Observational Study Report - Study Information

Acronym/Title	**TRE**atment Pattern of **N**OACs (non-vitamin K oral anticoagulants) in Outpatient Users in Colombian **D**atabases – TREND Colombia
Report version and date	Version 1.0 07 May 2019
Study type / Study phase	Observational, Phase IV PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	EUPAS23099
Active substance	B01A Antithrombotic agents, direct Factor Xa Inhibitors (B01A F01 RIVAROXABAN, B01A F02 APIXABAN and B01A E07 DABIGATRAN)
Medicinal product	Xarelto, Pradaxa, and Eliquis
Product reference	EU/1/08/472/001-041
Procedure number	EMEA/H/C/00944
Study Initiator and Funder	Bayer AG
Research question and objectives	There are limited data on the patterns of use of non-vitamin K antagonist oral anticoagulants (NOACs) in stroke prevention in atrial fibrillation (SPAF) patients in routine care in Colombia. However these data are important to evaluate how they are being used to manage SPAF patients in Colombia and whether they are being prescribed in accordance with the drug labelling information. This population-based descriptive study aimed to characterize first-time users of three NOACs (rivaroxaban, dabigatran and apixaban) in SPAF in patients in routine patient care in Colombia, and to assess the patterns of NOAC utilization among these patients. The primary objectives were to: • provide a detailed description of SPAF patients who were prescribed a NOAC (rivaroxaban, dabigatran and apixaban) for the first time use in an outpatient

	setting • assess the pattern of outpatient use of NOACs in SPAF patients The secondary objective was to: • determine time-trends in the characteristics of first-time use of rivaroxaban, dabigatran and apixaban in outpatient SPAF patients.
Country of study	Colombia
Author	[redacted]

Marketing authorization holder

Marketing authorization holder(s)	Bayer AG, 51368 Leverkusen
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1. Abstract

Acronym/Title	**TRE**atment Pattern of **N**OACs (non-vitamin K oral anticoagulants) in Outpatient Users in Colombian **D**atabases – TREND Colombia
Report version and date **Author**	07 MAY 2019 and v1.0 [redacted]
Keywords	Direct Oral Anticoagulants (DOACs), Atrial Fibrillation, Drug Utilization
Rationale and background	Non-vitamin K antagonist oral anticoagulants (NOACs) have several advantages over vitamin K antagonists such as warfarin, including use of fixed dosing with no need for international normalized ratio monitoring, and fewer drug-drug interactions. Data on the patterns of use of NOACs in SPAF patients in routine care in Colombia are lacking. Such data, however, are important in order to study their use in the management of patients with non-valvular atrial fibrillation (NVAF) and whether they are being prescribed in accordance with the drug labelling information.
Research question and objectives	This population-based descriptive study aimed to characterize first-time users of three NOACs (rivaroxaban, dabigatran and apixaban) in patients with NVAF in Colombia, and to assess the patterns of drug utilization in these patients in routine general practice. The primary objectives were to: • provide a detailed description of SPAF patients who are prescribed a NOAC (rivaroxaban, dabigatran and apixaban) for the first time use in an outpatient setting • assess the pattern of outpatient use of NOACs in SPAF patients The secondary objective was to: • determine time-trends in the characteristics of first-time use of rivaroxaban, dabigatran and apixaban in outpatient SPAF patients
Study design	This was a population-based study designed to describe patterns of first-time NOAC use in patients with NVAF in Colombia.

Setting	The study was carried out in a primary care setting in Colombia, South America. The study period was from 01 JUL 2009 to 31 JUN 2017 (the latest date of data collection).
Subjects and study size, including dropouts	All patients aged ≥18 years with a diagnosis of NVAF and with at least 1 year of enrollment with their primary care physician (PCP) in the Audifarma S.A database and with 1 year since their first recorded health contact r were eligible for inclusion. Three mutually exclusive cohorts of first-time users of a NOAC (rivaroxaban, apixaban or dabigatran) with the date of first prescription the NOAC (index drug) being the index date, and followed all patients for at least 1 year.
Variables and data sources	**Patient characteristics**: demographics, comorbidities, co-medications (including prior anticoagulant use – naïve/non-naïve status), and healthcare use **Index NOAC characteristics**: dose, dose posology, duration of use **Data source**: Audifarma S.A outpatient primary care database, the main drug dispensing company within the Health System of Colombia
Results	10,528 patients with NVAF were identified as first-time users of a NOAC during the study period. The incidence rate of patients with NVAF who were started on apixaban or rivaroxaban increased steadily over the study period, whereas for dabigatran, the rate declined after a peak in 2013. The sex distribution of patients was broadly similar between NOAC cohorts with males accounting for more than half: apixaban 56.0%, dabigatran 54.9% and rivaroxaban 59.0%. The mean age was also similar across cohorts: apixaban 78.5 years, dabigatran 76.5 years and rivaroxaban 76.0 years. The apixaban cohort had the highest percentage of anticoagulant naïve patients (70.5%) compared with dabigatran (64.7%) and rivaroxaban (65.8%). Over half of patients were still prescribed their index NOAC at 6 months (apixaban 54.0%, dabigatran 58.5% and rivaroxaban 58.0%). Among patients starting on apixaban just over half (51.7%) received a daily dose of 5 mg, and just over at third (36.0%) had a first episode of continuous apixaban use of ≥180 days. Among patients starting on dabigatran, just over a third (34.7%) received a daily dose of 220 mg, while 42.1% received a daily dose of either 110 mg or 150 mg.

	Approximately half of patients starting on dabigatran (46.7%) had a first episode of continuous use that lasted more than 180 days while 28.4% had a first episode of continuous use that lasted for at least a year. Among patients starting on rivaroxaban, a total daily dose of 20 mg was the most frequent prescribed (43.9%), followed by a daily of 15 mg (28.4%). A little under half (43.5%) had a first episode of continuous use that lasted more than 180 days.
Discussion	The increasing use of NOACs in patients with NVAF in Colombia likely reflects the growing confidence in NOACs among PCPs in Colombia. The characteristics of these patients are in line with those seen in comparable European and American cohorts.
Marketing Authorization Holder(s)	Bayer AG
Names and affiliations of principal investigators	**Investigators:** [redacted] **Co-investigators:** • [redacted] Grupo de Investigación en Farmacoepidemiología y Farmacovigilancia. Universidad Tecnológica de Pereira y Audifarma S.A. Pereira, Colombia, South America [redacted] • [redacted] Spanish Centre for Pharmacoepidemiologic Research (CEIFE) Almirante, 28, 2 28004 Madrid, Spain Phone: +34-91-531 3404 Email: lagarcia@ceife.es

2. List of abbreviations

ACE	Angiotensin-Converting enzyme
CEIFE	Centro Español de Investigación Farmacoepidemiológica
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
DMARD	Disease-Modifying Antirheumatic Drug
IHD	Ischaemic Heart Disease
LMWH	Low-Molecular-Weight Heparin
MAH	Marketing Authorization Holder
N/A	Not Applicable
NOAC	Non-vitamin K Antagonist Oral Anticoagulant
NSAID	Non-Steroidal Anti-Inflammatory Drug
NVAF	Non-Valvular Atrial Fibrillation
OR	Odds Ratio
PAD	Peripheral Artery Disease
PAS	Post-Authorization Study
PCPs	Primary Care Physicians
PPI	Proton Pump Inhibitor
SD	Standard Deviation
SPAF	Stroke Prevention in Atrial Fibrillation
TIA	Transient Ischaemic Attack
VKA	Vitamin K Antagonist
VTE	Venous Thromboembolism

3. Investigators

Principal Investigator: [redacted]

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4. Other responsible parties

None.

5. Milestones

Table 1. Milestones

Milestone	Planned date	Actual Date	Comments
Ethics Submission & Approval	June 2017	July 2017	
Study Start	Feb 2018	Feb 2018	Collecting data retrospective from 1st January 2009
Start of data analysis	Mar 2018	Mar 2018	Collecting data up to last available database update (June 2017)
Registration in the EU PAS register	Feb 2018	Feb 2018	
Final report of study results	November 2017	May 2019	Sub-analysis

6. Rationale and background

Vitamin K antagonists (VKAs) have been the standard treatment for the prevention of stroke in patients with non-valvular atrial fibrillation (NVAF) for the last 60 years. Newer oral anticoagulants – non-vitamin K antagonist oral anticoagulants (NOACs) – have shown to have a more favourable efficacy and safety profile than VKAs. Two classes of NOACs are currently available, the oral direct thrombin inhibitors (dabigatran) and oral direct factor Xa inhibitors (e.g. rivaroxaban, and apixaban). Unlike VKAs, which block the formation of multiple active vitamin K-dependent coagulation factors (factors II, VII, IX, and X), these drugs block the activity of one single step in the coagulation cascade. Three NOACs (rivaroxaban, dabigatran, and apixaban) are now available and approved in Colombia for the prevention of stroke in non-valvular atrial fibrillation.

There is a shortage of real-world data on prescription and usage patterns of NOACs in stroke prevention in atrial fibrillation (SPAF) patients in routine care in Colombia. However, monitoring patterns of NOACs use in the general population is necessary to assess compliance with labelling information of these drugs. This population-based study aimed to characterize patients with NVAF in Colombia who were first-time users of either apixaban, dabigatran or rivaroxaban, and to assess patterns of NOAC use among these patients in routine general practice using the Audifarma Colombian database.

7. Research question and objectives

This population-based descriptive study aimed to characterize first-time users of three NOACs (rivaroxaban, dabigatran and apixaban) in patients with NVAF in Colombia, and to assess the patterns of drug utilization in these patients in routine general practice.

7.1 Primary objectives

The primary objectives were to:

- provide a detailed description of SPAF patients who are prescribed NOACs (rivaroxaban, dabigatran and apixaban) for first time use in an outpatient setting
- assess the pattern of outpatient use of NOACs in SPAF patients

7.2 Secondary objectives

The secondary objective was to:

- determine time-trends in the characteristics of first-time use of rivaroxaban, dabigatran and apixaban in outpatient SPAF patients

8. Amendments and updates

None

9. Research methods

9.1 Study design

This was a population-based descriptive study with the aim of characterizing first-time users of NOACs among patients with NVAF in Colombia and assessing use of these medications, including type and dose of the initial NOAC prescription.

9.1.1 Primary end points

- Baseline characteristics (comorbidities, co-medications and healthcare use) of patients with NVAF identified from a Colombian database and who were prescribed either rivaroxaban, dabigatran or apixaban for the first time for stroke prevention.
- Daily dose, dose posology, naïve status and treatment duration of the NOAC newly prescribed for patients with NVAF (including those with renal impairment) for stroke prevention.

9.2 Setting

The study was carried out in Colombia, South America using primary care data from the Audifarma S.A, the main drug dispensing company within the Health System of Colombia. The study period started on 01 JUL 2009 and ended on 31 JUN 2017 (the latest date of data collection). In Colombia the approved dosage for the prevention of stroke and systemic embolism in adults with NVAF is as follows: the recommended standard dosages are 5 mg twice daily for apixaban, 150 mg twice daily for dabigatran and 20 mg once daily for rivaroxaban; the recommended reduced dosages are 2.5 mg twice daily for apixaban, 110 mg twice daily for dabigatran and 15 mg once daily for rivaroxaban.

9.3 Subjects

All patients aged ≥18 years with at least 1 year of enrollment with their primary care physician (PCP) in the Audifarma S.A database and with 1 year since their first recorded health contact were eligible for inclusion in the study. From within this study population, three mutually exclusive cohorts of first-time users of NOACS – rivaroxaban, apixaban or dabigatran – were identified, with the date of first prescription the NOAC (index drug) being the index date. The study therefore applied a new-user (initiators) design.**(1)** Patients who qualified as members of more than one cohort on the same day, were excluded. If a patient qualified as first-time user of more than one study drug during the study period with different index dates they were assigned to the cohort of study drug first prescribed. From the three mutually exclusive NOAC study cohorts, patients with a record of atrial fibrillation (ICD-10 code I48) before the index date or in the 2 weeks after the index date were retained. As there is no specific code for NVAF in the International Classification of Diseases-10 coding system, patients with a record of valvular replacement or mitral stenosis before the index date or up to 2 weeks after the index date were excluded. Patients may have used other anticoagulants (e.g. warfarin) before their index date (first NOAC prescription during the study period); these patients were classed as non-naïve, while patients with no use of any other

anticoagulant before their index date were classed as naïve. All patients were followed up for at least 1 year from the index date.

9.4 Variables

9.4.1 NOAC dose and dose posology

The strength of the NOAC tablet was derived from the description of the prescribed NOAC, and dosing frequency/posology per day was derived from recorded instructions in the free text. A posology of three or more doses per day (derived from instructions) was considered to be invalid. If unclear, the daily dose of the first prescription was assigned by applying the algorithm for deduplication and daily dose assignment described as follows:

9.4.1.1 Deduplication

For two or more prescriptions for the same NOAC issued on the same day (concurrent prescriptions), deduplication was performed based on the following criteria:

- If concurrent prescriptions were of the same strength then the prescription with the greatest quantity of tablets was selected.
- If concurrent prescriptions were for rivaroxaban but were for different strengths with one prescription being for 15 mg, then this 15 mg prescription was selected.
- If the above did not apply and if there was another prescription for the same NOAC within a window of 30 days after the end of supply of the longest concurrent prescription, and this prescription was for the same strength as the original concurrent prescription, then this prescription selected.
- If the above did not apply then the first prescription issued as recorded in the database was selected.

9.4.1.2 Daily dose assignment

Following the deduplication process (where required), the daily NOAC was computed as follows:

- If the posology derived directly from the text-based dosage instructions had a value of 1 or 2 then the corresponding value of posology of 1 or 2 was assigned.
- If the above didn't apply and if the NOAC was apixaban or dabigatran then the posology was assigned to 2.
- If the above didn't apply and if the NOAC was rivaroxaban then the posology was assigned to 1, unless one of the following scenarios was present:
    - when there were concurrent prescriptions for 15 mg strength and 20 mg strength tablets then the posology was assigned to 2 for the 15 mg strength tablet prescription (this rule applied even when dosage instructions gave valid values of 1).

- when the rivaroxaban prescription was for tablets of 15 mg strength with a quantity of 42 tablets (irrespective of another concurrent rivaroxaban prescription) then the posology was assigned to 2.

Following these steps, the daily dose was derived as the product of the posology value and the strength of the selected NOAC prescription. This was followed by a process of manually changing the assigned daily dose of 40 mg rivaroxaban to 20 mg when the posology derived from dividing the number of tablets by the days in the time interval between consecutive prescriptions (gap between prescriptions of less than 90 days) resulted in a 20 mg daily dose (in this scenario, any information from the instructions field was disregarded).

9.4.2 Duration of NOAC use

For all patients, we calculated the duration of the first episode of continuous NOAC treatment. Continuous treatment was when there was either no gap in treatment of >30 days between the end of the supply of a prescription and the start of the next prescription for the same NOAC, or no further prescription after the end of the previous one.

9.4.2.1 Patient characteristics

Information on the following patient characteristics was extracted from the database:

- Demographics: age and sex at the index date
- Type and duration of use of other anticoagulants including warfarin and low-molecular-weight heparin (LMWH) before the index date.
- Prescriptions for the following medications in the year before the index date: antiplatelet drugs (low-dose aspirin, clopidogrel, dipyridamole, prasugrel, ticlopidine and ticagrelor), antiarrhythmics, antihypertensives, statins, anti-diabetic agents, non-steroidal anti-inflammatory drugs (NSAIDs), oral steroids, acid-suppressive drugs (proton pump inhibitors [PPIs] and histamine H_2-receptor antagonists), disease-modifying anti-rheumatic drugs (DMARDs), antidepressants, antipsychotic drugs, oral contraceptives, hormone replacement therapy, strong inhibitors of either cytochrome P450 3A4 or P-glycoprotein (e.g. the systemic azole antimycotics ketoconazole, itraconazole, voriconazole and posaconazole and the HIV-protease inhibitor ritonavir), strong CYP3A4 inducers (e.g. rifampicin, phenytoin, carbamazepine or phenobarbital) and fluconazole.
- Comorbidities (any time before, and including, the index date): severe renal disease, intracranial haemorrhage, urogenital bleeding, gastrointestinal bleeding, liver disease, pancreatic disease, cancer, cardiovascular (CV) disease (acute myocardial infarction, ischaemic heart disease (IHD), congestive heart failure, ventricular arrhythmia, peripheral arterial disease [PAD], venous thromboembolism [VTE]), CV risk factors (hypertension, diabetes mellitus, hyperlipidaemia and obesity), stroke/transient ischaemic attack (TIA), respiratory disease (asthma and chronic obstructive pulmonary disease [COPD]), rheumatoid arthritis, osteoarthritis, peptic ulcer disease, and alcohol-related disorders.
- Healthcare utilization: number of PCP visits, outpatient visits and hospital admissions in the year before the index date.

9.5 Data sources and measurement

The study was performed using the Audifarma S.A outpatient database, the database of the largest drug dispensing company in Colombia. Audifarma contains patient information for 4.8 million people affiliated to five health insurance companies in the Colombian healthcare system, which provides universal coverage through two regimes. The contributory regime is paid by the worker and the employer, while the subsidized regime is paid by the government free of charge. Both have a benefit plan covering warfarin for anticoagulant therapy but this does not include NOACs. To access these, the doctor may request them through a mechanism called MIPRES, making a request to the Health System and giving a justification of the need for the new anticoagulant.

Information on drug dispensing is stored on a server with daily dispensing data (approximately 2.8 million formulas per month). Data are available from 1 JAN 2006 to the present. Drugs are coded according to their Anatomical Therapeutic Chemical classification included in the Manual of Medicines of the Colombian Health System and medicines dispensed through scientific technical committees, “tutelas” and Mipres. Diagnoses linked to prescriptions are coded according to the International Classification of Diseases version 10.

The age and sex distribution of the population in Audifarma database in 2016 based on data from two of the 5 insurance companies – Salud total and Compensar, both of which have reliable and complete data of all Colombian patients affiliated with them and corresponding to 3.6 of the 4.8 million patients in this study – are shown in **Figure 1**.

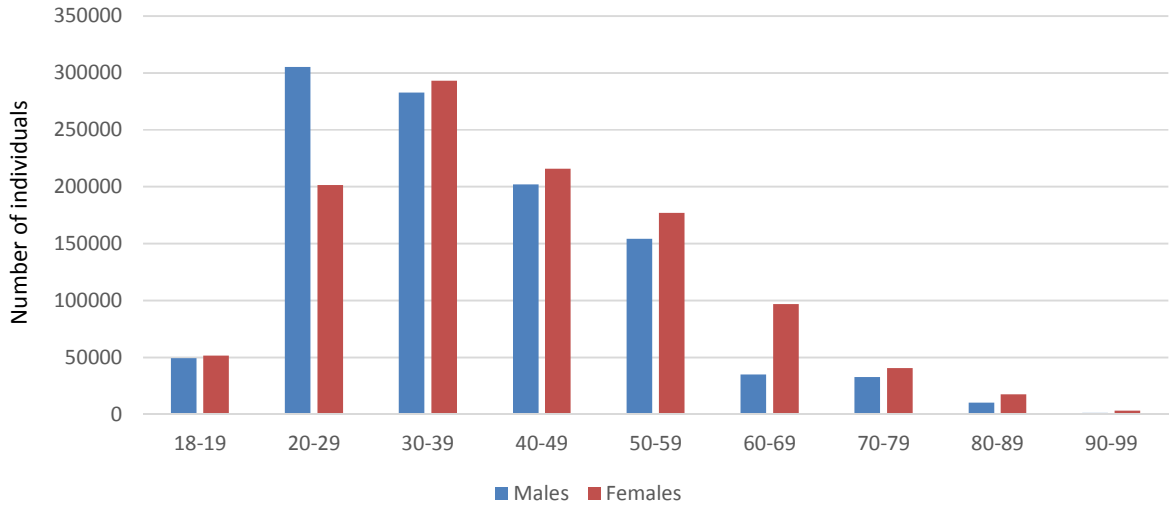


Figure 1. Age and sex distribution of the population in Audifarma database in 2016 based on data from two of the 5 insurance companies (Salud total and Compensar).

A comparison of the age distribution of the male and female populations in the Audifarma database and the general male/female population of Colombia in 2016 (according to the National Department of Statistics) is shown in **Figure 2** and **Figure 3**, respectively.

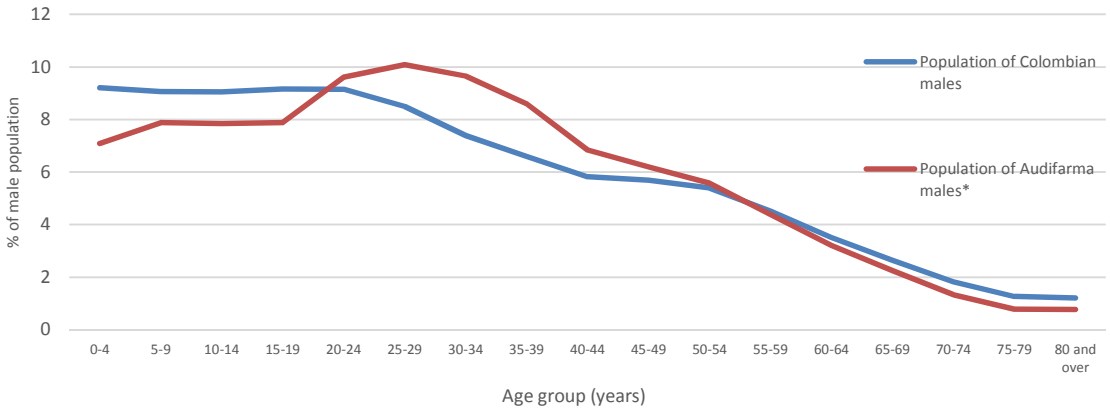


Figure 2. Age distribution of the male population in the Audifarma database (Salud total and Compensar) and the general female population of Colombia: data for 2016.

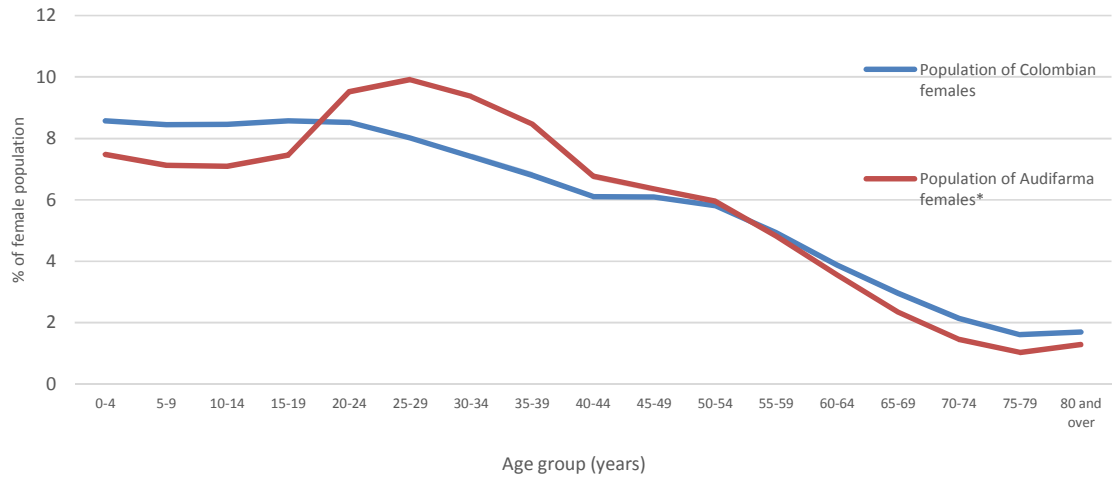


Figure 3. Age distribution of the female population in the Audifarma database (Salud total and Compensar) and the general female population of Colombia: data for 2016.

9.6 Bias

This drug utilization study was based on data from PCPs and physician specialists providing complete coverage of all age groups and with no selection bias. As all data recorded was independent of patients' recollection, recall bias would not be present. There is the possibility that some indications for NOACs use were misclassified if there were inaccuracies in recording.

9.7 Study size

This study was based on all data available during the study period (1 JAN 2009 to 30 JUN 2017), and was based on all patients with NVAF who were first-time users of apixaban, dabigatran or rivaroxaban.

9.8 Data transformation

All material, including the study protocol, a copy of Scientific Review Committee approval, algorithms and data collections, datasets, SPSS programs, results from validation exercises and questionnaires, final SPSS programs, and final report and publications, were kept in one folder cross-shared by the Grupo de Investigación en Farmacoepidemiología y Farmacovigilancia team. All data were kept in a secure location (all material is kept for a minimum of 10 years) and monthly back-ups were performed. As is standard practice, one researcher prepared the list of codes, tested the computer algorithms to be used and ran the statistical analysis after agreement on all phases of analyses with the rest of the team. As one measure of quality control (to minimise data errors), a researcher from CEIFE independently performed several checks by reviewing commands and analyses.

9.9 Statistical methods

9.9.1 Main summary measures

The main summary measures were the number and percentage (for categorical variables) and the number and mean with standard deviation (SD)(for age) of patients in each NOAC cohort for each characteristic studied. Potential changes in the prevalence of patient/index NOAC characteristics over time were quantified with the calculation of odds ratios (ORs) with 95% confidence intervals (CIs).

9.9.2 Main statistical methods

All data analysis was conducted using SPSS Statistics Version 25 (IBM, USA) for Windows. Standard methods of obtaining descriptive statistics were used for the main outcome summary measures. Crude ORs with 95% CIs to identify potential changes in characteristics over time were calculated using logistic regression.We estimated cumulative incidence rates of new use of NOACs among patients with NVAF per 1000 individuals for each study year, and also by age group and sex

in the last full year of the study period (2016). We also calculated the proportion of patients prescribed each NOAC among all new users of NOACS with NVAF for each study year.

9.9.3 Missing values

No data imputation strategies were applied to handle missing data. However, missing values for non-critical variables may have occurred in a small proportion of patients. Individuals with missing values were retained in the analyses using a separate category for those with missing values of the respective variable.

9.9.4 Sensitivity analyses

None.

9.9.5 Amendments to the statistical analysis plan

None.

9.10 Quality control

Standard operating procedures at the research centre (CEIFE) were used to guide the conduct of the study. These procedures included internal quality audits, rules for secure and confidential data storage, methods to maintain and archive project documents, quality control procedures for programming, standards for writing analysis plans, and requirements for senior scientific review. All programming written by the executing researcher were reviewed independently by a senior researcher. All key study documents, such as study reports, underwent quality control and senior scientific review. Privacy issues were addressed and respected at each stage of the study. All analyses and reporting were conducted on appropriately de-identified data. The Company did not receive any patient or provider identifiable information from CEIFE at any time. Conduct of study adhered with the Guidelines for Good Pharmacoepidemiology Practices.

10. Results

10.1 Participants

The steps involved in identification of the three NOAC cohorts are shown in **Figure 4**. A total of 18,551 patients met the inclusion criteria in Step 2. After creating mutually exclusive cohorts and retaining only patients with a diagnosis of NVAF, there were a total of 10,528 patients left for analysis: 2153 in the apixaban cohort, 3089 in the dabigatran cohort and 5286 in the rivaroxaban cohort.

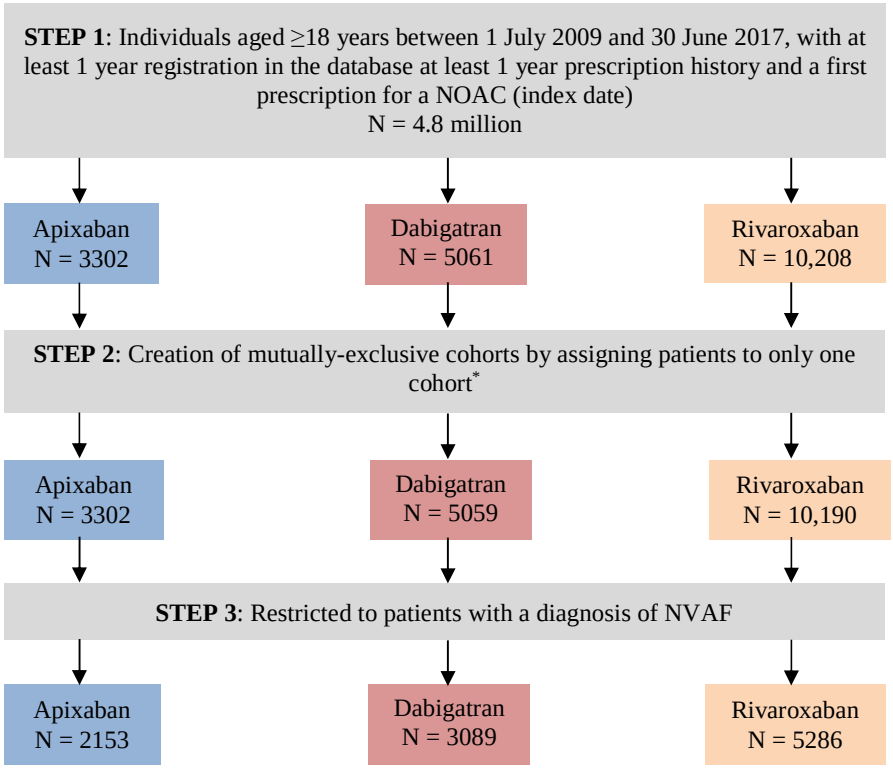


Figure 4. Flowchart depicting the identification of the three NOAC study cohorts.

*Mutually exclusive cohorts were created by excluding patients who were prescribed two different NOACs on the same day, and by assigning patients prescribed two different NOACs on different dates during the study period to the cohort of the first prescribed NOAC.

10.2 Descriptive data

As shown in **Figure 5a**, the number of patients with NVAF starting NOAC therapy on apixaban (36 in 2013, 780 in 2016) or rivaroxaban (310 in 2012, 813 in 2017) increased markedly over study years, while the number of patients with NVAF starting NOAC therapy on dabigatran (477 in 2012, 325 in 2017) decreased (in Colombia, dabigatran was approved in 2008, rivaroxaban was approved in 2011, and apixaban was approved in 2013). The same trends were seen in terms of incidence rates as shown in **Figure 6**. Of all patients with NVAF newly prescribed a NOAC, the percentage of use of each specific NOAC is shown in **Figure 5b**.

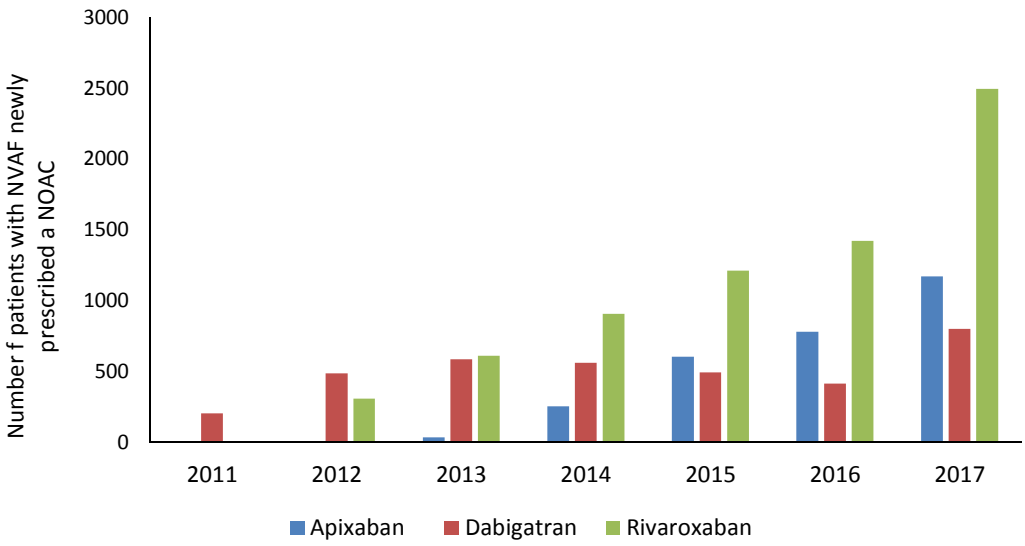


Figure 5a. Number of patients with NVAF newly prescribed apixaban, dabigatran or rivaroxaban by study year. Note: Data are for 2017 are up to December 2017.

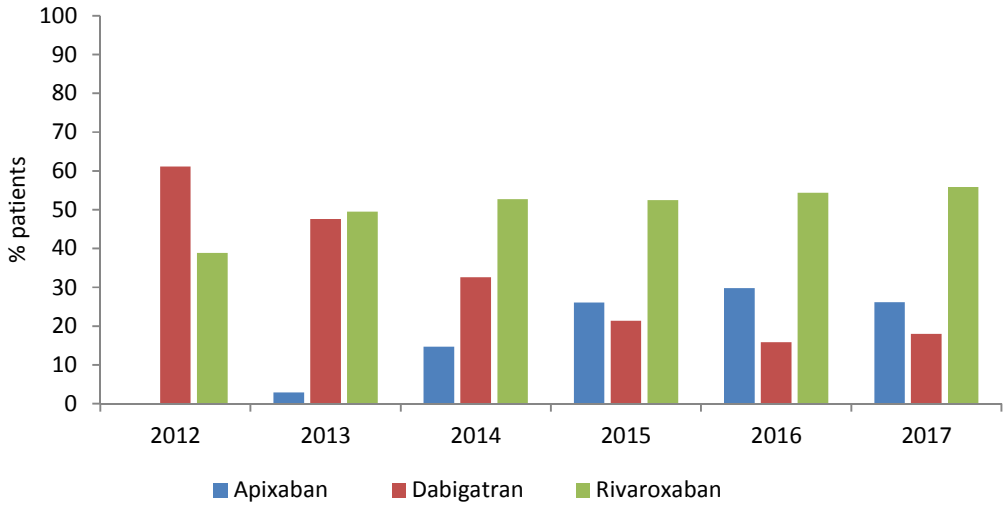
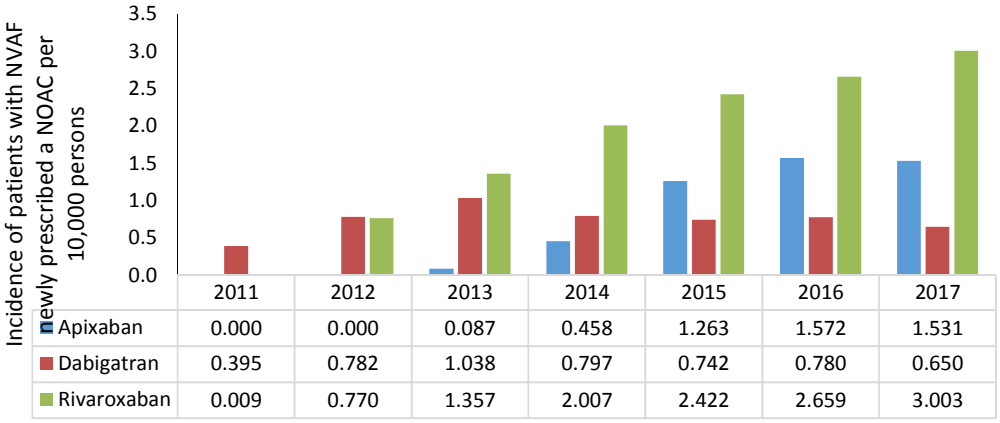


Figure 5b. Number of patients with NVAF newly prescribed apixaban, dabigatran or rivaroxaban by study year.
Note: Data are for 2017 are up to December 2017.



	2011	2012	2013	2014	2015	2016	2017
Apixaban	0.000	0.000	0.087	0.458	1.263	1.572	1.531
Dabigatran	0.395	0.782	1.038	0.797	0.742	0.780	0.650
Rivaroxaban	0.009	0.770	1.357	2.007	2.422	2.659	3.003

Figure 6. Incidence of NOAC use among patients with NVAF per 1000 patients by study year.
Note: Data are from only two clinical benefit providers (Salud Total and Compensar).

As shown in **Figure 7**, the most common the highest rates of NOAC use among patients with NVAF occurred among those aged 80–89 years.

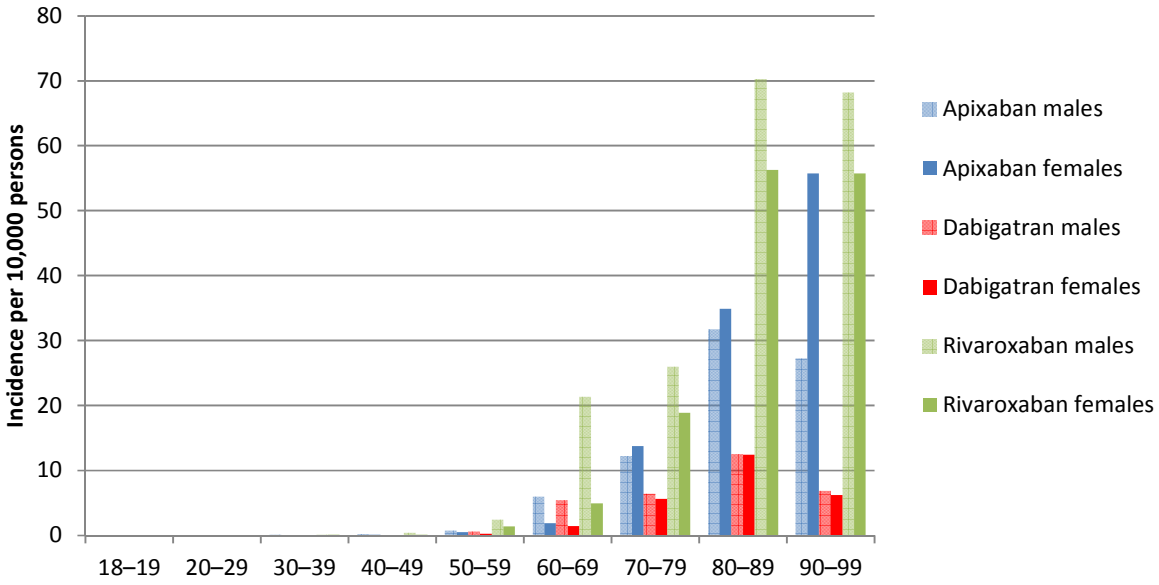


Figure 7. Incidence of patients with NVAF newly prescribed apixaban, dabigatran or rivaroxaban by age and sex in 2016.
Note: Data were from two clinical providers (Salud total and Compensar).

As shown in **Figure 8**, among patients with NVAF newly prescribed a NOAC, rivaroxaban became and remained the most commonly prescribed NOAC following its introduction in 2012. From 2015, apixaban became more commonly prescribed than dabigatran among patients with NVAF.

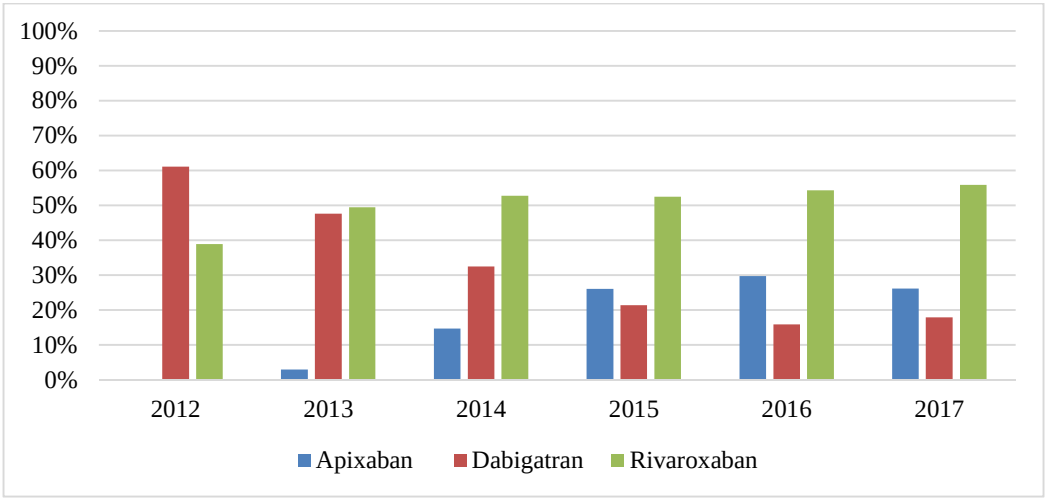


Figure 8. Percentage of patients prescribed each NOAC among all new users of NOACs with NVAF by study year (2012–2017).

10.3 Outcome data

Outcome data are described in **Section 10.4** (main results).

10.4 Main results

10.4.1 Patient characteristics

A total of 18,571 patients were identified with a first prescription for a NOAC (with or without a diagnosis of NVAF): 3,302 new users of apixaban, 5,061 new users of dabigatran and 10,208 new users of rivaroxaban. General characteristics of these 18,571 patients are shown in the **Appendix Table**. Among these, there were 10,528 patients with NVAF newly prescribed a NOAC: 2153 new users of apixaban (20.4%), 3089 new users of dabigatran (29.4%) and 5286 new users of rivaroxaban (50.2%).

General characteristics of these 10,528 patients are shown in **Table 2** by NOAC cohort. The percentage of males was broadly similar across NOAC cohorts: apixaban 56.0%, dabigatran 54.9% and rivaroxaban 59.0%. The mean age of patients was also similar across cohorts: apixaban 78.5 years, dabigatran 76.5 years and rivaroxaban 76.0 years. There was a higher percentage of patients who were anticoagulant naïve among the apixaban cohort (70.5%) compared with the dabigatran cohort (64.7%) and the rivaroxaban cohort (65.8%).

The frequency distribution of healthcare visits (including PCP visits, hospital referrals and hospital admission) and of polypharmacy (number of different medication in the 2 months before the index date) is shown in **Table 3** by NOAC cohort. In each NOAC cohort, around 40% of patients had fewer than 10 healthcare visits in the year before the index date. About a third of patients in each cohort had between 10 and 19 healthcare visits during this time period, while approximately 10% in each cohort had ≥30 healthcare visits. There was a significant percentage of patients in each cohort with polypharmacy. Close to 60% of patients in each cohort received between 5 and 9 different medications (including their NOAC) in the 2 months before the index date, and about a quarter of patients in each cohort received at least 10 different medications during this time period.

Table 2. General characteristics of patients with NVAF newly prescribed a NOAC.

	Apixaban N= 2153		**Dabigatran N= 3089**		**Rivaroxaban N= 5286**	
Sex						
Male	1206	56.0	1696	54.9	3117	59.0
Female	947	44.0	1393	45.1	2169	41.0
Age (years)						
<39	8	0.4	15	0.5	28	0.5
40–59	100	4.6	187	6.1	393	7.4
60–69	259	12.0	501	16.2	858	16.2
70–79	633	29.4	946	30.6	1667	31.5
≥80	1102	51.2	1288	41.7	2163	40.9
Unknown	51	2.4	152	4.9	177	3.3
Mean age (SD)	78.5 (11.0)		76.5 (11.0)		76.0 (11.0)	
Anticoagulant naïve status						
Naive	1517	70.5	1999	64.7	3480	65.8
Non-naive	636	29.5	1090	35.3	1806	34.2
Year of first prescription						
2009	0	0.0	0	0.0	1	0.0
2010	0	0.0	10	0.3	3	0.1
2011	0	0.0	206	6.7	2	0.0
2012	0	0.0	477	15.4	310	5.9
2013	36	1.7	588	19.0	612	11.6
2014	254	11.8	561	18.2	909	17.2
2015	604	28.1	495	16.0	1213	22.9
2016	780	36.2	416	13,.5	1423	26.9
2017 (Jan to end of June)	479	22.2	325	10.5	813	15.4
2017	1171	41.2	802	22.4	2497	35.8
Mean duration of follow-up (days)		**541.9**		**1030.8**		**747.9**

Data are n (%) unless otherwise specified.

Table 3. Healthcare visits and polypharmacy among patients with NVAF newly prescribed a NOAC.

	Apixaban N=2153		Dabigatran N=3089		Rivaroxaban N=5286	
	n	**%**	**n**	**%**	**n**	**%**
Healthcare visits*						
<3	546	25.4	829	26.8	1280	24.2
4–9	303	14.1	496	16.1	780	14.8
10–19	708	32.9	1002	32.4	1768	33.4
20–29	338	15.7	459	14.9	855	16.2
≥30	258	12.0	303	9.8	603	11.4
Polypharmacy†						
None	473	22.0	722	23.4	1007	19.1
1–4	428	19.9	620	20.1	1077	20.4
5–9	704	32.7	1016	32.9	1785	33.8
≥10	548	25.5	731	23.7	1417	26.8

*Health care visits in the year before the index date.
†Number of different medications (including NOACs) in the 2 months before the index date.

Comorbidities among patients with NVAF newly prescribed a NOAC are shown in **Table 4** for each NOAC cohort. The frequencies of most comorbidity, including hypertension, PAD, obesity, diabetes, asthma, COPD, rheumatoid arthritis, cancer and severe renal disease, were broadly similar across NOAC cohorts. Hypertension was recorded in the vast majority (>80% in each cohort), heart failure in about one third of patients in each cohort and diabetes mellitus in about one fifth of patients in each cohort. Heart failure, myocardial infarction, IHD, VTE and hyperlipidaemia were all more prevalent among the rivaroxaban cohort. The dabigatran cohort had the highest percentage of patients with a previous record of ischaemic stroke and urogenital bleeding but also the lower percentage of patients with a previous record of gastrointestinal bleeding. A previous record of VTE occurred more frequently among patients starting on rivaroxaban (6.3%) compared with those starting on apixaban (2.5%) or dabigatran (3.5%).

Medication use in the year before the index date is shown for the three NOAC study cohorts in **Table 5**. The most frequently prescribed medications in the year before starting NOAC therapy were beta-blockers, statins, low-dose aspirin, proton pump inhibitors and diuretics. For several medications, including low-dose aspirin, NSAIDS, antiarrhythmics, antihypertensives, diuretics, and statins, the highest level of previous use was among patients in the rivaroxaban cohort. The apixaban cohort had the lowest level of previous anticoagulant use as well as previous antiarrhythmic drugs use. The frequency of previous use of antidiabetics, PPIs, ranitidine, antipsychotics and antidepressants was similar between the cohorts.

Table 4. Comorbidities among patients with NVAF newly prescribed a NOAC.

	Apixaban N=2153		Dabigatran N=3089		Rivaroxaban N=5286	
COMORBIDITY*	**n**	**%**	**n**	**%**	**n**	**%**
CV disease/risk factors						
Myocardial infarction	96	4.5	119	3.9	274	5.2
IHD	57	2.6	108	3.5	188	3.6
Heart failure	683	31.7	1115	36.1	2010	38.0
Ventricular arrhythmia	121	5.6	274	8.9	380	7.2
PAD	10	0.5	26	0.8	39	0.7
VTE	55	2.5	107	3.5	334	6.3
Hypertension	1724	80.1	2533	82.0	4359	82.5
Hyperlipidaemia	288	13.4	468	15.2	955	18.1
Ischaemic stroke	150	7.0	300	9.7	395	7.5
TIA	33	1.5	73	2.4	126	2.4
Bleeding disorders						
Intracranial bleeding	9	0.4	20	0.6	33	0.6
Gastrointestinal bleeding	81	3.8	25	0.8	195	3.7
Urogenital bleeding	22	1.0	80	2.6	58	1.1
Endocrine/metabolic disease						
Obesity	131	6.1	199	6.4	412	7.8
Diabetes mellitus	432	20.1	710	23.0	1161	22.0
Respiratory disease						
COPD	320	14.9	456	14.8	870	16.5
Asthma	72	3.3	112	3.6	215	4.1
Gastrointestinal disease						
Liver disease	8	0.4	19	0.6	42	0.8
Pancreatic disease	0	0.0	0	0.0	1	0.0
Peptic ulcer disease	3	0.1	0	0.0	7	0.1
Other diseases						
Rheumatoid arthritis	61	2.8	69	2.2	133	2.5
Osteoarthritis	244	11.3	322	10.4	706	13.4
Cancer	138	6.4	190	6.2	347	6.6
Solid cancer	121	5.6	165	5.3	295	5.6
Hematological cancer	9	0.4	13	0.4	33	0.6
Unknown cancer	8	0.4	12	0.4	19	0.4
Severe renal disease	350	16.3	452	14.6	831	15.7
Alcohol-related disorders	10	0.5	16	0.5	24	0.5

*Any time before (and including) the index date.

Table 5. Medication use in the year before the index date among patients with NVAF newly prescribed a NOAC.

	Apixaban N=2153		Dabigatran N=3089		Rivaroxaban N=5286	
MEDICATION	**n**	**%**	**n**	**%**	**n**	**%**
Antiplatelet agents	974	45.2	1422	46.0	2511	47.5
Low-dose aspirin	924	42.9	1349	43.7	2386	45.1
Clopidogrel	240	11.1	329	10.7	543	10.3
NSAIDs	216	10.0	343	11.1	695	13.1
Oral steroids	140	6.5	161	5.2	347	6.6
Anticoagulants	695	32.3	1217	39.4	1939	36.7
Antiarrhythmic	323	15.0	533	17.3	932	17.6
Propafenone	39	1.8	80	2.6	125	2.4
Amiodarone	287	13.3	462	15.0	824	15.6
Dronedarone	1	0.0	4	0.1	4	0.1
Antihypertensives	1601	74.4	2222	71.9	4047	76.6
Beta-blockers	1258	58.4	1792	58.0	3177	60.1
ACE inhibitors	373	17.3	553	17.9	988	18.7
Diuretics	882	41.0	1230	39.8	2290	43.3
Statins	1193	55.4	1665	53.9	3020	57.1
Antidiabetic drugs	370	17.2	499	16.2	893	16.9
Oral contraceptives[*]	0	0.0	1	0.0	1	0.0
Hormone replacement therapy[*]	0	0.0	3	0.1	4	0.1
PPIs	950	44.1	1322	42.8	2388	45.2
H_2-receptor antagonists	170	7.9	306	9.9	521	9.9
DMARDs	49	2.3	61	2.0	122	2.3
Antidepressants	375	17.4	472	15.3	886	16.8
Antipsychotic drugs	76	3.5	91	2.9	155	2.9
Strong inhibitors of either cytochrome P450 3A4 or P-glycoprotein[†]	0	0.0	0	0.0	0	0.0
Strong CYP3A4 inducers[$]	122	5.7	185	6.0	382	7.2

[*]Among 4509 women.
[†]Including the following drugs: ketoconazole, voriconazole, posaconazole, ritonavir, lopinavir plus ritonavir and itraconazole.
[$]Including the following drugs: fluconazole, rifampicin, rifampicin w isoniazid, phenytoin, phenytoin w phenobarbitone, carbamazepine and phenobarbital.

10.4.1.1 Time-trends in patient characteristics

Demographics and anticoagulation naïve status among patients with NVAF newly prescribed a NOAC by study year is shown in **Table 6** for apixaban, **Table 7** for dabigatran and **Table 8** for rivaroxaban.

Among new users of apixaban (**Table 6**), the majority in 2013 were female yet the majority in later study years were male (55.6% in 2016). The percentage of patients over 80 years of age increased from 33.3% in 2013 to 50.3% in 2016. The proportion of patients aged <60 years also increased over study years from 2.8% in 2013 to 6.4% in 2016, as did the percentage of patients who were anticoagulant naïve (50.0% in 2013 and 70.6% in 2016).

Among new users of dabigatran (**Table 7**), males accounted for less than half of patients in 2011 (48.1%) but for more than half in later study years (56.0% in 2016). The percentage of patients over 80 years of age decreased from 56.8% in 2011 to 30.5% in 2016, while the percentage of patients aged <60 years almost doubled rising from 4.9% in 2011 to 9.6% in 2016. The percentage of patients who were anticoagulant naïve increased significantly from 57.3% in 2011 to 73.8% in 2016, OR 2.07 (95% CI: 1.56–2.75)

Among new users of rivaroxaban (**Table 8**), males increasingly accounted for the majority of patients across study years (55.8% in 2012 and 62.1% in 2016). The percentage of patients over 80 years of age decreased from 44.2% in 2012 to 37.5% in 2016, OR 0.39 (95% CI: 0.22–0.67), while the percentage of patients aged <60 years more than doubled increasing from 5.2% in 2012 to 11.2% in 2016. The percentage of patients who were anticoagulant naïve increased from 54.2% in 2012 to 69.4% in 2016, OR 1.91 (95% CI: 1.49–2.46).

Table 6. General characteristics of patients with NVAF newly prescribed apixaban by calendar year.

	2011		2012		2013 N=36		2014 N=254		2015 N=604		2016 N=780		2017 N=479		Crude OR (95% CI) (2016–2014)
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	
Sex															
Male	–	–	–	–	16	44.4	147	57.9	349	57.8	434	55.6	261	54.5	0.91 (0.68–1.22)
Female	–	–	–	–	20	55.6	107	42.1	256	42.4	346	44.4	218	45.5	1.0 (reference)
Age (years)															
<60	–	–	–	–	1	2.8	12	4.7	24	4.0	50	6.4	35	7.3	1.0 (reference)
60–69	–	–	–	–	6	16.7	27	10.6	69	11.4	91	11.7	66	13.8	0.81 (0.38–1.73)
70–79	–	–	–	–	15	41.7	72	28.3	178	29.5	243	31.2	125	26.1	0.81 (0.41–1.60)
≥80	–	–	–	–	12	33.3	138	54.3	321	53.1	392	50.3	239	49.9	0.68 (0.35–1.31)
Anticoagulation naïve status															
Naïve	–	–	–	–	18	50.0	169	66.5	439	72.7	551	70.6	340	71.0	1.20 (0.89–1.63)
Non-naïve	–	–	–	–	18	50.0	85	33.5	165	27.3	230	29.5	139	29.0	1.0 (reference)

Table 7. General characteristics of patients with NVAF newly prescribed dabigatran by calendar year.

	2011 N=206		2012 N=488		2013 N=588		2014 N=561		2015 N=495		2016 N=416		2017 N=325		Crude OR (95% CI) (2016–2012)
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	
Sex															
Male	99	48.1	259	53.1	316	53.7	310	55.3	273	55.2	233	56.0	200	61.5	1.12 (0.86–1.46)
Female	107	51.9	229	46.9	272	46.3	251	44.7	222	44.8	183	44.0	125	38.5	1.0 (reference)
Age (years)															
<60	10	4.9	22	4.5	46	7.8	35	6.2	38	7.7	40	9.6	28	8.6	1.0 (reference)
60–69	15	7.3	63	12.9	86	14.6	85	15.2	89	18.0	98	23.6	63	19.4	0.86 (0.46–1.57)
70–79	49	23.8	117	24.0	171	29.1	194	34.6	158	31.9	148	35.6	106	32.6	0.70 (0.39–1.24)
≥80	117	56.8	239	49.0	256	43.5	223	39.8	200	40.4	127	30.5	122	37.5	0.29 (0.17–0.51)
Anticoagulation naïve status															
Naïve	118	57.3	281	57.6	374	63.6	364	64.9	338	68.3	307	73.8	214	65.8	2.07 (1.56–2.75)
Non-naïve	88	42.7	207	42.4	214	36.4	197	35.1	157	31.7	109	26.2	111	34.2	1.0 (reference)

Table 8. General characteristics of patients with NVAF newly prescribed rivaroxaban by calendar year.

	2012 N=310		2013 N=612		2014 N=909		2015 N=1213		2016 N=1423		2017 N=813		Crude OR (95% CI) (2016–2012)
	n	%	n	%	n	%	n	%	n	%	n	%	
Sex													
Male	173	55.8	331	54.1	515	56.7	706	58.2	884	62.1	506	62.2	1.30 (1.01–1.67)
Female	137	44.2	281	45.9	394	43.3	507	41.8	539	37.9	307	37.8	1.0 (reference)
Age (years)													
<60	16	5.2	31	5.1	72	7.9	107	8.8	160	11.2	81	10.0	1.0 (reference)
60–69	34	11.0	68	11.1	147	16.2	213	17.6	257	18.1	139	17.1	0.76 (0.40–1.41)
70–79	101	32.6	174	28.4	258	28.4	399	32.9	463	32.5	267	32.8	0.46 (0.26–0.80)
≥80	137	44.2	305	49.8	410	45.1	469	38.7	534	37.5	307	37.8	0.39 (0.22–0.67)
Anticoagulation naïve status													
Naïve	168	54.2	360	58.8	562	61.8	815	67.2	987	69.4	583	71.7	1.91 (1.49–2.46)
Non-naïve	142	45.8	252	41.2	347	38.2	398	32.8	436	30.6	230	28.3	1.0 (reference)

Comorbidities among patients with NVAF newly prescribed a NOAC are shown for each study year in **Table 9** for apixaban, **Table 10** for dabigatran and **Table 11** for rivaroxaban.

Among new users of apixaban (**Table 9**) several comorbidities became less prevalent over study years (2016 vs. 2014): hypertension (OR: 0.65, 95% CI: 0.42–0.98), heart failure (OR: 0.69, 95% CI: 0.52–0.93), ventricular arrhythmias (OR: 0.51, 95% CI: 0.30–0.88), TIA (OR: 0.38, 95% CI: 0.16–0.89), diabetes mellitus (OR: 0.64, 95% CI: 0.46–0.89) and severe renal disease (OR: 0.46, 95% CI: 0.33–0.68). The percentage of patients with dyslipidaemia and the percentage of those with the other comorbidities evaluated remained stable.

Similarly to apixaban, among new users of dabigatran (**Table 10**), several comorbidities became less prevalent over study years (2016 vs. 2012): myocardial infarction (OR: 0.46, 95% CI: 0.22–0.96), heart failure (OR: 0.55, 95% CI: 0.41–0.72), hypertension (OR: 0.47, 95% CI: 0.33–0.66), ventricular arrhythmias (OR: 0.26, 95% CI: 0.15–0.44), ischaemic stroke (OR: 0.33, 95% CI: 0.21–0.54), TIA (OR: 0.23, 95% CI: 0.04–0.81), asthma (OR: 0.36, 95% CI: 0.15–0.86), COPD (OR: 0.53, 95% CI: 0.46–0.78) and severe renal disease (OR: 0.44, 95% CI: 0.29–0.65). The percentage of patients with obesity, diabetes mellitus and rheumatoid arthritis remained stable over study years.

As with patients in the apixaban and dabigatran cohorts, among new users of rivaroxaban (**Table 11**) there was a reduction in the percentage of patients with certain comorbidities over study years (2016 vs. 2012): myocardial infarction (OR: 0.54, 95% CI: 0.33–0.88), heart failure (OR: 0.45, 95% CI: 0.35–0.57), hypertension (OR: 0.54, 95% CI: 0.38–0.77), ventricular arrhythmias (OR: 0.28, 95% CI: 0.19–0.44), VTE (OR: 0.51, 95% CI: 0.33–0.79), ischaemic stroke (OR: 0.30, 95% CI:0.21–0.43), TIA (OR: 0.42, 95% CI: 0.23–0.78), intracranial bleeding (OR: 0.16, 95% CI: 0.05–0.46), diabetes mellitus (OR: 0.70, 95% CI:0.53–0.93), COPD (OR: 0.58, 95% CI: 0.43–0.80), rheumatoid arthritis (OR: 0.34, 95% CI: 0.17–0.64) and severe renal disease (OR: 0.60, 95% CI: 0.44–0.82). The percentage of patients with obesity remained stable over study years.

Table 9. Comorbidities among patients with NVAF newly prescribed apixaban by calendar year.

	2013 N=36		2014 N=254		2015 N=604		2016 N=780		2017 N=479		Crude OR 95% CI (2016–2014)	
	n	%	n	%	n	%	n	%	n	%		
CV disease												
Myocardial infarction	1	2.8	6	2.4	28	4.6	34	4.4	27	5.6	1.88	0.78–4.54
IHD	2	5.6	10	3.9	17	2.8	18	2.3	10	2.1	0.58	0.26–1.26
Heart failure	11	30.6	101	39.8	205	33.9	245	31.4	121	25.3	0.69	0.52–0.93
Ventricular arrhythmia	4	11.1	23	9.1	42	7.0	38	4.9	14	2.9	0.51	0.30–0.88
PAD (lower extremity)	0	0.0	3	1.2	3	0.5	4	0.5	9	1.9	0.44	0.10–1.94
VTE	3	8.3	6	2.4	19	3.1	22	2.8		0.0	1.20	0.48–2.99
Hypertension	33	91.7	223	87.8	461	76.3	642	82.3	365	76.2	0.65	0.42–0.98
Hyperlipidaemia	5	13.9	24	9.4	87	14.4	105	13.5	67	14.0	1.49	0.93–2.38
Ischaemic stroke	1	2.8	24	9.4	50	8.3	50	6.4	7	1.5	0.66	0.39–1.09
TIA	0	0.0	10	3.9	7	1.2	12	1.5	4	0.8	0.38	0.16–0.89
Bleeding disorders												
Intracranial bleeding	0	0.0	2	0.8	4	0.7	2	0.3	1	0.2	0.32	0.04–2.31
Gastrointestinal bleeding	1	2.8	13	5.14	26	4.3	29	3.7	12	2.5	0.72	0.37–1.40
Urogenital bleeding	1	2.8	3	1.2	5	0.8	7	0.9	6	1.3	0.76	0.19–2.95
Endocrine/metabolic disease												
Obesity	1	2.8	15	5.9	38	6.3	51	6.5	26	5.4	1.11	0.62–2.02
Diabetes mellitus	8	22.2	69	27.2	129	21.4	150	19.2	78	16.3	0.64	0.46–0.89
Respiratory disease												
COPD	4	11.1	40	15.7	103	17.1	125	16.0	48	10.0	1.02	0.69–1.51
Asthma	2	5.6	7	2.8	21	3.5	28	3.6	14	2.9	1.31	0.57–3.04
Gastrointestinal disease												
Liver disease	0	0.0	0	0.0	1	0.2	3	0.4	4	0.8	–	–

	2013 N=36		2014 N=254		2015 N=604		2016 N=780		2017 N=479		Crude OR 95% CI (2016–2014)	
	n	%	n	%	n	%	n	%	n	%		
Pancreatic disease	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	–	–
Peptic ulcer disease	0	0.0	0	0.0	2	0.3	0	0.0	1	0.2	–	–
Other diseases												
Rheumatoid arthritis	2	5.6	8	3.1	15	2.5	21	2.7	15	3.1	0.85	0.37–1.94
Osteoarthritis	3	8.3	30	11.8	73	12.1	87	11.2	51	10.6	0.94	0.60–1.46
Cancer	4	11.1	20	7.9	44	7.3	47	6.0	23	4.8	0.75	0.44–1.29
Severe renal disease	2	5.6	11	4.3	13	2.2	6	0.8	74	15.4	0.46	0.33–0.68

Table 10. Comorbidities among patients with NVAF newly prescribed dabigatran by calendar year.

	2012 N=488		2013 N=588		2014 N=561		2015 N=495		2016 N=416		2017 N=325		Crude OR (95% CI) (2016 –2012)	
	n	%	n	%	n	%	n	%	n	%	n	%		
CV disease/risk factors														
Myocardial infarction	25	5.1	22	3.7	23	4.1	21	4.2	10	2.4	7	2.2	0.46	0.22–0.96
IHD	22	4.5	28	4.8	16	2.9	13	2.6	13	3.1	6	1.8	0.68	0.34–1.37
Heart failure	218	44.7	251	42.7	205	36.5	155	31.3	128	30.8	63	19.4	0.55	0.41–0.72
Ventricular arrhythmia	75	15.4	69	11.7	48	8.6	28	5.7	19	4.6	9	2.8	0.26	0.15–0.44
PAD (lower extremity)	15	3.1	13	2.2	13	2.3	7	1.4	8	1.9	7	2.2	0.62	0.26–1.47
VTE	9	1.8	16	2.7	27	4.8	26	5.2	20	4.8		0.0	2.69	1.21–5.97
Hypertension	423	86.7	513	87.2	469	83.6	397	80.2	313	75.2	227	69.8	0.47	0.33–0.66
Atrial fibrillation	488	100.0	588	100.0	561	100.0	495	100.0	416	100.0		0.0		
Hyperlipidaemia	80	16.4	97	16.5	87	15.5	77	15.6	51	12.3	35	10.8	0.71	0.49–1.04
Ischaemic stroke	76	15.6	59	10.0	64	11.4	34	6.9	24	5.8	4	1.2	0.33	0.21–0.54
TIA	15	3.1	17	2.9	17	3.0	10	2.0	3	0.7	5	1.5	0.23	0.04–0.81
Bleeding disorders														
Intracranial bleeding	2	0.4	8	1.4	3	0.5	1	0.2	2	0.5	1	0.3	1.17	0.08–16.25
Gastrointestinal bleeding	17	3.5	15	2.6	21	3.7	11	2.2	7	1.7	0	0.0	0.47	0.19–1.15
Urogenital bleeding	8	1.6	3	0.5	6	1.1	3	0.6	3	0.7	0	0.0	0.43	0.07–1.83
Endocrine/metabolic disease														
Obesity	34	7.0	51	8.7	38	6.8	40	8.1	17	4.1	11	3.4	0.57	0.31–1.03
Diabetes mellitus	114	23.4	143	24.3	132	23.5	117	23.6	81	19.5	68	20.9	0.79	0.57–1.09
Respiratory disease														
COPD	94	19.3	81	13.8	72	12.8	79	16.0	47	11.3	32	9.8	0.53	0.36–0.78
Asthma	22	4.5	26	4.4	18	3.2	20	4.0	7	1.7	7	2.2	0.36	0.15–0.86
Gastrointestinal disease														

	2012 N=488		2013 N=588		2014 N=561		2015 N=495		2016 N=416		2017 N=325		Crude OR (95% CI) (2016 –2012)	
	n	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**		
Liver disease	3	0.6	4	0.7	7	1.2	2	0.4	1	0.2	1	0.3	0.39	0.01–4.88
Pancreatic disease	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	–	–
Peptic ulcer disease	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	–	–
Other diseases														
Rheumatoid arthritis	16	3.3	15	2.6	7	1.2	13	2.6	9	2.2	2	0.6	0.65	0.28–1.49
Osteoarthritis	49	10.0	76	12.9	55	9.8	59	11.9	37	8.7	14	4.3	0.87	0.56–1.37
Cancer	32	6.6	43	7.3	42	7.5	26	5.3	21	5.0	14	4.3	0.76	0.43–1.33
Severe renal disease	19	3.9	15	2.6	8	1.4	6	1.2	4	1.0	1	0.3	0.44	0.29–0.65

Table 11. Comorbidities among patients with NVAF newly prescribed rivaroxaban by calendar year.

	2012 N=310		2013 N=612		2014 N=909		2015 N=1213		2016 N=1423		2017 N=813		Crude OR (95% CI) (2016–2012)	
	n	%	n	%	n	%	n	%	n	%	n	%		
CV disease/risk factors														
Myocardial infarction	24	7.7	32	5.2	52	5.7	72	5.9	62	4.4	32	3.9	0.54	(0.33–0.88)
IHD	16	5.2	32	5.2	26	2.9	48	4.0	43	3.0	21	6.5	0.57	0.32–1.03
Heart failure	162	52.3	298	48.7	400	44.0	487	40.1	469	33.0	191	58.8	0.45	(0.35–0.57)
Ventricular arrhythmia	41	13.2	74	12.1	75	8.3	106	8.7	60	4.2	23	7.1	0.28	0.19–0.44
PAD (lower extremity)	1	0.3	5	0.8	6	0.7	9	0.7	15	1.1	16	4.9	3.29	0.50–139.0
VTE	31	10.0	52	8.5	79	8.7	75	6.2	76	5.3		0.0	0.51	0.33–0.79
Hypertension	271	87.4	544	88.9	787	86.6	1046	86.2	1123	78.9	582	179.1	0.54	0.38–0.77
Hyperlipidaemia	63	23.0	127	20.8	162	17.8	227	18.7	258	18.1	114	35.1	0.87	0.64–1.18
Ischaemic stroke	53	17.1	68	11.1	69	7.6	91	7.5	84	5.9	9	2.8	0.30	0.21–0.43
TIA	16	5.2	17	2.8	27	3.0	25	2.1	32	2.2	9	2.8	0.42	0.23–0.78
Bleeding disorders														
Intracranial bleeding	8	2.6	9	1.5	7	0.8	3	0.2	6	0.4	0	0.0	0.16	0.05–0.46
Gastrointestinal bleeding	16	5.2	30	4.9	28	3.1	56	4.6	47	3.3	18	5.5	0.63	0.35–1.12
Urogenital bleeding	5	1.6	4	0.7	10	1.1	13	1.1	20	1.4	6	1.8	0.87	0.31–2.99
Endocrine/metabolic disease														
Obesity	21	6.8	53	8.7	81	8.9	87	7.2	115	8.1	55	16.9	1.21	0.74–1.96
Diabetes mellitus	80	25.8	148	24.2	214	23.5	273	22.5	280	19.7	164	50.5	0.70	0.53–0.93
Respiratory disease														
COPD	67	21.6	109	17.8	197	21.7	212	17.5	199	14.0	85	26.2	0.58	0.43–0.80
Asthma	12	3.9	30	4.9	48	5.3	56	4.6	49	3.4	20	6.2	0.88	0.46–1.68
Gastrointestinal disease														
Liver disease	5	1.6	4	0.7	5	0.6	11	0.9	13	0.9	3	0.9	0.56	0.19–2.03
Pancreatic disease	0	0.0	0	0.0	0	0.0	0	0.0	1	0.1	0	0.0	–	–

	2012 N=310		2013 N=612		2014 N=909		2015 N=1213		2016 N=1423		2017 N=813		Crude OR (95% CI) (2016–2012)	
	n	%	n	%	n	%	n	%	n	%	n	%		
Peptic ulcer disease	0	0.0	0	0.0	4	0.4	0	0.0	2	0.1	1	0.3	–	–
Other diseases														
Rheumatoid arthritis	17	5.5	21	3.4	27	3.0	30	2.5	28	2.0	10	3.1	0.34	0.17–0.64
Osteoarthritis	39	12.6	91	14.9	129	14.2	161	13.3	200	14.1	82	25.2	1.14	0.79–1.64
Cancer	27	8.7	43	7.0	59	6.5	77	6.3	102	7.2	39	12.0	0.81	0.52–1.26
Severe renal disease	13	4.2	19	3.1	18	2.0	28	2.3	27	1.9	87	26.8	0.60	0.44–0.82

Medication use in the year before the index date among patients with NVAF for each calendar year is shown in **Table 12**, **Table 13** and **Table 14** for new users of apixaban, dabigatran and rivaroxaban, respectively.

Among new users of apixaban (**Table 12**), there was a reduction between 2014 and 2016 in the use of low-dose aspirin (OR: 0.70, 95% CI: 0.53–0.93), antiarrhythmics (OR: 0.66, 95% CI: 0.45–0.96), diuretics (OR: 0.67 (95% CI: 0.51–0.89) and statins (OR: 0.69, 95% CI: 0.52–0.93).

Among new users of dabigatran (**Table 13)** there was a decrease in the use of several medications between 2012 and 2016: antiplatelet agents (OR: 0.75, 95% CI: 0.58–0.98), antiarrhythmics (OR: 0.40, 95% CI: 0.27–0.58), antihypertensive agents (OR: 0.60, 95% CI: 0.45–0.80), beta-blockers (OR: 0.60, 95% CI: 0.46–0.78), diuretics (OR: 0.62, 95% CI: 0.47–0.81), and H_2RAs (OR: 0.55, 95% CI: 0.34–0.89). The use of antidepressants and antipsychotics was stable across study years, while the use of NSAIDs (OR: 1.63, 95% CI: 1.08–2.46) and antidiabetics increased (OR: 1.64, 95% CI: 1.11–2.43).

Among new users of rivaroxaban (**Table 14)**, there was a decrease in the use of several medication across study years (2012 to 2016): antiplatelet agents (OR: 0.74, 95% CI: 0.58–0.95), antiarrhythmic drugs (OR: 0.63, 95% CI: 0.47–0.84), antihypertensives (OR: 0.59, 95% CI: 0.43–0.80), beta-blockers (OR: 0.74, 95% CI: 0.58–0.96), ACE inhibitors (OR: 0.61, 95% CI: 10.46–0.82), diuretics (OR: 0.58, 95% CI: 0.45–0.75), statins (OR: 0.62, 95% CI: 0.48–0.80), PPIs (OR: 0.72, 95% CI: 0.56–0.92), antipsychotics (OR: 0.57, 95% CI: 0.32–0.99) and strong CYP3A4 inducers (OR: 0.52, 95% CI: 0.34–0.81).

Table 12. Medication use among patients with NVAF newly prescribed apixaban by calendar year.

	2013 N=36		2014 N=254		2015 N=604		2016 N=780		2017 N=479		Crude OR (95% CI) 2016 vs. 2014	
	n	%	n	%	n	%	n	%	n	%		
Antiplatelet agents	21	53.3	137	53.9	259	42.9	352	45.1	205	42.8	0.70	0.53–0.93
Low-dose aspirin	17	47.2	131	51.6	244	40.4	334	42.8	198	41.3	0.70	0.53–0.93
Clopidogrel	7	19.4	31	12.2	62	10.3	96	12.3	44	9.2	1.00	0.66–1.56
NSAIDs	7	19.4	23	9.1	66	10.9	75	9.6	45	9.4	1.07	0.65–1.74
Oral steroids	3	8.3	11	4.3	45	7.5	55	7.1	26	5.4	1.68	0.86–3.25
Anticoagulants drugs	22	61.1	87	34.3	233	38.6	220	28.2	133	27.8	0.75	0.56–1.02
Antiarrhythmic drugs	6	16.7	49	19.3	75	12.4	106	13.6	87	18.2	0.66	0.45–0.96
Antihypertensive drugs	30	83.3	199	78.3	414	68.5	591	75.8	367	76.6	0.86	0.61–1.21
Beta-blockers	25	69.4	160	63.0	325	53.8	456	58.5	292	61.0	0.82	0.62–1.11
ACE inhibitors	8	22.2	52	20.5	103	17.1	124	15.9	86	18.0	0.73	0.51–1.05
Diuretics	18	50.0	126	49.6	231	38.2	311	39.9	196	40.9	0.67	0.51–0.89
Statins	25	69.4	160	63.0	330	54.6	422	54.1	256	53.4	0.69	0.52–0.93
Antidiabetic drugs	5	13.9	58	22.8	104	17.2	135	17.3	68	14.2	0.71	0.50–1.00
Oral contraceptives	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	–	–
Hormone replacement therapy	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	–	–
PPIs	22	61.1	121	47.6	251	41.6	340	43.6	216	45.1	0.85	0.64–1.13
H_2-receptor antagonists	5	13.9	24	9.4	46	7.6	67	8.6	28	5.8	0.90	0.55–1.47
DMARDs	2	5.6	3	1.2	12	2.0	21	2.7	11	2.3	2.31	0.68–7.83
Antidepressants	8	22.2	48	18.9	99	16.4	130	16.7	90	18.8	0.86	0.60–1.24
Antipsychotic drugs	0	0.0	8	3.1	23	3.8	32	4.1	13	2.7	1.32	0.47–2.89
Strong inhibitors of either cytochrome P450 3A4 or P-glycoprotein	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	–	–
Strong CYP3A4 inducers	1	2.8	20	7.9	22	3.6	45	5.8	34	7.1	0.72	0.41–1.24

Table 13. Medication use among patients with NVAF newly prescribed dabigatran by calendar year.

	2012 N=488		2013 N=588		2014 N=561		2015 N=495		2016 N=416		2017 N=325		Crude OR 2016 vs. 2012	
	n	%	n	%	n	%	n	%	n	%	n	%	OR	95% CI
Antiplatelet agents	226	46.3	312	53.1	264	47.1	226	45.7	164	39.4	129	39.7	0.75	0.58–0.98
Low-dose aspirin	211	43.2	299	50.9	253	45.1	216	43.6	157	37.7	123	37.8	0.80	0.61–1.04
Clopidogrel	67	13.7	89	15.1	52	9.3	32	6.5	36	8.7	24	7.4	0.60	0.39–0.91
NSAIDs	45	9.2	77	13.1	51	9.1	57	11.5	59	14.2	32	9.8	1.63	1.08–2.46
Oral steroids	25	5.1	34	5.8	21	3.7	32	6.5	19	4.6	18	5.5	0.89	0.48–1.63
Anticoagulants drugs	264	54.1	255	43.4	212	37.8	163	32.9	115	27.6	76	23.4	0.32	0.24–0.43
Antiarrhythmic drugs	110	22.5	119	20.2	89	15.9	76	15.4	43	10.3	43	13.2	0.40	0.27–0.58
Antihypertensive drugs	362	74.2	451	76.7	400	71.3	350	70.7	264	63.5	250	76.9	0.60	0.45–0.80
Beta-blockers	297	60.9	361	61.4	320	57.0	283	57.2	201	48.3	212	65.2	0.60	0.46–0.78
ACE inhibitors	102	20.9	131	22.3	105	18.7	68	13.7	42	10.1	50	15.4	0.42	0.29–0.62
Diuretics	213	43.6	258	43.9	220	39.2	187	37.8	135	32.5	143	44.0	0.62	0.47–0.81
Statins	250	51.2	343	58.3	318	56.7	271	54.7	192	46.2	187	57.5	0.82	0.63–1.06
Antidiabetic drugs	51	10.5	97	16.5	102	18.2	92	18.6	67	16.1	67	20.6	1.64	1.11–2.43
Oral contraceptives	1	0.2	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	–	
Hormone replacement therapy	1	0.2	0	0.0	0	0.0	1	0.2	1	0.2	0	0.0	1.17	0.07–18.82
PPIs	216	44.3	280	47.6	236	42.1	204	41.2	158	38.0	135	41.5	0.77	0.59–1.01
H2-receptor antagonists	53	10.9	79	13.4	63	11.2	42	8.5	26	6.3	17	5.2	0.55	0.34–0.89
DMARDs	5	1.0	11	1.9	11	2.0	17	3.4	9	2.2	7	2.2	2.14	0.71–6.42
Antidepressants	65	13.3	98	16.7	79	14.1	83	16.8	55	13.2	46	14.2	0.99	0.67–1.46
Antipsychotic drugs	12	2.5	20	3.4	19	3.4	12	2.4	12	2.9	8	2.5	1.18	0.52–2.65
Strong inhibitors of either cytochrome P450 3A4 or P-glycoprotein	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	–	
Strong CYP3A4 inducers	28	5.7	45	7.7	37	6.6	32	6.5	16	3.8	17	5.2	0.66	0.35–1.23

Table 14. Medication use among patients with NVAF newly prescribed rivaroxaban by calendar year.

	2012 N=310		2013 N=612		2014 N=909		2015 N=1213		2016 N=1423		2017 N=813		Crude OR (2016 vs. 2012)	
	n	%	n	%	n	%	n	%	n	%	n	%	OR	95%CI
Antiplatelet agents	157	50.6	346	56.5	469	51.6	588	48.5	616	43.3	333	41.0	0.74	0.58–0.95
Low-dose aspirin	151	48.7	335	54.7	440	48.4	562	46.3	584	41.0	312	38.4	0.73	0.57–0.94
Clopidogrel	38	12.3	86	14.1	111	12.2	113	9.3	122	8.6	72	8.9	0.67	0.46–0.99
NSAIDs	45	14.5	107	17.5	116	12.8	150	12.4	170	11.9	102	12.5	0.80	0.56–1.14
Oral steroids	19	6.1	60	9.8	69	7.6	79	6.5	80	5.6	40	4.9	0.91	0.54–1.53
Anticoagulants drugs	189	61.0	343	56.0	389	42.8	419	34.5	190	13.4	190	23.4	0.10	0.07–0.13
Antiarrhythmic drugs	75	24.2	145	23.7	165	18.2	189	15.6	238	16.7	116	14.3	0.63	0.47–0.84
Antihypertensive drugs	251	81.0	504	82.4	724	79.6	935	77.1	1018	71.5	611	75.2	0.59	0.43–0.80
Beta-blockers	193	62.3	398	65.0	577	63.5	735	60.6	784	55.1	488	60.0	0.74	0.58–0.96
ACE inhibitors	79	25.5	148	24.2	171	18.8	221	18.2	246	17.3	123	15.1	0.61	0.46–0.82
Diuretics	154	49.7	315	51.5	451	49.6	530	43.7	520	36.5	318	39.1	0.58	0.45–0.75
Statins	198	63.9	394	64.4	554	60.9	890	73.4	744	52.3	437	53.8	0.62	0.48–0.80
Antidiabetic drugs	49	15.8	109	17.8	164	18.0	192	15.8	228	16.0	151	18.6	1.02	0.72–1.42
Oral contraceptives	0	0.0	1	0.2	0	0.0	0	0.0	0	0.0	0	0.0	–	–
Hormone replacement therapy	0	0.0	1	0.2	0	0.0	1	0.1	2	0.1	0	0.0	–	–
PPIs	151	48.7	335	54.7	451	49.6	544	44.8	579	40.7	326	40.1	0.72	0.56–0.92
H_2-receptor antagonists	35	11.3	85	13.9	125	13.8	100	8.2	119	8.4	56	6.9	0.72	0.48–1.07
DMARDs	8	2.6	20	3.3	23	2.5	24	2.0	31	2.2	16	2.0	0.84	0.38–1.85
Antidepressants	55	17.7	113	18.5	173	19.0	200	16.5	219	15.4	124	15.3	0.84	0.61–1.17
Antipsychotic drugs	18	5.8	15	2.5	23	2.5	31	2.6	48	3.4	20	2.5	0.57	0.32–0.99
Strong inhibitors of either cytochrome P450 3A4 or P-glycoprotein	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	–	–
Strong CYP3A4 inducers	31	10.0	56	9.2	62	6.8	84	6.9	78	5.5	50	6.2	0.52	0.34–0.81

10.4.2 NOAC prescription patterns among patients with NVAF

10.4.2.1 Index NOAC prescription

Characteristics of the index NOAC prescription among patients with NVAF newly prescribed a NOAC are shown in **Table 15** for apixaban, **Table 16** for dabigatran and **Table 17** for rivaroxaban.

Among patients starting on apixaban **(Table 15)**, about a quarter (26.2%) were started on the standard 10 mg daily dose, with over half prescribed a reduced dose of 5 mg/day and about a fifth (21.2%) prescribed a further reduced dose of 2.5 mg/day. Although the most frequent posology for apixaban was twice daily, this applied to less than 60% of patients (58.1%), showing that for a substantial percentage of patients starting OAC therapy on apixaban, the posology was once daily and therefore not in-line with the instructions on the drug label. Just over at third of patients (36.0%) had a first episode of continuous apixaban use that lasted more than 180 days.

Among patients starting on dabigatran (**Table 16**), 21.7% of patients were prescribed the standard dose of 300mg/day, while over a third of patients (34.7%) were prescribed a reduced dose of 220 mg/day with the remaining patients (42.3%) receiving a dose of 150mg/day or less. As with apixaban, although the most frequent posology for dabigatran was twice daily, this applied to less than 60% of the patients (58.1%), indicating that a large percentage of patients starting OAC therapy on dabigatran received the medication with a posology of once daily, i.e. not in-line with the instructions on the drug label. Approximately half of patients (46.7%) had a first episode of continuous use that lasted more than 180 days while 28.4% had a first episode of continuous use that lasted for at least a year.

Among patients starting on rivaroxaban (**Table 17**), a daily dose of 20 mg (standard daily dose) was the most frequent prescribed (43.9%), followed by a reduced daily dose of 15 mg (28.4%). Rivaroxaban was mostly prescribed once daily (74.6%), which is the correct posology for stroke prevention in AF. A little under half (43.5%) had a first episode of continuous use that lasted more than 180 days. There were 688 patients with an initial recorded rivaroxaban dose of 40 mg/day. Of these, 609 (88.5%) were still prescribed rivaroxaban at 3 months from starting NOAC therapy; only 13 (2.1%) were still prescribed 40 mg/day; in the majority (92.3%) the dose at 3 months was 20 mg/day. Twenty four patients prescribed rivaroxaban 40 mg at the index date switched to another NOAC at 3 months.

Over half of patients were still prescribed their index NOAC at 6 months (apixaban 54.0%, dabigatran 58.5% and rivaroxaban 58.0%). As shown in **Table 18**, irrespective of the index NOAC, the majority of the NOAC prescriptions had either no gap between them (i.e. they were immediately next to each other or were overlapping prescriptions) or a small gap (0–7 days) between them during follow-up.

Table 15. Characteristics of the index prescription among patients with NVAF newly prescribed apixaban.

	Apixaban N=2153		**Apixaban (prescription at least one year after the index date) N=1331**	
	n	**%**	**n**	**%**
Apixaban tablet strength (mg)				
2.5	1152	53.5	671	50.4
5	1001	46.5	660	49.6
Dose frequency per day (based on the recorded posology for first prescription)				
Once daily	882	41.0	568	42.7
Twice daily	1251	58.1	750	56.3
Unknown	20	0.9	13	1.0
Daily dose of the index prescription (mg)				
2.5	456	21.2	284	21.3
5	1113	51.7	666	50.0
10	564	26.2	368	27.6
Unknown	20	0.9	13	1.0
Length of the index prescription (days)				
1–15	58	2.7	40	3.0
16–30	1251	58.1	745	56.0
31–60	817	37.9	527	39.6
61–90	4	0.2	3	0.2
≥91	3	0.1	3	0.2
Unknown	20	0.9	13	1.0
Duration of the first episode of use (days)				
1–30	396	18.4	131	9.8
31–60	116	5.4	42	3.2
61–90	353	16.4	182	13.7
91–180	512	23.8	257	19.3
181–365	375	17.4	248	18.6
>365	401	18.6	471	35.4

Table 16. Characteristics of the index prescription patients with NVAF newly prescribed dabigatran.

	Dabigatran N=3089		**(prescription at least one year after the index date) N=2459**	
	n	**%**	**n**	**%**
Dabigatran tablet strength (mg)				
75	87	2.8	72	2.9
110	1860	60.2	1496	60.8
150	1142	37.0	891	36.2
Dose frequency per day (based on the recorded posology for first prescription)				
Once daily	1254	40.6	1027	41.8
Twice daily	1794	58.1	1398	56.9
Unknown	41	1.3	34	1.4
Daily dose of the index prescription (mg)				
75	34	1.1	29	1.2
110	768	24.9	645	26.2
150	505	16.3	396	16.1
220	1072	34.7	833	33.9
300	669	21.7	522	21.2
Unknown	41	1.3	34	1.4
Length of the index prescription (days)				
1–15	81	2.6	71	2.9
16–30	1812	58.7	1402	57.0
31–60	1152	37.3	949	38.6
61–90	0	0.0	0	0.0
≥91	3	0.1	3	0.1
Unknown	41	1.3	34	1.4
Duration of the first episode of use (days)				
1–30	512	16.6	217	8.8
31–60	116	3.8	65	2.6
61–90	412	13.3	307	12.5
91–180	607	19.7	432	17.6
181–365	565	18.3	471	19.2
>365	877	28.4	967	39.3

Table 17. Characteristics of the index prescription patients with NVAF newly prescribed rivaroxaban.

	Rivaroxaban N=5286		**Rivaroxaban (prescription at least one year after the index date) N=3825**	
	n	**%**	**n**	**%**
Rivaroxaban tablet strength (mg)				
2.5	9	0.2	6	0.2
10	233	4.4	182	4.8
15	2028	38.4	1408	36.8
20	3016	57.1	2229	58.3
Dose frequency per day (based on the recorded posology for first prescription)				
Once daily	3944	74.6	2808	73.4
Twice daily	1253	23.7	944	24.7
Unknown	89	1.7	73	1.9
Daily dose of the index prescription (mg)				
2.5	6	0.1	5	0.1
5	3	0.1	1	0.0
10	173	3.3	138	3.6
15	1501	28.4	1020	26.7
20	2319	43.9	1686	44.1
30	507	9.6	373	9.8
40	688	13.0	529	13.8
Unknown	89	1.7	73	1.9
Length of the index prescription (days)				
1–15	1196	22.6	905	23.7
16–30	3850	72.8	2723	71.2
31–60	147	2.8	120	3.1
61–90	1	0.0	1	0.0
≥91	3	0.1	3	0.1
Unknown	89	1.7	73	1.9
Duration of the first episode of use (days)				
1–30	871	16.5	309	8.1
31–60	300	5.7	155	4.1
61–90	860	16.3	565	14.8
91–180	957	18.1	577	15.1
181–365	1002	19.0	764	20.0
>365	1296	24.5	1455	38.0

Table 18. Distribution of the time interval between prescriptions among patients with NVAF newly prescribed a NOAC.

Interval (days)	Apixaban prescriptions N=19,534		Dabigatran prescriptions N=53,441		Rivaroxaban prescriptions N=74,100	
	n	%	n	%	n	%
<0 (overlapping)	7015	35.9	18,306	34.3	17,603	23.8
0–7	7886	40.4	22,821	42.7	37,314	50.4
8–30	3124	16.0	8092	15.1	13,721	18.5
31–90	1126	5.8	3050	5.7	4134	5.6
>90	383	2.0	1172	2.2	1328	1.8

10.4.2.2 Time trends in the index NOAC prescription

Characteristics of the index NOAC among patients with NVAF newly prescribed a NOAC are shown for each study year in **Table 19** for apixaban, **Table 20** for dabigatran and **Table 21** for rivaroxaban.

Among new users of apixaban, (**Table 19**), 5 mg tablets were the most commonly prescribed in the early study years but this was replaced by 2.5 mg tablets being the most commonly prescribed from 2015. Across study years, the most common dosing frequency was twice daily and the most common length of the index apixaban prescription was between 16 and 30 days. Across study years, about a third of patients had a first continuous episode of apixaban use that lasted more than a year.

Among new users of dabigatran, (**Table 20**), 110 mg tablets were the most commonly prescribed across study years, although 150 mg tablets became increasingly issued. Twice daily was the most common dosing frequency across study years. A substantial percentage (between 39% and 45%) of patients had a first continuous episode of use that lasted more than a year.

Among new users of rivaroxaban, (**Table 21**), 20 mg tablets were the most commonly issued across study years, although 15 mg tablets became increasingly issued over time. The most common dosing frequency was always once a day. More than 40% of new users of dabigatran had a first continuous episode of use that lasted more than a year.

Table 19. Characteristics of the index prescription among patients with NVAF newly prescribed apixaban.

	2013 N=36		2014 N=254		2015 N=604		2016 N=780		2017 N=479		Crude OR (95% CI) (2016 vs. 2014)	
	n	%	n	%	n	%	n	%	n	%		
Apixaban tablet strength (mg)												
2.5	12	33.3	120	47.2	346	57.3	412	52.8	262	54.7	1.0 (reference)	
5	24	66.7	134	52.8	258	42.7	368	47.2	217	45.3	0.80	0.60–1.06
Dose frequency per day (based on the recorded posology for the first prescription)												
Once daily	11	30.6	110	43.3	262	43.4	312	40.0	187	39.0	1.0 (reference)	
Twice daily	25	69.4	142	55.9	339	56.1	458	58.7	287	59.9	1.13	0.85–1.52
Unknown	0	0.0	2	0.8	3	0.5	10	1.3	5	1.0	1.76	0.38–8.17
Daily dose of the index prescription (mg)												
2.5	6	16.7	46	18.1	147	24.3	165	21.2	92	19.2	1.0 (reference)	
5	11	30.6	138	54.3	312	51.7	390	50.0	262	54.7	0.79	0.54–1.15
10	19	52.8	68	26.8	142	23.5	215	27.6	120	25.1	0.88	0.58–1.35
Unknown	0	0.0	2	0.8	3	0.5	10	1.3	5	1.0	1,39	0.30–6.57
Length of the index prescription (days)												
1–15	0	0.0	7	2.8	16	2.6	25	3.2	9	1.9	1.0 (reference)	
16–30	27	75.0	142	55.9	341	56.5	455	58.3	289	60.3	0.90	0.38–2.12
31–60	11	30.6	100	39.4	241	39.9	290	37.2	175	36.5	0.81	0.34–1.94
61–90	0	0.0	3	1.2	0	0.0	0	0.0	1	0.2	–	
≥91	0	0.0	0	0.0	3	0.5	0	0.0	0	0.0	–	
Unknown	0	0.0	2		3	0.5	10	1.3	5	1.0	1.4	0.24–7.93
Duration of the first continuous episode of use (days)												
1–30	5	13.9	43	16.9	93	15.4	131	16.8	124	25.9	1.0 (reference)	
31–60	4	11.1	10	3.9	21	3.5	36	4.6	45	9.4	1.18	0.54–2.58
61–90	3	8.3	36	14.2	91	15.1	110	14.1	113	23.6	1.00	0.60–1.67

	2013 N=36		2014 N=254		2015 N=604		2016 N=780		2017 N=479		Crude OR (95% CI) (2016 vs. 2014)	
	n	%	n	%	n	%	n	%	n	%		
91–180	5	13.9	62	24.4	118	19.5	176	22.6	151	31.5	0.93	0.59–1.46
181–365	7	19.4	32	12.6	85	14.1	205	26.3	46	9.6	2.10	1.27–3.49
>365 days	12	33.3	71	28.0	196	32.5	122	15.6	0	0.0	0.56	0.36–0.89
Duration of first continuous episode of use (at least one year data collection after start date) (days)												
1–30	4	12.1	22	9.4	47	9.8	58	9.9			1.0 (reference)	
31–60	3	9.1	7	3.0	12	2.5	20	3.4			1.08	0.40–2.92
61–90	3	9.1	33	14.2	64	13.3	64	11.0			0.74	0.39–1.40
91–180	4	12.1	54	23.2	72	15.0	127	21.7			0.89	0.50–1.60
181–365	7	21.2	28	12.0	68	14.1	145	24.8			1.96	1.04–3.71
>365	12	36.4	89	38.2	218	45.3	170	29.1			0.72	0.42–1.26

Table 20. Characteristics of the index prescription among patients with NVAF newly prescribed dabigatran.

	2012 N=488		2013 N=588		2014 N=561		2015 N=495		2016 N=416		2017 N=325		Crude OR (95% CI) (2016 vs. 2012)	
	n	%	n	%	n	%	n	%	n	%	n	%		
Dabigatran tablet strength (mg)														
75	11	2.3	13	2.2	8	1.4	11	2.2	9	2.2	9	2.8	1.0 (reference)	
110	324	66.4	367	62.4	345	61.5	285	57.6	225	54.1	173	53.2	0.85	0.35–2.08
150	153	31.4	208	35.4	208	37.1	199	40.2	182	43.8	143	44.0	1.45	0.59–3.60
Dose frequency per day (based on the recorded posology for the first prescription)														
Once daily	230	47.1	237	40.3	216	38.5	213	43.0	160	38.5	105	32.3	1.0 (reference)	
Twice daily	255	52.3	343	58.3	334	59.5	274	55.4	251	60.3	216	66.5	1.42	1.08–1.85
Unknown	3	0.6	8	1.4	11	2.0	8	1.6	5	1.2	4	1.2	2.40	0.56–10.17
Daily dose of the index prescription (mg)														
75	2	0.4	5	0.9	4	0.7	5	1.0	6	1.4	1	0.3	2.00	0.39–10.15
110	156	32.0	149	25.3	124	22.1	128	25.9	95	22.8	53	16.3	0.41	0.28–0.59
150	81	16.6	91	15.5	92	16.4	86	17.4	62	14.9	59	18.2	0.51	0.33–0.79
220	166	34.0	213	36.2	214	38.1	155	31.3	128	30.8	119	36.6	0.51	0.36–0.74
300	80	16.4	122	20.7	116	20.7	113	22.8	120	28.8	89	27.4	1.0 (reference)	
Unknown	3	0.6	8	1.4	11	2.0	8	1.6	5	1.2	4	1.2	1.11	0.26–4.78
Length of the index prescription (days)														
1–15	17	3.5	11	1.9	11	2.0	13	2.6	15	3.6	3	0.9	1.0 (reference)	
16–30	259	53.1	350	59.5	339	60.4	280	56.6	247	59.4	224	68.9	1.08	0.53–2.21
31–60	208	42.6	219	37.2	200	35.7	194	39.2	149	35.8	94	28.9	0.81	0.39–1.68
61–90	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	–	
≥91	1	0.2	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	–	
Unknown	3	0.6	8	1.4	11	2.0	8	1.6	5	1.2	4	1.2	1.89	0.38–9.27
Duration of the first continuous episode of use (days)														

	2012 N=488		2013 N=588		2014 N=561		2015 N=495		2016 N=416		2017 N=325		Crude OR (95% CI) (2016 vs. 2012)	
	n	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**		
1–30	65	13.3	75	12.8	81	14.4	85	17.2	76	18.3	98	30.2	1.0 (reference)	
31–60	15	3.1	15	2.6	18	3.2	12	2.4	16	3.8	34	10.5	0.91	0.42–1.99
61–90	59	12.1	83	14.1	65	11.6	69	13.9	60	14.4	54	16.6	0.87	0.53–1.42
91–180	83	17.0	89	15.1	108	19.3	87	17.6	91	21.9	104	32.0	0.94	0.60–1.46
181–365	77	15.8	111	18.9	112	20.0	86	17.4	105	25.2	35	10.8	1.16	0.75–1.82
>365	189	38.7	215	36.6	177	31.6	156	31.5	68	16.3	0	0.0	0.31	0.20–0.47
Duration of first continuous episode of use (at least one year data collection after start date) (days)														
1–30	36	7.7	41	7.5	41	8.0	43	10.3	35	11.2			1.0 (reference)	
31–60	15	3.2	14	2.6	16	3.1	9	2.1	8	2.6			0.55	0.20–1.45
61–90	55	11.8	75	13.7	58	11.4	54	12.9	45	14.4			0.84	0.46–1.54
91–180	78	16.7	80	14.6	97	19.0	75	17.9	60	19.2			0.79	0.44–1.40
181–365	72	15.5	103	18.8	102	20.0	75	17.9	84	26.8			1.34	0.76–2.34
>365	210	45.1	236	43.0	196	38.4	163	38.9	81	25.9			0.40	0.23–0.67

Table 21. Characteristics of the index prescription among patients with NVAF newly prescribed rivaroxaban.

	2012 N=310		2013 N=612		2014 N=909		2015 N=1213		2016 N=1423		2017 N=813		Crude OR (95% CI) (2016 vs. 2012)	
	n	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**		
Rivaroxaban tablet strength (mg)														
2.5	0	0.0	0	0.0	0	0.0	3	0.2	5	0.4	1	0.1	–	–
10	25	8.1	62	10.1	40	4.4	41	3.4	40	2.8	19	2.3	1.0 (reference)	
15	89	28.7	202	33.0	353	38.8	481	39.7	574	40.3	329	40.5	4.03	2.33–6.97
20	196	63.2	348	56.9	516	56.8	688	56.7	804	56.5	464	57.1	2.56	1.52–4.33
Dose frequency per day (based on the recorded posology for the first prescription)														
Once daily	219	70.6	448	73.2	687	75.6	901	74.3	1059	74.4	626	77.0	1.0 (reference)	
Twice daily	87	28.1	156	25.5	200	22.0	295	24.3	337	23.7	177	21.8	0.80	0.61–1.06
Unknown	4	1.3	8	1.3	22	2.4	17	1.4	27	1.9	10	1.2	1.40	0.48–4.03
Daily dose of the index prescription (mg)														
2.5	0	0.0	0	0.0	0	0.0	2	0.2	4	0.3	0	0.0	–	
5	0	0.0	0	0.0	0	0.0	1	0.1	1	0.1	1	0.1	–	
10	19	6.1	51	8.3	29	3.2	28	2.3	28	2.0	14	1.7	1.0 (reference)	
15	54	17.4	140	22.9	272	29.9	362	29.8	419	29.4	254	31.2	5.27	2.75–10.06
20	152	49.0	266	43.5	397	43.7	522	43.0	618	43.4	363	44.6	2.76	1.50–5.07
30	34	11.0	62	10.1	78	8.6	115	9.5	146	10.3	72	8.9	2.91	1.46–5.82
40	47	15.2	85	13.9	111	12.2	166	13.7	180	12.6	99	12.2	2.60	1.34–5.05
Unknown	4	1.3	8	1.3	22	2.4	17	1.4	27	1.9	10	1.2	4.58	1.38–15.22
Length of the index prescription (days)														
1–15	79	25.5	152	24.8	186	20.5	289	23.8	317	22.3	171	21.0	1.0 (reference)	
16–30	209	67.4	419	68.5	675	74.3	876	72.2	1046	73.5	622	76.5	1.25	0.94–1.66

	2012 N=310		2013 N=612		2014 N=909		2015 N=1213		2016 N=1423		2017 N=813		Crude OR (95% CI) (2016 vs. 2012)	
	n	%	n	%	n	%	n	%	n	%	n	%		
31–60	18	5.8	32	5.2	26	2.9	29	2.4	32	2.2	10	1.2	0.44	0.24–0.83
61–90	0	0.0	0	0.0	0	0.0	1	0.1	0	0.0	0	0.0	–	
≥91	0	0.0	1	0.2	0	0.0	1	0.1	1	0.1	0	0.0	–	
Unknown	4		8	1.3	22	2.4	17	1.4	27	1.9	10	1.2	1.68	0.57–4.95
Duration of the first continuous episode of use (days)														
1–30	42	13.5	84	13.7	128	14.1	170	14.0	213	15.0	228	28.0	1.0 (reference)	
31–60	10	3.2	25	4.1	35	3.9	59	4.9	70	4.9	101	12.4	1.38	0.66–2.89
61–90	46	14.8	85	13.9	147	16.2	187	15.4	210	14.8	185	22.8	0.90	0.57–1.42
91–180	48	15.5	69	11.3	145	16.0	199	16.4	275	19.3	221	27.2	1.13	0.72–1.77
181–365	53	17.1	95	15.5	150	16.5	205	16.9	421	29.6	78	9.6	1.57	1.01–2.42
>365	111	35.8	254	41.5	304	33.4	393	32.4	234	16.4	0	0.0	0.42	0.28–0.62
Duration of first continuous episode of use (at least one year users) (days)														
1–30	19	6.5	41	7.2	78	9.5	79	7.4	87	8.2			1.0 (reference)	
31–60	8	2.7	23	4.0	31	3.8	47	4.4	46	4.3			1.26	0.51–3.09
61–90	44	15.1	77	13.5	127	15.4	161	15.0	156	14.7			0.77	0.42–1.41
91–180	43	14.8	67	11.8	127	15.4	161	15.0	179	16.9			0.91	0.50–1.65
181–365	50	17.2	80	14.1	131	15.9	181	16.9	322	30.3			1.41	0.79–2.51
>365	127	43.6	281	49.4	331	40.1	443	41.3	272	127			0.47	0.27–0.80

10.5 Other analyses

N/A

10.6 Safety data (Adverse events/adverse reactions)

N/A. The aim of this study was to describe patterns of NOAC use among patients with NVAF in Colombia and to describe patient user characteristics.

11. Discussion

11.1 Key results

There were a total of 10,528 patients with NVAF newly prescribed a NOAC during the study period: 2153 new users of apixaban (20.4%), 3089 new users of dabigatran (29.4%) and 5286 new users of rivaroxaban (50.2%). Prescribing of NOACs among patients with NVAF was seen to increase over the study period, with the observed time-trends clearly reflecting the time of introduction of the different NOACs in Colombia. The decline in the incidence of patients with NVAF starting NOAC treatment on dabigatran – the first NOAC approved in Colombia for NVAF – was accompanied by an increase in the use of rivaroxaban and apixaban, which possibly reflects concerns about adverse gastrointestinal bleeding among prescribers although one study has reported that they have equivalent risks.**(2)** Several studies in the United States **(3, 4)** and Europe **(5-10)** have shown similar time trends in the use of these three NOACs in patients with NVAF.

The age and gender distribution of our study population were broadly comparable to those in similar populations in other countries, with a mean age at first NOAC prescription a little over 75 years, and a slight predominance of men.**(7, 11-13)** A high level of polypharmacy was apparent in our predominantly elderly study population, as also shown by Mueller et *al* among NOAC users with NVAF in Scotland.**(7)** As expected, and in line with other studies, **(11-15)** hypertension – the predominant risk factor for AF – was the most common comorbidity among patients in our study, being recorded for about 80%. The presence of diabetes mellitus in about one-fifth of patients in our study is also in line with findings among patients with NVAF in other countries,**(11-13, 15)** although estimates have been slightly higher in some American cohorts.**(11, 13)** The prevalence of heart failure among about one-third of patients with NVAF represents a higher percentage than seen elsewhere.**(11-13, 15)** Interestingly, we found a higher percentage of patients with a record of previous VTE among patients starting NOAC therapy on rivaroxaban compared with those starting on apixaban or dabigatran. All three NOACs are indicated for the prevention of VTE recurrence,**(16)** yet our data suggest that previous occurrence of a VTE may have prompted a preference for rivaroxaban for stroke prevention in NVAF among prescribers in Colombia. As expected by patients' comorbidity profile the most frequently prescribed medications in the year before starting NOAC therapy were beta-blockers, statins, low-dose aspirin, PPIs and diuretics.

Rivaroxaban became the most commonly prescribed NOAC to patients with NVAF during the study period. This preference for rivaroxaban could be due to its simple once-a-day administration, which could appeal to many prescribers in Colombia who recognize the importance of patient adherence to therapy to gain the full benefits of protection against ischaemic cerebrovascular events. The growing

confidence in NOACs in Colombia can also be inferred from our finding that approximately two-thirds of the new users of NOACs in our study were anticoagulant naïve. Also, over half of first-time NOAC users still received treatment with their index NOAC after 6 months, indicating a certain level of adherence and tolerability among patients, providing a level of reassurance to physicians about prescribing this class of drugs. With respect to the initial NOAC dose prescribed in our patient population, only about a quarter of patients starting NOAC therapy on apixaban received the standard daily dose compared with 44% of patients starting on rivaroxaban and 42% on dabigatran. This shows that a large number of NOAC users with NVAF in Colombia, especially those starting preventative treatment on apixaban, are prescribed a reduced dose, as has been shown to be common in other countries,**(17-19)** but that patients receiving a reduced dose do not always satisfy the dose reduction criteria on the drug label.(**13, 20-23)** Further investigation would be needed to see whether this is also the case in Colombia.

11.2 Limitations

- Given the nature of real-world data, missing data were likely to be present in only a minority of instances, for example under-recording of hospitalizations.
- We were unable to characterize patients according to lifestyle factors such as smoking status, alcohol status and body mass index (from height and weight measurements) because these are not recorded in the database
- Although we were able to identify patients with severe renal failure from ICD-10 codes, we could not characterize patients in terms of mild or moderate renal failure because this information was not available in the database.
- Only prescriptions captured in the Audifarma database were available. Medications prescribed at hospital may have been captured in a small subset linked to the inpatient databases but over-the-counter medications are not recorded in the Audifarma database.

11.3 Interpretation

The increasing use of NOACs in patients with NVAF in Colombia as seen in our study is suggestive of a decline in warfarin use – the mainstay of oral anticoagulant therapy in this patient population prior to the introduction of NOACs – as shown in several studies across the world.**(3-5, 7, 8, 10, 24, 25)** These findings suggest that the benefits of NOACs over warfarin – both in terms of their favourable efficacy and safety profile as well as avoiding the need for regular clinic visits for coagulation monitoring – is recognized by outpatient prescribers in Colombia.

11.4 Generalizability

Our study population was representative in terms of the sex and age distribution of the Colombian population, and because the data source made selection bias unlikely, the results of the study are likely to reflect routine clinical practice in Colombia. However it should be noted that patterns of

NOAC use described in this study are those of patients in the contributory healthcare regime and not necessarily those of patients in the government subsidized healthcare regime, who may have a different distribution of comorbidities and co-medication use. Studies are now needed focusing on the real-world effectiveness and safety of NOACs in Colombia, as well as an evaluation of the appropriateness of reduced dosing.

12. Other information

None.

13. Conclusion

The increasing use of NOACs in patients with NVAF in Colombia likely reflects the growing confidence in NOACs among PCPs in Colombia. The characteristics of these patients and characteristics of NOAC prescribing, including the observation that a large percentage of patients are prescribed a reduced dose, are in line with those seen in comparable European and American cohorts.

14. References

1. Ray WA. Evaluating medication effects outside of clinical trials: new-user designs. Am J Epidemiol. 2003 Nov 1;158(9):915–20.

2. Graham DJ, Reichman ME, Wernecke M, Zhang R, Southworth MR, Levenson M, et al. Cardiovascular, bleeding, and mortality risks in elderly Medicare patients treated with dabigatran or warfarin for nonvalvular atrial fibrillation. Circulation. 2015 Jan 13;131(2):157–64.

3. Alalwan AA, Voils SA, Hartzema AG. Trends in utilization of warfarin and direct oral anticoagulants in older adult patients with atrial fibrillation. Am J Health Syst Pharm. 2017 Aug 15;74(16):1237–44.

4. Barnes GD, Lucas E, Alexander GC, Goldberger ZD. National Trends in Ambulatory Oral Anticoagulant Use.2015/07/07. eng.

. Am J Med. 2015;128(12):1300–5.e2.

5. Ruigomez A, Brobert G, Vora P, Suzart-Woischnik K, Balabanova Y, Garcia Rodriguez LA. Trends in use of rivaroxaban for prophylaxis and treatment in general practice in the United Kingdom between 2012 and 2015. Pharmacoepidemiology and Drug Safety. 2018;27(S2).

6. Loo SY, Dell'Aniello S, Huiart L, Renoux C. Trends in the prescription of novel oral anticoagulants in UK primary care. Br J Clin Pharmacol. 2017 Sep;83(9):2096–106.

7. Mueller T, Alvarez-Madrazo S, Robertson C, Bennie M. Use of direct oral anticoagulants in patients with atrial fibrillation in Scotland: Applying a coherent framework to drug utilisation studies. Pharmacoepidemiol Drug Saf. 2017 Nov;26(11):1378–86.

8. Bjerring Olesen JB, Sorensen R, Hansen ML, Lamberts M, Weeke P, Mikkelsen AP, et al. Non-vitamin K antagonist oral anticoagulation agents in anticoagulant naive atrial fibrillation patients: Danish nationwide descriptive data 2011-2013. Europace. 2015 Feb;17(2):187–93.

9. Fay MR, Martins JL, Czekay B. Oral anticoagulant prescribing patterns for stroke prevention in atrial fibrillation among general practitioners and cardiologists in three European countries. European Heart Journal. 2016;37(Supplement 1 (August 2016)):510 (P2597 Abstract).

10. Kjerpeseth LJ, Ellekjaer H, Selmer R, Ariansen I, Furu K, Skovlund E. Trends in use of warfarin and direct oral anticoagulants in atrial fibrillation in Norway, 2010 to 2015. Eur J Clin Pharmacol. 2017 Nov;73(11):1417–25.

11. Lip GYH, Pan X, Kamble S, Kawabata H, Mardekian J, Masseria C, et al. Discontinuation risk comparison among 'real-world' newly anticoagulated atrial fibrillation patients: Apixaban, warfarin, dabigatran, or rivaroxaban. PLoS One. 2018;13(4):e0195950.

12. Vinogradova Y, Coupland C, Hill T, Hippisley-Cox J. Risks and benefits of direct oral anticoagulants versus warfarin in a real world setting: cohort study in primary care. BMJ. 2018 Jul 4;362:k2505.

13. Yao X, Shah ND, Sangaralingham LR, Gersh BJ, Noseworthy PA. Non-Vitamin K Antagonist Oral Anticoagulant Dosing in Patients With Atrial Fibrillation and Renal Dysfunction. J Am Coll Cardiol. 2017 Jun 13;69(23):2779–90.

14. García Rodríguez LA, Schink T, Bezemer ID, Herings RM, Friberg L, Balabanova Y, et al. High cardiovascular risk and frequent cardiovascular medication use among new users of rivaroxaban and vitamin K antagonists. Poster presentation at the American Heart Association Scientific Session 2018, November 10–14, 2018, Chicago, IL, USA. 2018.

15. Forslund T, Wettermark B, Hjemdahl P. Comparison of treatment persistence with different oral anticoagulants in patients with atrial fibrillation. Eur J Clin Pharmacol. 2016 Mar;72(3):329–38.

16. Kearon C, Akl EA, Ornelas J, Blaivas A, Jimenez D, Bounameaux H, et al. Antithrombotic Therapy for VTE Disease: CHEST Guideline and Expert Panel Report. Chest. 2016 Feb;149(2):315-52.

17. Steinberg BA, Shrader P, Pieper K, Thomas L, Allen LA, Ansell J, et al. Frequency and Outcomes of Reduced Dose Non-Vitamin K Antagonist Anticoagulants: Results From ORBIT-AF II (The Outcomes Registry for Better Informed Treatment of Atrial Fibrillation II). J Am Heart Assoc. 2018 Feb 16;7(4).

18. Staerk L, Gerds TA, Lip GYH, Ozenne B, Bonde AN, Lamberts M, et al. Standard and reduced doses of dabigatran, rivaroxaban and apixaban for stroke prevention in atrial fibrillation: a nationwide cohort study. J Intern Med. 2018 Jan;283(1):45–55.

19. Buchholz A, Ueberham L, Gorczynska K, Dinov B, Hilbert S, Dagres N, et al. Initial apixaban dosing in patients with atrial fibrillation. Clin Cardiol. 2018 May;41(5):671–6.

20. Steinberg BA, Shrader P, Thomas L, Ansell J, Fonarow GC, Gersh BJ, et al. Off-Label Dosing of Non-Vitamin K Antagonist Oral Anticoagulants and Adverse Outcomes: The ORBIT-AF II Registry. J Am Coll Cardiol. 2016 Dec 20;68(24):2597–604.

21. Barra ME, Fanikos J, Connors JM, Sylvester KW, Piazza G, Goldhaber SZ. Evaluation of Dose-Reduced Direct Oral Anticoagulant Therapy. Am J Med. 2016 Nov;129(11):1198–204.

22. Lavoie K, Turgeon MH, Brais C, Larochelle J, Blais L, Farand P, et al. Inappropriate dosing of direct oral anticoagulants in patients with atrial fibrillation. J Atr Fibrillation. 2016 Dec;9(4):1478.

23. Pisters R, van Vugt SPG, Brouwer MA, Elvan A, Ten Holt WL, Zwart PAG, et al. Real-life use of Rivaroxaban in the Netherlands: data from the Xarelto for Prevention of Stroke in Patients with Atrial Fibrillation (XANTUS) registry. Neth Heart J. 2017 Oct;25(10):551–8.

24. Camm AJ, Accetta G, Ambrosio G, Atar D, Bassand JP, Berge E, et al. Evolving antithrombotic treatment patterns for patients with newly diagnosed atrial fibrillation. Heart. 2017 Feb 15;103(4):307–14.

25. Zhu J, Alexander GC, Nazarian S, Segal JB, Wu AW. Trends and Variation in Oral Anticoagulant Choice in Patients with Atrial Fibrillation, 2010-2017. Pharmacotherapy. 2018 Sep;38(9):907–20.

Appendices

Appendix Table. Baseline characteristics of new users of NOACs (any indication) meeting the study inclusion criteria.

	Apixaban N=3302		**Dabigatran N=5061**		**Rivaroxaban N=10,208**	
Sex						
Male	1790	54.2	2762	54.6	5672	55.6
Female	1512	45.8	2299	45.4	4536	44.4
Age (years)						
<39	29	0.9	75	1.5	331	3.2
40–59	212	6.4	465	9.2	1358	13.3
60–69	449	13.6	774	15.3	1700	16.7
70–79	903	27.3	1412	27.9	2752	27.0
≥80	1556	47.1	1845	36.5	3431	33.6
Unknown	153	4.6	490	9.7	636	6.2
Mean age (SD)	77.3 (13.6)		74.8 (13.6)		72.4 (13.6)	
Anticoagulant naïve status						
Naive	2351	71.2	3394	67.1	6883	67.4
Non-naive	951	28.8	1667	32.9	3325	32.6
NVAF	2153	65.2	3089	61.0	5286	51.8
Atrial fibrillation with mitral stenosis/valvular replacement	28	0.8	49	1.0	103	1.0
Indication for NOAC use not specified	1121	33.9	1923	38.0	4819	47.2
Year of first NOAC prescription						
2009	0	0.0	7	0.1	27	0.3
2010	0	0.0	47	0.9	114	1.1
2011	0	0.0	416	8.2	71	0.7
2012	0	0.0	761	15.0	677	6.6
2013	52	1.6	853	16.9	1221	12.0
2014	339	10.3	853	16.9	1642	16.1
2015	826	25.0	765	15.1	2081	20.4
2016	1235	37.4	763	15.1	2584	25.3
2017 (Jan to end of June)	850	25.7	596	11.8	1791	17.5
2017	1544	38.6	1073	19.4	3476	29.2

Data are n (%) unless otherwise specified.

Annex 1: List of stand-alone documents

Not applicable

Annex 2 Additional information.

Not applicable