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CLINICAL RESEARCH

Apixaban for prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation in France: The PAROS cross-sectional study of routine clinical practice

Apixaban pour la prévention de l'accident vasculaire cérébral et des embolies systémiques chez les patients avec fibrillation atriale non valvulaire en France : résultats de l'étude cross -sectionnelle PAROS en pratique clinique quotidienne

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Abbreviations: AF, atrial fibrillation; CI, confidence interval; NOAC, non-vitamin K antagonist oral anticoagulant; NVAF, non-valvular atrial fibrillation; SmPC, summary of product characteristics; VKA, vitamin K antagonist.

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KEYWORDS
Anticoagulation;
Atrial fibrillation;
Non-vitamin K antagonist oral anticoagulants;
Observational study;
Vitamin K antagonists

Summary
Background. — Non-vitamin K antagonist oral anticoagulants (NOACs), including apixaban, are recommended for prevention of stroke and systemic embolism in non-valvular atrial fibrillation (NVAF).
Aims. — To describe the characteristics of patients starting anticoagulant treatment, identify the characteristics associated with apixaban prescription, and describe apixaban use in France.
Methods. — This was a non-interventional multicentre French study. Patients with NVAF (aged $\geq$ 18 years) with anticoagulant treatment started in the preceding 3 months were evaluated in four groups (NOAC [apixaban, dabigatran or rivaroxaban] or vitamin K antagonist [VKA]).
Results. — Data from 2027 patients were eligible for analysis. Mean age was 73.0 $\pm$ 11.2 years, 56.6% were men and 80.2% were anticoagulant naïve. Stage $\geq$ 4 chronic kidney disease was present in 2.2% of patients prescribed apixaban, none of those prescribed dabigatran or rivaroxaban, and 16.8% of those prescribed VKAs. The median CHA_2DS_2-VASc score was 3 for all three NOACs and 4 for VKAs; the median HAS-BLED score was $\geq$ 3 for 2.5—5.9% of patients prescribed NOACs and 12.0% of those prescribed VKAs. Apixaban was more likely to be prescribed than other NOACs in older patients with higher bleeding risk and decreased renal function, and VKAs in patients with lower bleeding risk and better renal function. Patients received a reduced dose (5 mg/day; 30.4% patients) or a full dose (10 mg/day; 69.6% patients) of apixaban. Only 79.3% of patients prescribed apixaban had doses consistent with the summary of product characteristics; underdosing was more frequent than overdosing. Off-label use of apixaban was observed, mainly in elderly patients, despite normal renal function and weight.
Conclusions. — Initiation of apixaban versus NOACs was more common among patients with increased age, higher bleeding risk and decreased renal function, whereas initiation of apixaban versus VKAs was more common among patients with lower bleeding risk and better renal function.

MOTS CLÉS
Anticoagulation ;
Fibrillation auriculaire ;
Anticoagulants directs oraux ;
Étude observationnelle ;
Antivitamine K

Résumé
Contexte. — Les anticoagulants oraux directs (AOD) sont recommandés dans la prévention de l'AVC et de l'embolie systémique chez des patients atteints de FANV.
Objectifs. — Décrire les caractéristiques des patients initiant un traitement anticoagulant, les caractéristiques associées à la prescription et les conditions d'utilisation d'apixaban.
Méthodes. — Étude multicentrique non-interventionnelle, menée en France. Patients atteints de FANV ($\geq$ 18 ans), ayant initié un anticoagulant dans les 3 derniers mois, évalués en 4 groupes.
Résultats 2027 patients, âge moyen 73,0 $\pm$ 11,2 ans, 56,6 % d'hommes et 80,2 % de patients naïfs d'anticoagulant. Une insuffisance rénale stade $\geq$ 4 concernait 2,2 % des patients apixaban (aucun avec les autres AOD) et 16,8 % des patients AVK. Le HA_2DS_2-VASc médian était de 3 (AOD) et de 4 (AVK) et le HAS-BLED était $\geq$ 3 pour 2,5—5,9 % des patients (AOD) et 12,0 % (AVK). Il était plus probable qu'apixaban soit prescrit qu'un autre AOD chez les patients âgés avec un risque de saignement plus élevé et une fonction rénale diminuée, et plus probable qu'un AVK chez les patients avec un risque de saignement diminué et une meilleure fonction rénale. Les patients ont reçu une dose d'apixaban réduite (5 mg/jour; 30,4 % des patients) ou complète (10 mg/jour; 69,6 % des patients). Au total, 79,3 % des patients apixaban ont reçu des doses conformes au RCP.
Conclusions. — L'initiation d'apixaban versus AOD dans la FANV était associée à un âge plus élevé, un risque saignement plus important, et une fonction rénale diminuée, alors que l'initiation d'apixaban versus AVK était associée à un faible risque de saignement et une meilleur fonction rénale.

Background

Atrial fibrillation (AF) is an important public health problem and the most common arrhythmia worldwide [1], with an overall incidence of approximately 2% in Europe, and incurs significant healthcare costs [2]. AF is associated with significant mortality and morbidity: the incidence of stroke is fivefold higher and the incidence of death is twofold higher in patients with AF [3–6]. The incidence of AF increases with age, and it is more common in men than women [2]. With an ageing population in Europe, AF is likely to become more common, which will have major implications in terms of disease burden as well as public health expenditure.

Vitamin K antagonists (VKAs) have been the reference oral anticoagulant treatment in patients with AF for over 50 years. However, VKAs are associated with a range of food and drug interactions and, because of their narrow therapeutic window, require regular monitoring.

Over the last decade, non-VKA oral anticoagulants (NOACs) that target the enzymatic activity of thrombin or factor Xa have been developed. The NOACs marketed currently in France include the direct thrombin inhibitor dabigatran and the direct factor Xa inhibitors rivaroxaban and apixaban [7]. These new drugs offer advantages over VKAs, with no need for routine coagulation monitoring or individual dosing because they have predictable pharmacokinetics, low drug-drug and dietary interactions, short half-lives and wide therapeutic windows. Randomized clinical trials comparing these agents with VKAs in non-valvular AF (NVAF) have shown a favorable risk-benefit profile overall [8–12], and the European Society of Cardiology guidelines recommend the use of these agents in first-line prevention of stroke and systemic embolism in patients with NVAF [13].

In June 2013, the French Health Authority Transparency Commission (Commission de la Transparence de la Haute Autorité de Santé) approved the reimbursement of apixaban for the indications of stroke prevention and systemic embolism in patients with NVAF with one or more risk factors, including previous stroke or transient ischaemic attack, age $\geq$ 75 years, hypertension, diabetes mellitus and symptomatic heart failure [14]. However, existing data pertaining to NOACs were obtained from an often highly selected population of randomized trial participants, who can differ substantially from patients encountered in routine clinical practice [15,16]. There are few real-life data on NOACs in France; these are needed to describe the characteristics of patients prescribed apixaban and information about apixaban dosing in real-life practice (as two doses are currently recommended, depending on the patient profile).

The rationale and design of the PAROS study have been published previously [17]. This non- interventional study was conducted in patients with AF in France who had recently started anticoagulant treatment with a NOAC (apixaban, dabigatran or rivaroxaban) or a VKA. The main aims were to compare real-life data on patient characteristics in each anticoagulant group, and to describe the dosing characteristics in patients with newly initiated apixaban treatment.

Methods

Study design and patients

This was a non-interventional cross-sectional multicentre study conducted in France [17]. The study protocol was approved by the appropriate French authorities (Autorité Nationale de la Protection de la Vie Privée, Commission Nationale de l'Informatique et des Libertés and Conseil National de l'Ordre des Médecins) and by the relevant ethics committees and/or local governance bodies for each site. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and Good Epidemiological Practice. As the study was non-interventional, it did not affect the patient-physician relationship or the care and follow-up provided to the patient, and the physicians (investigators) were the sole deciders about drug prescriptions and patient follow-up. According to French law, patient identity was protected, but patients' informed consent was not required. The study was conducted between January 2016 and August 2016 with cardiologists in mainland France. To minimize a potential bias in centre selection, stratification of the participating physicians was performed according to the type of practice (hospital/mixed or office based) and geographical region.

Male and female patients aged $\geq$ 18 years with a diagnosis of NVAF and with NOAC (apixaban, dabigatran or rivaroxaban) or VKA treatment initiated in the preceding 3 months or on the day of enrolment were eligible for inclusion. The main exclusion criteria were AF resulting from reversible causes, a diagnosis of valvular AF (i.e. AF related to rheumatic valvular disease [predominantly mitral stenosis] or prosthetic heart valves) [13] or ongoing participation in a separate AF clinical study. Patient enrolment was planned to be limited to 12 patients per study site, and was stratified on treatment initiated, with up to six patients with newly initiated apixaban treatment, up to three patients with newly initiated treatment with another NOAC and up to three patients with newly initiated VKA treatment.

Study objectives

The primary objective of the study was to describe patient and disease characteristics, co-morbidities and treatment history in patients with NVAF starting a new anticoagulant treatment, and to compare these characteristics between apixaban and other anticoagulant treatments (other NOACs and VKAs) in anticoagulant-naïve patients. Secondary objectives included a description of dose characteristics in patients with NVAF with newly initiated apixaban treatment.

Study assessments

To evaluate the primary and secondary objectives, and to allow calculation of renal clearance using the Cockcroft formula, the CHA_2DS_2-VASc score [18], the HAS-BLED score (excluding the labile international normalized ratio component) [19] the Charlson Comorbidity Index (adjusted for age) score [20], the presence of concomitant treatments with a potential interaction with the anticoagulant treatment, detailed patient and disease characteristics, co-morbidities,

treatment history and apixaban prescription details were recorded. The data collected have been described previously [17].

Statistical analyses

For the primary objective, subgroups were defined based on the newly initiated anticoagulant treatment (i.e. apixaban, another NOAC or a VKA). Continuous variables are described using means ± standard deviations, medians (interquartile ranges) and maximum and minimum values; categorical variables are described using the numbers and percentages of patients in each category. For analyses of the primary objective, missing data were imputed using multiple imputation by fully conditional specification (or multivariable imputation by chained equations) [21]. For anticoagulant-naïve patients (i.e. those not previously treated with an anticoagulant), patient characteristics were compared between subgroups using multivariable logistic regression to identify potential characteristics associated with the choice of the newly initiated anticoagulant treatment. Two separate multivariable logistic regression models were used: one comparing the characteristics of patients treated with apixaban versus the other NOACs; and one comparing patients treated with apixaban versus a VKA. In both cases, treatment with apixaban was considered the event of interest. All covariates and modalities included in each model were selected *a priori* based on clinical relevance only, and no further selection, including on statistical considerations, was performed. The absence of co-linearity between covariates was assessed before the analyses. Analyses for the secondary objectives were only descriptive.

Because of the stratified enrolment of patients and the risk of selection bias, population weighting methods were used for all descriptive analyses, with the exception of the description of apixaban dose characteristics, based on three distinct aspects: at the patient level, based on the frequency of visits by the patient to the centre over the last year, to account for unbalanced probability of sampling across patients; at the site level, based on the overall activity of the centre, to account for the predetermined cap of 12 enrolled patients; and at the subgroup level, based on the observed distribution of anticoagulant newly prescribed to patients with NVAF by cardiologists (data on file from a database analysis), to account for the stratified structure of the patient sample. A single weight, corresponding to the product of the three aspects described above, was applied for each patient.

A sample size of 1800 patients ($n = 1000$ for apixaban, $n = 400$ for the other NOACs and $n = 400$ for VKAs) was calculated based on the descriptive analyses for the primary objective. The sample size calculation has been described fully [17], and ensured a precision (95% confidence interval [CI] width) of ± 5% around the proportion of each patient/disease characteristic, co-morbidity and treatment history variable.

Statistical analyses were performed using SAS® software, version 9.4 (SAS Institute, Cary, NC, USA).

Results

Investigators and patients

Approximately 90% of French cardiologists ($n = 6109$) were contacted, of whom 177 (2.9%) agreed to take part in the study and enrolled at least one patient. The main regions of France were represented equally: 17.5% in Paris and the surrounding area; 16.4% in the north west; 23.2% in the north east; 24.3% in the south east; and 18.6% in the south west. No differences in age and sex were found between participating and non-participating physicians. There was, however, an over-representation of physicians from private practices among participating compared with non-participating physicians (58.2% and 36.4%, respectively).

A median of 11 (9, 12) patients were included by each investigator, with most (71.8%) recruiting 7—12 patients. A total of 27 investigators (15.2%) recruited more than the maximum of 12 patients planned per investigator; in each case the Sponsor authorized the extra inclusion (s), and ensured that the same stratification was used as was defined for the first 12 patients.

A total of 2081 patients were enrolled in the study, of whom 2027 (97.4%) were considered eligible and included in the analysis population (reasons for exclusion were: no anticoagulant initiated at the visit or in the previous 3 months [$n = 49$]; no diagnosis of NVAF available [$n = 3$]; and missing selection criteria [$n = 2$]). Patient disposition is summarized in Fig. 1.

Among eligible patients, apixaban, dabigatran, rivaroxaban and VKAs were initiated in 52.2%, 4.9%, 20.8% and 22.0% of patients, respectively. After weighting, the corresponding proportions were 38.6%, 10.0%, 36.2% and 15.1%, respectively, meaning that 84.8% of patients overall received NOACs (apixaban, dabigatran, rivaroxaban), with 46.2% receiving dabigatran or rivaroxaban.

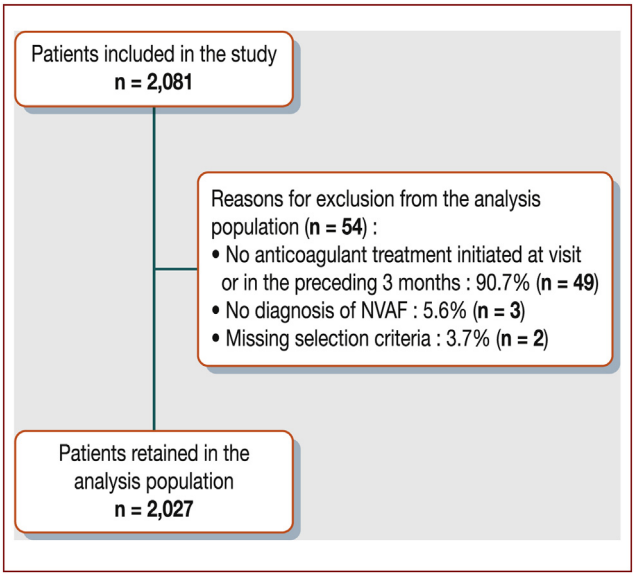

Figure 1. Patient disposition. NVAF: non-valvular atrial fibrillation.

Characteristics of the population

Patient characteristics are presented in Table 1. The mean age was 73.2 ± 11.4 years, 72.2 ± 9.5 years and 71.1 ± 11.2 years for the apixaban, dabigatran and rivaroxaban subgroups, respectively, and 77.7 ± 10.5 years for the VKA group. There was also a numerically higher percentage of patients aged > 80 years in the VKA group (49.9%) compared with the apixaban, dabigatran and rivaroxaban groups (33.7%, 24.8% and 23.4%, respectively). In each group, most patients (56.6% overall) were men. Mean body mass index was similar in each group (overall 27.5 ± 5.3 kg/m^2). Most patients (89.5% overall) in each group were living at home with no assistance.

The NVAF diagnosis had been made in the 6 months preceding study entry for 76.9% of patients overall. For most patients in each group, NVAF was either paroxysmal (43.5% overall) or persistent (45.8% overall).

Chronic kidney disease, assessed through creatinine clearance calculated using the Cockcroft and Gault formula (Stage 1: ≥ 90 mL/min; Stage 2: ≥ 60 and < 90 mL/min; Stage 3: ≥ 30 and < 60 mL/min; Stage 4: ≥ 15 and < 30 mL/min; Stage 5: < 15 mL/min), was Stage 1 or Stage 2 for the majority of patients in the apixaban (66.8%), dabigatran (65.7%) and rivaroxaban groups (78.6%). For patients treated with NOACs, all patients with Stage 4 (2.1%) and Stage 5 (0.1%) chronic kidney disease were in the apixaban group. Among patients treated with VKAs, none was Stage 1, 33.9% were Stage 2, 40.2% were Stage 3, 15.7% were Stage 4 and 1.1% were Stage 5.

The mean CHA_2DS_2-VASc score was 3.2 ± 1.6, 3.1 ± 1.6 and 2.9 ± 1.5 for the apixaban, dabigatran and rivaroxaban groups, respectively, and 3.8 ± 1.6 for the VKA group. The proportion of patients with a score ≥ 3 was 67.7%, 62.3% and 60.6% for the apixaban, dabigatran and rivaroxaban groups, respectively, and 83.0% for the VKA group. The most common factors leading to an elevated CHA_2DS_2-VASc score for each group were arterial hypertension (overall 69.1%) and age ≥ 75 years (overall 47.8%).

The HAS-BLED score was measured without considering the labile international normalized ratio component; the theoretical range was therefore 0–8. The mean HAS-BLED score was 1.2 ± 0.8, 1.2 ± 0.7 and 1.1 ± 0.8 for the apixaban, dabigatran and rivaroxaban groups, respectively, and 1.5 ± 0.8 for the VKA group. The most common factor leading to an elevated HAS-BLED score in each group was age ≥ 65 years (overall 77.7%). Concomitant treatments that could induce bleeding (not otherwise specified) and renal insufficiency were numerically more common for VKAs than for NOACs (19.9% vs. 10.0–12.2% and 12.8% vs. 0.2–2.1%).

The mean Charlson score was 4.7 ± 2.4, 4.4 ± 2.2 and 4.1 ± 2.1 for the apixaban, dabigatran and rivaroxaban groups, respectively, and 6.1 ± 2.6 for the VKA group. The proportion of patients with a score of ≥ 5 was 51.0%, 40.1% and 36.6% for the apixaban, dabigatran and rivaroxaban groups, respectively, and 78.0% for the VKA group. Factors leading to an elevated Charlson score that were numerically higher in the VKA group than in the apixaban, dabigatran and rivaroxaban groups, respectively, included creatinine clearance < 60 mL/min (56.9% vs. 33.1%, 34.3% and 21.4%), cardiac failure (33.0% vs. 18.7%, 25.2% and 21.0%), peripheral vascular disease (26.7% vs. 16.7%, 7.9% and 14.1%), transient ischaemic attack/cerebrovascular accident/systemic embolism (13.7% vs. 9.8%, 9.7% and 10.3%) and myocardial infarction (15.4% vs. 9.6%, 3.2% and 5.8%). Age was also an important factor associated with higher Charlson scores, particularly in the VKA group, with 49.9% of patients aged ≥ 80 years.

The majority of patients in each group were anticoagulant naïve (i.e. had not received any previous anticoagulant treatment): 78.2%, 70.6%, 83.9% and 82.6% in the apixaban, dabigatran, rivaroxaban and VKA groups, respectively (Table 2). In the NOAC treatment groups, VKAs were the most common previous anticoagulant treatments (65.4%, 68.6% and 78.5% of patients in the apixaban, dabigatran and rivaroxaban groups, respectively)—most commonly fluindione (86.4% of previous VKA treatment overall). In the VKA treatment group, apixaban (39.3%) and rivaroxaban (33.7%) were the most common previous anticoagulant treatments (Table 2).

Characteristics associated with choice of newly initiated anticoagulant treatment

The multivariable analysis of patient characteristics for anticoagulant-naïve patients treated with apixaban versus other NOACs (dabigatran and rivaroxaban) (Fig. 2 and Table A.1) indicated overall that prescription of apixaban was associated with patient profiles with a slightly higher risk of bleeding. Patients with creatinine clearance < 50 mL/min were 1.8 times more likely to receive apixaban (95% CI 1.2–2.6), and patients with diabetes were 1.4 times more likely to be treated with apixaban (95% CI 1.0–1.9). Study investigators were more likely to prescribe apixaban than another NOAC compared with GPs; however, this is likely to result from aspects of the study design, and this variable was added for adjustment purposes. No other tested covariate was considered significant in this model (Table A.1).

The multivariable analysis of patient characteristics for anticoagulant-naïve patients treated with apixaban versus VKAs (Fig. 3 and Table A.2) indicates, in contrast with the previous model, that apixaban prescription was associated with patient profiles with a lower risk of bleeding. Patients with creatinine clearance ≥ 50 mL/min were 4.1 times more likely to receive apixaban than a VKA (95% CI 3.0–5.6), those living at home without assistance were 1.6 times more likely to receive apixaban (95% CI: 1.0–2.4), those without a previous bleeding episode or disposition to bleeding were 4.4 times more likely to receive apixaban (95% CI 1.9–9.8), those without a peripheral vascular illness were 1.6 times more likely to receive apixaban (95% CI 1.1–2.4) and those who had not received at least one concomitant antiplatelet agent were 1.5 times more likely to be treated with apixaban (95% CI 1.0–2.1). As for the comparison of apixaban with other NOACs (above), study investigators were more likely to prescribe apixaban than a VKA compared with GPs.

In these multivariable models, there was no association of sex, age, weight, risk of stroke (transient ischaemic attack/cerebrovascular accident/systemic embolism), hepatic insufficiency or peptic ulcer with the likelihood of apixaban use compared with other NOACs or VKAs.

Table 1 Patient characteristics by treatment.

	Treatment				
	Apixaban	Dabigatran	Rivaroxaban	VKA	Total
Age (years)					
Mean ± SD	73.2 ± 11.4	72.2 ± 9.5	71.1 ± 11.2	77.7 ± 10.5	73.0 ± 11.2
Median (IQR)	74 (67.0, 92.0)	72 (66.9, 79.0)	72 (65.0, 79.0)	79 (70.0, 86.0)	74 (66.0, 82.0)
Range	25–95	34–89	22–96	24–102	22–102
18–49	4.2	1.7	4.5	0.8	3.5
50–64	14.4	17.2	20.5	10.0	16.2
65–74	31.6	37.5	35.6	23.7	32.5
75–79	16.1	18.8	16.0	15.6	16.3
≥ 80	33.7	24.8	23.4	49.9	31.5
Sex					
Male	56.4	56.8	57.3	55.3	56.6
Female	43.6	43.2	42.7	44.7	43.4
BMI (kg/m^2)					
< 18.5	1.4	4.6	0.9	1.4	1.6
18.5–24.9	33.8	19.2	34.1	35.3	32.7
25–29.9	39.9	51.1	39.2	38.4	40.5
≥ 30	24.8	25.0	25.8	24.9	25.2
Degree of dependence					
Living at home (no assistance)	89.8	88.5	93.6	79.8	89.5
Living at home (with assistance)	8.4	1.2	5.5	6.8	8.9
Living in nursing home	1.9	0.3	0.9	3.4	1.6
Time since NAVF diagnosis					
< 6 months	76.3	72.7	78.1	78.4	76.9
6 months to 1 year	3.7	6.6	4.0	5.0	4.3
> 1 year	20.0	20.8	18.0	16.6	18.8
Type of NAVF					
Paroxysmal	43.2	41.8	46.6	37.9	43.5
Persistent	45.7	36.8	46.5	50.2	45.8
Permanent	11.1	21.4	7.0	11.9	10.8
Renal function (creatinine clearance[a], mL/min)					
Stage 1 (≥ 90 mL/min)	20.4	22.1	27.2	0.0	NC
Stage 2 (≥ 60 to < 90 mL/min)	46.4	43.6	51.4	33.9	NC
Stage 3 (≥ 30 to < 60 mL/min)	30.9	34.3	21.4	40.2	NC
Stage 4 (≥ 15 to < 30 mL/min)	2.1	0.0	0.0	15.7	NC
Stage 5 (< 15 mL/min)	0.1	0.0	0.0	1.1	NC
CHA_2DS_2-VASc score					
Mean ± SD	3.2 ± 1.6	3.1 ± 1.6	2.9 ± 1.5	3.8 ± 1.6	3.2 ± 1.6
Median	3	3	3	4	3
Range	0–8	0–8	0–8	0–8	0–8
≤ 1	14.7	10.3	19.3	7.5	14.8
2	17.7	27.4	20.2	9.6	18.3
≥ 3	67.7	62.3	60.6	83.0	66.9
HAS-BLED score					
Mean ± SD	1.2 ± 0.8	1.2 ± 0.7	1.1 ± 0.8	1.5 ± 0.8	1.2 ± 0.8
Median	1	1	1	1	1
Range	0–4	0–3	0–4	0–5	0–5
< 3	94.1	97.4	94.6	88.0	93.7
≥ 3	5.9	2.5	5.4	12.0	6.3
Charlson score (adjusted for age)					
Mean ± SD	4.7 ± 2.4	4.4 ± 2.2	4.1 ± 2.1	6.1 ± 2.6	4.7 ± 2.4
Median	5	4	4	6	4
Range	0–16	0–12	0–13	0–14	0–16
≤ 1	7.2	4.4	8.1	2.8	6.6
2	11.3	13.1	13.1	4.1	11.0
3	12.1	19.4	21.8	10.2	16.0
4	18.4	23.0	20.5	12.2	18.7
≥ 5	51.0	40.1	36.6	70.8	47.7

Data are expressed as percentage of patients, unless otherwise indicated. BMI: body mass index; IQR: interquartile range; NAVF: non-valvular atrial fibrillation; NC: not calculated; SD: standard deviation; VKA: vitamin K antagonist.

[a] Creatinine clearance calculated using Cockcroft and Gault formula.

Table 2 Previous anticoagulant treatments.

	Current AC treatment				
	Apixaban	Dabigatran	Rivaroxaban	VKA	Total
Previous AC treatment	21.8	29.4	16.1	17.4	19.8
Type of AC treatment					
Apixaban	0.0	6.1	10.8	39.3	9.3
Dabigatran	8.3	8.0	4.2	18.0	8.3
Rivaroxaban	18.8	8.4	3.9	33.7	14.8
VKA[a]	65.4	68.6	78.5	2.0	61.3
Other AC	7.6	8.9	2.5	6.9	6.2

Data are expressed as percentage of patients. AC: anticoagulant; VKA, vitamin K antagonist.
[a] Fluindione (86.4%); coumadin (8.8%); acenocoumarol (4.8%).

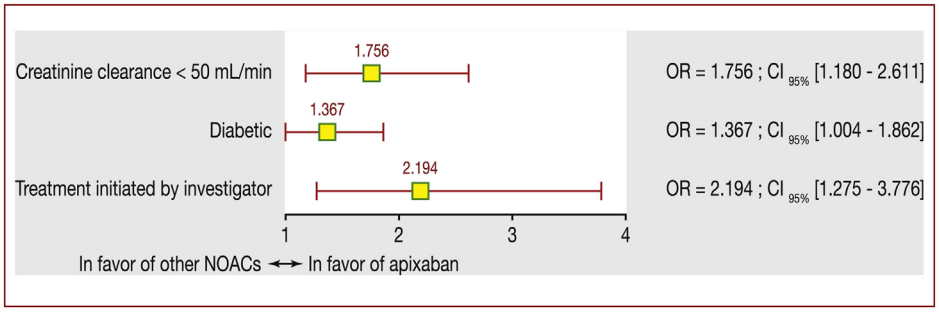

Figure 2. Multivariable logistic regression model of anticoagulant-naïve patient characteristics associated with treatment with apixaban versus other non-vitamin K antagonist oral anticoagulants (NOACs). CI: confidence interval; OR: odds ratio.

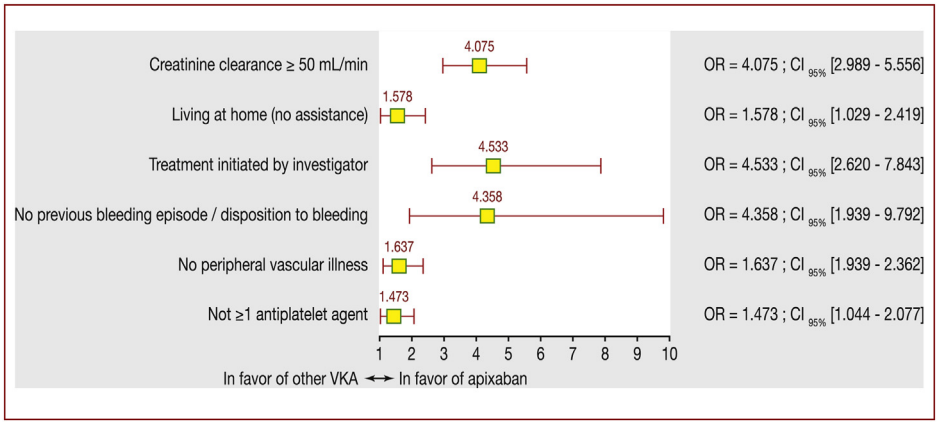

Figure 3. Multivariable logistic regression model of anticoagulant-naïve patient characteristics associated with treatment with apixaban versus vitamin K antagonists (VKAs). CI: confidence interval; OR: odds ratio.

Apixaban dosing characteristics

Among the 1059 patients treated with apixaban, 30.4% received a total daily dose of 5 mg (2.5 mg twice daily [adjusted dose]) and 69.6% received 10 mg (5 mg twice daily [full dose]).

The criteria justifying the use of an adjusted dose are described in the summary of product characteristics (SmPC) for apixaban. Dose adjustment required at least two of the following three criteria: age $\geq$ 80 years; weight $\leq$ 60 kg; serum creatinine $\geq$ 1.5 mg/dL; or creatinine clearance < 30 mL/min. Among patients treated with an adjusted dose, 36.3% had the appropriate criteria for this dosage, while among those treated with a full dose, 98.1% had the appropriate criteria for this dosage. Overall, 79.3% of patients were treated in accordance with SmPC dosing recommendations (Fig. 4 and Table A.3). For patients receiving an adjusted dose without fulfilling the corresponding criteria, 24.1% had at least one concomitant antiplatelet agent, while 16.9% of patients receiving a full dose (and not fulfilling the adjusted-dose criteria) were treated concomitantly with these agents. For those treated with an adjusted dose fulfilling only one reduced-dose criterion, the most common criterion was age $\geq$ 80 years. Among patients treated with an adjusted dose and only fulfilling the age criterion ($\geq$ 80

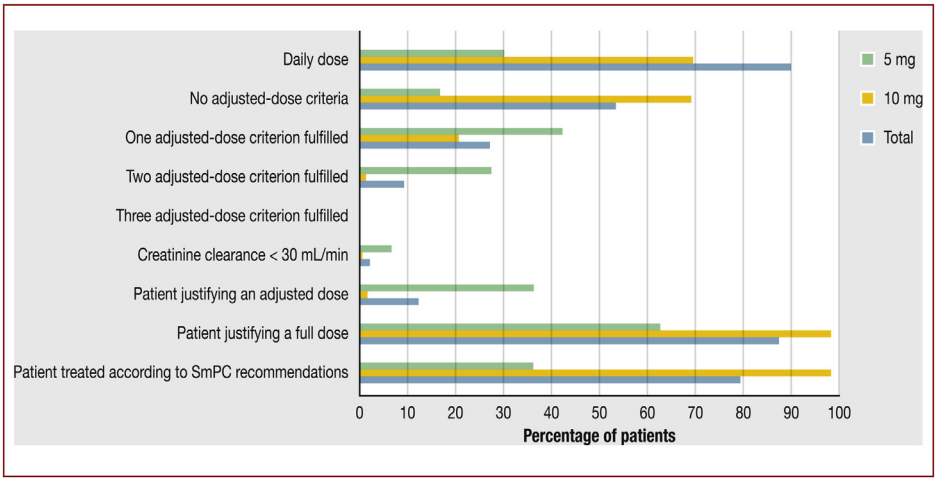

Figure 4. Apixaban dose characteristics. SmPC: summary of product characteristics.

years), median creatinine clearance was 58.3 (47.1, 70.0) mL/min.

Discussion

This observational study provides data on the use of apixaban in France in more than 2000 patients with NVAF, whose demography was consistent with that previously described for NVAF [22,23].

The prescription of VKAs and NOACs based on the risk of stroke in patients with NVAF using the CHA_2DS_2-VASc score was generally in line with European Society of Cardiology recommendations [13]. The slightly higher CHA_2DS_2-VASc score in the apixaban group compared with the dabigatran and rivaroxaban groups was probably a reflection of the increased risk of diabetes in these patients and their slightly older age. There was some off-label use of anticoagulants, with prescription to a small number of patients with a CHA_2DS_2-VASc score of 0; however, in these cases, it is possible that the prescribing physician took into account factors other than those included in the calculation of the CHA_2DS_2-VASc score.

Overall, VKAs were preferred to NOACs in patients at higher risk, and the patient co-morbidity risk was higher for patients prescribed VKAs than for those prescribed NOACs. The older age of patients in the VKAs group is likely to account in part for the increased scores for the risks of stroke, major bleeding and co-morbidity. In particular, VKAs were preferred to apixaban in patients with a higher risk of bleeding, which could be explained by the availability of an antidote for VKAs, but not for apixaban, as reported previously with dabigatran and rivaroxaban [24,25]. In this context, renal impairment is recognized as a risk factor for bleeding and cerebrovascular accident [26,27], and the data from this study show greater use of VKAs compared with NOACs in these patients. Although NOACs are not recommended in Stage 4 or 5 renal impairment, a reduced dose of apixaban can be used with an acceptable benefit-risk balance in these patients [14], and this was observed in a small number of patients in this study, with underdosing of apixaban being more frequent than overdosing. This could account for its increased use in patients with diabetes, who are at increased risk of renal impairment [28].

Overall, an adjusted dose of apixaban was used in approximately one third of patients, and was generally associated with old age and/or reduced renal function. While the apixaban SmPC patient criteria [14] were generally adhered to by the prescribing physician, patients receiving an adjusted dose of apixaban were mainly treated off-label. This is probably because of difficulty or hesitation in choosing the dose as a result of the complexity of concomitant criteria. In particular, serum creatinine can be elevated on admission as a result of impaired cardiac rather than reduced renal function, and biomarkers could be used to provide a more accurate measure of renal function. Additional analyses performed following these results indicated, among patients not fulfilling SmPC criteria for an adjusted dose, that old age and reduced renal function (more specifically creatinine clearance < 60 mL/min) were associated with receipt of an adjusted dose. It is possible that the physicians considered these patients as ''borderline'' in terms of the relevant criteria, and treated them pre-emptively with an adjusted dose. It is also possible that physicians applied the creatinine clearance threshold for rivaroxaban (50 mL/min), which was available several months before apixaban approval, for the decision to use an adjusted dose of apixaban [14]. Indeed, data from the GARFIELD-AF [29] registry highlight the fact that French physicians might be watchful regarding bleeding risk. In this French cohort, anticoagulant prescription declined with increasing bleeding risk, from 82.1% in patients with a HAS-BLED score of 0 to 64.5% in patients with a HAS-BLED score of 4—9.

Study limitations

Despite stratification by type of practice, geographical region and treatment prescribed, a limitation of the study was the potential bias in the selection of both investigators and patients, whose distribution cannot be strictly controlled in any observational study. However, weighting methods were used to limit the extent of this bias for the descriptive analyses, by shifting the study population characteristics closer to those of the target population [30]. A

further limitation was the use in the multivariable analysis of covariates that were considered to be clinically relevant, with both apixaban doses being included together; it is possible that other factors that were not measured could have been of clinical interest, and that a separate analysis for each apixaban dose could have provided different results.

Conclusions

This non-interventional study showed extensive use of NOACs, including apixaban, in France as first-line treatment for NVAF; it is the first such observational study to evaluate apixaban in France. The choice of apixaban rather than other NOACs was more common among patients with increased age, a higher risk of bleeding and decreased renal function, whereas the choice of apixaban rather than VKAs was more common among patients with a lower risk of bleeding and better renal function. Overall, 79.3% of patients were treated in accordance with SmPC recommendations, meaning that one in five patients did not receive doses consistent with the SmPC. Careful assessment of appropriate dose should therefore be encouraged. Off-label use of apixaban was observed, mainly in elderly patients, despite normal renal function and weight, which could result in lower protection against stroke and systemic embolism in these patients.

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Disclosure of interest

B. F. Consultant for the companies Eli Lilly, Bristol-Myers Squibb, Servier, Sanofi, GlaxoSmithKline, HRA Pharma, Roche, Boehringer Ingelheim, Bayer, Almirall, Allergan, Stallergene, Genzyme, Pierre Fabre, AstraZeneca, Novartis, Janssen, Astellas, Biotronik, Daiichi Sankyo, Gilead, Merck Sharp & Dohme, Lundbeck, Actelion, UCB, Otsuka and Grunenthal.

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The other authors declare that they have no conflicts of interest concerning this article.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.acvd.2019.02.003.

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