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Non-adherence and non-persistence of Direct Oral Anticoagulants among patients with non-valvular atrial fibrillation: a French retrospective cohort study

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Non-adherence and non-persistence of direct oral anticoagulants (DOAC) in patients with non-valvular atrial fibrillation remain major concerns. Most studies on non-persistence and non-adherence during the implementation phase (i.e., from the first to the last dose of DOAC) focus only on new DOAC users. We conducted a retrospective cohort study in France in 2018–2019 using the real-world THIN database to determine non-adherence during the implementation phase, non-persistence, and their associated factors among all DOAC users. Non-adherence was defined as the proportion of days covered < 80% and non-persistence as a supply gap > 30 days. Factors associated with non-adherence or non-persistence were identified using logistic regressions. We included a total of 5,059 DOAC users: 1,358 new users and 3,701 prevalent users. Non-adherence was 18.7% at 6 months and 24.2% at 1 year and non-persistence was 16.1% and 28.4%, respectively. Non-adherence was almost the same in new and prevalent DOAC users and non-persistence was slightly higher in new users. Factors associated with non-adherence and non-persistence were: age < 65 years and having < 5 comedications. Further studies will be needed to quantify the impact of non-adherence or non-persistence.

Keywords Adherence, Persistence, Anticoagulants, Atrial fibrillation, Real word data

Atrial fibrillation is one of the most common arrhythmias and a major risk factor of stroke and other thromboembolic events[1]. To prevent these events, all scientific societies recommend the lifelong use of an oral anticoagulant comprising Direct Oral Anticoagulants (DOAC) or Vitamin K Antagonist (VKA)[2]. DOAC comprise dabigatran, rivaroxaban, apixaban and edoxaban, and have been authorized in the EU for this indication (i.e., the prevention of thromboembolism risk) in 2012 for the first one. Current European guidelines now recommend DOAC as first-line therapy in patients with non-valvular atrial fibrillation (NVAF) in moderate to high risk patients[2].

Compared to VKA, DOAC have shown non-inferiority in terms of efficacy[3,4] with a lower risk of cerebral hemorrhage[3,4]. Although they are administered using fixed-dose regimens with no need for regular monitoring[5–10] and have lower potential interactions with food or drugs[5,7–10], they have a shorter half-life than VKA, and therefore a more rapidly reversible anticoagulant effect[7–9,11–14]. For this reason, their efficacy depends not only on strict adherence (i.e., by respecting the drug administration schedule[15,16] during the implementation phase (i.e., from the first dose of the prescribed DOAC to the last dose); but also on strict persistence (i.e., by respecting the prescribed treatment duration[15]).

Non-adherence and/or non-persistence remain major concerns, as they have been associated with higher risks of thromboembolic events and all-cause mortality[9,14,17]. Many studies in various countries have evaluated DOAC non-adherence and non-persistence. The results show a wide variation in non-adherence (between 5% and 59% over 1 year[18]) and non-persistence (between 14% and 64% over 1 year[5,19]). In the literature, different

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definitions and methods are used to estimate non-adherence and non-persistence. In addition, the particularities of each country such as healthcare reimbursement policies and population differences also render it difficult to transfer and compare the results from one country to another. To our knowledge, only one study on DOAC non-adherence has been conducted in France in 2013[6]. This study did not include apixaban which was not on the market at that time, and only focused on new DOAC users[6]. Regarding non-persistence, only three studies have evaluated it in France: one study did not include apixaban[20] and two studies focused only on new DOAC users[19,21]. Hence, data on DOAC non-adherence and non-persistence, their associated factors, and the impact of the use of different definitions are needed in France.

Therefore, the present study aims at assessing (i) DOAC non-adherence during the implementation phase, (ii) DOAC non-persistence and (iii) factors associated with both of them in all, new and prevalent adult users of DOAC with NVAF in 2018–2019 in a retrospective cohort study in France. As a secondary aim, we will conduct different sensitivity analyses to assess the impact of the use of different definitions of non-adherence and non-persistence.

Methods

This was a retrospective cohort study. For the description of our study, we used the ESPACOMP Medication Adherence Reporting Guideline (EMERGE)[22] (Table S1) in addition to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement[23] (Table S2).

Data source

We used a French primary care database from The Health Improvement Network (THIN)[24] marketed by GERS DATA (description in Supplementary note). The THIN database in France collects anonymized longitudinal real-world data from doctors using the CrossWay® prescription assistance software marketed by GERS DATA. About 2,000 general practitioners (GP) and 1,000 specialists make up a representative panel of primary care physicians in terms of age, gender and geographical area. The database covers more than 3 million patients representative of the French population in terms of age, gender and geographical area. Of all the data available for each patient in the THIN database, we used demographic and diagnostic data encoded by the physician (general practitioner (GP) or cardiologist), dispensing data for drugs and hospitalisation charges. THIN database is registered and holds an ethical approval from the French Data Protection Authority (CNIL). As we only used anonymized data, no additional ethical approval was required.

Study timeframe and eligibility criteria

We extracted from the THIN database all patients who met the following criteria between October 2012 (the year DOAC were marketed in France) and December 2021 (the last period available at the time of data extraction): (1) aged ≥ 18 years, (2) with a diagnosis of atrial fibrillation [International Classification of Diseases, 10th revision (ICD-10) code: I48], and (3) with at least one DOAC dispensing (apixaban, rivaroxaban or dabigatran [Anatomical Therapeutic Chemical (ATC)-code: B01AF02, B01AF01, B01AE07]). Since edoxaban was not yet marketed in France during the study period, it was not included. Then, we identified 2 mutually exclusive cohorts.

Patients with at least one DOAC dispensing in 2019 and one DOAC dispensing in 2018 and 2017 (2 years prior use) were categorized as prevalent DOAC users. The index date for prevalent users was January 1, 2019 (Fig. 1). Patients with at least one DOAC dispensing in 2018 and no DOAC dispensing in 2017 were categorized as new DOAC users. The date of first DOAC dispensing in 2018 became their index date (Fig. 1). We did not choose 2019 for the first dispensation, as we preferred to avoid follow-up during the Covid-19 period in order to avoid potential information bias (e.g., misclassification).

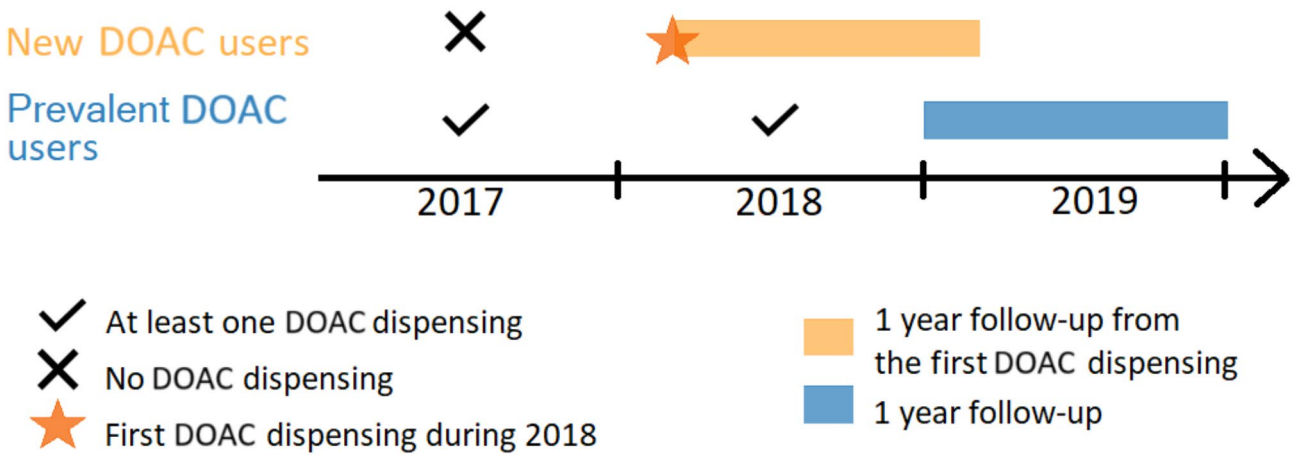

Fig. 1. Definition of the 2 mutually exclusive cohorts among non-valvular atrial fibrillation patients: new DOAC users and prevalent DOAC users and their follow-up periods. *DOAC: Direct Oral Anticoagulant.*

Then, we only included patients with a diagnosis of atrial fibrillation before or no later than 1 month after the index date, and with no diagnosis of valvular heart diseases or valvular replacement at any time prior to the index date (Table S3) to take only patients with NVAF. Finally, to avoid competing treatment indications for DOAC, we did not include patients with a record of deep vein thrombosis, cardiac catherization, pulmonary embolism, or hip/knee surgery (Table S3) in the 6 months before the index date.

Outcomes

We used the taxonomy of European ABC (Ascertaining Barriers to Compliance) group for medication adherence[15]. As previously mentioned, adherence to DOAC during the implementation reflects if the patient follows the dosing regimen prescribed by the physician from the first dose to the last one, i.e., if he follows the number of daily doses to be administered[15]. Persistence is the action of continuing the drug for the prescribed duration[15] and in patients with NVAF this usually equates to a lifetime treatment.

In line with the above, in all, new and prevalent adult users of DOAC, we measured non-adherence during the implementation phase and non-persistence after 1 year as primary outcome (duration most often found in the literature[5]) and after 6 months as secondary outcome.

Adherence was estimated using the Proportion of Days Covered (PDC) which is the proportion of days that a person has access to the drug over a given period[25]. It was calculated using the CMA9 function of the AdhereR package of R software[26]. For each fill, the function computes a ratio of days of supply which is based on the quantity dispensed and dosage unit per day. Then, it weights all days by their corresponding ration to generate an average PDC value for the observation period[26]. We used a value < 80% as non-adherence, the definition most frequently used in studies[18]. In case of overlaps between 2 consecutive refills, the corresponding number of days was carried forward to the end of the exhaustion date of the previous refill, based on the number of pills dispensed and the frequency of administration[25]. In addition, for prevalent users, we used a retrospective period to check whether they had any leftover drugs before the index date, so that we could carry them forward. In case of hospitalization, the patient was considered as adherent, since the drugs are provided by the hospital. During the study period, switching between different DOAC was allowed.

Regarding persistence, the supply gaps most frequently observed in the literature are the 60-day gap and the 30-day gap[5]. Because of its clinical relevance and since missing even a single pill may play a role in the consequences of this disease[27,28], we chose the > 30-day supply gap as non-persistence. In the same way as for adherence calculation, the patient was considered persistent in the case of hospitalization; switching between different DOAC was allowed, and overlaps and leftover drugs were taken into account in the non-persistence calculation.

As a sensitivity analysis, we defined a PDC < 90% for non-adherence during the implementation phase and a > 60-day supply gap for non-persistence.

Follow-up

At the time of data extraction, dates of death were not yet available in the database. To avoid potential bias, a proxy was created to reflect whether a patient was lost to follow-up or dead without distinction. If the patient had no further dispensing of any drug and no reimbursement for hospitalisation during the follow-up, he was considered lost to follow-up or dead. The censor date was the date on which the refill was exhausted, calculated on the basis of the number of pills dispensed and the frequency of administration, or the end of hospitalisation, whichever comes last. Therefore, participants were followed from the index date to death/lost to follow-up (exit from the THIN database), or up to 12 months, whichever occurs first. Patients were not followed up beyond December 31, 2019 (cut-off date of the database).

Covariates

We considered a large panel of covariates of interest including age, sex, comorbidities identified using ICD-10 codes (Table S4) and medication history during the 3 month-period before the index date, identified in dispensing claims using ATC codes, 5th level (Table S4). We computed $CHAD_2DS_2$-VASc score, HAS-BLED score (endorsed by European guidelines and which better identifies patients at very low risk of bleeding[29]), age-adjusted Charlson Comorbidity Index and the number of comedications (Table S4). We created a new variable to reflect whether the patient was a new DOAC user or a prevalent DOAC user. Finally, among the new users, we created a variable for descriptive purposes by redefining 2 sub-populations: former VKA users, if the patient had at least one VKA dispensation prior the first use of DOAC (i.e., from the database extraction date to the date of the first dispensation), and anticoagulant naïve patients.

Statistical analyses

Data are presented as mean ± standard deviation (SD) or median (p25, p75) for continuous variables, according to the normality of the distribution, and counts (%) for categorical variables.

Depending on the normality of the data distribution, comparison of continuous variables between 2 groups was done using unpaired Student's t-test or Wilcoxon-Mann-Whitney test. Categorical variables were compared between 2 groups using Pearson's chi-squared or Fisher's exact test, as appropriate.

Binary logistic regression was used to assess variables independently associated with non-adherence and non-persistence within the whole cohort and among each sub-cohort (new and prevalent users), and OR (95% CI) were computed. For multivariable analyses, a conservative approach was used to avoid overestimation[30,31]. In the multivariable model, we included all clinically relevant variables (sex, age, frequency of DOAC use, the prescriber's specialty, and the number of comedications) and comorbidities with $p < 0.15$ in univariate analysis (instead of medication history and clinical risk score). Collinearity was assessed by computing the variance

inflation factor (VIF). A variable with a VIF > 2 was excluded from the model and the final model was assessed using the Hosmer-Lemeshow test. Finally, we computed adjusted OR (aOR) with 95% CI.

All the variables included in the analyses had no missing data. All p-values were two-tailed and $p < 0.05$ was considered statistically significant. Statistical analyses were performed with R software version 1.4.1717.

Results

Study population

A total of 7,468 patients with a diagnosis of atrial fibrillation had at least one DOAC dispensing in the THIN database between October 2012 and December 2021 (Fig. 2). After removing patients with no DOAC use in the study period, identifying the two mutually exclusive cohorts and applying the eligibility criteria, we identified 1,358 new users and 3,701 prevalent users (Fig. 2) for a total of 5,059 DOAC users. Overall, the mean age was 75.9 ± 9.6 years, with prevalent DOAC users slightly older than new users (76.4 ± 9.3 vs. 74.5 ± 10.3 years). The total proportion of males was 57.1%, with 55.4% in new users and 57.7% in prevalent users (Table 1). Baseline characteristics are summarized in Table 1.

DOAC non-adherence and associated factors

When we used a PDC < 80%, non-adherence was 18.7% at 6 months and 24.2% at 1 year. In new users, it was 17.8% at 6 months and 24.4% at 1 year; in prevalent users, it was 19.0% and 24.1%, respectively. Using a PDC < 90%, non-adherence was 31.1% at 6 months and 36.9% at 1 year. In new users, it was 25.9% at 6 months and 33.2% at 1 year; in prevalent users, it was 33.0% and 38.2%, respectively (Table S5).

Regarding associations between patient characteristics and non-adherence (PDC < 80%) at 1 year, people < 65 years old were more likely to be non-adherent. People having a prescription from a cardiologist were more likely to be non-adherent [aOR 1.21, 95%CI (1.02–1.44)] while those using at least 5 drugs [aOR 0.75, 95%CI (0.65–0.86)] or having hypertension [aOR 0.84, 95%CI (0.73–0.97)] were less likely to be (Fig. 3, Table S6). Results for

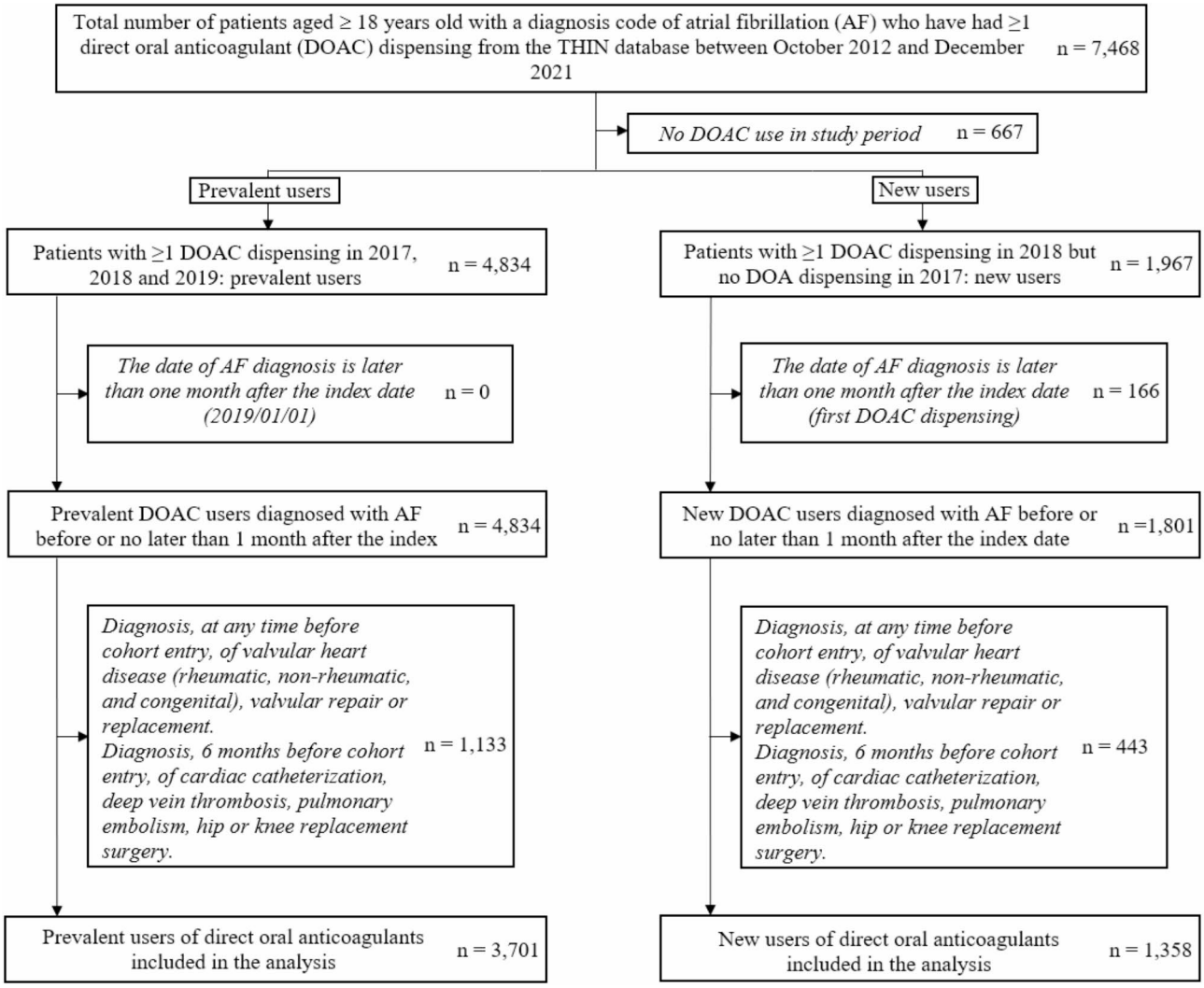

Fig. 2. Flow chart describing the sample selection.

Patient characteristics	All DOAC users, *n* (%) (*N* = 5,059)	New DOAC users, *n* (%) (*N* = 1,358)	Prevalent DOAC users, *n* (%) (*N* = 3,701)
Male	2,889 (57.1)	753 (55.4)	2,136 (57.7)
Age at baseline (years), mean ± SD	75.9 ± 9.6	74.5 ± 10.3	76.4 ± 9.3
< 65	607 (12.0)	229 (16.9)	378 (10.2)
65–74	1,502 (29.7)	394 (29.0)	1,108 (29.9)
75–84	1,941 (38.4)	500 (36.8)	1,441 (38.9)
≥ 85	1,009 (19.9)	235 (17.3)	774 (20.9)
Specialty of the prescriber			
General practitioner	4,082 (80.7)	1,050 (77.3)	3,032 (81.9)
Cardiologist	977 (19.3)	308 (22.7)	669 (18.1)
Comorbidities			
Cancer	1,171 (23.1)	291 (21.4)	880 (23.8)
Peripheral vascular disease	394 (7.8)	107 (7.9)	287 (7.8)
Coagulopathy	106 (2.1)	33 (2.4)	73 (2.0)
Congestive heart failure	474 (9.4)	115 (8.5)	359 (9.7)
Coronary heart diseases	643 (12.7)	174 (12.8)	469 (12.7)
Hypertension	3,430 (67.8)	870 (64.1)	2,560 (69.2)
Renal disease	273 (5.4)	58 (4.3)	215 (5.8)
Liver disease	189 (3.7)	49 (3.6)	140 (3.8)
Diabetes	1,067 (21.1)	269 (19.8)	798 (21.6)
Gastrointestinal disease	1,269 (25.1)	302 (22.2)	967 (26.1)
Hypercholesterolemia or hyperlipidemia	1,813 (35.8)	463 (34.1)	1,350 (36.5)
Chronic pulmonary disease	1,768 (34.9)	448 (33.0)	1,320 (35.7)
Psychiatric disorders except dementia	869 (17.2)	221 (16.3)	648 (17.5)
Dementia	52 (1.0)	17 (1.3)	35 (0.9)
Anemia	354 (7.0)	73 (5.4)	281 (7.6)
History of ischemic stroke, TIA, arterial systemic embolism	686 (13.6)	152 (11.2)	534 (14.4)
History of bleeding	897 (17.7)	193 (14.2)	704 (19.0)
Clinical risk score			
CHA_2DS_2-VASc score, mean ± SD	3.3 ± 1.5	3.2 ± 1.6	3.4 ± 1.5
0–1	569 (11.2)	204 (15.0)	365 (9.9)
2	931 (18.4)	262 (19.3)	669 (18.1)
3	1,273 (25.2)	321 (23.6)	952 (25.7)
≥ 4	2,286 (45.2)	571 (42.0)	1,715 (46.3)
HAS-BLED score, mean ± SD	2.1 ± 1.0	2.2 ± 1.1	2.1 ± 1.0
0–1	1,321 (26.1)	360 (26.5)	961 (26.0)
2	2,085 (41.2)	527 (38.8)	1,558 (42.1)
≥ 3	1,653 (32.7)	471 (34.7)	1,182 (31.9)
Charlson Comorbidity Index Score, mean ± SD	4.8 ± 2.2	4.6 ± 2.2	4.9 ± 2.1
0–2	535 (10.6)	202 (14.9)	333 (9.0)
3–4	1,999 (39.5)	554 (40.8)	1,445 (39.0)
5–6	1,528 (30.2)	363 (26.7)	1,165 (31.5)
≥ 7	997 (19.7)	239 (17.6)	758 (20.5)
Medication history			
Number of comedications*, median (p25, p75)	7 (4, 9)	7 (4, 10)	7 (4, 9)
Polypharmacy (≥ 5 drugs*)	3,632 (71.8)	1,002 (73.8)	2,630 (71.1)
Antiplatelet agents	556 (11.0)	387 (28.5)	169 (4.6)
NSAIDs	285 (5.6)	126 (9.3)	159 (4.3)
Lipid modifying agents	1,885 (37.3)	499 (36.7)	1,386 (37.4)
Antihypertensive drugs	4,243 (83.9)	1,135 (83.6)	3,108 (84.0)
Proton pump inhibitors	1,745 (34.5)	529 (39.0)	1,216 (32.9)

Continued

Patient characteristics	All DOAC users, *n* (%) (*N* = 5,059)	New DOAC users, *n* (%) (*N* = 1,358)	Prevalent DOAC users, *n* (%) (*N* = 3,701)
Antidiabetic drug	878 (17.4)	237 (17.5)	641 (17.3)
Antiarrhythmics	2,098 (41.5)	555 (40.9)	1,543 (41.7)
Antiepileptics	212 (4.2)	59 (4.3)	153 (4.1)
Psychotropic drugs	1,172 (23.2)	339 (25.0)	833 (22.5)
Prior use of VKA (only for new users)	N/A	296 (21.8)	N/A

Table 1. Baseline characteristics of all users, new users and prevalent users of direct oral anticoagulant (DOAC) in patients with non-valvular atrial fibrillation. *Excluding DOAC. Details of the ICD-10 codes used for diagnostics and ATC codes used for drugs are presented in *Table S4*. *DOAC: direct oral anticoagulant; NSAIDs: non-steroidal anti-inflammatory drug; TIA: transient ischemic attack; SD: standard deviation; VKA: vitamin K antagonist*.

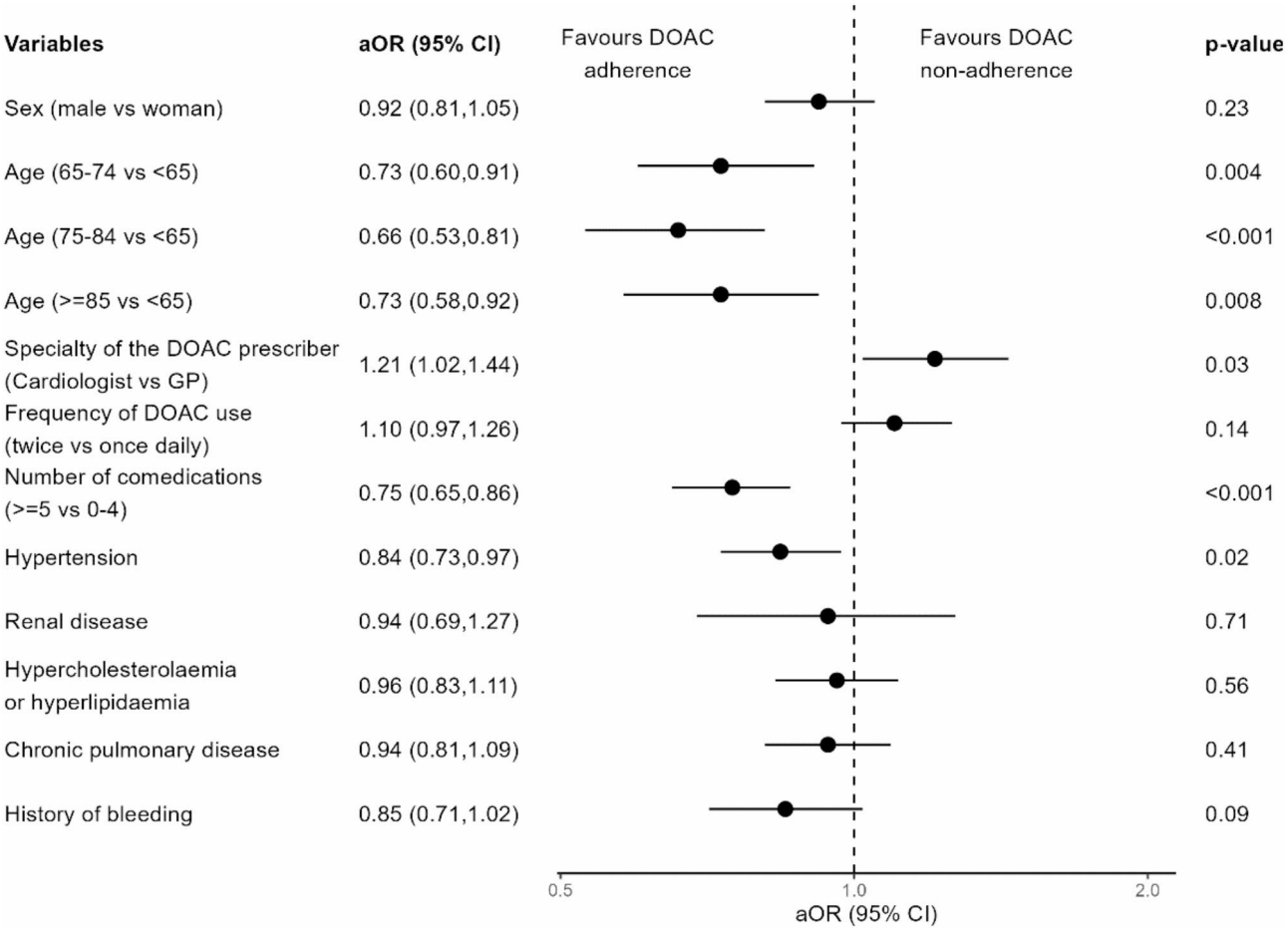

Fig. 3. Factors associated with non-adherence to DOAC using an 80% threshold at 1 year in all users (*N* = 5,059). *aOR: adjusted odds ratio; DOAC: direct oral anticoagulants GP: general practitioner.* Details of the ICD-10 codes used for diagnostics are presented in Table S4.

sensitivity analyses, i.e. factors associated with non-adherence for PDC < 80% at 6 months and PDC < 90% at 6 months and 1 year, are presented in Table S6 and Figure S1-S2.

DOAC non-persistence and associated factors

Overall, non-persistence with the > 30-day supply gap was 16.1% at 6 months and 28.4% at 1 year; with the > 60-day supply gap it was 9.0% and 19.7%, respectively (Table S7). In new users, non-persistence (> 30-day supply gap) was 18.0% at 6 months and 29.8% at 1 year; with the > 60-day supply gap it was 11.9% and 22.8%, respectively (Table S7). In prevalent users, non-persistence (> 30-day supply gap) was 15.3% at 6 months and 27.9% at 1 year; with the > 60-day supply gap it was 7.9% and 18.5%, respectively (Table S7).

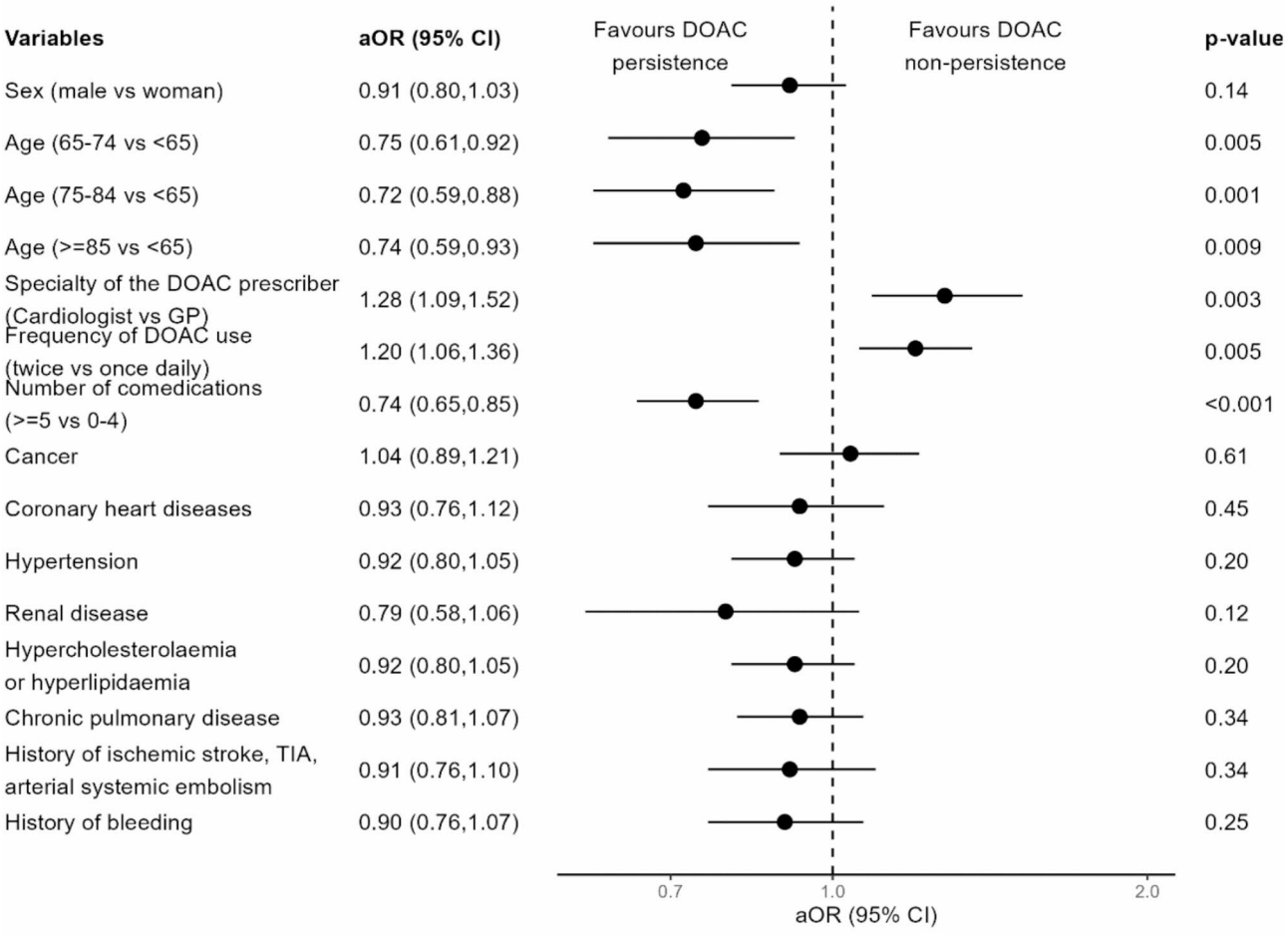

Fig. 4. Factors associated with non-persistence of DOAC using a 30-day gap at 1 year in all users ($N = 5{,}059$). *aOR: adjusted odds ratio; DOAC: direct oral anticoagulants GP: general practitioner.* Details of the ICD-10 codes used for diagnostics are presented in Table S4.

Regarding the associations with non-persistence (>30-day supply gap) at 1 year, people using at least 5 drugs were less likely to be non-persistent [aOR 0.74, 95%CI (0.65–0.85)] while those < 65 years of age, having a prescription from a cardiologist [aOR 1.28, 95%CI (1.09–1.52)] or taking twice-daily dosing [aOR 1.20, 95%CI (1.06–1.36)] were more likely to be (Fig. 4). Results for sensitivity analyses, i.e. factors associated with non-persistence for >30-day supply gap at 6 months and >60-day supply gap at 6 months and 1 year, are presented in Table S6 and Figure S3-S4.

Discussion

In this French study of 5,059 DOAC users (1,358 new DOAC users and 3,701 prevalent DOAC users), overall non-adherence during the implementation phase was rather high. At 6 months, it was slightly higher in prevalent users than in new users (19.0% vs. 17.8%) and at 1 year, almost the same (24.1% vs. 24.4%). Unlike the French study conducted among new users in 2013[6], which did not include apixaban, we found that non-adherence at 1 year was lower, both using a PDC < 80% (24.4% vs. 39.1%[6]) or a PDC < 90% (33.2% vs. 52.1%[6]). Although our results were comparable in terms of PDC < 80% at 1 year (24.4% vs. 24.5%[27]) to those of a more recent study among new users in the Netherlands[27], they were lower when using a PDC < 90% (33.2% vs. 39.4%[27]).

While short DOAC half-lives make adherence essential to reducing the thromboembolic risk[10,27,32], a quarter of the patients in our study had sub-optimal adherence. As clinical results are better using a 90% threshold, some authors have questioned the arbitrary 80% threshold for DOAC[28,33,34]. By using a PDC < 90% as the new definition of non-adherence, we showed that more than one-third of NVAF patients were non-adherent at 1 year, thereby highlighting the importance of reducing non-adherence.

With regard to non-persistence, levels were slightly higher in new users than prevalent users. Extending the length of the admissible gap without drug supply from 30 to 60 days considerably reduced non-persistence from 16.1% to 9.0% at 6 months and from 28.4% to 19.7% at 1 year. A study among new users in 6 European countries showed that non-persistence (30-day gap) at 1 year ranged from 16.0% for the UK to 63.9% for Germany[19]. France had a non-persistence rate of 26.6%[19], which was similar to our rate of 28.4%. Although treatment should ideally be continuous to obtain the optimum clinical results[27], a significant proportion of patients were not

persistent. It is important to stress that even short interruptions in treatment, e.g., for 7 consecutive days, can lead to a risk of stroke due to a potential rebound phenomenon, and that, without reducing the risk of major bleeding[35].

Regarding associated factors, non-adherence and non-persistence were associated with people < 65 years old, an association that is known from the literature[14,27,35–38]. One explanation could be that older patients have a better understanding of their disease and of the benefits of their treatment[6] than younger patients, whose busy lifestyles make them more likely to forget to take their medication[38]. Another factor associated with better adherence and persistence was having ≥ 5 comedications. While this might be surprising, it has already been found in other studies with DOAC[27,35,37,39]. One possible hypothesis is that polymedicated patients often have chronic pathologies and might already have been made aware of the importance of treatment adherence and persistence. With regard to DOAC user types, there was no significant association in primary outcomes. However, when we use a PDC < 90% as definition of non-adherence and > 60-day supply gap as definition of non-persistence, prevalent users were more likely to be non-adherent than new users, but less likely to be non-persistent. Finally, in some studies, a history of stroke was previously reported to be associated with increased adherence[35,40], and a history of bleeding was previously reported to be associated with poor adherence and/or persistence[35,41,42]. However, in our study, we found no significant association.

The main strength of our study lies in the use of real-world data (RWD) from routine clinical practice. As the THIN database includes data from a panel of physicians and patients that is representative in terms of sex, age and geographical area, these results can be extrapolated nationwide. Two other strengths are our coverage of a broad spectrum of patients with NVAF comprising new and prevalent DOAC users, and our use of data to take home stockpiling into account to identify supply gaps. However, this study also has some limitations. First, adherence was measured on the basis of dispensing data; while this assumed that any drugs dispensed were taken, there was no possibility of checking actual drug intake. Secondly, as our database contained no information on the reasons for non-adherence or non-persistence, we were unable to determine whether either resulted from a patient's decision or a physician's recommendation. Thirdly, at the time of data extraction, dates of death were not yet available in the database. Finally, the lifestyle characteristics (e.g., smoking status) contained too many missing values and were not usable.

Regarding implications for clinical practice and perspectives, the stroke-risk reduction expected from DOAC may not be optimal for all patients in daily clinical practice. Using a PDC < 80% at 1 year, we found that 1 out of 4 patients was non-adherent; using a PDC < 90%, we found that more than 1 out of 3 was non-adherent. Almost 30% of patients were non-persistent. We also found that being aged < 65 years was associated with non-adherence or non-persistence. Sufficient therapeutic education could therefore enable this population to understand the need for optimal adherence and persistence and their effects on the disease. In everyday practice, adherence could be improved by developing individualized strategies for each patient[14] and also by an active multidisciplinary patient-centered approach[3,14,35]. Patients' regular scheduled contact with their physician[14,32,43], their patient's inclusion in the care process (not just in therapeutic education) and their improved knowledge of their disease have all been shown to improve adherence and persistence[2,14,43]. In future, further studies will be needed to quantify the impact of non-adherence or non-persistence, and the duration of both, on the risk of thromboembolic events, major bleedings and death.

Data availability

The data that support the findings of this study are available from GERS DATA but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of GERS DATA.

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Author contributions

VF and SH conceived and designed the study. VF performed the statistical analysis, interpreted the data, and drafted the article. SH, AS and LZ critically revised the manuscript. All authors contributed to the article and approved the submitted version.

Declarations

Competing interests
The authors declare no competing interests.

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