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ORIGINAL REPORT

Adherence with direct oral anticoagulants in nonvalvular atrial fibrillation new users and associated factors: a French nationwide cohort study

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Abstract

Purpose: Direct oral anticoagulants (DOACs) have been promoted in patients with nonvalvular atrial fibrillation (nv-AF) as a more convenient alternative to vitamin K antagonists. We estimated 1-year dabigatran and rivaroxaban adherence rates in nv-AF patients and assessed associations between baseline patient characteristics and nonadherence.

Methods: This cohort study included OAC-naive nv-AF patients with no contraindications to OAC, who initiated dabigatran and rivaroxaban, using nationwide data from French national health care databases. One-year adherence was defined by the proportion of days covered of 80% or more over a fixed 1-year period after treatment initiation. Associations between nonadherence and baseline patient characteristics were assessed using multivariate logistic regression models.

Results: The population was composed of 11 141 dabigatran (women: 48%; mean age: 74 ± 10.7 y; ≥80 y: 34.9%) and 11 126 rivaroxaban (46.5%; 74 ± 10.9 y; 34.8%) new users. One-year adherence was 53.3% in dabigatran-treated and 59.9% in rivaroxaban-treated patients, consistent with numerous subgroup analyses. A switch to vitamin K antagonist was observed in 14.5% of dabigatran and 11.7% of rivaroxaban patients; 10.2% and 5.9% of patients switched to another DOAC, respectively; and 4.3% of patients died in the 2 cohorts. In patients who did not die or switch during the follow-up, 1-year adherence was 69.6% in dabigatran-treated and 72.3% in rivaroxaban-treated patients. Having concomitant ischemic heart diseases was associated with an increased risk of nonadherence in the 2 cohorts.

Conclusion: In this real-life study, 1-year adherence to DOAC is poor in nv-AF new users. Despite the introduction of DOAC, adherence to OACs may remain a significant challenge in AF patients.

KEYWORDS

adherence, atrial fibrillation, direct oral anticoagulants, French health care databases, pharmacoepidemiology

1 | INTRODUCTION

Oral anticoagulants (OACs) are widely recommended as lifetime treatment in atrial fibrillation (AF), the most common form of sustained cardiac arrhythmia and a major health and economic challenge.[1-3]

Vitamin K antagonists (VKAs), the standard OAC for many years, are associated with nonoptimal use that can be mainly explained by the fear of bleeding and the need for multiple treatment adjustments.[4-6] In recent years, direct oral anticoagulants (DOACs) have been developed, such as the direct thrombin inhibitor dabigatran and

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the factor Xa inhibitors rivaroxaban and apixaban. These drugs are considered to be more convenient, fixed-dose alternatives to VKA for stroke prevention in nonvalvular AF (nv-AF) patients. Their relative safety and efficacy versus warfarin have been demonstrated in large-scale randomized trials in nv-AF patients.[7,8] Laboratory monitoring is not required with the DOACs, which makes them an attractive option compared to VKA therapy. European guidelines have recently expressed a preference for DOACs over VKAs in stroke prevention for AF patients.[2]

Although these medications may have several advantages over VKAs, they have their own drawbacks, including renal clearance, the very limited ability to monitor their anticoagulant effect, the lack of a factor Xa inhibitor antidote, and their questionable economic value compared to VKA. Above all, they are associated with rapid offset of action due to their shorter half-life, which implies that the efficacy of DOACs in nv-AF patients in clinical practice is likely to be closely dependent on strict adherence.[1,2,9] However, only a few large-scale, academic real-life studies on DOAC adherence have been published and concerns have been raised regarding potential poor adherence with DOAC, as well as potential overuse.[10,11]

Using the large French health care databases, an incident cohort study was therefore conducted to estimate the 1-year adherence to DOAC therapies and to assess a possible association between baseline patient characteristics and adherence rates.

KEY POINTS

- In stroke prevention for AF patients, 2016 European guidelines have expressed a preference for DOACs over VKAs, commonly associated with poor adherence;
- DOACs have short half-life implying rapid onset and offset of action.
- Among nearly 22 500 dabigatran or rivaroxaban new users with nv-AF, 2 of 5 were classified as 1-year nonadherent, suggesting that adherence to anticoagulation therapy may remain a significant challenge;
- Having concomitant ischemic heart diseases was strongly associated with an increased risk of nonadherence with these DOACs.

2 | METHODS

2.1 | Data sources

This study was conducted by using data from the French health insurance system database (SNIIRAM) linked to the French hospital discharge database (PMSI). French national health insurance covers the entire French population (65.3 million inhabitants in 2012) and is divided into several specific schemes according to beneficiary profiles, the largest scheme being the *Régime Général* (around 50 million beneficiaries).

The SNIIRAM database contains individualized, anonymous, and comprehensive data on health spending reimbursements. Demographic data include date of birth, gender, and vital status. Dates of death available in the SNIIRAM database are provided by the French National Institute of Statistics and Economic Studies (INSEE); drugs are coded according to the Anatomical Therapeutic Chemical classification.

The PMSI database provides detailed medical information on all French hospitals.

The medical indication for drug reimbursements and the results of medical procedures or laboratory tests are not available in these databases. However, medical diagnosis information is available from 2 independent sources: (1) diagnosis corresponding to patient eligibility for 100% reimbursement of severe and costly long-term diseases (LTD) and (2) discharge diagnosis from hospitalization data and medical procedures performed during hospital stays. Discharge and LTD diagnoses are coded according to the International Classification of Diseases, 10th edition (ICD-10).

The French health care databases (SNIIRAM and PMSI) have already been described and successfully used in epidemiological and pharmacoepidemiological research.[12]

2.2 | Study design and population

A cohort of nv-AF patients who initiated treatment with dabigatran or rivaroxaban between January 1, 2013, and June 30, 2013, was identified from *Régime général* data. Patients' index date was the date of first DOAC reimbursement, as identified during this inclusion period.

To be eligible for inclusion, patients had to meet the following criteria: (1) at least one reimbursement for DOAC indicated for AF between January 1, 2013, and June 30, 2013 (dabigatran 110 and 150 mg or rivaroxaban 15 and 20 mg; apixaban was not available in France during this inclusion period, it was introduced in January 2014) and no reimbursement for any OAC (VKA or DOAC) in the previous 24 months; (2) treated for nv-AF; and (3) continuous general scheme health insurance coverage for at least 4 years before the index date and over the 1-year follow-up period. To ensure this last condition, patients with no identified drug reimbursement during a period of 90 consecutive days or longer during the 360 + 90 days period following the index date were excluded, except when they had died between the index date and the end of this 90-day period.

To ensure inclusion of AF patients, patients who underwent a lower limb orthopaedic procedure or with a history of deep vein thrombosis or pulmonary embolism (DVT/PE) during the 6 weeks before the index date were excluded. The AF patients were identified from the resulting cohort as (1) patients with a diagnosis of AF (ICD-10 code I48) or specific AF management procedures identified from LTD or hospitalization discharge information during the 4-year period preceding the index date ("confirmed AF") and (2) patients identified using an algorithm based on proxies discriminating AF from DVT/PE with 95% specificity, to identify "probable AF outpatients" when neither ICD-10 code I48 diagnoses nor DVT/PE codes or specific procedures were found in the preindex period.[13]

Finally, nv-AF patients were identified by excluding patients with a history of valvular heart disease, identified from either LTD or

hospitalization discharge information. Patients presenting a contraindication to OAC treatment were excluded from the resulting cohort of DOAC new users with nv-AF (Table S1).

2.3 | Exposure to DOACs and definition of adherence

2.3.1 | Estimation of the number of days of treatment covered

From each identified reimbursement during the 1-year period following the index date, the number of days of treatment covered was calculated by dividing the number of tablets delivered by the recommended daily dosage, assuming a twice-daily and once-daily one-pill regimen for dabigatran and rivaroxaban, respectively. Patients were considered to be covered for treatment on days spent in hospital. When an overlap was observed between 2 consecutive refills, the corresponding number of pills was carried over. However, when the time to the next refill was shorter than the number of days of treatment covered by the overlap, the excess overlap was considered to correspond to lost pills.

2.3.2 | Estimation of adherence

Medication adherence was assessed by the fixed proportion of days covered (PDC), ie, the total number of days covered by the quantities of drug delivered divided by a fixed observed time interval identical for all patients.[14,15] The total number of days covered by treatment (numerator) was calculated for each patient by adding the number of days of treatment covered and the number of days of hospitalization. The fixed time interval (denominator) was defined as a 360-day period following the index date/treatment initiation. The number of days of treatment extending beyond the observation period was not taken into account for estimation of medication adherence. Consistently with the published literature, 1-year adherence to treatment was defined using the cut-point for PDC of 80% or more.[16]

2.4 | Patient characteristics

The variables examined at baseline included demographic characteristics (age, gender, and deprivation index of the patient's municipality of residence[17]), type of initial prescriber, comorbidities including a frailty score, comedications, and the number of visits to a general practitioner in the 1-year period preceding the index date. (See definitions in Table S1).

Clinical scores predicting the risk of stroke (CHA_2DS_2-VASc) or bleeding (HAS-BLED) in nv-AF patients adapted to claims data were calculated. As information on smoking status and alcohol abuse is not available from the databases, these characteristics were assessed by using proxies (Table S1).

2.5 | Data analysis

2.5.1 | Adherence analyses

Descriptive analyses examined baseline patient characteristics expressed as mean and standard deviation (SD) for continuous variables, and numbers and percentages for categorical variables.

One-year adherence rates (PDC ≥ 80%) in the full cohort and in subcohorts of dabigatran and rivaroxaban new users were age (<75 and >75 years old) and gender stratified. Subgroup analyses included (1) patients with nv-AF identified by hospital discharge diagnosis I48 ICD-10 code only, (2) patients with CHA_2DS_2VASc score ≥ 2, (3) patients with HAS-BLED score ≥ 3, and (4) patients with at least 2 consecutive reimbursements.

Two additional subgroup analyses were performed after excluding (a) patients who died during the 360-day follow-up and (b) patients who died or switched to another OAC treatment (to VKA in the full cohort or to VKA or dabigatran/rivaroxaban or apixaban in the rivaroxaban/dabigatran subcohorts). The objective of these subgroup analyses was (1) to provide information about patients with complete follow-up over the 1-year period following treatment initiation and (2) to try to take into account some discontinuations due to switches not related to medical reasons, including marketing transitions from DOAC towards VKA or between DOACs (eg, apixaban introduction). A patient who switched during the 1-year follow-up was defined as a patient with, during this period, at least one reimbursement for VKA (full cohort) or one reimbursement for a VKA or for a DOAC different from that initiated at the index date (dabigatran and rivaroxaban subcohorts).

Three sensitivity analyses for the definition of adherence were performed: (1) PDC ≥ 80% but estimated without considering days of hospitalization as days covered, (2) PDC ≥ 50%, and (2) PDC ≥ 90%.

As adherence rates were calculated over a 1-year period irrespective of how long patients remained on treatment, the time interval between the dates of DOAC initiation and the last refill over the 1-year follow-up period was provided as additional information.

Finally, as episodes of bleeding could have a major impact on adherence rates, hospitalization rates for bleeding during the follow-up period were described.

2.5.2 | Determinants of adherence

Associations between nonadherence (PDC < 80%) and baseline patient characteristics (except CHA_2DS_2VASc score, smoking and alcohol abuse) were assessed using multivariate logistic regression models in the dabigatran and rivaroxaban subcohorts, respectively. This analysis was repeated in the subgroup of patients who did not die or switch to another OAC treatment, for the same reasons as those indicated above. Covariates were included in the final model when they were selected by stepwise regression ($P < .05$) in at least 1 of the 4 subgroups and then based on expert clinical knowledge. Odds ratios and their 95% confidence intervals (95% CI) were reported. The variance inflation factor was used to test multicollinearity. Model calibration was assessed by an Osius-Rojek test due to the sample size, and model discrimination was assessed by c-index.

All analyses were performed with SAS software, version 9.2 (SAS Institute, Inc., Cary, North Carolina).

3 | RESULTS

3.1 | Patient selection and characteristics

A total of 22 267 dabigatran or rivaroxaban new users treated for nv-AF were included, 11 141 of whom initiated treatment with dabigatran, and 11 126 initiated treatment with rivaroxaban (Figure 1).

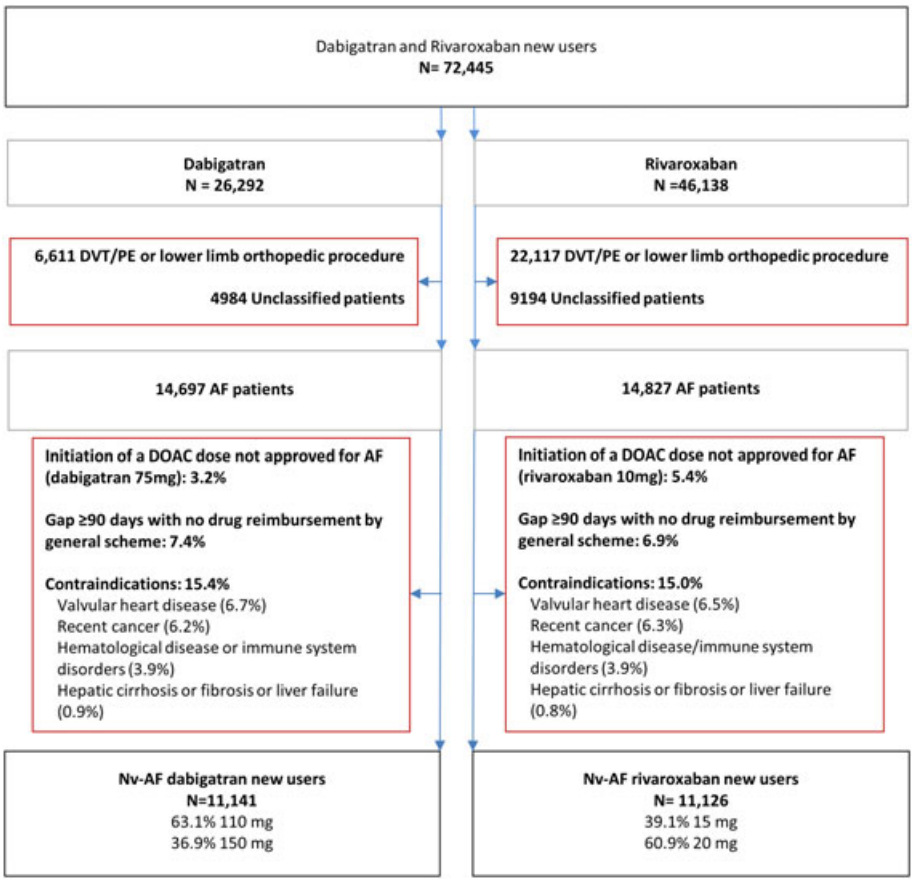

FIGURE 1 Study population flowchart. DOAC, direct oral anticoagulant; DVT/PE, deep vein thrombosis or pulmonary embolism; nv-AF, nonvalvular atrial fibrillation [Colour figure can be viewed at wileyonlinelibrary.com]

Baseline patient characteristics are shown in Table 1. Nearly one half of DOAC treatments were initiated by private cardiologists in the 2 subcohorts. About 9% of DOAC patients had a history of stroke, and about 20% had a history of ischemic heart diseases (IHDs). Although one-half of the full cohort patients were using antiplatelet agents at baseline, only 18% (13%) of dabigatran patients and 17% (13%) of rivaroxaban patients had received at least one (3) reimbursement for antiplatelet agents during the 1-year follow-up period. The hospitalization rates for bleeding during the 1-year follow-up period were close to 2% in both subcohorts.

3.2 | Adherence patterns

Nine percent of the patients included in the study had received only one reimbursement for DOAC. During the follow-up, 25.6% of patients only received dabigatran 110 mg and 22.9% of patients only received rivaroxaban 20 mg. Conversely, 23% of patients were treated with at least 2 DOACs or at different dosages. A switch to another DOAC (including apixaban) was observed in 10.2% of dabigatran patients and 5.9% of rivaroxaban patients; switches to VKA were observed in 14.5% and 11.7% of patients, respectively. Mortality rates during follow-up were similar in the 2 subcohorts, ie, 4.3%.

Table 2 shows the estimated proportion of 1-year adherent patients (PDC ≥ 80%) in the various populations. One-year adherence was 53.3% in dabigatran-treated and 59.9% in rivaroxaban-treated patients, consistent with numerous subgroup analyses. In patients who did not die or switch during the follow-up, 1-year adherence was 69.6% in dabigatran-treated and 72.3% in rivaroxaban-treated patients.

Figure 2 displays the proportion of patients classified as adherent according to the PDC cut-point used to define adherence.

The median interval between DOAC initiation and last refill over the 1-year follow-up period was 335 days in the full cohort (Table S2).

3.3 | Association between adherence and baseline characteristics

Older age, history of stroke, preventive treatment for chronic cardiovascular disease, and living in more deprived municipalities versus less deprived municipalities were all independently associated with adherence (PDC ≥ 80%). Having chronic kidney disease or IHDs was associated with nonadherence in both dabigatran- and rivaroxaban-treated patients. Associations remained significant after excluding patients who died or who switched to VKA or another DOAC except for chronic kidney disease. Only having IHDs was therefore associated with nonadherence in the 2 cohorts. (See forest plot in Figures 3 and 4).

Interactions for age and IHD and for age and history of stroke were significant ($P < .05$) in both the dabigatran and rivaroxaban models; interaction for IHD and history of stroke was significant only in the dabigatran model. Age and history of stroke were no longer independently associated with higher adherence in patients with IHD in dabigatran- and rivaroxaban-treated patients (Table S3).

TABLE 1 Baseline patient characteristics

Characteristics	Dabigatran All Doses N = 11 141 N (%)[a]	Rivaroxaban All Doses N = 11 126 N (%)[a]	Total N = 22 267 N (%)[a]
Female	5350 (48.0)	5177 (46.5)	10527 (47.3)
Age, mean (SD)	74.0 (10.7)	74.0 (10.9)	74.0 (10.8)
<65 y	2044 (18.3)	2039 (18.3)	4083 (18.3)
65-74 y	3087 (27.7)	3089 (27.8)	6176 (27.7)
75-79 y	2122 (19.0)	2125 (19.1)	4247 (19.1)
80-84 y	2155 (19.3)	2105 (18.9)	4260 (19.1)
≥85 y	1733 (15.6)	1768 (15.9)	3501 (15.7)
Deprivation index			
Quintile 1 (least deprived)	1900 (17.1)	2189 (19.7)	4089 (18.4)
Quintile 2	2092 (18.8)	2316 (20.8)	4408 (19.8)
Quintile 3	2261 (20.3)	2130 (19.1)	4391 (19.7)
Quintile 4	2374 (21.3)	2186 (19.6)	4560 (20.5)
Quintile 5 (most deprived)	2414 (21.7)	2217 (19.9)	4631 (20.8)
Overseas departments	100 (0.9)	88 (0.8)	188 (0.8)
First prescriber's specialty			
Private cardiologist	4581 (41.1)	5351 (48.1)	9932 (44.6)
Hospital practitioner	3952 (35.5)	3094 (27.8)	7046 (31.6)
General practitioner	2405 (21.6)	2508 (22.5)	4913 (22.1)
Other private physicians	203 (1.8)	173 (1.6)	376 (1.7)
CHA_2DS_2-VASc, mean (SD)	3.0 (1.6)	3.0 (1.5)	3.0 (1.6)
HAS-BLED, mean (SD)	2.2 (1.0)	2.2 (1.0)	2.2 (1.0)
Comorbidities			
Heart failure	1527 (13.7)	1428 (12.8)	2955 (13.3)
Diabetes	2201 (19.8)	2178 (19.6)	4379 (19.7)
Chronic kidney disease[b]	271 (2.4)	300 (2.7)	571 (2.6)
History of ATE	1046 (9.4)	940 (8.4)	1986 (8.9)
History of DVT/PE	73 (0.7)	85 (0.8)	158 (0.7)
Ischemic heart disease	2244 (20.1)	2323 (20.9)	4567 (20.5)
Dementia/Parkinson's disease	500 (4.5)	464 (4.2)	964 (4.3)
Peripheral vascular disease[b]	693 (6.2)	706 (6.3)	1399 (6.3)
History of bleeding[b]	253 (2.3)	263 (2.4)	516 (2.3)
Chronic hepatitis B or C or HIV patients	26 (0.2)	33 (0.3)	59 (0.3)
Osteoporosis[b]	126 (1.1)	139 (1.2)	265 (1.2)
Psychiatric disorders	1645 (14.8)	1544 (13.9)	3189 (14.3)
Other chronic and debilitating diseases	688 (6.2)	694 (6.2)	1382 (6.2)
Frailty	850 (7.6)	855 (7.7)	1705 (7.7)
Alcohol abuse[c]	181 (1.6)	146 (1.3)	327 (1.5)
Smoking[c]	983 (8.8)	974 (8.8)	1957 (8.8)
Comedications			
Antihypertensives	9706 (87.1)	9579 (86.1)	19285 (86.6)
Antiarrhythmics and cardiac glycosides	8152 (73.2)	8338 (74.9)	16490 (74.1)
Lipid-lowering agents	5281 (47.4)	5309 (47.7)	10590 (47.6)
Antiplatelet drugs	5791 (52.0)	6000 (53.9)	11791 (53.0)
Corticosteroids	1736 (15.6)	1762 (15.8)	3498 (15.7)
Antiulcer agents	4708 (42.3)	4616 (41.5)	9324 (41.9)
Hypnotics and anxiolytics	2901 (26.0)	2846 (25.6)	5747 (25.8)
Anti-inflammatory/antirheumatic agents	2209 (19.8)	2162 (19.4)	4371 (19.6)
Opioid analgesics	1646 (14.8)	1684 (15.1)	3330 (15.0)
Homeopathy	736 (6.6)	740 (6.7)	1476 (6.6)
Influenza vaccination[d]	5780 (51.9)	5958 (53.6)	11738 (52.7)

(Continues)

TABLE 1 (Continued)

Characteristics	Dabigatran All Doses N = 11 141 N (%)[a]	Rivaroxaban All Doses N = 11 126 N (%)[a]	Total N = 22 267 N (%)[a]
Visits to a GP in the previous year[e]			
<6 visit(s)	4124 (37.0)	4293 (38.6)	8417 (37.8)
6-11 visits	4647 (41.7)	4511 (40.5)	9158 (41.1)
≥12 visits	2370 (21.3)	2322 (20.9)	4692 (21.1)

Abbreviations: ATE, arterial thromboembolic events (ischemic stroke, arterial systemic embolism, or transient ischemic attack); DVT/PE, deep vein thrombosis/pulmonary embolism; GP, general practitioner; HIV, human immunodeficiency virus; SD, standard deviation.

[a]Dichotomous variables are expressed as N (%); continuous variables are expressed as mean (standard deviation).

[b]Comorbidities mainly defined by inpatient data (hospital discharge diagnosis ICD-10 codes).

[c]Smoking or alcoholism data: measured using proxies such as reimbursements for nicotine replacement therapy/drugs used in alcohol dependence and hospital discharge diagnoses mainly related to tobacco use or alcohol abuse.

[d]During the first "flu vaccination campaign" preceding the index date.

[e]Frequency of visits to a general practitioner was measured in the year before the index date.

TABLE 2 Number and rate of 1-year adherent patients (PDC ≥ 80%) by type of DOAC and according to subgroup analyses

	Dabigatran		Rivaroxaban		Total	
Incident Cohorts	N	Adherent Patients, N (%)	N	Adherent Patients, N (%)	N	Adherent Patients, N (%)
Main study population	11 141	5938 (53.3)	11 126	6670 (59.9)	22 267	13 560 (60.9)
Women	5350	2814 (52.6)	5177	3148 (60.8)	10 527	6527 (61.0)
Men	5791	3124 (53.9)	5949	3,522 (9.2)	11 740	7133 (60.8)
<75 y	5131	2798 (54.5)	5128	3097 (60.4)	10 259	6345 (61.8)
≥75 y	6010	3140 (52.2)	5998	3573 (59.6)	12 008	7215 (60.1)
Patients hospitalized for nv-AF	6433	3521 (54.7)	5836	3583 (61.4)	12 269	7611 (62.0)
Patients with $CHA_2DS_2VASc \geq 2$	9111	4982 (54.7)	9124	5605 (61.4)	18 235	11 376 (62.4)
Patients with HAS-BLED ≥3	4796	2657 (55.4)	4896	2984 (60.9)	9692	6050 (62.4)
Patients with at least 2 reimbursements	10 150	5938 (58.5)	10 189	6670 (65.5)	20 339	13 560 (66.7)
Additional subgroup analysis 1[a]	10 657	5904 (55.4)	10 653	6628 (62.2)	21 310	13 479 (63.2)
Additional subgroup analysis 2[b]	8167	5681 (69.6)	8890	6426 (72.3)	18 509	13 160 (71.1)
Complementary analysis[c]	11 141	5869 (52.7)	11 126	6616 (59.5)	22 267	13 430 (60.3)

Abbreviations: DOAC, direct oral anticoagulant, Nv-AF, nonvalvular atrial fibrillation; PDC, proportion of days covered; VKA, vitamin K antagonist.

[a]Patients who died were excluded from the study population.

[b]Patients who died or who switched to VKA and towards other DOAC were excluded from the study population. Only switches to VKA were considered for the overall cohort analysis.

[c]Days of hospitalization were not considered as days covered in this analysis.

Thirty-five percent of nv-AF patients with IHD at DOAC initiation had at least one reimbursement, and 29.5% had at least 3 reimbursements of antiplatelet agents during the 1-year follow-up period.

4 | DISCUSSION

In this cohort study examining data for more than 22 000 OAC-naive patients with nv-AF, 2 of 5 DOAC new users were found to be nonadherent to treatment (dabigatran: 46.7%; rivaroxaban: 40.1%), when adherence was defined as medication coverage of at least 80% of a fixed 1-year follow-up period. Among patients who neither died nor switched during the 1-year follow-up period, nonadherence remained high (dabigatran: 30.4%; rivaroxaban: 27.8%). Regardless of the DOAC used at initiation, adherence was higher among patients with a history of stroke provided they did not also present concomitant IHDs, which was associated with an increased risk of nonadherence in both dabigatran and rivaroxaban new users.

This is the first study to assess the real-life 1-year adherence with DOACs using French health care databases and one of the rare studies to have focused on both rivaroxaban and dabigatran adherence on such a large, almost nationwide, scale. We provided numerous subgroup analyses and took into account the impact of mortality and switches. Direct comparisons with adherence rates reported in other observational studies are difficult due to methodological issues.[18-25] However, in those studies that were also based on claims data, adherence rates were situated in the range of 40% to 70%, which are consistent with our findings.[18,19,25,26]

This study suggest that adherence to DOAC is poor in the real-life setting. One hypothesis for this result could be related to the absence of laboratory monitoring that may imply less intensive follow-up of

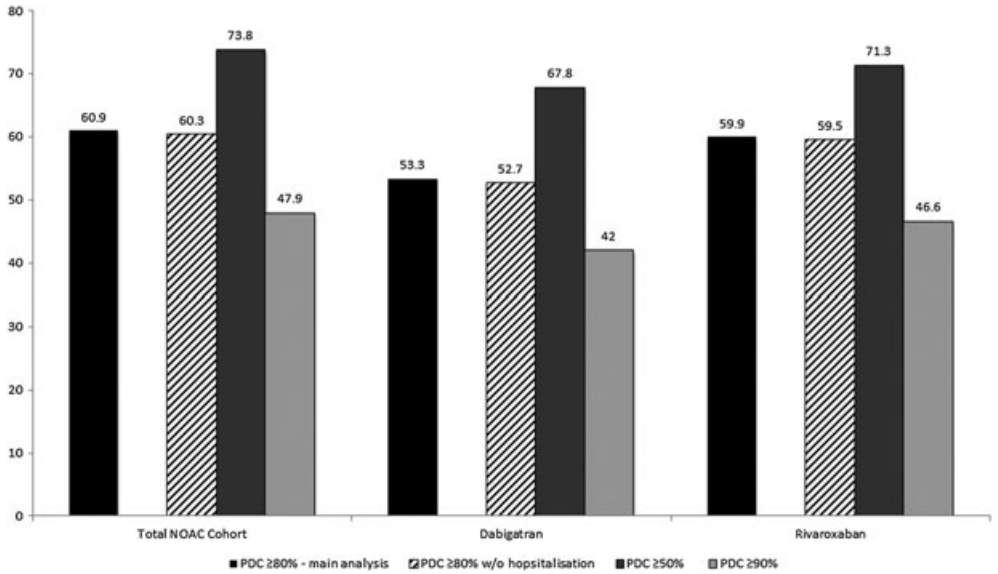

FIGURE 2 Proportion of patients classified as 1-year adherent according to the proportion of days covered (PDC) cut-point and the type of direct oral anticoagulant (DOAC) (sensitivity analysis)

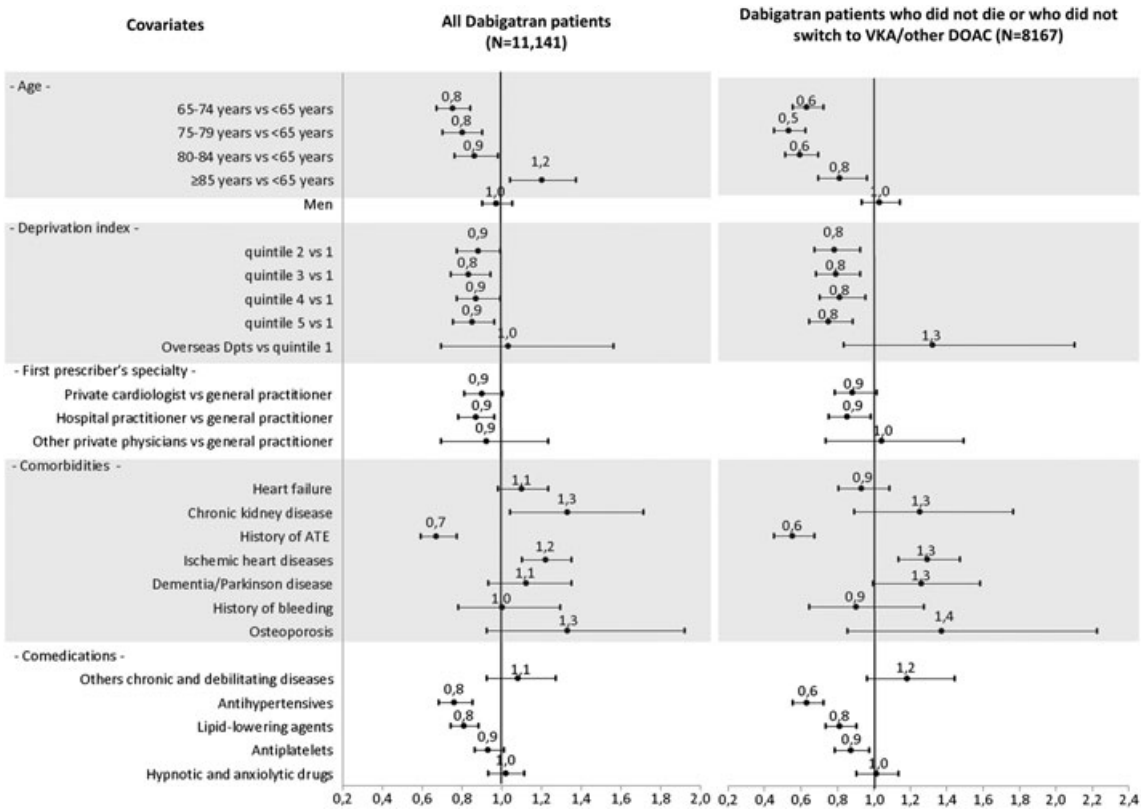

FIGURE 3 Results from multivariate logistic regression analysis modelling the association between nonadherence (PDC < 80%) to dabigatran and baseline covariates. Multicollinearity assessment, model calibration, and discrimination: All variance inflation factor values were less than 2; *P* values for Osius-Rojek test were .67 and .65 for the overall dabigatran study population and subgroup analysis, respectively; c-index for the same groups were c = 0.58 and c = 0.61, respectively. ATE, arterial thromboembolic event; DOAC, direct oral anticoagulant; PDC, proportion of days covered; VKA, vitamin K antagonist

patients by physicians than that required for VKA therapy. Adverse event may be responsible for nonadherence, but their nature and seriousness need to be further investigated, as the serious bleeding cannot provide an explanation for such high levels of nonadherence in this study. Minor but frequent side effects, such as gastrointestinal adverse effects described with dabigatran, may explain poorer adherence.[27,28] Limited access of patients to more expensive DOAC therapy is not a possible explanation for these non-adherence rates as, in France, National Health Insurance covers the entire population and most people also subscribe a private complementary health insurance.[29]

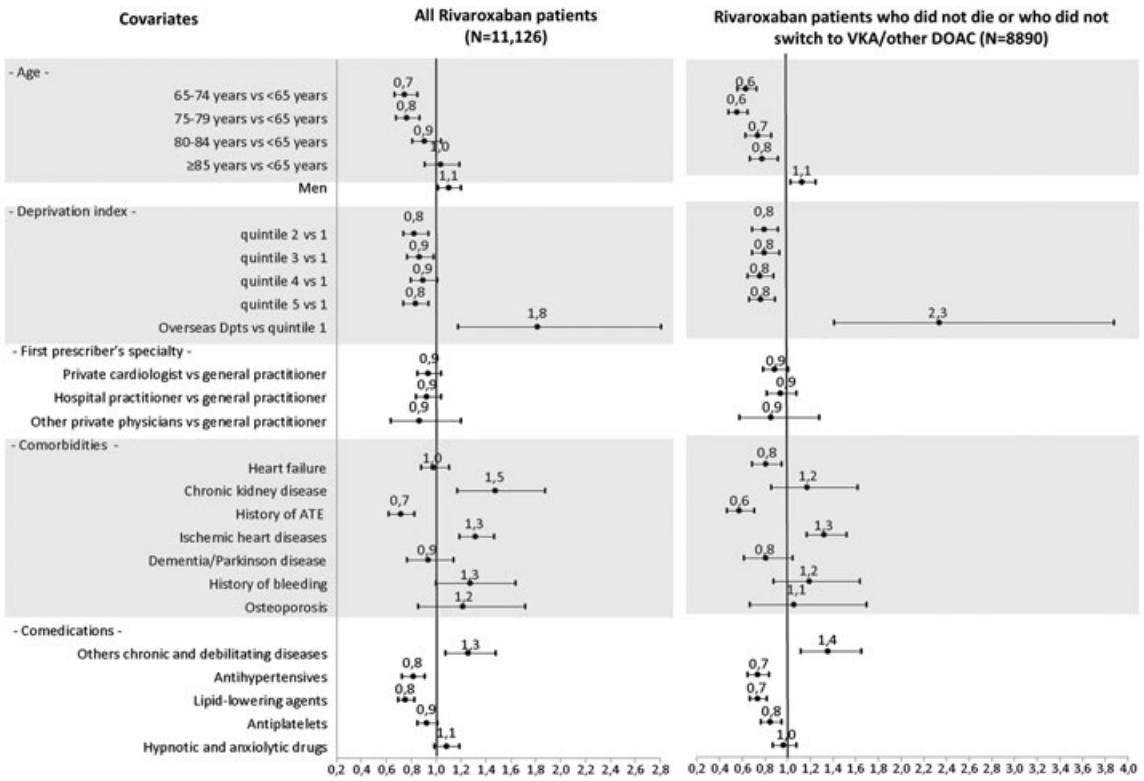

FIGURE 4 Results from multivariate logistic regression analysis modelling the association between nonadherence (PDC < 80%) to rivaroxaban and baseline covariates. Multicollinearity assessment, model calibration, and discrimination: All variance inflation factor values were less than 2; *P* values for Osius-Rojek test were .09 and .07 for the overall rivaroxaban study population and the subgroup analysis, respectively; c-index for the same groups were c = 0.58 and c = 0.61, respectively. ATE, arterial thromboembolic event; DOAC, direct oral anticoagulant; PDC, proportion of days covered; VKA, vitamin K antagonist

Although consequences of poor adherence in terms of adverse outcomes were not assessed in this study, DOAC nonadherence has already been shown to be associated with an increased risk of adverse outcomes.[30,31] Our results therefore imply that adherence counselling should be systematically encouraged at the time of initiation of DOAC and repeatedly during the course of therapy. Adherence strategies integrating a multilevel and patient-centered approach have been proposed to improve adherence and related health outcomes.[15,32] Among possible interventions, pharmacist-led monitoring was shown to have dramatic effects,[19,22,33] and this type of intervention was introduced in France for DOAC patients in 2016.[34]

The baseline covariates associated with better adherence all tend to reflect the severity of the patient's state of health (more advanced age, history of stroke, and receiving preventive cardiovascular treatments), in line with numerous studies.[21,25,26,35,36] The better adherence observed in these patients may be explained by a better understanding of their nv-AF condition and the rationale behind the benefits of long-term adherence with OAC.[36] The apparent association between deprivation index and improved adherence could be interpreted in a similar way, as people living in more deprived municipalities may also have a poorer state of health than those living in less deprived areas.

Concomitant IHD was the only covariate associated with nonadherence in both dabigatran and rivaroxaban nv-AF patients after exclusion of patients who died or switched during follow-up. To our knowledge, this association has never been previously demonstrated with DOAC use and is a subject of concern. However, patients with a history of coronary heart disease were shown to be less likely to be given warfarin.[37] Guidelines for optimal antithrombotic treatment (antiplatelet therapy and/or OAC) may be insufficiently known or unclear in the case of concomitant AF and stable coronary artery disease.[38-41] The results of recent studies support long-term monotherapy anticoagulation rather than antiplatelet and OAC combinations, which are associated with an increased bleeding risk with no improvement of outcomes.[40,41]

Among the main limitations of this study, adherence rates were assessed from claims data, for which it is impossible to verify whether medication reimbursement actually corresponds to medication consumption. However, drug exposure estimated from claims data was shown consistent with exposure assessed from the medications actually taken by patients.[42,43]

The same applies to the relevance of using PDC and selecting 80% coverage as a cut-point to distinguish adherent from nonadherent patients.[16,44] The use of a fixed PDC measure is recommended in preference to variable adherence measures in which adherence is calculated using a variable duration denominator, usually between the first and the last refill, ie, in persistent patients as variable adherence measures have been shown to bias upwards adherence values in conditions such as nv-AF requiring long-term treatment. Furthermore, fixed PDC includes information on patients who discontinued

treatment, a common pattern that would be useful to quantify in the clinical setting.[14,45,46]

Due to nature of the data used, it cannot be determined whether patients stopped treatment on their own, following an intercurrent health event or following a medical decision. Guidelines for AF patients recommend long-term anticoagulant therapy.[1,2] However, in some AF patients, albeit a minority, radiofrequency ablation or cardioversion may achieve sinus rhythm, resulting in discontinuation of DOACs.

Adherence is a complex human behavior influenced by environmental factors, including the daily living of patients and health care quality.[15,32,47] This study, based on claims data, was not able to capture all these factors and adjust estimates for all of these factors, ie, residual confounding cannot be excluded.

Finally, this study was not designed to compare adherence between the 2 DOACs by considering differences between the 2 groups and potential competing events. Considering our results, the next step would be to compare DOAC and VKA adherence. However, VKA adherence could not be reliably assessed due to dynamic dosing on claims data. While the literature reports mixed results on the comparative persistence of DOAC versus VKA,[48-50] whether or not DOAC patients have better persistence rates than VKA patients in no way lessens the issue of poor adherence with DOACs, now recommended as first-line treatment over VKA for stroke prevention.[2] In contrast, for clinical practice, our results suggest that initiating DOAC as first-line treatment might not necessarily result in good adherence in nv-AF patients.

5 | CONCLUSION

In this real-life study, 1-year adherence to DOAC therapy is poor in nv-AF new users, which implies that the efficacy of DOAC observed in clinical trials may not be achieved in clinical practice. Despite the introduction of DOAC, adherence to oral anticoagulation therapy may remain a significant challenge in the management of AF patients. Reinforced teaching for both patients and prescribers regarding the benefits of optimal DOAC adherence is urgently needed, particularly focusing on patients with IHDs.

ETHICS STATEMENT

The authors state that no ethical approval was needed.

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CONFLICT OF INTEREST

The authors are employees of the French National Health Insurance (CNAMTS) or belong to the French National Institute of Health and Medical Research (Inserm) and have no conflicts of interest with the Pharmaceutical Industry.

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