BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-018180
Article Type:	Research
Date Submitted by the Author:	12-Jun-2017
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Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Cardiovascular medicine, Pharmacology and therapeutics, Public health
Keywords:	Cohort, Atrial Fibrilation, anticoagulants, Vitamine K antagonist, direct oral anti-coagulants

Direct oral anticoagulant therapies for atrial fibrillation: changing profiles of newly treated patients

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Abstract (300 words)

Objective

Unlike several other national health agencies, French health authorities recommended that the newer direct oral anticoagulant (DOAC) agents only be prescribed as second choice for the treatment of newly diagnosed non-valvular atrial fibrillation (NVAF), with vitamin K antagonists (VKA) remaining the first choice. We investigated the patterns of use of DOACs versus VKA in the treatment of NVAF in France over the first five years of DOAC availability. We also identified the changes in patient characteristics of those who initiated DOAC treatment over this time period.

Methods

Based on the French National Health Administrative Database, we constituted a population-based cohort of all patients who were newly treated for NVAF between January 2011 and December 2015. Trends in drug use were described as the percentage of patients initiating each drug at the time of treatment initiation. A multivariate analysis using logistic regression model was performed to identify independent sociodemographic and clinical predictors of initial anticoagulant choice.

Results

The cohort comprised 814,446 patients who had received a new anticoagulant treatment for NVAF. The proportion of patients using DOACs as initial anticoagulant therapy reached 54% three months after the Health Ministry approved the reimbursement of dabigatran for NVAF, and 61% by the end of 2015, versus VKA use. In the multivariate analysis, we found that DOAC initiators were younger and healthier overall than VKA initiators, and this tendency was reinforced over the 2011-2014 period. DOACs were more frequently

prescribed by cardiologists in 2012 and after (adjusted-OR in 2012: 2.47; 95% Confidence Interval: 2.40-2.54).

Conclusion

Despite recommendations from health authorities, DOACs have been rapidly and massively adopted as initial therapy for NVAF in France. Observational studies should account for the fact that patients selected to initiate DOAC treatment are healthier overall, as failure to do so may bias the risk-benefit assessment of DOACs.

Keywords (6 max)

Cohort, atrial fibrillation, anticoagulants, vitamin K antagonist, direct oral anticoagulants

Tables: 2

Figures: 5

Supplementary material: 6 tables

Strength and limitations:

- With a source database covering 63 million inhabitants and exhaustive information on anticoagulant deliveries in France, our study is the largest to report penetration of DOACs on the market. This is particularly the case for apixaban, which is the most recent DOAC available
- The administrative database used does not include clinical results; nor does it include outpatients' diagnosis codes. To account for outpatients, we based our definition of NVAF on drug dispensation, using the most likely treatment scheme for NVAF. We conducted sensitivity analyses to ensure that our results are consistent.

Introduction

Non-Valvular Atrial fibrillation (NVAF) is the most common sustained cardiac arrhythmia, and its age-adjusted prevalence has been increasing over time.[1,2] NVAF is associated with high morbidity and mortality, as it increases the risks of stroke and systemic thromboembolic events.[2] In light of this, the use of an oral anticoagulant is recommended in patients with NVAF at medium or high risk of stroke.[3-7] For more than 50 years, vitamin K antagonists (VKA) such as warfarin were the only effective therapy available for stroke prevention in patients with NVAF.[8] However, the efficacy and safety of VKAs are closely related to the quality of anticoagulation, which is open to substantial inter- and intra-patient variability and requires close biological monitoring.[9, 8, 10]

In order to respond to physicians' and patients' expectations of more user-friendly drugs, research on new drugs has intensified over the last few years. This has prompted the development of direct oral anticoagulants (DOAC) that inhibit thrombin or factor Xa. Large randomised clinical trials (RCTs) have compared the efficacy of DOACs to that of warfarin in patients with NVAF.[11,12,13] A recent meta-analysis of these RCTs has shown that the frequency of strokes and/or systemic embolic events is 19% lower with DOACs than it is with warfarin. Moreover, compared with warfarin, DOACs have been shown to present similar risks of major bleeding but higher risks of gastrointestinal bleeding.[14] The risk-benefit ratio of DOACs nevertheless varies according to patient profile.[15, 16]

In France, the direct thrombin inhibitor dabigatran was the first DOAC to be approved for the primary prevention of venous thromboembolism in orthopedic surgery (in 2008) and stroke in NVAF (in 2011). Reimbursement of dabigatran for the treatment of NVAF was

approved in July 2012. Two new oral direct factor Xa inhibitors, rivaroxaban and apixaban, were made available for patients with NVAF in September 2012 and January 2014, respectively. Given the initial lack of specific antidotes and of data on these drugs' efficacy and safety in real life, French Health Authorities recommended that VKAs remain the standard therapy. They also recommended that DOACs be offered as an alternative therapy only to patients with low adherence to VKAs or unstable INRs (International Normalised Ratios) on VKAs.[17] To date, it is not clear how the expectations of clinicians and the recommendations of health authorities have impacted the choice of anticoagulant for newly treated patients with NVAF. Nor is it clear how patients' characteristics have influenced treatment choice.

In view of the above, this study aimed to identify the initial oral anticoagulant therapy used in a cohort of patients newly diagnosed with NVAF for the prevention of stroke and systemic thromboembolism. It also sought to describe changes in the characteristics of patients who initiated treatment during the first five years of DOAC availability in France.

Method

Study design and source of data

The retrospective population-based cohort of patients with NVAF was formed from data provided by the French National Health Insurance System (NHIS). The NHIS guarantees universal health coverage to all segments of the population, and includes both a drug delivery database and a hospital discharge database. The NHIS comprises health insurance schemes for salaried workers, self-employed workers, agricultural workers and farmers, as well as 12 other insurance schemes. Together, these schemes provide health insurance to

approximately 63 million inhabitants, which corresponds to 93% of the French population. Detailed description of the NHIS database is provided elsewhere.[18,19]

In France, drugs are available only in pharmacies, and a medical prescription is required to obtain anticoagulant drugs. All reimbursement claims for prescriptions processed and filled in pharmacies are submitted to the NHIS via a single electronic system. This drug delivery database is linked to the hospital discharge database through a unique personal identifier allocated to every individual. The second database provides medical information on all patients discharged from hospitals, along with associated ICD-10 diagnosis codes (10th version of International Classification of Diseases). However, no clinical diagnosis is provided in this database for outpatient consultations with general practitioners and specialists.

Cohort definition

We defined a cohort of all patients 18 years and older who were newly treated for NVAF between January 1, 2011 and December 31, 2015. Cohort entry was defined by the delivery of anticoagulant therapy (VKA or DOAC) combined with an antiarrhythmic agent (flecainide, propafenone, amiodarone, quinidine, disopyramide or sotalol) or a rate control treatment (beta-blocker, calcium channel agonists or digoxin) within a time window of +/- 30 days. The date of cohort entry was the latest date of delivery of either drug, within the 30 day window. We excluded patients with less than 1 year of data available in the database before cohort entry, as well as patients who had received anticoagulant treatment or had a history of cardiac valvular replacement in the 12 months before inclusion. Lastly, we excluded patients who had undergone lower limb orthopedic surgery within 30 days of inclusion.

Exposure

We identified patients' exposure to initial anticoagulant treatment. We compared patients initiating VKA treatment—acenocoumarol, fluindione, warfarin (the 3 most commonly used VKAs in France), as well as phenindione and tioclomarol—to patients receiving any of the 3 DOACs available during the study period (dabigatran, rivaroxaban or apixaban).

Study covariates

The following characteristics of patients were identified in the year prior to cohort entry using treatment and/or hospital discharge code: high blood pressure, coronary artery disease (including myocardial infarction and ischemic heart disease), congestive heart failure, diabetes, a personal history of cancer, renal failure, liver failure, dementia, a history of bleeding, and history of ischemic stroke. Exposure to treatment other than anticoagulants—aspirin or other nonsteroidal anti-inflammatory drugs, antiplatelet agents (other than aspirin), corticosteroids—was identified in the 3 months prior to cohort entry. We also determined whether initial anticoagulant therapy was prescribed by a general practitioner, a cardiologist or a physician with another specialty. To estimate the risk of major bleeding, we calculated a modified HAS-BLED score (hypertension, abnormal renal and/or liver function, stroke/TIA, bleeding, labile international normalised ratio (INR), age >65, antiplatelet/NSAID use, or alcohol abuse).[20] Labile INR was not included in the score because it is both unavailable in the database and irrelevant for new DOAC users. Alcohol abuse was determined based on the hospital discharge database. To estimate the risk of stroke, we calculated the CHA2DS2-VASc2 score (congestive heart failure, hypertension, age ≥75, diabetes mellitus, stroke/transient ischemic attack, vascular disease, age 65–74, and sex).[21]

Data analysis

Descriptive statistics were computed for continuous data (mean, +/- standard deviation (sd) or median and range) and for categorical data (frequency and proportion). Trends in drugs use were described as the number of new patients treated each month and as the percentage of each anticoagulant prescribed at the time of treatment initiation.

Patients' characteristics were described according to initial anticoagulant therapy received. In bivariate comparisons, the characteristics of patients and prescribers were compared according to the type of anticoagulant, using a t-test for continuous variables, and a chi-square test for categorical variables. To identify independent predictors of initial anticoagulant choice, we performed a multivariate analysis using a logistic regression model stratified by calendar year of anticoagulant initiation. The model included all the variables that were associated with a p-value <0.20 in the bivariate comparisons. These variables were selected using a backward selection approach. Further, we defined 2 other cohorts for the sensitivity analyses: 1) one cohort was defined more restrictively: it included patients who were newly treated with an anticoagulant combined with an antiarrhythmic agent or a rate control treatment other than beta-blocker agents within a time window of +/- 30 days; 2) the other cohort was defined according to broader inclusion criteria: it comprised all patients newly treated with an anticoagulant, regardless of other potential concomitant therapies.

Statistical significance was set at 0.05. All p-values were two sided.

All statistical analyses were performed using SAS version 9.4 (SAS institute, Cary Inc).

Results

In France, 1,772,399 individuals were delivered a prescription for either a VKA or a DOAC between January 1, 2011 and December 31, 2015 (Figure 1). Out of this sample, we identified 872,970 individuals who received a new prescription for an anticoagulant (VKA or DOAC) combined with a prescription for an antiarrhythmic agent or a rate control treatment within a time window of +/- 30 days. Ultimately, the cohort comprised 814,446 patients newly treated for NVAF: 506,821 subjects initiated VKA, 94,468 dabigatran, 169,524 rivorixaban, and 43,633 apixaban.

Figure 2 illustrates the percentages of patients initiating one of the different anticoagulant treatments over the study period. A sharp rise in DOAC use was observed starting in mid-2012. As of October 2012, DOACs were used more frequently than VKAs as initial anticoagulant therapy, representing 54% of all anticoagulant prescriptions (30% for dabigatran and 24% for rivaroxaban). In the last quarter of 2015, this percentage reached 61% (4% for dabigatran, 34% for rivaroxaban, and 24% for apixaban). The proportion of patients initiating dabigatran began to decline 6 months after reimbursement was approved, and even more so after October 2013. Rivaroxaban use increased sharply as early as September 2012. This drug was the most frequently initiated DOAC in early 2013, and it remained so until December 2015, when it was surpassed by apixaban (26% vs 28% in December 2015).

The mean age of newly treated patients was 74.9 (sd: 11.7), and 50.2% of patients were male (table 1). Most subjects were treated for high blood pressure (94.4%), and 22.2% were treated for diabetes. Patients who received DOACs had less comorbidities and were on average younger than those who were prescribed VKAs (73.8 years (sd: 11.5) versus 75.6 years (sd: 11.9) $p<0.0001$). General practitioners prescribed VKAs (67.5%) more frequently

than DOACs (32.5%) as initial anticoagulant therapy, whereas cardiologist favored DOACs (51.2%). Patients receiving apixaban were older than those receiving other DOACs (76.2 vs. 72.9 for rivaroxaban and 74.1 for dabigatran). They also had more comorbidities, such as high blood pressure and heart or renal failure (table 2). Patients with lower HAS-BLED or lower CHA2DS2-VASc scores were more likely to initiate DOACs (figure 3).

The characteristics and associated treatments of DOAC initiators as compared with VKA initiators changed over the 5-year period (Figure 4 and 5). Older subjects (>= 75 years) were less likely to initiate DOAC treatment than VKA treatment. The adjusted OR decreased from 0.86 in 2011 (95% Confidence Interval (95%CI): 0.80 to 0.92) to 0.62 in 2014 (95%CI: 0.61 to 0.64). Overall, patients with comorbidities—especially renal failure—were less likely to receive DOAC treatment, and this negative association was reinforced over the study period (adjusted OR for 2014: 0.22; 95%CI: 0.21-0.23). The negative association was not reinforced in 2015, likely due the fact that a larger proportion of patients received apixaban. Patients with a history of bleeding prior to cohort entry were less likely to receive DOAC treatment (adjusted OR for 2015: 0.56; 95%CI: 0.53-0.59). Since 2012, cardiologists have been strongly associated with initial prescription of DOACs, after accounting the patients' characteristics.

The sensitivity analyses conducted for the 2 other cohorts provided similar results: a rapid increase in the use of DOAC over time, and a healthier profile of patients receiving DOACs compared with those receiving VKAs (supplementary material cohort 1 and cohort 2).

Discussion

Less than 6 months after reimbursement was approved, DOACs became the most frequently prescribed initial anticoagulant therapy for NVAF in France. Starting in the third quarter of 2012, DOACs were delivered to over 60% of all patients newly treated for NVAF. Dabigatran,

rivaroxaban and, in late 2015, apixaban were used one after the other as the most frequent initial DOAC therapy for NVAF. The proportion of dabigatran initiators declined largely after 2013. DOAC initiators were younger and healthier than VKA users, and this tendency was reinforced over time. The use of DOACs varied over time depending on the availability of new drugs and on the national recommendations and safety warnings in place.

National trends in anticoagulant sales volumes have also been reported in other countries, revealing an important upsurge in DOAC use.[22, 23] Most studies based on registries or cohorts of patients with NVAF have reported dabigatran use rates ranging from 5% to 25%, which is lower than what we found in our study.[24-27] However, in the US, Desai *et al*. have reported an increase in DOAC use for the 2010-2013 period which is similar to the one we observed, with a peak of 62% of patients initiating DOAC treatment among a cohort of anticoagulant initiators.[28] This convergence of results is surprising given the differences in populations, health systems, drug coverage, and, most importantly, clinical recommendations on the use of DOACs for the treatment of NVAF between countries. Thus, in France, health authorities do not recommend DOACs as initial anticoagulant therapy, unless the patient has poor adherence to VKAs or unless biological monitoring of VKA treatment is difficult.[17]

The sharp rise in DOAC use in France was observed as of mid-2012, shortly after the NHIS approved the reimbursement of dabigatran. Specifically, dabigatran was authorised as an anticoagulant for the treatment of NVAF in August 2011; reimbursement of treatment was pre-approved in February 2012, and it was fully approved in July 2012. Starting in November 2012, DOACs were used more frequently than VKAs as initial anticoagulant therapy. The reimbursement of rivaroxaban was fully approved in September 2012, and the drug was

used more frequently than dabigatran as initial anticoagulant therapy as of January 2013. This rapid uptake of DOACs in the drug market may be explained by the fact that alternatives to VKAs had long been expected. Indeed, a recent study indicates that DOACs were preferred to VKAs by more than a third of surveyed physicians.[29] The speed of adoption of DOACs is similar to that described for other new drugs, which usually reaches a plateau 6 to 12 months after they are launched.[30] This speed varies according to the specialty of the prescriber, and specialists are generally more prompt to adopt new drugs[30]—as was the case in our study. Nevertheless, some studies have reported no impact of physician specialty on the prescription of DOACs.[24,27] The differences we observed between the prescriptions of general practitioners (GP) and those of cardiologists may reflect the gap between national and European clinical guidelines. Indeed, French Health Authorities recommend VKAs as initial anticoagulant therapy, whereas the European Society of Cardiology favors DOACs.[3] GPs in the rest of Europe have taken a more cautious approach towards DOACs. This is especially the case in the treatment of elderly populations, most likely because there remains substantial uncertainty concerning the effectiveness and safety of DOACs in unselected elderly patients with NVAF.[31]

Our results indicate that the characteristics of patients who initiated treatment with DOACs rather than VKAs evolved over the first few years of drug commercialisation. In the first year, we observed a similar selection process as that described by Desai *et al.,* with healthier patients using DOACs more frequently than VKAs as initial therapy.[28] This tendency was reinforced as DOAC initiators became healthier over time. The prescription of DOACs to healthier patients is an issue that needs to be addressed, as these molecules may offer

higher-risk patients greater benefits than VKAs,[32] but also because their cost effectiveness depends on the severity of patients' condition.[33] Observational studies that aim to evaluate the risks and benefits associated with DOACs as well as cost effectiveness studies should carefully account for the fact that patients selected to initiate DOAC treatment are healthier overall, as well as for the selection of patients on the different types of DOACs.[34] Failure to do so may lead to underestimating the potential risks associated with DOACs in real life studies.

The fact that DOAC initiation is less frequent among patients with comorbidities may result from a warning issued by different health agencies in France.[35] This tendency seems to be linked to the diminishing use of dabigatran observed at the end of 2013, when the French medicine safety agency released warnings on bleeding risks associated with the drug.[36,37,38] At the time, French health authorities informed health professionals that DOACs are not recommended as initial therapy for NVAF, unless the patient has poor adherence to VKAs or unless biological monitoring of VKA treatment is difficult. However, while these recommendations were followed by a temporary decrease in DOAC use, a few months later DOACs were once again the most frequently prescribed anticoagulants for patients newly treated for NVAF.

Our study has several strengths. The source database covers 63 million inhabitants and over 93% of the French population, which means that our findings are independent of individual health coverage. Moreover, we had access to exhaustive information on anticoagulant delivery because these treatments are delivered on prescription alone. As a result, our study is the largest to report penetration of DOACs on the market (particularly in the case of

apixaban, which is the most recent DOAC available) and to describe variations in the characteristics of patients over time.

Nevertheless, some limitations must also be acknowledged. The NHIS administrative database does not include clinical or biological results; nor does it include outpatients' diagnosis codes. To capture outpatient diagnosis of AF, we based our definition of NVAF on drug dispensation, using the most likely treatment scheme for NVAF. Insofar as the results of our sensitivity analyses are consistent, we can be confident that our findings are not sensitive to the definition of NVAF. Moreover, 69% of patients who were hospitalised during follow-up had a diagnostic code of NVAF in the hospital discharge database (data not shown). Another limitation of our study is due to the 2015 data that may be partially incomplete. Indeed, for patients who do not have their NHIS card and attend a pharmacy that is not their regular pharmacy - a paper reimbursement form may be issued. The data are then recorded when the paper form is send to the NHIS and integrated later in the database. When the 2015 data were made available, paper claims were likely to have not all been included. However, this changes the total number of users but not the proportion of users of the different drugs.

The rapid and massive adoption of DOACs as initial therapy for NVAF could potentially challenge the French health care system because of the important increase in costs associated with these new drugs (in the US, these costs accounted for more than 90% of insurer spending on anticoagulants in 2014[28]) and because of the uncertainty concerning the cost-effectiveness of these drugs in real life. Future observational studies should carefully

account for the fact that patients selected to initiate DOAC treatment are healthier overall, and that this tendency is reinforced over the first few years of drug commercialization. Failure to do so may bias the risk-benefit assessment of DOACs.

Contributor ship statement

LH, XR, CF designed the study. All authors have contributed substantially to the interpretation of results. In addition: LH and AB drafted the article; - CF conducted the statistical analysis; CF, CR, SL, LB, SS, OM, XR 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

Pr. Suissa has participated in advisory board meetings and received research grants from Bayer, Boehringer Ingelheim, Bristol-Myers-Squibb and Novartis. These activities are conducted outside this submitted study.

All other co-authors have no conflict of interest.

Funding

This research was supported by a 2012 research grant from the Agence Nationale de Sécurité du Médicament (ANSM).

Data sharing statement

No additional data are available directly from the authors. The datasource of the study is the French National Health Insurance. Data ara available from the Caisse National de l'Assurance Maladie des Travailleurs Salariés (CNAMTS) for academic research.

Ethics approval

The study was approved by the French National Institute of Data, and by the National Commission for Data Protection and Liberties (CNIL-France: authorization number: 1637014).

Acknowledgements

We thank the Caisse National de l'Assurance Maladie des Travailleurs Salariés (CNAMTS) and the Institut des Données de Santé (IDS) for their assistance in obtaining the study database.

We personally thank Ms. Valérie EDEL from the IDS, as well as Mr. Laurent DUCHET and Mr. Medhi GABBAS from the department in charge of the SNIIRAM DATA at CNAM-TS.

We are indebted to Arianne Dorval for proofreading the English manuscript. C Renoux is the recipient of a Chercheur-Boursier Award from the Fonds de la recherche du Québec - santé (FRQ-S). S Suissa is the recipient of the James McGill Chair.

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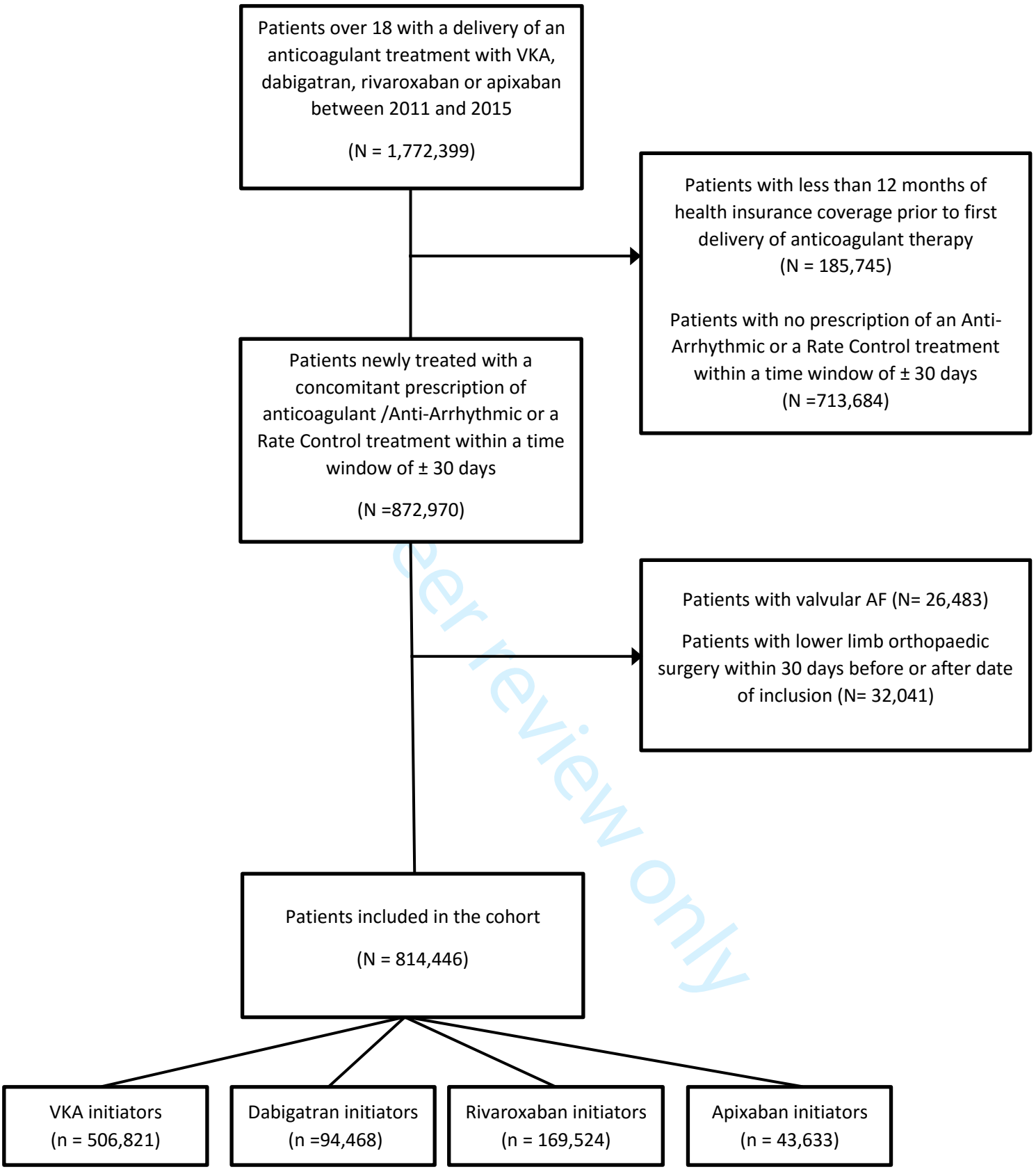

Figure 1 – Flow-chart describing cohort constitution

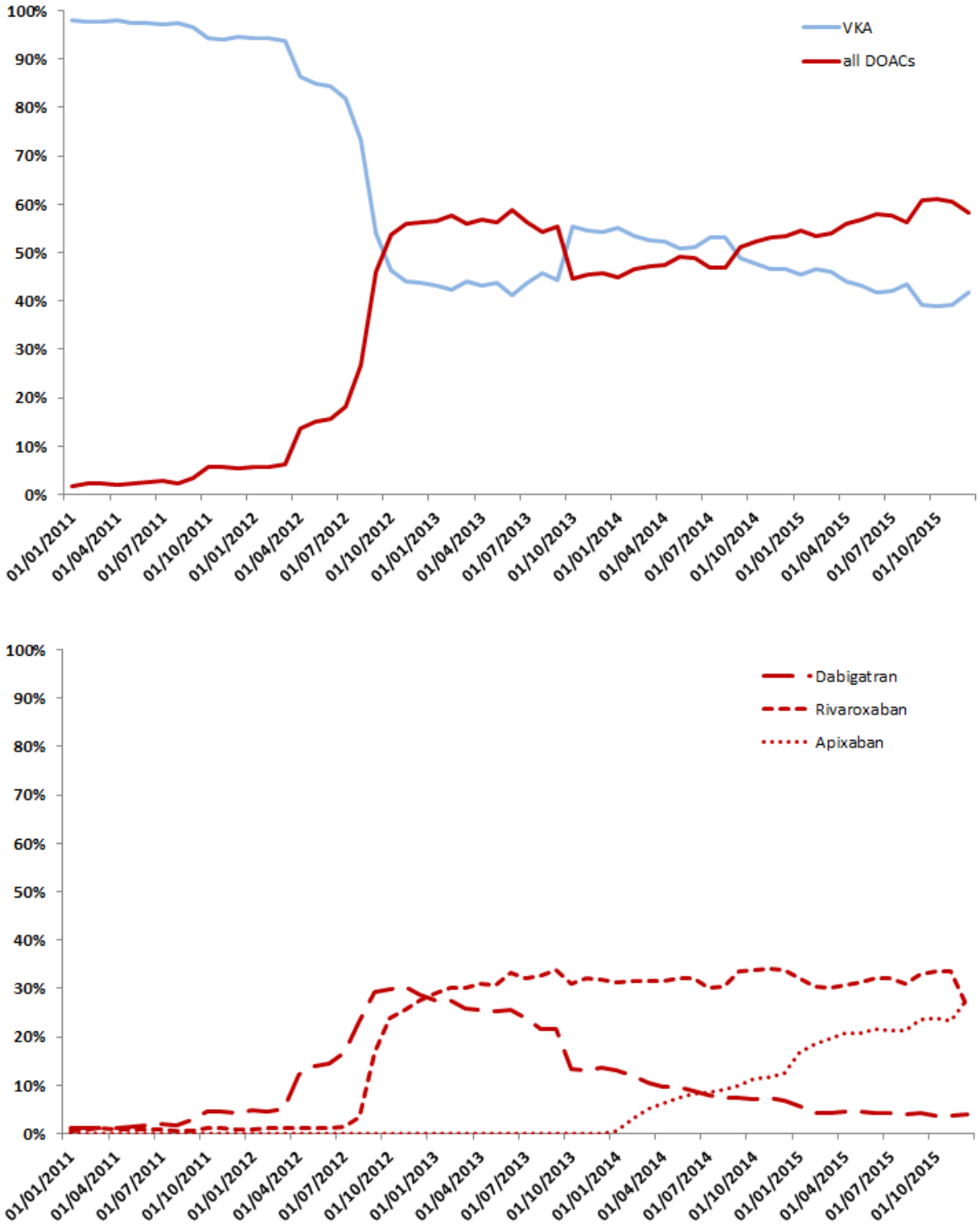

Figure 2 – Time trends in the prescription of anticoagulants in newly treated patients with Atrial Fibrilation between 2011 and 2015 in France (n = 814,446)

(VKA: vitamin K antagonist, DOAC: direct oral anticoagulant)

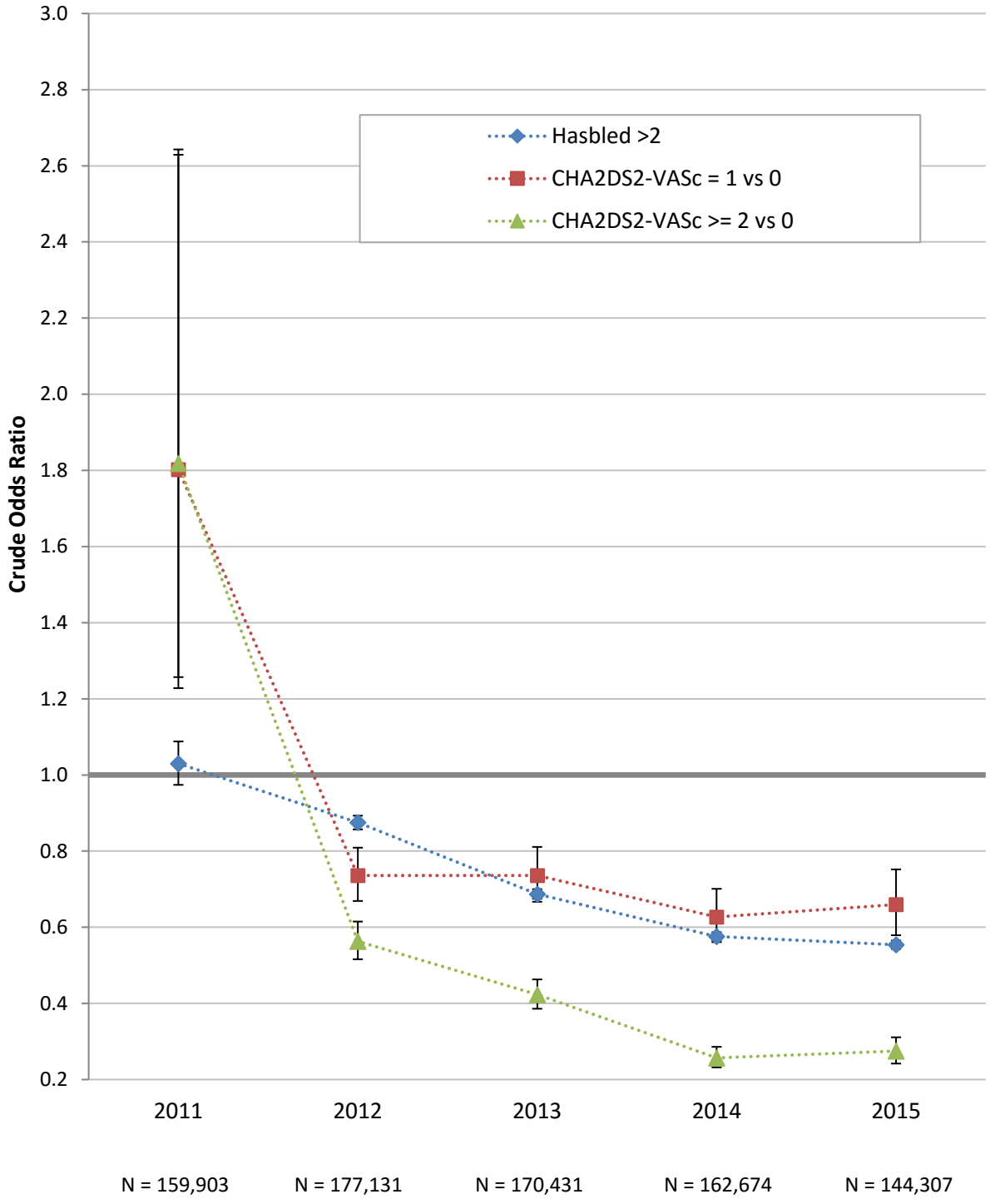

Figure 3 – HAS-BLED and CHA2DS2-VASc scores associated with DOAC vs VKA initiation according to year of therapy initiation. Crude Odds Ratio and 95% confidence interval

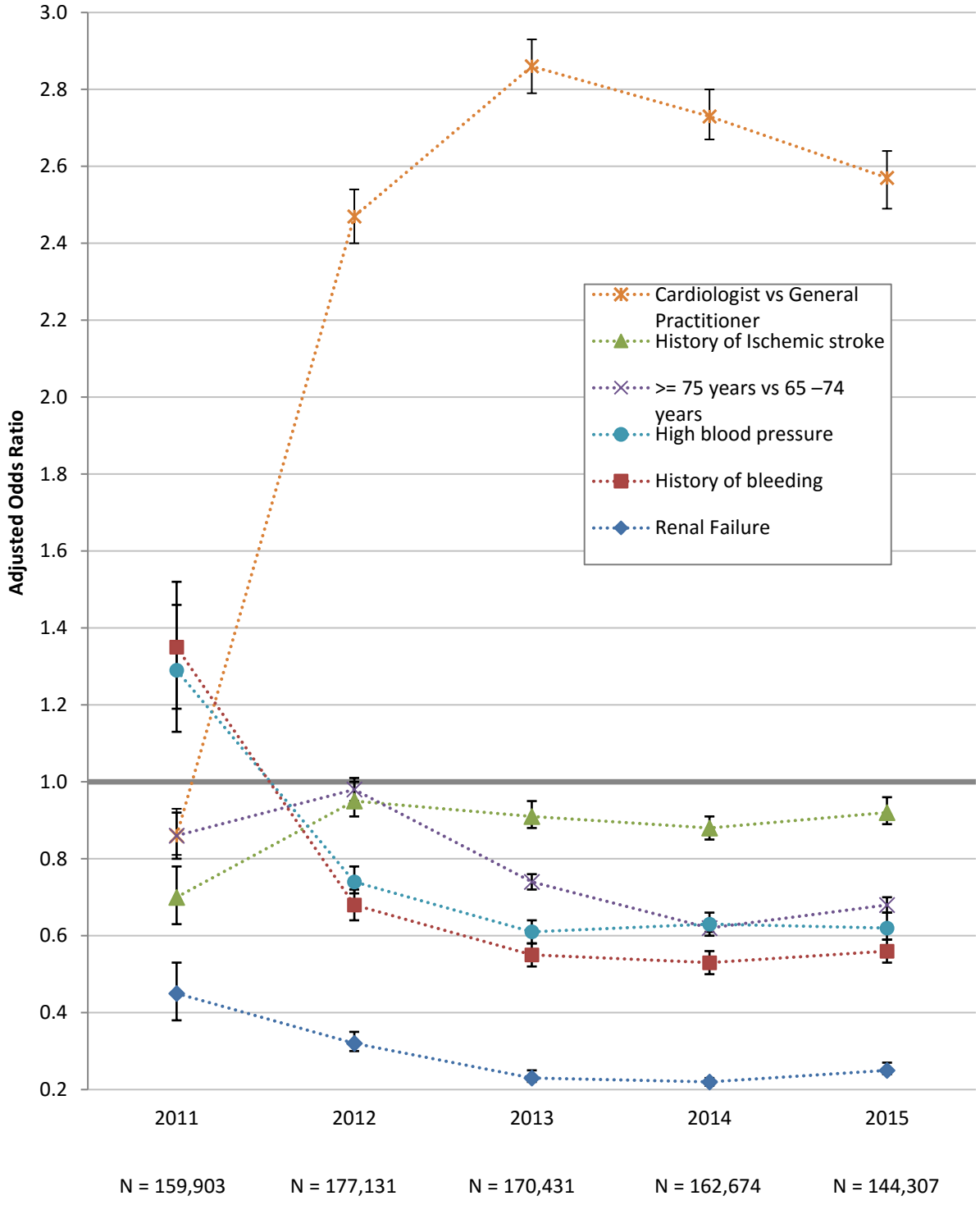

Figure 4 – Determinants associated with DOAC vs VKA initiation according to year of therapy initiation in the multivariate analyses. Adjusted OR and 95% confidence interval

Other variables in the logistic regression model: sex, ischemic heart disease, heart failure, diabetes, cancer, liver failure, dementia, treatment at cohort entry - Aspirin, NSAID, Antiplatelet agents and corticosteroids. (Results on figure 4 and 5 are issued from the same statistical model)

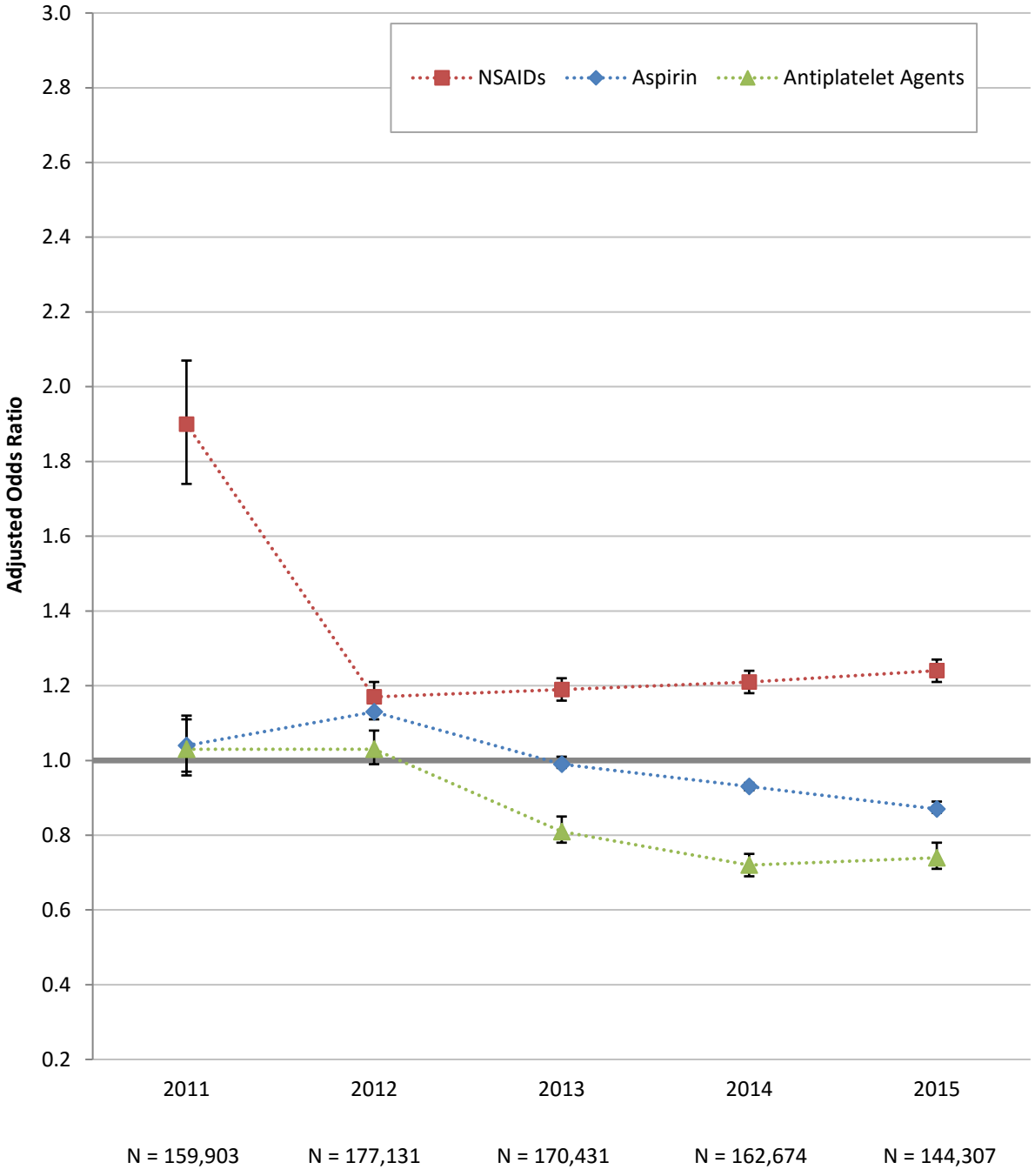

Figure 5 – Treatments at cohort entry associated with DOAC vs VKA initiation according to year of therapy initiation in the multivariate analyses. Adjusted OR and 95% confidence interval

Other variables in the logistic regression model: age, sex, blood pressure, ischemic heart disease, heart failure, diabetes, cancer, renal failure, liver failure, dementia, history of ischemic stroke, history of bleeding, medical specialty of first prescriber of anticoagulant. (Results on figure 4 and 5 are issued from the same statistical model)

Table 1 – Characteristics of Patients and Prescribers at Anticoagulant Treatment Initiation (2011-2015)

	VKA* N = 506,821	DOACs† N = 307,625
Demographic characteristics		
Mean age (sd‡)	75.6 (11.9)	73.8 (11.5)
Male	49.3%	51.7%
Clinical characteristics§		
High blood pressure	95.4%	92.7%
Ischemic heart disease	28.6%	18.1%
Heart failure	27.8%	17.2%
Diabetes	23.6%	19.6%
Cancer	16.5%	12.9%
Renal failure	10.9%	2.6%
Liver failure	1.7%	0.7%
Dementia	5.2%	3.0%
History Ischemic stroke	9.6%	7.1%
History of bleeding	6.3%	3.1%
HAS-BLED score, mean (sd)	2.7 (0.9)	2.4 (0.9)
CHA_2DS_2- $VASc_2$ score, mean (sd)	3.9 (1.5)	3.4 (1.4)
Other treatment at cohort entry‖		
Aspirin	45.8%	42.0%
Nonsteroidal anti-inflammatory drugs	13.7%	16.3%
Antiplatelet Agents (other than Aspirin)	15.8%	11.5%
Corticosteroids	14.0%	12.5%
Prescriber of first anticoagulant		
General Practitioner	64.4%	51.2%
Among General Practitioners	*67.5%*	*32.5%*
Cardiologist	22.2%	38.3%
Among Cardiologists	*48.8%*	*51.2%*
Other specialist	4.8%	4.6%
Unknown	8.6%	6.0%

* Vitamin K agonist; † Direct oral anticoagulants; ‡ sd: standard deviation; § defined in the 12 months prior to cohort entry; ‖ defined in the 3 months prior to cohort entry

Table 2 – Characteristics of Patients and Prescribers at Anticoagulant Treatment Initiation in the Sub-Group of Patients Receiving a Direct Oral Anticoagulant (2011-2015)

	Dabigatran N = 94,468	Rivaroxaban N = 169,524	Apixaban N = 43,633
Demographic characteristics			
Mean age (sd†)	74.1 (11.3)	73.0 (11.5)	76.2 (11.1)
Male	52.3%	52.0%	49.5%
Clinical characteristics‡			
High blood pressure	92.1%	92.5%	94.7%
Ischemic heart disease	19.7%	17.4%	17.6%
Heart failure	18.9%	15.2%	21.5%
Diabetes	19.9%	19.7%	20.8%
Cancer	14.0%	12.8%	11.1%
Renal failure	2.3%	2.4%	4.1%
Liver failure	0.7%	0.7%	0.6%
Dementia	3.1%	2.9%	3.3%
History of ischemic stroke	8.4%	6.0%	9.0%
History of bleeding	2.9%	3.1%	3.9%
HAS-BLED score, mean (sd)	2.4 (0.9)	2.4 (0.9)	2.5 (0.9)
CHA_2DS_2- $VASc_2$, mean (sd)	3.5 (1.5)	3.3 (1.4)	3.7 (1.4)
Other treatments at cohort entry§			
Aspirin	43.3%	40.9%	43.6%
Nonsteroidal anti-inflammatory drugs	16.6%	16.9%	13.0%
Antiplatelet Agents (other than Aspirin)	12.1%	10.9%	12.4%
Corticosteroids	12.2%	12.7%	12.1%
Prescriber of first anticoagulant			
General Practitioner	50.2%	51.9%	50.4%
Cardiologist	38.9%	38.0%	37.9%
Other specialist	4.4%	4.7%	4.6%
Unknown	6.5%	5.4%	7.1%

* *Direct oral anticoagulants*, † Standard deviation, ‡ defined in the 12 months prior to cohort entry, § defined in the 3 months prior to cohort entry

Supplemental material – Sensitivity analysis – Cohort 1 - patients newly treated with an anticoagulant combined with an antiarrhythmic agent or a rate control treatment excluding beta-blockers, within a time window of +/- 30 days

Table 1 – Characteristics of Patients and Prescribers at Anticoagulant Treatment Initiation (2011-2015)

	VKA* N = 289,430	DOACs† N = 199,016
Demographic characteristics		
Mean age (sd§)	76.1 (11.2)	73.7 (11.3)
Male	49.8%	52.5%
Clinical characteristics‖		
High blood pressure	91.9%	88.7%
Ischemic heart disease	26.3%	16.6%
Heart failure	34.4%	21.6%
Diabetes	21.9%	18.6%
Cancer	16.1%	13.0%
Renal failure	9.7%	2.4%
Liver failure	1.3%	0.7%
Dementia	4.6%	2.7%
History Ischemic stroke	8.5%	6.2%
History of bleeding	5.5%	2.9%
HAS-BLED score, mean (sd)	2.6 (0.9)	2.4 (0.9)
CHA_2DS_2- $VASc_2$ score, mean (sd)	3.9 (1.5)	3.4 (1.5)
Other treatment at cohort entry¶		
Aspirin	45.9%	42.2%
Nonsteroidal anti-inflammatory drugs	13.8%	15.9%
Antiplatelet Agents (other than Aspirin)	14.4%	10.9%
Corticosteroids	13.9%	12.8%
Prescriber of first anticoagulant		
General Practitioner	59.7%	46.7%
Among general practitioners	*65.0%*	*35.0%*
Cardiologist	27.7%	43.8%
Among cardiologists	*47.9%*	*52.1%*
Other specialist	4.2%	3.8%
Unknown	8.4%	5.6%

* Vitamin K agonist; † Direct oral anticoagulants; ‡, p value comparing VKA vs DOACs; § sd: standard deviation; ‖ defined in the 12 months prior to cohort entry; ¶ defined in the 3 months prior to cohort entry

Supplemental material – Sensitivity analysis – Cohort 1 - patients newly treated with an anticoagulant combined with an antiarrhythmic agent or a rate control treatment excluding beta-blockers, within a time window of +/- 30 days

Table 2 – Characteristics of Patients and Prescribers at Anticoagulant Treatment Initiation in the Sub-Group of Patients Receiving a Direct Oral Anticoagulant (2011-2015)

	Dabigatran N = 65,851	Rivaroxaban N = 104,936	Apixaban N = 28,229
Demographic characteristics			
Mean age (sd†)	73.7 (11.4)	73.0 (11.3)	76.0 (11.0)
Male	52.3%	53.4%	49.6%
Clinical characteristics‡			
High blood pressure	88.7%	87.8%	91.8%
Ischemic heart disease	17.9%	15.8%	17.0%
Heart failure	22.8%	19.9%	25.2%
Diabetes	18.6%	18.3%	20.0%
Cancer	14.0%	12.8%	11.3%
Renal failure	2.1%	2.2%	3.8%
Liver failure	0.7%	0.6%	0.6%
Dementia	2.8%	2.6%	2.9%
History of ischemic stroke	7.2%	5.4%	7.1%
History of bleeding	2.7%	2.7%	3.6%
HAS-BLED score, mean (sd)	2.4 (0.9)	2.3 (0.9)	2.5 (0.9)
CHA_2DS_2- $VASc_2$, mean (sd)	3.4 (1.5)	3.2 (1.5)	3.6 (1.4)
Other treatments at cohort entry§			
Aspirin	43.0%	41.4%	43.2%
Nonsteroidal anti-inflammatory drugs	16.6%	16.1%	13.2%
Antiplatelet Agents (other than Aspirin)	11.3%	10.4%	12.1%
Corticosteroids	12.8%	12.8%	12.6%
Prescriber of first anticoagulant			
General Practitioner	47.0%	46.3%	47.5%
Cardiologist	43.1%	44.9%	41.7%
Other specialist	3.7%	3.8%	4.1%
Unknown	6.2%	5.0%	6.7%

* *Direct oral anticoagulants*, † Standard deviation, ‡ defined in the 12 months prior to cohort entry, § defined in the 3 months prior to cohort entry

Supplemental material – Sensitivity analysis – Cohort 1 - patients newly treated with an anticoagulant combined with an antiarrhythmic agent or a rate control treatment excluding beta-blockers, within a time window of +/- 30 days

Table 3 – Multivariate analysis of the determinants associated with DOAC initiation according to year of therapy initiation

Characteristics at treatment initiation	2011 N = 101,817		2012 N = 110,571		2013 N = 103,594		2014 N = 94,180		2015 N = 78,284	
	Adjusted OR	**CI 95%***	**Adjusted OR**	**CI 95%**	**Adjusted OR**	**CI 95%**	**Adjusted OR**	**CI 95%**	**Adjusted OR**	**CI 95%**
Demographic characteristics										
Age										
< 65 years	0.89	0.78 – 1.01	0.93	0.88 – 0.97	1.02	0.98 – 1.06	1.15	1.10 – 1.21	1.08	1.03 – 1.14
65 –74 years	1.0		1.0		1.0		1.0		1.0	
>= 75 years	1.15	1.04 – 1.27	0.98	0.94 – 1.01	0.69	0.67 – 0.71	0.59	0.57 – 0.61	0.65	0.63 – 0.68
Sex (Male)	0.86	0.79 – 0.94	0.97	0.94 – 1.01	1.09	1.06 – 1.13	1.10	1.06 – 1.13	1.08	1.05 – 1.12
Clinical characteristics†										
High blood pressure	0.87	0.76 – 1.00	0.82	0.78 – 0.86	0.79	0.75 – 0.83	0.78	0.74 – 0.82	0.79	0.74 – 0.84
Ischemic heart disease	0.88	0.79 – 0.97	0.83	0.80 – 0.86	0.76	0.74 – 0.79	0.74	0.72 – 0.77	0.76	0.72 – 0.79
Heart failure	0.60	0.55 – 0.67	0.70	0.68 – 0.72	0.61	0.59 – 0.63	0.59	0.57 – 0.61	0.63	0.60 – 0.65
Diabetes	0.88	0.79 – 0.98	0.89	0.86 – 0.93	0.88	0.85 – 0.91	0.93	0.89 – 0.96	0.92	0.89 – 0.96
Cancer	0.98	0.88 – 1.10	0.96	0.92 – 1.00	0.85	0.81 – 0.88	0.85	0.81 – 0.88	0.84	0.80 – 0.89
Renal failure	0.50	0.39 – 0.63	0.34	0.31 – 0.36	0.23	0.22 – 0.25	0.22	0.20 – 0.23	0.24	0.23 – 0.26
Liver failure	0.59	0.33 – 1.05	0.74	0.63 – 0.88	0.59	0.52 – 0.68	0.58	0.50 – 0.66	0.49	0.41 – 0.58
Dementia	0.96	0.77 – 1.19	0.84	0.77 – 0.92	0.75	0.70 – 0.80	0.81	0.76 – 0.88	0.74	0.68 – 0.81
History of Ischemic Stroke	1.01	0.87 – 1.16	0.99	0.94 – 1.05	0.88	0.84 – 0.93	0.88	0.84 – 0.93	0.92	0.86 – 0.98
History of bleeding	1.28	1.06 – 1.55	0.70	0.64 – 0.76	0.52	0.48 – 0.55	0.52	0.49 – 0.56	0.57	0.53 – 0.61
Prescriber of first anticoagulant										
General Practitioner	1.0		1.0		1.0		1.0		1.0	
Cardiologist	1.30	1.19 – 1.42	2.33	2.25 – 2.41	2.63	2.55 – 2.71	2.57	2.49 – 2.65	2.46	2.37 – 0.56
Other specialists/Unknown	1.72	1.52 – 1.93	1.03	0.97 – 1.08	1.00	0.96 – 1.05	1.03	0.98 – 1.07	1.03	0.98 – 1.08
Other treatments at cohort entry‡										
Aspirin	1.28	1.18 – 1.42	1.16	1.12 – 1.19	0.98	0.85 – 1.00	0.93	0.90 – 0.95	0.87	0.84 – 0.90
NSAID	1.37	1.24 – 1.52	1.16	1.11 – 1.21	1.18	1.13 – 1.22	1.21	1.17 – 1.27	1.20	1.14 – 1.26
Antiplatelet Agents	1.30	1.15 – 1.46	1.06	1.01 – 1.11	0.85	0.82 – 0.89	0.73	0.70 – 0.76	0.78	0.74 – 0.82
Corticosteroids	0.90	0.79 – 1.02	0.96	0.92– 1.00	0.93	0.89 – 0.96	0.98	0.94 – 1.02	0.92	0.88 – 0.96
Time of anticoagulant intiation										
1st term of the year	1.0		1.0		1.0		1.0		1.0	
2nd term of the year	1.13	0.96 – 1.32	3.17	2.98 – 3.37	1.00	0.96 -1.04	1.08	1.04 – 1.13	1.11	1.06 – 1.15
3rd term of the year	2.05	1.77 – 2.37	9.37	8.84 – 9.94	0.93	0.89 – 0.96	1.09	1.05 – 1.14	1.17	1.11 – 1.22
4th term of the year	4.71	4.14 – 5.36	31.06	29.34 – 32.88	0.54	0.52 – 0.56	1.35	1.30 – 1.40	1.39	1.33 – 1.45

* 95% Confidence interval; † defined in the 12 months prior to cohort entry; ‡ defined in the 3 months prior to cohort entry

Supplemental material – Sensitivity analysis – Cohort 2 - Cohort all patients newly treated with an anticoagulant therapy regardless of other potential concomitant therapies

Table 1 – Characteristics of Patients and Prescribers at Anticoagulant Treatment Initiation (2011-2015).

	VKA* N = 952,565	DOACs† N = 661,089
Demographic characteristics		
Mean age (sd§)	71.7 (15.3)	69.5 (13.8)
Male	48.4%	49.2%
Clinical characteristics‖		
High blood pressure	78.5%	71.3%
Ischemic heart disease	21.0%	11.9%
Heart failure	18.6%	8.8%
Diabetes	19.9%	15.7%
Cancer	16.7%	11.6%
Renal failure	9.3%	1.9%
Liver failure	1.6%	0.6%
Dementia	5.5%	2.4%
History Ischemic stroke	8.6%	5.0%
History of bleeding	6.8%	3.6%
HAS-BLED score, mean (sd)	2.3 (1.1)	2.0 (1.1)
CHA_2DS_2- $VASc_2$ score, mean (sd)	3.3 (1.7)	2.8 (1.6)
Other treatment at cohort entry¶		
Aspirin	35.8%	28.9%
Nonsteroidal anti-inflammatory drugs	17.1%	28.4%
Antiplatelet Agents (other than Aspirin)	11.7%	7.4%
Corticosteroids	15.1%	12.7%
Prescriber of first anticoagulant		
General Practitioner	70.7%	54.1%
Among General Practitioners	*64.7%*	*35.3%*
Cardiologist	15.6%	21.7%
Among Cardiologists	*50.0%*	*50.0%*
Other specialist	5.8%	18.2%
Unknown	7.9%	6.0%

* Vitamin K agonist; † Direct oral anticoagulants; ‡, p value comparing VKA vs DOACs; § sd: standard deviation; ‖ defined in the 12 months prior to cohort entry; ¶ defined in the 3 months prior to cohort entry

Supplemental material – Sensitivity analysis – Cohort 2 - Cohort all patients newly treated with an anticoagulant therapy regardless of other potential concomitant therapies

Table 2 – Characteristics of Patients and Prescribers at Anticoagulant Treatment Initiation in the Sub-Group of Patients Receiving a Direct Oral Anticoagulant (2011-2015) AC

	Dabigatran N = 174,423	Rivaroxaban N = 419,780	Apixaban N = 66,886
Demographic characteristics			
Mean age (sd†)	71.5 (12.5)	67.8 (14.3)	74.5 (11.8)
Male	49.6%	49.0%	49.4%
Clinical characteristics‡			
High blood pressure	76.9%	66.9%	84.4%
Ischemic heart disease	14.8%	10.4%	14.0%
Heart failure	11.0%	6.9%	15.3%
Diabetes	16.9%	14.6%	18.8%
Cancer	12.7%	11.3%	10.8%
Renal failure	1.9%	1.7%	3.7%
Liver failure	0.6%	0.6%	0.6%
Dementia	2.6%	2.2%	3.1%
History of ischemic stroke	6.5%	3.9%	8.4%
History of bleeding	3.5%	3.6%	4.0%
HAS-BLED score, mean (sd)	2.2 (1.0)	1.9 (1.1)	2.4 (1.0)
CHA_2DS_2- $VASc_2$, mean (sd)	3.0 (1.6)	2.6 (1.6)	3.4 (1.5)
Other treatments at cohort entry§			
Aspirin	32.8%	25.9%	37.6%
Nonsteroidal anti-inflammatory drugs	28.3%	29.8%	19.4%
Antiplatelet Agents (other than Aspirin)	8.7%	6.4%	10.1%
Corticosteroids	11.9%	13.1%	11.7%
Prescriber of first anticoagulant			
General Practitioner	48.2%	56.9%	51.4%
Cardiologist	24.1%	19.6%	29.2%
Other specialist	20.9%	18.0%	12.0%
Unknown	6.8%	5.5%	7.4%

* *Direct oral anticoagulants*, † Standard deviation, ‡ defined in the 12 months prior to cohort entry, § defined in the 3 months prior to cohort entry

Supplemental material – Sensitivity analysis – Cohort 2 - Cohort all patients newly treated with an anticoagulant therapy regardless of other potential concomitant therapies

Table 3 – Multivariate analysis of the determinants associated with DOAC initiation according to year of therapy initiation.

Characteristics at treatment initiation	2011 N = 319*,372		2012 N = 353,242		2013 N = 327,150		2014 N = 311,352		2015 N =275,538	
	Adjusted OR	**CI 95%***	**Adjusted OR**	**CI 95%**	**Adjusted OR**	**CI 95%**	**Adjusted OR**	**CI 95%**	**Adjusted OR**	**CI 95%**
Demographic characteristics										
Age										
< 65 years	0.57	0.56 – 0.59	0.63	0.62 – 0.64	0.74	0.72 – 0.76	0.81	0.79 – 0.82	0.81	0.79 – 0.83
65 –74 years	1.0		1.0		1.0		1.0		1.0	
>= 75 years	0.56	0.55 – 0.58	0.76	0.75 – 0.78	0.69	0.68 – 0.70	0.59	0.58 – 0.60	0.66	0.65 – 0.67
Sex (Male)	0.86	0.84 – 0.88	0.98	0.96 – 0.99	1.09	1.07 – 1.11	1.08	1.06 – 1.09	1.06	1.04 – 1.08
Clinical characteristics†										
High blood pressure	0.76	0.74 – 0.78	0.90	0.88 – 0.92	0.95	0.93 – 0.97	0.89	0.87 – 0.91	0.87	0.85 – 0.89
Ischemic heart disease	0.78	0.76 – 0.81	0.81	0.79 – 0.83	0.76	0.75 – 0.78	0.74	0.72 – 0.76	0.77	0.75 – 0.80
Heart failure	0.15	0.14 – 0.16	0.56	0.54 – 0.57	0.63	0.62 – 0.64	0.58	0.56 – 0.59	0.64	0.63 – 0.66
Diabetes	0.89	0.86 – 0.92	0.90	0.88 – 0.92	0.89	0.87 – 0.91	0.89	0.87 – 0.91	0.91	0.89 – 0.93
Cancer	0.71	0.69 – 0.73	0.81	0.79 – 0.83	0.75	0.73 – 0.76	0.73	0.72 – 0.75	0.70	0.68 – 0.72
Renal failure	0.29	0.27 – 0.32	0.30	0.29 – 0.32	0.23	0.22 – 0.24	0.22	0.21 – 0.23	0.26	0.25 – 0.27
Liver failure	0.50	0.44 – 0.57	0.50	0.46 – 0.55	0.47	0.43 – 0.50	0.43	0.40 – 0.47	0.40	0.37 – 0.44
Dementia	0.29	0.26 – 0.31	0.56	0.54 – 0.59	0.61	0.59 – 0.63	0.60	0.58 – 0.63	0.63	0.60 – 0.66
History of Ischemic Stroke	0.24	0.22 – 0.26	0.66	0.64 – 0.68	0.76	0.74 – 0.78	0.74	0.72 – 0.76	0.81	0.78 – 0.84
History of bleeding	1.00	0.95 – 1.05	0.70	0.68 – 0.73	0.54	0.52 – 0.56	0.53	0.51 – 0.55	0.54	0.52 – 0.56
Prescriber of first anticoagulant										
General Practitioner	1.0		1.0		1.0		1.0		1.0	
Cardiologist	0.26	0.25 – 0.28	1.91	1.87 – 1.95	2.86	2.80 – 2.92	2.78	2.72 – 2.84	2.67	2.60 – 2.73
Other specialists/Unknown	7.01	6.85 – 7.18	3.76	3.69 – 3.84	1.83	1.79 – 1.87	1.79	1.75 – 1.82	1.55	1.51 – 1.58
Other treatments at cohort entry‡										
Aspirin	0.71	0.69 – 0.73	1.00	0.98 – 1.02	0.98	0.96 – 1.00	0.91	0.90 – 0.93	0.87	0.85 – 0.88
NSAID	2.77	2.71 – 2.83	1.93	1.90 – 1.97	1.57	1.54 – 1.60	1.56	1.53 – 1.59	1.57	1.53 – 1.60
Antiplatelet Agents	0.64	0.61 – 0.68	0.94	0.91 – 0.97	0.83	0.81 – 0.85	0.75	0.72 – 0.77	0.76	0.73 – 0.78
Corticosteroids	0.60	0.58 – 0.62	0.70	0.68 – 0.72	0.79	0.77 – 0.80	0.84	0.82 – 0.86	0.87	0.85 – 0.89
Time of anticoagulant intiation										
1st term of the year	1.0		1.0		1.0		1.0		1.0	
2nd term of the year	1.02	0.99 – 1.05	1.35	1.32 – 1.38	1.05	1.03 – 1.07	1.12	1.10 – 1.14	1.10	1.08 – 1.13
3rd term of the year	0.81	0.78 – 0.83	2.22	2.17 – 2.28	0.96	0.94 – 0.98	1.09	1.07 – 1.12	1.12	1.10 – 1.15
4th term of the year	1.32	1.29 – 1.37	5.92	5.79 – 6.05	0.69	0.68 – 0.70	1.38	1.35 – 1.41	1.31	1.28 – 1.34

* 95% Confidence interval; † defined in the 12 months prior to cohort entry; ‡ defined in the 3 months prior to cohort entry

STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5-6
Objectives	3	State specific objectives, including any pre-specified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7-8
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	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	8
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	*8*
Bias	9	Describe any efforts to address potential sources of bias	9
Study size	10	Explain how the study size was arrived at	Database study – NA
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9
		(*b*) Describe any methods used to examine subgroups and interactions	9
		(*c*) Explain how missing data were addressed	Administrative database study – no missing variable

		(*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	Only variable at cohort entry were used
		(*e*) Describe any sensitivity analyses	9
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	11
		(b) Give reasons for non-participation at each stage	11 and figure 1
		(c) Consider use of a flow diagram	Fig 1
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 – admin database study – no missing variables
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	Variables only at cohort entry
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
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	Figure 4-5
		(*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	Supplementary table
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	14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	15
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	14

		which the present article is based	

*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

Trends in initiation of direct oral anticoagulant therapies for atrial fibrillation in the French Health Insurance databases

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-018180.R1
Article Type:	Research
Date Submitted by the Author:	13-Oct-2017
Complete List of Authors:	Huiart, Laetitia; CIC 1410 Ferdynus, Cyril; CHU de la Réunion, Unité de Soutien Méthodologique; CHU Réunion, CIC INSERM 1410 Renoux, Christel; McGill University, Neurology & Neurosurgery Beaugrand, Amélie; Centre Hospitalier National d'Ophtalmologie des Quinze-Vingts Lafarge, Sophie; CHU Réunion, CIC INSERM 1410 Bruneau, Léa; CHU de la Réunion, Unité de Soutien Méthodologique Suissa, Samy; McGill University, Maillard, Olivier; CHU Réunion, CIC INSERM 1410 Ranouil, Xavier; CHU de la Réunion, Service de Cardiologie
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Cardiovascular medicine, Pharmacology and therapeutics, Public health
Keywords:	Cohort, Atrial Fibrilation, anticoagulants, Vitamine K antagonist, direct oral anti-coagulants

Trends in initiation of direct oral anticoagulant therapies for atrial fibrillation in the French Health Insurance databases

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Abstract (300 words)

Objective

Unlike several other national health agencies, French health authorities recommended that the newer direct oral anticoagulant (DOAC) agents only be prescribed as second choice for the treatment of newly diagnosed non-valvular atrial fibrillation (NVAF), with vitamin K antagonists (VKA) remaining the first choice. We investigated the patterns of use of DOACs versus VKA in the treatment of NVAF in France over the first five years of DOAC availability. We also identified the changes in patient characteristics of those who initiated DOAC treatment over this time period.

Methods

Based on the French National Health Administrative Database, we constituted a population-based cohort of all patients who were newly treated for NVAF between January 2011 and December 2015. Trends in drug use were described as the percentage of patients initiating each drug at the time of treatment initiation. A multivariate analysis using logistic regression model was performed to identify independent sociodemographic and clinical predictors of initial anticoagulant choice.

Results

The cohort comprised 814,446 patients who had received a new anticoagulant treatment for NVAF. The proportion of patients using DOACs as initial anticoagulant therapy reached 54% three months after the Health Ministry approved the reimbursement of dabigatran for NVAF, and 61% by the end of 2015, versus VKA use. In the multivariate analysis, we found that DOAC initiators were younger and healthier overall than VKA initiators, and this tendency was reinforced over the 2011-2014 period. DOACs were more frequently

prescribed by cardiologists in 2012 and after (adjusted-OR in 2012: 2.47; 95% Confidence Interval: 2.40-2.54).

Conclusion

Despite recommendations from health authorities, DOACs have been rapidly and massively adopted as initial therapy for NVAF in France. Observational studies should account for the fact that patients selected to initiate DOAC treatment are healthier overall, as failure to do so may bias the risk-benefit assessment of DOACs.

Keywords (6 max)

Cohort, atrial fibrillation, anticoagulants, vitamin K antagonist, direct oral anticoagulants

Tables: 2

Figures: 3

Supplementary material: 6 tables

Strength and limitations:

- With a source database covering 66 million inhabitants and exhaustive information on anticoagulant deliveries in France, our study is the largest to report penetration of DOACs on the market. This is particularly the case for apixaban, which was the most recent DOAC available at the time of the study
- The administrative database used does not include clinical results; nor does it include outpatients' diagnosis codes. To account for outpatients, we based our definition of NVAF on drug dispensation, using the most likely treatment scheme for NVAF. We conducted sensitivity analyses to ensure that our results are consistent.

Introduction

Non-Valvular Atrial fibrillation (NVAF) is the most common sustained cardiac arrhythmia, and its age-adjusted prevalence has been increasing over time.[1,2] NVAF is associated with high morbidity and mortality, as it increases the risks of stroke and systemic thromboembolic events.[2] In light of this, the use of an oral anticoagulant is recommended in patients with NVAF at medium or high risk of stroke.[3-7] For more than 50 years, vitamin K antagonists (VKA) such as warfarin were the only effective therapy available for stroke prevention in patients with NVAF.[8] However, the efficacy and safety of VKAs are closely related to the quality of anticoagulation, which is open to substantial inter- and intra-patient variability and requires close biological monitoring.[9, 8,10]

In order to respond to physicians' and patients' expectations of more user-friendly drugs, research on new drugs has intensified over the last few years. This has prompted the development of direct oral anticoagulants (DOAC) that inhibit thrombin or factor Xa. Large randomised clinical trials (RCTs) have compared the efficacy of DOACs to that of warfarin in patients with NVAF.[11 ,12,13] A recent meta-analysis of these RCTs has shown that the frequency of strokes and/or systemic embolic events is 19% lower with DOACs than it is with warfarin. Moreover, compared with warfarin, DOACs have been shown to present similar risks of major bleeding but higher risks of gastrointestinal bleeding.[14] The benefit-risk ratio of DOACs nevertheless varies across individual agents, and also according to patient profile.[15,16]

In France, the direct thrombin inhibitor dabigatran was the first DOAC to be approved for the primary prevention of venous thromboembolism in orthopedic surgery (in 2008) and stroke in NVAF (in 2011). Reimbursement of dabigatran for the treatment of NVAF was

approved in July 2012. Two new oral direct factor Xa inhibitors, rivaroxaban and apixaban, were made available for patients with NVAF in September 2012 and January 2014, respectively. Given the initial lack of specific antidotes and of data on these drugs' efficacy and safety in real life, French Health Authorities recommended that VKAs remain the standard therapy. They also recommended that DOACs be offered as an alternative therapy only to patients with low adherence to VKAs or unstable INRs (International Normalised Ratios) on VKAs.[17] To date, it is not clear how the expectations of clinicians and the recommendations of health authorities have impacted the choice of anticoagulant for newly treated patients with NVAF. Nor is it clear how patients' characteristics have influenced treatment choice.

In view of the above, we conducted a study in the French National health administrative database. This study based on claims data, aimed to identify the initial oral anticoagulant therapy used in a cohort of patients newly diagnosed with NVAF for the prevention of stroke and systemic thromboembolism. It also sought to describe changes in the characteristics of patients who initiated treatment during the first five years of DOAC availability in France.

Method

Study design and source of data

The retrospective population-based cohort of patients with NVAF was formed from data provided by the French National Health Insurance System (NHIS).[18] The NHIS guarantees universal health coverage to all segments of the population, and includes both a drug delivery database and a hospital discharge database. The NHIS comprises health insurance schemes for salaried workers, self-employed workers, agricultural workers and farmers, as

well as 12 other insurance schemes. Together, these schemes provide health insurance to approximately 66 million inhabitants, which corresponds to approximately 99% of the French population.[19] Detailed description of the NHIS database is provided elsewhere.[20,21]

In France, drugs are available only in pharmacies, and a medical prescription is required to obtain anticoagulant drugs. All reimbursement claims for prescriptions processed and filled in pharmacies are submitted to the NHIS via a single electronic system. This drug delivery database is linked to the hospital discharge database through a unique personal identifier allocated to every individual. The second database provides medical information on all patients discharged from hospitals, along with associated ICD-10 diagnosis codes (10th version of International Classification of Diseases). However, no clinical diagnosis is provided in this database for consultations by health professionals in an ambulatory care setting.

Cohort definition

We defined a cohort of all patients 18 years and older who were newly treated for NVAF between January 1, 2011 and December 31, 2015. Cohort entry was defined by the delivery of anticoagulant therapy (VKA or DOAC) combined with either an antiarrhythmic agent (flecainide, propafenone, amiodarone, quinidine, disopyramide or sotalol) or a rate control treatment (beta-blocker, calcium channel blockers - verapamil and diltiazem -, or digoxin) within a time window of +/- 30 days. The date of cohort entry was the latest date of delivery of either drug, within the 30 day window. We excluded patients with less than 1 year of data available in the database before cohort entry, as well as patients who had received anticoagulant treatment or had a history of cardiac valvular replacement in the 12 months before inclusion. Therefore, the anticoagulant therapy received at cohort inclusion

corresponded to a new anticoagulant therapy. Lastly, we excluded patients who had undergone lower limb orthopedic surgery within +/- 30 days of inclusion.

Exposure

We identified patients' exposure to initial anticoagulant treatment. We compared patients initiating VKA treatment—acenocoumarol, fluindione, warfarin (the 3 most commonly used VKAs in France)—to patients receiving any of the 3 DOACs available during the study period (dabigatran, rivaroxaban or apixaban).

Study covariates

The following characteristics of patients were identified in the year prior to cohort entry using treatment and/or hospital discharge code (supplementary table): high blood pressure, coronary artery disease (including myocardial infarction and ischemic heart disease), congestive heart failure, diabetes, a personal history of cancer, renal failure, liver failure, dementia, a history of bleeding, and history of ischemic stroke. Exposure to treatment other than anticoagulants—aspirin or other nonsteroidal anti-inflammatory drugs, antiplatelet agents (other than aspirin), corticosteroids—was identified in the 3 months prior to cohort entry. We also determined whether initial anticoagulant therapy was prescribed by a general practitioner, a cardiologist or a physician with another specialty. To estimate the risk of major bleeding, we calculated a modified HAS-BLED score (hypertension, abnormal renal and/or liver function, stroke/TIA, bleeding, labile international normalised ratio (INR), age >65, antiplatelet/NSAID use, or alcohol abuse).[22] Labile INR was not included in the score because it is unavailable in the database. Alcohol abuse was determined based on the hospital discharge database. To estimate the risk of stroke, we calculated the CHA2DS2-

VASc2 score (congestive heart failure, hypertension, age ≥75, diabetes mellitus, stroke/transient ischemic attack, vascular disease, age 65–74, and sex).[23]

Data analysis

Descriptive statistics were computed for continuous data (mean, +/- standard deviation (SD) or median and range) and for categorical data (frequency and proportion). Trends in drugs use were described as the number of new patients treated each month and as the percentage of each anticoagulant prescribed at the time of treatment initiation.

Patients' characteristics were described according to initial anticoagulant therapy received. In bivariate comparisons, the characteristics of patients and prescribers were compared according to the type of anticoagulant, using a t-test for continuous variables, and a chi-square test for categorical variables. To identify independent predictors of initial anticoagulant choice, we performed a multivariate analysis using 5 logistic regression models, one for each calendar year of anticoagulant initiation. The model included all the variables that were associated with a p-value <0.20 in the bivariate comparisons. These variables were selected using a backward selection approach. Further, we defined 2 other cohorts for the sensitivity analyses: 1) one cohort was defined more restrictively: it included patients who were newly treated with an anticoagulant combined with an antiarrhythmic agent or a rate control treatment other than beta-blocker agents within a time window of +/- 30 days; 2) the other cohort was defined according to broader inclusion criteria: it comprised all patients newly treated with an anticoagulant, regardless of other potential concomitant therapies.

To assess the impact of timeline events on the uptake process (i.e. market authorization of each drug, reimbursement approval/downgrade and security warnings from national health

agency), we fitted a segmented regression model, adjusted on: 1) drug coded into four categories (VKA, dabigatran, rivaroxaban and apixaban), 2) time (linear and square terms) and 3) each timeline event. A timeline event was coded as a dichotomous variable valued 0 before the event and 1 after. All these covariates were included in a primary model, then a backward selection procedure was applied to select covariates associated at a significant level ($p < 0.05$). To evaluate the trends and the impact of timeline events on each drug, we entered an interaction term for each drug and other covariates (time and timeline events).

Statistical significance was set at 0.05. All p-values were two sided.

All statistical analyses were performed using SAS version 9.4 (SAS institute, Cary Inc).

Results

In France, 1,772,399 individuals were delivered a prescription for either a VKA or a DOAC between January 1, 2011 and December 31, 2015 (Figure 1). Out of this sample, we identified 872,970 individuals who received a new prescription for an anticoagulant (VKA or DOAC) combined with a prescription for an antiarrhythmic agent or a rate control treatment within a time window of +/- 30 days. Ultimately, the cohort comprised 814,446 patients newly treated for NVAF: 506,821 subjects initiated VKA, 94,468 dabigatran, 169,524 rivaroxaban, and 43,633 apixaban.

Figure 2 illustrates the percentages of patients initiating one of the different anticoagulant treatments over the study period. A sharp rise in DOAC use was observed starting in mid-2012. As of October 2012, DOACs were used more frequently than VKAs as initial anticoagulant therapy, representing 54% of all anticoagulant prescriptions (30% for dabigatran and 24% for rivaroxaban). In the last quarter of 2015, this percentage reached

61% (4% for dabigatran, 34% for rivaroxaban, and 24% for apixaban). The proportion of patients initiating dabigatran began to decline 6 months after reimbursement was approved, and even more so after October 2013. Rivaroxaban use increased sharply as early as September 2012. This drug was the most frequently initiated DOAC in early 2013, and it remained so until December 2015, when it was surpassed by apixaban (26% vs 28% in December 2015).

Figure 2 illustrates the percentages of patients initiating one of the different anticoagulant treatments over the study period. The segmented regression model identified 5 significant changepoints. The two first changepoints (line a and b in figure 2) corresponded to a sharp rise in DOAC initiation in July 2012 and in September 2012, corresponding respectively to dabigatran and rivaroxaban reimbursement approval time. As of October 2012, DOACs were used more frequently than VKAs as initial anticoagulant therapy, representing 54% of all anticoagulant prescriptions (30% for dabigatran and 24% for rivaroxaban). The third changepoint identified was in September 2013 (ligne d, Figure 2) with a significant decrease in the use of DOACs at the time security warnings were issued by the French health authorities. From January 2014 (4th change point – line c on figure 2), DOACs initiation increased again, corresponding to the time point where apixaban received reimbursement approval. A final significant changepoint (line e) was identified in September 2015 and was linked to a reduction in dabigatran reimbursement. In December 2015, apixaban was the most prescribed DOAC (28% versus 26% for rivaroxaban).

The mean age of newly treated patients was 74.9 (SD: 11.7), and 50.2% of patients were male (table 1). Most subjects were treated for high blood pressure (94.4%), and 22.2% were

treated for diabetes. Patients who received DOACs had less comorbidities and were on average younger than those who were prescribed VKAs (73.8 years (SD: 11.5) versus 75.6 years (SD: 11.9) p<0.0001). General practitioners prescribed VKAs (67.5%) more frequently than DOACs (32.5%) as initial anticoagulant therapy, whereas cardiologist favored DOACs (51.2%). Patients receiving apixaban were older than those receiving other DOACs (76.2 vs. 72.9 for rivaroxaban and 74.1 for dabigatran). They also had more comorbidities, such as high blood pressure and heart or renal failure (table 1). Patients with lower HAS-BLED or lower CHA2DS2-VASc scores were more likely to initiate DOACs (figure 3).

The characteristics and associated treatments of DOAC initiators as compared with VKA initiators changed over the 5-year period (table 2). Older subjects (>= 75 years) were less likely to initiate DOAC treatment than VKA treatment. The adjusted OR decreased from 0.86 in 2011 (95% Confidence Interval (95%CI): 0.80 to 0.92) to 0.62 in 2014 (95%CI: 0.61 to 0.64). Overall, patients with comorbidities—especially renal failure—were less likely to receive DOAC treatment, and this negative association was reinforced over the study period (adjusted OR for 2014: 0.22; 95%CI: 0.21-0.23). The negative association was not reinforced in 2015, likely due the fact that a larger proportion of patients received apixaban. However, because apixaban was only available at the end of the study period, further data are needed to confirm this hypothesis. Patients with a history of bleeding prior to cohort entry were less likely to receive DOAC treatment (adjusted OR for 2015: 0.56; 95%CI: 0.53-0.59). Since 2012, cardiologists have been strongly associated with initial prescription of DOACs, after accounting the patients' characteristics.

The sensitivity analyses conducted for the 2 other cohorts provided similar results: a rapid increase in the use of DOAC over time, and a healthier profile of patients receiving DOACs compared with those receiving VKAs (supplementary material cohort 1 and cohort 2).

Table 1 – Characteristics of Patients and Prescribers at Anticoagulant Treatment Initiation (2011-2015)

	VKA* N = 506,821	Dabigatran N = 94,468	Rivaroxaban N = 169,524	Apixaban N = 43,633
Demographic characteristics				
Mean age (sd†)	75.6 (11.9)	74.1 (11.3)	73.0 (11.5)	76.2 (11.1)
Male	49.3%	52.3%	52.0%	49.5%
Clinical characteristics‡				
High blood pressure	95.4%	92.1%	92.5%	94.7%
Ischemic heart disease	28.6%	19.7%	17.4%	17.6%
Heart failure	27.8%	18.9%	15.2%	21.5%
Diabetes	23.6%	19.9%	19.7%	20.8%
Cancer	16.5%	14.0%	12.8%	11.1%
Renal failure	10.9%	2.3%	2.4%	4.1%
Liver failure	1.7%	0.7%	0.7%	0.6%
Dementia	5.2%	3.1%	2.9%	3.3%
History of ischemic stroke	9.6%	8.4%	6.0%	9.0%
History of bleeding	6.3%	2.9%	3.1%	3.9%
HAS-BLED score, mean (sd)	2.7 (0.9)	2.4 (0.9)	2.4 (0.9)	2.5 (0.9)
CHA_2DS_2- $VASc_2$, mean (sd)	3.9 (1.5)	3.5 (1.5)	3.3 (1.4)	3.7 (1.4)
Other treatments at cohort entry§				
Aspirin	45.8%	43.3%	40.9%	43.6%
Nonsteroidal anti-inflammatory drugs	13.7%	16.6%	16.9%	13.0%
Antiplatelet Agents (other than Aspirin)	15.8%	12.1%	10.9%	12.4%
Corticosteroids	14.0%	12.2%	12.7%	12.1%
Prescriber of first anticoagulant				
General Practitioner	64.4%	50.2%	51.9%	50.4%
Cardiologist	22.2%	38.9%	38.0%	37.9%
Other specialist	4.8%	4.4%	4.7%	4.6%
Unknown	8.6%	6.5%	5.4%	7.1%

* Vitamin K agonist; † Direct oral anticoagulants; ‡ sd: standard deviation; § defined in the 12 months prior to cohort entry; ‖ defined in the 3 months prior to cohort entry

Table 2 – Multivariate analysis of the determinants associated with DOAC initiation according to year of therapy initiation.

Characteristics at treatment initiation	2011 N = 159,903		2012 N = 177,131		2013 N = 170,431		2014 N = 162,674		2015 N = 144,307	
	Adjusted OR	CI 95%*	Adjusted OR	CI 95%	Adjusted OR	CI 95%	Adjusted OR	CI 95%	Adjusted OR	CI 95%
Demographic characteristics										
Age										
< 65 years	0.88	0.81 – 0.96	0.82	0.79 – 0.86	0.87	0.84 – 0.90	0.99	0.95 – 1.02	0.94	0.91 – 0.98
65 –74 years	1.0		1.0		1.0		1.0		1.0	
>= 75 years	0.86	0.80 – 0.92	0.98	0.95 – 1.01	0.74	0.72 – 0.76	0.62	0.61 – 0.64	0.68	0.66 – 0.70
Sex (Male)	0.73	0.69 – 0.77	1.01	0.99 – 1.04	1.15	1.12 – 1.17	1.13	1.11 – 1.16	1.11	1.08 – 1.13
Clinical characteristics†										
High blood pressure	1.29	1.13 – 1.46	0.74	0.71 – 0.78	0.61	0.58 – 0.64	0.63	0.60 – 0.66	0.62	0.59 – 0.66
Ischemic heart disease	0.89	0.84 – 0.96	0.80	0.78 – 0.83	0.74	0.72 – 0.76	0.70	0.69 – 0.72	0.75	0.73 – 0.77
Heart failure	0.43	0.40 – 0.47	0.73	0.71 – 0.76	0.68	0.66 – 0.69	0.64	0.62 – 0.65	0.69	0.66 – 0.70
Diabetes	0.89	0.83 – 0.96	0.91	0.88 – 0.94	0.89	0.86 – 0.91	0.90	0.88 – 0.92	0.91	0.89 – 0.94
Cancer	0.93	0.86 – 1.01	0.92	0.89 – 0.95	0.82	0.80 – 0.85	0.81	0.79 – 0.83	0.80	0.77 – 0.83
Renal failure	0.45	0.38 – 0.53	0.32	0.30 – 0.35	0.23	0.22 – 0.25	0.22	0.21 – 0.23	0.25	0.24 – 0.27
Liver failure	0.58	0.41 – 0.80	0.58	0.51 – 0.66	0.48	0.44 – 0.53	0.41	0.38 – 0.46	0.40	0.35 – 0.44
Dementia	0.72	0.61 – 0.85	0.79	0.74 – 0.84	0.73	0.69 – 0.77	0.74	0.70 – 0.78	0.72	0.68 – 0.76
History of Ischemic Stroke	0.70	0.63 – 0.78	0.95	0.91– 1.00	0.91	0.88 – 0.95	0.88	0.85 – 0.91	0.92	0.89 – 0.96
History of bleeding	1.35	1.19 – 1.52	0.68	0.64 – 0.72	0.55	0.52 – 0.58	0.53	0.50 – 0.56	0.56	0.53 – 0.59
Prescriber of first anticoagulant										
General Practitioner	1.0		1.0		1.0		1.0		1.0	
Cardiologist	0.86	0.81 – 0.93	2.47	2.40 – 2.54	2.86	2.79 – 2.93	2.73	2.67 – 2.80	2.57	2.49 – 2.64
Other specialists/Unknown	2.53	2.36 – 2.71	1.15	1.10 – 1.19	1.00	0.96 – 1.03	1.04	1.00 – 1.07	1.03	0.99 – 1.06
Other treatments at cohort entry‡										
Aspirin	1.04	0.98 – 1.10	1.13	1.10 – 1.16	0.99	0.97 – 1.01	0.93	0.91 – 0.95	0.87	0.85 – 0.89
NSAID	1.90	1.78 – 2.02	1.17	1.13 – 1.21	1.19	1.16 – 1.22	1.21	1.18 – 1.25	1.24	1.20 – 1.28
Antiplatelet Agents	1.03	0.94 – 1.12	1.03	0.99 – 1.07	0.81	0.79 – 0.84	0.72	0.70 – 0.75	0.74	0.71 – 0.77
Corticosteroids	0.76	0.69 – 0.83	0.87	0.84 – 0.94	0.89	0.86 – 0.91	0.93	0.90 – 0.96	0.93	0.90 – 0.96
Time of anticoagulant intiation										
1st term of the year	1.0		1.0		1.0		1.0		1.0	
2nd term of the year	1.12	1.02 – 1.23	2.85	2.72 – 2.99	1.01	0.98 – 1.04	1.10	1.07 – 1.14	1.13	1.09 – 1.16
3rd term of the year	1.40	1.28 – 1.53	7.53	7.19– 7.88	0.94	0.91 – 0.97	1.13	1.09 – 1.16	1.19	1.15 – 1.23
4th term of the year	2.75	2.53 – 2.94	22.52	21.55 – 23.54	0.58	0.56 – 0.59	1.38	1.34 – 1.42	1.40	1.36 – 1.44

* 95% Confidence interval; † defined in the 12 months prior to cohort entry; ‡ defined in the 3 months prior to cohort entry

Discussion

Less than 6 months after reimbursement was approved, DOACs became the most frequently prescribed initial anticoagulant therapy for NVAF in France. Starting in the third quarter of 2012, DOACs were delivered to over 60% of all patients newly treated for NVAF. Dabigatran, rivaroxaban and, in late 2015, apixaban were used one after the other as the most frequent initial DOAC therapy for NVAF. The proportion of dabigatran initiators declined largely after 2013. DOAC initiators were younger and healthier than VKA users, and this tendency was reinforced over time. The use of DOACs varied over time depending on the availability of new drugs and on the national recommendations and safety warnings in place.

National trends in anticoagulant sales volumes have also been reported in other countries, revealing an important upsurge in DOAC use.[24-26] Most studies based on registries or cohorts of patients with NVAF have reported dabigatran use rates ranging from 5% to 25%, which is lower than what we found in our study.[27-30] However, in the US, Desai *et al*. have reported an increase in DOAC use for the 2010-2013 period which is similar to the one we observed, with a peak of 62% of patients initiating DOAC treatment among a cohort of anticoagulant initiators.[31] These common trends in results observed are surprising given the differences in populations, health systems, drug coverage, and, most importantly, clinical recommendations on the use of DOACs for the treatment of NVAF between countries. Indeed, in France, health authorities do not recommend DOACs as initial anticoagulant therapy, unless the patient has poor adherence to VKAs or unless biological monitoring of VKA treatment is difficult.[17] However, physicians are still free to opt for any of the available treatment and their personal beliefs on efficacy and safety influences their choices.

The sharp rise in DOAC use in France was observed as of mid-2012, shortly after the NHIS approved the reimbursement of dabigatran. Specifically, dabigatran was authorised as an anticoagulant for the treatment of NVAF in August 2011; reimbursement of treatment was pre-approved in February 2012, and it was fully approved in July 2012. Starting in November 2012, DOACs were used more frequently than VKAs as initial anticoagulant therapy. The reimbursement of rivaroxaban was fully approved in September 2012, and the drug was used more frequently than dabigatran as initial anticoagulant therapy as of January 2013. This rapid uptake of DOACs in the drug market may be explained by the fact that alternatives to VKAs had long been expected. Indeed, a recent study indicates that DOACs were considered equal or preferred to VKAs by respectively 48.5% and 33.3% of surveyed physicians.[32] The speed of adoption of DOACs is similar to that described for other new drugs, which usually reaches a plateau 6 to 12 months after they are launched.[33] This speed varies according to the specialty of the prescriber, and specialists are generally more prompt to adopt new drugs[33]—as was the case in our study. Nevertheless, some studies have reported no impact of physician specialty on the prescription of DOACs.[27,30] The differences we observed between the prescriptions of general practitioners (GP) and those of cardiologists may reflect the gap between national and European clinical guidelines. Indeed, French Health Authorities recommend VKAs as initial anticoagulant therapy, whereas the European Society of Cardiology favors DOACs.[3] GPs in the rest of Europe have taken a more cautious approach towards DOACs. This is especially the case in the treatment of elderly populations, most likely because there remains substantial uncertainty concerning the effectiveness and safety of DOACs in unselected elderly patients with NVAF.[34]

Our results indicate that the characteristics of patients who initiated treatment with DOACs rather than VKAs evolved over the first few years of drug commercialisation. In the first year, we observed a selection process with healthier patients using DOACs more frequently than VKAs as initial therapy.[31] This tendency was reinforced as DOAC initiators became healthier over time. It may reflect the evolution of the perception of efficacy and safety of these new drugs by physicians. The prescription of DOACs to healthier patients is an issue that needs to be addressed, as these molecules may offer higher-risk patients greater benefits than VKAs,[35] but also because their cost effectiveness depends on the severity of patients' condition.[36] Observational studies that aim to evaluate the risks and benefits associated with DOACs as well as cost effectiveness studies should carefully account for the fact that patients selected to initiate DOAC treatment are healthier overall, as well as for the selection of patients on the different types of DOACs.[37] Failure to do so may lead to underestimating the potential risks associated with DOACs in real life studies.

The fact that DOAC initiation is less frequent among patients with comorbidities may result from a warning issued by different health agencies such as in France, Europe or US.[35] This tendency seems to be linked to the diminishing use of dabigatran observed at the end of 2013, when the French medicine safety agency released warnings on bleeding risks associated with the drug.[38,39,40] At the time, French health authorities informed health professionals that DOACs are not recommended as initial therapy for NVAF, unless the patient has poor adherence to VKAs or unless biological monitoring of VKA treatment is difficult. However, while these recommendations were followed by a temporary decrease in

DOAC use, a few months later DOACs were once again the most frequently prescribed anticoagulants for patients newly treated for NVAF.

Our study has several strengths. The source database covers 66 million inhabitants and nearly 99% of the French population, which means that our findings are independent of individual health coverage. Moreover, we had access to exhaustive information on anticoagulant delivery because these treatments are delivered on prescription alone. As a result, our study is the largest to report penetration of DOACs on the market (particularly in the case of apixaban, which is the most recent DOAC available) and to describe variations in the characteristics of patients over time.

Nevertheless, some limitations must also be acknowledged. The NHIS administrative database does not include clinical or biological results; nor does it include outpatients' diagnosis codes. To capture outpatient diagnosis of AF, we based our definition of NVAF on drug dispensation, using the most likely treatment scheme for NVAF. Insofar as the results of our sensitivity analyses are consistent, we can be confident that our findings are not too sensitive to the definition of NVAF. Moreover, 69% of patients who were hospitalised during follow-up had a diagnostic code of NVAF in the hospital discharge database (data not shown). Another limitation of our study is due to the 2015 data that may be partially incomplete. Indeed, for patients who do not have their NHIS card and attend a pharmacy that is not their regular pharmacy - a paper reimbursement form may be issued. The data are then recorded when the paper form is send to the NHIS and integrated later in the database. When the 2015 data were made available, paper claims were likely to have not all

been included. However, this changes the total number of users but not the proportion of users of the different drugs.

The rapid and massive adoption of DOACs as initial therapy for NVAF will impact treatment expenditures because of the important increase in costs associated with these new drugs (in the US, these costs accounted for more than 90% of insurer spending on anticoagulants in 2014[31]). Future observational studies should carefully account for the fact that patients selected to initiate DOAC treatment are healthier overall, and that this tendency is reinforced over the first few years of drug commercialization. Failure to do so may bias the risk-benefit assessment of DOACs.

Contributor ship statement

LH, XR, CF designed the study. All authors have contributed substantially to the interpretation of results. In addition: LH and AB drafted the article; - CF conducted the statistical analysis; CF, CR, SL, LB, SS, OM, XR 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

Pr. Suissa has participated in advisory board meetings and received research grants from Bayer, Boehringer Ingelheim, Bristol-Myers-Squibb and Novartis. These activities are conducted outside this submitted study.

All other co-authors have no conflict of interest.

Funding

This research was supported by a 2012 research grant from the Agence Nationale de Sécurité du Médicament (ANSM).

Data sharing statement

No additional data are available directly from the authors. The datasource of the study is the French National Health Insurance. Data ara available from the Caisse National de l'Assurance Maladie des Travailleurs Salariés (CNAMTS) for academic research.

Ethics approval

The study was approved by the French National Institute of Data, and by the National Commission for Data Protection and Liberties (CNIL-France: authorization number: 1637014).

Acknowledgements

We thank the Caisse National de l'Assurance Maladie des Travailleurs Salariés (CNAMTS) and the Institut des Données de Santé (IDS) for their assistance in obtaining the study database.

We personally thank Ms. Valérie EDEL from the IDS, as well as Mr. Laurent DUCHET and Mr. Medhi GABBAS from the department in charge of the SNIIRAM DATA at CNAM-TS.

We are indebted to Arianne Dorval for proofreading the English manuscript. C Renoux is the recipient of a Chercheur-Boursier Award from the Fonds de la recherche du Québec - santé (FRQ-S). S Suissa is the recipient of the James McGill Chair.

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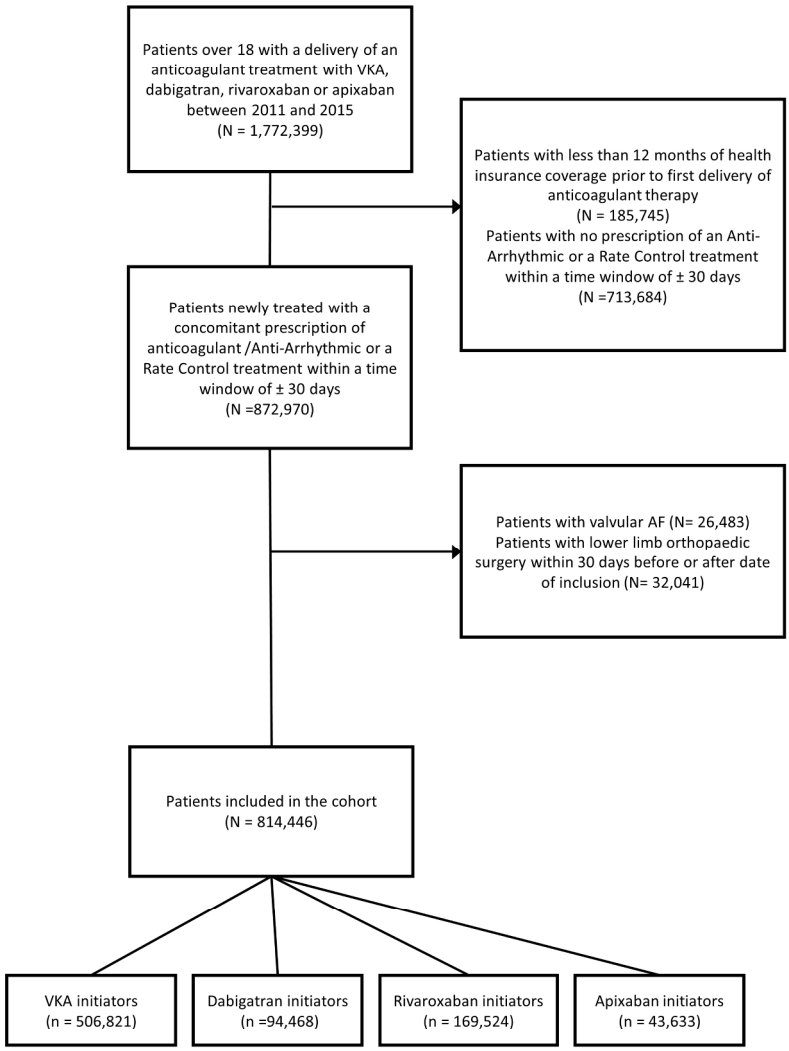
Figure 1 – Flow-chart describing cohort constitution

Figure 2 – Time trends in the prescription of anticoagulants in newly treated patients with Atrial Fibrilation between 2011 and 2015 in France (n = 814,446)

(VKA: vitamin K antagonist, DOAC: direct oral anticoagulant)

Significant changepoints in trends identified a segmented regression model (a): Dabigatran reimbursement approval, (b): Rivaroxaban reimbursement approval, (c): and Apixaban reimbursement approval, (d): Security warning (risks of bleeding hemorrhages) from the National Health Agency, (e): Downgrade of Dabigatran reimbursement.

Figure 3 – HAS-BLED and CHA2DS2-VASc scores associated with DOAC vs VKA initiation according to year of therapy initiation. Crude Odds Ratio and 95% confidence interval



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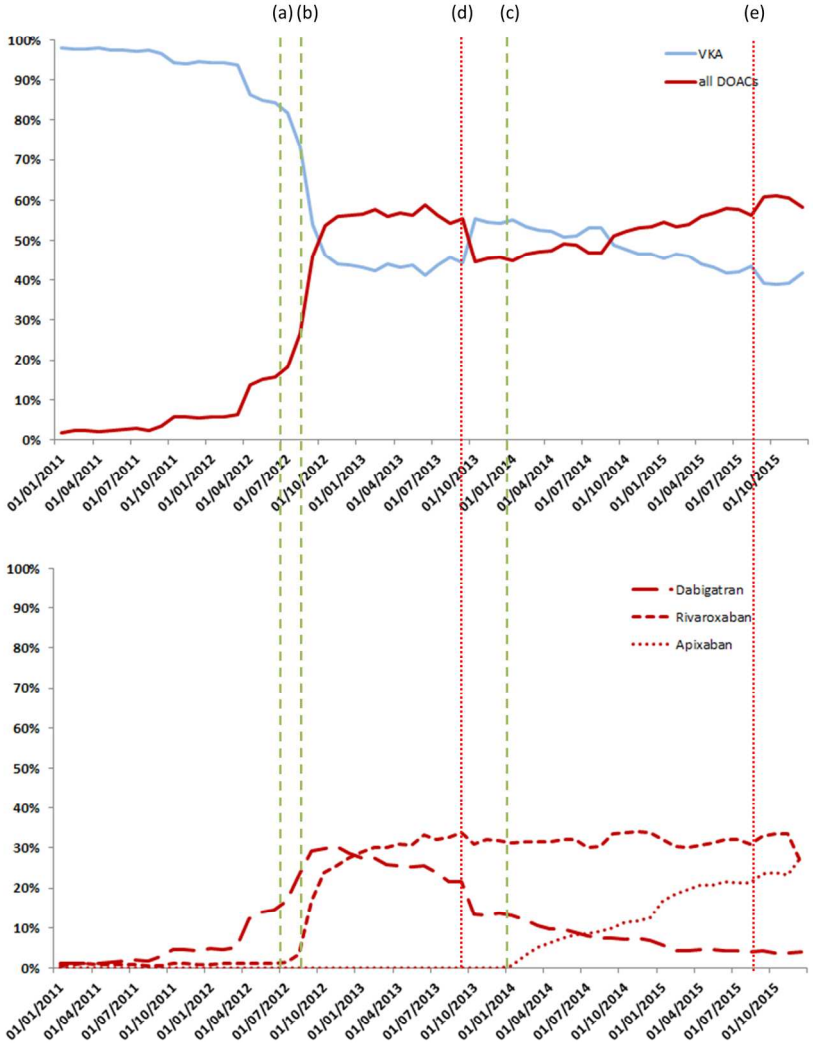

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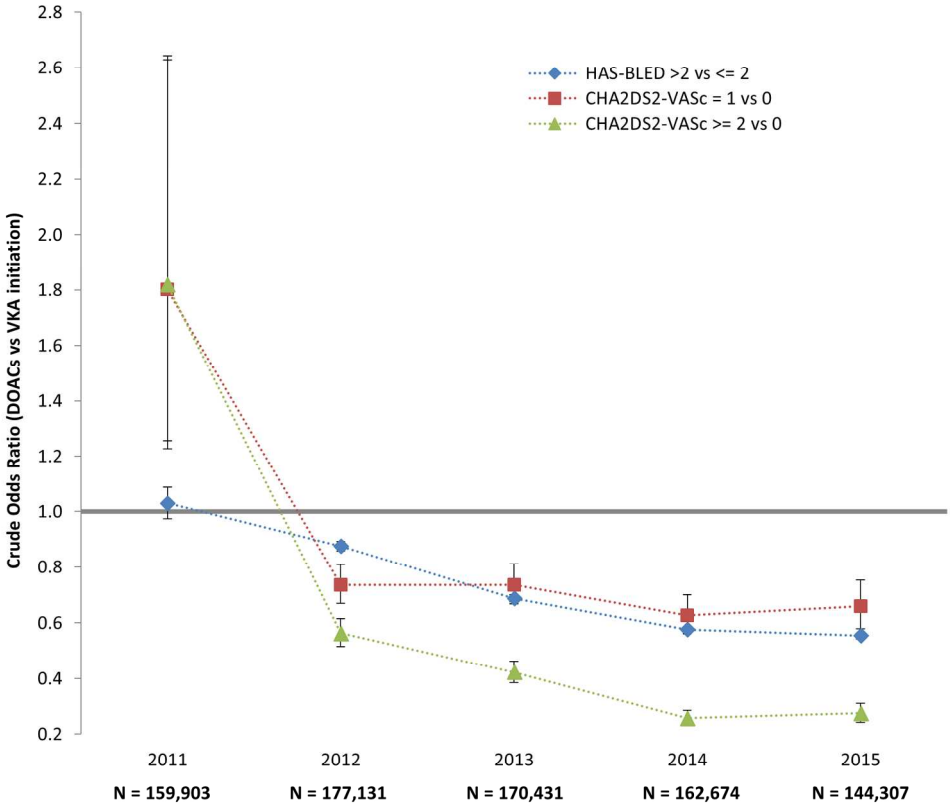

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Supplemental material – Sensitivity analysis – Cohort 1 - patients newly treated with an anticoagulant combined with an antiarrhythmic agent or a rate control treatment excluding beta-blockers, within a time window of +/- 30 days

Table 1 – Characteristics of Patients and Prescribers at Anticoagulant Treatment Initiation (2011-2015)

	VKA* N = 289,430	DOACs† N = 199,016
Demographic characteristics		
Mean age (sd§)	76.1 (11.2)	73.7 (11.3)
Male	49.8%	52.5%
Clinical characteristics‖		
High blood pressure	91.9%	88.7%
Ischemic heart disease	26.3%	16.6%
Heart failure	34.4%	21.6%
Diabetes	21.9%	18.6%
Cancer	16.1%	13.0%
Renal failure	9.7%	2.4%
Liver failure	1.3%	0.7%
Dementia	4.6%	2.7%
History Ischemic stroke	8.5%	6.2%
History of bleeding	5.5%	2.9%
HAS-BLED score, mean (sd)	2.6 (0.9)	2.4 (0.9)
CHA_2DS_2- $VASc_2$ score, mean (sd)	3.9 (1.5)	3.4 (1.5)
Other treatment at cohort entry¶		
Aspirin	45.9%	42.2%
Nonsteroidal anti-inflammatory drugs	13.8%	15.9%
Antiplatelet Agents (other than Aspirin)	14.4%	10.9%
Corticosteroids	13.9%	12.8%
Prescriber of first anticoagulant		
General Practitioner	59.7%	46.7%
Among general practitioners	*65.0%*	*35.0%*
Cardiologist	27.7%	43.8%
Among cardiologists	*47.9%*	*52.1%*
Other specialist	4.2%	3.8%
Unknown	8.4%	5.6%

* Vitamin K agonist; † Direct oral anticoagulants; ‡, p value comparing VKA vs DOACs; § sd: standard deviation; ‖ defined in the 12 months prior to cohort entry; ¶ defined in the 3 months prior to cohort entry

Supplemental material – Sensitivity analysis – Cohort 1 - patients newly treated with an anticoagulant combined with an antiarrhythmic agent or a rate control treatment excluding beta-blockers, within a time window of +/- 30 days

Table 2 – Characteristics of Patients and Prescribers at Anticoagulant Treatment Initiation in the Sub-Group of Patients Receiving a Direct Oral Anticoagulant (2011-2015)

	Dabigatran N = 65,851	Rivaroxaban N = 104,936	Apixaban N = 28,229
Demographic characteristics			
Mean age (sd†)	73.7 (11.4)	73.0 (11.3)	76.0 (11.0)
Male	52.3%	53.4%	49.6%
Clinical characteristics‡			
High blood pressure	88.7%	87.8%	91.8%
Ischemic heart disease	17.9%	15.8%	17.0%
Heart failure	22.8%	19.9%	25.2%
Diabetes	18.6%	18.3%	20.0%
Cancer	14.0%	12.8%	11.3%
Renal failure	2.1%	2.2%	3.8%
Liver failure	0.7%	0.6%	0.6%
Dementia	2.8%	2.6%	2.9%
History of ischemic stroke	7.2%	5.4%	7.1%
History of bleeding	2.7%	2.7%	3.6%
HAS-BLED score, mean (sd)	2.4 (0.9)	2.3 (0.9)	2.5 (0.9)
CHA_2DS_2- $VASc_2$, mean (sd)	3.4 (1.5)	3.2 (1.5)	3.6 (1.4)
Other treatments at cohort entry§			
Aspirin	43.0%	41.4%	43.2%
Nonsteroidal anti-inflammatory drugs	16.6%	16.1%	13.2%
Antiplatelet Agents (other than Aspirin)	11.3%	10.4%	12.1%
Corticosteroids	12.8%	12.8%	12.6%
Prescriber of first anticoagulant			
General Practitioner	47.0%	46.3%	47.5%
Cardiologist	43.1%	44.9%	41.7%
Other specialist	3.7%	3.8%	4.1%
Unknown	6.2%	5.0%	6.7%

* *Direct oral anticoagulants*, † Standard deviation, ‡ defined in the 12 months prior to cohort entry, § defined in the 3 months prior to cohort entry

Supplemental material – Sensitivity analysis – Cohort 1 - patients newly treated with an anticoagulant combined with an antiarrhythmic agent or a rate control treatment excluding beta-blockers, within a time window of +/- 30 days

Table 3 – Multivariate analysis of the determinants associated with DOAC initiation according to year of therapy initiation

Characteristics at treatment initiation	2011 N = 101,817		2012 N = 110,571		2013 N = 103,594		2014 N = 94,180		2015 N = 78,284	
	Adjusted OR	**CI 95%***	**Adjusted OR**	**CI 95%**	**Adjusted OR**	**CI 95%**	**Adjusted OR**	**CI 95%**	**Adjusted OR**	**CI 95%**
Demographic characteristics										
Age										
< 65 years	0.89	0.78 – 1.01	0.93	0.88 – 0.97	1.02	0.98 – 1.06	1.15	1.10 – 1.21	1.08	1.03 – 1.14
65 –74 years	1.0		1.0		1.0		1.0		1.0	
>= 75 years	1.15	1.04 – 1.27	0.98	0.94 – 1.01	0.69	0.67 – 0.71	0.59	0.57 – 0.61	0.65	0.63 – 0.68
Sex (Male)	0.86	0.79 – 0.94	0.97	0.94 – 1.01	1.09	1.06 – 1.13	1.10	1.06 – 1.13	1.08	1.05 – 1.12
Clinical characteristics†										
High blood pressure	0.87	0.76 – 1.00	0.82	0.78 – 0.86	0.79	0.75 – 0.83	0.78	0.74 – 0.82	0.79	0.74 – 0.84
Ischemic heart disease	0.88	0.79 – 0.97	0.83	0.80 – 0.86	0.76	0.74 – 0.79	0.74	0.72 – 0.77	0.76	0.72 – 0.79
Heart failure	0.60	0.55 – 0.67	0.70	0.68 – 0.72	0.61	0.59 – 0.63	0.59	0.57 – 0.61	0.63	0.60 – 0.65
Diabetes	0.88	0.79 – 0.98	0.89	0.86 – 0.93	0.88	0.85 – 0.91	0.93	0.89 – 0.96	0.92	0.89 – 0.96
Cancer	0.98	0.88 – 1.10	0.96	0.92 – 1.00	0.85	0.81 – 0.88	0.85	0.81 – 0.88	0.84	0.80 – 0.89
Renal failure	0.50	0.39 – 0.63	0.34	0.31 – 0.36	0.23	0.22 – 0.25	0.22	0.20 – 0.23	0.24	0.23 – 0.26
Liver failure	0.59	0.33 – 1.05	0.74	0.63 – 0.88	0.59	0.52 – 0.68	0.58	0.50 – 0.66	0.49	0.41 – 0.58
Dementia	0.96	0.77 – 1.19	0.84	0.77 – 0.92	0.75	0.70 – 0.80	0.81	0.76 – 0.88	0.74	0.68 – 0.81
History of Ischemic Stroke	1.01	0.87 – 1.16	0.99	0.94 – 1.05	0.88	0.84 – 0.93	0.88	0.84 – 0.93	0.92	0.86 – 0.98
History of bleeding	1.28	1.06 – 1.55	0.70	0.64 – 0.76	0.52	0.48 – 0.55	0.52	0.49 – 0.56	0.57	0.53 – 0.61
Prescriber of first anticoagulant										
General Practitioner	1.0		1.0		1.0		1.0		1.0	
Cardiologist	1.30	1.19 – 1.42	2.33	2.25 – 2.41	2.63	2.55 – 2.71	2.57	2.49 – 2.65	2.46	2.37 – 0.56
Other specialists/Unknown	1.72	1.52 – 1.93	1.03	0.97 – 1.08	1.00	0.96 – 1.05	1.03	0.98 – 1.07	1.03	0.98 – 1.08
Other treatments at cohort entry‡										
Aspirin	1.28	1.18 – 1.42	1.16	1.12 – 1.19	0.98	0.85 – 1.00	0.93	0.90 – 0.95	0.87	0.84 – 0.90
NSAID	1.37	1.24 – 1.52	1.16	1.11 – 1.21	1.18	1.13 – 1.22	1.21	1.17 – 1.27	1.20	1.14 – 1.26
Antiplatelet Agents	1.30	1.15 – 1.46	1.06	1.01 – 1.11	0.85	0.82 – 0.89	0.73	0.70 – 0.76	0.78	0.74 – 0.82
Corticosteroids	0.90	0.79 – 1.02	0.96	0.92– 1.00	0.93	0.89 – 0.96	0.98	0.94 – 1.02	0.92	0.88 – 0.96
Time of anticoagulant intiation										
1st term of the year	1.0		1.0		1.0		1.0		1.0	
2nd term of the year	1.13	0.96 – 1.32	3.17	2.98 – 3.37	1.00	0.96 -1.04	1.08	1.04 – 1.13	1.11	1.06 – 1.15
3rd term of the year	2.05	1.77 – 2.37	9.37	8.84 – 9.94	0.93	0.89 – 0.96	1.09	1.05 – 1.14	1.17	1.11 – 1.22
4th term of the year	4.71	4.14 – 5.36	31.06	29.34 – 32.88	0.54	0.52 – 0.56	1.35	1.30 – 1.40	1.39	1.33 – 1.45

* 95% Confidence interval; † defined in the 12 months prior to cohort entry; ‡ defined in the 3 months prior to cohort entry

Supplemental material – Sensitivity analysis – Cohort 2 - Cohort all patients newly treated with an anticoagulant therapy regardless of other potential concomitant therapies

Table 1 – Characteristics of Patients and Prescribers at Anticoagulant Treatment Initiation (2011-2015).

	VKA* N = 952,565	DOACs† N = 661,089
Demographic characteristics		
Mean age (sd§)	71.7 (15.3)	69.5 (13.8)
Male	48.4%	49.2%
Clinical characteristics‖		
High blood pressure	78.5%	71.3%
Ischemic heart disease	21.0%	11.9%
Heart failure	18.6%	8.8%
Diabetes	19.9%	15.7%
Cancer	16.7%	11.6%
Renal failure	9.3%	1.9%
Liver failure	1.6%	0.6%
Dementia	5.5%	2.4%
History Ischemic stroke	8.6%	5.0%
History of bleeding	6.8%	3.6%
HAS-BLED score, mean (sd)	2.3 (1.1)	2.0 (1.1)
CHA_2DS_2- $VASc_2$ score, mean (sd)	3.3 (1.7)	2.8 (1.6)
Other treatment at cohort entry¶		
Aspirin	35.8%	28.9%
Nonsteroidal anti-inflammatory drugs	17.1%	28.4%
Antiplatelet Agents (other than Aspirin)	11.7%	7.4%
Corticosteroids	15.1%	12.7%
Prescriber of first anticoagulant		
General Practitioner	70.7%	54.1%
Among General Practitioners	*64.7%*	*35.3%*
Cardiologist	15.6%	21.7%
Among Cardiologists	*50.0%*	*50.0%*
Other specialist	5.8%	18.2%
Unknown	7.9%	6.0%

* Vitamin K agonist; † Direct oral anticoagulants; ‡, p value comparing VKA vs DOACs; § sd: standard deviation; ‖ defined in the 12 months prior to cohort entry; ¶ defined in the 3 months prior to cohort entry

Supplemental material – Sensitivity analysis – Cohort 2 - Cohort all patients newly treated with an anticoagulant therapy regardless of other potential concomitant therapies

Table 2 – Characteristics of Patients and Prescribers at Anticoagulant Treatment Initiation in the Sub-Group of Patients Receiving a Direct Oral Anticoagulant (2011-2015) AC

	Dabigatran N = 174,423	Rivaroxaban N = 419,780	Apixaban N = 66,886
Demographic characteristics			
Mean age (sd†)	71.5 (12.5)	67.8 (14.3)	74.5 (11.8)
Male	49.6%	49.0%	49.4%
Clinical characteristics‡			
High blood pressure	76.9%	66.9%	84.4%
Ischemic heart disease	14.8%	10.4%	14.0%
Heart failure	11.0%	6.9%	15.3%
Diabetes	16.9%	14.6%	18.8%
Cancer	12.7%	11.3%	10.8%
Renal failure	1.9%	1.7%	3.7%
Liver failure	0.6%	0.6%	0.6%
Dementia	2.6%	2.2%	3.1%
History of ischemic stroke	6.5%	3.9%	8.4%
History of bleeding	3.5%	3.6%	4.0%
HAS-BLED score, mean (sd)	2.2 (1.0)	1.9 (1.1)	2.4 (1.0)
CHA_2DS_2- $VASc_2$, mean (sd)	3.0 (1.6)	2.6 (1.6)	3.4 (1.5)
Other treatments at cohort entry§			
Aspirin	32.8%	25.9%	37.6%
Nonsteroidal anti-inflammatory drugs	28.3%	29.8%	19.4%
Antiplatelet Agents (other than Aspirin)	8.7%	6.4%	10.1%
Corticosteroids	11.9%	13.1%	11.7%
Prescriber of first anticoagulant			
General Practitioner	48.2%	56.9%	51.4%
Cardiologist	24.1%	19.6%	29.2%
Other specialist	20.9%	18.0%	12.0%
Unknown	6.8%	5.5%	7.4%

* *Direct oral anticoagulants*, † Standard deviation, ‡ defined in the 12 months prior to cohort entry, § defined in the 3 months prior to cohort entry

Supplemental material – Sensitivity analysis – Cohort 2 - Cohort all patients newly treated with an anticoagulant therapy regardless of other potential concomitant therapies

Table 3 – Multivariate analysis of the determinants associated with DOAC initiation according to year of therapy initiation.

Characteristics at treatment initiation	2011 N = 319*,372		2012 N = 353,242		2013 N = 327,150		2014 N = 311,352		2015 N =275,538	
	Adjusted OR	**CI 95%***	**Adjusted OR**	**CI 95%**	**Adjusted OR**	**CI 95%**	**Adjusted OR**	**CI 95%**	**Adjusted OR**	**CI 95%**
Demographic characteristics										
Age										
< 65 years	0.57	0.56 – 0.59	0.63	0.62 – 0.64	0.74	0.72 – 0.76	0.81	0.79 – 0.82	0.81	0.79 – 0.83
65 –74 years	1.0		1.0		1.0		1.0		1.0	
>= 75 years	0.56	0.55 – 0.58	0.76	0.75 – 0.78	0.69	0.68 – 0.70	0.59	0.58 – 0.60	0.66	0.65 – 0.67
Sex (Male)	0.86	0.84 – 0.88	0.98	0.96 – 0.99	1.09	1.07 – 1.11	1.08	1.06 – 1.09	1.06	1.04 – 1.08
Clinical characteristics†										
High blood pressure	0.76	0.74 – 0.78	0.90	0.88 – 0.92	0.95	0.93 – 0.97	0.89	0.87 – 0.91	0.87	0.85 – 0.89
Ischemic heart disease	0.78	0.76 – 0.81	0.81	0.79 – 0.83	0.76	0.75 – 0.78	0.74	0.72 – 0.76	0.77	0.75 – 0.80
Heart failure	0.15	0.14 – 0.16	0.56	0.54 – 0.57	0.63	0.62 – 0.64	0.58	0.56 – 0.59	0.64	0.63 – 0.66
Diabetes	0.89	0.86 – 0.92	0.90	0.88 – 0.92	0.89	0.87 – 0.91	0.89	0.87 – 0.91	0.91	0.89 – 0.93
Cancer	0.71	0.69 – 0.73	0.81	0.79 – 0.83	0.75	0.73 – 0.76	0.73	0.72 – 0.75	0.70	0.68 – 0.72
Renal failure	0.29	0.27 – 0.32	0.30	0.29 – 0.32	0.23	0.22 – 0.24	0.22	0.21 – 0.23	0.26	0.25 – 0.27
Liver failure	0.50	0.44 – 0.57	0.50	0.46 – 0.55	0.47	0.43 – 0.50	0.43	0.40 – 0.47	0.40	0.37 – 0.44
Dementia	0.29	0.26 – 0.31	0.56	0.54 – 0.59	0.61	0.59 – 0.63	0.60	0.58 – 0.63	0.63	0.60 – 0.66
History of Ischemic Stroke	0.24	0.22 – 0.26	0.66	0.64 – 0.68	0.76	0.74 – 0.78	0.74	0.72 – 0.76	0.81	0.78 – 0.84
History of bleeding	1.00	0.95 – 1.05	0.70	0.68 – 0.73	0.54	0.52 – 0.56	0.53	0.51 – 0.55	0.54	0.52 – 0.56
Prescriber of first anticoagulant										
General Practitioner	1.0		1.0		1.0		1.0		1.0	
Cardiologist	0.26	0.25 – 0.28	1.91	1.87 – 1.95	2.86	2.80 – 2.92	2.78	2.72 – 2.84	2.67	2.60 – 2.73
Other specialists/Unknown	7.01	6.85 – 7.18	3.76	3.69 – 3.84	1.83	1.79 – 1.87	1.79	1.75 – 1.82	1.55	1.51 – 1.58
Other treatments at cohort entry‡										
Aspirin	0.71	0.69 – 0.73	1.00	0.98 – 1.02	0.98	0.96 – 1.00	0.91	0.90 – 0.93	0.87	0.85 – 0.88
NSAID	2.77	2.71 – 2.83	1.93	1.90 – 1.97	1.57	1.54 – 1.60	1.56	1.53 – 1.59	1.57	1.53 – 1.60
Antiplatelet Agents	0.64	0.61 – 0.68	0.94	0.91 – 0.97	0.83	0.81 – 0.85	0.75	0.72 – 0.77	0.76	0.73 – 0.78
Corticosteroids	0.60	0.58 – 0.62	0.70	0.68 – 0.72	0.79	0.77 – 0.80	0.84	0.82 – 0.86	0.87	0.85 – 0.89
Time of anticoagulant intiation										
1st term of the year	1.0		1.0		1.0		1.0		1.0	
2nd term of the year	1.02	0.99 – 1.05	1.35	1.32 – 1.38	1.05	1.03 – 1.07	1.12	1.10 – 1.14	1.10	1.08 – 1.13
3rd term of the year	0.81	0.78 – 0.83	2.22	2.17 – 2.28	0.96	0.94 – 0.98	1.09	1.07 – 1.12	1.12	1.10 – 1.15
4th term of the year	1.32	1.29 – 1.37	5.92	5.79 – 6.05	0.69	0.68 – 0.70	1.38	1.35 – 1.41	1.31	1.28 – 1.34

* 95% Confidence interval; † defined in the 12 months prior to cohort entry; ‡ defined in the 3 months prior to cohort entry

Supplementary table – Sources of codes used for the definition of covariates

Covariates at cohort entry	Definitions			
	Drug claims	Hospital discharge diagnoses (main or associated)	Hospital Inpatient procedures	Long duration disease codes
High blood pressure	X	X		X
Ischemic heart disease		X		
Heart failure	X	X		X
Diabetes	X	X		X
Cancer	X	X		X
Renal failure		X	X	X
Liver failure		X		X
Dementia	X	X		X
History Ischemic stroke		X		X
History of bleeding	X	X		
HAS-BLED score	X	X	X	X
CHA_2DS_2- $VASc_2$ score	X	X		X
Aspirin	X			
Nonsteroidal anti-inflammatory drugs	X			
Antiplatelet Agents (other than Aspirin)	X			
Corticosteroids	X			

STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5-6
Objectives	3	State specific objectives, including any pre-specified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7-8
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	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	8
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	*8*
Bias	9	Describe any efforts to address potential sources of bias	9
Study size	10	Explain how the study size was arrived at	Database study – NA
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9
		(*b*) Describe any methods used to examine subgroups and interactions	9
		(*c*) Explain how missing data were addressed	Administrative database study – no missing variable

		(*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	Only variable at cohort entry were used
		(*e*) Describe any sensitivity analyses	9
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	11
		(b) Give reasons for non-participation at each stage	11 and figure 1
		(c) Consider use of a flow diagram	Fig 1
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 – admin database study – no missing variables
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	Variables only at cohort entry
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
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 1
		(*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	Supplementary table
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	14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	15
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	14

		which the present article is based	

*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

Trends in initiation of direct oral anticoagulant therapies for atrial fibrillation in a national population-based cross-sectional study in the French Health Insurance databases

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-018180.R2
Article Type:	Research
Date Submitted by the Author:	12-Dec-2017
Complete List of Authors:	Huiart, Laetitia; CIC 1410 Ferdynus, Cyril; CHU de la Réunion, Unité de Soutien Méthodologique; CHU Réunion, CIC INSERM 1410 Renoux, Christel; McGill University, Neurology & Neurosurgery Beaugrand, Amélie; Centre Hospitalier National d'Ophtalmologie des Quinze-Vingts Lafarge, Sophie; CHU Réunion, CIC INSERM 1410 Bruneau, Léa; CHU de la Réunion, Unité de Soutien Méthodologique Suissa, Samy; McGill University, Maillard, Olivier; CHU Réunion, CIC INSERM 1410 Ranouil, Xavier; CHU de la Réunion, Service de Cardiologie
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Cardiovascular medicine, Pharmacology and therapeutics, Public health
Keywords:	Cohort, Atrial Fibrilation, anticoagulants, Vitamine K antagonist, direct oral anti-coagulants

Trends in initiation of direct oral anticoagulant therapies for atrial fibrillation in a national population-based cross-sectional study in the French Health Insurance databases

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Abstract (300 words)

Objective

Unlike several other national health agencies, French health authorities recommended that the newer direct oral anticoagulant (DOAC) agents only be prescribed as second choice for the treatment of newly diagnosed non-valvular atrial fibrillation (NVAF), with vitamin K antagonists (VKA) remaining the first choice. We investigated the patterns of use of DOACs versus VKA in the treatment of NVAF in France over the first five years of DOAC availability. We also identified the changes in patient characteristics of those who initiated DOAC treatment over this time period.

Methods

Based on the French National Health Administrative Database, we constituted a population-based cohort of all patients who were newly treated for NVAF between January 2011 and December 2015. Trends in drug use were described as the percentage of patients initiating each drug at the time of treatment initiation. A multivariate analysis using logistic regression model was performed to identify independent sociodemographic and clinical predictors of initial anticoagulant choice.

Results

The cohort comprised 814,446 patients who had received a new anticoagulant treatment for NVAF. The proportion of patients using DOACs as initial anticoagulant therapy reached 54% three months after the Health Ministry approved the reimbursement of dabigatran for NVAF, and 61% by the end of 2015, versus VKA use. In the multivariate analysis, we found that DOAC initiators were younger and healthier overall than VKA initiators, and this tendency was reinforced over the 2011-2014 period. DOACs were more frequently

prescribed by cardiologists in 2012 and after (adjusted-OR in 2012: 2.47; 95% Confidence Interval: 2.40-2.54).

Conclusion

Despite recommendations from health authorities, DOACs have been rapidly and massively adopted as initial therapy for NVAF in France. Observational studies should account for the fact that patients selected to initiate DOAC treatment are healthier overall, as failure to do so may bias the risk-benefit assessment of DOACs.

Keywords (6 max)

Cohort, atrial fibrillation, anticoagulants, vitamin K antagonist, direct oral anticoagulants

Tables: 2

Figures: 3

Supplementary material: 6 tables

Strength and limitations:

- With a source database covering 66 million inhabitants and exhaustive information on anticoagulant deliveries in France, our study is the largest to report penetration of DOACs on the market. This is particularly the case for apixaban, which was the most recent DOAC available at the time of the study
- The administrative database used does not include clinical results; nor does it include outpatients' diagnosis codes. To account for outpatients, we based our definition of NVAF on drug dispensation, using the most likely treatment scheme for NVAF. We conducted sensitivity analyses to ensure that our results are consistent.

Introduction

Non-Valvular Atrial fibrillation (NVAF) is the most common sustained cardiac arrhythmia, and its age-adjusted prevalence has been increasing over time.[1,2] NVAF is associated with high morbidity and mortality, as it increases the risks of stroke and systemic thromboembolic events.[2] In light of this, the use of an oral anticoagulant is recommended in patients with NVAF at medium or high risk of stroke.[3-7] For more than 50 years, vitamin K antagonists (VKA) such as warfarin were the only effective therapy available for stroke prevention in patients with NVAF.[8] However, the efficacy and safety of VKAs are closely related to the quality of anticoagulation, which is open to substantial inter- and intra-patient variability and requires close biological monitoring.[9, 8,10]

In order to respond to physicians' and patients' expectations of more user-friendly drugs, research on new drugs has intensified over the last few years. This has prompted the development of direct oral anticoagulants (DOAC) that inhibit thrombin or factor Xa. Large randomised clinical trials (RCTs) have compared the efficacy of DOACs to that of warfarin in patients with NVAF.[11 ,12,13] A recent meta-analysis of these RCTs has shown that the frequency of strokes and/or systemic embolic events is 19% lower with DOACs than it is with warfarin. Moreover, compared with warfarin, DOACs have been shown to present similar risks of major bleeding but higher risks of gastrointestinal bleeding.[14] The benefit-risk ratio of DOACs nevertheless varies across individual agents, and also according to patient profile.[15,16]

In France, the direct thrombin inhibitor dabigatran was the first DOAC to be approved for the primary prevention of venous thromboembolism in orthopedic surgery (in 2008) and stroke in NVAF (in 2011). Reimbursement of dabigatran for the treatment of NVAF was approved in July 2012. Two new oral direct factor Xa inhibitors, rivaroxaban and apixaban, were made available for patients with NVAF in September 2012 and January 2014,

respectively. Given the initial lack of specific antidotes and of data on these drugs' efficacy and safety in real life, French Health Authorities recommended that VKAs remain the standard therapy. They also recommended that DOACs be offered as an alternative therapy only to patients with low adherence to VKAs or unstable INRs (International Normalised Ratios) on VKAs.[17] To date, it is not clear how the expectations of clinicians and the recommendations of health authorities have impacted the choice of anticoagulant for newly treated patients with NVAF. Nor is it clear how patients' characteristics have influenced treatment choice.

In view of the above, we conducted a study in the French National health administrative database. This study based on claims data, aimed to identify the initial oral anticoagulant therapy used in a cohort of patients newly diagnosed with NVAF for the prevention of stroke and systemic thromboembolism. It also sought to describe changes in the characteristics of patients who initiated treatment during the first five years of DOAC availability in France.

Method

Study design and source of data

The retrospective population-based cohort of patients with NVAF was formed from data provided by the French National Health Insurance System (NHIS).[18] The NHIS guarantees universal health coverage to all segments of the population, and includes both a drug delivery database and a hospital discharge database. The NHIS comprises health insurance schemes for salaried workers, self-employed workers, agricultural workers and farmers, as well as 12 other insurance schemes. Together, these schemes provide health insurance to approximately 66 million inhabitants, which corresponds to approximately 99% of the French population.[19] Detailed description of the NHIS database is provided elsewhere.[20,21]

In France, drugs are available only in pharmacies, and a medical prescription is required to obtain anticoagulant drugs. All reimbursement claims for prescriptions processed and filled in pharmacies are submitted to the NHIS via a single electronic system. This drug delivery database is linked to the hospital discharge database through a unique personal identifier allocated to every individual. The second database provides medical information on all patients discharged from hospitals, along with associated ICD-10 diagnosis codes (10th version of International Classification of Diseases). However, no clinical diagnosis is provided in this database for consultations by health professionals in an ambulatory care setting.

Cohort definition

We defined a cohort of all patients 18 years and older who were newly treated for NVAF between January 1, 2011 and December 31, 2015. Cohort entry was defined by the delivery of anticoagulant therapy (VKA or DOAC) combined with either an antiarrhythmic agent (flecainide, propafenone, amiodarone, quinidine, disopyramide or sotalol) or a rate control treatment (beta-blocker, calcium channel blockers - verapamil and diltiazem -, or digoxin) within a time window of +/- 30 days. The date of cohort entry was the latest date of delivery of either drug, within the 30 day window. We excluded patients with less than 1 year of data available in the database before cohort entry, as well as patients who had received anticoagulant treatment or had a history of cardiac valvular replacement in the 12 months before inclusion. Therefore, the anticoagulant therapy received at cohort inclusion corresponded to a new anticoagulant therapy. Lastly, we excluded patients who had undergone lower limb orthopedic surgery within +/- 30 days of inclusion.

Exposure

We identified patients' exposure to initial anticoagulant treatment. We compared patients initiating VKA treatment—acenocoumarol, fluindione, warfarin (the 3 most commonly used VKAs in France)—to patients receiving any of the 3 DOACs available during the study period (dabigatran, rivaroxaban or apixaban).

Study covariates

The following characteristics of patients were identified in the year prior to cohort entry using treatment and/or hospital discharge code (supplementary table): high blood pressure, coronary artery disease (including myocardial infarction and ischemic heart disease), congestive heart failure, diabetes, a personal history of cancer, renal failure, liver failure, dementia, a history of bleeding, and history of ischemic stroke. Exposure to treatment other than anticoagulants—aspirin or other nonsteroidal anti-inflammatory drugs, antiplatelet agents (other than aspirin), corticosteroids—was identified in the 3 months prior to cohort entry. We also determined whether initial anticoagulant therapy was prescribed by a general practitioner, a cardiologist or a physician with another specialty. To estimate the risk of major bleeding, we calculated a modified HAS-BLED score (hypertension, abnormal renal and/or liver function, stroke/TIA, bleeding, labile international normalised ratio (INR), age >65, antiplatelet/NSAID use, or alcohol abuse).[22] Labile INR was not included in the score because it is unavailable in the database. Alcohol abuse was determined based on the hospital discharge database. To estimate the risk of stroke, we calculated the CHA2DS2-VASc2 score (congestive heart failure, hypertension, age ≥75, diabetes mellitus, stroke/transient ischemic attack, vascular disease, age 65–74, and sex).[23]

Data analysis

Descriptive statistics were computed for continuous data (mean, +/- standard deviation (SD) or median and range) and for categorical data (frequency and proportion). Trends in drugs

use were described as the number of new patients treated each month and as the percentage of each anticoagulant prescribed at the time of treatment initiation.

Patients' characteristics were described according to initial anticoagulant therapy received. In bivariate comparisons, the characteristics of patients and prescribers were compared according to the type of anticoagulant, using a t-test for continuous variables, and a chi-square test for categorical variables. To identify independent predictors of initial anticoagulant choice, we performed a multivariate analysis using 5 logistic regression models, one for each calendar year of anticoagulant initiation. The model included all the variables that were associated with a p-value <0.20 in the bivariate comparisons. These variables were selected using a backward selection approach. Further, we defined 2 other cohorts for the sensitivity analyses: 1) one cohort was defined more restrictively: it included patients who were newly treated with an anticoagulant combined with an antiarrhythmic agent or a rate control treatment other than beta-blocker agents within a time window of +/- 30 days; 2) the other cohort was defined according to broader inclusion criteria: it comprised all patients newly treated with an anticoagulant, regardless of other potential concomitant therapies.

To assess the impact of timeline events on the uptake process (i.e. market authorization of each drug, reimbursement approval/downgrade and security warnings from national health agency), we fitted a segmented regression model, adjusted on: 1) drug coded into four categories (VKA, dabigatran, rivaroxaban and apixaban), 2) time (linear and square terms) and 3) each timeline event. A timeline event was coded as a dichotomous variable valued 0 before the event and 1 after. All these covariates were included in a primary model, then a backward selection procedure was applied to select covariates associated at a significant

level ($p < 0.05$). To evaluate the trends and the impact of timeline events on each drug, we entered an interaction term for each drug and other covariates (time and timeline events).

Statistical significance was set at 0.05. All p-values were two sided.

All statistical analyses were performed using SAS version 9.4 (SAS institute, Cary Inc).

Results

In France, 1,772,399 individuals were delivered a prescription for either a VKA or a DOAC between January 1, 2011 and December 31, 2015 (Figure 1). Out of this sample, we identified 872,970 individuals who received a new prescription for an anticoagulant (VKA or DOAC) combined with a prescription for an antiarrhythmic agent or a rate control treatment within a time window of +/- 30 days. Ultimately, the cohort comprised 814,446 patients newly treated for NVAF: 506,821 subjects initiated VKA, 94,468 dabigatran, 169,524 rivaroxaban, and 43,633 apixaban.

Figure 2 illustrates the percentages of patients initiating one of the different anticoagulant treatments over the study period. A sharp rise in DOAC use was observed starting in mid-2012. As of October 2012, DOACs were used more frequently than VKAs as initial anticoagulant therapy, representing 54% of all anticoagulant prescriptions (30% for dabigatran and 24% for rivaroxaban). In the last quarter of 2015, this percentage reached 61% (4% for dabigatran, 34% for rivaroxaban, and 24% for apixaban). The proportion of patients initiating dabigatran began to decline 6 months after reimbursement was approved, and even more so after October 2013. Rivaroxaban use increased sharply as early as September 2012. This drug was the most frequently initiated DOAC in early 2013, and it remained so until December 2015, when it was surpassed by apixaban (26% vs 28% in December 2015).

Figure 2 illustrates the percentages of patients initiating one of the different anticoagulant treatments over the study period. The segmented regression model identified 5 significant changepoints. The two first changepoints (line a and b in figure 2) corresponded to a sharp rise in DOAC initiation in July 2012 and in September 2012, corresponding respectively to dabigatran and rivaroxaban reimbursement approval time. As of October 2012, DOACs were used more frequently than VKAs as initial anticoagulant therapy, representing 54% of all anticoagulant prescriptions (30% for dabigatran and 24% for rivaroxaban). The third changepoint identified was in September 2013 (ligne d, Figure 2) with a significant decrease in the use of DOACs at the time security warnings were issued by the French health authorities. From January 2014 (4th change point – line c on figure 2), DOACs initiation increased again, corresponding to the time point where apixaban received reimbursement approval. A final significant changepoint (line e) was identified in September 2015 and was linked to a reduction in dabigatran reimbursement. In December 2015, apixaban was the most prescribed DOAC (28% versus 26% for rivaroxaban).

The mean age of newly treated patients was 74.9 (SD: 11.7), and 50.2% of patients were male (table 1). Most subjects were treated for high blood pressure (94.4%), and 22.2% were treated for diabetes. Patients who received DOACs had less comorbidities and were on average younger than those who were prescribed VKAs (73.8 years (SD: 11.5) versus 75.6 years (SD: 11.9) p<0.0001). General practitioners prescribed VKAs (67.5%) more frequently than DOACs (32.5%) as initial anticoagulant therapy, whereas cardiologist favored DOACs (51.2%). Patients receiving apixaban were older than those receiving other DOACs (76.2 vs. 72.9 for rivaroxaban and 74.1 for dabigatran). They also had more comorbidities, such as

high blood pressure and heart or renal failure (table 1). Patients with lower HAS-BLED or lower CHA2DS2-VASc scores were more likely to initiate DOACs (figure 3).

The characteristics and associated treatments of DOAC initiators as compared with VKA initiators changed over the 5-year period (table 2). Older subjects (>= 75 years) were less likely to initiate DOAC treatment than VKA treatment. The adjusted OR decreased from 0.86 in 2011 (95% Confidence Interval (95%CI): 0.80 to 0.92) to 0.62 in 2014 (95%CI: 0.61 to 0.64). Overall, patients with comorbidities—especially renal failure—were less likely to receive DOAC treatment, and this negative association was reinforced over the study period (adjusted OR for 2014: 0.22; 95%CI: 0.21-0.23). The negative association was not reinforced in 2015, likely due the fact that a larger proportion of patients received apixaban. However, because apixaban was only available at the end of the study period, further data are needed to confirm this hypothesis. Patients with a history of bleeding prior to cohort entry were less likely to receive DOAC treatment (adjusted OR for 2015: 0.56; 95%CI: 0.53-0.59). Since 2012, cardiologists have been strongly associated with initial prescription of DOACs, after accounting the patients' characteristics.

The sensitivity analyses conducted for the 2 other cohorts provided similar results: a rapid increase in the use of DOAC over time, and a healthier profile of patients receiving DOACs compared with those receiving VKAs (supplementary material cohort 1 and cohort 2).

Table 1 – Characteristics of Patients and Prescribers at Anticoagulant Treatment Initiation (2011-2015)

	VKA* N = 506,821	Dabigatran N = 94,468	Rivaroxaban N = 169,524	Apixaban N = 43,633
Demographic characteristics				
Mean age (sd†)	75.6 (11.9)	74.1 (11.3)	73.0 (11.5)	76.2 (11.1)
Male	49.3%	52.3%	52.0%	49.5%
Clinical characteristics‡				
High blood pressure	95.4%	92.1%	92.5%	94.7%
Ischemic heart disease	28.6%	19.7%	17.4%	17.6%
Heart failure	27.8%	18.9%	15.2%	21.5%
Diabetes	23.6%	19.9%	19.7%	20.8%
Cancer	16.5%	14.0%	12.8%	11.1%
Renal failure	10.9%	2.3%	2.4%	4.1%
Liver failure	1.7%	0.7%	0.7%	0.6%
Dementia	5.2%	3.1%	2.9%	3.3%
History of ischemic stroke	9.6%	8.4%	6.0%	9.0%
History of bleeding	6.3%	2.9%	3.1%	3.9%
HAS-BLED score, mean (sd)	2.7 (0.9)	2.4 (0.9)	2.4 (0.9)	2.5 (0.9)
CHA_2DS_2- $VASc_2$, mean (sd)	3.9 (1.5)	3.5 (1.5)	3.3 (1.4)	3.7 (1.4)
Other treatments at cohort entry§				
Aspirin	45.8%	43.3%	40.9%	43.6%
Nonsteroidal anti-inflammatory drugs	13.7%	16.6%	16.9%	13.0%
Antiplatelet Agents (other than Aspirin)	15.8%	12.1%	10.9%	12.4%
Corticosteroids	14.0%	12.2%	12.7%	12.1%
Protons-Pump Inhibitors	48.9%	40.7%	41.2%	43.9%
Prescriber of first anticoagulant				
General Practitioner	64.4%	50.2%	51.9%	50.4%
Cardiologist	22.2%	38.9%	38.0%	37.9%
Other specialist	4.8%	4.4%	4.7%	4.6%
Unknown	8.6%	6.5%	5.4%	7.1%

* Vitamin K agonist; † Direct oral anticoagulants; ‡ sd: standard deviation; § defined in the 12 months prior to cohort entry; ‖ defined in the 3 months prior to cohort entry

Table 2 – Multivariate analysis of the determinants associated with DOAC initiation according to year of therapy initiation.

Characteristics at treatment initiation	2011 N = 159,903		2012 N = 177,131		2013 N = 170,431		2014 N = 162,674		2015 N = 144,307	
	Adjusted OR	CI 95%*	Adjusted OR	CI 95%	Adjusted OR	CI 95%	Adjusted OR	CI 95%	Adjusted OR	CI 95%
Demographic characteristics										
Age										
< 65 years	0.88	0.81 – 0.96	0.82	0.79 – 0.86	0.87	0.84 – 0.90	0.99	0.95 – 1.02	0.94	0.91 – 0.98
65 –74 years	1.0		1.0		1.0		1.0		1.0	
>= 75 years	0.86	0.80 – 0.92	0.98	0.95 – 1.01	0.74	0.72 – 0.76	0.62	0.61 – 0.64	0.68	0.66 – 0.70
Sex (Male)	0.73	0.69 – 0.77	1.01	0.99 – 1.04	1.15	1.12 – 1.17	1.13	1.11 – 1.16	1.11	1.08 – 1.13
Clinical characteristics†										
High blood pressure	1.29	1.13 – 1.46	0.74	0.71 – 0.78	0.61	0.58 – 0.64	0.63	0.60 – 0.66	0.62	0.59 – 0.66
Ischemic heart disease	0.89	0.84 – 0.96	0.80	0.78 – 0.83	0.74	0.72 – 0.76	0.70	0.69 – 0.72	0.75	0.73 – 0.77
Heart failure	0.43	0.40 – 0.47	0.73	0.71 – 0.76	0.68	0.66 – 0.69	0.64	0.62 – 0.65	0.69	0.66 – 0.70
Diabetes	0.89	0.83 – 0.96	0.91	0.88 – 0.94	0.89	0.86 – 0.91	0.90	0.88 – 0.92	0.91	0.89 – 0.94
Cancer	0.93	0.86 – 1.01	0.92	0.89 – 0.95	0.82	0.80 – 0.85	0.81	0.79 – 0.83	0.80	0.77 – 0.83
Renal failure	0.45	0.38 – 0.53	0.32	0.30 – 0.35	0.23	0.22 – 0.25	0.22	0.21 – 0.23	0.25	0.24 – 0.27
Liver failure	0.58	0.41 – 0.80	0.58	0.51 – 0.66	0.48	0.44 – 0.53	0.41	0.38 – 0.46	0.40	0.35 – 0.44
Dementia	0.72	0.61 – 0.85	0.79	0.74 – 0.84	0.73	0.69 – 0.77	0.74	0.70 – 0.78	0.72	0.68 – 0.76
History of Ischemic Stroke	0.70	0.63 – 0.78	0.95	0.91– 1.00	0.91	0.88 – 0.95	0.88	0.85 – 0.91	0.92	0.89 – 0.96
History of bleeding	1.35	1.19 – 1.52	0.68	0.64 – 0.72	0.55	0.52 – 0.58	0.53	0.50 – 0.56	0.56	0.53 – 0.59
Prescriber of first anticoagulant										
General Practitioner	1.0		1.0		1.0		1.0		1.0	
Cardiologist	0.86	0.81 – 0.93	2.47	2.40 – 2.54	2.86	2.79 – 2.93	2.73	2.67 – 2.80	2.57	2.49 – 2.64
Other specialists/Unknown	2.53	2.36 – 2.71	1.15	1.10 – 1.19	1.00	0.96 – 1.03	1.04	1.00 – 1.07	1.03	0.99 – 1.06
Other treatments at cohort entry‡										
Aspirin	1.04	0.98 – 1.10	1.13	1.10 – 1.16	0.99	0.97 – 1.01	0.93	0.91 – 0.95	0.87	0.85 – 0.89
NSAID	1.90	1.78 – 2.02	1.17	1.13 – 1.21	1.19	1.16 – 1.22	1.21	1.18 – 1.25	1.24	1.20 – 1.28
Antiplatelet Agents	1.03	0.94 – 1.12	1.03	0.99 – 1.07	0.81	0.79 – 0.84	0.72	0.70 – 0.75	0.74	0.71 – 0.77
Corticosteroids	0.76	0.69 – 0.83	0.87	0.84 – 0.94	0.89	0.86 – 0.91	0.93	0.90 – 0.96	0.93	0.90 – 0.96
Time of anticoagulant intiation										
1st term of the year	1.0		1.0		1.0		1.0		1.0	
2nd term of the year	1.12	1.02 – 1.23	2.85	2.72 – 2.99	1.01	0.98 – 1.04	1.10	1.07 – 1.14	1.13	1.09 – 1.16
3rd term of the year	1.40	1.28 – 1.53	7.53	7.19– 7.88	0.94	0.91 – 0.97	1.13	1.09 – 1.16	1.19	1.15 – 1.23
4th term of the year	2.75	2.53 – 2.94	22.52	21.55 – 23.54	0.58	0.56 – 0.59	1.38	1.34 – 1.42	1.40	1.36 – 1.44

* 95% Confidence interval; † defined in the 12 months prior to cohort entry; ‡ defined in the 3 months prior to cohort entry

Discussion

Less than 6 months after reimbursement was approved, DOACs became the most frequently prescribed initial anticoagulant therapy for NVAF in France. Starting in the third quarter of 2012, DOACs were delivered to over 60% of all patients newly treated for NVAF. Dabigatran, rivaroxaban and, in late 2015, apixaban were used one after the other as the most frequent initial DOAC therapy for NVAF. The proportion of dabigatran initiators declined largely after 2013. DOAC initiators were younger and healthier than VKA users, and this tendency was reinforced over time. The use of DOACs varied over time depending on the availability of new drugs and on the national recommendations and safety warnings in place.

National trends in anticoagulant sales volumes have also been reported in other countries, revealing an important upsurge in DOAC use.[24-26] Most studies based on registries or cohorts of patients with NVAF have reported dabigatran use rates ranging from 5% to 25%, which is lower than what we found in our study.[27-30] However, in the US, Desai *et al*. have reported an increase in DOAC use for the 2010-2013 period which is similar to the one we observed, with a peak of 62% of patients initiating DOAC treatment among a cohort of anticoagulant initiators.[31] These common trends in results observed are surprising given the differences in populations, health systems, drug coverage, and, most importantly, clinical recommendations on the use of DOACs for the treatment of NVAF between countries. Indeed, in France, health authorities do not recommend DOACs as initial anticoagulant therapy, unless the patient has poor adherence to VKAs or unless biological monitoring of VKA treatment is difficult.[17] However, physicians are still free to opt for any of the available treatment and their personal beliefs on efficacy and safety influences their choices.

The sharp rise in DOAC use in France was observed as of mid-2012, shortly after the NHIS approved the reimbursement of dabigatran. Specifically, dabigatran was authorised as an anticoagulant for the treatment of NVAF in August 2011; reimbursement of treatment was pre-approved in February 2012, and it was fully approved in July 2012. Starting in November 2012, DOACs were used more frequently than VKAs as initial anticoagulant therapy. The reimbursement of rivaroxaban was fully approved in September 2012, and the drug was used more frequently than dabigatran as initial anticoagulant therapy as of January 2013. This rapid uptake of DOACs in the drug market may be explained by the fact that alternatives to VKAs had long been expected. Indeed, a recent study indicates that DOACs were considered equal or preferred to VKAs by respectively 48.5% and 33.3% of surveyed physicians.[32] The speed of adoption of DOACs is similar to that described for other new drugs, which usually reaches a plateau 6 to 12 months after they are launched.[33] This speed varies according to the specialty of the prescriber, and specialists are generally more prompt to adopt new drugs[33]—as was the case in our study. Nevertheless, some studies have reported no impact of physician specialty on the prescription of DOACs.[27,30] The differences we observed between the prescriptions of general practitioners (GP) and those of cardiologists may reflect the gap between national and European clinical guidelines. Indeed, French Health Authorities recommend VKAs as initial anticoagulant therapy, whereas the European Society of Cardiology favors DOACs.[3] GPs in the rest of Europe have taken a more cautious approach towards DOACs. This is especially the case in the treatment of elderly populations, most likely because there remains substantial uncertainty concerning the effectiveness and safety of DOACs in unselected elderly patients with NVAF.[34]

Our results indicate that the characteristics of patients who initiated treatment with DOACs rather than VKAs evolved over the first few years of drug commercialisation. In the first year, we observed a selection process with healthier patients using DOACs more frequently than VKAs as initial therapy.[31] This tendency was reinforced as DOAC initiators became healthier over time. It may reflect the evolution of the perception of efficacy and safety of these new drugs by physicians. The prescription of DOACs to healthier patients is an issue that needs to be addressed, as these molecules may offer higher-risk patients greater benefits than VKAs,[35] but also because their cost effectiveness depends on the severity of patients' condition.[36] Observational studies that aim to evaluate the risks and benefits associated with DOACs as well as cost effectiveness studies should carefully account for the fact that patients selected to initiate DOAC treatment are healthier overall, as well as for the selection of patients on the different types of DOACs.[37] Failure to do so may lead to underestimating the potential risks associated with DOACs in real life studies.

The fact that DOAC initiation is less frequent among patients with comorbidities may result from a warning issued by different health agencies such as in France, Europe or US.[35] This tendency seems to be linked to the diminishing use of dabigatran observed at the end of 2013, when the French medicine safety agency released warnings on bleeding risks associated with the drug.[38,39,40] At the time, French health authorities informed health professionals that DOACs are not recommended as initial therapy for NVAF, unless the patient has poor adherence to VKAs or unless biological monitoring of VKA treatment is difficult. However, while these recommendations were followed by a temporary decrease in

DOAC use, a few months later DOACs were once again the most frequently prescribed anticoagulants for patients newly treated for NVAF.

Our study has several strengths. The source database covers 66 million inhabitants and nearly 99% of the French population, which means that our findings are independent of individual health coverage. Moreover, we had access to exhaustive information on anticoagulant delivery because these treatments are delivered on prescription alone. As a result, our study is the largest to report penetration of DOACs on the market (particularly in the case of apixaban, which is the most recent DOAC available) and to describe variations in the characteristics of patients over time.

Nevertheless, some limitations must also be acknowledged. The NHIS administrative database does not include clinical or biological results; nor does it include outpatients' diagnosis codes. To capture outpatient diagnosis of AF, we based our definition of NVAF on drug dispensation, using the most likely treatment scheme for NVAF. Insofar as the results of our sensitivity analyses are consistent, we can be confident that our findings regarding the choice of the initial therapy and the patients' characteristics are not too sensitive to the definition of NVAF. Moreover, 69% of patients who were hospitalised during follow-up had a diagnostic code of NVAF in the hospital discharge database (data not shown). We did not use long duration diseases codes to define AF as these codes have various limitation, for example their use has been shown to differ between the different insurance schemes included in the database [41] and there was an important discrepancy between them and hospital discharge codes. These long duration disease codes were only used to define some

covariates but only in combination with drugs delivery and/or hospital codes. We did not exclude patients with Deep Vein Thrombosis or Pulmonary Embolism at inclusion. They represented 4.4 % of the study sample. We conducted a sensitivity analysis excluding these patients and obtained similar results (data not shown). Another limitation of our study is due to the 2015 data that may be partially incomplete. Indeed, for patients who do not have their NHIS card and attend a pharmacy that is not their regular pharmacy - a paper reimbursement form may be issued. The data are then recorded when the paper form is send to the NHIS and integrated later in the database. When the 2015 data were made available, paper claims were likely to have not all been included. However, this changes the total number of users but not the proportion of users of the different drugs.

The rapid and massive adoption of DOACs as initial therapy for NVAF will impact treatment expenditures because of the important increase in costs associated with these new drugs (in the US, these costs accounted for more than 90% of insurer spending on anticoagulants in 2014[31]). Future observational studies should carefully account for the fact that patients selected to initiate DOAC treatment are healthier overall, and that this tendency is reinforced over the first few years of drug commercialization. Failure to do so may bias the risk-benefit assessment of DOACs.

Contributor ship statement

LH, XR, CF designed the study. All authors have contributed substantially to the interpretation of results. In addition: LH and AB drafted the article; - CF conducted the statistical analysis; CF, CR, SL, LB, SS, OM, XR 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

Pr. Suissa has participated in advisory board meetings and received research grants from Bayer, Boehringer Ingelheim, Bristol-Myers-Squibb and Novartis. These activities are conducted outside this submitted study.

All other co-authors have no conflict of interest.

Funding

This research was supported by a 2012 research grant from the Agence Nationale de Sécurité du Médicament (ANSM).

Data sharing statement

No additional data are available directly from the authors. The datasource of the study is the French National Health Insurance. Data ara available from the Caisse National de l'Assurance Maladie des Travailleurs Salariés (CNAMTS) for academic research.

Ethics approval

The study was approved by the French National Institute of Data, and by the National Commission for Data Protection and Liberties (CNIL-France: authorization number: 1637014).

Acknowledgements

We thank the Caisse National de l'Assurance Maladie des Travailleurs Salariés (CNAMTS) and the Institut des Données de Santé (IDS) for their assistance in obtaining the study database.

We personally thank Ms. Valérie EDEL from the IDS, as well as Mr. Laurent DUCHET and Mr. Medhi GABBAS from the department in charge of the SNIIRAM DATA at CNAM-TS.

We are indebted to Arianne Dorval for proofreading the English manuscript. C Renoux is the recipient of a Chercheur-Boursier Award from the Fonds de la recherche du Québec - santé (FRQ-S). S Suissa is the recipient of the James McGill Chair.

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Figure 1 – Flow-chart describing cohort constitution

Figure 2 – Time trends in the prescription of anticoagulants in newly treated patients with Atrial Fibrilation between 2011 and 2015 in France (n = 814,446)

(VKA: vitamin K antagonist, DOAC: direct oral anticoagulant)

Significant changepoints in trends identified a segmented regression model (a): Dabigatran reimbursement approval, (b): Rivaroxaban reimbursement approval, (c): and Apixaban reimbursement approval, (d): Security warning (risks of bleeding hemorrhages) from the National Health Agency, (e): Downgrade of Dabigatran reimbursement.

Figure 3 – HAS-BLED and CHA2DS2-VASc scores associated with DOAC vs VKA initiation according to year of therapy initiation. Crude Odds Ratio and 95% confidence interval

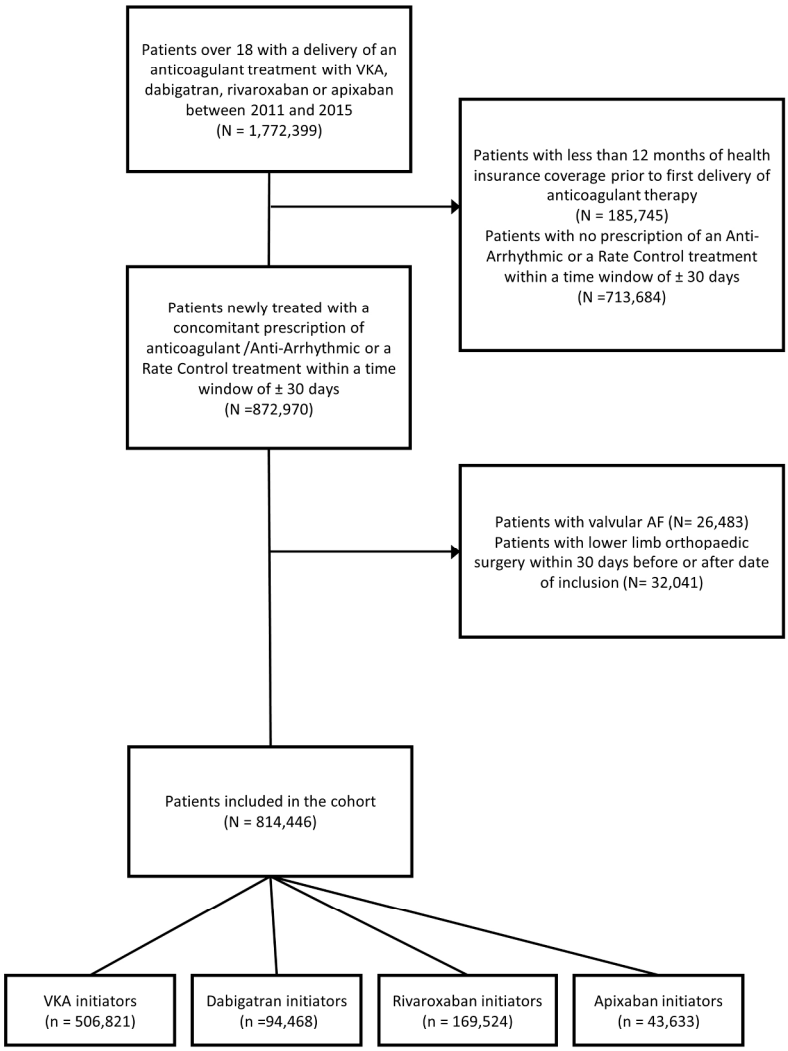
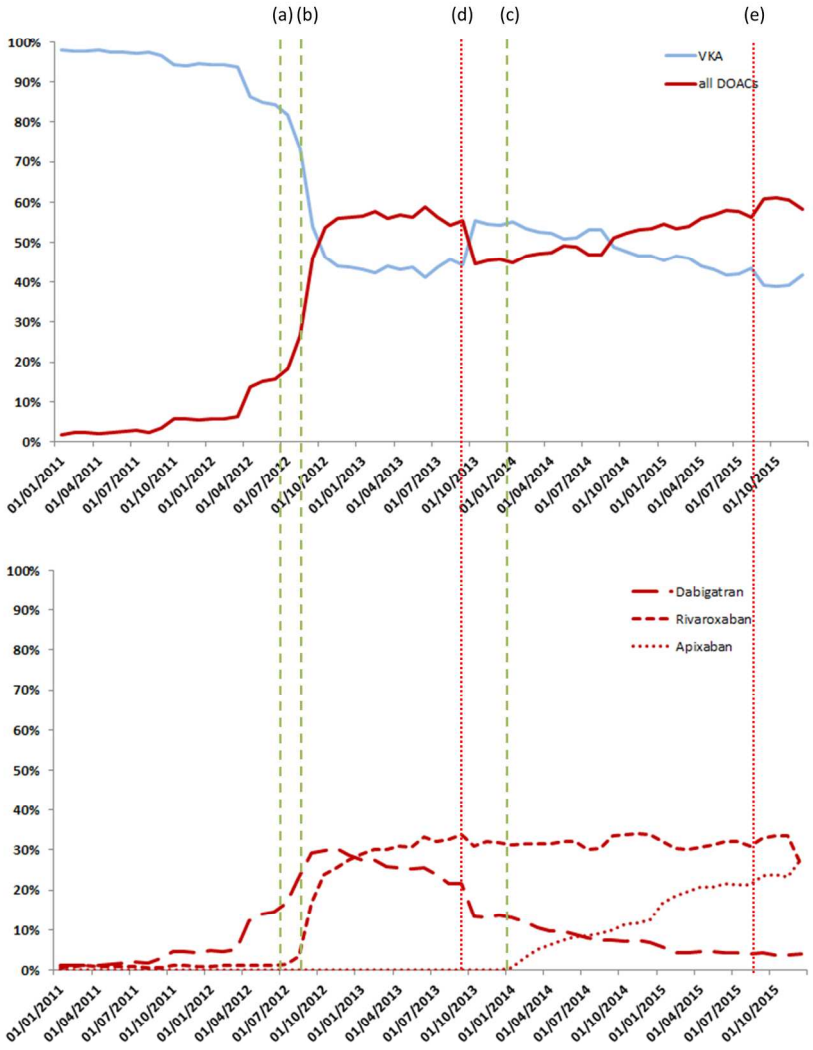


Figure 1 – Flow-chart describing cohort constitution

180x260mm (300 x 300 DPI)



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164x220mm (300 x 300 DPI)

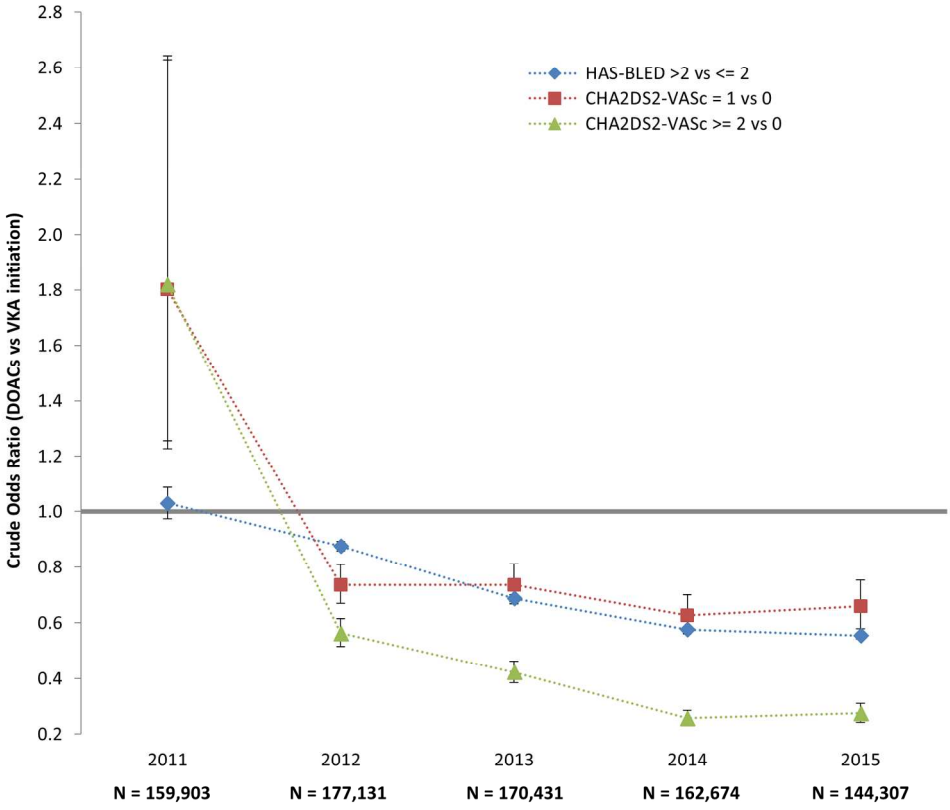

Figure 3 – HAS-BLED and CHA2DS2-VASc scores associated with DOAC vs VKA initiation according to year of therapy initiation. Crude Odds Ratio and 95% confidence interval

168x150mm (300 x 300 DPI)

Supplemental material – Sensitivity analysis – Cohort 1 - patients newly treated with an anticoagulant combined with an antiarrhythmic agent or a rate control treatment excluding beta-blockers, within a time window of +/- 30 days

Table 1 – Characteristics of Patients and Prescribers at Anticoagulant Treatment Initiation (2011-2015)

	VKA* N = 289,430	DOACs† N = 199,016
Demographic characteristics		
Mean age (sd§)	76.1 (11.2)	73.7 (11.3)
Male	49.8%	52.5%
Clinical characteristics‖		
High blood pressure	91.9%	88.7%
Ischemic heart disease	26.3%	16.6%
Heart failure	34.4%	21.6%
Diabetes	21.9%	18.6%
Cancer	16.1%	13.0%
Renal failure	9.7%	2.4%
Liver failure	1.3%	0.7%
Dementia	4.6%	2.7%
History Ischemic stroke	8.5%	6.2%
History of bleeding	5.5%	2.9%
HAS-BLED score, mean (sd)	2.6 (0.9)	2.4 (0.9)
CHA_2DS_2- $VASc_2$ score, mean (sd)	3.9 (1.5)	3.4 (1.5)
Other treatment at cohort entry¶		
Aspirin	45.9%	42.2%
Nonsteroidal anti-inflammatory drugs	13.8%	15.9%
Antiplatelet Agents (other than Aspirin)	14.4%	10.9%
Corticosteroids	13.9%	12.8%
Prescriber of first anticoagulant		
General Practitioner	59.7%	46.7%
Among general practitioners	*65.0%*	*35.0%*
Cardiologist	27.7%	43.8%
Among cardiologists	*47.9%*	*52.1%*
Other specialist	4.2%	3.8%
Unknown	8.4%	5.6%

* Vitamin K agonist; † Direct oral anticoagulants; ‡, p value comparing VKA vs DOACs; § sd: standard deviation; ‖ defined in the 12 months prior to cohort entry; ¶ defined in the 3 months prior to cohort entry

Supplemental material – Sensitivity analysis – Cohort 1 - patients newly treated with an anticoagulant combined with an antiarrhythmic agent or a rate control treatment excluding beta-blockers, within a time window of +/- 30 days

Table 2 – Characteristics of Patients and Prescribers at Anticoagulant Treatment Initiation in the Sub-Group of Patients Receiving a Direct Oral Anticoagulant (2011-2015)

	Dabigatran N = 65,851	Rivaroxaban N = 104,936	Apixaban N = 28,229
Demographic characteristics			
Mean age (sd†)	73.7 (11.4)	73.0 (11.3)	76.0 (11.0)
Male	52.3%	53.4%	49.6%
Clinical characteristics‡			
High blood pressure	88.7%	87.8%	91.8%
Ischemic heart disease	17.9%	15.8%	17.0%
Heart failure	22.8%	19.9%	25.2%
Diabetes	18.6%	18.3%	20.0%
Cancer	14.0%	12.8%	11.3%
Renal failure	2.1%	2.2%	3.8%
Liver failure	0.7%	0.6%	0.6%
Dementia	2.8%	2.6%	2.9%
History of ischemic stroke	7.2%	5.4%	7.1%
History of bleeding	2.7%	2.7%	3.6%
HAS-BLED score, mean (sd)	2.4 (0.9)	2.3 (0.9)	2.5 (0.9)
CHA_2DS_2- $VASc_2$, mean (sd)	3.4 (1.5)	3.2 (1.5)	3.6 (1.4)
Other treatments at cohort entry§			
Aspirin	43.0%	41.4%	43.2%
Nonsteroidal anti-inflammatory drugs	16.6%	16.1%	13.2%
Antiplatelet Agents (other than Aspirin)	11.3%	10.4%	12.1%
Corticosteroids	12.8%	12.8%	12.6%
Prescriber of first anticoagulant			
General Practitioner	47.0%	46.3%	47.5%
Cardiologist	43.1%	44.9%	41.7%
Other specialist	3.7%	3.8%	4.1%
Unknown	6.2%	5.0%	6.7%

* *Direct oral anticoagulants*, † Standard deviation, ‡ defined in the 12 months prior to cohort entry, § defined in the 3 months prior to cohort entry

Supplemental material – Sensitivity analysis – Cohort 1 - patients newly treated with an anticoagulant combined with an antiarrhythmic agent or a rate control treatment excluding beta-blockers, within a time window of +/- 30 days

Table 3 – Multivariate analysis of the determinants associated with DOAC initiation according to year of therapy initiation

Characteristics at treatment initiation	2011 N = 101,817		2012 N = 110,571		2013 N = 103,594		2014 N = 94,180		2015 N = 78,284	
	Adjusted OR	**CI 95%***	**Adjusted OR**	**CI 95%**	**Adjusted OR**	**CI 95%**	**Adjusted OR**	**CI 95%**	**Adjusted OR**	**CI 95%**
Demographic characteristics										
Age										
< 65 years	0.89	0.78 – 1.01	0.93	0.88 – 0.97	1.02	0.98 – 1.06	1.15	1.10 – 1.21	1.08	1.03 – 1.14
65 –74 years	1.0		1.0		1.0		1.0		1.0	
>= 75 years	1.15	1.04 – 1.27	0.98	0.94 – 1.01	0.69	0.67 – 0.71	0.59	0.57 – 0.61	0.65	0.63 – 0.68
Sex (Male)	0.86	0.79 – 0.94	0.97	0.94 – 1.01	1.09	1.06 – 1.13	1.10	1.06 – 1.13	1.08	1.05 – 1.12
Clinical characteristics†										
High blood pressure	0.87	0.76 – 1.00	0.82	0.78 – 0.86	0.79	0.75 – 0.83	0.78	0.74 – 0.82	0.79	0.74 – 0.84
Ischemic heart disease	0.88	0.79 – 0.97	0.83	0.80 – 0.86	0.76	0.74 – 0.79	0.74	0.72 – 0.77	0.76	0.72 – 0.79
Heart failure	0.60	0.55 – 0.67	0.70	0.68 – 0.72	0.61	0.59 – 0.63	0.59	0.57 – 0.61	0.63	0.60 – 0.65
Diabetes	0.88	0.79 – 0.98	0.89	0.86 – 0.93	0.88	0.85 – 0.91	0.93	0.89 – 0.96	0.92	0.89 – 0.96
Cancer	0.98	0.88 – 1.10	0.96	0.92 – 1.00	0.85	0.81 – 0.88	0.85	0.81 – 0.88	0.84	0.80 – 0.89
Renal failure	0.50	0.39 – 0.63	0.34	0.31 – 0.36	0.23	0.22 – 0.25	0.22	0.20 – 0.23	0.24	0.23 – 0.26
Liver failure	0.59	0.33 – 1.05	0.74	0.63 – 0.88	0.59	0.52 – 0.68	0.58	0.50 – 0.66	0.49	0.41 – 0.58
Dementia	0.96	0.77 – 1.19	0.84	0.77 – 0.92	0.75	0.70 – 0.80	0.81	0.76 – 0.88	0.74	0.68 – 0.81
History of Ischemic Stroke	1.01	0.87 – 1.16	0.99	0.94 – 1.05	0.88	0.84 – 0.93	0.88	0.84 – 0.93	0.92	0.86 – 0.98
History of bleeding	1.28	1.06 – 1.55	0.70	0.64 – 0.76	0.52	0.48 – 0.55	0.52	0.49 – 0.56	0.57	0.53 – 0.61
Prescriber of first anticoagulant										
General Practitioner	1.0		1.0		1.0		1.0		1.0	
Cardiologist	1.30	1.19 – 1.42	2.33	2.25 – 2.41	2.63	2.55 – 2.71	2.57	2.49 – 2.65	2.46	2.37 – 0.56
Other specialists/Unknown	1.72	1.52 – 1.93	1.03	0.97 – 1.08	1.00	0.96 – 1.05	1.03	0.98 – 1.07	1.03	0.98 – 1.08
Other treatments at cohort entry‡										
Aspirin	1.28	1.18 – 1.42	1.16	1.12 – 1.19	0.98	0.85 – 1.00	0.93	0.90 – 0.95	0.87	0.84 – 0.90
NSAID	1.37	1.24 – 1.52	1.16	1.11 – 1.21	1.18	1.13 – 1.22	1.21	1.17 – 1.27	1.20	1.14 – 1.26
Antiplatelet Agents	1.30	1.15 – 1.46	1.06	1.01 – 1.11	0.85	0.82 – 0.89	0.73	0.70 – 0.76	0.78	0.74 – 0.82
Corticosteroids	0.90	0.79 – 1.02	0.96	0.92– 1.00	0.93	0.89 – 0.96	0.98	0.94 – 1.02	0.92	0.88 – 0.96
Time of anticoagulant intiation										
1st term of the year	1.0		1.0		1.0		1.0		1.0	
2nd term of the year	1.13	0.96 – 1.32	3.17	2.98 – 3.37	1.00	0.96 -1.04	1.08	1.04 – 1.13	1.11	1.06 – 1.15
3rd term of the year	2.05	1.77 – 2.37	9.37	8.84 – 9.94	0.93	0.89 – 0.96	1.09	1.05 – 1.14	1.17	1.11 – 1.22
4th term of the year	4.71	4.14 – 5.36	31.06	29.34 – 32.88	0.54	0.52 – 0.56	1.35	1.30 – 1.40	1.39	1.33 – 1.45

* 95% Confidence interval; † defined in the 12 months prior to cohort entry; ‡ defined in the 3 months prior to cohort entry

Supplemental material – Sensitivity analysis – Cohort 2 - Cohort all patients newly treated with an anticoagulant therapy regardless of other potential concomitant therapies

Table 1 – Characteristics of Patients and Prescribers at Anticoagulant Treatment Initiation (2011-2015).

	VKA* N = 952,565	DOACs† N = 661,089
Demographic characteristics		
Mean age (sd§)	71.7 (15.3)	69.5 (13.8)
Male	48.4%	49.2%
Clinical characteristics‖		
High blood pressure	78.5%	71.3%
Ischemic heart disease	21.0%	11.9%
Heart failure	18.6%	8.8%
Diabetes	19.9%	15.7%
Cancer	16.7%	11.6%
Renal failure	9.3%	1.9%
Liver failure	1.6%	0.6%
Dementia	5.5%	2.4%
History Ischemic stroke	8.6%	5.0%
History of bleeding	6.8%	3.6%
HAS-BLED score, mean (sd)	2.3 (1.1)	2.0 (1.1)
CHA_2DS_2- $VASc_2$ score, mean (sd)	3.3 (1.7)	2.8 (1.6)
Other treatment at cohort entry¶		
Aspirin	35.8%	28.9%
Nonsteroidal anti-inflammatory drugs	17.1%	28.4%
Antiplatelet Agents (other than Aspirin)	11.7%	7.4%
Corticosteroids	15.1%	12.7%
Prescriber of first anticoagulant		
General Practitioner	70.7%	54.1%
Among General Practitioners	*64.7%*	*35.3%*
Cardiologist	15.6%	21.7%
Among Cardiologists	*50.0%*	*50.0%*
Other specialist	5.8%	18.2%
Unknown	7.9%	6.0%

* Vitamin K agonist; † Direct oral anticoagulants; ‡, p value comparing VKA vs DOACs; § sd: standard deviation; ‖ defined in the 12 months prior to cohort entry; ¶ defined in the 3 months prior to cohort entry

Supplemental material – Sensitivity analysis – Cohort 2 - Cohort all patients newly treated with an anticoagulant therapy regardless of other potential concomitant therapies

Table 2 – Characteristics of Patients and Prescribers at Anticoagulant Treatment Initiation in the Sub-Group of Patients Receiving a Direct Oral Anticoagulant (2011-2015) AC

	Dabigatran N = 174,423	Rivaroxaban N = 419,780	Apixaban N = 66,886
Demographic characteristics			
Mean age (sd†)	71.5 (12.5)	67.8 (14.3)	74.5 (11.8)
Male	49.6%	49.0%	49.4%
Clinical characteristics‡			
High blood pressure	76.9%	66.9%	84.4%
Ischemic heart disease	14.8%	10.4%	14.0%
Heart failure	11.0%	6.9%	15.3%
Diabetes	16.9%	14.6%	18.8%
Cancer	12.7%	11.3%	10.8%
Renal failure	1.9%	1.7%	3.7%
Liver failure	0.6%	0.6%	0.6%
Dementia	2.6%	2.2%	3.1%
History of ischemic stroke	6.5%	3.9%	8.4%
History of bleeding	3.5%	3.6%	4.0%
HAS-BLED score, mean (sd)	2.2 (1.0)	1.9 (1.1)	2.4 (1.0)
CHA_2DS_2- $VASc_2$, mean (sd)	3.0 (1.6)	2.6 (1.6)	3.4 (1.5)
Other treatments at cohort entry§			
Aspirin	32.8%	25.9%	37.6%
Nonsteroidal anti-inflammatory drugs	28.3%	29.8%	19.4%
Antiplatelet Agents (other than Aspirin)	8.7%	6.4%	10.1%
Corticosteroids	11.9%	13.1%	11.7%
Prescriber of first anticoagulant			
General Practitioner	48.2%	56.9%	51.4%
Cardiologist	24.1%	19.6%	29.2%
Other specialist	20.9%	18.0%	12.0%
Unknown	6.8%	5.5%	7.4%

* *Direct oral anticoagulants*, † Standard deviation, ‡ defined in the 12 months prior to cohort entry, § defined in the 3 months prior to cohort entry

Supplemental material – Sensitivity analysis – Cohort 2 - Cohort all patients newly treated with an anticoagulant therapy regardless of other potential concomitant therapies

Table 3 – Multivariate analysis of the determinants associated with DOAC initiation according to year of therapy initiation.

Characteristics at treatment initiation	2011 N = 319*,372		2012 N = 353,242		2013 N = 327,150		2014 N = 311,352		2015 N =275,538	
	Adjusted OR	**CI 95%***	**Adjusted OR**	**CI 95%**	**Adjusted OR**	**CI 95%**	**Adjusted OR**	**CI 95%**	**Adjusted OR**	**CI 95%**
Demographic characteristics										
Age										
< 65 years	0.57	0.56 – 0.59	0.63	0.62 – 0.64	0.74	0.72 – 0.76	0.81	0.79 – 0.82	0.81	0.79 – 0.83
65 –74 years	1.0		1.0		1.0		1.0		1.0	
>= 75 years	0.56	0.55 – 0.58	0.76	0.75 – 0.78	0.69	0.68 – 0.70	0.59	0.58 – 0.60	0.66	0.65 – 0.67
Sex (Male)	0.86	0.84 – 0.88	0.98	0.96 – 0.99	1.09	1.07 – 1.11	1.08	1.06 – 1.09	1.06	1.04 – 1.08
Clinical characteristics†										
High blood pressure	0.76	0.74 – 0.78	0.90	0.88 – 0.92	0.95	0.93 – 0.97	0.89	0.87 – 0.91	0.87	0.85 – 0.89
Ischemic heart disease	0.78	0.76 – 0.81	0.81	0.79 – 0.83	0.76	0.75 – 0.78	0.74	0.72 – 0.76	0.77	0.75 – 0.80
Heart failure	0.15	0.14 – 0.16	0.56	0.54 – 0.57	0.63	0.62 – 0.64	0.58	0.56 – 0.59	0.64	0.63 – 0.66
Diabetes	0.89	0.86 – 0.92	0.90	0.88 – 0.92	0.89	0.87 – 0.91	0.89	0.87 – 0.91	0.91	0.89 – 0.93
Cancer	0.71	0.69 – 0.73	0.81	0.79 – 0.83	0.75	0.73 – 0.76	0.73	0.72 – 0.75	0.70	0.68 – 0.72
Renal failure	0.29	0.27 – 0.32	0.30	0.29 – 0.32	0.23	0.22 – 0.24	0.22	0.21 – 0.23	0.26	0.25 – 0.27
Liver failure	0.50	0.44 – 0.57	0.50	0.46 – 0.55	0.47	0.43 – 0.50	0.43	0.40 – 0.47	0.40	0.37 – 0.44
Dementia	0.29	0.26 – 0.31	0.56	0.54 – 0.59	0.61	0.59 – 0.63	0.60	0.58 – 0.63	0.63	0.60 – 0.66
History of Ischemic Stroke	0.24	0.22 – 0.26	0.66	0.64 – 0.68	0.76	0.74 – 0.78	0.74	0.72 – 0.76	0.81	0.78 – 0.84
History of bleeding	1.00	0.95 – 1.05	0.70	0.68 – 0.73	0.54	0.52 – 0.56	0.53	0.51 – 0.55	0.54	0.52 – 0.56
Prescriber of first anticoagulant										
General Practitioner	1.0		1.0		1.0		1.0		1.0	
Cardiologist	0.26	0.25 – 0.28	1.91	1.87 – 1.95	2.86	2.80 – 2.92	2.78	2.72 – 2.84	2.67	2.60 – 2.73
Other specialists/Unknown	7.01	6.85 – 7.18	3.76	3.69 – 3.84	1.83	1.79 – 1.87	1.79	1.75 – 1.82	1.55	1.51 – 1.58
Other treatments at cohort entry‡										
Aspirin	0.71	0.69 – 0.73	1.00	0.98 – 1.02	0.98	0.96 – 1.00	0.91	0.90 – 0.93	0.87	0.85 – 0.88
NSAID	2.77	2.71 – 2.83	1.93	1.90 – 1.97	1.57	1.54 – 1.60	1.56	1.53 – 1.59	1.57	1.53 – 1.60
Antiplatelet Agents	0.64	0.61 – 0.68	0.94	0.91 – 0.97	0.83	0.81 – 0.85	0.75	0.72 – 0.77	0.76	0.73 – 0.78
Corticosteroids	0.60	0.58 – 0.62	0.70	0.68 – 0.72	0.79	0.77 – 0.80	0.84	0.82 – 0.86	0.87	0.85 – 0.89
Time of anticoagulant intiation										
1st term of the year	1.0		1.0		1.0		1.0		1.0	
2nd term of the year	1.02	0.99 – 1.05	1.35	1.32 – 1.38	1.05	1.03 – 1.07	1.12	1.10 – 1.14	1.10	1.08 – 1.13
3rd term of the year	0.81	0.78 – 0.83	2.22	2.17 – 2.28	0.96	0.94 – 0.98	1.09	1.07 – 1.12	1.12	1.10 – 1.15
4th term of the year	1.32	1.29 – 1.37	5.92	5.79 – 6.05	0.69	0.68 – 0.70	1.38	1.35 – 1.41	1.31	1.28 – 1.34

* 95% Confidence interval; † defined in the 12 months prior to cohort entry; ‡ defined in the 3 months prior to cohort entry

Supplementary table – Sources of codes used for the definition of covariates

Covariates at cohort entry	Definitions			
	Drug claims	Hospital discharge diagnoses (main or associated)	Hospital Inpatient procedures	Long duration disease codes
High blood pressure	X	X		X
Ischemic heart disease		X		
Heart failure	X	X		X
Diabetes	X	X		X
Cancer	X	X		X
Renal failure		X	X	X
Liver failure		X		X
Dementia	X	X		X
History Ischemic stroke		X		X
History of bleeding	X	X		
HAS-BLED score	X	X	X	X
CHA_2DS_2- $VASc_2$ score	X	X		X
Aspirin	X			
Nonsteroidal anti-inflammatory drugs	X			
Antiplatelet Agents (other than Aspirin)	X			
Corticosteroids	X			

STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5-6
Objectives	3	State specific objectives, including any pre-specified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7-8
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	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	8
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	*8*
Bias	9	Describe any efforts to address potential sources of bias	9
Study size	10	Explain how the study size was arrived at	Database study – NA
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9
		(*b*) Describe any methods used to examine subgroups and interactions	9
		(*c*) Explain how missing data were addressed	Administrative database study – no missing variable

		(*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	Only variable at cohort entry were used
		(*e*) Describe any sensitivity analyses	9
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	11
		(b) Give reasons for non-participation at each stage	11 and figure 1
		(c) Consider use of a flow diagram	Fig 1
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 – admin database study – no missing variables
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	Variables only at cohort entry
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
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 1
		(*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	Supplementary table
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	14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	15
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	14

		which the present article is based	

*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.