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CARDIOVASCULAR DISEASE

Annual rate of newly treated atrial fibrillation by age and gender in France, 2010–2016

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Abstract

Few studies are available on atrial fibrillation (AF) burden at a whole country scale. The objective was to estimate the rate of AF patients newly treated with oral anticoagulants (OAC) in France each year between 2010 and 2016 and to describe age and gender differences. We used the French national health data system. For each year between 2010 and 2016, we identified patients aged over 20 initiating OAC. OAC indicated for the treatment of AF was determined by hospitalization diagnoses, specific procedures and registered long-term disease status, or a multiple imputation process for patients with no recorded information as to why they initiated OAC. Among the 421,453 individuals initiating OAC treatment in 2016, the estimated number of newly treated AF patients was 210,131, women accounting for 46%, patients under 65 years old 17%, and 21.4% of patients living in most deprived area. Age-standardized rates reached 400/100,000 inhabitants. Approximately 19% of patients were recently hospitalized for heart failure and 7% for stroke. Age-standardized rates increased by 35% over the study period in both genders, with a marked increase in patients under 55 (+ 41%) and those over 85 years old (+ 60%). Annual rates of AF patients newly treated with OAC increased by 35% between 2010 and 2016. Important differences in rates were observed according to age, gender and the deprivation level of the living area.

Keywords Atrial fibrillation · Temporal trends · Anticoagulant · Gender · Aging

Introduction

Atrial fibrillation (AF) is a frequent medical condition associated with several complications, stroke being the most serious [1]. The Global Burden of Diseases reported a 30% increase in AF incidence between 1990 and 2010 in developed countries, with significant public health implications [2]. The forecasted increase in strokes attributable to AF due to the ageing of the general population underlines the importance of stroke prevention. Until 2011, vitamin K antagonists (VKA) were the most effective and recommended long-term oral anticoagulant treatment (OAC) for AF patients. Furthermore, the French Stroke Registry of Dijon showed that they were associated with a decreased incidence of AF-related stroke treatment in AF patients [3]. In 2012, the therapeutic arsenal for secondary prevention was enlarged when direct OAC (DOAC) was indicated for stroke prevention in AF patients. Today, DOAC are preferred in most western countries including France due to their easiest use and lower hemorrhagic risk [4, 5], although VKA continued to be the officially recommended first line treatment in France until 2018. Given this context, understanding the evolution of the epidemiology of AF treatment with OAC in France is important. A study by the Oxford Stroke Registry showed that the incidence of AF-related stroke remained stable and pointed out the under-use of OAC [6].

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Nationwide rates of AF treated by OAC can be estimated from the French national healthcare data system (*Système national des données de san*té—SNDS), which collects, among other things, in- and out-patient medical data for hospitalizations and drug reimbursements [7] for the entire general population. The objective of the present study was to estimate the rate of AF patients newly treated with OAC in France for each year between 2010 and 2016, to describe age and gender differences as well as patient characteristics, and to analyze time-trends.

Methods

Sources

Individual data were extracted from the SNDS. This database comprehensively collects individual outpatient data (age, sex, etc.), as well as healthcare prescriptions and procedures reimbursed by the French national health insurance system, for almost all of the 66 million persons living in France. Data collected in the SNDS is linked, via the national hospital discharge database (Programme de médicalisation des systèmes d'information: PMSI), to data concerning public and private hospital stays throughout all French territories. However, the SNDS does not provide any clinical data regarding the reasons for examinations or prescriptions, or regarding the results of examinations or physicians' diagnoses in an outpatient context (i.e., not discharged from hospital). The data used in our analyses were exhaustive for almost 100% of the study population for the study period [7, 8]. The SNDS also records long-term disease (LTD) status. Patients with this status benefit from 100% reimbursement for all healthcare expenditures related to the particular disease.

Identification of AF patients newly treated with OAC (Fig. 1)

All patients newly treated with OAC and aged over 20 years old were identified. We were able to record all OAC drugs delivered by pharmacies to outpatient and discharged inpatients in France, as these drugs are reimbursed by the French national health insurance system once prescribed [7, 8]. Furthermore, for our analysis, we did not use the prescription date but the date of OAC delivery at pharmacies, which is much more accurate. A patient was considered newly treated in a given calendar year, if he/she was reimbursed for OAC in the same calendar year with no reimbursement in the previous 24 months. OAC might be prescribed for different conditions. Those who, in the 24 months preceding reimbursement for OAC, had a diagnosis of AF (main or associated hospital-based diagnosis) or ablation/cardioversion or had LTD status for an AF, were considered to have an OAC indication for AF, while those who were hospitalized for Deep Venous Thrombosis/Pulmonary Embolism (DVT/PE) or who had a specific procedure for DVT/PE in the 6 weeks preceding OAC reimbursement were considered to have an OAC indication for DVT/PE. The SNDS exhaustively records orthopedic- and valvulophathy-related procedures. Patients with one of these two types of procedure concomitant with AF diagnosis were included in the study population, whereas patients who had one of these procedures without concomitant AF diagnosis were excluded.

Patients with no diagnosis information were labeled "missing diagnosis". Given that these patients had to have either AF or DVT/PE (mostly DVT given the fact that an

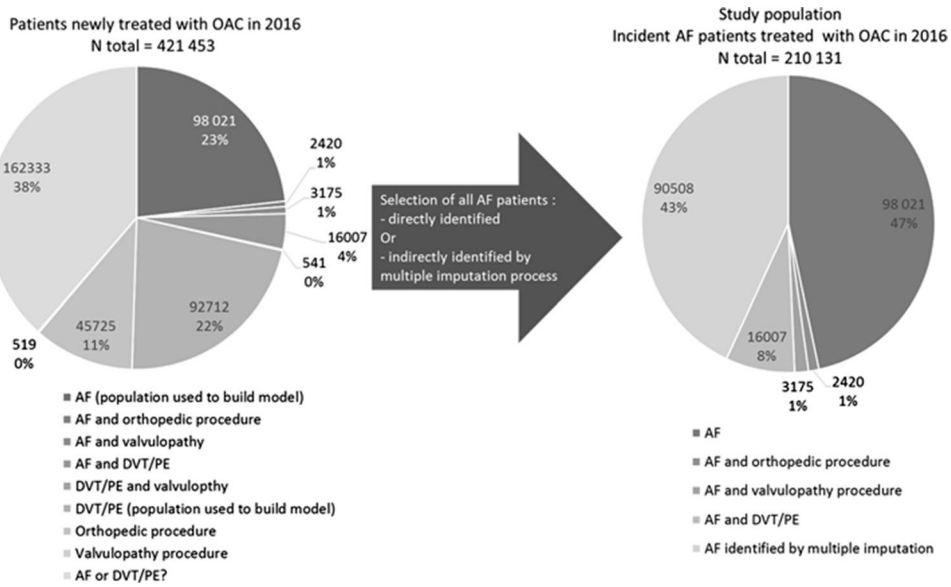

Fig. 1 Identification of AF patients newly treated with OAC. *AF* atrial fibrillation, *OAC* oral anticoagulant, *DVT/PE* deep venous thrombosis/pulmonary embolism

PE would have been hospitalized), the lack of diagnosis suggests they had received out of hospital OAC treatment. We used multiple imputations of missing data to attribute AF or DVT/PE diagnosis to these patients. To do this, a prediction model was first adapted from a logistic model developed by Billonnet et al. [9] which discriminated the probability of being treated with OAC for AF from DVT/PE using AF and DVT/PE cases with known diagnosis (see online Supplement).

For each patient with a missing diagnosis, AF or DVT/PE diagnosis was then imputed using a binomial distribution, with the predicted probability of being newly treated with OAC for AF being the parameter. Fifteen imputed data sets were generated and analyzed within a multiple imputation framework. Increasing the number of imputations above 15 helps to reduce the size of variance estimates and confidence intervals. However, given the large size of our database, the sizes of confidence intervals were not of great concern. Furthermore, our large size dataset would have required a lot of computing power if there had been many more imputations [10]. To compute rates of patients newly treated with OAC for an AF, population estimations published by the French national institute of statistics (*Institut National de la Statistique et des Etudes Economiques*, INSEE) were used as a denominator. Age-standardized rates were calculated using the age structure of the European population in 2010.

Social deprivation level of the town of residence was estimated using the index developed by Rey et al. [11]: the first quintile group (Q1) represented the 20% of the population with the lowest deprivation level while the fifth quintile group (Q5) represented the 20% with the highest. The degree of individual social deprivation was estimated by evaluating the number of people benefiting from free complementary universal health insurance coverage (CMUc), which is available for persons aged under 60 years old resident in France who live under the poverty line. CMUc provides access to care without advance payment or extra billing, and covers total medical expenditures.

In the 24 months preceding the index date of OAC reimbursement, we recorded hospitalization for: stroke, heart failure, acute coronary syndrome, hemorrhages, chronic kidney diseases (CKD), mainly defined by using hospital data, and treatment for hypertension and diabetes mellitus (eTable 3). We also calculated the CHA2-DS2-VASc score for each patient. This is a stroke risk score for AF patients which takes into account congestive heart failure, hypertension, vascular diseases, stroke/transient ischemic attack/systemic embolism history, diabetes, age and gender [12].

Analysis

Gender differences in patient characteristics were tested using χ^2 tests for binary variables and Wilcoxon and Kruskall–Wallis tests for continuous variables with no normal distribution. To assess AF newly treated with OAC rate changes over the study period according to age group and gender, we performed a Poisson regression model with the number of cases as a dependent variable and years since OAC initiation as independent variables. The log of the average population size of each age group was used as an offset variable for each year. Gender differences were tested for by using interaction tests between gender and year. Overdispersion was also taken into account. Time-trends in the proportion of the different comorbidities were assessed using logistic regression adjusted for age and gender. Analyses were performed using SAS Enterprise Guide 7.1 and R software.

Ethics approval

In line with French governmental regulations and the National Ethics Committee, no patient consent was required. Database used contained de-identified patient information.

Results

Characteristics of AF patients newly treated with OAC in 2016

The estimated number of newly treated AF patients with OAC in 2016 was 210,131, women accounting for 46%. Patients under 65 years accounted for 16.6% of the population (22.2% in men and 10.2% in women) (Table 1). The percentage of patients in the highest deprivation quintile was higher (21.4%) than that in the lowest deprivation quintile (17.3%), particularly in women (22.2% vs 16.9%). Moreover, 11.6% of patients under 60 years of age received CMUc, with a higher proportion of women (13.5%) than men (11.0%).

The distribution of new cases with age differed greatly between both sexes (Fig. 2). A maximum proportion was observed at approximately 85 years in women, and over a larger age interval (70–80 years) in men (Fig. 2). The crude rate of new cases was 417.6/100,000 inhabitants and was higher in men (471.7) than in women (368.6) (Table 1). The crude rates constantly rose with age: rates were 56.7/100,000 and 19.0/100,000, respectively, in men and women aged under 55 years old, and reached 3100.7/100,000 and 2449.2/100,000 inhabitants, respectively, in men and women aged 85 years or over. Gender differences were bigger after standardizing for age, with rates of 409.7 in men and 244.5 in women (Table 1).

Overall, 56.9% of identified AF patients newly treated with OAC had hospital diagnosed AF, LTD status or a specific medical procedure. This proportion was higher in women (59.4%). Indeed women were more likely to have

Table 1 Characteristics of AF patients newly treated with OAC in 2010 and 2016

	2010				2016			
	Men	Women	p_{gender}	Total	Men	Women	p_{gender}	Total
No.	75,037	63,706		138,743	112,817	97,314		210,131
Mean age	71.8 (10.1)	77.8 (8.5)	***	74.6 (9.7)	73.0 (10.6)	79.0 (9.3)	***	75.8 (10.3)
% Under 65 years old	26.3	11.1	***	19.3	22.2	10.2	***	16.6
Crude rates per 100,000								
Total	324.0	249.0		284.6	471.7	368.6		417.6
20–64	105.7	36.7		70.7	135.4	51.8		92.9
≥65	1235.2	895.5		1036.3	1614.7	1203.8		1379.7
Age-standardized rates per 100,000[a]	388.1	225.1	***	296.4	516.7	307.5	***	399.9
Deprivation Index[b], % column			*				***	
Q1	21.4	20.3		20.8	17.6	16.9		17.3
Q2	19.8	19.8		19.8	19.6	18.8		19.2
Q3	19.0	19.5		19.3	20.5	20.3		20.4
Q4	21.4	20.8		21.1	21.6	21.8		21.7
Q5	18.5	19.6		19.0	20.7	22.2		21.4
CMUc[c]	8.4	11.8	**	9.4	11.0	13.5	***	11.6
CHA_2-DS_2-VASc score			***				***	
0–1	21.1	3.0		12.7	20.2	3.4		12.4
2–3	49.2	26.7		38.9	48.7	28.1		39.2
4	18.7	35.3		26.3	19.1	34.8		26.4
≥5	11.1	35.0		22.1	11.9	33.9		22.0
Ischemic stroke	5.4	6.7	**	6.0	5.5	6.5	***	6.0
All strokes	6.8	8.4	**	7.5	6.6	7.9	***	7.2
Heart failure	21.2	23.1	***	22.1	18.8	20.7	***	19.7
Acute coronary syndrome	5.0	3.2	***	4.2	5.4	3.2	***	4.4
Hemorrhages	1.8	1.4	**	1.6	1.7	1.3	***	1.5
Chronic kidney diseases	0.9	0.8	NS	0.9	1.2	0.9	**	1.1
Arterial hypertension	75.0	78.9	***	76.8	73.2	76.6	***	74.7
Diabetes mellitus	19.5	15.3	***	17.6	22.0	17.0	***	19.7
% Of AF patients directly identified	55.9	60.9	***	58.2	54.8	59.4	***	56.9
% Hospital diagnosis	47.7	52.3	***	49.8	44.7	48.2	***	46.3
% Long-term disease status	14.2	16.5	***	15.2	16.9	20.0	***	18.3
% Specific procedure (ablation or cardioversion)	4.8	2.5	***	3.8	3.6	1.8	***	2.8
% Of patients identified by the model	44.1	39.1	***	41.8	45.2	40.6	***	43.1

AF atrial fibrillation, *OAC* oral anticoagulant, *CI* confidence interval, *Q1* quintile1, *CMUc* free complementary universal health insurance coverage

[a]Rates standardized according to the age of the European population of 2010

[b]Of the municipality of residence for patients living in metropolitan France (97% of the overall French population)

[c]In patients under 60 years of age

***P-value < 0.0001, **0.0001 ≤ P-value < 0.01, *0.01 ≤ P-value < 0.05

hospital diagnosed AF or have LTD status for AF. Furthermore, women were twice less likely to have specific in-hospital AF procedures than men (1.8% vs 3.6% in 2016).

In 2016, 12.4% of patients had a CHA_2-DS_2-VASc score of 0 or 1. The distribution of the score differed substantially between genders, even after adjusting for age. The history of AF comorbidities is reported in Table 1. Stroke was recorded for 7.2% of patients in 2016, and for 6.0% of patients when considering ischemic stroke only. Hypertension and diabetes were recorded for 74.7% and 19.7%, respectively. Heart failure was also a very common comorbidity (19.7%). Women were more likely to have previously had stroke, heart failure and treatment for arterial hypertension. After adjustment for age and year of OAC initiation, we observed that men

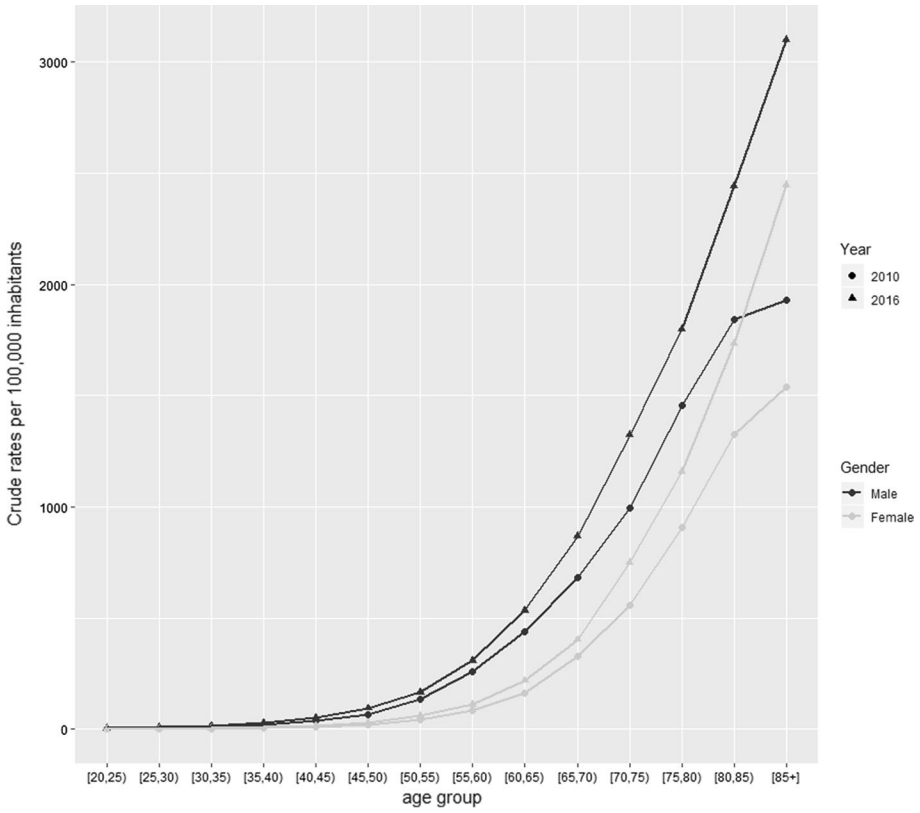

Fig. 2 Crude rates by age and gender of AF patients treated with OAC in 2010 and 2016. *AF* atrial fibrillation, *OAC* oral anticoagulant

were more likely to have heart failure and arterial hypertension but women had higher rates of stroke history (data not shown).

Time trends

The estimated number of newly treated AF patients substantially increased between 2010 (N = 138,743) and 2016 (N = 210,131). The corresponding age-standardized rates rose from 296.4/100,000 inhabitants in 2010 to 399.9/100,000 inhabitants in 2016, i.e., a 35% rise. However, a non-linear increase was observed over the study period, with a peak being observed in 2012. More specifically, rates increased by 33% in men and 37% in women. Rise in rates was much important in inhabitants aged 85 years old or over (+ 60%), and in persons aged under 55 years old (+ 41%). The deprivation index quintile distribution changed between 2010 and 2016. In 2010 the quintiles were similarly distributed in the affected population. However, in 2016, a much higher proportion of patients, particularly women, were living in one of the most deprived areas (Fig. 3).

We observed no change in the distribution of the CHA_2-DS_2-VASc score over the study period. However, it significantly increased for acute coronary syndromes (ACS) and diabetes, while it decreased or remained stable for all other comorbidities. These trends remained significant after adjusting for age and gender. Moreover no association between gender and trends was found.

Discussion

This nationwide study estimated that 210,131 AF patients were newly treated with OAC in 2016 in France, corresponding to an age-standardized rate of 400/100,000 habitants. The rate was higher in men than in women. Globally, the rate increased by 35% between 2010 and 2016 (33% in men and 37% in women). The profile of these patients changed over the study period. More specifically, for 2016, we observed higher proportions of elderly patients, very young patients, people living in deprived areas, individuals treated with diabetes and patients with a recent history of ACS. Conversely, fewer cases of recent heart failure, hemorrhages and treated hypertension were recorded over the same period, even after adjustment for age and gender.

Various methodologies have been used to estimate the burden of AF in France, leading to differences in selected patient characteristics and conflicting results. We adapted the algorithm used by Billionnet et al. [9]. Our study is the first to report nationwide annual rates of AF patients newly treated with OAC in the overall French population. Huiart et al. estimated the number of AF patients treated by OAC by considering that a patient had AF if he/she was reimbursed

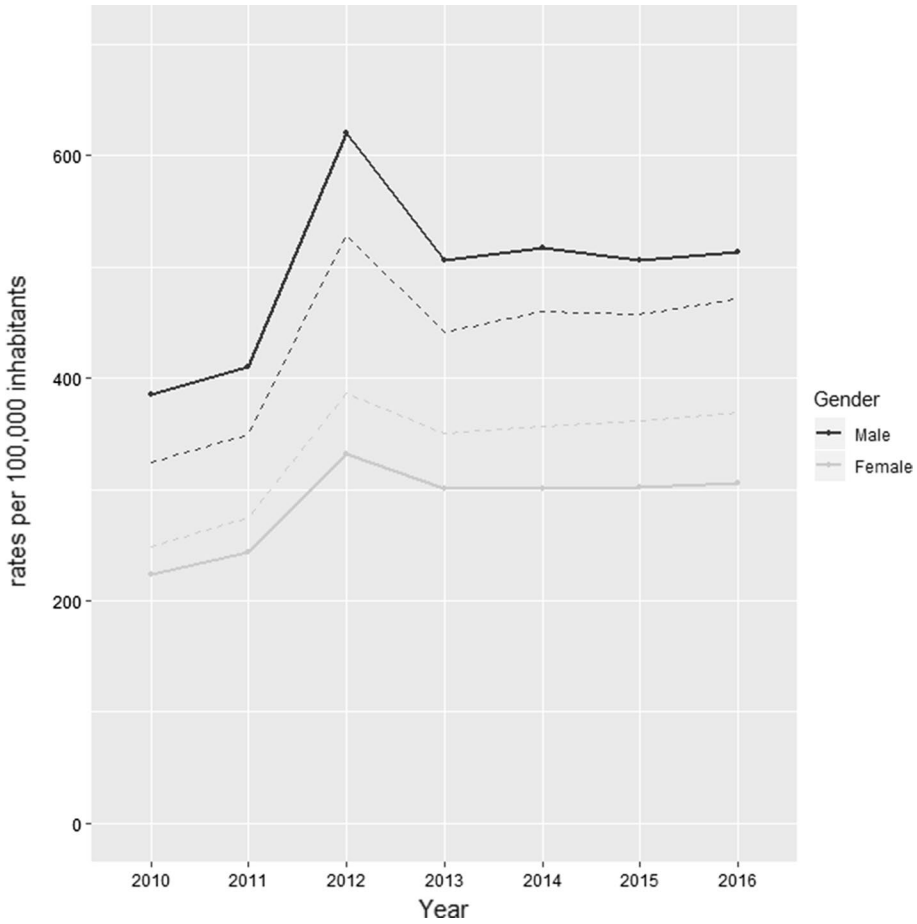

Fig. 3 Age-standardized (standardized according to the 2010 European census population; solid line) and crude (dashed line) rates of AF patients treated with OAC from 2010 to 2016 by gender. *AF* atrial fibrillation, *OAC* oral anticoagulant

for OAC in addition to being reimbursed for antiarrhythmic or rate-control treatment [13]. In 2011, Charlemagne et al. published an estimation of AF incidence in France extrapolating from cohort studies implemented in other countries [14]. Finally, other French studies using only hospital databases analyzed the incidence of hospitalizations mentioning AF diagnosis [15, 16]. Reported AF incidences using healthcare databases in Sweden [17], Germany [18], and in the United-States [19] were higher than rates of AF patients initiating OAC, as were results from population-based cohort studies in the Netherlands, the USA, the UK and Iceland [20–23], underlying the difficulties to ascertain data on OAC even in developed countries. Internationally, not all patients newly diagnosed with AF are treated with OAC, as shown in population-based AF registries in Denmark, England and the international GARFIELD-AF cohort [24–27]. In the latter, between 2010 and 2016, approximately 12% of newly diagnosed AF cases did not receive antithrombotic treatment [27].

While we cannot exclude that the increase in AF patients on OAC in France over the study period was at least partly related to improved screening and increased frequency of disease diagnosis, the observed trends may be the result of a change in AF management. The introduction of DOAC treatments in 2012 contributed to increased prescription for a greater number of patients, particularly the most elderly (≥ 85 years old), and mainly explained the peak of rates observed in 2012. Therefore, AF cases newly treated in 2012 comprised incident (i.e., newly diagnosed AF cases) and prevalent (i.e., diagnosed but not on treatment) AF patients. The decrease in OAC initiation observed just after 2012 is most likely due to the fact that only incident cases were newly treated at that moment, and to a warning published by French health authorities regarding the risk of bleeding associated with new OAC, especially as no reversal agents were available at the time. Furthermore, the gap between rates observed in 2013–2016 and those observed in 2010–2011 was mainly explained by the fact that these new OAC led to the treatment of more AF patients including incident AF patients. The increase in the proportion of AF patients newly treated with OAC at age of 85 or over could partly explain the increase in the CHA2-DS2-VASc score, in the mean age and in the presence of some of the main AF comorbidities. Earlier diagnosis of AF may also explain the trend toward fewer comorbidities. However, one study including diagnosed AF patients who were on OAC and others who were not, warned about too frequent a use of OAC in patients at low risk of stroke and too infrequent a use in those at high

risk [28]. The increased proportion of recent hospitalizations for ACS is likely due to the increased simultaneous use of DOAC and antiplatelet therapy in ACS patients, as the risk of bleeding is lower with this combined therapy than with an antiplatelet-VKA combination [27].

Gender differences in our study were similar to those observed in previous reports: fewer women with AF were newly treated. Furthermore women were much older and had more comorbidities than men except for ACS and diabetes [29]. A French study conducted among general practitioners showed that women over 75 years old were a third less likely to be treated with recommended anticoagulants than men of a similar age [30]. This observation was confirmed in a recent study. Moreover, it has been suggested that women may be more frequently treated than men with antiplatelet therapy (instead of OAC) [31]. As a consequence, women may have been underrepresented in our study. However, many studies showed that women were less likely to be treated with OAC than men in a presence of AF and the gap seems to persist even with the introduction of DOAC [32]. The thromboembolic risk in AF women might often be underestimated and not taken as seriously as other thromboembolic risk factors while it has been shown in many studies [33].

Another important finding is the change over time in the distribution of deprivation index quintiles: in 2010 no clear trend was observed, while in 2016 a large difference was found. This may be partly explained by increased access to DOAC than to VKA treatment, leading to more people in highly deprived areas being treated. VKA use requires strict follow-up of patients given that repeated and regular INR measures need to be performed frequently. Deprived populations may be less able to comply with these needs. Highly deprived patients are more likely to have more severe AF and therefore more likely to be treated by OAC. Some studies showed that high deprivation or low education level were independently associated with lower OAC prescription in Sweden and Italy [34, 35] while a study in UK stated that the prescription of OAC for AF was not associated with deprivation level [36]. Another study in Sweden showed conflicting results as authors concluded that neighborhood deprivation and socioeconomic disparities were not independently associated with hospitalized AF, in contrast to many other cardiovascular diseases [37].

Strengths and limitations

The quality of the French national health data system has been previously assessed, even if AF diagnostic codes have not been properly validated yet [7]. For patients in our study population who did not have a clear diagnosis of AF, a specific medical procedure for AF, or AF-specific LTD status in their hospital discharge data, we used a model a including multiple imputation process to estimate the probability that they had AF as opposed to DVT/PE. The multiple imputation process implied a missing at random (MAR) mechanism in the diagnosis of AF versus DVT/PE: i.e., for a given combination of the covariates included in the prediction model, the AF/VTE patient ratio was the same for outpatients as for inpatients. The covariates with the greatest influence in terms of discriminating between AF and VTE in hospitalized patients were those related to therapeutic strategies and diagnostic procedures (anti-arrhythmic drugs and beta-blockers being very predictive of AF, whereas D-Dimer dosage was very predictive of VTE, see supplemental data). The MAR hypothesis holds when therapeutic strategies and diagnostic procedures targeting either AF or VTE are comparable between inpatients and outpatients, as was the case in our context. The good discriminant properties of our prediction model meant that we could satisfactorily impute the missing diagnostic status (i.e., AF or VTE) (See supplemental data eTable 1, eFigure 1, eFigure 2). Another limitation was the unavailability of medical information for a small percentage of healthcare beneficiaries before 2012. More specifically, the rates of AF cases newly treated with OAC may have been underestimated for the years 2010 and 2011 as data may not have been exhaustive for a maximum of 2–3% of the study population for that period. Social deprivation of the patient was estimated using the deprivation index of the town of residence. This may have introduced a bias, in particular for patients living in large cities with great social diversity. Finally, we used only hospitalization to report some AF comorbidities in the 24 months preceding OAC initiation and therefore, underestimated AF comorbidities. However, we focused on acute events for these comorbidities. Only a small proportion of patients had LTD status for AF in our study. This is explained by the fact that for many patients, LTD status was not a requirement to access treatment. This is true for example for those treated with vitamin-K antagonist OAC (this treatment is not expensive) and those who already had LTD status for an AF-related disease, and therefore already benefitted from 100% healthcare reimbursement [8]. Indeed, it is well known that a large proportion of AF patients have comorbidities (heart failure, hypertension, stroke, etc.).

Conclusion

Annual rates of AF patients newly treated with OAC increased substantially between 2010 and 2016. Our study highlights the burden of AF in France in terms of epidemiology and the current healthcare system. With regard to the increased proportion of AF patients treated with OAC, we might expect a decrease in the incidence of AF-related stroke, providing that adherence to OAC treatment is

satisfactory and that patients at high risk of stroke are adequately treated. Differences in rates according to age, gender and social environment should lead further research to deal with potential under use of OAC in women, the important increase in both very young and very old AF patients treated by OAC, and the particular high rates and increased proportion of patients living in the most deprived area.

Author contributions AG directed research, wrote the manuscript; AG and EC performed the statistical analyses; EC, GM, CB and MG contributed to the discussion and reviewed the manuscript; YB and VO directed research, contributed to discussion and reviewed the manuscript. AG takes full responsibility for the data, the analyses and interpretation, and the conduct of the research.

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Compliance with ethical standards

Coflict of interest Dr. Béjot reports grants and personal fees from AstraZeneca, personal fees from Pfizer, personal fees from MSD, personal fees from Medtronic, personal fees from BMS, personal fees from Amgen, grants and personal fees from Boehringer-Ingelheim, outside the submitted work.

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