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Title page

Oral anticoagulation therapy use in patients with atrial fibrillation after the introduction of direct oral anticoagulants: findings from the French healthcare databases, 2011-2016.

Running title: Patterns of OAC use

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Abstract

Objectives: To describe i) the trend in oral anticoagulant (OAC) use following the introduction of direct oral anticoagulant (DOAC) therapy for stroke prevention in atrial fibrillation (AF) patients; ii) the current patterns of use of DOAC therapy in new users with AF in France.

Design: i) Repeated cross-sectional study; ii) Population-based cohort study.

Setting: French National Healthcare databases (Régime général, 50 million beneficiaries).

Participants: i) Patients with identified AF in 2011, 2013, and 2016; ii) Patients with AF initiating OAC therapy in 2015-2016.

Primary and secondary outcome measures: i) Trend in oral anticoagulant therapy use in patients with AF; ii) Patterns of use of DOAC therapy in new users with AF.

Results: Between 2011 and 2016, use of OAC therapy moderately increased (+16%), while use of antiplatelet therapy decreased (-22%) among all patients with identified AF. In 2016, among the 1.1 million AF patients, 66% used OAC therapy and were more likely to be treated by VKA than DOAC therapy, including patients at higher risk of stroke (63.5%), while 33% used antiplatelet therapy. Among 192,851 new users of OAC therapy in 2015-2016 with identified AF, DOAC therapy (66.3%) was initiated more frequently than VKA therapy, including in patients at higher risk of stroke (57.8%). Reduced doses were prescribed in 40% of DOAC new users. Several situations of inappropriate use at DOAC initiation were identified, including concomitant use of drugs increasing the risk of bleeding (one in three new users) and potential DOAC underdosing.

Conclusions: OAC therapy use in AF patients remains suboptimal 4 years after the introduction of DOACs for stroke prevention in France and improvement in appropriate prescribing regarding DOAC initiation is needed. However, DOAC therapy is now the preferred drug class for initiation of OAC therapy in patients with AF, including in patients at higher risk of stroke.

Strengths and limitations of this study

- This study is the first to report both the 2011-2016 trend in oral anticoagulant (OAC) coverage in patients with atrial fibrillation (AF) following the introduction of direct oral anticoagulant (DOAC) therapy in France and the current patterns of use of DOACs in new users including assessment of potential inappropriate use;
- This study is based on reimbursement data for 50 million beneficiaries with access to all OAC prescriptions filled in the ambulatory setting;
- As indications for treatment are not available in the databases, AF was mostly identified on the basis of discharge and long-term disease diagnosis codes and an algorithm previously validated in the French healthcare databases that helped to further identify AF in outpatients.

Introduction

Direct Oral Anticoagulants (DOACs) have been gradually introduced over the past decade as a more convenient, fixed-dose alternative to vitamin K antagonists (VKAs), the only oral anticoagulant therapy available up until now for long-term stroke prevention in patients with non-valvular atrial fibrillation (AF) [1]. Compared to VKA, DOAC therapy avoids the need for regular laboratory monitoring of patients by INR testing due to a wider therapeutic window, allows once (rivaroxaban, edoxaban) or twice (dabigatran, apixaban) daily intake and is associated with fewer drug-drug interactions to date [2–6]. DOACs have been demonstrated to have similar or superior efficacy to warfarin for stroke prevention in nv-AF patients, and these findings have recently been implemented in the 2016 European Society of Cardiology (ESC) guidelines that recommended DOAC over VKA therapy in this indication [7]. Moreover, antiplatelet therapy is no longer recommended in these patients [7,8]. The use of DOAC therapy, massively adopted worldwide including in France [9–15], is expected to overcome the suboptimal use of oral anticoagulant (OAC) therapy extensively reported with VKA therapy, including underprescribing and high discontinuation rates [16,17].

Despite their improved ease of use, DOAC prescribed dose needs to be adjusted to the patient's clinical profile with regards to age, renal function, weight, and risks of bleeding and drug-drug interactions. Two dose regimens are therefore proposed for each DOAC: standard dose regimen (*i.e.* dabigatran 150mg/12h, rivaroxaban 20mg/24h; apixaban 5mg/12h), and reduced-dose regimen (i.e. dabigatran 75mg or 110mg/12h, rivaroxaban 10mg or 15mg/24h; apixaban 2.5mg/12h). The reasons for prescribing a reduced-dose regimen are listed in the summary of product characteristics (SmPCs) of each DOAC with differences across DOACs as well as in the ESC [7,8] and European Heart Rhythm Association (EHRA) guidelines [18]. Recent publications have suggested that the frequency of use of reduced-dose DOACs in clinical practice could largely exceed that expected on the basis of the conditions summarized in these guidelines [11,19–21]. However, national data are lacking concerning the current French patterns of DOAC use, including the potential issue of DOAC underdosing.

A steady increase in the initiation of DOAC therapy has already been reported in AF patients in France [14], but trends in OAC coverage of AF patients following the introduction of DOACs and a description of the current national patterns of DOAC use have not yet been reported. This study, based on the French nationwide healthcare databases, therefore had a twofold objective: 1) to describe the trends in OAC use following the introduction of DOAC for stroke prevention in AF patients during the 2011-2016 period; 2) to describe the current patterns of use of OAC therapies with particular focus on DOAC use in new users with AF.

Methods

Data source

French national health insurance (*Assurance Maladie*) covers the entire French population by means of several specific schemes according to the beneficiary's occupational sector, the largest scheme being the '*Régime général*' (around 50 million beneficiaries).

This study was conducted using data from the French health insurance system database (SNIIRAM) linked to the French hospital discharge database (PMSI) [22,23]. The SNIIRAM database contains individualized, anonymous, and comprehensive data on health spending reimbursements. Demographic data include date of birth, gender, and vital status. Drugs are coded according to the Anatomical Therapeutic Chemical (ATC) classification. Each packaging of each product is identified by means of a national specific pack identifier code providing information on the name of the product, active ingredient and dose per unit, number of units, and route of administration; but, the exact dosage prescribed and the indication are not available. However, for most drugs, particularly OACs, each dispensing of the prescribed drug cannot exceed the quantity necessary for one month of treatment. The PMSI database provides detailed information about discharge diagnoses and medical procedures related to all hospitalizations in France. This information regarding morbidities is completed by diagnoses corresponding to patient eligibility for 100% reimbursement of severe and costly long-term diseases (LTD) and disability, such as AF, coronary heart disease, certain debilitating diseases (such as multiple sclerosis or rheumatoid arthritis), HIV infection, cancer, etc. All information concerning medical diagnosis is encoded according to the International Classification of Diseases, 10th revision (ICD-10). Finally, the SNIIRAM-PMSI databases also indicate medical procedures performed in the ambulatory setting, including information about the type and date of all laboratory tests performed, but not including their results.

The French healthcare databases have been previously described and used in epidemiological and pharmacoepidemiological studies [22,24–26].

Study populations and study designs

A study population was defined for each objective. First, in a repeated cross-sectional study, patients with AF were identified for each of the following calendar years: 2011 (no DOAC available for stroke prevention in France), 2013 (first calendar year with both rivaroxaban and dabigatran reimbursed for stroke prevention in July 2012) and 2016 (the most recent data available at the time of writing the study protocol; dabigatran, rivaroxaban and apixaban were all reimbursed for stroke prevention in France, as apixaban was reimbursed from January 2014 onwards). For each of these calendar years, a patient was considered to have AF when at least one diagnosis of AF (ICD-10 code I48) was identified

from discharge and LTD diagnoses in the SNIIRAM-PMSI database in the calendar year considered or during the previous 5 years. Patients with no continuous '*Régime général*' health insurance coverage for at least six years before the calendar year considered were excluded.

Second, a retrospective population-based cohort study was performed in patients with AF among those initiating DOAC therapy in 2015-2016. To be included in this cohort, patients with continuous '*Régime général*' health insurance coverage had to be identified as DOAC new users: at least one reimbursement for DOAC therapy in 2015-2016 and no reimbursement for any OAC (VKA or DOAC) in the previous 24 months. The patient's index date was the date of first DOAC reimbursement identified during the 2015-2016 period. After exclusion of patients treated for other OAC indications *i.e.* patients treated for deep vein thrombosis/pulmonary embolism (DVT/PE) or with lower limb orthopaedic procedures, DOAC new users treated for AF were identified from the resulting cohort as: (a) "DOAC new users with confirmed AF" for those with a diagnosis of AF (ICD-10 code I48) or specific AF management procedures identified from LTD or hospitalization discharge data during a six-year pre-index period; and (b) "DOAC new users with probable AF" for outpatients identified using an algorithm discriminating AF from DVT/PE with 95% specificity [27]. The remaining patients were not classified as probable FA patients and were excluded. Codes used for identification of AF and all of the patient characteristics considered, including comorbidities, are displayed in **Supplementary Table 1**.

Exposure

DOAC (dabigatran, rivaroxaban, apixaban) and VKA therapies (fluindione, warfarin and acenocoumarol) were identified using ATC codes; edoxaban was not available in France during the period considered.

Outcomes

Trends in oral anticoagulant therapy use in patients with AF

The proportion of AF patients treated by OAC therapy was assessed before and after approval of DOAC therapies for stroke prevention in France. Trends in the use of antiplatelet agents were also assessed in AF patients over the same timeframe.

Patterns of use of DOAC therapy in new users with AF

The description of patterns of DOAC use in new users treated for AF in 2015-2016 included comparison of the baseline characteristics among DOAC new users and compared to those of VKA new users and potential inappropriate use of DOAC therapy was then investigated by identifying:

(i) DOAC off-label use or non-approved indication/dose: contraindications to DOAC therapy according to SmPCs [concomitant coagulopathy, purpura and other haemorrhagic conditions, liver fibrosis and

cirrhosis, recent gastrointestinal ulceration or intracranial haemorrhage], valvular atrial fibrillation [DOAC are only approved for non-valvular AF], prosthetic heart valve [contraindicated for dabigatran], cancer [DOAC are not approved for prevention of thromboembolism in patients with cancer] and prescription of DOAC doses not approved for stroke prevention in Europe [dabigatran 75 mg and rivaroxaban 10 mg are not approved for stroke prevention in Europe and are therefore off-label doses in AF patients]; (ii) non-compliance with guidelines with respect to follow-up and clinical work-up of patients during the first year following DOAC initiation: no monitoring of patients' renal function [renal function should be assessed at initiation and annually during DOAC therapy [28]], discontinuation of DOAC therapy [OAC therapy is recommended as lifetime treatment in most patients with AF] (iii) clinically relevant drug-drug interactions at initiation increasing the bleeding risk at initiation; (iv) potential inappropriate underdosing, i.e. patients in whom the DOAC dose prescribed at initiation was inappropriately reduced in view of their individual stroke and bleeding risks.

Data analysis

Descriptive analyses are expressed as mean and standard deviation (SD) for continuous variables, and numbers and percentages for categorical variables.

Trends in oral anticoagulant therapy use in patients with AF

For each calendar year, the proportion of patients treated by a drug was defined by the number of patients with at least one reimbursement for this drug in the calendar year considered over the total number of patients identified as having AF in the same year. Proportions are reported according to the type of OAC first reimbursed in the year considered. Antiplatelet drugs and OAC therapies were considered to be coprescribed when they were reimbursed at least once on the same day during the calendar year studied. Analyses were replicated in subgroups of AF patients: (i) aged 75 years and over; (ii) female and male, separately; (iii) with a history of hospitalization for arterial thromboembolic events (ATE); (iv) with concomitant ischaemic heart disease (IHD) or prosthetic heart valve.

Patterns of use of DOAC therapy in new users with AF

Baseline characteristics of DOAC new users with AF included sociodemographic data, including deprivation index of the patient's municipality of residence [29], type of initial prescriber, clinical scores predicting the risk of stroke (CHA_2DS_2-VASc score) or bleeding (HAS-BLED score) [30,31], adapted to claims data and the other main comorbidities and comedications, including proxies of frailty.

Compliance with guidelines regarding renal function monitoring and treatment persistence patterns were assessed in new users for whom data for at least one year of follow-up were available, i.e. patients included in 2015 and who had not died and had not been hospitalized for 3 months or longer. Compliance with renal function monitoring was assessed at DOAC initiation (no reimbursement for renal function monitoring during the three months before and the three months after DOAC initiation) and during the first year following treatment initiation. OAC non-persistence patterns were assessed over the one-year period following the index date by calculating proxies of OAC discontinuation: number of patients with only one reimbursement and those with five or less reimbursements.

Drugs increasing the risk of bleeding were those responsible for clinically relevant pharmacodynamic interactions with OAC therapy, i.e. concomitant reimbursement of other parenteral and oral antithrombotic drugs, non-steroidal anti-inflammatory drugs (NSAIDs); selective serotonin reuptake inhibitors and selective serotonin-norepinephrine reuptake inhibitors (SSRIs and SSNRIs) [7,18,32]. Patients taking concomitant drugs with OAC therapy were defined as those with a reimbursement for the drug of interest during the period corresponding to the index date and the following 45 days. Analyses were replicated in VKA new users for descriptive purposes.

Finally, potential inappropriate underdosing with DOACs was defined as initiation of DOAC therapy in patients at risk of stroke in whom reduced doses of DOAC were prescribed with no identified justification. As this study was based on claims data and as, up until 2016, ESC guidelines recommended prescribing reduced-dose DOAC in patients with HAS-BLED≥3 [8], the proportion of AF patients initiating reduced-dose DOAC with an HAS-BLED score<3 among all DOAC new users with a CHA_2DS_2-VASc score ≥2 was used to quantify potential inappropriate underdosing in DOAC new users. Analyses were replicated in patients i) with CHA_2DS_2-VASc score ≥4, ii) aged 75 and over with a history of ATE.

Results

Trends in oral anticoagulant therapy use in patients with AF

The number of patients identified from French healthcare databases as having AF increased between 2011 (N=853,440) and 2016 (N=1,098,657). A high proportion of these patients were identified exclusively by hospitalization discharge diagnosis and this proportion decreased only slightly over this time interval from 90.2% (N=770,002) to 86.2% (N=946,657).

Between 2011 and 2016, the proportion of patients with at least one reimbursement for OAC therapy among all AF patients moderately increased (+16%) from 56.7% to 65.8%, corresponding to a steady decrease in VKA use (from 56.6% to 40.8% of all AF patients) associated with the introduction of DOACs (from 0.6% to 27.7%). In 2016, among patients with identified AF, VKA therapy remained the preferred OAC therapy (62.0%), including in patients aged 75 years and over (67.0%) and in those with a history of ATE (63.5%).

Between 2011 and 2016, the use of antiplatelet therapy decreased in AF patients (-22%), but the proportion of patients with concomitant OAC and antiplatelet therapy remained stable (9.7% in 2016). In 2016, 32.5% of AF patients had at least one reimbursement for antiplatelet therapy during the year.

Similar trends were observed in the subgroup analyses. A slightly higher rate of OAC therapy was observed in patients with a history of ATE (68.4% vs 65.8% in the total cohort in 2016). However, OAC coverage was lower in women than in men with AF (64.7% vs 66.8% in 2016) (**Figure 1**).

Patterns of use of DOAC therapy in new users with AF

Baseline characteristics of OAC new users

Among 540,914 patients initiating OAC therapy in 2015-2016, a total of 192,851 (35.7%) patients were included in the study population, corresponding to 127,841 DOAC new users and 65,010 VKA new users with AF. The mains reasons for ineligibility were other indications or uncertain identification of the indication for DOAC (**Figure 2**).

The mean age of the DOAC new users cohort was 74.1±11.6 years; patients over the age of 80 represented 37.3% of the total cohort. One-half of the DOAC new users were women, mean CHA_2DS_2-VASc and HAS-BLED scores were 3.7±1.6 and 2.0±0.9, respectively, and 40.0% received a reduced dose at initiation (62.2% for dabigatran new users). DOAC were mostly initiated by hospital practitioners and private cardiologists. Apixaban was the DOAC most commonly initiated; apixaban new users were older and had more comorbidities than the other two groups of DOAC new users. VKA new users were older with much more severe disease than each of the three DOAC new users.

DOAC therapy was more likely to be initiated than VKA therapy among patients aged 75 years and older (59.4%) and in patients with a history of ATE (57.8%) (**Table 1**).

Potential inappropriate use of DOAC therapy

About 15% of DOAC new users with AF were considered to be using DOAC off-label or for a non-approved indication. In particular, 8.5% of DOAC new users with AF had valvular heart disease (8.5%), including prosthetic heart valve (1.5%) and 4.6% had a recently or currently treated cancer (**Table 2**).

About 15% and 9% of DOAC new users had no reimbursement for renal function tests at initiation and during the one-year period post-initiation, respectively. Discontinuation during the one-year period following initiation was frequent, as more than 20% of patients had five or less reimbursements (**Table 2**).

Nearly 30% of DOAC new users were using at least one concomitant drug increasing the risk of bleeding (52% in VKA new users). The most common concomitant drugs concerned at initiation were antiplatelet agents or parenteral anticoagulants (**Table 2**).

Among the 116,391 DOAC new users with AF with a CHA_2DS_2-VASc score ≥2, 42.9% (N=49,935) of patients were prescribed a reduced dose at initiation, and 29.1% (N=33,845) also had an HAS-BLED score <3 meaning that nearly 1 in 3 DOAC new users with AF and at risk of stroke were therefore potentially prescribed an inappropriately reduced dose of DOAC at initiation. The proportion of patients potentially underdosed was 33% (N=24,281) in patients with a CHA_2DS_2-VASc score ≥4 and 14.5% in patients aged 75 and over with a history of ATE (**Figure 3**).

Among the patients with no criterion justifying dose reduction, i.e. patients with HAS-BLED<3 only, these proportions were 39.3%, 51.9% and 58.4%, respectively. Differences in baseline characteristics were observed in patients with HAS-BLED<3 according to the type of DOAC dose prescribed, e.g. patients with reduced-dose DOAC were frailer than those with standard-dose DOAC (**Supplementary Table 2**).

Discussion

Main findings

OAC therapy use among patients with AF improved in France between 2011 and 2016, but remained suboptimal with about 66% of the 1.1 million patients with identified AF treated by OAC therapy in 2016. Use of antiplatelet therapy in AF patients decreased over the same period, but still concerned 33% of all AF patients in 2016. Patients with AF were more likely to be treated by VKA than DOAC therapy, including older patients and those at higher risk of stroke.

Nearly 193,000 patients with AF were identified as OAC new users in 2015-2016: patients were more likely to be treated by DOAC than VKA therapy, including older patients and those at higher risk of stroke. Results on current patterns of use of DOAC therapy in new users with AF suggest several situations of inappropriate use, including frequent concomitant use of drugs increasing the risk of bleeding and potential inappropriate underdosing.

Comparison with postmarketing literature and clinical implications

The overall improvement of management of AF patients observed with regards to OAC therapy after the introduction of DOACs has been reported in many countries [33–36]. The same applies to the steady decrease in VKA use in favour of DOAC therapies [12,37,38], and the gaps remaining in optimal OAC coverage and high antiplatelet drug use [39–41].

This study demonstrated channelling of DOAC therapy towards patients at lower risk of stroke and bleeding when considering all patients with AF, in line with what has become a common feature reported worldwide in clinical practice by many observational studies on the current patterns of use of DOACs [15,42–45]. However, DOAC therapy is now the preferred OAC therapy at initiation in the oldest patients and those at higher risk of stroke. This French pattern of OAC use has never been previously reported and contrasts with published results concerning earlier periods [46]. This emerging pattern is encouraging for AF management, as older and high-risk patients are those who should derive most benefit from DOAC *versus* VKA therapy [47].

Reduced doses were often prescribed in OAC new users, including dabigatran 75mg and rivaroxaban 10mg, which are not approved for stroke prevention in Europe [48]. In addition to the overall channelling mentioned above, these findings may reflect a “bleeding avoidance” strategy of prescribers (i.e. overestimation of the potential bleeding risk *versus* the likely benefit of stroke reduction) and the differential perception of the comparative safety of DOACs *versus* VKA and between DOACs. The early safety alert on bleeding in dabigatran-treated patients, followed by the contraindication of this DOAC in patients with prosthetic heart valves, may have reinforced the fears of prescribers in relation to the safety of dabigatran, which would explain the difference in reduced-

dose prescription rates between the three DOACs in this study, despite the intermediate stroke and bleeding risk profile of dabigatran compared to that of rivaroxaban and apixaban in new users. Similarly, among DOAC new users, apixaban was prescribed to the oldest and most severe patients. Apixaban was the only DOAC found to be superior to warfarin for all types of bleeding outcome and all-cause mortality, which would also illustrate the tendency of physicians to prescribe OAC therapies according to bleeding risk [5]. This may also explain the potential inappropriate underdosing observed in DOAC users in this study. This pattern of DOAC use has been previously reported, but mostly in field and registry studies based on small sample sizes. The reported inappropriate underdosing rate varies according to studies and the definition used. DOAC underdosing concerned 30.4% of Turkish patients in the RAMSES study (N=2,086) [49], 18.4% of Japanese patients of the *KiCS* AF registry (N=1,284) [50,51], between 19.7% and 27.6% of patients in the SAKURA AF registry (N= 3,266) [52], and 9.4% to 16% of patients in the ORBIT-AF II registry (N=7925) [21,53]. In the subgroup of Dutch patients (N=899) enrolled in the XANTUS registry, 33% of patients were also treated with reduced-dose rivaroxaban despite presenting normal renal function [54]. Using a large U.S. administrative database, Yao *et al* found that 13.3% of the 13,392 DOAC new users with no renal indication for dose reduction were potentially underdosed [55]. Taken together with our results, these data suggest that inappropriate underdosing might be a common issue in DOAC new users that should be systematically assessed when studying DOAC patterns of use. This is of particular concern, as recent data have suggested a relationship between DOAC dose and clinical outcomes [56]. In particular, DOAC underdosing has been shown to be associated with increased risk for adverse outcomes [21,55].

These patterns of DOAC use contrast with the other patterns concomitantly observed in this study, such as the high level of concomitant prescription of antiplatelet agents and parenteral anticoagulants or, to a lesser extent, DOAC use in non-approved indications such as prosthetic heart valves that are both associated with an increased risk of bleeding [57–59].

Strengths and limitations

This study is the first to report the improved trend in OAC coverage in French patients with AF over the last five years as well as the recent patterns of use of OAC therapy in new users, particularly including a nationwide assessment of the growing issue of DOAC underdosing, based on health data for more than 50 million beneficiaries. Moreover, all OAC prescriptions filled in the ambulatory setting are captured in the databases and are reimbursed with no restriction of coverage: selection bias related to the access of patients to more expensive DOAC therapy is therefore not an issue with the use of French healthcare databases [22,60].

However, several limitations related to the nature of the data used should be underlined. First of all, it cannot be verified whether patients actually took the drugs for which they were reimbursed. Secondly, as the indication for treatment is not available in the databases, and despite the use of an algorithm to identify AF among outpatients in the French healthcare databases, identification of AF was mostly based on non-validated discharge and LTD diagnoses recorded in the databases. Moreover, it cannot be excluded that the increase in the identified number of patients with AF over the 2011-2016 period could be partially explained by changes in LTD legislation in 2011 (e.g. hypertension was removed from the list of LTD, while access to LTD was facilitated for patients with severe arrhythmia and valvular heart diseases) which could have helped identify patients with AF. Thirdly, identification of inappropriate underdosing at DOAC initiation was also indirectly assessed by using stroke and bleeding risk scores computed from claims data. Important medical data such as patient's weight, renal function assessment and exact alcohol consumption are not available in the French healthcare databases. Furthermore, the agreement between these empirical scores in patients with AF and the prescriber-assessed stroke and bleeding risk is a subject of discussion [61]. However, DOAC misuse and underdosing have also been reported in a French prospective field study based on patients' medical charts [62]. Of note, as INR values were not available in the databases, underdosing with VKA therapy was not assessed in this study, but has been frequently reported and must not be overlooked [52,63]. In addition, the results for DOAC and VKA new users are difficult to compare, as they were not adjusted for significant differences in baseline characteristics and this comparison was not the purpose of this study.

Conclusion

OAC therapy use has modestly increased after the introduction of the DOACs for stroke prevention in patients with AF in France and DOAC therapy is now the preferred OAC therapy at initiation in older patients at higher risk of stroke. However, results from this nationwide drug utilization study suggest the need for improvement in appropriate prescription of OAC therapy in these patients, especially regarding the use of concomitant interacting drugs and the choice of initial DOAC dose.

Contributor ship statement

GM, AP, CB and AN designed the study. All authors have contributed substantially to the interpretation of results. In addition: GM, AP and AN drafted the article; CB, JD and AN conducted the statistical analysis; GM, AP, AN, CB, JD, AW provided critical revision of the manuscript for important intellectual content. All authors had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis. All authors approved the version to be published.

Competing interests

All authors have no conflict of interest.

GM, CB, JD, AN and AW are employees of the French National Health Insurance (Cnam, Assurance Maladie); AP belongs to the French National Institute of Health and Medical Research (Inserm).

All authors have no conflicts of interest with the Pharmaceutical Industry.

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Data sharing statement

Data are available from the French National Health Insurance (*Caisse National de l'Assurance Maladie,* Cnam) for academic research and the data access permission policy prohibits making the data set publicly available. All databases used in this study only contained anonymous patient records.

Ethics approval

The study was approved by the French data protection agency (*Commission Nationale de l'Informatique et des Libertés*, Cnil).

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Figure titles and legends

Figure 1. Time trends in the use of oral antithrombotic therapy between 2011 and 2016 in patients with atrial fibrillation in France

Abbreviations: AF: atrial fibrillation; OAC: oral anticoagulant; VKA: vitamin K antagonist; DOAC: direct oral anticoagulant

Legend: For Figures 1.b., 1.d and 1.e., estimates from all AF patients already presented in figure 1.a. are indicated by dashed lines for the purposes of comparison.

Figure 2. Patient flow chart.

Abbreviations: OAC: oral anticoagulant; DOAC: direct oral anticoagulant; VKA: vitamin K antagonist; DVT/PE: deep vein thrombosis/pulmonary embolism; AF: atrial fibrillation

Figure 3. Potential DOAC underdosing in new users with AF

Abbreviations: DOAC: direct oral anticoagulant; AF: atrial fibrillation

Table 1. Baseline characteristics of anticoagulant-naive patients with atrial fibrillation initiating oral anticoagulants in 2015-2016

Characteristics (N; %*)	DOAC				VKA
	Dabigatran N= 9,085	Rivaroxaban N= 54,456	Apixaban N= 64,300	Total DOAC N= 127,841	N= 65,010
DOAC: reduced doses	5,652 (62.2)	19,429 (35.7)	26,003 (40.4)	51,084 (40.0)	NA
Female sex	4,546 (50.0)	26,147 (48.0)	33,375 (51.9)	64,068 (50.1)	33,865 (52.1)
Age (years), mean (SD)	74.1 (11.6)	72.8 (11.9)	75.3 (11.3)	74.1 (11.6)	78.0 (11.3)
18-54	548 (6.0)	4,007 (7.4)	3,172 (4.9)	7,727 (6.0)	2,361 (3.6)
55-64	1,117 (12.3)	7,651 (14.0)	7,117 (11.1)	15,885 (12.4)	5,680 (8.7)
65-74	2,514 (27.7)	16,057 (29.5)	16,645 (25.9)	35,216 (27.5)	12,969 (19.9)
75-79	1,554 (17.1)	9,053 (16.6)	10,692 (16.6)	21,299 (16.7)	9,587 (14.7)
≥80	3,352 (36.9)	17,688 (32.5)	26,674 (41.5)	47,714 (37.3)	34,413 (52.9)
≥90	493 (5.4)	2,559 (4.7)	4,654 (7.2)	7,706 (6.0)	8,399 (12.9)
Deprivation index					
Quintile 1 (least deprived)	1,394 (15.3)	10,265 (18.9)	11,266 (17.5)	22,925 (17.9)	10,263 (15.8)
Quintile 2	1,586 (17.5)	10,678 (19.6)	12,496 (19.4)	24,760 (19.4)	11,884 (18.3)
Quintile 3	1,780 (19.6)	10,701 (19.7)	12,799 (19.9)	25,280 (19.8)	12,811 (19.7)
Quintile 4	1,917 (21.1)	10,794 (19.8)	13,142 (20.4)	25,853 (20.2)	14,272 (22.0)
Quintile 5 (most deprived))	2,113 (23.3)	11,172 (20.5)	13,825 (21.5)	27,110 (21.2)	14,699 (22.6)
Overseas departments	295 (3.2)	846 (1.6)	772 (1.2)	1,913 (1.5)	1,081 (1.7)
First prescriber's specialty					
Hospital practitioner	3,720 (40.9)	22,905 (42.1)	29,316 (45.6)	55,941 (43.8)	39,083 (60.1)
General practitioner	2,062 (22.7)	11,145 (20.5)	11,590 (18.0)	24,797 (19.4)	15,539 (23.9)
Private cardiologist	3,093 (34.0)	18,978 (34.9)	21,843 (34.0)	43,914 (34.4)	8,511 (13.1)
Private orthopaedic surgeon	16 (0.2)	100 (0.2)	95 (0.1)	211 (0.2)	73 (0.1)
Other private specialist	168 (1.8)	1,149 (2.1)	1,276 (2.0)	2,593 (2.0)	1,583 (2.4)
CHA_2DS_2-VASc score[†]					
Mean score (SD)	3.7 (1.6)	3.5 (1.6)	3.9 (1.6)	3.7 (1.6)	4.5 (1.6)
0	183 (2.0)	1,294 (2.4)	847 (1.3)	2,324 (1.8)	309 (0.5)
1	635 (7.0)	4,854 (8.9)	3,637 (5.7)	9,126 (7.1)	1,607 (2.5)
≥ 2	8,267 (91.0)	48,308 (88.7)	59,816 (93.0)	116,391 (90.1)	63,094 (97.0)
C (Heart failure)	2,849 (31.4)	17,805 (32.7)	23,548 (36.6)	44,202 (34.6)	32,727 (50.3)
H (antihypertensive drugs)	7,547 (83.1)	44,260 (81.3)	54,596 (84.9)	106,403 (83.2)	59,139 (91.0)
D(iabetes)	1,959 (21.6)	11,279 (20.7)	14,087 (21.9)	27,325 (21.4)	18,806 (28.9)
S(troke: ATE)	1,207 (13.3)	4,930 (9.1)	8,448 (13.1)	14,585 (11.4)	10,638 (16.4)
V(ascular diseases)	2,242 (24.7)	13,924 (25.6)	18,766 (29.2)	34,932 (27.3)	28,894 (44.4)
Age≥75 and arterial thromboembolic events[†]	769 (8.5)	3,126 (5.7)	5,608 (8.7)	9,503 (7.4)	7,762 (11.9)
Age<65 and no arterial thromboembolic events[†]	1,510 (16.6)	11,074 (20.3)	9,396 (14.6)	21,980 (17.2)	7,035 (10.8)

Table 1. Baseline characteristics of oral anticoagulant-naive patients with atrial fibrillation initiating oral anticoagulants in 2015-2016 (continued)

Characteristics (N; %)	DOAC				VKA
	Dabigatran N= 9,085	Rivaroxaban N= 54,456	Apixaban N= 64,300	Total DOAC N= 127,841	N= 65,010
HAS-BLED score†					
Mean score (SD)	2.0 (0.9)	1.9 (0.9)	2.1 (0.9)	2.0 (0.9)	2.7 (1.0)
≥ 3	2,169 (23.9)	11,388 (20.9)	16,834 (26.2)	30,391 (23.8)	36,417 (56.0)
A(bnormal)					
Renal function	345 (3.8)	2,426 (4.5)	3,822 (5.9)	6,593 (5.2)	14,260 (21.9)
Liver function	169 (1.9)	967 (1.8)	1,106 (1.7)	2,242 (1.8)	2,372 (3.6)
B(leeding)					
Predisposition	182 (2.0)	1,161 (2.1)	1,605 (2.5)	2,948 (2.3)	5,873 (9.0)
Major bleeding	692 (7.6)	3,729 (6.8)	5,134 (8)	9,555 (7.5)	9,348 (14.4)
D(rug/alcohol)					
Alcohol abuse‡	272 (3.0)	1,698 (3.1)	1,730 (2.7)	3,700 (2.9)	2,923 (4.5)
Drug-drug interactions	947 (10.4)	5,838 (10.7)	7,570 (11.8)	14,355 (11.2)	23,451 (36.1)
Parenteral anticoagulant (heparin)	64 (0.7)	331 (0.6)	361 (0.6)	756 (0.6)	9,824 (15.1)
Antiplatelet drugs	826 (9.1)	5,225 (9.6)	6,951 (10.8)	13,002 (10.2)	15,433 (23.7)
NSAIDs	72 (0.8)	365 (0.7)	344 (0.5)	781 (0.6)	212 (0.3)
Other comorbidities†					
Ischaemic heart disease	1,821 (20.0)	11,321 (20.8)	15,439 (24.0)	28,581 (22.4)	23,657 (36.4)
Frailty (proxies)	1,666 (18.3)	8,971 (16.5)	12,730 (19.8)	23,367 (18.3)	24,175 (37.2)
Dementia or Parkinson's disease	524 (5.8)	3,204 (5.9)	4,125 (6.4)	7,853 (6.1)	7,437 (11.4)
Psychiatric disorders	1,722 (19.0)	10,593 (19.5)	12,844 (20.0)	25,159 (19.7)	16,598 (25.5)
Smoking‡	1,024 (11.3)	6,481 (11.9)	7,442 (11.6)	14,947 (11.7)	11,434 (17.6)
Comedications§					
Antiarrhythmics or cardiac glycosides	5,996 (66.0)	35,761 (65.7)	41,031 (63.8)	82,788 (64.8)	35,600 (54.8)
Lipid-lowering agents	3,913 (43.1)	22,250 (40.9)	28,812 (44.8)	54,975 (43.0)	31,903 (49.1)
Oral corticosteroids	1,105 (12.2)	6,964 (12.8)	8,079 (12.6)	16,148 (12.6)	8,967 (13.8)
Antiulcer agents	4,295 (47.3)	24,842 (45.6)	31,469 (48.9)	60,606 (47.4)	39,842 (61.3)
Polymedication (≥5 ATC classes)	3,750 (41.3)	21,725 (39.9)	28,196 (43.9)	53,671 (42.0)	45,153 (69.5)
Polymedication (≥10 ATC classes)	738 (8.1)	4,653 (8.5)	6,246 (9.7)	11,637 (9.1)	14,947 (23.0)

DOAC: direct oral anticoagulant; VKA: vitamin K antagonist; SD: standard deviation; ATE: arterial thromboembolic events (ischaemic stroke, arterial systemic embolism or transient ischaemic attack); NSAIDs: non-steroidal anti-inflammatory drugs

* Unless otherwise stated

† Comorbidities were defined using a rolling 1-year period following the initiation of OAC therapy

‡ Smoking or alcohol data: measured by using proxies such as reimbursements for specific therapy or hospitalizations related to smoking or alcohol consumption/diseases

§ Comorbidities were defined using a rolling 4-month period preceding the initiation of OAC therapy

Table 2. Potential inappropriate use of DOAC therapy in oral anticoagulant-naive patients with atrial fibrillation in 2015-2016

Characteristics (N; %)	DOAC				VKA
	Dabigatran N= 9,085	Rivaroxaban N= 54,456	Apixaban N= 64,300	Total DOAC N= 127,841	N= 65,010
Contraindications or non-approved indication/dose	**1,457 (16.0)**	**8,614 (15.8)**	**9,542 (14.8)**	**19,613 (15.3)**	**NA**
Any valvular heart disease	649 (7.1)	4,146 (7.6)	6,122 (9.5)	10,917 (8.5)	16,461 (25.3)
Prosthetic heart valve	106 (1.2)	665 (1.2)	1,096 (1.7)	1,867 (1.5)	6,726 (10.3)
Recently hospitalized for coagulopathy, purpura and other haemorrhagic conditions*	90 (1.0)	479 (0.9)	596 (0.9)	1,165 (0.9)	2,142 (3.3)
Liver fibrosis and cirrhosis*	50 (0.6)	282 (0.5)	367 (0.6)	699 (0.5)	1,174 (1.8)
Recent gastrointestinal ulceration or intracranial haemorrhage†	40 (0.4)	120 (0.2)	248 (0.4)	408 (0.3)	350 (0.5)
Recently or currently treated cancer*	417 (4.6)	2,531 (4.6)	2,898 (4.5)	5,846 (4.6)	4,252 (6.5)
Reduced-dose DOAC not approved for stroke prevention in AF patients in Europe	357 (3.9)	1,844 (3.4)	NA	2,201 (3.5)	NA
Inappropriate use during follow-up‡					
No monitoring of renal function at initiation	637 (16.8)	3804 (15.5)	3642 (14.5)	8083 (15.1)	5401 (17.0)
No monitoring of renal function in the year post-initiation	378 (10.0)	2,347 (9.6)	2,138 (8.5)	4,863 (9.1)	2,984 (9.4)
Non-persistence patterns, N (%)					
One reimbursement only	605 (15.9)	2,666 (10.9)	1,771 (7.1)	5,042 (9.4)	2,426 (7.6)
≤5 reimbursements	1,229 (32.4)	6,557 (26.8)	4,515 (18.0)	12,301 (23.0)	7,456 (23.5)
Concomitant use of drug increasing the risk of bleeding§	**2,639 (29.3)**	**15,797 (29.3)**	**18,556 (29.2)**	**36,992 (29.3)**	**33,025 (52.3)**
Antiplatelet agents or parenteral anticoagulants	1,728 (19.2)	10,386 (19.3)	12,382 (19.5)	24,496 (19.4)	28,112 (44.5)
Parenteral anticoagulants	287 (3.2)	1,577 (2.9)	1,520 (2.4)	3,384 (2.7)	12,078 (19.1)
Antiplatelet agents	1,490 (16.6)	9,179 (17.0)	11,170 (17.6)	21,839 (17.3)	19,710 (31.2)
Aspirin	1,336 (14.8)	8,215 (15.2)	10,026 (15.8)	19,577 (15.5)	17,770 (28.1)
NSAIDs	375 (4.2)	2,111 (3.9)	2,017 (3.2)	4,503 (3.6)	1,030 (1.6)
SSRIs and SSNRIs	836 (9.3)	4,852 (9.0)	5,880 (9.2)	11,568 (9.1)	7,317 (11.6)

DOAC: direct oral anticoagulant; VKA: vitamin K antagonist; AF: atrial fibrillation; NA: not applicable; NSAIDs: non-steroidal anti-inflammatory drugs; SSRIs: selective serotonin reuptake inhibitors and SSNRIs: selective serotonin-norepinephrine reuptake inhibitors

* Comorbidities identified using hospitalization and/or LTD data, and/or specific procedures during a rolling 1-year period preceding the initiation of OAC therapy

† Comorbidities identified using hospitalization data during a rolling 6-week period preceding the initiation of OAC therapy

‡ Data on patients with at least a one year of follow-up i.e. patients initiating OAC in 2015 after excluding patients who died and those hospitalized for 3 months or longer (N= 3,796; 24,483; 25,118; 53,397 and 31,777 for dabigatran-, rivaroxaban, apixaban, total DOAC- and total VKA new users, respectively); period considered (unless otherwise stated): rolling 1-year period following the initiation of OAC therapy (index date included)

§ Data for new users still alive after a 45-day period following the index date (N= 9,001; 53,885; 63,578; 126,464 and 63,180 for dabigatran-, rivaroxaban, apixaban, total DOAC- and total VKA new users , respectively); period considered: rolling 6-week period following the initiation of OAC therapy (index date included)

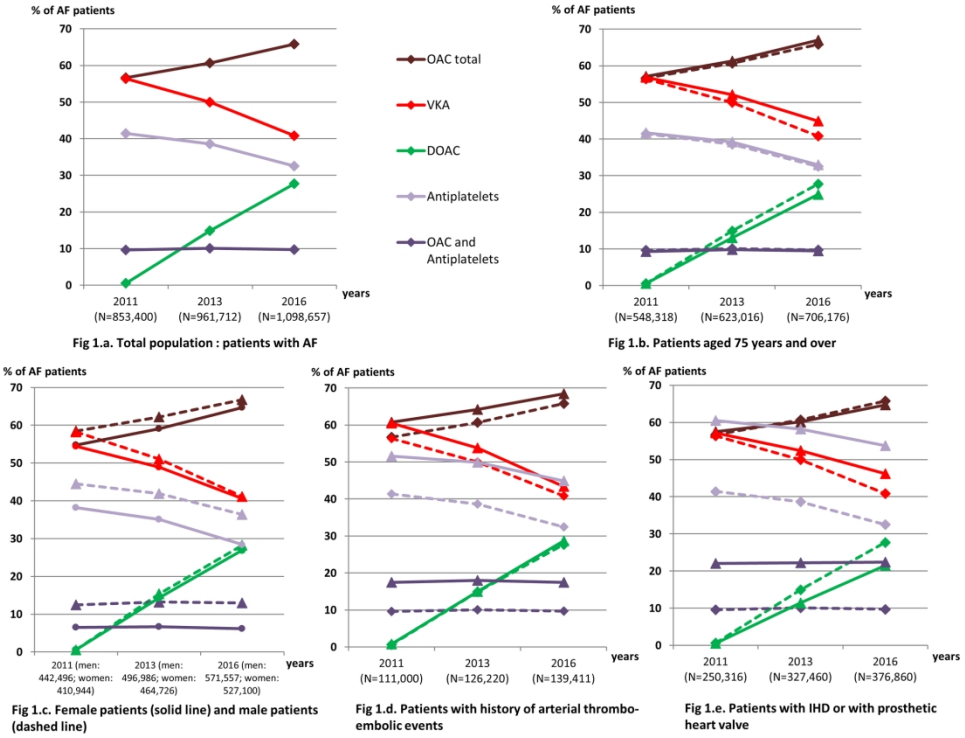

Figure 1

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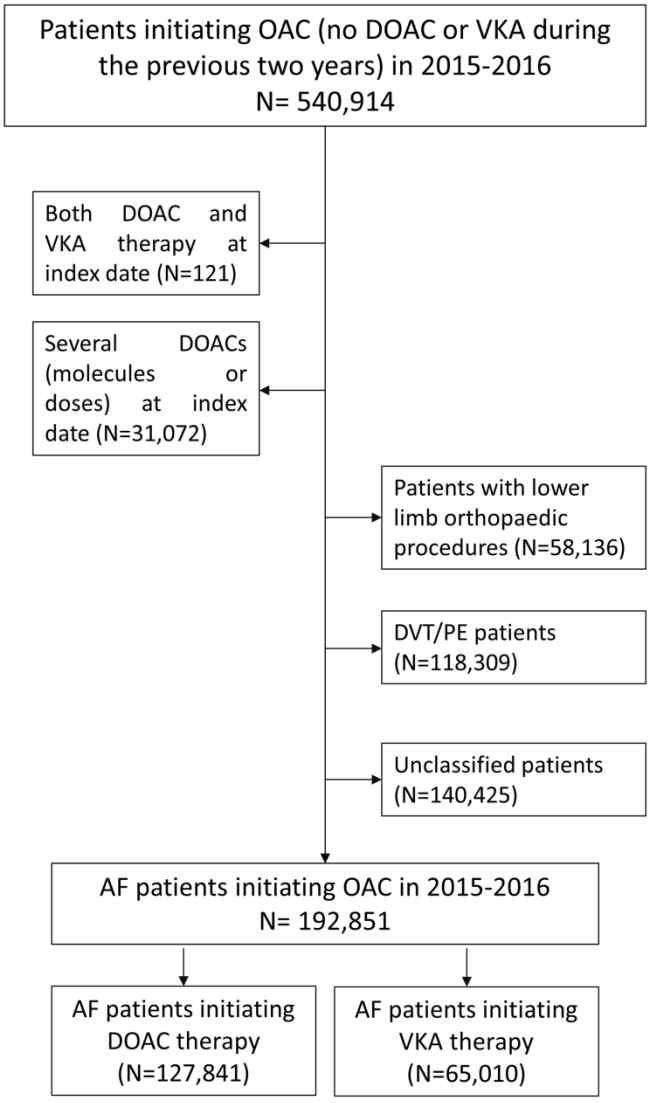

Figure 2

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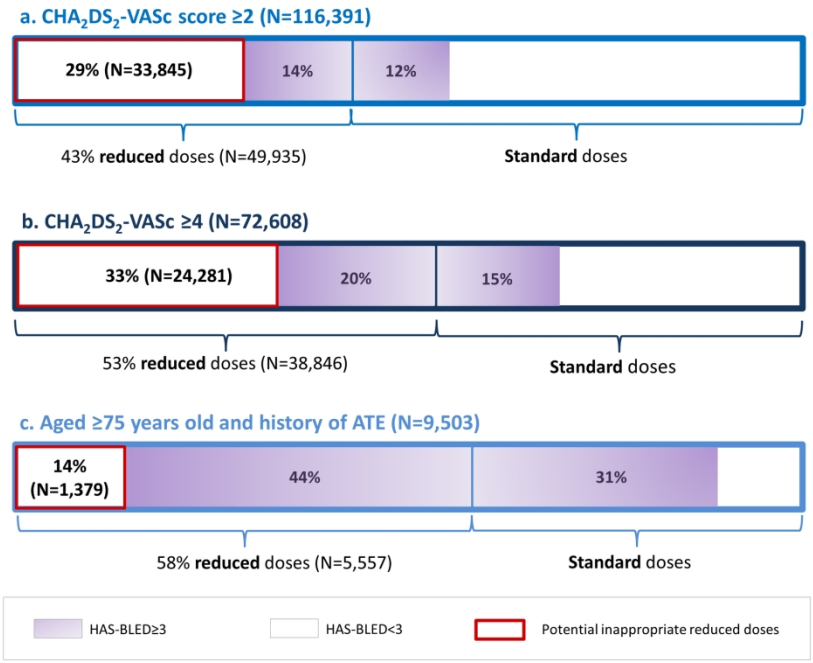

Figure 3

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Supplementary Materials

Supplementary Table 1. Definitions used to identify comorbid conditions and comedications in the French healthcare databases.

Supplementary Table 2. Comparison of selected baseline characteristics of DOAC new users with AF at risk of stroke according to level of HAS-BLED score and type of DOAC dose.

Supplementary Table 1. Definitions used to identify comorbid conditions and comedications in the SNIIRAM-PMSI databases.

Covariates*	Hospital discharge diagnoses†	LTD diagnoses†	Specific procedures or drug reimbursements
AF definition (Patterns of use of DOAC therapy in new users with AF)			
Nonvalvular atrial fibrillation	I48	I48	Radiofrequency ablation, cardioversion
Lower limb orthopaedic procedures			Lower limb orthopaedic surgery or procedures
History of valvular heart disease/Prosthetic heart valve	I05-I09, I33-I39/ Z95.2, Z95.3 ou Z95.4		Heart valve surgery
Deep vein thrombosis/pulmonary embolism	I26, I80 (except I80.0), I81, I82	I26, I80-I82	Lower limb venous ultrasonography, pulmonary/lower limb angiography, ventilation/perfusion scan
CHA_2DS_2-VASc and HAS-BLED scores			
Heart failure	I50 or I11.0, I13.0, I13.2, I13.9, K76.1, J81 related to I50	I50	Specific medications approved for heart failure including beta-blockers (bisoprolol, carvedilol, metoprolol), eplerenone, bumetanide, furosemide when licensed for heart failure only
Antihypertensive drugs			Diuretics, beta blockers, calcium channel blockers, agents acting on the renin-angiotensin system and other antiadrenergic agents
Diabetes	E10-E14	E10-E14	Insulins and blood glucose lowering drugs
History of ATE (ischemic stroke, arterial systemic embolism or transient ischemic attack)	I63 (except I63.6), G46 related to I63 or I69.3; I74, G45 (except G45.4)	I63, I74, G45	
Peripheral vascular disease	I20, I21, I22, I23, I24, I25, I70, I71, I72, I73, E10.5, E11.5, E12.5, E13.5, E14.5	I70-I73 , I20-I25	
Abnormal renal function	N18, I12.0, I13.1, I13.2, E10.2, E11.2, E13.2, E14.2, N08.3	N18, I12	
Abnormal liver function	R18, I85, K70, K71.3, K71.4, K71.5, K71.7, K72.1, K73, K74, K76.1, B18, C22, C78.7	K70, K73, K74, B18, C22	Antiviral agents for systemic use HCV (ribavirin, [peg]interferon alpha and DAA), and against HCB ([peg]interferon alpha and NnRTIs).
Major bleeding	I60-I62, S06.3-S06.6, I85, K25-K29, K62.5, K92, D62, N02, R31, R58, H11.3, H35.6, H43.1, H45.0, H92.2, J94.2, K66.1, M25.0, N92, N93.8, N93.9, N95.0, R04.0		
Predisposition for bleeding	Anemias : D50, D51, D52, D53, D55, D56, D57, D58, D59, D60, D62, D63, D64 or coagulation defects, purpura and other hemorrhagic: D65, D66, D67, D68, D69		
Alcohol abuse	F10, K70, T51, K6, G31.2, G62.1, G72.1, I42.6, K29.2, Z71.4, Z72.1, Z50.2.		disulfiram, acamprosate, nalmefene and products with naltrexone licensed in adult patients with alcohol dependence
Drug-drug interaction			Platelet aggregation inhibitors (including low-dose acetylsalicylic acid), heparins, NSAIDs
Other comorbidities			
Ischemic heart disease (including myocardial infarction)	I20-I25	I20-I25	Nitrovasodilator agents
Frailty	G81-G83	G81-G83	Home hospital bed, wheelchair, high level of nursing home stay
Dementia or Parkinson's disease	F00-F03, G30, G20	F00-F03, G30, G20	Anticholinesterases or NMDA receptor antagonists: anticholinergic and dopaminergic agents
Psychiatric disorders	F20-29, F30-39	F20-29, F30-39	Antidepressants, antipsychotics, conventional mood stabilizers
Smoking	F17, Z71.6, Z72.0; J43-J44	J43-J44	Nicotine replacement therapy
Recently hospitalized for coagulopathy, purpura and other haemorrhagic conditions	D65-D69		
Liver fibrosis and cirrhosis	K70.0, K70.2, K70.3, K70.4, K71.7, K72, K74		

Recent gastrointestinal ulceration or intracranial haemorrhage	K25, K26, K27, K28, K29.0, I60, I61, I62, S06.4, S06.5, S06.6		
Recently or currently treated cancer	C00-D09, D37-D48, Z510, Z511	C00-D09, D37-D48	Radiotherapy procedures
Baseline comedications			
Antiarrhythmics and cardiac glycosides			Antiarrhythmics: class I and III, verapamil, digitalis glycosides
Lipid-lowering agents			HMG CoA reductase inhibitors, fibrates, ezetimibe
Antiplatelet drugs			Platelet aggregation inhibitors including low-dose acetylsalicylic acid
Oral corticosteroids			Mineralo- and gluco-corticoids
Antiulcer agents			Mainly proton pump inhibitors and H2-receptor antagonists

LTD: long-term diseases; ATE: arterial thromboembolic events (mainly stroke); DVT/PE: deep vein thrombosis/pulmonary embolism; NMDA: N-methyl-D-aspartate; HIV: human immunodeficiency virus; PI: Protease inhibitor; NNRTIs: Non-nucleoside reverse transcriptase inhibitors; NnRTI: Nucleoside and nucleotide reverse transcriptase inhibitors; DAA: direct-acting antiviral; HMG CoA: 3-hydroxy-3-methyl-glutaryl-CoA; NSAIDs: Non-steroidal anti-inflammatory drugs.

* Comorbidities were identified using ICD-10 diagnosis codes for hospital discharge/LTD, or specific procedures, or drug reimbursements. Concomitant medications were identified as those dispensed at least once during the 4-month period preceding the index date. Influenza vaccination was determined during the first 'flu vaccination campaign preceding the index date.
†ICD-10 codes

Supplementary Table 2. Comparison of selected baseline characteristics of DOAC new users with AF at risk of stroke according to level of HAS-BLED score and type of DOAC dose

N (%)	Patients with CHA2DS2-VASc ≥ 2 (N=116,391)				Patients aged ≥75 years old and history of ATE (N=9,503)			
	HAS-BLED≥3 (N=30 273)		HAS-BLED<3 (N=86 118)		HAS-BLED≥3 (N=7,143)		HAS-BLED<3 (N=2,360)	
	Reduced doses* (N=16,090)	Standard doses* (N=14,183)	Reduced doses* (N=33,845)	Standard doses* (N=52,273)	Reduced doses* (N=4,178)	Standard doses* (N=2,965)	Reduced doses* (N=1,379)	Standard doses* (N=981)
Age (years), mean	81.8	74.8	81.3	70.9	84,8	81.1	81.3	70.9
Age ≥ 80 years	10,786 (67.0)	3,982 (28.1)	22,962 (67.8)	9,984 (19.1)	3,496 (83.7)	1,720 (58.0)	1,188 (86.1)	567 (57.8)
First prescriber's specialty								
Hospital practitioner or private cardiologist	12,315 (76.6)	11,364 (80.1)	25,221 (74.5)	41,728 (79.8)	3216 (77.0)	2965 (80.2)	1013 (73.5)	798 (81.3)
General practitioner	3321 (20.6)	2426 (17.1)	7836 (23.2)	9302 (17.8)	860 (20.6)	503 (17.0)	322 (23.4)	157 (16.0)
Frailty (proxies)	6,689 (41.6)	4,600 (32.4)	6,932 (20.5)	4,779 (9.1)	2,599 (62.2)	1,642 (55.4)	589 (42.7)	316 (32.2)
Dementia or Parkinson's disease	2121 (13.2)	935 (6.6)	3169 (9.4)	1555 (3.0)	789 (18.9)	355 (12.0)	259 (18.8)	111 (11.3)
Any valvular diseases†	2,640 (16.4)	1,809 (12.8)	2,740 (8.1)	3,342 (6.4)	566 (13.5)	330 (11.1)	144 (10.4)	95 (9.7)
Prosthetic heart valve†	544 (3.4)	384 (2.7)	425 (1.3)	474 (0.9)	94 (2.2)	52 (1.8)	19 (1.4)	14 (1.4)
Ischaemic heart disease	7,232 (44.9)	5,274 (37.2)	6,827 (20.2)	9,142 (17.5)	1,338 (32.0)	758 (25.6)	336 (24.4)	185 (18.9)
Antiplatelet agents at initiation	6,035 (37.5)	4,891 (34.5)	620 (1.8)	1,264 (2.4)	874 (20.9)	510 (17.2)	11 (0.8)	7 (0.7)
Lipid-lowering agents	9252 (57.5)	9213 (65.0)	12836 (37.9)	21820 (41.7)	2606 (62.4)	2132 (71.9)	697 (50.5)	611 (62.3)
Polymedication (≥10 ATC classes)	3,627 (22.5)	2,946 (20.8)	2,150 (6.4)	2,798 (5.4)	788 (18.9)	473 (16.0)	104 (7.5)	67 (6.8)

* Reduced-dose DOAC: dabigatran 150mg, Rivaroxaban 20 and apixaban 5mg; reduced-dose DOAC: dabigatran 75mg and 110mg, rivaroxaban 10mg and 15mg and apixaban 2.5mg
† Covariates defined by hospitalization data only

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5,6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5,6
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*6,7,8*
Bias	9	Describe any efforts to address potential sources of bias	7,8
Study size	10	Explain how the study size was arrived at	9, Fig 2
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7,8
		(*b*) Describe any methods used to examine subgroups and interactions	7,8
		(*c*) Explain how missing data were addressed	NA
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	NA
		(*e*) Describe any sensitivity analyses	7,8

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9 Fig 2
		(b) Give reasons for non-participation at each stage	9
		(c) Consider use of a flow diagram	Fig 2
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 1
		(b) Indicate number of participants with missing data for each variable of interest	NA
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	*NA*
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	*NA*
		Cross-sectional study—Report numbers of outcome events or summary measures	*Fig2,3* *Table2*
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Table 2
		(*b*) Report category boundaries when continuous variables were categorized	Table 2
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	9, 10
Discussion			
Key results	18	Summarise key results with reference to study objectives	11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11, 12
Generalisability	21	Discuss the generalisability (external validity) of the study results	12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	14

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Oral anticoagulation therapy use in patients with atrial fibrillation after the introduction of non-vitamin K antagonist oral anticoagulants: findings from the French healthcare databases, 2011-2016

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Keywords:	Anticoagulation < HAEMATOLOGY, EPIDEMIOLOGY, PUBLIC HEALTH, dabigatran, rivaroxaban, apixaban

Title page

Oral anticoagulation therapy use in patients with atrial fibrillation after the introduction of non-vitamin K antagonist oral anticoagulants: findings from the French healthcare databases, 2011-2016.

Running title: Patterns of OAC use

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Abstract

Objectives: To describe i) the trend in oral anticoagulant (OAC) use following the introduction of Non-vitamin K antagonist oral anticoagulant (NOAC) therapy for stroke prevention in atrial fibrillation (AF) patients; ii) the current patterns of use of NOAC therapy in new users with AF in France.

Design: i) Repeated cross-sectional study; ii) Population-based cohort study.

Setting: French National Healthcare databases (50 million beneficiaries).

Participants: i) Patients with identified AF in 2011, 2013, and 2016; ii) Patients with AF initiating OAC therapy in 2015-2016.

Primary and secondary outcome measures: i) Trend in oral anticoagulant therapy use in patients with AF; ii) Patterns of use of NOAC therapy in new users with AF.

Results: Between 2011 and 2016, use of OAC therapy moderately increased (+16%), while use of antiplatelet therapy decreased (-22%) among all patients with identified AF. In 2016, among the 1.1 million AF patients, 66% used OAC therapy and were more likely to be treated by VKA than NOAC therapy, including patients at higher risk of stroke (63.5%), while 33% used antiplatelet therapy. Among 192,851 new users of OAC therapy in 2015-2016 with identified AF, NOAC therapy (66.3%) was initiated more frequently than VKA therapy, including in patients at higher risk of stroke (57.8%). Reduced doses were prescribed in 40% of NOAC new users. Several situations of inappropriate use at NOAC initiation were identified, including concomitant use of drugs increasing the risk of bleeding (one in three new users) and potential NOAC underdosing.

Conclusions: OAC therapy use in AF patients remains suboptimal 4 years after the introduction of NOACs for stroke prevention in France and improvement in appropriate prescribing regarding NOAC initiation is needed. However, NOAC therapy is now the preferred drug class for initiation of OAC therapy in patients with AF, including in patients at higher risk of stroke.

Strengths and limitations of this study

- This study is the first to report both the 2011-2016 trend in oral anticoagulant (OAC) coverage in patients with atrial fibrillation (AF) following the introduction of Non-vitamin K antagonist oral anticoagulant (NOAC) therapy in France and the current patterns of use of NOACs in new users including assessment of potential inappropriate use;
- This study is based on reimbursement data for 50 million beneficiaries with access to all OAC prescriptions filled in the ambulatory setting;
- As indications for treatment are not available in the databases, AF was mostly identified on the basis of discharge and long-term disease diagnosis codes and an algorithm previously validated in the French healthcare databases that helped to further identify AF in outpatients.

Introduction

Non-vitamin K antagonist Oral AntiCoagulants (NOACs) have been gradually introduced over the past decade as a more convenient, fixed-dose alternative to vitamin K antagonists (VKAs), the only oral anticoagulant therapy available up until now for long-term stroke prevention in patients with non-valvular atrial fibrillation (AF) [1]. Compared to VKA, NOAC therapy avoids the need for regular laboratory monitoring of patients by INR testing due to a wider therapeutic window, allows once (rivaroxaban, edoxaban) or twice (dabigatran, apixaban) daily intake and is associated with fewer drug-drug interactions to date [2–6]. NOACs have been demonstrated to have similar or superior efficacy to warfarin for stroke prevention in nv-AF patients, and these findings have recently been implemented in the 2016 European Society of Cardiology (ESC) guidelines that recommended NOAC over VKA therapy in this indication [7]. Moreover, antiplatelet therapy is no longer recommended in these patients [7,8]. The use of NOAC therapy, massively adopted worldwide including in France [9–15], is expected to overcome the suboptimal use of oral anticoagulant (OAC) therapy extensively reported with VKA therapy, including underprescribing and high discontinuation rates [16,17].

Despite their improved ease of use, NOAC prescribed dose needs to be adjusted to the patient's clinical profile with regards to age, renal function, weight, and risks of bleeding and drug-drug interactions. Two dose regimens are therefore proposed for each NOAC: standard dose regimen (*i.e.* dabigatran 150mg/12h, rivaroxaban 20mg/24h; apixaban 5mg/12h), and reduced-dose regimen (i.e. dabigatran 75mg or 110mg/12h, rivaroxaban 10mg or 15mg/24h; apixaban 2.5mg/12h). The reasons for prescribing a reduced-dose regimen are listed in the summary of product characteristics (SmPCs) of each NOAC with differences across NOACs as well as in the ESC [7,8] and European Heart Rhythm Association (EHRA) guidelines [18]. Recent publications have suggested that the frequency of use of reduced-dose NOACs in clinical practice could largely exceed that expected on the basis of the conditions summarized in these guidelines [11,19–21]. However, national data are lacking concerning the current French patterns of NOAC use, including the potential issue of NOAC underdosing.

A steady increase in the initiation of NOAC therapy has already been reported in AF patients in France [14], but trends in OAC coverage of AF patients following the introduction of NOACs and a description of the current national patterns of NOAC use have not yet been reported. This study, based on the French nationwide healthcare databases, therefore had a twofold objective: 1) to describe the trends in OAC use following the introduction of NOAC for stroke prevention in AF patients during the 2011-2016 period; 2) to describe the current patterns of use of OAC therapies with particular focus on NOAC use in new users with AF.

Methods

Data source

French national health insurance (*Assurance Maladie*) covers the entire French population by means of several specific schemes according to the beneficiary's occupational sector, the largest scheme being the '*Régime général*' (around 50 million beneficiaries).

This study was conducted using data from the French health insurance system database (*Système national d'information inter-régimes de l'Assurance maladie*, SNIIRAM) linked to the French hospital discharge database (*Programme de médicalisation des systèmes d'information*, PMSI) [22,23]. The SNIIRAM database contains individualized, anonymous, and comprehensive data on health spending reimbursements. Demographic data include date of birth, gender, and vital status. Drugs are coded according to the Anatomical Therapeutic Chemical (ATC) classification. Each packaging of each product is identified by means of a national specific pack identifier code providing information on the name of the product, active ingredient and dose per unit, number of units, and route of administration; but, the exact dosage prescribed and the indication are not available. However, for most drugs, particularly OACs, each dispensing of the prescribed drug cannot exceed the quantity necessary for one month of treatment. The PMSI database provides detailed information about discharge diagnoses and medical procedures related to all hospitalizations in France. This information regarding morbidities is completed by diagnoses corresponding to patient eligibility for 100% reimbursement of severe and costly long-term diseases (LTD) and disability, such as AF, coronary heart disease, certain debilitating diseases (such as multiple sclerosis or rheumatoid arthritis), HIV infection, cancer, etc. All information concerning medical diagnosis is encoded according to the International Classification of Diseases, 10th revision (ICD-10). Finally, the SNIIRAM-PMSI databases also indicate medical procedures performed in the ambulatory setting, including information about the type and date of all laboratory tests performed, but not including their results.

The French healthcare databases have been previously described and used in epidemiological and pharmacoepidemiological studies [22,24–26].

Study populations and study designs

Two study populations were defined; one for each objective.

To answer the first objective, a repeated cross-sectional study was performed to describe the trends in OAC use following the introduction of NOAC in AF patients. Patients with AF were identified in 2011 (as none of the NOACs was available for stroke prevention in France) and 2016 (the most recent data available at the time of writing the study protocol; dabigatran, rivaroxaban and apixaban were all reimbursed for stroke prevention in France, as apixaban was reimbursed from January 2014

onwards). OAC coverage was also calculated for year 2013 as this year represented the first calendar year for which the first two NOACs were available in France, i.e. a pivotal year for the pharmacological management of AF by oral anticoagulants. For each of these calendar years, a patient was considered to have AF when at least one diagnosis of AF (ICD-10 code I48) was identified from discharge and LTD diagnoses in the SNIIRAM-PMSI database in the calendar year considered or during the previous 5 years. Patients with no continuous '*Régime général*' health insurance coverage for at least six years before the calendar year considered were excluded.

To answer the second objective, a population-based cohort study was performed including patients with AF initiating OAC therapy in 2015-2016. First, OAC new users were identified among patients with continuous '*Régime général*' health insurance coverage as those with at least one reimbursement for OAC therapy in 2015-2016 and no reimbursement for any OAC (VKA or NOAC) in the previous 24 months. The patient's index date was the date of first OAC reimbursement identified during the 2015-2016 period. Second, the cohort of NOAC news users was restricted to those treated for AF: (i) patients treated for other OAC indications *i.e.* patients treated for deep vein thrombosis/pulmonary embolism (DVT/PE) or with lower limb orthopaedic procedures were excluded; (ii) OAC new users treated for AF were identified from the resulting cohort as the sum of "OAC new users with confirmed AF" for those with a diagnosis of AF (ICD-10 code I48) or specific AF management procedures identified from LTD or hospitalization discharge data during a six-year pre-index period, and "OAC new users with probable AF" for outpatients identified using an algorithm discriminating AF from DVT/PE with 95% specificity [27]. The remaining patients were not classified as probable FA patients and were excluded. Codes used for identification of AF and all of the patient characteristics considered, including comorbidities, are displayed in **Supplementary Table 1**.

Patient and public involvement

Patients and or public were not involved.

Exposure

NOAC (dabigatran, rivaroxaban, apixaban) and VKA therapies (fluindione, warfarin and acenocoumarol) were identified using ATC codes; edoxaban was not available in France during the period considered.

Outcomes

Trends in oral anticoagulant therapy use in patients with AF

The proportion of AF patients treated by OAC therapy was assessed before and after approval of NOAC therapies for stroke prevention in France. Trends in the use of antiplatelet agents were also assessed in AF patients over the same timeframe.

Patterns of use of NOAC therapy in new users with AF

The description of patterns of NOAC use in new users treated for AF in 2015-2016 included comparison of the baseline characteristics among NOAC new users and compared to those of VKA new users and potential inappropriate use of NOAC therapy was then investigated by identifying:

(i) NOAC off-label use or non-approved indication/dose: contraindications to NOAC therapy according to SmPCs [concomitant coagulopathy, purpura and other haemorrhagic conditions, liver fibrosis and cirrhosis, recent gastrointestinal ulceration or intracranial haemorrhage], valvular atrial fibrillation [NOAC are only approved for non-valvular AF], prosthetic heart valve [contraindicated for dabigatran], cancer [NOAC are not approved for prevention of thromboembolism in patients with cancer] and prescription of NOAC doses not approved for stroke prevention in Europe [dabigatran 75 mg and rivaroxaban 10 mg are not approved for stroke prevention in Europe and are therefore off-label doses in AF patients]; (ii) non-compliance with guidelines with respect to follow-up and clinical work-up of patients during the first year following NOAC initiation: no monitoring of patients' renal function [renal function should be assessed at initiation and annually during NOAC therapy [28]], discontinuation of NOAC therapy [OAC therapy is recommended as lifetime treatment in most patients with AF] (iii) clinically relevant drug-drug interactions at initiation increasing the bleeding risk at initiation; (iv) potential inappropriate underdosing, i.e. patients in whom the NOAC dose prescribed at initiation was inappropriately reduced in view of their individual stroke and bleeding risks.

Data analysis

Descriptive analyses are expressed as mean and standard deviation (SD) for continuous variables, and numbers and percentages for categorical variables.

Trends in oral anticoagulant therapy use in patients with AF

For each calendar year, the proportion of patients treated by a drug was defined by the number of patients with at least one reimbursement for this drug in the calendar year considered over the total number of patients identified as having AF in the same year. Proportions are reported according to the type of OAC first reimbursed in the year considered. Antiplatelet drugs and OAC therapies were considered to be coprescribed when they were reimbursed at least once on the same day during the calendar year studied. Analyses were replicated in subgroups of AF patients: (i) aged 75 years and over; (ii) female and male, separately; (iii) with a history of hospitalization for arterial thromboembolic events (ATE); (iv) with concomitant ischaemic heart disease (IHD) or prosthetic heart valve.

Patterns of use of NOAC therapy in new users with AF

Baseline characteristics of NOAC new users with AF included sociodemographic data, including deprivation index of the patient's municipality of residence [29], type of initial prescriber, clinical scores predicting the risk of stroke (CHA_2DS_2-VASc score) or bleeding (HAS-BLED score) [30,31], adapted to claims data and the other main comorbidities and comedications, including proxies of frailty. A negative binomial regression analysis for each NOAC therapy and each baseline characteristic was performed to assess the association between these characteristics and the choice of NOAC therapy *versus* VKA therapy, while adjusting for age and sex.

Compliance with guidelines regarding renal function monitoring and treatment persistence patterns were assessed in new users for whom data for at least one year of follow-up were available, i.e. patients included in 2015 and who had not died and had not been hospitalized for 3 months or longer. Compliance with renal function monitoring was assessed at NOAC initiation (no reimbursement for renal function monitoring during the three months before and the three months after NOAC initiation) and during the first year following treatment initiation. OAC non-persistence patterns were assessed over the one-year period following the index date by calculating proxies of OAC discontinuation: number of patients with only one reimbursement and one-year crude discontinuation rates.

Drugs increasing the risk of bleeding were those responsible for clinically relevant pharmacodynamic interactions with OAC therapy, i.e. concomitant reimbursement of other parenteral and oral antithrombotic drugs, non-steroidal anti-inflammatory drugs (NSAIDs); selective serotonin reuptake inhibitors and selective serotonin-norepinephrine reuptake inhibitors (SSRIs and SSNRIs) [7,18,32]. Patients taking concomitant drugs with OAC therapy were defined as those with a reimbursement for the drug of interest during the period corresponding to the index date and the following 45 days. Analyses were replicated in VKA new users for descriptive purposes.

Finally, potential inappropriate underdosing with NOACs was defined as initiation of NOAC therapy in patients at risk of stroke in whom reduced doses of NOAC were prescribed with no identified justification. As this study was based on claims data and as, up until 2016, ESC guidelines recommended prescribing reduced-dose NOAC in patients with HAS-BLED≥3 [8], the proportion of AF patients initiating reduced-dose NOAC with an HAS-BLED score<3 among all NOAC new users with a CHA_2DS_2-VASc score ≥2 was used to quantify potential inappropriate underdosing in NOAC new users. Analyses were replicated in patients i) with CHA_2DS_2-VASc score ≥4, ii) aged 75 and over with a history of ATE.

Results

Trends in oral anticoagulant therapy use in patients with AF

The number of patients identified from French healthcare databases as having AF increased between 2011 (N=853,440) and 2016 (N=1,098,657). A high proportion of these patients were identified exclusively by hospitalization discharge diagnosis and this proportion decreased only slightly over this time interval from 90.2% (N=770,002) to 86.2% (N=946,657).

Between 2011 and 2016, the proportion of patients with at least one reimbursement for OAC therapy among all AF patients moderately increased (+16%) from 56.7% to 65.8%, corresponding to a steady decrease in VKA use (from 56.6% to 40.8% of all AF patients) associated with the introduction of NOACs (from 0.6% to 27.7%). In 2016, among patients with identified AF, VKA therapy remained the preferred OAC therapy (62.0%), including in patients aged 75 years and over (67.0%) and in those with a history of ATE (63.5%).

Between 2011 and 2016, the use of antiplatelet therapy decreased in AF patients (-22%), but the proportion of patients with concomitant OAC and antiplatelet therapy remained stable (9.7% in 2016). In 2016, 32.5% of AF patients had at least one reimbursement for antiplatelet therapy during the year.

Similar trends were observed in the subgroup analyses. A slightly higher rate of OAC therapy was observed in patients with a history of ATE (68.4% vs 65.8% in the total cohort in 2016). However, OAC coverage was lower in women than in men with AF (64.7% vs 66.8% in 2016) (**Figure 1**).

Patterns of use of NOAC therapy in new users with AF

Baseline characteristics of OAC new users

Among 540,914 patients initiating OAC therapy in 2015-2016, a total of 192,851 (35.7%) patients were included in the study population, corresponding to 127,841 NOAC new users and 65,010 VKA new users with AF. The mains reasons for ineligibility were other indications or uncertain identification of the indication for NOAC (**Figure 2**).

The mean age of the NOAC new users cohort was 74.1±11.6 years; patients over the age of 80 represented 37.3% of the total cohort. One-half of the NOAC new users were women, and 40.0% received a reduced dose at initiation (62.2% for dabigatran new users). Apixaban was the NOAC most commonly initiated; apixaban new users were older and had more comorbidities than the other two groups of NOAC new users. NOAC therapy was more likely to be initiated than VKA therapy among patients aged 75 years and older (59.4%) and in patients with a history of ATE (57.8%) (**Table 1**).

Characteristics associated with bleeding risk, such as older age, renal impairment, history of bleeding or bleeding predisposition, and treatment with a concomitant drug increasing the risk of bleeding at

OAC initiation, were strong predictors of being treated with VKA therapy *versus* NOAC therapies (**Supplementary Table 2**).

Potential inappropriate use of NOAC therapy

About 15% of NOAC new users with AF were considered to be using NOAC off-label or for a non-approved indication. In particular, 8.5% of NOAC new users with AF had valvular heart disease (8.5%), including prosthetic heart valve (1.5%) and 4.6% had a recently or currently treated cancer (**Table 2**).

About 15% and 9% of NOAC new users had no reimbursement for renal function tests at initiation and during the one-year period post-initiation, respectively. Discontinuation during the one-year period following initiation was frequent, as more than 20% of patients had five or less reimbursements (**Table 2**).

Nearly 30% of NOAC new users were using at least one concomitant drug increasing the risk of bleeding (52% in VKA new users). The most common concomitant drugs concerned at initiation were antiplatelet agents or parenteral anticoagulants (**Table 2**).

Among the 116,391 NOAC new users with AF with a CHA_2DS_2-VASc score ≥2, 29.1% (N=33,845) were prescribed a reduced dose although they had an HAS-BLED score <3. This meant that nearly 1 in 3 NOAC new users with AF and at risk of stroke were therefore potentially prescribed an inappropriately reduced dose of NOAC at initiation. This proportion was 33% (N=24,281) and 14.5% when defining patients at risk of stroke as patients with a CHA_2DS_2-VASc score ≥4 and aged 75 and over with a history of ATE, respectively (**Figure 3**).

Differences in baseline characteristics were observed in patients with HAS-BLED<3 according to the type of NOAC dose prescribed, e.g. patients with reduced-dose NOAC were older and frailer than those with standard-dose NOAC (**Supplementary Table 3**).

Discussion

Main findings

OAC therapy use among patients with AF improved in France between 2011 and 2016, but remained suboptimal with about 66% of the 1.1 million patients with identified AF treated by OAC therapy in 2016. Use of antiplatelet therapy in AF patients decreased over the same period, but still concerned 33% of all AF patients in 2016. Patients with AF were more likely to be treated by VKA than NOAC therapy, including older patients and those at higher risk of stroke.

Nearly 193,000 patients with AF were identified as OAC new users in 2015-2016: patients were more likely to be treated by NOAC than VKA therapy, including older patients and those at higher risk of stroke. Results on current patterns of use of NOAC therapy in new users with AF suggest several situations of inappropriate use, including frequent concomitant use of drugs increasing the risk of bleeding and potential inappropriate underdosing.

Comparison with postmarketing literature and clinical implications

The overall improvement of management of AF patients observed with regards to OAC therapy after the introduction of NOACs has been reported in many countries [33–36]. The same applies to the steady decrease in VKA use in favour of NOAC therapies [12,37,38], and the gaps remaining in optimal OAC coverage and high antiplatelet drug use [39–41].

This study demonstrated channelling of NOAC therapy towards patients at lower risk of stroke and bleeding when considering all patients with AF, in line with what has become a common feature reported worldwide in clinical practice by many observational studies on the current patterns of use of NOACs [15,42–45]. In particular, data from EORP-AF registry showed that younger age and non-valvular heart diseases were also found to be clinical predictors for being treated with NOAC in other South countries (Greece, Italy, Portugal) [46].

However, NOAC therapy is now the preferred OAC therapy at initiation in the oldest patients and those at higher risk of stroke. This French pattern of OAC use has never been previously reported and contrasts with published results concerning earlier periods [47]. This emerging pattern is encouraging for AF management, as older and high-risk patients are those who should derive most benefit from NOAC *versus* VKA therapy [48].

Reduced doses were often prescribed in OAC new users, including dabigatran 75mg and rivaroxaban 10mg, which are not approved for stroke prevention in Europe [49]. In addition to the overall channelling mentioned above, these findings may reflect a “bleeding avoidance” strategy of prescribers (i.e. overestimation of the potential bleeding risk *versus* the likely benefit of stroke reduction) and the differential perception of the comparative safety of NOACs *versus* VKA and

between NOACs. The early safety alert on bleeding in dabigatran-treated patients, followed by the contraindication of this NOAC in patients with prosthetic heart valves, may have reinforced the fears of prescribers in relation to the safety of dabigatran, which would explain the difference in reduced-dose prescription rates between the three NOACs in this study, despite the intermediate stroke and bleeding risk profile of dabigatran compared to that of rivaroxaban and apixaban in new users. Similarly, among NOAC new users, apixaban was prescribed to the oldest and most severe patients. Apixaban was the only NOAC found to be superior to warfarin for all types of bleeding outcome and all-cause mortality, which would also illustrate the tendency of physicians to prescribe OAC therapies according to bleeding risk [5]. This may also explain the potential inappropriate underdosing observed in NOAC users in this study. This pattern of NOAC use has been previously reported, but mostly in field and registry studies based on small sample sizes. The reported inappropriate underdosing rate varies according to studies and the definition used. NOAC underdosing concerned 30.4% of Turkish patients in the RAMSES study (N=2,086) [50], 18.4% of Japanese patients of the *KiCS* AF registry (N=1,284) [51,52], between 19.7% and 27.6% of patients in the SAKURA AF registry (N= 3,266) [53], and 9.4% to 16% of patients in the ORBIT-AF II registry (N=7925) [21,54]. In the subgroup of Dutch patients (N=899) enrolled in the XANTUS registry, 33% of patients were also treated with reduced-dose rivaroxaban despite presenting normal renal function [55]. Using a large U.S. administrative database, Yao *et al* found that 13.3% of the 13,392 NOAC new users with no renal indication for dose reduction were potentially underdosed [56]. Taken together with our results, these data suggest that inappropriate underdosing might be a common issue in NOAC new users that should be systematically assessed when studying NOAC patterns of use. This is of particular concern, as recent data have suggested a relationship between NOAC dose and clinical outcomes [57]. In particular, NOAC underdosing has been shown to be associated with increased risk for adverse outcomes [21,56].

These patterns of NOAC use contrast with the other patterns concomitantly observed in this study, such as the high level of concomitant prescription of antiplatelet agents and parenteral anticoagulants or, to a lesser extent, NOAC use in non-approved indications such as prosthetic heart valves that are both associated with an increased risk of bleeding [58–60].

Strengths and limitations

This study is the first to report the improved trend in OAC coverage in French patients with AF over the last five years as well as the recent patterns of use of OAC therapy in new users, particularly including a nationwide assessment of the growing issue of NOAC underdosing, based on health data for more than 50 million beneficiaries. Moreover, all OAC prescriptions filled in the ambulatory setting are captured in the databases and are reimbursed with no restriction of coverage: selection

bias related to the access of patients to more expensive NOAC therapy is therefore not an issue with the use of French healthcare databases [22,61].

However, several limitations related to the nature of the data used should be underlined. First of all, it cannot be verified whether patients actually took the drugs for which they were reimbursed. Secondly, as the indication for treatment is not available in the databases, and despite the use of an algorithm to identify AF among outpatients in the French healthcare databases, identification of AF was mostly based on non-validated discharge and LTD diagnoses recorded in the databases. Moreover, it cannot be excluded that the increase in the identified number of patients with AF over the 2011-2016 period could be partially explained by changes in LTD legislation in 2011 (e.g. hypertension was removed from the list of LTD, while access to LTD was facilitated for patients with severe arrhythmia and valvular heart diseases) which could have helped identify patients with AF. Thirdly, identification of inappropriate underdosing at NOAC initiation was also indirectly assessed by using stroke and bleeding risk scores computed from claims data. Important medical data such as patient's weight, glomerular filtration rate and exact alcohol consumption are not available in the French healthcare databases, which may have led to underestimation of the HAS-BLED score and therefore to overestimation of the proportion of patients potentially underdosed at initiation. These missing clinical data may also explain the prescription of reduced dose NOAC at treatment initiation in clinical practice. Furthermore, the agreement between these empirical scores in patients with AF and the prescriber-assessed stroke and bleeding risk is a subject of discussion [62]. Consequently, the rate of inappropriate underdosing should be interpreted with caution and must be confirmed by further studies. However, NOAC misuse and underdosing have also been reported in a French prospective field study based on patients' medical charts [63]. Of note, as INR values were not available in the databases, underdosing with VKA therapy was not assessed in this study, but has been frequently reported and must not be overlooked [53,64]. In addition, the results for NOAC and VKA new users are difficult to compare, as they were not adjusted for significant differences in baseline characteristics and this comparison was not the purpose of this study.

Conclusion

OAC therapy use has modestly increased after the introduction of the NOACs for stroke prevention in patients with AF in France and NOAC therapy is now the preferred OAC therapy at initiation in older patients at higher risk of stroke. However, results from this nationwide drug utilization study suggest the need for improvement in appropriate prescription of OAC therapy in these patients, especially regarding the use of concomitant interacting drugs and the choice of initial NOAC dose.

Contributor ship statement

GM, AP, CB and AN designed the study. All authors have contributed substantially to the interpretation of results. In addition: GM, AP and AN drafted the article; CB, JD and AN conducted the statistical analysis; GM, AP, AN, CB, JD, AW provided critical revision of the manuscript for important intellectual content. All authors had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis. All authors approved the version to be published.

Competing interests

All authors have no conflict of interest.

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Data sharing statement

No additional data are available directly from the authors. Permanent access to the French healthcare databases is automatically granted to certain government agencies, public institutions and public service authorities. Temporary access for studies and research is possible upon request from the national health data institute (INDS). All databases used in this study only contained anonymous patient records.

Ethics approval

This observational study based on the French healthcare databases was approved by the French Data Protection Agency (*Commission Nationale de l'Informatique et des Libertés*, Cnil) and did not require patient consents or ethics committee approval.

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Figure titles and legends

Figure 1. Time trends in the use of oral antithrombotic therapy between 2011 and 2016 in patients with atrial fibrillation in France

Abbreviations: AF: atrial fibrillation; OAC: oral anticoagulant; VKA: vitamin K antagonist; NOAC: Non vitamin K antagonist oral anticoagulant

Legend: For Figures 1.b., 1.d and 1.e., estimates from all AF patients already presented in figure 1.a. are indicated by dashed lines for the purposes of comparison.

Figure 2. Patient flow chart.

Abbreviations: OAC: oral anticoagulant; NOAC: Non-vitamin K antagonist oral anticoagulant; VKA: vitamin K antagonist; DVT/PE: deep vein thrombosis/pulmonary embolism; AF: atrial fibrillation

Figure 3. Potential NOAC underdosing in new users with AF

Abbreviations: NOAC: Non-vitamin K antagonist oral anticoagulant; AF: atrial fibrillation

Table 1. Baseline characteristics of anticoagulant-naive patients with atrial fibrillation initiating oral anticoagulants in 2015-2016

Characteristics (N; %*)	NOAC				VKA
	Dabigatran N= 9,085	Rivaroxaban N= 54,456	Apixaban N= 64,300	Total NOAC N= 127,841	N= 65,010
NOAC: reduced doses	5,652 (62.2)	19,429 (35.7)	26,003 (40.4)	51,084 (40.0)	NA
Female sex	4,546 (50.0)	26,147 (48.0)	33,375 (51.9)	64,068 (50.1)	33,865 (52.1)
Age (years), mean (SD)	74.1 (11.6)	72.8 (11.9)	75.3 (11.3)	74.1 (11.6)	78.0 (11.3)
18-54	548 (6.0)	4,007 (7.4)	3,172 (4.9)	7,727 (6.0)	2,361 (3.6)
55-64	1,117 (12.3)	7,651 (14.0)	7,117 (11.1)	15,885 (12.4)	5,680 (8.7)
65-74	2,514 (27.7)	16,057 (29.5)	16,645 (25.9)	35,216 (27.5)	12,969 (19.9)
75-79	1,554 (17.1)	9,053 (16.6)	10,692 (16.6)	21,299 (16.7)	9,587 (14.7)
≥80	3,352 (36.9)	17,688 (32.5)	26,674 (41.5)	47,714 (37.3)	34,413 (52.9)
≥90	493 (5.4)	2,559 (4.7)	4,654 (7.2)	7,706 (6.0)	8,399 (12.9)
Deprivation index					
Quintile 1 (least deprived)	1,394 (15.3)	10,265 (18.9)	11,266 (17.5)	22,925 (17.9)	10,263 (15.8)
Quintile 2	1,586 (17.5)	10,678 (19.6)	12,496 (19.4)	24,760 (19.4)	11,884 (18.3)
Quintile 3	1,780 (19.6)	10,701 (19.7)	12,799 (19.9)	25,280 (19.8)	12,811 (19.7)
Quintile 4	1,917 (21.1)	10,794 (19.8)	13,142 (20.4)	25,853 (20.2)	14,272 (22.0)
Quintile 5 (most deprived))	2,113 (23.3)	11,172 (20.5)	13,825 (21.5)	27,110 (21.2)	14,699 (22.6)
Overseas departments	295 (3.2)	846 (1.6)	772 (1.2)	1,913 (1.5)	1,081 (1.7)
First prescriber's specialty					
Hospital practitioner	3,720 (40.9)	22,905 (42.1)	29,316 (45.6)	55,941 (43.8)	39,083 (60.1)
General practitioner	2,062 (22.7)	11,145 (20.5)	11,590 (18.0)	24,797 (19.4)	15,539 (23.9)
Private cardiologist	3,093 (34.0)	18,978 (34.9)	21,843 (34.0)	43,914 (34.4)	8,511 (13.1)
Private orthopaedic surgeon	16 (0.2)	100 (0.2)	95 (0.1)	211 (0.2)	73 (0.1)
Other private specialist	168 (1.8)	1,149 (2.1)	1,276 (2.0)	2,593 (2.0)	1,583 (2.4)
CHA_2DS_2-VASc score[†]					
Mean score (SD)	3.7 (1.6)	3.5 (1.6)	3.9 (1.6)	3.7 (1.6)	4.5 (1.6)
0	183 (2.0)	1,294 (2.4)	847 (1.3)	2,324 (1.8)	309 (0.5)
1	635 (7.0)	4,854 (8.9)	3,637 (5.7)	9,126 (7.1)	1,607 (2.5)
≥ 2	8,267 (91.0)	48,308 (88.7)	59,816 (93.0)	116,391 (90.1)	63,094 (97.0)
C (Heart failure)	2,849 (31.4)	17,805 (32.7)	23,548 (36.6)	44,202 (34.6)	32,727 (50.3)
H (antihypertensive drugs)	7,547 (83.1)	44,260 (81.3)	54,596 (84.9)	106,403 (83.2)	59,139 (91.0)
D(iabetes)	1,959 (21.6)	11,279 (20.7)	14,087 (21.9)	27,325 (21.4)	18,806 (28.9)
S(troke: ATE)	1,207 (13.3)	4,930 (9.1)	8,448 (13.1)	14,585 (11.4)	10,638 (16.4)
V(ascular diseases)	2,242 (24.7)	13,924 (25.6)	18,766 (29.2)	34,932 (27.3)	28,894 (44.4)
Age≥75 and arterial thromboembolic events[†]	769 (8.5)	3,126 (5.7)	5,608 (8.7)	9,503 (7.4)	7,762 (11.9)
Age<65 and no arterial thromboembolic events[†]	1,510 (16.6)	11,074 (20.3)	9,396 (14.6)	21,980 (17.2)	7,035 (10.8)

Table 1. (continued)

Characteristics (N; %)	NOAC				VKA
	Dabigatran N= 9,085	Rivaroxaban N= 54,456	Apixaban N= 64,300	Total NOAC N= 127,841	N= 65,010
HAS-BLED score†					
Mean score (SD)	2.0 (0.9)	1.9 (0.9)	2.1 (0.9)	2.0 (0.9)	2.7 (1.0)
≥ 3	2,169 (23.9)	11,388 (20.9)	16,834 (26.2)	30,391 (23.8)	36,417 (56.0)
A(bnormal)					
Renal function	345 (3.8)	2,426 (4.5)	3,822 (5.9)	6,593 (5.2)	14,260 (21.9)
Liver function	169 (1.9)	967 (1.8)	1,106 (1.7)	2,242 (1.8)	2,372 (3.6)
B(leeding)					
Predisposition	182 (2.0)	1,161 (2.1)	1,605 (2.5)	2,948 (2.3)	5,873 (9.0)
Major bleeding	692 (7.6)	3,729 (6.8)	5,134 (8)	9,555 (7.5)	9,348 (14.4)
D(rug/alcohol)					
Alcohol abuse‡	272 (3.0)	1,698 (3.1)	1,730 (2.7)	3,700 (2.9)	2,923 (4.5)
Drug-drug interactions	947 (10.4)	5,838 (10.7)	7,570 (11.8)	14,355 (11.2)	23,451 (36.1)
Parenteral anticoagulant (heparin)	64 (0.7)	331 (0.6)	361 (0.6)	756 (0.6)	9,824 (15.1)
Antiplatelet drugs	826 (9.1)	5,225 (9.6)	6,951 (10.8)	13,002 (10.2)	15,433 (23.7)
NSAIDs	72 (0.8)	365 (0.7)	344 (0.5)	781 (0.6)	212 (0.3)
Other comorbidities†					
Ischaemic heart disease	1,821 (20.0)	11,321 (20.8)	15,439 (24.0)	28,581 (22.4)	23,657 (36.4)
Frailty (proxies)	1,666 (18.3)	8,971 (16.5)	12,730 (19.8)	23,367 (18.3)	24,175 (37.2)
Dementia or Parkinson's disease	524 (5.8)	3,204 (5.9)	4,125 (6.4)	7,853 (6.1)	7,437 (11.4)
Psychiatric disorders	1,722 (19.0)	10,593 (19.5)	12,844 (20.0)	25,159 (19.7)	16,598 (25.5)
Smoking‡	1,024 (11.3)	6,481 (11.9)	7,442 (11.6)	14,947 (11.7)	11,434 (17.6)
Comedications§					
Antiarrhythmics or cardiac glycosides	5,996 (66.0)	35,761 (65.7)	41,031 (63.8)	82,788 (64.8)	35,600 (54.8)
Lipid-lowering agents	3,913 (43.1)	22,250 (40.9)	28,812 (44.8)	54,975 (43.0)	31,903 (49.1)
Oral corticosteroids	1,105 (12.2)	6,964 (12.8)	8,079 (12.6)	16,148 (12.6)	8,967 (13.8)
Antiulcer agents	4,295 (47.3)	24,842 (45.6)	31,469 (48.9)	60,606 (47.4)	39,842 (61.3)
Polymedication (≥5 ATC classes)	3,750 (41.3)	21,725 (39.9)	28,196 (43.9)	53,671 (42.0)	45,153 (69.5)
Polymedication (≥10 ATC classes)	738 (8.1)	4,653 (8.5)	6,246 (9.7)	11,637 (9.1)	14,947 (23.0)

NOAC: Non-vitamin K antagonist oral anticoagulant; VKA: vitamin K antagonist; SD: standard deviation; ATE: arterial thromboembolic events (ischaemic stroke, arterial systemic embolism or transient ischaemic attack); NSAIDs: non-steroidal anti-inflammatory drugs

* Unless otherwise stated

† Comorbidities were defined using a rolling 1-year period following the initiation of OAC therapy

‡ Smoking or alcohol data: measured by using proxies such as reimbursements for specific therapy or hospitalizations related to smoking or alcohol consumption/diseases

§ Comorbidities were defined using a rolling 4-month period preceding the initiation of OAC therapy

Table 2. Potential inappropriate use of NOAC therapy in oral anticoagulant-naïve patients with atrial fibrillation in 2015-2016

Characteristics (N; %)	NOAC				VKA
	Dabigatran N= 9,085	Rivaroxaban N= 54,456	Apixaban N= 64,300	Total NOAC N= 127,841	N= 65,010
Contraindications or non-approved indication/dose	**1,457 (16.0)**	**8,614 (15.8)**	**9,542 (14.8)**	**19,613 (15.3)**	**NA**
Any valvular heart disease	649 (7.1)	4,146 (7.6)	6,122 (9.5)	10,917 (8.5)	16,461 (25.3)
Prosthetic heart valve (mechanical or bioprosthetic valves)	106 (1.2)	665 (1.2)	1,096 (1.7)	1,867 (1.5)	6,726 (10.3)
Recently hospitalized for coagulopathy, purpura and other haemorrhagic conditions*	90 (1.0)	479 (0.9)	596 (0.9)	1,165 (0.9)	2,142 (3.3)
Liver fibrosis and cirrhosis*	50 (0.6)	282 (0.5)	367 (0.6)	699 (0.5)	1,174 (1.8)
Recent gastrointestinal ulceration or intracranial haemorrhage†	40 (0.4)	120 (0.2)	248 (0.4)	408 (0.3)	350 (0.5)
Recently or currently treated cancer*	417 (4.6)	2,531 (4.6)	2,898 (4.5)	5,846 (4.6)	4,252 (6.5)
Reduced-dose NOAC not approved for stroke prevention in AF patients in Europe	357 (3.9)	1,844 (3.4)	NA	2,201 (3.5)	NA
Inappropriate use during follow-up‡					
No monitoring of renal function at initiation	637 (16.8)	3804 (15.5)	3642 (14.5)	8083 (15.1)	5401 (17.0)
No monitoring of renal function in the year post-initiation	378 (10.0)	2,347 (9.6)	2,138 (8.5)	4,863 (9.1)	2,984 (9.4)
Non-persistence patterns, N (%)					
One reimbursement only	605 (15.9)	2,666 (10.9)	1,771 (7.1)	5,042 (9.4)	2,426 (7.6)
One-year treatment discontinuation rates§	984 (25.9)	6210 (25.4)	4524 (18,0)	11,718 (21,9)	8399 (26.4)
Concomitant use of drug increasing the risk of bleeding¶	**2,639 (29.3)**	**15,797 (29.3)**	**18,556 (29.2)**	**36,992 (29.3)**	**33,025 (52.3)**
Antiplatelet agents or parenteral anticoagulants	1,728 (19.2)	10,386 (19.3)	12,382 (19.5)	24,496 (19.4)	28,112 (44.5)
Parenteral anticoagulants	287 (3.2)	1,577 (2.9)	1,520 (2.4)	3,384 (2.7)	12,078 (19.1)
Antiplatelet agents	1,490 (16.6)	9,179 (17.0)	11,170 (17.6)	21,839 (17.3)	19,710 (31.2)
Aspirin	1,336 (14.8)	8,215 (15.2)	10,026 (15.8)	19,577 (15.5)	17,770 (28.1)
NSAIDs	375 (4.2)	2,111 (3.9)	2,017 (3.2)	4,503 (3.6)	1,030 (1.6)
SSRIs and SSNRIs	836 (9.3)	4,852 (9.0)	5,880 (9.2)	11,568 (9.1)	7,317 (11.6)

NOAC: Non-vitamin K antagonist oral anticoagulant; VKA: vitamin K antagonist; AF: atrial fibrillation; NA: not applicable; NSAIDs: non-steroidal anti-inflammatory drugs; SSRIs: selective serotonin reuptake inhibitors and SSNRIs: selective serotonin-norepinephrine reuptake inhibitors

* Comorbidities identified using hospitalization and/or LTD data, and/or specific procedures during a rolling 1-year period preceding the initiation of OAC therapy

† Comorbidities identified using hospitalization data during a rolling 6-week period preceding the initiation of OAC therapy

‡ Data on patients with at least a one year of follow-up i.e. patients initiating OAC in 2015 after excluding patients who died and those hospitalized for 3 months or longer (N= 3,796; 24,483; 25,118; 53,397 and 31,777 for dabigatran-, rivaroxaban, apixaban, total NOAC- and total VKA new users, respectively); period considered (unless otherwise stated): rolling 1-year period following the initiation of OAC therapy (index date included)

§ One-year crude discontinuation rate for patients initiating OAC in 2015 who died and those hospitalized for 3 months or longer, defined as prolonged treatment discontinuation i.e. 90-day gap with no medication coverage after the 30-day coverage period of a refill

¶ Data for new users still alive after a 45-day period following the index date (N= 9,001; 53,885; 63,578; 126,464 and 63,180 for dabigatran-, rivaroxaban, apixaban, total NOAC- and total VKA new users , respectively); period considered: rolling 6-week period following the initiation of OAC therapy (index date included)

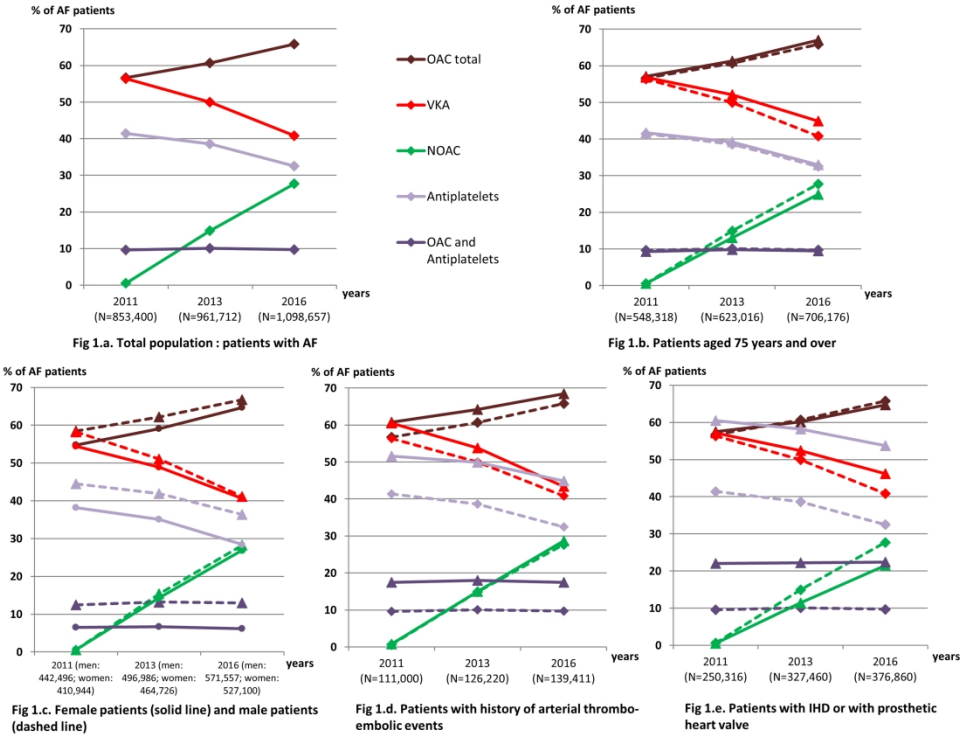

Figure 1

253x190mm (300 x 300 DPI)

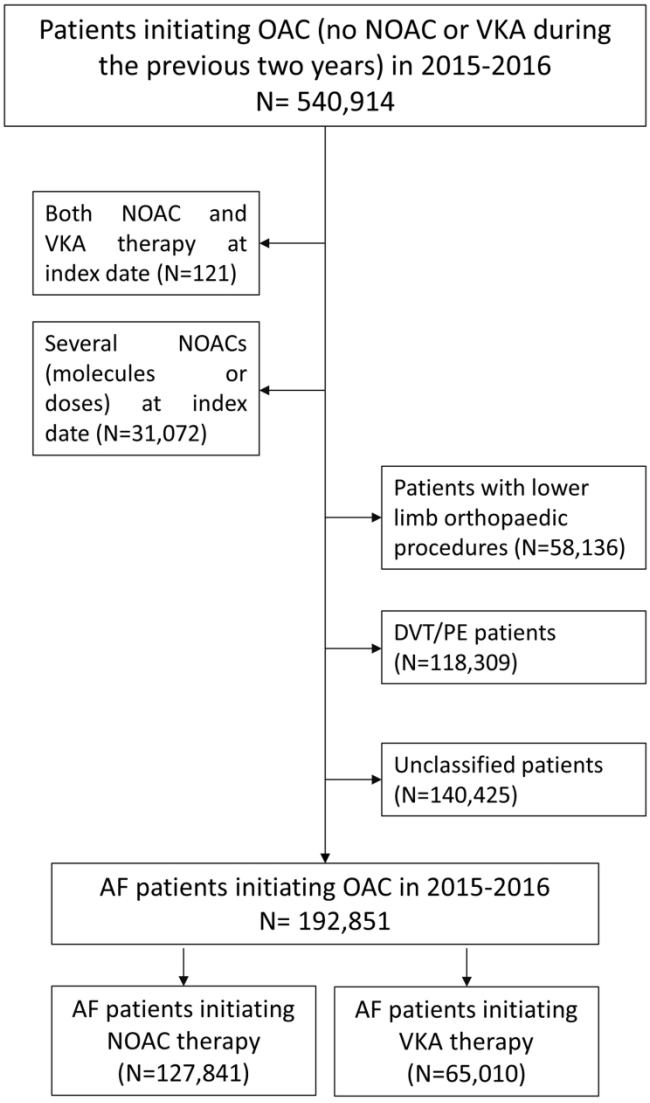

Figure 2

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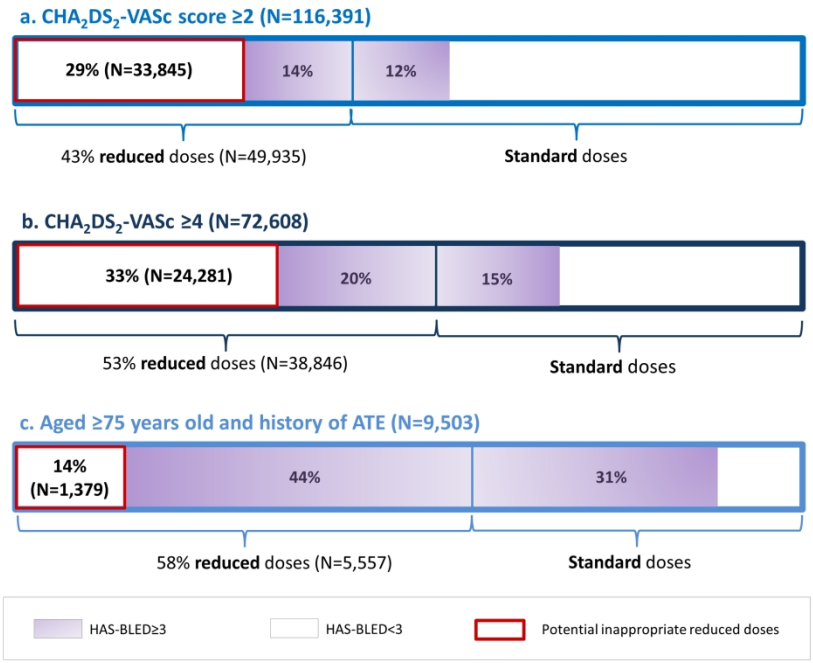

Figure 3

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Supplementary Materials

Supplementary Table 1. Definitions used to identify comorbid conditions and comedications in the French healthcare databases.

Supplementary Table 2. Age- and sex-adjusted association between baseline characteristics and the choice of NOAC therapy compared to VKA therapy in OAC new users.

Supplementary Table 3. Comparison of selected baseline characteristics of DOAC new users with AF at risk of stroke according to level of HAS-BLED score and type of DOAC dose.

Supplementary Table 1. Definitions used to identify comorbid conditions and comedications in the SNIIRAM-PMSI databases.

Covariates*	Hospital discharge diagnoses†	LTD diagnoses†	Specific procedures or drug reimbursements
AF definition (Patterns of use of DOAC therapy in new users with AF)			
Nonvalvular atrial fibrillation	I48	I48	Radiofrequency ablation, cardioversion
Lower limb orthopaedic procedures			Lower limb orthopaedic surgery or procedures
History of valvular heart disease/Prosthetic heart valve	I05-I09, I33-I39/ Z95.2, Z95.3 ou Z95.4		Heart valve surgery
Deep vein thrombosis/pulmonary embolism	I26, I80 (except I80.0), I81, I82	I26, I80-I82	Lower limb venous ultrasonography, pulmonary/lower limb angiography, ventilation/perfusion scan
CHA_2DS_2-VASc and HAS-BLED scores			
Heart failure	I50 or I11.0, I13.0, I13.2, I13.9, K76.1, J81 related to I50	I50	Specific medications approved for heart failure including beta-blockers (bisoprolol, carvedilol, metoprolol), eplerenone, bumetanide, furosemide when licensed for heart failure only
Antihypertensive drugs			Diuretics, beta blockers, calcium channel blockers, agents acting on the renin-angiotensin system and other antiadrenergic agents
Diabetes	E10-E14	E10-E14	Insulins and blood glucose lowering drugs
History of ATE (ischemic stroke, arterial systemic embolism or transient ischemic attack)	I63 (except I63.6), G46 related to I63 or I69.3; I74, G45 (except G45.4)	I63, I74, G45	
Peripheral vascular disease	I20, I21, I22, I23, I24, I25, I70, I71, I72, I73, E10.5, E11.5, E12.5, E13.5, E14.5	I70-I73 , I20-I25	
Abnormal renal function	N18, I12.0, I13.1, I13.2, E10.2, E11.2, E13.2, E14.2, N08.3	N18, I12	
Abnormal liver function	R18, I85, K70, K71.3, K71.4, K71.5, K71.7, K72.1, K73, K74, K76.1, B18, C22, C78.7	K70, K73, K74, B18, C22	Antiviral agents for systemic use HCV (ribavirin, [peg]interferon alpha and DAA), and against HCB ([peg]interferon alpha and NnRTIs).
Major bleeding	I60-I62, S06.3-S06.6, I85, K25-K29, K62.5, K92, D62, N02, R31, R58, H11.3, H35.6, H43.1, H45.0, H92.2, J94.2, K66.1, M25.0, N92, N93.8, N93.9, N95.0, R04.0		
Predisposition for bleeding	Anemias : D50, D51, D52, D53, D55, D56, D57, D58, D59, D60, D62, D63, D64 or coagulation defects, purpura and other hemorrhagic: D65, D66, D67, D68, D69		
Alcohol abuse	F10, K70, T51, K6, G31.2, G62.1, G72.1, I42.6, K29.2, Z71.4, Z72.1, Z50.2.		disulfiram, acamprosate, nalmefene and products with naltrexone licensed in adult patients with alcohol dependence
Drug-drug interaction			Platelet aggregation inhibitors (including low-dose acetylsalicylic acid), heparins, NSAIDs
Other comorbidities			
Ischemic heart disease (including myocardial infarction)	I20-I25	I20-I25	Nitrovasodilator agents
Frailty	G81-G83	G81-G83	Home hospital bed, wheelchair, high level of nursing home stay
Dementia or Parkinson's disease	F00-F03, G30, G20	F00-F03, G30, G20	Anticholinesterases or NMDA receptor antagonists: anticholinergic and dopaminergic agents
Psychiatric disorders	F20-29, F30-39	F20-29, F30-39	Antidepressants, antipsychotics, conventional mood stabilizers
Smoking	F17, Z71.6, Z72.0; J43-J44	J43-J44	Nicotine replacement therapy
Recently hospitalized for coagulopathy, purpura and other haemorrhagic conditions	D65-D69		
Liver fibrosis and cirrhosis	K70.0, K70.2, K70.3, K70.4, K71.7, K72, K74		

Recent gastrointestinal ulceration or intracranial haemorrhage	K25, K26, K27, K28, K29.0, I60, I61, I62, S06.4, S06.5, S06.6		
Recently or currently treated cancer	C00-D09, D37-D48, Z510, Z511	C00-D09, D37-D48	Radiotherapy procedures
Baseline comedications			
Antiarrhythmics and cardiac glycosides			Antiarrhythmics: class I and III, verapamil, digitalis glycosides
Lipid-lowering agents			HMG CoA reductase inhibitors, fibrates, ezetimibe
Antiplatelet drugs			Platelet aggregation inhibitors including low-dose acetylsalicylic acid
Oral corticosteroids			Mineralo- and gluco-corticoids
Antiulcer agents			Mainly proton pump inhibitors and H2-receptor antagonists

LTD: long-term diseases; ATE: arterial thromboembolic events (mainly stroke); DVT/PE: deep vein thrombosis/pulmonary embolism; NMDA: N-methyl-D-aspartate; HIV: human immunodeficiency virus; PI: Protease inhibitor; NNRTIs: Non-nucleoside reverse transcriptase inhibitors; NnRTI: Nucleoside and nucleotide reverse transcriptase inhibitors; DAA: direct-acting antiviral; HMG CoA: 3-hydroxy-3-methyl-glutaryl-CoA; NSAIDs: Non-steroidal anti-inflammatory drugs.

* Comorbidities were identified using ICD-10 diagnosis codes for hospital discharge/LTD, or specific procedures, or drug reimbursements. Concomitant medications were identified as those dispensed at least once during the 4-month period preceding the index date. Influenza vaccination was determined during the first 'flu vaccination campaign preceding the index date.
†ICD-10 codes

Supplementary Table 2. Age- and sex-adjusted association between baseline characteristics and the choice of NOAC therapy compared to VKA therapy in OAC new users.

Baseline characteristics	Dabigatran *vs* VKA				Rivaroxaban *vs* VKA				Apixaban *vs* VKA			
	RR*	*95% CI*		p-value†	RR*	*95% CI*		p-value†	RR*	*95% CI*		p-value†
Female sex	1.11	1.05	1.17	***	1.03	1.00	1.07	*	1.07	1.04	1.09	***
Age (years)												
18-54 (Ref)	1.00	1.00	1.00		1.00	1.00	1.00		1.00	1.00	1.00	
55-64	0.87	0.78	0.98	*	0.92	0.87	0.97	**	0.97	0.92	1.02	
65-74	0.86	0.77	0.95	**	0.89	0.84	0.94	***	0.98	0.93	1.03	
75-79	0.73	0.65	0.81	***	0.77	0.73	0.82	***	0.91	0.87	0.96	***
80-84	0.58	0.52	0.65	***	0.65	0.61	0.68	***	0.83	0.79	0.87	***
85-89	0.44	0.39	0.49	***	0.50	0.48	0.54	***	0.74	0.70	0.77	***
>=90	0.28	0.25	0.32	***	0.37	0.35	0.40	***	0.61	0.57	0.65	***
Deprivation index												
quintile 1 (least deprived) (Ref)	1.00	1.00	1.00		1.00	1.00	1.00		1.00	1.00	1.00	
quintile 2	0.97	0.91	1.05		0.94	0.92	0.97	***	0.97	0.95	1.00	*
quintile 3	0.99	0.93	1.07		0.90	0.87	0.92	***	0.94	0.92	0.97	***
quintile 4	0.96	0.89	1.03		0.85	0.83	0.87	***	0.90	0.88	0.93	***
quintile 5 (most deprived)	1.00	0.94	1.07		0.85	0.83	0.87	***	0.91	0.89	0.93	***
Overseas departments	1.60	1.41	1.82	***	0.83	0.77	0.89	***	0.77	0.72	0.83	***
First prescriber's specialty												
Hospital practitioner (Ref)	1.00	1.00	1.00		1.00	1.00	1.00		1.00	1.00	1.00	
General practitioner	1.37	1.29	1.46	***	1.16	1.10	1.23	***	1.00	0.96	1.04	
Private cardiologist	2.92	2.76	3.08	***	1.80	1.70	1.90	***	1.65	1.59	1.71	***
Private orthopedic surgeon	1.96	1.20	3.21	**	1.48	1.20	1.81	***	1.32	1.07	1.61	**
Other private specialist	1.07	0.93	1.24		1.12	1.04	1.21	**	1.03	0.97	1.10	
From CHA_2DS_2-VASc score												
Heart Failure	0.52	0.49	0.54	***	0.70	0.68	0.71	***	0.77	0.75	0.78	***
Antihypertensive drugs	0.60	0.57	0.63	***	0.74	0.72	0.76	***	0.80	0.78	0.82	***
Diabetes	0.67	0.63	0.71	***	0.76	0.74	0.77	***	0.80	0.79	0.82	***
ATE	0.85	0.79	0.92	***	0.71	0.68	0.74	***	0.90	0.88	0.92	***

Vascular diseases	0.47	0.42	0.53	***	0.63	0.61	0.66	***	0.71	0.67	0.74	***
From HAS-BLED score												
Abnormal renal function	0.17	0.15	0.19	***	0.31	0.30	0.33	***	0.40	0.38	0.42	***
Abnormal liver function	0.46	0.39	0.54	***	0.58	0.54	0.62	***	0.60	0.57	0.64	***
Bleeding predisposition	0.53	0.47	0.59	***	0.63	0.60	0.65	***	0.70	0.67	0.72	***
Major bleeding	0.23	0.20	0.26	***	0.36	0.33	0.39	***	0.41	0.38	0.45	***
Alcohol abuse	0.55	0.48	0.62	***	0.69	0.65	0.72	***	0.68	0.65	0.72	***
Drug-drug interactions	0.22	0.20	0.24	***	0.36	0.34	0.37	***	0.40	0.37	0.43	***
Parenteral anticoagulants	0.04	0.03	0.06	***	0.07	0.06	0.07	***	0.07	0.06	0.07	***
Antiplatelets drugs	0.34	0.31	0.37	***	0.49	0.47	0.51	***	0.56	0.53	0.60	***
NSAIDs	1.80	1.43	2.28	***	1.24	1.12	1.38	***	1.18	1.06	1.32	**
Other comorbidities												
Valvular heart diseases	0,25	0,20	0,31	***	0,40	0,36	0,45	***	0,47	0,41	0,54	***
Ischemic heart diseases	0.51	0.46	0.56	***	0.65	0.63	0.67	***	0.74	0.71	0.77	***
Frailty (proxies)	0.48	0.45	0.51	***	0.58	0.55	0.61	***	0.64	0.62	0.66	***
Dementia or Parkinson's disease	0.66	0.60	0.72	***	0.82	0.78	0.85	***	0.77	0.75	0.80	***
Psychiatric disorders	0.74	0.70	0.78	***	0.86	0.84	0.88	***	0.86	0.84	0.88	***
Smoking	0.56	0.52	0.60	***	0.71	0.69	0.74	***	0.74	0.71	0.76	***
Comedications												
Antiarrhythmics or cardiac glycosides	1.42	1.35	1.50	***	1.22	1.19	1.25	***	1.18	1.16	1.20	***
Lipid-lowering agents	0.76	0.71	0.81	***	0.81	0.79	0.84	***	0.90	0.87	0.92	***
Oral corticosteroids	0.85	0.80	0.91	***	0.94	0.91	0.97	***	0.94	0.91	0.96	***
Antiulcer agents	0.61	0.56	0.66	***	0.73	0.71	0.75	***	0.78	0.75	0.81	***
Polymedication (≥5 ATC classes)	0.37	0.35	0.40	***	0.55	0.54	0.57	***	0.60	0.59	0.62	***
Polymedication (≥10 ATC classes)	0.33	0.30	0.36	***	0.49	0.46	0.52	***	0.54	0.51	0.57	***

NOAC: Non vitamin K antagonist oral anticoagulant; VKA: vitamin K antagonist; OAC: oral anticoagulant; RR: Relative risk; IC; Confidence interval; ATE: arterial thromboembolic events (ischaemic stroke, arterial systemic embolism or transient ischaemic attack); NSAIDs: non-steroidal anti-inflammatory drugs

* RR determined using negative binomial regression analysis adjusting for age and sex(except for age and sex covariates, adjusted for sex and for age only, respectively).

† p-values : *** $p < 0{,}001$; ** $p < 0{,}01$; * $p < 0{,}05$

Reading example: Age and sex being equal, frailty reduced the probability for a prescription of dabigatran (instead of VKA) by 52% (1 minus the estimated RR of 0.48). For rivaroxaban and apixaban, this reduction was 42% and 36%, respectively.

Supplementary Table 3. Comparison of selected baseline characteristics of DOAC new users with AF at risk of stroke according to level of HAS-BLED score and type of DOAC dose.

N (%)	Patients with CHA2DS2-VASc ≥ 2 (N=116,391)				Patients aged ≥75 years old and history of ATE (N=9,503)			
	HAS-BLED≥3 (N=30 273)		HAS-BLED<3 (N=86 118)		HAS-BLED≥3 (N=7,143)		HAS-BLED<3 (N=2,360)	
	Reduced doses* (N=16,090)	Standard doses* (N=14,183)	Reduced doses* (N=33,845)	Standard doses* (N=52,273)	Reduced doses* (N=4,178)	Standard doses* (N=2,965)	Reduced doses* (N=1,379)	Standard doses* (N=981)
Age (years), mean	81.8	74.8	81.3	70.9	84,8	81.1	81.3	70.9
Age ≥ 80 years	10,786 (67.0)	3,982 (28.1)	22,962 (67.8)	9,984 (19.1)	3,496 (83.7)	1,720 (58.0)	1,188 (86.1)	567 (57.8)
First prescriber's specialty								
Hospital practitioner or private cardiologist	12,315 (76.6)	11,364 (80.1)	25,221 (74.5)	41,728 (79.8)	3216 (77.0)	2965 (80.2)	1013 (73.5)	798 (81.3)
General practitioner	3321 (20.6)	2426 (17.1)	7836 (23.2)	9302 (17.8)	860 (20.6)	503 (17.0)	322 (23.4)	157 (16.0)
Frailty (proxies)	6,689 (41.6)	4,600 (32.4)	6,932 (20.5)	4,779 (9.1)	2,599 (62.2)	1,642 (55.4)	589 (42.7)	316 (32.2)
Dementia or Parkinson's disease	2121 (13.2)	935 (6.6)	3169 (9.4)	1555 (3.0)	789 (18.9)	355 (12.0)	259 (18.8)	111 (11.3)
Any valvular diseases†	2,640 (16.4)	1,809 (12.8)	2,740 (8.1)	3,342 (6.4)	566 (13.5)	330 (11.1)	144 (10.4)	95 (9.7)
Prosthetic heart valve†	544 (3.4)	384 (2.7)	425 (1.3)	474 (0.9)	94 (2.2)	52 (1.8)	19 (1.4)	14 (1.4)
Ischaemic heart disease	7,232 (44.9)	5,274 (37.2)	6,827 (20.2)	9,142 (17.5)	1,338 (32.0)	758 (25.6)	336 (24.4)	185 (18.9)
Antiplatelet agents at initiation	6,035 (37.5)	4,891 (34.5)	620 (1.8)	1,264 (2.4)	874 (20.9)	510 (17.2)	11 (0.8)	7 (0.7)
Lipid-lowering agents	9252 (57.5)	9213 (65.0)	12836 (37.9)	21820 (41.7)	2606 (62.4)	2132 (71.9)	697 (50.5)	611 (62.3)
Polymedication (≥10 ATC classes)	3,627 (22.5)	2,946 (20.8)	2,150 (6.4)	2,798 (5.4)	788 (18.9)	473 (16.0)	104 (7.5)	67 (6.8)

* Reduced-dose DOAC: dabigatran 150mg, Rivaroxaban 20 and apixaban 5mg; reduced-dose DOAC: dabigatran 75mg and 110mg, rivaroxaban 10mg and 15mg and apixaban 2.5mg
† Covariates defined by hospitalization data only

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5,6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5,6
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*6,7,8*
Bias	9	Describe any efforts to address potential sources of bias	7,8
Study size	10	Explain how the study size was arrived at	9, Fig 2
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7,8
		(*b*) Describe any methods used to examine subgroups and interactions	7,8
		(*c*) Explain how missing data were addressed	NA
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	NA
		(*e*) Describe any sensitivity analyses	7,8

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9 Fig 2
		(b) Give reasons for non-participation at each stage	9
		(c) Consider use of a flow diagram	Fig 2
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 1
		(b) Indicate number of participants with missing data for each variable of interest	NA
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	*NA*
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	*NA*
		Cross-sectional study—Report numbers of outcome events or summary measures	*Fig2,3* *Table2*
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Table 2
		(*b*) Report category boundaries when continuous variables were categorized	Table 2
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	9, 10
Discussion			
Key results	18	Summarise key results with reference to study objectives	11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11, 12
Generalisability	21	Discuss the generalisability (external validity) of the study results	12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	14

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Oral anticoagulation therapy use in patients with atrial fibrillation after the introduction of non-vitamin K antagonist oral anticoagulants: findings from the French healthcare databases, 2011-2016

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Title page

Oral anticoagulation therapy use in patients with atrial fibrillation after the introduction of non-vitamin K antagonist oral anticoagulants: findings from the French healthcare databases, 2011-2016.

Running title: Patterns of OAC use

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Number of supplementary tables: 3

Abstract

Objectives: To describe i) the trend in oral anticoagulant (OAC) use following the introduction of Non-vitamin K antagonist oral anticoagulant (NOAC) therapy for stroke prevention in atrial fibrillation (AF) patients; ii) the current patterns of use of NOAC therapy in new users with AF in France.

Design: i) Repeated cross-sectional study; ii) Population-based cohort study.

Setting: French National Healthcare databases (50 million beneficiaries).

Participants: i) Patients with identified AF in 2011, 2013, and 2016; ii) Patients with AF initiating OAC therapy in 2015-2016.

Primary and secondary outcome measures: i) Trend in oral anticoagulant therapy use in patients with AF; ii) Patterns of use of NOAC therapy in new users with AF.

Results: Between 2011 and 2016, use of OAC therapy moderately increased (+16%), while use of antiplatelet therapy decreased (-22%) among all patients with identified AF. In 2016, among the 1.1 million AF patients, 66% used OAC therapy and were more likely to be treated by VKA than NOAC therapy, including patients at higher risk of stroke (63.5%), while 33% used antiplatelet therapy. Among 192,851 new users of OAC therapy in 2015-2016 with identified AF, NOAC therapy (66.3%) was initiated more frequently than VKA therapy, including in patients at higher risk of stroke (57.8%). Reduced doses were prescribed in 40% of NOAC new users. Several situations of inappropriate use at NOAC initiation were identified, including concomitant use of drugs increasing the risk of bleeding (one in three new users) and potential NOAC underdosing.

Conclusions: OAC therapy use in AF patients remains suboptimal 4 years after the introduction of NOACs for stroke prevention in France and improvement in appropriate prescribing regarding NOAC initiation is needed. However, NOAC therapy is now the preferred drug class for initiation of OAC therapy in patients with AF, including in patients at higher risk of stroke.

Strengths and limitations of this study

- This study is the first to report both the 2011-2016 trend in oral anticoagulant (OAC) coverage in patients with atrial fibrillation (AF) following the introduction of Non-vitamin K antagonist oral anticoagulant (NOAC) therapy in France and the current patterns of use of NOACs in new users including assessment of potential inappropriate use;
- This study is based on reimbursement data for 50 million beneficiaries with access to all OAC prescriptions filled in the ambulatory setting;
- As indications for treatment are not available in the databases, AF was mostly identified on the basis of discharge and long-term disease diagnosis codes and an algorithm previously validated in the French healthcare databases that helped to further identify AF in outpatients.

Introduction

Non-vitamin K antagonist Oral AntiCoagulants (NOACs) have been gradually introduced over the past decade as a more convenient, fixed-dose alternative to vitamin K antagonists (VKAs), the only oral anticoagulant therapy available up until now for long-term stroke prevention in patients with non-valvular atrial fibrillation (AF) [1]. Compared to VKA, NOAC therapy avoids the need for regular laboratory monitoring of patients by INR testing due to a wider therapeutic window, allows once (rivaroxaban, edoxaban) or twice (dabigatran, apixaban) daily intake and is associated with fewer drug-drug interactions to date [2–6]. NOACs have been demonstrated to have similar or superior efficacy to warfarin for stroke prevention in nv-AF patients, and these findings have recently been implemented in the 2016 European Society of Cardiology (ESC) guidelines that recommended NOAC over VKA therapy in this indication [7]. Moreover, antiplatelet therapy is no longer recommended in these patients [7,8]. The use of NOAC therapy, massively adopted worldwide including in France [9–15], is expected to overcome the suboptimal use of oral anticoagulant (OAC) therapy extensively reported with VKA therapy, including underprescribing and high discontinuation rates [16,17].

Despite their improved ease of use, NOAC prescribed dose needs to be adjusted to the patient's clinical profile with regards to age, renal function, weight, and risks of bleeding and drug-drug interactions. Two dose regimens are therefore proposed for each NOAC: standard dose regimen (*i.e.* dabigatran 150mg/12h, rivaroxaban 20mg/24h; apixaban 5mg/12h), and reduced-dose regimen (i.e. dabigatran 75mg or 110mg/12h, rivaroxaban 10mg or 15mg/24h; apixaban 2.5mg/12h). The reasons for prescribing a reduced-dose regimen are listed in the summary of product characteristics (SmPCs) of each NOAC with differences across NOACs as well as in the ESC [7,8] and European Heart Rhythm Association (EHRA) guidelines [18]. Recent publications have suggested that the frequency of use of reduced-dose NOACs in clinical practice could largely exceed that expected on the basis of the conditions summarized in these guidelines [11,19–21]. However, national data are lacking concerning the current French patterns of NOAC use, including the potential issue of NOAC underdosing.

A steady increase in the initiation of NOAC therapy has already been reported in AF patients in France [14], but trends in OAC coverage of AF patients following the introduction of NOACs and a description of the current national patterns of NOAC use have not yet been reported. This study, based on the French nationwide healthcare databases, therefore had a twofold objective: 1) to describe the trends in OAC use following the introduction of NOAC for stroke prevention in AF patients during the 2011-2016 period; 2) to describe the current patterns of use of OAC therapies with particular focus on NOAC use in new users with AF.

Methods

Data source

French national health insurance (*Assurance Maladie*) covers the entire French population by means of several specific schemes according to the beneficiary's occupational sector, the largest scheme being the '*Régime général*' (around 50 million beneficiaries).

This study was conducted using data from the French health insurance system database (*Système national d'information inter-régimes de l'Assurance maladie*, SNIIRAM) linked to the French hospital discharge database (*Programme de médicalisation des systèmes d'information*, PMSI) [22,23]. The SNIIRAM database contains individualized, anonymous, and comprehensive data on health spending reimbursements. Demographic data include date of birth, gender, and vital status. Drugs are coded according to the Anatomical Therapeutic Chemical (ATC) classification. Each packaging of each product is identified by means of a national specific pack identifier code providing information on the name of the product, active ingredient and dose per unit, number of units, and route of administration; but, the exact dosage prescribed and the indication are not available. However, for most drugs, particularly OACs, each dispensing of the prescribed drug cannot exceed the quantity necessary for one month of treatment. The PMSI database provides detailed information about discharge diagnoses and medical procedures related to all hospitalizations in France. This information regarding morbidities is completed by diagnoses corresponding to patient eligibility for 100% reimbursement of severe and costly long-term diseases (LTD) and disability, such as AF, coronary heart disease, certain debilitating diseases (such as multiple sclerosis or rheumatoid arthritis), HIV infection, cancer, etc. All information concerning medical diagnosis is encoded according to the International Classification of Diseases, 10th revision (ICD-10). Finally, the SNIIRAM-PMSI databases also indicate medical procedures performed in the ambulatory setting, including information about the type and date of all laboratory tests performed, but not including their results.

The French healthcare databases have been previously described and used in epidemiological and pharmacoepidemiological studies [22,24–26].

Study populations and study designs

Two study populations were defined; one for each objective.

To answer the first objective, a repeated cross-sectional study was performed to describe the trends in OAC use following the introduction of NOAC in AF patients. Patients with AF were identified in 2011 (as none of the NOACs was available for stroke prevention in France) and 2016 (the most recent data available at the time of writing the study protocol; dabigatran, rivaroxaban and apixaban were all reimbursed for stroke prevention in France, as apixaban was reimbursed from January 2014

onwards). OAC coverage was also calculated for year 2013 as this year represented the first calendar year for which the first two NOACs were available in France, i.e. a pivotal year for the pharmacological management of AF by oral anticoagulants. For each of these calendar years, a patient was considered to have AF when at least one diagnosis of AF (ICD-10 code I48) was identified from discharge and LTD diagnoses in the SNIIRAM-PMSI database in the calendar year considered or during the previous 5 years. Patients with no continuous '*Régime général*' health insurance coverage for at least six years before the calendar year considered were excluded.

To answer the second objective, a population-based cohort study was performed including patients with AF initiating OAC therapy in 2015-2016. First, OAC new users were identified among patients with continuous '*Régime général*' health insurance coverage as those with at least one reimbursement for OAC therapy in 2015-2016 and no reimbursement for any OAC (VKA or NOAC) in the previous 24 months. The patient's index date was the date of first OAC reimbursement identified during the 2015-2016 period. Second, the cohort of NOAC news users was restricted to those treated for AF: (i) patients treated for other OAC indications *i.e.* patients treated for deep vein thrombosis/pulmonary embolism (DVT/PE) or with lower limb orthopaedic procedures were excluded; (ii) OAC new users treated for AF were identified from the resulting cohort as the sum of "OAC new users with confirmed AF" for those with a diagnosis of AF (ICD-10 code I48) or specific AF management procedures identified from LTD or hospitalization discharge data during a six-year pre-index period, and "OAC new users with probable AF" for outpatients identified using an algorithm discriminating AF from DVT/PE with 95% specificity [27]. The remaining patients were not classified as probable FA patients and were excluded. Codes used for identification of AF and all of the patient characteristics considered, including comorbidities, are displayed in **Supplementary Table 1**.

Patient and public involvement

Patients and or public were not involved.

Exposure

NOAC (dabigatran, rivaroxaban, apixaban) and VKA therapies (fluindione, warfarin and acenocoumarol) were identified using ATC codes; edoxaban was not available in France during the period considered.

Outcomes

Trends in oral anticoagulant therapy use in patients with AF

The proportion of AF patients treated by OAC therapy was assessed before and after approval of NOAC therapies for stroke prevention in France. Trends in the use of antiplatelet agents were also assessed in AF patients over the same timeframe.

Patterns of use of NOAC therapy in new users with AF

The description of patterns of NOAC use in new users treated for AF in 2015-2016 included comparison of the baseline characteristics among NOAC new users and compared to those of VKA new users and potential inappropriate use of NOAC therapy was then investigated by identifying:

(i) NOAC off-label use or non-approved indication/dose: contraindications to NOAC therapy according to SmPCs [concomitant coagulopathy, purpura and other haemorrhagic conditions, liver fibrosis and cirrhosis, recent gastrointestinal ulceration or intracranial haemorrhage], valvular atrial fibrillation [NOAC are only approved for non-valvular AF], prosthetic heart valve [contraindicated for dabigatran], cancer [NOAC are not approved for prevention of thromboembolism in patients with cancer] and prescription of NOAC doses not approved for stroke prevention in Europe [dabigatran 75 mg and rivaroxaban 10 mg are not approved for stroke prevention in Europe and are therefore off-label doses in AF patients]; (ii) non-compliance with guidelines with respect to follow-up and clinical work-up of patients during the first year following NOAC initiation: no monitoring of patients' renal function [renal function should be assessed at initiation and annually during NOAC therapy [28]], discontinuation of NOAC therapy [OAC therapy is recommended as lifetime treatment in most patients with AF] (iii) clinically relevant drug-drug interactions at initiation increasing the bleeding risk at initiation; (iv) potential inappropriate underdosing, i.e. patients in whom the NOAC dose prescribed at initiation was inappropriately reduced in view of their individual stroke and bleeding risks.

Data analysis

Descriptive analyses are expressed as mean and standard deviation (SD) for continuous variables, and numbers and percentages for categorical variables.

Trends in oral anticoagulant therapy use in patients with AF

For each calendar year, the proportion of patients treated by a drug was defined by the number of patients with at least one reimbursement for this drug in the calendar year considered over the total number of patients identified as having AF in the same year. Proportions are reported according to the type of OAC first reimbursed in the year considered. Antiplatelet drugs and OAC therapies were considered to be coprescribed when they were reimbursed at least once on the same day during the calendar year studied. Analyses were replicated in subgroups of AF patients: (i) aged 75 years and over; (ii) female and male, separately; (iii) with a history of hospitalization for arterial thromboembolic events (ATE); (iv) with concomitant ischaemic heart disease (IHD) or prosthetic heart valve.

Patterns of use of NOAC therapy in new users with AF

Baseline characteristics of NOAC new users with AF included sociodemographic data, including deprivation index of the patient's municipality of residence [29], type of initial prescriber, clinical scores predicting the risk of stroke (CHA_2DS_2-VASc score) or bleeding (HAS-BLED score) [30,31], adapted to claims data and the other main comorbidities and comedications, including proxies of frailty. A negative binomial regression analysis for each NOAC therapy and each baseline characteristic was performed to assess the association between these characteristics and the choice of NOAC therapy *versus* VKA therapy, while adjusting for age and sex.

Compliance with guidelines regarding renal function monitoring and treatment persistence patterns were assessed in new users for whom data for at least one year of follow-up were available, i.e. patients included in 2015 and who had not died and had not been hospitalized for 3 months or longer. Compliance with renal function monitoring was assessed at NOAC initiation (no reimbursement for renal function monitoring during the three months before and the three months after NOAC initiation) and during the first year following treatment initiation. OAC non-persistence patterns were assessed over the one-year period following the index date by calculating proxies of OAC discontinuation: number of patients with only one reimbursement and one-year crude discontinuation rates.

Drugs increasing the risk of bleeding were those responsible for clinically relevant pharmacodynamic interactions with OAC therapy, i.e. concomitant reimbursement of other parenteral and oral antithrombotic drugs, non-steroidal anti-inflammatory drugs (NSAIDs); selective serotonin reuptake inhibitors and selective serotonin-norepinephrine reuptake inhibitors (SSRIs and SSNRIs) [7,18,32]. Patients taking concomitant drugs with OAC therapy were defined as those with a reimbursement for the drug of interest during the period corresponding to the index date and the following 45 days. Analyses were replicated in VKA new users for descriptive purposes.

Finally, potential inappropriate underdosing with NOACs was defined as initiation of NOAC therapy in patients at risk of stroke in whom reduced doses of NOAC were prescribed with no identified justification. As this study was based on claims data and as, up until 2016, ESC guidelines recommended prescribing reduced-dose NOAC in patients with HAS-BLED≥3 [8], the proportion of AF patients initiating reduced-dose NOAC with an HAS-BLED score<3 among all NOAC new users with a CHA_2DS_2-VASc score ≥2 was used to quantify potential inappropriate underdosing in NOAC new users. Analyses were replicated in patients i) with CHA_2DS_2-VASc score ≥4, ii) aged 75 and over with a history of ATE.

Results

Trends in oral anticoagulant therapy use in patients with AF

The number of patients identified from French healthcare databases as having AF increased between 2011 (N=853,440) and 2016 (N=1,098,657). A high proportion of these patients were identified exclusively by hospitalization discharge diagnosis and this proportion decreased only slightly over this time interval from 90.2% (N=770,002) to 86.2% (N=946,657).

Between 2011 and 2016, the proportion of patients with at least one reimbursement for OAC therapy among all AF patients moderately increased (+16%) from 56.7% to 65.8%, corresponding to a steady decrease in VKA use (from 56.6% to 40.8% of all AF patients) associated with the introduction of NOACs (from 0.6% to 27.7%). In 2016, among patients with identified AF, VKA therapy remained the preferred OAC therapy (62.0%), including in patients aged 75 years and over (67.0%) and in those with a history of ATE (63.5%).

Between 2011 and 2016, the use of antiplatelet therapy decreased in AF patients (-22%), but the proportion of patients with concomitant OAC and antiplatelet therapy remained stable (9.7% in 2016). In 2016, 32.5% of AF patients had at least one reimbursement for antiplatelet therapy during the year.

Similar trends were observed in the subgroup analyses. A slightly higher rate of OAC therapy was observed in patients with a history of ATE (68.4% vs 65.8% in the total cohort in 2016). However, OAC coverage was lower in women than in men with AF (64.7% vs 66.8% in 2016) (**Figure 1**).

Patterns of use of NOAC therapy in new users with AF

Baseline characteristics of OAC new users

Among 540,914 patients initiating OAC therapy in 2015-2016, a total of 192,851 (35.7%) patients were included in the study population, corresponding to 127,841 NOAC new users and 65,010 VKA new users with AF. The mains reasons for ineligibility were other indications or uncertain identification of the indication for NOAC (**Figure 2**).

The mean age of the NOAC new users cohort was 74.1±11.6 years; patients over the age of 80 represented 37.3% of the total cohort. One-half of the NOAC new users were women, and 40.0% received a reduced dose at initiation (62.2% for dabigatran new users). Apixaban was the NOAC most commonly initiated; apixaban new users were older and had more comorbidities than the other two groups of NOAC new users. NOAC therapy was more likely to be initiated than VKA therapy among patients aged 75 years and older (59.4%) and in patients with a history of ATE (57.8%) (**Table 1**).

Characteristics associated with bleeding risk, such as older age, renal impairment, history of bleeding or bleeding predisposition, and treatment with a concomitant drug increasing the risk of bleeding at

OAC initiation, were strong predictors of being treated with VKA therapy *versus* NOAC therapies (**Supplementary Table 2**).

Potential inappropriate use of NOAC therapy

About 15% of NOAC new users with AF were considered to be using NOAC off-label or for a non-approved indication. In particular, 8.5% of NOAC new users with AF had valvular heart disease (8.5%), including prosthetic heart valve (1.5%) and 4.6% had a recently or currently treated cancer (**Table 2**).

About 15% and 9% of NOAC new users had no reimbursement for renal function tests at initiation and during the one-year period post-initiation, respectively. Discontinuation during the one-year period following initiation was frequent, as more than 20% of patients had five or less reimbursements (**Table 2**).

Nearly 30% of NOAC new users were using at least one concomitant drug increasing the risk of bleeding (52% in VKA new users). The most common concomitant drugs concerned at initiation were antiplatelet agents or parenteral anticoagulants (**Table 2**).

Among the 116,391 NOAC new users with AF with a CHA_2DS_2-VASc score ≥2, 29.1% (N=33,845) were prescribed a reduced dose although they had an HAS-BLED score <3. This meant that nearly 1 in 3 NOAC new users with AF and at risk of stroke were therefore potentially prescribed an inappropriately reduced dose of NOAC at initiation. This proportion was 33% (N=24,281) and 14.5% when defining patients at risk of stroke as patients with a CHA_2DS_2-VASc score ≥4 and aged 75 and over with a history of ATE, respectively (**Figure 3**).

Differences in baseline characteristics were observed in patients with HAS-BLED<3 according to the type of NOAC dose prescribed, e.g. patients with reduced-dose NOAC were older and frailer than those with standard-dose NOAC (**Supplementary Table 3**).

Discussion

Main findings

OAC therapy use among patients with AF improved in France between 2011 and 2016, but remained suboptimal with about 66% of the 1.1 million patients with identified AF treated by OAC therapy in 2016. Use of antiplatelet therapy in AF patients decreased over the same period, but still concerned 33% of all AF patients in 2016. Patients with AF were more likely to be treated by VKA than NOAC therapy, including older patients and those at higher risk of stroke.

Nearly 193,000 patients with AF were identified as OAC new users in 2015-2016: patients were more likely to be treated by NOAC than VKA therapy, including older patients and those at higher risk of stroke. Results on current patterns of use of NOAC therapy in new users with AF suggest several situations of inappropriate use, including frequent concomitant use of drugs increasing the risk of bleeding and potential inappropriate underdosing.

Comparison with postmarketing literature and clinical implications

The overall improvement of management of AF patients observed with regards to OAC therapy after the introduction of NOACs has been reported in many countries [33–36]. The same applies to the steady decrease in VKA use in favour of NOAC therapies [12,37,38], and the gaps remaining in optimal OAC coverage and high antiplatelet drug use [39–41].

This study demonstrated channelling of NOAC therapy towards patients at lower risk of stroke and bleeding when considering all patients with AF, in line with what has become a common feature reported worldwide in clinical practice by many observational studies on the current patterns of use of NOACs [15,42–45]. In particular, data from the ESC-sponsored 'EURObservational Research Programme on AF' (EORP-AF) General Long-Term Registry showed that younger age, having fewer risk factors or a history of non-valvular heart diseases were also found to be clinical predictors for being treated with NOACs vs. VKAs [46].

However, NOAC therapy is now the preferred OAC therapy at initiation in the oldest patients and those at higher risk of stroke. This French pattern of OAC use has never been previously reported and contrasts with published results concerning earlier periods [47]. This emerging pattern is encouraging for AF management, as older and high-risk patients are those who should derive most benefit from NOAC *versus* VKA therapy [48].

Reduced doses were often prescribed in OAC new users, including dabigatran 75mg and rivaroxaban 10mg, which are not approved for stroke prevention in Europe [49]. In addition to the overall channelling mentioned above, these findings may reflect a "bleeding avoidance" strategy of prescribers (i.e. overestimation of the potential bleeding risk *versus* the likely benefit of stroke

reduction) and the differential perception of the comparative safety of NOACs *versus* VKA and between NOACs. The early safety alert on bleeding in dabigatran-treated patients, followed by the contraindication of this NOAC in patients with prosthetic heart valves, may have reinforced the fears of prescribers in relation to the safety of dabigatran, which would explain the difference in reduced-dose prescription rates between the three NOACs in this study, despite the intermediate stroke and bleeding risk profile of dabigatran compared to that of rivaroxaban and apixaban in new users. Similarly, among NOAC new users, apixaban was prescribed to the oldest and most severe patients. Apixaban was the only NOAC found to be superior to warfarin for all types of bleeding outcome and all-cause mortality, which would also illustrate the tendency of physicians to prescribe OAC therapies according to bleeding risk [5]. This may also explain the potential inappropriate underdosing observed in NOAC users in this study. This pattern of NOAC use has been previously reported, but mostly in field and registry studies based on small sample sizes. The reported inappropriate underdosing rate varies according to studies and the definition used. NOAC underdosing concerned 30.4% of Turkish patients in the RAMSES study (N=2,086) [50], 18.4% of Japanese patients of the *KiCS* AF registry (N=1,284) [51,52], between 19.7% and 27.6% of patients in the SAKURA AF registry (N= 3,266) [53], and 9.4% to 16% of patients in the ORBIT-AF II registry (N=7925) [21,54]. In the subgroup of Dutch patients (N=899) enrolled in the XANTUS registry, 33% of patients were also treated with reduced-dose rivaroxaban despite presenting normal renal function [55]. Using a large U.S. administrative database, Yao *et al* found that 13.3% of the 13,392 NOAC new users with no renal indication for dose reduction were potentially underdosed [56]. Taken together with our results, these data suggest that inappropriate underdosing might be a common issue in NOAC new users that should be systematically assessed when studying NOAC patterns of use. This is of particular concern, as recent data have suggested a relationship between NOAC dose and clinical outcomes [57]. In particular, NOAC underdosing has been shown to be associated with increased risk for adverse outcomes [21,56].

These patterns of NOAC use contrast with the other patterns concomitantly observed in this study, such as the high level of concomitant prescription of antiplatelet agents and parenteral anticoagulants or, to a lesser extent, NOAC use in non-approved indications such as prosthetic heart valves that are both associated with an increased risk of bleeding [58–60].

Strengths and limitations

This study is the first to report the improved trend in OAC coverage in French patients with AF over the last five years as well as the recent patterns of use of OAC therapy in new users, particularly including a nationwide assessment of the growing issue of NOAC underdosing, based on health data for more than 50 million beneficiaries. Moreover, all OAC prescriptions filled in the ambulatory

setting are captured in the databases and are reimbursed with no restriction of coverage: selection bias related to the access of patients to more expensive NOAC therapy is therefore not an issue with the use of French healthcare databases [22,61].

However, several limitations related to the nature of the data used should be underlined. First of all, it cannot be verified whether patients actually took the drugs for which they were reimbursed. Secondly, as the indication for treatment is not available in the databases, and despite the use of an algorithm to identify AF among outpatients in the French healthcare databases, identification of AF was mostly based on non-validated discharge and LTD diagnoses recorded in the databases. Moreover, it cannot be excluded that the increase in the identified number of patients with AF over the 2011-2016 period could be partially explained by changes in LTD legislation in 2011 (e.g. hypertension was removed from the list of LTD, while access to LTD was facilitated for patients with severe arrhythmia and valvular heart diseases) which could have helped identify patients with AF. Thirdly, identification of inappropriate underdosing at NOAC initiation was also indirectly assessed by using stroke and bleeding risk scores computed from claims data. Important medical data such as patient's weight, glomerular filtration rate and exact alcohol consumption are not available in the French healthcare databases, which may have led to underestimation of the HAS-BLED score and therefore to overestimation of the proportion of patients potentially underdosed at initiation. These missing clinical data may also explain the prescription of reduced dose NOAC at treatment initiation in clinical practice. Furthermore, the agreement between these empirical scores in patients with AF and the prescriber-assessed stroke and bleeding risk is a subject of discussion [62]. Consequently, the rate of inappropriate underdosing should be interpreted with caution and must be confirmed by further studies. However, NOAC misuse and underdosing have also been reported in a French prospective field study based on patients' medical charts [63]. Of note, as INR values were not available in the databases, underdosing with VKA therapy was not assessed in this study, but has been frequently reported and must not be overlooked [53,64]. In addition, as stated in the 2016 ESC guidelines [7], HAS-BLED score is not designed to evaluate prescription of NOAC type and dosage and no longer must be used for this purpose in clinical practice.

Finally, the results for NOAC and VKA new users are difficult to compare, as they were not adjusted for significant differences in baseline characteristics and this comparison was not the purpose of this study.

Conclusion

OAC therapy use has modestly increased after the introduction of the NOACs for stroke prevention in patients with AF in France and NOAC therapy is now the preferred OAC therapy at initiation in older

patients at higher risk of stroke. However, results from this nationwide drug utilization study suggest the need for improvement in appropriate prescription of OAC therapy in these patients, especially regarding the use of concomitant interacting drugs and the choice of initial NOAC dose.

Contributor ship statement

GM, AP, CB and AN designed the study. All authors have contributed substantially to the interpretation of results. In addition: GM, AP and AN drafted the article; CB, JD and AN conducted the statistical analysis; GM, AP, AN, CB, JD, AW provided critical revision of the manuscript for important intellectual content. All authors had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis. All authors approved the version to be published.

Competing interests

All authors have no conflict of interest.

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Data sharing statement

No additional data are available directly from the authors. Permanent access to the French healthcare databases is automatically granted to certain government agencies, public institutions and public service authorities. Temporary access for studies and research is possible upon request from the national health data institute (INDS). All databases used in this study only contained anonymous patient records.

Ethics approval

This observational study based on the French healthcare databases was approved by the French Data Protection Agency (*Commission Nationale de l'Informatique et des Libertés*, Cnil) and did not require patient consents or ethics committee approval.

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Figure titles and legends

Figure 1. Time trends in the use of oral antithrombotic therapy between 2011 and 2016 in patients with atrial fibrillation in France

Abbreviations: AF: atrial fibrillation; OAC: oral anticoagulant; VKA: vitamin K antagonist; NOAC: Non vitamin K antagonist oral anticoagulant

Legend: For Figures 1.b., 1.d and 1.e., estimates from all AF patients already presented in figure 1.a. are indicated by dashed lines for the purposes of comparison.

Figure 2. Patient flow chart.

Abbreviations: OAC: oral anticoagulant; NOAC: Non-vitamin K antagonist oral anticoagulant; VKA: vitamin K antagonist; DVT/PE: deep vein thrombosis/pulmonary embolism; AF: atrial fibrillation

Figure 3. Potential NOAC underdosing in new users with AF

Abbreviations: NOAC: Non-vitamin K antagonist oral anticoagulant; AF: atrial fibrillation

Table 1. Baseline characteristics of anticoagulant-naive patients with atrial fibrillation initiating oral anticoagulants in 2015-2016

Characteristics (N; %*)	NOAC				VKA
	Dabigatran N= 9,085	Rivaroxaban N= 54,456	Apixaban N= 64,300	Total NOAC N= 127,841	N= 65,010
NOAC: reduced doses	5,652 (62.2)	19,429 (35.7)	26,003 (40.4)	51,084 (40.0)	NA
Female sex	4,546 (50.0)	26,147 (48.0)	33,375 (51.9)	64,068 (50.1)	33,865 (52.1)
Age (years), mean (SD)	74.1 (11.6)	72.8 (11.9)	75.3 (11.3)	74.1 (11.6)	78.0 (11.3)
18-54	548 (6.0)	4,007 (7.4)	3,172 (4.9)	7,727 (6.0)	2,361 (3.6)
55-64	1,117 (12.3)	7,651 (14.0)	7,117 (11.1)	15,885 (12.4)	5,680 (8.7)
65-74	2,514 (27.7)	16,057 (29.5)	16,645 (25.9)	35,216 (27.5)	12,969 (19.9)
75-79	1,554 (17.1)	9,053 (16.6)	10,692 (16.6)	21,299 (16.7)	9,587 (14.7)
≥80	3,352 (36.9)	17,688 (32.5)	26,674 (41.5)	47,714 (37.3)	34,413 (52.9)
≥90	493 (5.4)	2,559 (4.7)	4,654 (7.2)	7,706 (6.0)	8,399 (12.9)
Deprivation index					
Quintile 1 (least deprived)	1,394 (15.3)	10,265 (18.9)	11,266 (17.5)	22,925 (17.9)	10,263 (15.8)
Quintile 2	1,586 (17.5)	10,678 (19.6)	12,496 (19.4)	24,760 (19.4)	11,884 (18.3)
Quintile 3	1,780 (19.6)	10,701 (19.7)	12,799 (19.9)	25,280 (19.8)	12,811 (19.7)
Quintile 4	1,917 (21.1)	10,794 (19.8)	13,142 (20.4)	25,853 (20.2)	14,272 (22.0)
Quintile 5 (most deprived))	2,113 (23.3)	11,172 (20.5)	13,825 (21.5)	27,110 (21.2)	14,699 (22.6)
Overseas departments	295 (3.2)	846 (1.6)	772 (1.2)	1,913 (1.5)	1,081 (1.7)
First prescriber's specialty					
Hospital practitioner	3,720 (40.9)	22,905 (42.1)	29,316 (45.6)	55,941 (43.8)	39,083 (60.1)
General practitioner	2,062 (22.7)	11,145 (20.5)	11,590 (18.0)	24,797 (19.4)	15,539 (23.9)
Private cardiologist	3,093 (34.0)	18,978 (34.9)	21,843 (34.0)	43,914 (34.4)	8,511 (13.1)
Private orthopaedic surgeon	16 (0.2)	100 (0.2)	95 (0.1)	211 (0.2)	73 (0.1)
Other private specialist	168 (1.8)	1,149 (2.1)	1,276 (2.0)	2,593 (2.0)	1,583 (2.4)
CHA_2DS_2-VASc score[†]					
Mean score (SD)	3.7 (1.6)	3.5 (1.6)	3.9 (1.6)	3.7 (1.6)	4.5 (1.6)
0	183 (2.0)	1,294 (2.4)	847 (1.3)	2,324 (1.8)	309 (0.5)
1	635 (7.0)	4,854 (8.9)	3,637 (5.7)	9,126 (7.1)	1,607 (2.5)
≥ 2	8,267 (91.0)	48,308 (88.7)	59,816 (93.0)	116,391 (90.1)	63,094 (97.0)
C (Heart failure)	2,849 (31.4)	17,805 (32.7)	23,548 (36.6)	44,202 (34.6)	32,727 (50.3)
H (antihypertensive drugs)	7,547 (83.1)	44,260 (81.3)	54,596 (84.9)	106,403 (83.2)	59,139 (91.0)
D(iabetes)	1,959 (21.6)	11,279 (20.7)	14,087 (21.9)	27,325 (21.4)	18,806 (28.9)
S(troke: ATE)	1,207 (13.3)	4,930 (9.1)	8,448 (13.1)	14,585 (11.4)	10,638 (16.4)
V(ascular diseases)	2,242 (24.7)	13,924 (25.6)	18,766 (29.2)	34,932 (27.3)	28,894 (44.4)
Age≥75 and arterial thromboembolic events[†]	769 (8.5)	3,126 (5.7)	5,608 (8.7)	9,503 (7.4)	7,762 (11.9)
Age<65 and no arterial thromboembolic events[†]	1,510 (16.6)	11,074 (20.3)	9,396 (14.6)	21,980 (17.2)	7,035 (10.8)

Table 1. (continued)

Characteristics (N; %)	NOAC				VKA
	Dabigatran N= 9,085	Rivaroxaban N= 54,456	Apixaban N= 64,300	Total NOAC N= 127,841	N= 65,010
HAS-BLED score†					
Mean score (SD)	2.0 (0.9)	1.9 (0.9)	2.1 (0.9)	2.0 (0.9)	2.7 (1.0)
≥ 3	2,169 (23.9)	11,388 (20.9)	16,834 (26.2)	30,391 (23.8)	36,417 (56.0)
A(bnormal)					
Renal function	345 (3.8)	2,426 (4.5)	3,822 (5.9)	6,593 (5.2)	14,260 (21.9)
Liver function	169 (1.9)	967 (1.8)	1,106 (1.7)	2,242 (1.8)	2,372 (3.6)
B(leeding)					
Predisposition	182 (2.0)	1,161 (2.1)	1,605 (2.5)	2,948 (2.3)	5,873 (9.0)
Major bleeding	692 (7.6)	3,729 (6.8)	5,134 (8)	9,555 (7.5)	9,348 (14.4)
D(rug/alcohol)					
Alcohol abuse‡	272 (3.0)	1,698 (3.1)	1,730 (2.7)	3,700 (2.9)	2,923 (4.5)
Drug-drug interactions	947 (10.4)	5,838 (10.7)	7,570 (11.8)	14,355 (11.2)	23,451 (36.1)
Parenteral anticoagulant (heparin)	64 (0.7)	331 (0.6)	361 (0.6)	756 (0.6)	9,824 (15.1)
Antiplatelet drugs	826 (9.1)	5,225 (9.6)	6,951 (10.8)	13,002 (10.2)	15,433 (23.7)
NSAIDs	72 (0.8)	365 (0.7)	344 (0.5)	781 (0.6)	212 (0.3)
Other comorbidities†					
Ischaemic heart disease	1,821 (20.0)	11,321 (20.8)	15,439 (24.0)	28,581 (22.4)	23,657 (36.4)
Frailty (proxies)	1,666 (18.3)	8,971 (16.5)	12,730 (19.8)	23,367 (18.3)	24,175 (37.2)
Dementia or Parkinson's disease	524 (5.8)	3,204 (5.9)	4,125 (6.4)	7,853 (6.1)	7,437 (11.4)
Psychiatric disorders	1,722 (19.0)	10,593 (19.5)	12,844 (20.0)	25,159 (19.7)	16,598 (25.5)
Smoking‡	1,024 (11.3)	6,481 (11.9)	7,442 (11.6)	14,947 (11.7)	11,434 (17.6)
Comedications§					
Antiarrhythmics or cardiac glycosides	5,996 (66.0)	35,761 (65.7)	41,031 (63.8)	82,788 (64.8)	35,600 (54.8)
Lipid-lowering agents	3,913 (43.1)	22,250 (40.9)	28,812 (44.8)	54,975 (43.0)	31,903 (49.1)
Oral corticosteroids	1,105 (12.2)	6,964 (12.8)	8,079 (12.6)	16,148 (12.6)	8,967 (13.8)
Antiulcer agents	4,295 (47.3)	24,842 (45.6)	31,469 (48.9)	60,606 (47.4)	39,842 (61.3)
Polymedication (≥5 ATC classes)	3,750 (41.3)	21,725 (39.9)	28,196 (43.9)	53,671 (42.0)	45,153 (69.5)
Polymedication (≥10 ATC classes)	738 (8.1)	4,653 (8.5)	6,246 (9.7)	11,637 (9.1)	14,947 (23.0)

NOAC: Non-vitamin K antagonist oral anticoagulant; VKA: vitamin K antagonist; SD: standard deviation; ATE: arterial thromboembolic events (ischaemic stroke, arterial systemic embolism or transient ischaemic attack); NSAIDs: non-steroidal anti-inflammatory drugs

* Unless otherwise stated

† Comorbidities were defined using a rolling 1-year period following the initiation of OAC therapy

‡ Smoking or alcohol data: measured by using proxies such as reimbursements for specific therapy or hospitalizations related to smoking or alcohol consumption/diseases

§ Comorbidities were defined using a rolling 4-month period preceding the initiation of OAC therapy

Table 2. Potential inappropriate use of NOAC therapy in oral anticoagulant-naïve patients with atrial fibrillation in 2015-2016

Characteristics (N; %)	NOAC				VKA
	Dabigatran N= 9,085	Rivaroxaban N= 54,456	Apixaban N= 64,300	Total NOAC N= 127,841	N= 65,010
Contraindications or non-approved indication/dose	**1,457 (16.0)**	**8,614 (15.8)**	**9,542 (14.8)**	**19,613 (15.3)**	**NA**
Any valvular heart disease	649 (7.1)	4,146 (7.6)	6,122 (9.5)	10,917 (8.5)	16,461 (25.3)
Prosthetic heart valve (mechanical or bioprosthetic valves)	106 (1.2)	665 (1.2)	1,096 (1.7)	1,867 (1.5)	6,726 (10.3)
Recently hospitalized for coagulopathy, purpura and other haemorrhagic conditions*	90 (1.0)	479 (0.9)	596 (0.9)	1,165 (0.9)	2,142 (3.3)
Liver fibrosis and cirrhosis*	50 (0.6)	282 (0.5)	367 (0.6)	699 (0.5)	1,174 (1.8)
Recent gastrointestinal ulceration or intracranial haemorrhage†	40 (0.4)	120 (0.2)	248 (0.4)	408 (0.3)	350 (0.5)
Recently or currently treated cancer*	417 (4.6)	2,531 (4.6)	2,898 (4.5)	5,846 (4.6)	4,252 (6.5)
Reduced-dose NOAC not approved for stroke prevention in AF patients in Europe	357 (3.9)	1,844 (3.4)	NA	2,201 (3.5)	NA
Inappropriate use during follow-up‡					
No monitoring of renal function at initiation	637 (16.8)	3804 (15.5)	3642 (14.5)	8083 (15.1)	5401 (17.0)
No monitoring of renal function in the year post-initiation	378 (10.0)	2,347 (9.6)	2,138 (8.5)	4,863 (9.1)	2,984 (9.4)
Non-persistence patterns, N (%)					
One reimbursement only	605 (15.9)	2,666 (10.9)	1,771 (7.1)	5,042 (9.4)	2,426 (7.6)
One-year treatment discontinuation rates§	984 (25.9)	6210 (25.4)	4524 (18,0)	11,718 (21,9)	8399 (26.4)
Concomitant use of drug increasing the risk of bleeding¶	**2,639 (29.3)**	**15,797 (29.3)**	**18,556 (29.2)**	**36,992 (29.3)**	**33,025 (52.3)**
Antiplatelet agents or parenteral anticoagulants	1,728 (19.2)	10,386 (19.3)	12,382 (19.5)	24,496 (19.4)	28,112 (44.5)
Parenteral anticoagulants	287 (3.2)	1,577 (2.9)	1,520 (2.4)	3,384 (2.7)	12,078 (19.1)
Antiplatelet agents	1,490 (16.6)	9,179 (17.0)	11,170 (17.6)	21,839 (17.3)	19,710 (31.2)
Aspirin	1,336 (14.8)	8,215 (15.2)	10,026 (15.8)	19,577 (15.5)	17,770 (28.1)
NSAIDs	375 (4.2)	2,111 (3.9)	2,017 (3.2)	4,503 (3.6)	1,030 (1.6)
SSRIs and SSNRIs	836 (9.3)	4,852 (9.0)	5,880 (9.2)	11,568 (9.1)	7,317 (11.6)

NOAC: Non-vitamin K antagonist oral anticoagulant; VKA: vitamin K antagonist; AF: atrial fibrillation; NA: not applicable; NSAIDs: non-steroidal anti-inflammatory drugs; SSRIs: selective serotonin reuptake inhibitors and SSNRIs: selective serotonin-norepinephrine reuptake inhibitors

* Comorbidities identified using hospitalization and/or LTD data, and/or specific procedures during a rolling 1-year period preceding the initiation of OAC therapy

† Comorbidities identified using hospitalization data during a rolling 6-week period preceding the initiation of OAC therapy

‡ Data on patients with at least a one year of follow-up i.e. patients initiating OAC in 2015 after excluding patients who died and those hospitalized for 3 months or longer (N= 3,796; 24,483; 25,118; 53,397 and 31,777 for dabigatran-, rivaroxaban, apixaban, total NOAC- and total VKA new users, respectively); period considered (unless otherwise stated): rolling 1-year period following the initiation of OAC therapy (index date included)

§ One-year crude discontinuation rate for patients initiating OAC in 2015 who died and those hospitalized for 3 months or longer, defined as prolonged treatment discontinuation i.e. 90-day gap with no medication coverage after the 30-day coverage period of a refill

¶ Data for new users still alive after a 45-day period following the index date (N= 9,001; 53,885; 63,578; 126,464 and 63,180 for dabigatran-, rivaroxaban, apixaban, total NOAC- and total VKA new users , respectively); period considered: rolling 6-week period following the initiation of OAC therapy (index date included)

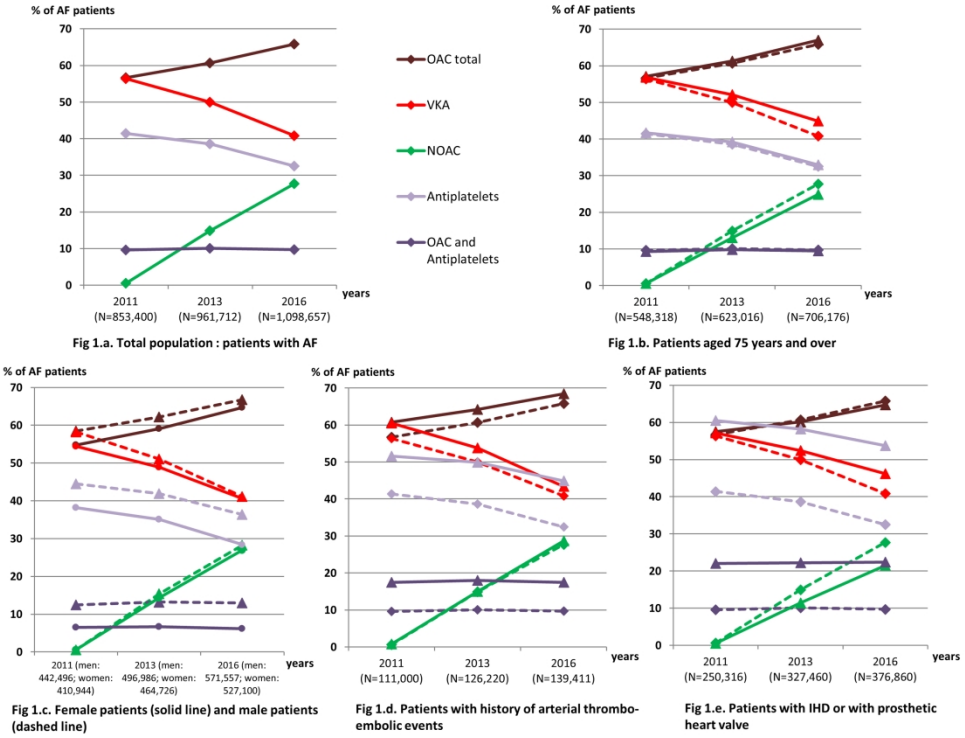

Figure 1

253x190mm (300 x 300 DPI)

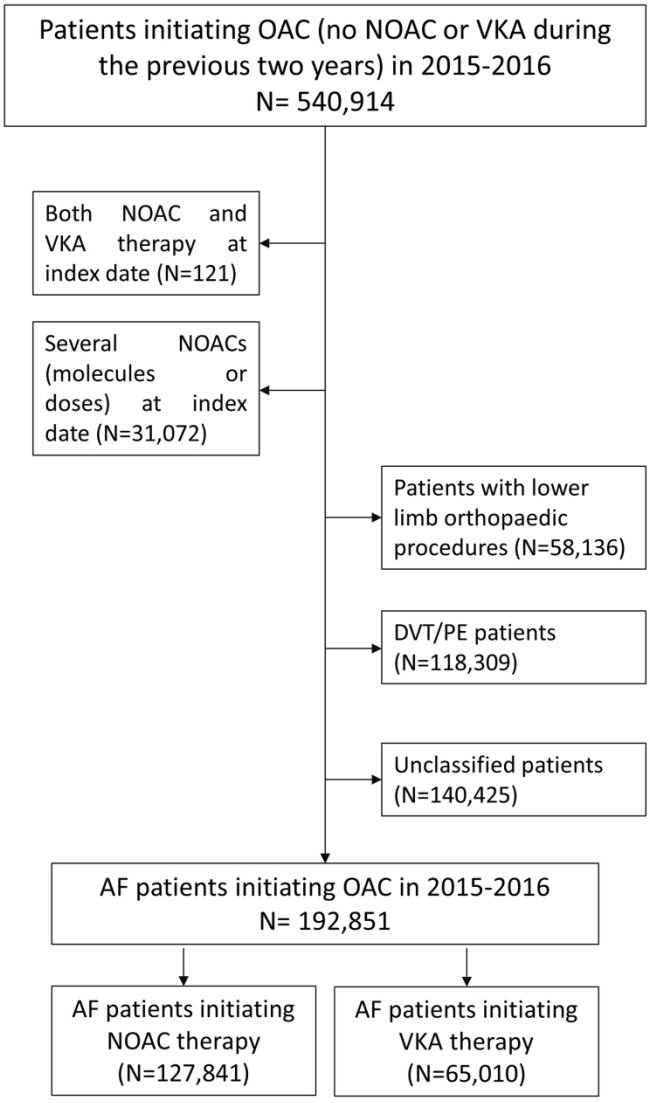

Figure 2

190x253mm (300 x 300 DPI)

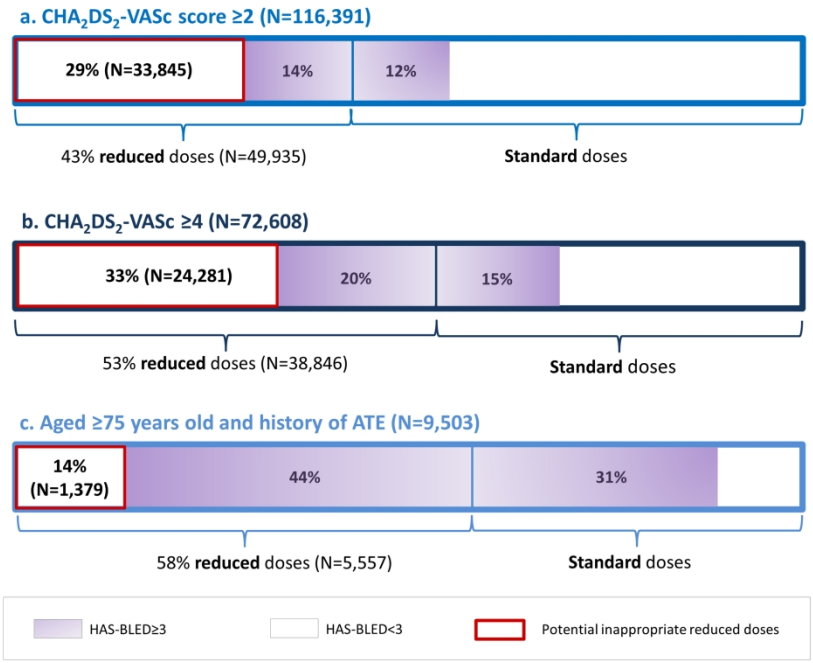

Figure 3

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Supplementary Materials

Supplementary Table 1. Definitions used to identify comorbid conditions and comedications in the French healthcare databases.

Supplementary Table 2. Age- and sex-adjusted association between baseline characteristics and the choice of NOAC therapy compared to VKA therapy in OAC new users.

Supplementary Table 3. Comparison of selected baseline characteristics of DOAC new users with AF at risk of stroke according to level of HAS-BLED score and type of DOAC dose.

Supplementary Table 1. Definitions used to identify comorbid conditions and comedications in the SNIIRAM-PMSI databases.

Covariates*	Hospital discharge diagnoses†	LTD diagnoses†	Specific procedures or drug reimbursements
AF definition (Patterns of use of DOAC therapy in new users with AF)			
Nonvalvular atrial fibrillation	I48	I48	Radiofrequency ablation, cardioversion
Lower limb orthopaedic procedures			Lower limb orthopaedic surgery or procedures
History of valvular heart disease/Prosthetic heart valve	I05-I09, I33-I39/ Z95.2, Z95.3 ou Z95.4		Heart valve surgery
Deep vein thrombosis/pulmonary embolism	I26, I80 (except I80.0), I81, I82	I26, I80-I82	Lower limb venous ultrasonography, pulmonary/lower limb angiography, ventilation/perfusion scan
CHA_2DS_2-VASc and HAS-BLED scores			
Heart failure	I50 or I11.0, I13.0, I13.2, I13.9, K76.1, J81 related to I50	I50	Specific medications approved for heart failure including beta-blockers (bisoprolol, carvedilol, metoprolol), eplerenone, bumetanide, furosemide when licensed for heart failure only
Antihypertensive drugs			Diuretics, beta blockers, calcium channel blockers, agents acting on the renin-angiotensin system and other antiadrenergic agents
Diabetes	E10-E14	E10-E14	Insulins and blood glucose lowering drugs
History of ATE (ischemic stroke, arterial systemic embolism or transient ischemic attack)	I63 (except I63.6), G46 related to I63 or I69.3; I74, G45 (except G45.4)	I63, I74, G45	
Peripheral vascular disease	I20, I21, I22, I23, I24, I25, I70, I71, I72, I73, E10.5, E11.5, E12.5, E13.5, E14.5	I70-I73 , I20-I25	
Abnormal renal function	N18, I12.0, I13.1, I13.2, E10.2, E11.2, E13.2, E14.2, N08.3	N18, I12	
Abnormal liver function	R18, I85, K70, K71.3, K71.4, K71.5, K71.7, K72.1, K73, K74, K76.1, B18, C22, C78.7	K70, K73, K74, B18, C22	Antiviral agents for systemic use HCV (ribavirin, [peg]interferon alpha and DAA), and against HCB ([peg]interferon alpha and NnRTIs).
Major bleeding	I60-I62, S06.3-S06.6, I85, K25-K29, K62.5, K92, D62, N02, R31, R58, H11.3, H35.6, H43.1, H45.0, H92.2, J94.2, K66.1, M25.0, N92, N93.8, N93.9, N95.0, R04.0		
Predisposition for bleeding	Anemias : D50, D51, D52, D53, D55, D56, D57, D58, D59, D60, D62, D63, D64 or coagulation defects, purpura and other hemorrhagic: D65, D66, D67, D68, D69		
Alcohol abuse	F10, K70, T51, K6, G31.2, G62.1, G72.1, I42.6, K29.2, Z71.4, Z72.1, Z50.2.		disulfiram, acamprosate, nalmefene and products with naltrexone licensed in adult patients with alcohol dependence
Drug-drug interaction			Platelet aggregation inhibitors (including low-dose acetylsalicylic acid), heparins, NSAIDs
Other comorbidities			
Ischemic heart disease (including myocardial infarction)	I20-I25	I20-I25	Nitrovasodilator agents
Frailty	G81-G83	G81-G83	Home hospital bed, wheelchair, high level of nursing home stay
Dementia or Parkinson's disease	F00-F03, G30, G20	F00-F03, G30, G20	Anticholinesterases or NMDA receptor antagonists: anticholinergic and dopaminergic agents
Psychiatric disorders	F20-29, F30-39	F20-29, F30-39	Antidepressants, antipsychotics, conventional mood stabilizers
Smoking	F17, Z71.6, Z72.0; J43-J44	J43-J44	Nicotine replacement therapy
Recently hospitalized for coagulopathy, purpura and other haemorrhagic conditions	D65-D69		
Liver fibrosis and cirrhosis	K70.0, K70.2, K70.3, K70.4, K71.7, K72, K74		

Recent gastrointestinal ulceration or intracranial haemorrhage	K25, K26, K27, K28, K29.0, I60, I61, I62, S06.4, S06.5, S06.6		
Recently or currently treated cancer	C00-D09, D37-D48, Z510, Z511	C00-D09, D37-D48	Radiotherapy procedures
Baseline comedications			
Antiarrhythmics and cardiac glycosides			Antiarrhythmics: class I and III, verapamil, digitalis glycosides
Lipid-lowering agents			HMG CoA reductase inhibitors, fibrates, ezetimibe
Antiplatelet drugs			Platelet aggregation inhibitors including low-dose acetylsalicylic acid
Oral corticosteroids			Mineralo- and gluco-corticoids
Antiulcer agents			Mainly proton pump inhibitors and H2-receptor antagonists

LTD: long-term diseases; ATE: arterial thromboembolic events (mainly stroke); DVT/PE: deep vein thrombosis/pulmonary embolism; NMDA: N-methyl-D-aspartate; HIV: human immunodeficiency virus; PI: Protease inhibitor; NNRTIs: Non-nucleoside reverse transcriptase inhibitors; NnRTI: Nucleoside and nucleotide reverse transcriptase inhibitors; DAA: direct-acting antiviral; HMG CoA: 3-hydroxy-3-methyl-glutaryl-CoA; NSAIDs: Non-steroidal anti-inflammatory drugs.

* Comorbidities were identified using ICD-10 diagnosis codes for hospital discharge/LTD, or specific procedures, or drug reimbursements. Concomitant medications were identified as those dispensed at least once during the 4-month period preceding the index date. Influenza vaccination was determined during the first 'flu vaccination campaign preceding the index date.
†ICD-10 codes

Supplementary Table 2. Age- and sex-adjusted association between baseline characteristics and the choice of NOAC therapy compared to VKA therapy in OAC new users.

Baseline characteristics	Dabigatran *vs* VKA				Rivaroxaban *vs* VKA				Apixaban *vs* VKA			
	RR*	*95% CI*		p-value†	RR*	*95% CI*		p-value†	RR*	*95% CI*		p-value†
Female sex	1.11	1.05	1.17	***	1.03	1.00	1.07	*	1.07	1.04	1.09	***
Age (years)												
18-54 (Ref)	1.00	1.00	1.00		1.00	1.00	1.00		1.00	1.00	1.00	
55-64	0.87	0.78	0.98	*	0.92	0.87	0.97	**	0.97	0.92	1.02	
65-74	0.86	0.77	0.95	**	0.89	0.84	0.94	***	0.98	0.93	1.03	
75-79	0.73	0.65	0.81	***	0.77	0.73	0.82	***	0.91	0.87	0.96	***
80-84	0.58	0.52	0.65	***	0.65	0.61	0.68	***	0.83	0.79	0.87	***
85-89	0.44	0.39	0.49	***	0.50	0.48	0.54	***	0.74	0.70	0.77	***
>=90	0.28	0.25	0.32	***	0.37	0.35	0.40	***	0.61	0.57	0.65	***
Deprivation index												
quintile 1 (least deprived) (Ref)	1.00	1.00	1.00		1.00	1.00	1.00		1.00	1.00	1.00	
quintile 2	0.97	0.91	1.05		0.94	0.92	0.97	***	0.97	0.95	1.00	*
quintile 3	0.99	0.93	1.07		0.90	0.87	0.92	***	0.94	0.92	0.97	***
quintile 4	0.96	0.89	1.03		0.85	0.83	0.87	***	0.90	0.88	0.93	***
quintile 5 (most deprived)	1.00	0.94	1.07		0.85	0.83	0.87	***	0.91	0.89	0.93	***
Overseas departments	1.60	1.41	1.82	***	0.83	0.77	0.89	***	0.77	0.72	0.83	***
First prescriber's specialty												
Hospital practitioner (Ref)	1.00	1.00	1.00		1.00	1.00	1.00		1.00	1.00	1.00	
General practitioner	1.37	1.29	1.46	***	1.16	1.10	1.23	***	1.00	0.96	1.04	
Private cardiologist	2.92	2.76	3.08	***	1.80	1.70	1.90	***	1.65	1.59	1.71	***
Private orthopedic surgeon	1.96	1.20	3.21	**	1.48	1.20	1.81	***	1.32	1.07	1.61	**
Other private specialist	1.07	0.93	1.24		1.12	1.04	1.21	**	1.03	0.97	1.10	
From CHA_2DS_2-VASc score												
Heart Failure	0.52	0.49	0.54	***	0.70	0.68	0.71	***	0.77	0.75	0.78	***
Antihypertensive drugs	0.60	0.57	0.63	***	0.74	0.72	0.76	***	0.80	0.78	0.82	***
Diabetes	0.67	0.63	0.71	***	0.76	0.74	0.77	***	0.80	0.79	0.82	***
ATE	0.85	0.79	0.92	***	0.71	0.68	0.74	***	0.90	0.88	0.92	***

Vascular diseases	0.47	0.42	0.53	***	0.63	0.61	0.66	***	0.71	0.67	0.74	***
From HAS-BLED score												
Abnormal renal function	0.17	0.15	0.19	***	0.31	0.30	0.33	***	0.40	0.38	0.42	***
Abnormal liver function	0.46	0.39	0.54	***	0.58	0.54	0.62	***	0.60	0.57	0.64	***
Bleeding predisposition	0.53	0.47	0.59	***	0.63	0.60	0.65	***	0.70	0.67	0.72	***
Major bleeding	0.23	0.20	0.26	***	0.36	0.33	0.39	***	0.41	0.38	0.45	***
Alcohol abuse	0.55	0.48	0.62	***	0.69	0.65	0.72	***	0.68	0.65	0.72	***
Drug-drug interactions	0.22	0.20	0.24	***	0.36	0.34	0.37	***	0.40	0.37	0.43	***
Parenteral anticoagulants	0.04	0.03	0.06	***	0.07	0.06	0.07	***	0.07	0.06	0.07	***
Antiplatelets drugs	0.34	0.31	0.37	***	0.49	0.47	0.51	***	0.56	0.53	0.60	***
NSAIDs	1.80	1.43	2.28	***	1.24	1.12	1.38	***	1.18	1.06	1.32	**
Other comorbidities												
Valvular heart diseases	0,25	0,20	0,31	***	0,40	0,36	0,45	***	0,47	0,41	0,54	***
Ischemic heart diseases	0.51	0.46	0.56	***	0.65	0.63	0.67	***	0.74	0.71	0.77	***
Frailty (proxies)	0.48	0.45	0.51	***	0.58	0.55	0.61	***	0.64	0.62	0.66	***
Dementia or Parkinson's disease	0.66	0.60	0.72	***	0.82	0.78	0.85	***	0.77	0.75	0.80	***
Psychiatric disorders	0.74	0.70	0.78	***	0.86	0.84	0.88	***	0.86	0.84	0.88	***
Smoking	0.56	0.52	0.60	***	0.71	0.69	0.74	***	0.74	0.71	0.76	***
Comedications												
Antiarrhythmics or cardiac glycosides	1.42	1.35	1.50	***	1.22	1.19	1.25	***	1.18	1.16	1.20	***
Lipid-lowering agents	0.76	0.71	0.81	***	0.81	0.79	0.84	***	0.90	0.87	0.92	***
Oral corticosteroids	0.85	0.80	0.91	***	0.94	0.91	0.97	***	0.94	0.91	0.96	***
Antiulcer agents	0.61	0.56	0.66	***	0.73	0.71	0.75	***	0.78	0.75	0.81	***
Polymedication (≥5 ATC classes)	0.37	0.35	0.40	***	0.55	0.54	0.57	***	0.60	0.59	0.62	***
Polymedication (≥10 ATC classes)	0.33	0.30	0.36	***	0.49	0.46	0.52	***	0.54	0.51	0.57	***

NOAC: Non vitamin K antagonist oral anticoagulant; VKA: vitamin K antagonist; OAC: oral anticoagulant; RR: Relative risk; IC; Confidence interval; ATE: arterial thromboembolic events (ischaemic stroke, arterial systemic embolism or transient ischaemic attack); NSAIDs: non-steroidal anti-inflammatory drugs

* RR determined using negative binomial regression analysis adjusting for age and sex(except for age and sex covariates, adjusted for sex and for age only, respectively).

† p-values : *** $p < 0{,}001$; ** $p < 0{,}01$; * $p < 0{,}05$

Reading example: Age and sex being equal, frailty reduced the probability for a prescription of dabigatran (instead of VKA) by 52% (1 minus the estimated RR of 0.48). For rivaroxaban and apixaban, this reduction was 42% and 36%, respectively.

Supplementary Table 3. Comparison of selected baseline characteristics of DOAC new users with AF at risk of stroke according to level of HAS-BLED score and type of DOAC dose.

N (%)	Patients with CHA2DS2-VASc ≥ 2 (N=116,391)				Patients aged ≥75 years old and history of ATE (N=9,503)			
	HAS-BLED≥3 (N=30 273)		HAS-BLED<3 (N=86 118)		HAS-BLED≥3 (N=7,143)		HAS-BLED<3 (N=2,360)	
	Reduced doses* (N=16,090)	Standard doses* (N=14,183)	Reduced doses* (N=33,845)	Standard doses* (N=52,273)	Reduced doses* (N=4,178)	Standard doses* (N=2,965)	Reduced doses* (N=1,379)	Standard doses* (N=981)
Age (years), mean	81.8	74.8	81.3	70.9	84,8	81.1	81.3	70.9
Age ≥ 80 years	10,786 (67.0)	3,982 (28.1)	22,962 (67.8)	9,984 (19.1)	3,496 (83.7)	1,720 (58.0)	1,188 (86.1)	567 (57.8)
First prescriber's specialty								
Hospital practitioner or private cardiologist	12,315 (76.6)	11,364 (80.1)	25,221 (74.5)	41,728 (79.8)	3216 (77.0)	2965 (80.2)	1013 (73.5)	798 (81.3)
General practitioner	3321 (20.6)	2426 (17.1)	7836 (23.2)	9302 (17.8)	860 (20.6)	503 (17.0)	322 (23.4)	157 (16.0)
Frailty (proxies)	6,689 (41.6)	4,600 (32.4)	6,932 (20.5)	4,779 (9.1)	2,599 (62.2)	1,642 (55.4)	589 (42.7)	316 (32.2)
Dementia or Parkinson's disease	2121 (13.2)	935 (6.6)	3169 (9.4)	1555 (3.0)	789 (18.9)	355 (12.0)	259 (18.8)	111 (11.3)
Any valvular diseases†	2,640 (16.4)	1,809 (12.8)	2,740 (8.1)	3,342 (6.4)	566 (13.5)	330 (11.1)	144 (10.4)	95 (9.7)
Prosthetic heart valve†	544 (3.4)	384 (2.7)	425 (1.3)	474 (0.9)	94 (2.2)	52 (1.8)	19 (1.4)	14 (1.4)
Ischaemic heart disease	7,232 (44.9)	5,274 (37.2)	6,827 (20.2)	9,142 (17.5)	1,338 (32.0)	758 (25.6)	336 (24.4)	185 (18.9)
Antiplatelet agents at initiation	6,035 (37.5)	4,891 (34.5)	620 (1.8)	1,264 (2.4)	874 (20.9)	510 (17.2)	11 (0.8)	7 (0.7)
Lipid-lowering agents	9252 (57.5)	9213 (65.0)	12836 (37.9)	21820 (41.7)	2606 (62.4)	2132 (71.9)	697 (50.5)	611 (62.3)
Polymedication (≥10 ATC classes)	3,627 (22.5)	2,946 (20.8)	2,150 (6.4)	2,798 (5.4)	788 (18.9)	473 (16.0)	104 (7.5)	67 (6.8)

* Reduced-dose DOAC: dabigatran 150mg, Rivaroxaban 20 and apixaban 5mg; reduced-dose DOAC: dabigatran 75mg and 110mg, rivaroxaban 10mg and 15mg and apixaban 2.5mg
† Covariates defined by hospitalization data only

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5,6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5,6
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*6,7,8*
Bias	9	Describe any efforts to address potential sources of bias	7,8
Study size	10	Explain how the study size was arrived at	9, Fig 2
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7,8
		(*b*) Describe any methods used to examine subgroups and interactions	7,8
		(*c*) Explain how missing data were addressed	NA
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	NA
		(*e*) Describe any sensitivity analyses	7,8

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9 Fig 2
		(b) Give reasons for non-participation at each stage	9
		(c) Consider use of a flow diagram	Fig 2
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 1
		(b) Indicate number of participants with missing data for each variable of interest	NA
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	*NA*
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	*NA*
		Cross-sectional study—Report numbers of outcome events or summary measures	*Fig2,3* *Table2*
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Table 2
		(*b*) Report category boundaries when continuous variables were categorized	Table 2
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	9, 10
Discussion			
Key results	18	Summarise key results with reference to study objectives	11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11, 12
Generalisability	21	Discuss the generalisability (external validity) of the study results	12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	14

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.