period, the annual average prevalence of DDA exposure in this population was 38.9%. Among the 10,392 patients, 223 (2.1%) were hospitalized for bleeding, of which 75 (33.6%) received the association and 148 (66.4%) received apixaban or rivaroxaban alone. There was no association between DDA exposure and risk of hospitalization for bleeding (aHR = 1.19, [95% CI: 0.90, 1.58]). Age (HR 1.03 [1.02, 1.05]) and male gender (HR 1.72 [1.28, 2.30]) were associated with an increased risk of hospitalization for bleeding.

Conclusion Exposure to antiarrhythmic drugs was not associated with an increased risk of hospitalization for bleeding in patients with AF under rivaroxaban or apixaban.

Keywords Pharmacovigilance · Drug interactions · Adverse drug reactions · Anticoagulants · Anti-arrhythmia agents

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Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia in adults [1]. It concerns about 1% of the French population [2]. The European Society of Cardiology recommends, in its 2020 guidelines for management of AF, the use of direct oral anticoagulant (DOAC) as first-line therapy for stroke prevention [1]. Many AF patients also take antiarrhythmic drugs (AAD) to control heart rhythm or heart rate.

Pharmacokinetic interactions exist between two DOAC, apixaban and rivaroxaban, and other medications that inhibit their metabolic or absorption pathways, such as CYP3A4 and P-glycoprotein (P-gp) inhibitors [3]. Pharmacokinetic studies have shown that the concomitant use of these two classes of drugs resulted in an increased plasmatic level of apixaban or rivaroxaban, which could lead to a potential risk of bleeding [4, 5]. Therefore, it is recommended to avoid the concomitant use of DOAC and strong CYP3A4 inhibitors but there are no clear recommendations for moderate CYP3A4 inhibitors (defined as a drug causing an increase between 2 and five-fold in the plasma area under curve value [6]). Among AAD, amiodarone, verapamil and diltiazem are P-gp and moderate CYP3A4 inhibitors. Some studies have shown that up to 20% of AF patients received simultaneously DOAC and one of these AAD [7–9]. The real-life clinical relevance of this drug-drug association (DDA) remains unclear.

The aim of this study was i/ to estimate the prevalence of simultaneous exposure to apixaban or rivaroxaban and P-gp and moderate CYP3A4 inhibitors given as anti-arrhythmic in AF patients and ii/ to assess the bleeding risk associated with this DDA, using pharmacy drug dispensing and hospital data from a representative subsample of the French healthcare insurance database.

Methods

This study was conducted on a cohort of AF patients exposed to apixaban or rivaroxaban and focused on the association between their concomitant exposure to the amiodarone, verapamil or diltiazem between 2014 and 2019.

Study design and data sources

This study was performed using the EGB (*échantillon généraliste des bénéficiaires*), a 1/97th random sample of the French healthcare insurance database that contains data for about 700,000 individuals [10]. The EGB is a pseudo-anonymized database representative of the French population containing demographic and medical information.

Socio-demographic information available for each patient were sex and year of birth. The medical data included status regarding long-term disease (LTD) eligible for 100% reimbursement and exhaustive information on care received and submitted to reimbursement. It contained drugs prescribed by a healthcare professional and dispensed in retail pharmacies identified according to the *Anatomical, Therapeutic and Chemical* (ATC) drug code system. Data included quantity dispensed, date of prescription, date of dispensing, and specialty of the prescriber. It also contained information on hospital stays collected by the French Hospital discharge database [11], which included dates of stay and discharge diagnoses, coded according to the *International Classification of diseases, Tenth Revision* (ICD-10).

Study population

Individuals eligible for inclusion in the study were those included in the EGB database, identified with AF, aged 18 years and over, and with at least one prescription of apixaban or rivaroxaban between 2014 and 2019.

A patient was considered to have AF, if he had at least one diagnosis of AF (code I48 of the ICD-10) as LTD in the calendar year or as a hospital discharge diagnosis in the five previous years. This definition was applied for all calendar years between 2014 and 2019. A patient was eligible for inclusion in the cohort from the year of the first detection of FA.

We excluded patients less than 18 years old since those drugs were not recommended or required special dose adjustments in this population, and patients receiving strong P-gp and CYP3A4 inhibitors on the date of inclusion because their co-administration with DOAC is not recommended due to an increased risk of bleeding [12].

We considered the drugs below as strong inhibitors: clarithromycin, erythromycin, telithromycin, itraconazole, ketoconazole, posaconazole, voriconazole, ritonavir, and cobicistat.

Each patient's inception date was the date of the first dispensation of apixaban or rivaroxaban identified in the database during their eligible study period. All patients were followed-up from the inception date until outcome or censoring due to death, prescription of strong P-gp and CYP3A4 inhibitors, first discontinuation of apixaban or rivaroxaban or the end of the study period (December 31st 2019).

Exposure definition

This study focused on the exposure to a DDA between apixaban or rivaroxaban and amiodarone, verapamil or diltiazem. Considering the pharmacokinetics properties and the rapid onset of the P-gp and CYP3A4 inhibition [13, 14], patients were considered as exposed to the DDA if they simultaneously received both drug classes for at least one day.

The duration of exposure to each drug class was estimated as the dispensed drug quantity divided by its daily dose. The average recommended dosage of the drugs studied was

apixaban 10 mg/day, rivaroxaban 20 mg/day, amiodarone 200 mg/day, verapamil 240 mg/day and diltiazem 240 mg/day. The daily dose of each drug was estimated by dividing the average recommended dosage by two in order to consider reduced dosage for specific patients (i.e. older patients with low-body weight or mild renal failure and apixaban).

For each dispensation, we assumed that drug intake started on the dispensing day and all dispensed quantity was consumed between two refills (no leftovers allowed).

Outcomes

The primary endpoint was hospitalization for bleeding, identified using ICD-10 codes registered as primary diagnosis. The codes were selected based on published studies [5, 7, 15] and reviewed by an expert group (eTable 1). For each patient, only the first episode of hospitalization during the follow-up was considered. In our secondary analysis, we focused on the type and severity of bleeding (hospital death).

Statistical analysis

Prevalence of the exposure to the DDA

The yearly prevalence of the DDA was estimated as the yearly number of individuals exposed to the DDA divided by the yearly number of individuals with AF exposed to apixaban or rivaroxaban. The index date of exposure to a drug was considered to be the day of drug dispensing. The trend in the evolution of the prevalence during the study period was assessed using a Chi-squared test for trend. To get complementary perspectives on the exposure to this DDA, its prevalence was studied on two levels: in our study population and as a person-time exposed prevalence in our cohort.

Evaluation of the bleeding risk associated with the exposure to the DDA

Baseline characteristics (age, sex, comorbidities, CHA_2DS_2-VASc score [1] and the specialty of the first prescriber of apixaban or rivaroxaban) were collected at inception. Patients with comorbidities were identified using algorithms predefined by the French Healthcare system for the database [16].

Differences between patients exposed or not to the DDA were assessed using *t*-test for continuous variables and chi-square-test for categorical variables.

The primary endpoint was measured as a time-to-event analysis of hospitalization for bleeding.

Because drug prescription may evolve during follow-up, we used a Cox model with time-dependent exposure to the DDA, to estimate hazard ratios (HR) for hospitalization and their confidence intervals. HR were adjusted for age, sex and comorbidities as fixed potential cofounders evaluated at baseline. CHA_2DS_2-VASc score was not included because all of its clinical characteristics were already included as individual factors in the model, while prescribers' speciality was not considered as a potential confounder.

To limit potential confounding, the exposure to the following drug classes known to increase the risk of bleeding was also taken into account: nonsteroidal anti-inflammatory drugs, corticosteroids and antiplatelet agents [4, 5, 15, 17]. More specifically, the distribution of the exposure to each of the three classes according to the DDA exposure status was assessed using chi-square-test, or if sample size were insufficient with Fisher exact test. Drug classes with a difference of more than 3% between groups were included in the final model as time-dependent variable.

A sensitivity analysis was performed to assess the robustness of our findings: we added a 7-day overlap to dispensation at the initiation of the AAD to consider a bleeding as possibly related to the DDA.

All analyses were performed using the statistical software R version 3.6 and the statistical significance level was set at $p = 0.05$.

Results

Characteristics of the cohort

Between 2014 and 2019, 10,392 patients were identified in the EGB with AF and at least one prescription of apixaban or rivaroxaban (Fig. 1).

Patient characteristics at inclusion are presented in Table 1. The mean age of the cohort was 76.2 years with 54.3% of males. The median duration of follow-up was 173 days (interquartile range [61–467]).

At inclusion, 4,999 (48.1%) of patients received rivaroxaban and 5,392 (51.9%) apixaban.

The mean CHA_2DS_2-VASc score was 2.68 ± 1.50. This score was significantly higher in the group receiving only apixaban or rivaroxaban.

Patients exposed to the DDA were younger than those not exposed (mean age 74.8 ± 11.1 vs 77.3 ± 11.8, $p < 0.001$) and more frequently males (56.3% vs 52.9%, $p < 0.001$). Concerning comorbidities, they had more often a history of coronary heart disease (23.6% vs 21.0%, $p = 0.003$) and of heart failure (24.3% vs 22.4%, $p = 0.002$), and less often a history of stroke or transient ischemic attack (8.3% vs 13.7%, $p < 0.001$), dementia (4.0% vs 8.0%, $p < 0.001$), cancer (19.9% vs 17.6%, $p = 0.004$) and exposure to antihypertensive drugs (6.3% vs 3.2%, $p < 0.001$).

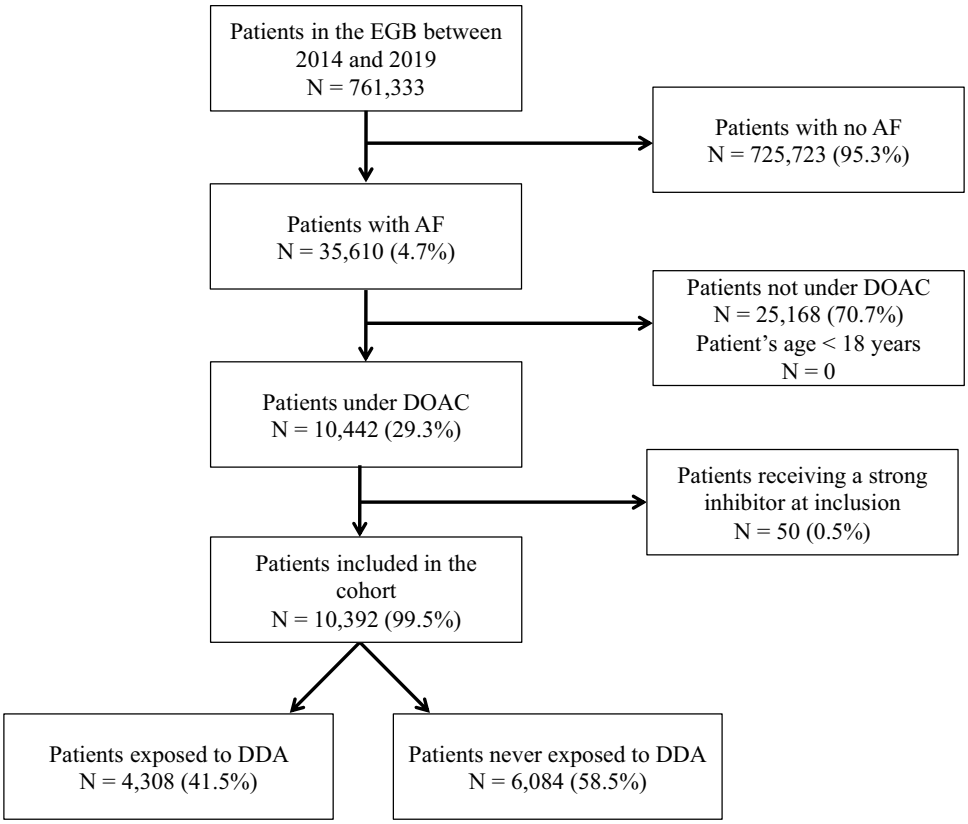

Fig. 1 Flow-chart of the cohort participants. *AF* atrial fibrillation; *DOAC* direct oral anticoagulant; *EGB* "échantillon généraliste des bénéficiaires"; *DDA* drug-drug association between DOAC and antiarrhythmic drugs

At inclusion, apixaban and rivaroxaban were mainly prescribed by general practitioners (61.0%). In the subgroup of patient exposed to the DDA, cardiologists were more frequently involved in the first prescription of apixaban or rivaroxaban (31.1% vs 21.7%, $p < 0.001$).

Prevalence

In the AF population, a significant decrease in the annual prevalence of the DDA was observed over the study period, from 43.6% [95%CI: 40.9, 46.4] in 2014 to 32.4% [95%CI: 31.3, 33.4] in 2019 ($p < 0.001$) (Table 2).

Bleeding in AF population and DDA exposition

Out of the 10,392 patients, 4,308 (41.5%) of patients were exposed to the DDA during the follow-up. Considering the length of the DDA exposure, we estimated the ratio of days during which patients were exposed to the DDA compared to the total days of follow-up in the entire cohort at 27.4% [95%CI: 27.34, 27.43]. The median duration of DDA exposure periods was 98 days (interquartile range [60–197]).

Between 2014 and 2019, 223 (2.2%) patients were hospitalized for bleeding. Out of them, 75 patients were exposed to the DDA (33.6%) (Table 3). In these patients, the median delay between the beginning of exposure to DDA and hospitalisation for bleeding was 74 days (interquartile range [30–192]). The mean duration of hospitalization did not differ significantly, 6.08 ± 10.2 days for patients exposed to the DDA versus 5.45 ± 6.37 days for those not exposed ($p = 0.6$). The mortality rate during hospitalization was 4.48% ($n = 10$), 1 patient died while exposed to DDA and 9 while exposed to apixaban or rivaroxaban only (no statistical difference $p = 0.17$).

We found that exposure to antiplatelet agents differed from more than 3% between patients who bled exposed to DDA or not (respectively 21.3% vs 17.6%, $p = 0.62$). The distribution did not differ for nonsteroidal anti-inflammatory drugs (1.3% vs 2.7%, $p = 0.67$) or corticosteroids (5.3% vs 3.4%, $p = 0.49$).

Therefore, exposure to antiplatelet agents was included in the final model as a time-dependent variable.

There was no significant difference in the risk of hospitalization for bleeding between patients exposed to the DDA compared to those not exposed (HR = 1.19, [95%CI 0.90, 1.58]) (Table 4). The risk of hospitalization for bleeding increased significantly with age (HR = 1.03 per year, [95%CI 1.02, 1.05]), and it was higher for males (HR = 1.72, [95%CI 1.28, 2.30] (Table 4). The results of the sensitivity analysis confirmed those obtained in the primary analysis: exposure to DDA was not significantly associated with a change in the risk of bleeding when adding a 7-day period to consider a patient exposed to the DDA (eTable 2).

Table 1 Characteristics of patients with AF and at least one prescription of apixaban or rivaroxaban in the EGB (N = 10,392), in France between 2014–2019

Characteristics	Total (n = 10,392)	DDA group (n = 4,308)	No DDA group (n = 6,084)	*p-value*
Age, mean ± sd, years	76.2 ± 11.6	74.8 ± 11.1	77.3 ± 11.8	< 0.001
18–49	235 (2.3)	95 (2.2)	140 (2.3)	
50–75	3,975 (38.3)	1,900 (44.1)	2,075 (34.1)	
≥ 75	6,182 (59.5)	2,313 (53.7)	3,869 (63.6)	
Female, No. (%)	4,747 (45.7)	1,882(43.7)	2,865 (47.1)	< 0.001
Prescriber's speciality, No. (%)				< 0.001
General practitioner	6,336 (61.0)	2,414 (56.0)	3,922 (64.5)	
Cardiologist	2,656 (25.6)	1,339 (31.1)	1,317 (21.7)	
Other specialty	671 (6.5)	250 (5.8)	421 (6.9)	
Missing values[a]	729 (7.0)	305 (7.1)	424 (7.0)	
CHA_2DS_2-VASc, mean ± sd	2.68 ± 1.50	2.50 ± 1.44	2.80 ± 1.52	< 0.001
Comorbidities, No. (%)				
Heart failure	2,408(23.2)	1,048 (24.3)	1,360 (22.4)	0.02
Coronary heart disease	2,294 (22.1)	1,014 (23.6)	1,280 (21.0)	0.003
Diabetes mellitus	1,852 (17.9)	768 (17.8)	1,084 (17.8)	1
Prior ischemic stroke or TIA	1,188 (11.4)	356 (8.3)	832 (13.7)	< 0.001
Peripheral vascular disease	904 (8.7)	354 (8.2)	550 (9.0)	0.15
Dementia	658 (6.3)	173 (4.0)	485 (8.0)	< 0.001
Chronic kidney disease	563 (5.4)	217 (5.0)	346 (5.7)	0.16
Cancer	1,970 (19.0)	760 (17.6)	1,210 (19.9)	0.004
Antihypertensive drugs	522 (5.0)	137 (3.2)	385 (6.3)	< 0.001

AF atrial fibrillation, *EGB* "échantillon généraliste des bénéficiaires", *DDA* drug-drug association, here DOAC + AAD, *TIA* transient ischemic attack

[a]Missing values were not included in the chi-square-test; Data presented are those at inclusion

Discussion

Between 2014 and 2019, the annual average prevalence of AAD exposure was 38.9% in the AF population under apixaban or rivaroxaban. Concomitant exposure to apixaban or rivaroxaban and AAD was not associated with an increased risk of hospitalization for bleeding in AF patients.

Pharmacokinetic studies have shown an increase in the blood concentration of DOAC when concomitantly used with P-gp and moderate CYP3A4 inhibitors [18, 19]. Even though this pharmacokinetic interaction seems modest, considering the number of AF patients exposed to this DDA, verifying its safety regarding bleeding risk seemed necessary.

Table 2 Prevalence and number of exposed to DDA in patients with AF receiving apixaban or rivaroxaban between 2014 and 2019 in the EGB in France

	Patients exposed to DDA	Total population	DDA prevalence (%) [95%CI]
2014	545	1,250	43.6 [40.9, 46.4]
2015	1,008	2,269	44.4 [42.4, 46.5]
2016	1,417	3,471	40.8 [39.2, 42.5]
2017	1,820	4,806	37.9 [36.5, 39.2]
2018	2,190	6,344	34.5 [33.6, 35.7]
2019	2,564	7,925	32.4 [31.3, 33.4]

AF atrial fibrillation; *EGB* "échantillon généraliste des bénéficiaires"; *DDA* drug-drug association, here DOAC + AAD

Studies have shown an increased risk of bleeding when DOAC were associated with potential interacting drugs. However they didn't focus on P-gp and moderate CYP3A4 inhibitors and studied simultaneously the effect of multiple inhibitors or were conducted on small samples [4, 7, 20].

Some of the published evidence suggests that this pharmacokinetic interaction does not translate into increased bleeding risk. A systematic review of pivotal trials in AF patients under DOAC showed a relative risk of bleeding of 0.91 [95% CI 0.77, 1.07] when concomitantly exposed to amiodarone compared to DOAC alone [21]. A case–control study nested in a cohort of new users of DOAC in England [5] found no significant increase in bleeding risk when simultaneously exposed to amiodarone (HR 0.67, [95% CI 0.28, 1.59]), verapamil (HR 1.76, [95% CI 0.58, 5.35]) or diltiazem (HR 0.26, [95% CI 0.11, 0.61]). However, in those two studies, dabigatran has also been included even though it has known interactions, through P-glycoprotein, with amiodarone and verapamil requiring dosage adaptations [12]. A US population-based cohort study was conducted to evaluate

Table 3 Bleeding outcome by type of bleed and exposure to the DDA and death during hospitalization

	Patient with DDA	Patient without DDA	Total
All bleeding, No. (%)	75 (33.6)	148 (66.4)	223
Intracranial bleeding	10 (40.0)	15 (60.0)	25
Gastro-intestinal bleeding	31 (28.2)	79 (71.8)	110
Uro-gynecological bleeding	12 (33.3)	24 (66.7)	36
Other bleeding	22 (42.3)	30 (57.7)	52
Death during hospitalization, No. (%)	1 (10.0)	9 (90.0)	10
Total of follow-up days for all patients, No. (%)	1,029,576 (27.4)	2,729,492 (72.6)	3,759,068

DDA drug-drug association

the overall bleeding risk in AF patients receiving DOAC with diltiazem or verapamil compared to amlodipine and to metoprolol. They showed no difference for rivaroxaban with diltiazem or verapamil vs amlodipine (HR 0.99, [95% CI 0.71, 1.38]) or vs metoprolol (HR 0.76, [95% CI 0.55, 1.06]) and for apixaban with diltiazem or verapamil vs amlodipine (HR 0.89, [95% CI 0.49, 1.63]) or vs metoprolol (HR 0.78, [95% CI 0.45, 1.36]) [22].

A case–control study found that the concomitant use of diltiazem in AF patients receiving rivaroxaban was not associated ($p = 0.34$) with an increased risk of major and clinically relevant non-major bleeding [23].

Our study confirms that this DDA concerns a large portion of AF patients and shows no association between bleeding risk and exposure to this DDA using real-life data in France.

Regarding the increased risk of bleeding for male patient with AF, it has already been observed in two other studies with DOAC [24, 25] and with other oral anticoagulants such as vitamin-K antagonist [26], but a clear association is yet to be proven. Moreover, many studies conducted on the risk of bleeding were built with a propensity-score matching [4, 7, 27] preventing any conclusion on the relationship between gender and bleeding risk.

The nature of the data from the EGB has led to some approximation in our study. First, regarding the definition of exposure to drugs, some assumptions had to be made. We had no direct measure of the drug consumption or treatment adherence, every pill dispensed was considered as consumed by patients between two refills. Also, having no information on the actual dosage prescribed by physicians at each dispensation, we had to use an estimated daily dosage of drugs in order to quantify the exposure periods. These two assumptions may have led to an overestimation of the number and duration of drug and DDA exposure periods. Measuring drug exposure

Table 4 Cox regression analysis on the occurrence of hospitalization for bleeding, in France, between 2014–2019 from the EGB (N = 10,392)

	Model without drugs interfering with bleeding risk		Final model including exposure to antiplatelet agents	
	Hazard ratios [95%CI]	*p-value*	Hazard ratios [95%CI]	*p-value*
Male sex	1.75 [1.30, 2.34]	< 0.001	1.72 [1.28, 2.30]	< 0.001
Age (per year)	1.03 [1.02, 1.05]	< 0.001	1.03 [1.02, 1.05]	< 0.001
Heart failure	1.12 [0.82, 1.54]	0.47	1.13 [0.82, 1.55]	0.46
Coronary heart disease	1.41 [1.04, 1.90]	0.03	1.22 [0.89, 1.67]	0.22
Diabetes mellitus	1.12 [0.81, 1.56]	0.50	1.10 [0.79, 1.52]	0.59
Ischemic stroke or TIA	0.98 [0.66, 1.47]	0.93	0.97 [0.65, 1.45]	0.88
Peripheral vascular disease	1.23 [0.80, 1.89]	0.35	1.12 [0.73, 1.73]	0.60
Dementia	2.36 [0.96, 5.79]	0.06	2.39 [0.97, 5.88]	0.06
Chronic kidney disease	0.84 [0.42, 1.65]	0.61	0.83 [0.42, 1.64]	0.60
Cancer	1.26 [0.92, 1.73]	0.14	1.28 [0.93, 1.75]	0.13
Antihypertensive drugs	0.58 [0.21, 1.64]	0.31	0.57 [0.20, 1.62]	0.30
DDA	1.21 [0.91, 1.60]	0.19	1.19 [0.90, 1.58]	0.23
Antiplatelet agent			1.79 [1.25, 2.58]	0.001

Hazards ratio were adjusted for the other covariates presented in the table; DDA and antiplatelet agent exposures were included as a time-dependant variables, other characteristics were included as fixed covariates at the inclusion in the cohort; age is considered as a continuous variable, female is reference for the sex, non-exposure is reference for other covariates

DDA drug-drug association, here DOAC + AAD, *TIA* transient ischemic attack, *EGB* "échantillon généraliste des bénéficiaires"

is a common limitation of pharmaco-epidemiological studies conducted on a medico-administrative database, we used the RECORD-PE checklist to be as thorough as possible in reporting its determination. Second, the database only contains data on drugs dispensed in retail pharmacy, information on drug administered in hospitals and in some nursing homes were not available which could lead to an underestimation of the exposure to drugs and DDA. However, the non-observable drug dispensations seem to be limited. Hospitalisations for other diagnostics than our outcome during follow-up accounted a total of 64,901 days (1.7% of total of follow-up days for all patients) and their median duration was 3 days (interquartile range [1–6]). Regarding drugs dispensed in nursing homes, only those with an internal pharmacy were not included in our study. In France in 2017, only 17.6% of nursing homes had internal pharmacies [28]. Some other medical data was not available such as patient's weight or glomerular filtration rate. The increased bleeding risk in patients with impaired renal function has been clearly documented [29] and DOAC's dose adjustment are recommended [1]. We adjusted our model to the presence of chronic kidney disease at inclusion but were unable to take into account changes in renal functions during follow-up. Third, to identify patients with comorbidities, we used algorithms provided with the database; unfortunately, some diseases do not have an associated algorithm, including hypertension. When an alternative definition of the comorbidity was available, such as exposure to antihypertensive drugs, we included it as a covariate in the model, even if its definition was less stringent compared to other comorbidities.

Another limit of this study was the lack of adjustment of the model on exposure to all drugs known to increase bleeding risk. As the study was designed with a Cox model and time-dependent exposure to the DDA, exposure to each drug that could interfere with the bleeding risk should have been considered in the model as individual time-dependent variables. Models including many time-dependent variables may not converge. Therefore, we focused on the three main drugs known to interfere with haemostasis.

The EGB is a large database, that enables monitoring and analysis of healthcare reimbursement in France. Its value for research has already been proven [10, 17, 30]. Patients' baseline characteristics found in this study were similar to those found in three studies conducted on medico-administrative databases in Australia [9], Taiwan [7] and France [17], regarding age (between 74 and 76.7 years) and sex (between 54.2 and 55.8% of male) in their AF population. Studies conducted in a single hospital center in Michigan [4], on a case–control study in UK [5] and a post-hoc analysis of a sample of the ROCKET trial population [27] had a mean age of, respectively, 68, 78 and 73 years old and between 58 and 62% of participants were males. These results seem to indicate that study conducted on similar population on medico-administrative database were comparable regarding sex and age, whereas they differed on studies conducted on cohorts created for research purposes.

The French healthcare system provides algorithms that help identifying patients with chronic diseases in their databases [16] allowing a reproducible identification of patients with AF and of their comorbidities. It also enables to limit a potential indication bias for apixaban or rivaroxaban in the study; we only included patients treated with apixaban or rivaroxaban after an AF diagnosis, excluding patients receiving those drugs for any other indication. Moreover, the ICD-10 codes used to identify hospitalization for bleeding were used in published studies [5, 7, 15] and have a good predictive value [31]. Only primary diagnoses were selected to maximize the specificity of the outcome. Observational studies on drugs effects are known to be prone to immortal-time bias: when patients have alternating periods of exposure to apixaban or rivaroxaban only and to DDA during follow-up, if the time of exposure to apixaban or rivaroxaban only is misclassified as time exposed to DDA or not considered in the analysis, it can lead to mistaken results and conclusions [32, 33]. To limit this bias and to account for possible variations in patient's treatment with AAD during the follow-up period in this study, we considered the exposure to the DDA as a time-dependant variable.

Conclusion

Among patients with AF given apixaban or rivaroxaban, each year, 38,9% were exposed concomitantly to a P-gp and moderate CYP3A4 inhibitor (amiodarone, verapamil, or diltiazem) and it was not associated with a significantly increased risk of hospitalization for bleeding. No dosage adjustment seems necessary when concomitantly prescribing these drugs in AF patients.

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Data availability The data that support the findings of this study are available from a third party (data owner). Restrictions apply to the availability of these data, which were used under license for this study. Aggregated data are available from the authors with the permission of the third party.

Declarations

Ethics National Institute for Health and Medical Research (INSERM) agreement for the research protocol was given in 2017–11-15. Neither ethics committee authorization nor request to national commissions for individual data protection is required according to French law to access this kind of anonymous and restricted-access database. Access to EGB is possible only through a secured connection to a specific server. Data are accessible online and are analyzed by the software SAS Enterprise Guide version 4.3 (Copyright © 2006–2010, SAS Institute Inc., Cary, NC, USA).

Conflict of interest The authors declared no competing interests for this work.

References

1. Hindricks G, Potpara T, Dagres N et al (2021) 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): The Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. Eur Heart J 42:373–498. https://doi.org/10.1093/eurheartj/ehaa612
2. Guide parcours de soins: Fibrillation atriale Février 2014. https://www.has-sante.fr/upload/docs/application/pdf/2014-05/guide_pds_fibrillation_atriale_vf.pdf. Accessed 29 Mar 2021
3. Hellwig T, Gulseth M (2013) Pharmacokinetic and pharmacodynamic drug interactions with new oral anticoagulants: what do they mean for patients with atrial fibrillation? Ann Pharmacother 47:1478–1487. https://doi.org/10.1177/1060028013504741
4. Hanigan S, Das J, Pogue K et al (2020) The real world use of combined P-glycoprotein and moderate CYP3A4 inhibitors with rivaroxaban or apixaban increases bleeding. J Thromb Thrombolysis. https://doi.org/10.1007/s11239-020-02037-3
5. Zhang Y, Souverein PC, Gardarsdottir H et al (2020) Risk of major bleeding among users of direct oral anticoagulants combined with interacting drugs: A population-based nested case–control study. Br J Clin Pharmacol 86:1150–1164. https://doi.org/10.1111/bcp.14227
6. Guideline on the investigation of drug interaction.pdf. https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-investigation-drug-interactions-revision-1_en.pdf. Accessed 5 Oct 2021
7. Chang S-H, Chou I-J, Yeh Y-H et al (2017) Association Between Use of Non-Vitamin K Oral Anticoagulants With and Without Concurrent Medications and Risk of Major Bleeding in Nonvalvular Atrial Fibrillation. JAMA 318:1250–1259. https://doi.org/10.1001/jama.2017.13883
8. Mo Y, Karakas-Torgut A, Pham AQ (2020) Evaluation of Potential Drug-Drug Interactions With Direct Oral Anticoagulants in a Large Urban Hospital. J Pharm Pract 33:136–141. https://doi.org/10.1177/0897190018788264
9. Bezabhe WM, Bereznicki LR, Radford J et al (2020) Five-Year Trends in Potential Drug Interactions with Direct-Acting Oral Anticoagulants in Patients with Atrial Fibrillation: An Australian-Wide Study. J Clin Med 9. https://doi.org/10.3390/jcm9113568
10. Tuppin P, Rudant J, Constantinou P et al (2017) Value of a national administrative database to guide public decisions: From the système national d'information interrégimes de l'Assurance Maladie (SNIIRAM) to the système national des données de santé (SNDS) in France. Rev DÉpidémiologie Santé Publique 65:S149–S167. https://doi.org/10.1016/j.respe.2017.05.004
11. Bezin J, Duong M, Lassalle R et al (2017) The national healthcare system claims databases in France, SNIIRAM and EGB: Powerful tools for pharmacoepidemiology. Pharmacoepidemiol Drug Saf 26:954–962. https://doi.org/10.1002/pds.4233
12. Thesaurus des interactions medicamenteuses (2020) https://ansm.sante.fr/var/ansm_site/storage/original/application/c8f2002151b0bb58d1936f9e50ed1d55.pdf. Accessed 11 Feb 2021
13. Hügl B, Horlitz M, Fischer K, Kreutz R (2023) Clinical significance of the rivaroxaban–dronedarone interaction: insights from physiologically based pharmacokinetic modelling. Eur Heart J Open 3:oead004. https://doi.org/10.1093/ehjopen/oead004
14. Cheong EJY, Goh JJN, Hong Y et al (2018) Rivaroxaban With and Without Amiodarone in Renal Impairment. J Am Coll Cardiol 71:1395–1397. https://doi.org/10.1016/j.jacc.2018.01.044
15. Friberg L (2018) Safety of apixaban in combination with dronedarone in patients with atrial fibrillation. Int J Cardiol 264:85–90. https://doi.org/10.1016/j.ijcard.2018.02.055
16. Méthodologie médicale de la cartographie des pathologies et des dépenses, version G7 (années 2012 à 2018) Mise à jour: 17 février 2020. https://www.ameli.fr/fileadmin/user_upload/documents/Methodologie_medicale_cartographie.pdf. Accessed 27 May 2021
17. Maura G, Blotière P-O, Bouillon K et al (2015) 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. Circulation 132:1252–1260. https://doi.org/10.1161/CIRCULATIONAHA.115.015710
18. Hirsh Raccah B, Rottenstreich A, Zacks N et al (2018) Drug interaction as a predictor of direct oral anticoagulant drug levels in atrial fibrillation patients. J Thromb Thrombolysis 46:521–527. https://doi.org/10.1007/s11239-018-1738-7
19. Frost CE, Byon W, Song Y et al (2015) Effect of ketoconazole and diltiazem on the pharmacokinetics of apixaban, an oral direct factor Xa inhibitor. Br J Clin Pharmacol 79:838–846. https://doi.org/10.1111/bcp.12541
20. Lee JY, Oh I-Y, Lee J-H et al (2021) Drug-drug interactions in atrial fibrillation patients receiving direct oral anticoagulants. Sci Rep 11:22403. https://doi.org/10.1038/s41598-021-01786-2
21. Lupercio F, Romero J, Peltzer B et al (2018) Efficacy and Safety Outcomes of Direct Oral Anticoagulants and Amiodarone in Patients with Atrial Fibrillation. Am J Med 131:573.e1-573.e8. https://doi.org/10.1016/j.amjmed.2017.11.047
22. Pham P, Schmidt S, Lesko L et al (2020) Association of Oral Anticoagulants and Verapamil or Diltiazem With Adverse Bleeding Events in Patients With Nonvalvular Atrial Fibrillation and Normal Kidney Function. JAMA Netw Open 3:e203593. https://doi.org/10.1001/jamanetworkopen.2020.3593
23. Bartlett JW, Renner E, Mouland E et al (2019) Clinical Safety Outcomes in Patients With Nonvalvular Atrial Fibrillation on Rivaroxaban and Diltiazem. Ann Pharmacother 53:21–27. https://doi.org/10.1177/1060028018795140
24. Proietti M, Cheli P, Basili S et al (2017) Balancing thromboembolic and bleeding risk with non-vitamin K antagonist oral anticoagulants (NOACs): A systematic review and meta-analysis on gender differences. Pharmacol Res 117:274–282. https://doi.org/10.1016/j.phrs.2017.01.004
25. Pancholy SB, Sharma PS, Pancholy DS et al (2014) Meta-Analysis of Gender Differences in Residual Stroke Risk and Major Bleeding in Patients With Nonvalvular Atrial Fibrillation Treated With Oral Anticoagulants. Am J Cardiol 113:485–490. https://doi.org/10.1016/j.amjcard.2013.10.035
26. Poli D, Antonucci E, Testa S et al (2013) Gender differences of bleeding and stroke risk in very Old atrial fibrillation patients on VKA treatment: Results of the EPICA study on the behalf of FCSA (Italian Federation of Anticoagulation Clinics). Thromb Res 131:12–16. https://doi.org/10.1016/j.thromres.2012.10.009

27. Washam JB, Hellkamp AS, Lokhnygina Y et al (2017) Efficacy and Safety of Rivaroxaban Versus Warfarin in Patients Taking Nondihydropyridine Calcium Channel Blockers for Atrial Fibrillation (from the ROCKET AF Trial). Am J Cardiol 120:588–594. https://doi.org/10.1016/j.amjcard.2017.05.026
28. La situation des EHPAD en 2017. Analyse de la gestion des établissements d'hébergement pour personnes âgées dépendantes et de la prise en charge des résidents. https://www.cnsa.fr/documentation/cnsa_portrait_ehpad_2017_vf.pdf. Accessed 21 Mar 2023
29. Potpara TS, Ferro CJ, Lip GYH (2018) Use of oral anticoagulants in patients with atrial fibrillation and renal dysfunction. Nat Rev Nephrol 14:337–351. https://doi.org/10.1038/nrneph.2018.19
30. Souty C, Launay T, Steichen O et al (2020) Use of the French healthcare insurance database to estimate the prevalence of exposure to potential drug-drug interactions. Eur J Clin Pharmacol 76:1675–1682. https://doi.org/10.1007/s00228-020-02952-7
31. Cunningham A, Stein CM, Chung CP et al (2011) An automated database case definition for serious bleeding related to oral anticoagulant use. Pharmacoepidemiol Drug Saf 20:560–566. https://doi.org/10.1002/pds.2109
32. Lévesque LE, Hanley JA, Kezouh A, Suissa S (2010) Problem of immortal time bias in cohort studies: example using statins for preventing progression of diabetes. BMJ 340:b5087. https://doi.org/10.1136/bmj.b5087
33. Suissa S (2007) Immortal time bias in observational studies of drug effects. Pharmacoepidemiol Drug Saf 16:241–249. https://doi.org/10.1002/pds.1357