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1. Abstract

Acronym/Title	Pattern of use of direct oral anticoagulants in non-valvular atrial fibrillation patients in UK general practices THIN-CPRD Study
Report version and date	Version 1.4, 21 May 2019
Authors	PPD, PPD Spanish Centre for Pharmacoepidemiologic Research (CEIFE), Madrid, Spain
Keywords	Non-vitamin K antagonist oral anticoagulants (NOACs), atrial fibrillation, drug utilization; dosing; discontinuation
Rationale and background	There are limited data on prescription and usage patterns of NOACs in the UK among patients with NVAF. This information is, however, needed to evaluate continuation with therapy and compliance with the drug labelling information.
Research question and objectives	This population-based descriptive study characterized first-time users of apixaban, dabigatran and rivaroxaban in NVAF patients and patterns of use in routine UK primary care. Primary objectives • To describe baseline characteristics of patients with NVAF who are prescribed apixaban, dabigatran or rivaroxaban) for the first time for stroke prevention, and to compare these with the corresponding characteristics of patients in clinical trials. • To assess the pattern of use (daily dose, dose posology, treatment duration, naïve status) of rivaroxaban, dabigatran and apixaban for stroke prevention in NVAF patients in the UK. • To assess the proportion of patients with NVAF and renal impairment who are prescribed rivaroxaban, dabigatran, or apixaban at the index date, and to assess the daily dose, dose posology and duration of NOAC treatment. Secondary objective • To determine time-trends in the characteristics of

	first-time use of rivaroxaban, dabigatran and apixaban in patients with NVAF.
Study design	Population-based cohort study.
Setting	UK primary care, 01 January 2011 to 31 December 2016.
Subjects and study size, including dropouts	The study population included 30,467 individuals with NVAF aged ≥18 years with a first recorded prescription (index date) for apixaban, dabigatran or rivaroxaban.
Variables and data sources	Patient characteristics at the index date: demographics, lifestyle variables, healthcare use, comorbidities (including renal function calculated from estimated glomerular filtration rates values), co-medications and oral anticoagulant (OAC) naïve status. NOAC prescriptions: dose, dose posology, duration of use of index NOAC, appropriateness of dosing, discontinuation, switching and reinitiation, predictors of discontinuation and inappropriate dosing. **Data sources:** The Health Improvement Network and Clinical Practice Research Datalink databases of primary care electronic health records**.**
Results	A total of 30,467 patients with NVAF starting OAC therapy on a NOAC: 15,252 (50.1%) patients started NOAC therapy on rivaroxaban, 10,834 (35.6%) on apixaban and 4381 (14.4%) on dabigatran. The majority of patients prescribed a reduced dose were aged 70 years or older (apixaban 93.6%, dabigatran 88.4%, rivaroxaban 91.4%), and were moderately or severely frail (apixaban, 70.2%, dabigatran 61.7%, rivaroxaban 74.0%) The mean age of patients was 74–75 years, which is just slightly higher than that seen among the three pivotal NOAC AF clinical trials. The gender ratio in our study population was more balanced (50–60% were male) than that in the NOAC AF trials where ≥60% were male. OAC naïve status was: apixaban 53% (vs. 43% in ARISTOTLE), dabigatran 42% (vs. 50% in RE-LY), rivaroxaban 47% (vs. 38% in ROCKET-AF). Hypertension was the most commonly recorded comorbidity (approx. two-thirds of patients in each NOAC cohort), which is less than that seen among participants in ARISTOTLE (87%), RE-LY (79%) and ROCKET-AF (90%). Heart failure was notably less prevalent (approximately 17% in each cohort)

	than patients in the clinical trials (36% in ARISTOTLE, 32% in RE-LY and 63% in ROCKET-AF). Approximately a third of patients in each cohort were obese, while a little under a third each had IHD and hyperlipidaemia. Most patients had normal renal function (apixaban 67.3%, dabigatran 74.4%, rivaroxaban 70.1%), a medium risk of bleeding (HAS-BLED score of 1–3) and a high mean CHA2DS2-VASc score (comorbidity index) of between 3.5 and 3.7. Approximately two-thirds of patients in each NOAC cohort (approx. two-thirds) had a $CHADS_2$ score of between 0 and 2, in line with scores seen among ARISTOTLE and RE-LY trial participants, but indicating a lower comorbidity profile than participants in ROCKET-AF. As expected from patients' comorbidity profile, the most frequently prescribed comedications were antihypertensives, statins, proton pump inhibitors, antiplatelets and diuretics. The majority of patients were prescribed an appropriate dose according to the EU labels: apixaban 74.9 %, dabigatran 74.4%, rivaroxaban 84.2%. There was a trend towards dose reduction with increasing renal impairment. Among patients with severe renal impairment, the majority received a reduced dose NOAC: apixaban 91.1%, dabigatran 80.0%, rivaroxaban 83.0%. Potential underdosing occurred in 21.6% of patients starting NOAC therapy on apixaban compared with 8.7% starting on dabigatran and 9.1% starting on rivaroxaban. potential overdosing was more frequent for dabigatran (16.9%) than for rivaroxaban (6.6%) or apixaban (3.5%). In the discontinuation analysis (N=11,481), one-year discontinuation rates were: apixaban 26.1%, dabigatran 40.0%, rivaroxaban 29.6%. One-year re-initiation rates were: apixaban 18.1%, dabigatran 21.7%, rivaroxaban 17.3%; (≥93% of re-initiations were with the index NOAC). Switching rates were: apixaban 2.8%, dabigatran 8.8%, rivaroxaban 4.9%; discontinuation with no reinitiation was: apixaban 5.2%, dabigatran 9.6%, rivaroxaban 7.4%. Compared with patients starting on apixaban, ORs (% CIs) for discontinuation due to switching were 4.28 (95% CI: 3.24–5.65) for dabigatran and 1.89 (95% CI: 1.49–2.39) for rivaroxaban. Severely reduced renal function was a predictor of any discontinuation, OR 1.77 (95% CI: 1.28–2.44). Only 7% of NVAF patients in our study permanently discontinued OAC therapy (i.e. discontinued their index NOAC and did not reinitiate and type of OAC).

Discussion	Our findings highlight the importance of monitoring the prescribing of NOACs in the post-marketing period. Further research is warranted into reasons for inappropriate prescribing of reduced and standard dose NOACs in UK primary care, the impact this has on risks of clinical outcomes, including stroke, systemic embolism and major bleeding in this setting, and ways to improve levels of correct dosing to ensure patients receive maximum benefit from treatment. Efforts are needed to increase NOAC continuation rates in order to increase the number of NVAF patients benefitting from NOAC-mediated stroke protection, and well-designed large cohort studies are warranted to quantify the impact of interrupting NOAC therapy on thromboembolism risk. Our findings also underscore the importance of considering differences in characteristics when comparing outcomes between real-world populations prescribed NOACs for SPAF and NOAC-AF clinical trials.
Marketing Authorization Holder(s)	Bayer AG, 51368 Leverkusen
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2. List of abbreviations

AF	Atrial fibrillation
ACE	Angiotensin-Converting Enzyme
ACR	Albumin to Creatinine Ratio
ATC	Anatomical Therapeutic Chemical (Classification System)
BMI	Body Mass Index
CEIFE	Centro Español de Investigación Farmacoepidemiológica
CI	Confidence Interval
CKD	Chronic Kidney Disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CVD	Cardiovascular Disease
DVT	Deep Vein Thrombosis
eGFR	estimated Glomerular Filtration Rate
EMA	European Medicine Agency
ENCePP	European Network of Centers in Pharmacoepidemiology and Pharmacovigilance
CPRD	Clinical Practice Research Datalink
GCP	Good Clinical Practice
HR	Hazard Ratio
IHD	Ischemic Heart Disease
INR	International Normalized Ratio
LMWH	Low molecular weight heparins
MAH	Marketing Authorization Holder
MDRD	Modification of Diet in Renal Disease Study
MI	Myocardial Infarction
MREC	Multicenter Research Ethics Committee
N/A	Not Applicable
NOACs	Non-Vitamin K antagonist oral anticoagulants
NSAIDs	non-steroidal anti-inflammatory drugs
NVAF	Non valvular Atrial Fibrillation
OAC	oral anticoagulant
OTC	over-the-counter
PAD	Peripheral Artery Disease
PAS	Post-Authorization Study
PASS	Post-Authorization Safety Study
PCPs	Primary Care Practitioners
SD	Standard deviation
SRC	Scientific Research Committee
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
THIN	The Health Improvement Network
TIA	Transient Ischaemic Attack

UK	United Kingdom
VKAs	Vitamin K Antagonists
VTE	Venous Thromboembolism

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4. Other responsible parties

None

5. Milestones

Table 1. Milestones

Milestone	Planned date	Actual Date	Comments
Ethics Submission & Approval	January 2017	March 2017	
Study Start	January 2017	March 2017	Collecting data retrospective from 1st January 2011
Start of data analysis	April 2017	July 2017	Collecting data up to last available database update (December 2016)
Registration in the EU PAS register	April 2017	April 2017	
Final report of study results	August 2017	March 2019	Sub-analyses

6. Rationale and background

Prior to the introduction of non-vitamin K antagonist oral anticoagulants (NOACs), vitamin K antagonists (VKAs) were the standard treatment for antithrombotic prevention in atrial fibrillation (AF).(1) Non-vitamin K antagonist oral anticoagulants have been shown to have a favourable efficacy and safety profile compared with VKAs. Four NOACs (apixaban, dabigatran, rivaroxaban and edoxaban) are currently approved in the United Kingdom (UK) for the prevention of stroke and systemic embolism in patients with non-valvular AF (NVAF). The NOACs have several advantages compared with VKAs, including the use of a fixed dosing regimen with no need for international normalized ratio (INR) monitoring, and fewer drug-drug interactions. Two classes of NOACs are currently available: oral direct thrombin inhibitors (dabigatran) and oral direct factor Xa inhibitors (apixaban, rivaroxaban and edoxaban). 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.

Anticoagulant treatment should be individualized based on patients' age, renal function, comorbidities, and concomitant treatments. There are limited data on prescription and usage patterns of NOACs in routine care for the prevention of stroke in patients with NVAF in the UK, yet evaluating the usage patterns of NOACs is essential to study continuation with therapy appropriateness with labelling information.

7. Research question and objectives

This population-based observational study aimed to characterize patients with NVAF (including those with renal impairment) who were new users of a NOAC (apixaban, dabigatran or rivaroxaban) for stroke prevention, and to assess patterns of NOAC use in these patients in routine UK primary care.

7.1 Primary objectives

Among patients with NVAF prescribed either apixaban, dabigatran or rivaroxaban for the first time in UK primary care, the primary and secondary study objectives were:

- To provide baseline characteristics of NVAF patients who are prescribed with any of the three NOACs (apixaban, dabigatran and rivaroxaban) for the first time for stroke prevention and contrast with the corresponding characteristics of patients in clinical trials.
- To assess the pattern of use (daily dose, dose posology, treatment duration, naïve status) of apixaban, dabigatran or rivaroxaban in the UK for stroke prevention in NVAF patients
- To assess the proportion of NVAF patients with renal impairment who are prescribed with apixaban, dabigatran or rivaroxaban at the index date including their treatment

characteristics (daily dose, dose posology, duration).

7.2 Secondary objective

- To determine time-trends in the characteristics of first-time use of rivaroxaban, dabigatran and apixaban in NVAF patients.

8. Amendments and updates

Nr.	*Date*	*Section of study protocol*	*Amendment or Update*	*Reason*
1	*15 March 2019*	*Section 9 to Annex 2*	*Revision of all the tables and text in the report*	*The underlying cohorts for the study drugs created had to be corrected as we identified an error in selection. This led to change in the number of patients in respective cohorts and hence the whole report had to be revised.*

9. Research methods

9.1 Study design

This was a population-based cohort study designed to describe the characteristics of patients with NVAF who were first-time users of a NOAC, and to describe patterns of NOAC use among these patients in UK primary care. This study applied a new-users (initiators) design.(2) New users were individuals with a first prescription for one of the NOAC medications of interest in the database. The study protocol was approved by independent Scientific Research Committees (reference SRC 17THIN014 for THIN, and ISAC 17_020R for CPRD).

9.1.1 Primary endpoints

The primary endpoints of the study were to determine in patients with NVAF (including those with renal impairment) prescribed either apixaban, dabigatran or rivaroxaban for the first time:

- Baseline characteristics of patients

- Daily dose, dose posology, oral anticoagulant (OAC) naïve status, treatment duration of NOACs prescribed
- Percentage of patients appropriately dosed – patients correctly prescribed a NOAC dose according to the European Union [EU] labels.(3,4,5)
- Percentage of patients inappropriately dosed – patients prescribed an initial NOAC dose not in line with the EU labels, which included both underdosed patients (patients eligible for a standard dose who were prescribed a reduced dose) and overdosed patients (prescribing of a higher than recommended dose or any dose when contraindicated).
- Percentage of patients prescribed an initial NOAC dose according to renal function status.
- Patient characteristics predictive of NOAC underdosing/overdosing.
- Percentage of patients discontinuing treatment with the index NOAC during the first year of treatment among patients with at least two prescriptions for their index NOAC and at least 1 year follow-up after the index date (using THIN database only for the period 01 JAN 2012 to 31 DEC 2016). Discontinuation of the index NOAC was defined as either a switch to another NOAC or to a VKA during the index NOAC treatment period or in the 30 days after, or if there was a gap in treatment of >30 days between the end of an index NOAC prescription and the issue date of the next index OAC prescription (if any). All other patients were considered to be continuous users of their index NOAC during the first year of treatment
    - Percentage of NOAC discontinuers who a) switched from their index NOAC to a different NOAC, (b) switched from their index NOAC to a VKA, c) reinitiated OAC therapy with either the same NOAC, a different NOAC or a VKA after a gap of >30 days between the end of the last index NOAC prescription and the next prescription for an OAC, d) who did not re-start OAC therapy at all.
    - Characteristics of patients predictive of NOAC discontinuation

9.1.2 Secondary endpoint

- Time-trends in the characteristics of patients with NVAF newly prescribed a NOAC and time-trends in characteristics of the index NOAC.

9.2 Setting

The study was set in UK primary care using data from two primary care databases of anonymized electronic health records (EHRs) – The Health Improvement Network and

Clinical Practice Research Datalink GOLD (CPRD GOLD) (see **Section 9.5** for details) during the period 01 JAN 2011 to 31 DEC 2016.

9.3 Subjects

9.3.1 First-time users of a NOAC

The study population included all patients aged ≥18 years with a first recorded prescription (index date) for apixaban, dabigatran or rivaroxaban between 01 JAN 2011 and 31 DEC 2016. Patients were required to have been registered with a primary care practitioner (PCP) for ≥1 year before their first NOAC prescription and to have ≥1 year prescription history. Only patients with NVAF were included for analysis. These were identified as those with a record of AF any time before the index date or in the 2 weeks after the index date, and with no record of heart valve replacement or mitral stenosis during this time. We also excluded patients with a record of deep vein thrombosis (DVT), pulmonary embolism (PE), or hip/knee surgery in the 3 months before the index date because these could all have been alternative reasons for NOAC initiation. As some general practices contribute data to both THIN and CPRD, we included patients from all practices contributing to THIN plus those exclusively contributing to CPRD. To identify and exclude duplicated practices, the method of matching of anonymized patient characteristics was applied.(3),(4)

9.3.2 Identification of the three NOAC cohorts

Three mutually exclusive study cohorts were identified based on the first prescribed NOAC (index NOAC) – apixaban, dabigatran or rivaroxaban (**Figure 1**). Patients who were prescribed two different NOACs on the same day were excluded. Patients qualifying as a new user of more than one NOAC during the study period with different index dates (i.e. switchers) were assigned to the cohort of the first prescribed NOAC.

9.3.3 Eligibility to receive standard of reduced dose NOAC

Patients were categorised as eligible for standard or reduced dose NOAC therapy or ineligible for NOAC therapy (i.e. contraindicated) based on the approved European Union (EU) label for each respective NOAC,(3-5) adapted to the information recorded in the databases (**Appendix Table 1**). For the prevention of stroke and systemic embolism in adults with NVAF, the recommended standard doses according to the EU labels are 5 mg twice daily for apixaban, 150 mg twice daily for dabigatran and 20 mg once daily for rivaroxaban; the recommended reduced doses are 2.5 mg twice daily for apixaban, 110 mg twice daily for dabigatran and 15 mg once daily for rivaroxaban. Hereafter, for simplicity, these doses are termed ‘daily dose’. Dose reduction recommendations for rivaroxaban are based on renal function,(5) while dose reduction for dabigatran considers renal function, age, concomitant medications and other comorbidities.(4) For apixaban, at least two of the following criteria are to be met for dose reduction: ≥80 years, body weight ≤60 kg, serum creatinine ≥1.5mg/dL.(3)

9.4 Variables

9.4.1 NOAC dose and dose posology

The dose of the index NOAC prescription and dose posology was derived from the description of the prescribed product. Dose posology was also derived from the recorded instructions in the free text (**see** **Section 9.5**). A posology of three or more doses per day was considered invalid. If unclear, the daily dose of the first prescription was assigned by applying the algorithms 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 algorithm:

- 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 didn't apply and if there was another prescription of 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 of one of the original concurrent prescriptions, then this prescription was selected.
- If the above didn't 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 dose was computed as follows:

- If the posology directly derived 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 prescription was apixaban or dabigatran, then 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 were 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 daily dose of rivaroxaban assigned to 40 mg to 20 mg when the posology derived from dividing the quantity (number of tablets) by the days between consecutive prescriptions (gap between prescriptions of less than 90 days) resulted in a 20 mg daily dose (in this scenario, any information in the instructions field was ignored).

9.4.2 Patient characteristics

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

- Demographics: age, sex and Townsend score measure of socioeconomic deprivation at the index date
- Lifestyle variables: smoking status, body mass index (BMI; from recorded height and weight measurements) and alcohol status, using the most recently recorded value/status before the index date
- OAC naïve status: patients were categorised as oral anticoagulant (OAC) non-naïve if they had a prescription for any OAC before their index NOAC (or a clinical entry implying previous use of any OAC, warfarin monitoring or international normalized ratio >2); otherwise they were considered to be OAC-naive.
- Other anticoagulant use: type and duration of another anticoagulant use before the index date (warfarin or low-molecular weight heparin [LMWH])
- Renal function: ascertained using the closest valid serum creatinine value to the index date (within the year before or in the week after) to estimate glomerular filtration rate (eGFR) expressed as mL/min/1.73m^2 applying the Chronic Kidney Disease (CKD) Epidemiology Collaboration equation,(6) but omitted ethnicity because this is not routinely recorded in UK primary care: **eGFR = 141 × min (Scr /κ, 1)α × max(Scr /κ, 1)-1.209 × 0.993Age × 1.018 [if female] × 1.159 [if black]**, where: Scr is serum creatinine in mg/dL; κ is 0.7 for females and 0.9 for males; α is –0.329 for females and –0.411 for males; min indicates the minimum of Scr /κ or 1, and max indicates the maximum of Scr/κ or 1. Coded clinical entries indicating CKD stage, renal dialysis or kidney transplant were also used to determine renal function. Renal function was categorised as normal (eGFR >50 ml/min/1.73 m^2), mild-to-moderate impairment (eGFR 30–50 ml/min/1.73m^2) and severe impairment (eGFR<30 ml/min/1.73m^2).

- CHA_2DS_2-VASc score for stroke risk: using patients' recorded history of congestive heart failure, hypertension, age, diabetes mellitus and prior stroke/ transient ischaemic attack [TIA] ($CHADS_2$ score was also calculated because this was assessed in the pivotal studies for the NOACs investigated in this study).
- HAS-BLED score for major bleeding risk: using the recorded history of hypertension, renal disease, liver disease, stroke history, prior major bleeding or predisposition to bleeding, age >65 years, medication use predisposing to bleeding, history of alcohol use).
- Frailty using a frailty index developed for research using primary care databases,(7) based on a wide range of symptoms, signs, diseases, disabilities, abnormal laboratory values and social circumstances, and categorising patients as fit, mildly frail, moderately frail or severely frail.
- Co-medication use: prescription of the following medications in the 12 months either side of the index date: antiplatelet drugs (low-dose aspirin, clopidogrel, dipyridamole, prasugrel, ticlopidine and ticagrelor), anticoagulants (including rivaroxaban, dabigatran, apixaban, warfarin, and LMWH), antiarrhythmic drugs, antihypertensive drugs, statins, anti-diabetic agents, non-steroidal anti-inflammatory drugs (NSAIDs), oral steroids, acid-suppressive drugs, disease-modifying anti-rheumatic drugs, 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): haemorrhagic disease, intracranial haemorrhage, urogenital bleeding, gastrointestinal bleeding, liver disease, pancreatic disease, cancer, cardiovascular disease (acute myocardial infarction, coronary artery disease, congestive heart failure, ventricular arrhythmia and peripheral arterial disease [PAD]), cardiovascular risk factors (hypertension, diabetes mellitus, hyperlipidaemia and obesity), stroke/TIA, respiratory disease (asthma and chronic obstructive pulmonary disease [COPD]), rheumatoid arthritis, osteoarthritis, gastrointestinal disease, liver disease, pancreatic disorders, and alcohol-related disorders
- Healthcare use in the year before the index date and in the year after the index date (number of PCP visits, outpatient visits and hospital admissions).

9.4.3 Appropriate dosing

Appropriate dosing was defined as patient being prescribed the correct recommended dose based on the approved EU label. Inappropriate dosing was defined as a patient being prescribed a dose not in line with the EU label – this included both underdosed patients (prescribing of a reduced dose NOAC to patients eligible for a standard dose) and overdosed

patients (prescribing of a higher dose than recommended or any dose when contraindicated).

9.4.4 Duration of NOAC use

For each NOAC cohort, the duration of first episode of continuous treatment was calculated. Continuous use was defined as when there was no gap between the end of supply of a prescription and the next prescription of >30 days or no prescription thereafter.

9.4.5 Discontinuation of NOAC use

1-year discontinuation patterns of NOAC use was evaluated using a subset of 11,481 patients in THIN database only who had at least 2 prescriptions for the index NOAC and at least 1 year follow-up from the index date during the period 01 JAN 2012 to 31 DEC 2016. Discontinuation of the index NOAC was defined as either a switch to another NOAC or to a VKA during the index NOAC treatment period or in the 30 days after, or if there was a gap in treatment of >30 days between an index NOAC prescription, if any (i.e. between the end of an index NOAC prescription and the issue date of the next index NOAC prescription). Discontinuers who did not switch were categorised as re-initiators, and these were further divided according to whether they reinitiated treatment on the index NOAC, on a different NOAC, on a VKA or whether they stopped OAC treatment (non-reinitiators). All other patients were considered to be continuous users of their index NOAC during the first year of therapy.

9.5 Data sources: Clinical Practice Research Datalink GOLD and The Heath Improvement Network

The Heath Improvement Network and CPRD GOLD are two similarly structured validated UK databases of anonymized primary care EHRs representative of the UK demographic.(8-11) The databases hold clinical and prescribing information entered by primary care practitioners (PCP) as part of routine patient care, and cover approximately 5% and 7% of the UK population, respectively. Medical events (e.g. symptoms, diagnosis, hospital referrals) are entered using Read codes,(12) although there is a free text field for manual data entry (currently available in THIN but not CPRD GOLD). Prescriptions are linked to multilex codes, (13) and are automatically recorded upon issue.

In this study, we used both databases because this enabled the acquisition of a larger database than would have been obtained if using only CPRD GOLD (approximately 25–30% greater). Therefore, we used all THIN practices and only included information from those CPRD practices that do not contribute to THIN. To identify and exclude duplicated practices between THIN and CPRD GOLD, matching of anonymized patient characteristics was applied.(14) Free-text comments entered by PCPs in patients' individual HER were available for patients registered in practices contributing to THIN but not in those exclusively contributing data to CPRD GOLD.

9.6 Bias

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

9.7 Study size

All data available during time of study (01 JAN, 2012–31 DEC, 2016) was used, i.e. all patients with NVAF who were and was based on all first-time users of either apixaban, dabigatran or rivaroxaban, who m*et al*l other study inclusion criteria.

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 CEIFE 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 a 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

For the primary objectives, descriptive analyses were carried out for each NOAC cohort using frequency counts and percentages for quantitative variables, and means with standard deviation (SD) and ranges for continuous variables. These analyses included a description of the following:

- patient characteristics (demographics, OAC naïve status, lifestyle factors, comorbidities, comedications and healthcare use) for the whole study period (2011–2016) for both the entire cohort as well as according to the daily dose of the index NOAC (standard or reduced).
- patient characteristics (as above) for the entire cohort for each individual study year.
- patient characteristics (including age, bodyweight and renal function) according to the dose of the index NOAC
- dose and dose posology of index NOAC for the whole study period as well as for each

study year.

- dose at 6 months following the index date among patients with either continuous or non-continuous NOAC treatment according to dose of index NOAC (only for patients who were current users of the index NOAC at 6 months).
- dose and dose posology of the index NOAC over whole study period stratified by renal function and by eligibility to receive standard or reduced dose NOAC.
- duration of continuous NOAC use.
- the percentage of patients appropriately dosed (see **Section 9.1.1**), both overall and according to i) eligibility to receive a standard or reduced dose NOAC, ii) whether the daily dose of the index NOAC was a standard or reduced dose, iii) renal function
- patient characteristics predictive of inappropriate underdosing/overdosing.

In addition, in the discontinuation analysis (using the subset of 11,481 patients in THIN) the following outcomes were described during the first year from start of NOAC therapy:

- the percentage of patients who i) discontinued treatment with the index NOAC, ii) switched from their index NOAC to another OAC (a different NOAC or a VKA), iii) discontinued their index NOAC and reinitiated treatment with the same NOAC, a different NOAC or a VKA, iv) discontinued their index NOAC and did not reinitiate with any OAC therapy
- time to NOAC discontinuation (among patients who discontinued with the index NOAC); time to OAC reinitiation (among patients who discontinued with the index NOAC but reinitiated OAC therapy).
- patient characteristics predictive of discontinuation with the index NOAC, calculating ORs with 95% CIs comparing the odds of discontinuers having a particular characteristic with the odds of non-discontinuers having that particular using logistic regression.

For the secondary study objective of describing time trends of new users of NOACs across the study period, the cumulative incidence of new users of each NOAC for SPAF were calculated using individual in THIN database only. We were unable to use GPRD-GOLD for this analysis because we did not have access to data on the population denominator. Cumulative incidence rates were calculated for each NOAC in each study year, as well as stratified by age and sex for the year 2016.

9.9.2 Main statistical methods

All analyses were undertaken using STATA version 12.0. Standard methods of obtaining descriptive statistics were used for the main outcome summary measures. Logistic regression was used to calculate crude ORs with 95% CIs to identify potential changes in patient

characteristics over time (i.e. odds of having that characteristic in 2016 with the odds of having that characteristic in earlier study years 2011–2013), and in analyses used to identify predictor outcomes.

9.9.3 Missing values

No data imputation strategies were applied to supplement missing data for patient characteristic variables such as smoking status, BMI or alcohol consumption. The requirement for inclusion was complete data for critical variables; otherwise this individual was not eligible to be a member of the study population. However, missing values may have occurred for a small proportion of patients. In this case, individuals with missing values were kept in the analysis and a separate category created for missing values of that variable.

9.9.4 Sensitivity analyses

Not applicable.

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 the flowchart in **Figure 1**. During the study period, there were a total of 11,047 patients with NVAF who were new users of apixaban, 4456 patients with NVAF who were new users of dabigatran, and 15,833 patients with NVAF who were new users of rivaroxaban. Among these, there were a total of 30,467 new users of a NOAC with a record of NVAF and no other recent indication for anticoagulation; 10,834 (35.6%) started on apixaban, 4381 (14.4%) started on dabigatran, and 15,252 (50.1%) started on rivaroxaban.

10.2 Descriptive data

Please refer to (Main Results) – **Section 10.4**. This study was descriptive in study design therefore all descriptive data constitute the main results.

10.3 Outcome data

All outcome data are shown in **Section 10.4**.

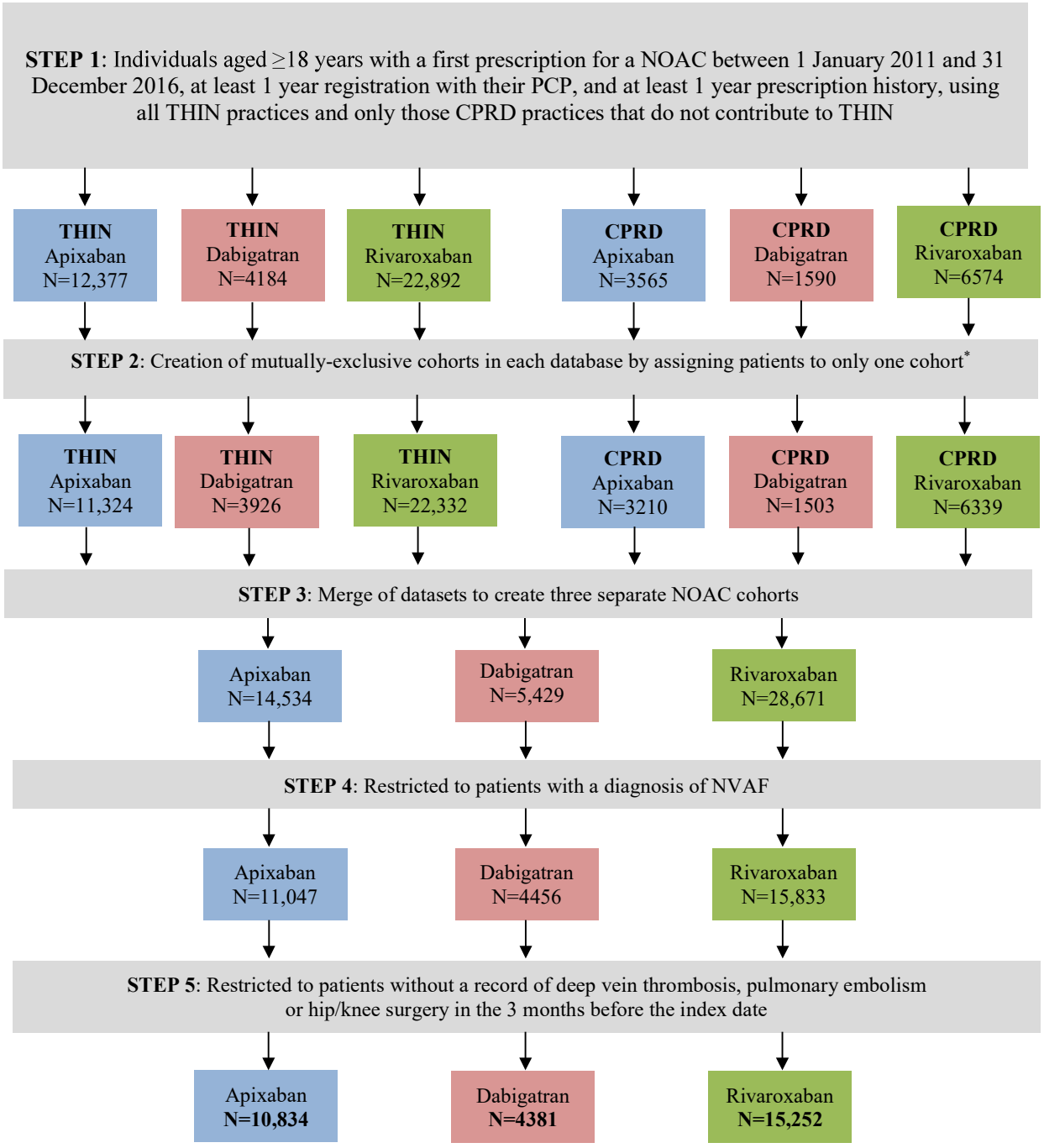

Figure 1. Flowchart depicting identification of the three NOAC study cohorts from THIN and CPRD GOLD.

10.4 Main results

10.4.1 Characteristics of the three NOAC study cohorts

Characteristics of the three NOAC study cohorts are shown in **Table 2**. Most patients in each cohort were male (apixaban 53.2%, dabigatran 57.6%, rivaroxaban 54.9%). The mean age of patients was similar across cohorts (apixaban 75 years, dabigatran 74 years, rivaroxaban 75 years. Most patients in the apixaban cohort were OAC naïve while most patients in the dabigatran and rivaroxaban cohort were OAC non-naïve. The most commonly observed comorbidity at the index date was hypertension, which was present in about two-thirds of patients in each NOAC cohort, while a third of patients in each cohort were obese. Other common comorbidities were ischaemic heart disease and hyperlipidaemia, which were both recorded in a little under a third of patients in each NOAC cohort. The majority of patients in each cohort (over 60%) had a $CHADS_2$ score of between 0 and 2, while around 30% of patients in each cohort had a CHA_2DS_2-VASc scores of between 0 and 2. The mean CHA_2DS_2-VASc and $CHADS_2$ score was 3.7 for the apixaban cohort, 3.5 for the dabigatran cohort 3.6 for the rivaroxaban cohort. The mean HAS-BLED score was 1.8 for the apixaban and dabigatran cohorts and 1.7 for the rivaroxaban cohort. Renal function was normal in the majority of patients (apixaban 67.3%, dabigatran 74.4%, rivaroxaban 70.1%). As might be expected from the comorbidity profile, the most common comedications were antihypertensives, statins, PPIs, antiplatelets and diuretics.

Characteristics of the study cohorts stratified by the daily dose of the index NOAC prescription (standard or reduced) are shown in **Table 3**. Among patients receiving a standard dose, the apixaban cohort had the highest proportion of OAC-naïve patients (55.4% vs. 45.0% for dabigatran and 48.6% for rivaroxaban). Most patients prescribed a standard dose had normal renal function (apixaban 75.4%, dabigatran 80.5%, rivaroxaban, 79.0%). The majority of patients prescribed a reduced dose were aged 70 years or older (apixaban 93.6%, dabigatran 88.4%; rivaroxaban 91.4%), and were moderately or severely frail (apixaban 70.2%, dabigatran 61.7%, rivaroxaban 74.0%). Bleeding risk (according to the HAS-BLED score) was similar between the three cohorts, and was higher among patients prescribed reduced NOAC doses (mean 2.0, SD 0.9 for all patients prescribed a reduced dose) than among patients receiving standard doses (mean 1.6, SD 0.9 for all patients prescribed a standard dose). Approximately three quarters of patients in each cohort who were prescribed a reduced dose had a high stroke risk index (CHA_2DS_2-VASc score of $\geq$4).

Table 2. Baseline characteristics of the cohort of 30,467 patients with NVAF starting NOAC therapy.

Characteristic	Apixaban N=10,834	Dabigatran N=4381	Rivaroxaban N=15,252
Sex	5759 (53.2)	25623 (57.6)	8374 (54.9)
Male	5075 (46.8)	1858 (42.4)	6878 (45.1)
Female			
Age (years)			
<39	47 (0.4)	16 (0.4)	46 (0.3)
40–59	849 (7.8)	437 (10.0)	1259 (8.3)
60–69	2080 (19.2)	928 (21.2)	2909 (19.1)
70–79	3536 (32.6)	1541 (35.2)	5140 (33.7)
≥80	4322 (39.9)	1459 (33.3)	5898 (38.7)
Mean age (SD)	75.4 (10.9)	74.0 (10.8)	75.2 (10.7)
OAC naïve status			
Naïve	5774 (53.3)	1827 (41.7)	7206 (47.2)
Non-naïve	5060 (46.7)	2554 (58.3)	8046 (52.8)
Year of first NOAC prescription			
2011	0 (0.0)	76 (1.7)	4 (0.0)
2012	0 (0.0)	838 (19.1)	312 (2.0)
2013	291 (2.7)	1260 (28.8)	1672 (11.0)
2014	1888 (17.4)	1010 (23.1)	3405 (22.3)
2015	3773(34.8)	739 (16.9)	5253 (34.4)
2016	4882 (45.1)	458 (10.5)	4606 (30.2)
Mean follow-up, days (SD)	371.9 (284.0)	718.3 (487.2)	462.4 (353.3)
BMI, kg/m^2			
10–19 (underweight)	448 (4.1)	174 (4.0)	647 (4.2)
20–24 (healthy weight)	2523 (23.3)	1008 (23.0)	3571 (23.4)
25–29 (overweight)	3827 (35.3)	1601 (36.5)	5297 (34.7)
≥30 (obese)	3602 (33.2)	1402 (32.0)	5165 (33.9)
Unknown	434 (4.0)	196 (4.5)	572 (3.8)
Smoking			
Non-smoker	4534 (41.8)	1799 (41.1)	6193 (40.6)
Smoker	826 (7.6)	304 (6.9)	1207 (7.9)
Ex-smoker	5463 (50.4)	2273 (51.9)	7842 (51.4)
Unknown	11 (0.1)	5 (0.1)	10 (0.1)
Alcohol (units/week)			
None	2485 (22.9)	770 (17.6)	3093 (20.3)
1–9	4707 (43.4)	1985 (45.3)	6983 (45.8)
10–20	1706 (15.7)	737 (16.8)	2302 (15.1)
21–41	598 (5.5)	318 (7.3)	920 (6.0)
≥42	275 (2.5)	137 (3.1)	405 (2.7)
Unknown	1063 (9.8)	434 (9.9)	1549 (10.2)
History of CVD			
MI	1461 (13.5)	496 (11.3)	1751 (11.5)
IHD	3248 (30.0)	1151 (26.3)	4132 (27.1)
Heart failure	1927 (17.8)	737 (16.8)	2518 (16.5)
Hypertension	7226 (66.7)	2883 (65.8)	10,285 (67.4)
Ventricular arrhythmia	253 (2.3)	117 (2.7)	327 (2.1)
Hyperlipidemia	3505 (32.4)	1250 (28.5)	4552 (29.8)
PAD	611 (5.6)	226 (5.2)	924 (6.1)
VTE	1050 (9.7)	447 (10.2)	1614 (10.6)
Ischaemic stroke	1764 (16.3)	689 (15.7)	2134 (14.0)

Characteristic	Apixaban N=10,834	Dabigatran (N=4381)	Rivaroxaban N=15,252
TIA	1335 (12.3)	585 (13.4)	1647 (10.8)
Diabetes mellitus	2364 (21.8)	832 (19.0)	3307 (21.7)
History of bleeding disorders			
Intracranial bleeding	204 (1.9)	71 (1.6)	193 (1.3)
GI bleeding	1530 (14.1)	581 (13.3)	2059 (13.5)
Urogenital bleeding	1394 (12.9)	523 (11.9)	2086 (13.7)
eGFR, ml/min/1.73m^2			
>50	7291 (67.3)	3259 (74.4)	10,699 (70.1)
30–50	1819 (16.8)	574 (13.1)	2389 (15.7)
<30	280 (2.6)	20 (0.5)	271 (1.8)
Unknown	1444 (13.3)	528 (12.1)	1893 (12.4)
CHA_2DS_2-VASc score,			
0	451 (4.2)	252 (5.8)	633 (4.2)
1	727 (6.7)	336 (7.7)	1183 (7.8)
2	1677 (15.5)	739 (16.9)	2387 (15.7)
3	2187 (20.2)	893 (20.4)	3202 (21.0)
4	5792 (53.5)	2161 (49.3)	7847 (51.4)
Mean (SD)	3.7 (1.9)	3.5 (1.9)	3.6 (1.8)
$CHADS_2$ score			
0	1230 (11.4)	594 (13.6)	1805 (11.8)
1	2714 (25.1)	1129 (25.8)	3909 (25.6)
2	3188 (29.4)	1254 (28.6)	4663 (30.6)
3	3702 (34.2)	1404 (32.0)	4875 (32.0)
Mean (SD)	3.7 (1.9)	3.5 (1.9)	3.6 (1.8)
HAS-BLED score	1.8 (1.0)	1.8 (1.0)	1.7 (1.0)
0	860 (7.9)	361 (8.2)	1282 (8.4)
1	3600 (33.2)	1425 (32.5)	5430 (35.6)
2	4024 (37.1)	(38.9)	5795 (38.0)
3	1878 (17.3)	733 (16.7)	2226 (14.6)
4	472 (4.4)	158 (3.6)	519 (3.4)
mean (SD)			
Medications*			
Antiplatelet agents	5094 (47.0)	2278 (52.0)	6855 (44.9)
Aspirin	4283 (39.5)	2020 (46.1)	5903 (38.7)
Clopidogrel	1332 (12.3)	486 (11.1)	1555 (10.2)
NSAIDs	1344 (12.4)	613 (14.0)	1782 (11.7)
Oral steroids	1465 (13.5)	570 (13.0)	2230 (14.6)
OACs	3174 (29.3)	1699 (38.8)	5361 (35.1)
Antiarrhythmics	1541 (14.2)	828 (18.9)	2180 (14.3)
Antihypertensives	9514 (87.8)	3890 (88.8)	13,517 (88.6)
Beta blockers	6146 (56.7)	2595 (59.2)	8688 (57.0)
ACE inhibitors	4084 (37.7)	1704 (38.9)	5784 (37.9)
Diuretics	4919 (45.4)	1956 (44.6)	6818 (44.7)
Statins	6220 (57.4)	2406 (54.9)	8441 (55.3)

Data are n (%) unless otherwise specified.
*Use in the year before (but not on) the index date.

Table 3. Baseline characteristics of the cohort of 30,467 patients with NVAF starting NOAC therapy stratified by dose of first NOAC prescription (standard or reduced dose).

	Apixaban (N=10,834)		Dabigatran (N=4381)		Rivaroxaban (N=15,252)*	
	Standard dose (n=7061; 65.2%)	**Reduced dose (n= 3773; 34.8%)**	**Standard dose (n=2018; 46.1%)**	**Reduced dose (n=2363; 53.9%)**	**Standard dose (n=12,091; 79.3%)**	**Reduced dose (n=3081; 20.2%)**
Sex						
Male	4271 (60.5)	1488 (39.4)	1380 (68.4)	1143 (48.4)	7042 (58.2)	1289 (41.8)
Female	2790 (39.5)	2285 (60.6)	638 (31.6)	1220 (51.6)	5049 (41.8)	1792 (58.2)
Age (years)						
<60	833 (11.8)	63 (1.7)	380 (18.8)	73 (3.1)	1233 (10.2)	66 (2.1)
60–69	1903 (27.0)	177 (4.7)	726 (36.0)	202 (8.5)	2696 (22.3)	199 (6.5)
70–79	2860 (40.5)	676 (17.9)	842 (41.7)	699 (29.6)	4400 (36.4)	715 (23.2)
≥80	1465 (20.7)	2857 (75.7)	70 (3.5)	1389 (58.8)	3762 (31.1)	2101 (68.2)
Mean age (SD)	71.4 (10.2)	82.8 (7.8)	67.2 (9.1)	79.7 (8.5)	73.6 (10.6)	81.8 (8.5)
OAC naïve status						
Naïve	3915 (55.4)	1859 (49.3)	909 (45.0)	918 (38.8)	5881 (48.6)	1295 (42.0)
Non-naïve	3146 (44.6)	1914 (50.7)	1109 (55.0)	1445 (61.2)	6210 (51.4)	1786 (58.0)
Year of first NOAC prescription						
2011–13	184 (2.6)	107 (2.8)	968 (48.0)	1206 (51.0)	1492 (12.3)	479 (15.5)
2014–16	6877 (97.4)	3666 (97.2)	1050 (52.0)	1157 (49.0)	10,599 (87.7)	2602 (84.5)
BMI, kg/m^2						
10–19 (underweight)	117 (1.7)	331 (8.8)	35 (1.7)	139 (5.9)	434 (3.6)	212 (6.9)
20–24 (healthy weight)	1322 (18.7)	1201 (31.8)	343 (17.0)	665 (28.1)	2679 (22.2)	875 (28.4)
25–29 (overweight)	2599 (36.8)	1228 (32.5)	735 (36.4)	866 (36.6)	4230 (35.0)	1035 (33.6)
≥30 (obese)	2766 (39.2)	836 (22.2)	809 (40.1)	593 (25.1)	4291 (35.5)	847 (27.5)
Unknown	257 (3.6)	177 (4.7)	96 (4.8)	100 (4.2)	457 (3.8)	112 (3.6)
Smoking						
Non-smoker	2851 (40.4)	1683 (44.6)	784 (38.9)	1015 (43.0)	4876 (40.3)	1282 (41.6)
Smoker	605 (8.6)	221 (5.9)	178 (8.8)	126 (5.3)	1015 (8.4)	182 (5.9)
Ex-smoker	3598 (51.0)	1865 (49.4)	1052 (52.1)	1221 (51.7)	6190 (51.2)	1617 (52.5)
Unknown	7 (0.1)	4 (0.1)	4 (0.2)	1 (0.0)	10 (0.1)	0 (0.0)

	Apixaban (N=10,834)		Dabigatran (N=4381)		Rivaroxaban (N=15,252)*	
	Standard dose (n=7061; 65.2%)	**Reduced dose (n= 3773; 34.8%)**	**Standard dose (n=2018; 46.1%)**	**Reduced dose (n=2363; 53.9%)**	**Standard dose (n=12,091; 79.3%)**	**Reduced dose (n=3081; 20.2%)**
Alcohol (units/week)						
None	1356 (19.2)	1129 (29.9)	244 (12.1)	526 (22.3)	2244 (18.6)	827 (26.8)
1–9	3044 (43.1)	1663 (44.1)	857 (42.5)	1128 (47.7)	5501 (45.5)	1448 (47.0)
10–20	1316 (18.6)	390 (10.3)	422 (20.9)	315 (13.3)	1975 (16.3)	316 (10.3)
21–41	470 (6.7)	128 (3.4)	219 (10.9)	99 (4.2)	821 (6.8)	95 (3.1)
≥42	227 (3.2)	48 (1.3)	92 (4.6)	45 (1.9)	354 (2.9)	50 (1.6)
Unknown	648 (9.2)	415 (11.0)	184 (9.1)	250 (10.6)	1196 (9.9)	345 (11.2)
History of CVD						
IHD	1939 (27.5)	1309 (34.7)	416 (20.6)	735 (31.1)	3014 (24.9)	1098 (35.6)
Heart failure	1080 (15.3)	847 (22.4)	268 (13.3)	469 (19.8)	1709 (14.1)	791 (25.7)
Hypertension	4464 (63.2)	2762 (73.2)	1192 (59.1)	1691 (71.6)	7888 (65.2)	2338 (75.9)
Ischaemic stroke	990 (14.0)	774 (20.5)	254 (12.6)	435 (18.4)	1567 (13.0)	553 (17.9)
History of bleeding disorders						
Intracranial bleeding	96 (1.4)	108 (2.9)	20 (1.0)	51 (2.2)	139 (1.1)	52 (1.7)
GI bleeding	957 (13.6)	573 (15.2)	232 (11.5)	349 (14.8)	1609 (13.3)	440 (14.3)
Urogenital bleeding	877 (12.4)	517 (13.7)	214 (10.6)	309 (13.1)	1629 (13.5)	449 (14.6)
eGFR, ml /min/1.73/m^2						
>50	5323 (75.4)	1968 (52.2)	1625 (80.5)	1634 (69.1)	9547 (79.0)	1105 (35.9)
30–50	694 (9.8)	1125 (29.8)	110 (5.5)	464 (19.6)	892 (7.4)	1475 (47.9)
<30	25 (0.4)	255 (6.8)	4 (0.2)	16 (0.7)	46 (0.4)	223 (7.2)
Unknown	1019 (14.4)	425 (11.3)	279 (13.8)	249 (10.5)	1606 (13.3)	278 (9.0)
Frailty index						
Fit	1306 (18.5)	191 (5.1)	517 (25.6)	201 (8.5)	2120 (17.5)	133 (4.3)
Mild frailty	2839 (40.2)	933 (24.7)	918 (45.5)	706 (29.9)	4624 (38.2)	668 (21.7)
Moderate frailty	1978 (28.0)	1395 (37.0)	448 (22.2)	833 (35.3)	3522 (29.1)	1182 (38.4)
Severe frailty	938 (13.3)	1254 (33.2)	135 (6.7)	623 (26.4)	1825 (15.1)	1098 (35.6)

	Apixaban (N=10,834)		Dabigatran (N=4381)		Rivaroxaban (N=15,252)*	
	Standard dose (n=7061; 65.2%)	**Reduced dose (n= 3773; 34.8%)**	**Standard dose (n=2018; 46.1%)**	**Reduced dose (n=2363; 53.9%)**	**Standard dose (n=12,091; 79.3%)**	**Reduced dose (n=3081; 20.2%)**
CHA_2DS_2-VASc-score						
0	42 (6.0)	25 (0.7)	220 (10.9)	32 (1.4)	608 (5.0)	23 (0.7)
1	675 (9.6)	52 (1.4)	260 (12.9)	76 (3.2)	1107 (9.2)	68 (2.2)
2	1425 (20.2)	252 (6.7)	517 (25.6)	222 (9.4)	2182 (18.0)	199 (6.5)
3	1564 (22.1)	623 (16.5)	418 (20.7)	475 (20.1)	2681 (22.2)	507 (16.5)
≥4	2971 (42.1)	2821 (74.8)	603 (29.9)	1558 (65.9)	5513 (45.6)	2284 (74.1)
Mean (SD)	3.2 (1.8)	4.6 (1.6)	2.7 (1.7)	4.2 (1.7)	3.4 (1.8)	4.6 (1.6)
$CHADS_2$ score						
0	1127 (16.0)	103 (2.7)	480 (23.8)	114 (4.8)	1696 (14.0)	103 (3.3)
1	2119 (30.0)	595 (15.8)	681 (33.7)	448 (19.0)	3440 (28.5)	452 (14.7)
2	1929 (27.3)	1259 (33.4)	468 (23.2)	786 (33.3)	3596 (29.7)	1044 (33.9)
≥3	1886 (26.7)	1816 (48.1)	389 (19.3)	1015 (43.0)	3359 (27.8)	1482 (48.1)
Mean (SD)	1.8 (1.3)	2.6 (1.3)	1.5 (1.2)	1.9 (1.3)	1.9 (1.3)	2.6 (1.3)
HAS-BLED score						
0	814 (11.5)	46 (1.2)	312 (15.5)	49 (2.1)	1224 (10.1)	54 (1.8)
1	2437 (34.5)	1163 (30.8)	704 (34.9)	721 (30.5)	4460 (36.9)	938 (30.4)
2	2510 (35.5)	1514 (40.1)	699 (34.6)	1005 (42.5)	4467 (36.9)	1305 (42.4)
3	1089 (15.4)	789 (20.9)	263 (13.0)	470 (19.9)	1612 (13.3)	596 (19.3)
≥4	211 (3.0)	261 (6.9)	40 (2.0)	118 (5.0)	328 (2.7)	188 (6.1)
Mean (SD)	1.6 (1.0)	2.0 (1.0)	1.6 (0.9)	2.0 (0.9)	1.6 (0.9)	2.0 (0.9)
Medications†						
Antiplatelets	3250 (46.0)	1844 (48.9)	993 (49.2)	1285 (54.4)	5299 (43.8)	1519 (49.3)
Antiarrhythmics	1074 (15.2)	467 (12.4)	403 (20.0)	425 (18.0)	1764 (14.6)	403 (13.1)
Antihypertensives	6114 (86.6)	3400 (90.1)	1743 (86.4)	2147(90.9)	10,591 (87.6)	2860 (92.8)

*80 patients starting therapy on rivaroxaban were prescribed an initial daily dose higher than standard daily dose (>20 mg day) and are not included in the table.

†Prescription within 1 year before or 1 year after the first NOAC prescription.

10.4.1.1 Time trends in the characteristics of patients with NVAF starting NOAC therapy

Characteristics of patients in each cohort are shown by study year in **Tables 4–12** along with the OR for each characteristic comparing patients having the characteristic in 2016 with those with the same characteristic in the years 2011–2013.

The distribution of age, sex and OAC naïve status across study years is shown in **Table 4** for patients starting NOAC therapy on apixaban, **Table 5** for patients starting on dabigatran and **Table 6** for those starting on rivaroxaban. There was a general trend of an increase in the percentage of apixaban and rivaroxaban new users who were male across study years, while for dabigatran, the percentage of males was stable over time. There were notable differences in the age distribution of the NOAC cohorts over time. Among patients starting on apixaban, there was a general trend of an increase in the percentage of patients aged ≥80 years and a decrease in the percentage of patients aged between 60 and 79 years. Among patients starting on dabigatran, there was an increase in the percentage of patients aged 60 years or more over time, while among patients starting on rivaroxaban, there was a marked decrease in the percentage of patients aged ≥80 years over time with a corresponding increase in the percentage of patients aged <60 years. In all three NOAC cohorts, there was an increase in the percentage of patients who were OAC naïve, and this was most evident for patients starting on either dabigatran (OR 1.48, 95% CI: 1.21–1.82) or rivaroxaban (OR 1.70, 95% CI: 1.53–1.90).

The distribution of comorbidities across study years is shown in **Table 7** for patients starting NOAC therapy on apixaban, **Table 8** for patients starting on dabigatran and **Table 9** for those starting on rivaroxaban. Among patients starting on apixaban, there were few notable changes in the distribution of patient comorbidities over time. There was some evidence of a decrease in the percentage of patients with hyperlipidaemia, ischaemic stroke, TIA, intracranial bleeding, and stronger evidence of a decrease in the percentage of patients with a HAS-BLED score of 2 (OR 0.65, 95% CI: 0.50–0.85) or ≥3 (OR 0.70, 95% CI: 0.51–0.97).

Among patients starting on dabigatran, there were a number of notable changes in the distribution of comorbidities over study years. Decreases were seen in the percentage of patients with myocardial infarction (OR 0.67, 95% CI: 0.48–0.96), ischaemic heart disease (IHD; OR 0.74, 95% CI: 0.59–0.94), VTE (OR 0.66, 95% CI: 0.45–0.96), moderate renal impairment (eGFR 30–50 ml/min/1.73m^2; OR 0.62, 95% CI: 0.44–0.87) and a HAS-BLED score ≥3 (OR 0.65, 95% CI: 0.49–0.86), while there was an increase in the percentage of patients with cancer (OR 1.41, 95% CI: 1.12–1.78).

Among patients starting on rivaroxaban, there were notable decreases in the distribution of many comorbidities over study years. This was seen in particular for the following: ventricular arrhythmia (OR 0.51, 95% CI: 0.36–0.72), ischaemic stroke (OR 0.59, 95% CI: 0.51–0.68), TIA (OR 0.69, 95% CI: 0.58–0.81), severe frailty (OR 0.59, 95% CI: 0.49–0.71), moderate frailty (OR 0.62, 95% CI: 0.52–0.74), mild frailty (OR 0.83, 95% CI: 0.70–0.99), a $CHADS_2$ scores of ≥3 (OR 0.56, 95% CI: 0.46–0.68) or 2 (OR 0.69, 95% CI: 0.57–0.84), a CHA_2DS_2-VASc score of 2 (OR 0.65, 95% CI: 0.57–0.73) or ≥3 (OR 0.65, 95% CI:

0.57–0.73). Other comorbidities that became less prevalent over time among patients starting on rivaroxaban were peptic ulcer disease, osteoarthritis, moderate renal impairment (eGFR 30–50/min/1.73m^2), and heart failure.

The distribution of comedications across study years is shown in **Table 10** for patients starting NOAC therapy on apixaban, **Table 11** for patients starting on dabigatran and **Table 12** for those starting on rivaroxaban. Among patients starting on apixaban, there were notable decreases in the prevalence of use of the following co-medications: low-dose aspirin (OR 0.51, 95% CI: 0.40–0.65), anticoagulants (OR 0.69, 95% CI: 0.54–0.88), antiarrhythmic drugs (OR 0.62, 95% CI: 0.46–0.84), and NSAIDs (OR 0.68, 95% CI: 0.49–0.94). Among patients starting on dabigatran or rivaroxaban, there were notable decreases in the prevalence of use of several comedications, in particular low-dose aspirin (dabigatran cohort, OR 0.51, 95% CI: 0.41–0.63; rivaroxaban cohort OR 0.53, 95% CI: 0.47–0.59), clopidogrel (dabigatran cohort, OR 0.55, 95% CI: 0.37–0.79; rivaroxaban cohort OR 0.67, 95% CI: 0.57–0.80), anticoagulant drugs (dabigatran cohort, OR 0.62, 95% CI: 0.50–0.77; rivaroxaban cohort OR 0.60, 95% CI: 0.54–0.67), and antiarrhythmics (dabigatran cohort, OR 0.56, 95% CI: 0.42–0.74; rivaroxaban cohort OR 0.63, 95% CI: 0.55–0.73). Decreases in the use of beta-blockers, ACE inhibitors, diuretics and strong CYP3A4 inducers were seen in both the dabigatran and rivaroxaban cohorts, while statins, antihypertensives, histamine-receptor-2 antagonists, and antipsychotics were also observed in the rivaroxaban cohort.

Table 4. Age, sex and OAC naive status patients with NVAF newly prescribed apixaban (N=10,834) by calendar year.

	2011 N=0		2012 N=0		2013 N=291		2014 N=1888		2015 N=3773		2016 N=4882		Crude OR 2016 (N=4882) vs. 2011–2013 (N=291)	
	n	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**OR**	**95% CI**
Sex														
Male	–	–	–	–	142	48.8	974	51.6	2041	54.1	2602	53.3	1.0	–
Female	–	–	–	–	149	51.2	914	48.4	1732	45.9	2280	46.7	0.84	0.66–1.06
Age (years)	–	–	–	–										
<60	–	–	–	–	16	5.5	158	8.4	351	9.3	371	7.6	1.0	
60–69	–	–	–	–	61	21.0	401	21.2	683	18.1	935	19.2	0.66	0.38–1.16
70–79	–	–	–	–	106	36.4	626	33.2	1228	32.5	1576	32.3	0.64	0.37–1.10
≥80	–	–	–	–	108	37.1	703	37.2	1511	40.0	2000	41.0	0.80	0.47–1.37
OAC naive status	–	–	–	–										
Naive	–	–	–	–	135	46.4	965	51.1	2061	54.6	2613	53.5	1.33	1.05–1.69
Non-naive	–	–	–	–	156	53.6	923	48.9	1712	45.4	2269	46.5	1.0	–

Table 5. Age, sex and OAC naive status among patients with NVAF newly prescribed dabigatran with NVAF (N=4381) by calendar year.

	2011		2012		2013		2014		2015		2016		Crude OR 2016 (N=458) vs. 2011–2013 (N=2174)	
	N=76		N=838		N=1260		N=1010		N=739		N=458			
	n	%	n	%	n	%	n	%	n	%	n	%	OR	95% CI
Sex														
Male	42	55.3	485	57.9	729	57.9	590	58.4	415	56.2	262	57.2	1.0	–
Female	34	44.7	353	42.1	531	42.1	420	41.6	324	43.8	196	42.8	1.02	0.83–1.25
Age (years)														
<60	7	9.2	87	10.4	147	11.7	101	10.0	77	10.4	34	7.4	1.0	–
60–69	17	22.4	167	19.9	245	19.4	235	23.3	158	21.4	106	23.1	1.75	1.15–2.66
70–79	29	38.2	331	39.5	441	35.0	336	33.3	237	32.1	167	36.5	1.48	0.99–2.20
≥80	23	30.3	253	30.2	427	33.9	338	33.5	267	36.1	151	33.0	1.52	1.02–2.27
OAC naive status														
Naive	25	32.9	283	33.8	491	39.0	453	44.9	363	49.1	212	46.3	1.48	1.21–1.82
Non-naive	51	67.1	555	66.2	769	61.0	557	55.1	376	50.9	246	53.7	1.0	–

Table 6. Age, sex and OAC naive status among patients with NVAF newly prescribed rivaroxaban with NVAF (N=15,252) by calendar year.

	2011 N=4		2012 N=312		2013 N=1672		2014 N=3405		2015 N=5253		2016 N=4606		Crude OR 2016 (N=4606) vs. 2011–2013 (N=1988)	
	n	%	n	%	n	%	n	%	n	%	n	%	OR	95 CI%
Sex														
Male	2	50.0	181	58.0	893	53.4	1854	54.4	2882	54.9	2562	55.6	1.0	–
Female	2	50.0	131	42.0	779	46.6	1551	45.6	2371	45.1	2044	44.4	0.94	0.85–1.05
Age (years)														
<60	0	0.0	24	7.7	112	6.7	284	8.3	444	8.5	441	9.6	1.0	–
60–69	1	25.0	60	19.2	281	16.8	637	18.7	1032	19.6	898	19.5	0.81	0.64–1.02
70–79	1	25.0	122	39.1	596	35.6	1116	32.8	1764	33.6	1541	33.5	0.66	0.53–0.82
≥80	2	50.0	106	34.0	683	40.8	1368	40.2	2013	38.3	1726	37.5	0.67	0.55–0.83
OAC naive status														
Naive	3	75.0	82	26.3	663	39.7	1529	44.9	2595	49.4	2334	50.7	1.70	1.53–1.90
Non–naive	1	25.0	230	73.7	1009	60.3	1876	55.1	2658	50.6	2272	49.3	1.0	–

Table 7. Comorbidities among patients with NVAF newly prescribed apixaban (N=10,834) by calendar year.

	2011 N=0		2012 N=0		2013 N=291		2014 N=1888		2015 N=3773		2016 N=4882		Crude OR 2016 (N=4882) vs. 2011–2013 (N=291)	
	n	%	n	%	n	%	n	%	n	%	n	%	OR	95% CI
Cardiovascular disease														
Myocardial infarction	–	–	–	–	39	13.4	238	12.6	533	14.1	651	13.3	0.99	0.70–1.41
IHD	–	–	–	–	89	30.6	554	29.3	1159	30.7	1446	29.6	0.96	0.74–1.23
Vascular disease (as in CHA_2DS_2-VASc)	–	–	–	–	90	30.9	566	30.0	1226	32.5	1547	31.7	1.04	0.80–1.34
Heart failure	–	–	–	–	48	16.5	316	16.7	688	18.2	875	17.9	1.11	0.80–1.52
Hypertension	–	–	–	–	191	65.6	1276	67.6	2506	66.4	3253	66.6	1.05	0.81–1.34
Atrial fibrillation	–	–	–	–	287	98.6	1869	99.0	3730	98.9	4804	98.4	0.86	0.31–2.36
Ventricular arrhythmia	–	–	–	–	6	2.1	55	2.9	87	2.3	105	2.2	1.04	0.45–2.40
Hyperlipidaemia	–	–	–	–	105	36.1	610	32.3	1240	32.9	1550	31.7	0.82	0.64–1.05
PAD (lower extremity)	–	–	–	–	14	4.8	94	5.0	234	6.2	269	5.5	1.15	0.67–2.00
VTE	–	–	–	–	27	9.3	189	10.0	399	10.6	435	8.9	0.96	0.64–1.44
Ischaemic stroke	–	–	–	–	53	18.2	303	16.0	664	17.6	744	15.2	0.81	0.59–1.10
TIA	–	–	–	–	42	14.4	235	12.4	495	13.1	563	11.5	0.77	0.55–1.08
History of bleeding disorders														
Intracranial bleeding	–	–	–	–	9	3.1	38	2.0	74	2.0	83	1.7	0.54	0.27–1.09
Gastrointestinal bleeding	–	–	–	–	38	13.1	281	14.9	545	14.4	666	13.6	1.05	0.74–1.49
Urogenital bleeding	–	–	–	–	43	14.8	252	13.3	472	12.5	627	12.8	0.85	0.61–1.19
Endocrine/metabolic disease														
Obesity	–	–	–	–	32	11.0	266	14.1	513	13.6	748	15.3	1.46	1.01–2.13
Diabetes mellitus	–	–	–	–	55	18.9	378	20.0	841	22.3	1090	22.3	1.23	0.91–1.67
Respiratory disease														
COPD	–	–	–	–	35	12.0	232	12.3	458	12.1	599	12.3	1.02	0.71–1.47
Asthma	–	–	–	–	65	22.3	406	21.5	768	20.4	1058	21.7	0.96	0.72–1.28
Gastrointestinal disease														
Liver disease	–	–	–	–	12	4.1	109	5.8	197	5.2	277	5.7	1.40	0.77–2.52
Pancreatic disease	–	–	–	–	2	0.7	36	1.9	60	1.6	83	1.7	2.50	0.61–10.21

	2011 N=0		2012 N=0		2013 N=291		2014 N=1888		2015 N=3773		2016 N=4882		Crude OR 2016 (N=4882) vs. 2011–2013 (N=291)	
	n	%	n	%	n	%	n	%	n	%	n	%	OR	95% CI
Peptic ulcer disease					28	9.6	196	10.4	377	10.0	514	10.5	1.11	0.74–1.65
Other diseases														
Rheumatoid arthritis	–	–	–	–	14	4.8	72	3.8	132	3.5	199	4.1	0.84	0.48–1.47
Osteoarthritis	–	–	–	–	142	48.8	874	46.3	1708	45.3	2332	47.8	0.96	0.76–1.22
Cancer	–	–	–	–	71	24.4	457	24.2	884	23.4	1174	24.0	0.98	0.74–1.29
Severe renal failure	–	–	–	–	6	2.1	43	2.3	68	1.8	73	1.5	0.72	0.31–1.67
eGFR, ml/min/1.73m^2														
> 50	–	–	–	–	197	67.7	1270	67.3	2547	67.5	3277	67.1	1.0	–
30–50	–	–	–	–	46	15.8	313	16.6	626	16.6	834	17.1	1.09	0.78–1.52
<30	–	–	–	–	9	3.1	57	3.0	97	2.6	117	2.4	0.78	0.39–1.56
Unknown	–	–	–	–	39	13.4	248	13.1	503	13.3	654	13.4	1.01	0.71–1.44
Frailty index														
Fit	–	–	–	–	37	12.7	285	15.1	492	13.0	683	14.0	1.0	–
Mild frailty	–	–	–	–	110	37.8	644	34.1	1312	34.8	1706	34.9	0.84	0.57–1.23
Moderate frailty	–	–	–	–	90	30.9	596	31.6	1194	31.6	1493	30.6	0.90	0.61–1.33
Severe frailty	–	–	–	–	54	18.6	363	19.2	775	20.5	1000	20.5	1.00	0.65–1.54
Cardiovascular scores														
$CHADS_2$ score														
0	–	–	–	–	31	10.7	218	11.5	419	11.1	562	11.5	1.0	–
1	–	–	–	–	71	24.4	501	26.5	890	23.6	1252	25.6	0.97	0.63–1.50
2	–	–	–	–	93	32.0	558	29.6	1111	29.4	1426	29.2	0.85	0.56–1.28
≥3	–	–	–	–	96	33.0	611	32.4	1353	35.9	1642	33.6	0.94	0.62–1.43
CHA_2DS_2-VASc score														
0–2	–	–	–	–	68	23.4	533	28.2	970	25.7	1284	26.3	1.0	–
3	–	–	–	–	67	23.0	376	19.9	744	19.7	1000	20.5	0.79	0.56–1.12
≥4	–	–	–	–	156	53.6	979	51.9	2059	54.6	2598	53.2	0.88	0.66–1.18

	2011 N=0		2012 N=0		2013 N=291		2014 N=1888		2015 N=3773		2016 N=4882		Crude OR 2016 (N=4882) vs. 2011–2013 (N=291)	
	n	%	n	%	n	%	n	%	n	%	n	%	OR	95% CI
HAS-BLED score														
0–1	–	–	–	–	101	34.7	691	36.6	1506	39.9	2162	44.3	1.0	–
2	–	–	–	–	126	43.3	734	38.9	1405	37.2	1759	36.0	0.65	0.50–0.85
≥3	–	–	–	–	64	22.0	463	24.5	862	22.8	961	19.7	0.70	0.51–0.97

Table 8. Comorbidities among patients with NVAF newly prescribed dabigatran (N=4381) by calendar year.

	2011		2012		2013		2014		2015		2016		Crude OR 2016 (N=458) vs. 2011–2013 (N=2174)	
	N=76		N=838		N=1260		N=1010		N=739		N=458			
	n	%	n	%	n	%	n	%	n	%	n	%	OR	95% CI
Cardiovascular disease														
Myocardial infarction	16	21.1	117	14.0	137	10.9	96	9.5	90	12.2	40	8.7	0.67	0.48–0.96
IHD	29	38.2	257	30.7	340	27.0	231	22.9	188	25.4	106	23.1	0.74	0.59–0.94
Vascular disease (as in CHA_2DS_2-VASc)	25	32.9	274	32.7	362	28.7	292	28.9	210	28.4	123	26.9	0.84	0.67–1.05
Heart failure	16	21.1	153	18.3	214	17.0	179	17.7	103	13.9	72	15.7	0.87	0.66–1.15
Hypertension	56	73.7	550	65.6	830	65.9	653	64.7	487	65.9	307	67.0	1.04	0.84–1.29
Atrial fibrillation	76	100.0	835	99.6	1258	99.8	1007	99.7	736	99.6	456	99.6	0.53	0.10–2.72
Ventricular arrhythmia	2	2.6	24	2.9	32	2.5	29	2.9	17	2.3	13	2.8	1.07	0.58–1.96
Hyperlipidaemia	23	30.3	260	31.0	353	28.0	285	28.2	200	27.1	129	28.2	0.95	0.76–1.19
PAD (lower extremity)	7	9.2	58	6.9	69	5.5	47	4.7	30	4.1	15	3.3	0.52	0.30–0.89
VTE	7	9.2	107	12.8	122	9.7	94	9.3	83	11.2	34	7.4	0.66	0.45–0.96
Ischaemic stroke	12	15.8	155	18.5	224	17.8	143	14.2	88	11.9	67	14.6	0.78	0.59–1.04
TIA	10	13.2	123	14.7	179	14.2	139	13.8	74	10.0	60	13.1	0.90	0.67–1.21
History of bleeding disorders														
Intracranial bleeding	1	1.3	12	1.4	21	1.7	16	1.6	11	1.5	10	2.2	1.40	0.69–2.86
Gastrointestinal bleeding	12	15.8	110	13.1	146	11.6	147	14.6	105	14.2	61	13.3	1.09	0.81–1.47
Urogenital bleeding	13	17.1	110	13.1	145	11.5	101	10.0	92	12.4	62	13.5	1.11	0.83–1.50
Endocrine/metabolic disease														
Obesity	13	17.1	99	11.8	138	11.0	112	11.1	91	12.3	46	10.0	0.86	0.62–1.20
Diabetes mellitus	14	18.4	154	18.4	245	19.4	201	19.9	148	20.0	70	15.3	0.77	0.58–1.01
Respiratory disease														
COPD	10	13.2	104	12.4	152	12.1	109	10.8	65	8.8	44	9.6	0.76	0.54–1.07
Asthma	19	25.0	195	23.3	286	22.7	216	21.4	155	21.0	94	20.5	0.86	0.67–1.11
Gastrointestinal disease														
Liver disease	3	3.9	36	4.3	55	4.4	44	4.4	41	5.5	28	6.1	1.44	0.93–2.23
Pancreatic disease	1	1.3	8	1.0	9	0.7	11	1.1	7	0.9	5	1.1	1.32	0.49–3.58
Peptic ulcer disease	11	14.5	83	9.9	120	9.5	82	8.1	51	6.9	37	8.1	0.80	0.56–1.16

	2011		2012		2013		2014		2015		2016		Crude OR 2016 (N=458) vs. 2011–2013 (N=2174)	
	N=76		N=838		N=1260		N=1010		N=739		N=458			
	n	%	n	%	n	%	n	%	n	%	n	%	OR	95% CI
Other diseases														
Rheumatoid arthritis	1	1.3	30	3.6	42	3.3	29	2.9	25	3.4	14	3.1	0.91	0.51–1.62
Osteoarthritis	38	50.0	374	44.6	569	45.2	443	43.9	341	46.1	224	48.9	1.16	0.95–1.42
Cancer	21	27.6	178	21.2	261	20.7	212	21.0	176	23.8	126	27.5	1.41	1.12–1.78
Severe renal failure	1	1.3	12	1.4	10	0.8	6	0.6	7	0.9	3	0.7	0.62	0.18–2.06
eGFR, ml/min/1.73m^2														
>50	48	63.2	625	74.6	949	75.3	733	72.6	547	74.0	357	77.9	1.0	–
30–50	17	22.4	125	14.9	168	13.3	129	12.8	93	12.6	42	9.2	0.62	0.44–0.87
<30	1	1.3	3	0.4	5	0.4	5	0.5	2	0.3	4	0.9	2.02	0.62–6.59
Unknown	10	13.2	85	10.1	138	11.0	143	14.2	97	13.1	55	12.0	1.07	0.78–1.47
Frailty index														
Fit	9	11.8	117	14.0	207	16.4	176	17.4	138	18.7	71	15.5	1.0	–
Mild frailty	32	42.1	318	37.9	448	35.6	385	38.1	259	35.0	182	39.7	1.07	0.79–1.45
Moderate frailty	19	25.0	250	29.8	388	30.8	268	26.5	214	29.0	142	31.0	1.01	0.74–1.39
Severe frailty	16	21.1	153	18.3	217	17.2	181	17.9	128	17.3	63	13.8	0.77	0.53–1.11
Cardiovascular scores														
$CHADS_2$ score														
0	7	9.2	109	13.0	156	12.4	165	16.3	97	13.1	60	13.1	1.0	–
1	16	21.1	207	24.7	323	25.6	235	23.3	219	29.6	129	28.2	1.07	0.76–1.50
2	24	31.6	228	27.2	363	28.8	284	28.1	220	29.8	135	29.5	1.00	0.71–1.39
≥3	29	38.2	294	35.1	418	33.2	326	32.3	203	27.5	134	29.3	0.82	0.59–1.15
CHA_2DS_2-VASc score														
0–2	22	28.9	225	26.8	371	29.4	327	32.4	245	33.2	137	29.9	1.0	–
3	12	15.8	192	22.9	245	19.4	183	18.1	150	20.3	111	24.2	1.12	0.84–1.47
≥4	42	55.3	421	50.2	644	51.1	500	49.5	344	46.5	210	45.9	0.86	0.68–1.08
HAS-BLED score														
0–1	34	44.7	319	38.1	467	37.1	439	43.5	326	44.1	201	43.9	1.0	–
2	26	34.2	333	39.7	494	39.2	385	38.1	289	39.1	177	38.6	0.85	0.68–1.06
≥3	16	21.1	186	22.2	299	23.7	186	18.4	124	16.8	80	17.5	0.65	0.49–0.86

Table 9. Comorbidities among patients with NVAF newly prescribed rivaroxaban (N=15,252) by calendar year.

	2011 N=4		2012 N=312		2013 N=1672		2014 N=3405		2015 N=5253		2016 N=4606		Crude OR 2016 (N=4606) vs. 2011–2013 (N=1988)	
	n	%	n	%	n	%	n	%	n	%	n	%	OR	95% CI
Cardiovascular disease														
Myocardial infarction	1	25.0	39	12.5	205	12.3	426	12.5	596	11.3	484	10.5	0.84	0.71–0.98
IHD	1	25.0	100	32.1	492	29.4	972	28.5	1420	27.0	1147	24.9	0.78	0.69–0.88
Vascular disease (as in CHA_2DS_2-VASc)	1	25.0	115	36.9	550	32.9	1011	29.7	1593	30.3	1257	27.3	0.75	0.67–0.83
Heart failure	0	0.0	70	22.4	323	19.3	554	16.3	884	16.8	687	14.9	0.71	0.62–0.82
Hypertension	2	50.0	215	68.9	1170	70.0	2303	67.6	3494	66.5	3101	67.3	0.89	0.80–1.00
Atrial fibrillation	4	100.0	310	99.4	1659	99.2	3381	99.3	5190	98.8	4563	99.1	0.81	0.45–1.46
Ventricular arrhythmia	0	0.0	10	3.2	50	3.0	66	1.9	119	2.3	72	1.6	0.51	0.36–0.72
Hyperlipidaemia	1	25.0	114	36.5	551	33.0	1033	30.3	1502	28.6	1351	29.3	0.82	0.74–0.92
PAD (lower extremity)	0	0.0	26	8.3	134	8.0	203	6.0	328	6.2	233	5.1	0.61	0.49–0.75
VTE	1	25.0	40	12.8	189	11.3	371	10.9	545	10.4	468	10.2	0.86	0.73–1.02
Ischaemic stroke	0	0.0	50	16.0	322	19.3	513	15.1	699	13.3	550	11.9	0.59	0.51–0.68
TIA	0	0.0	45	14.4	215	12.9	369	10.8	586	11.2	432	9.4	0.69	0.58–0.81
History of bleeding disorders														
Intracranial bleeding	1	25.0	3	1.0	28	1.7	54	1.6	52	1.0	55	1.2	0.74	0.48–1.15
Gastrointestinal bleeding	0	0.0	36	11.5	219	13.1	479	14.1	711	13.5	614	13.3	1.05	0.89–1.22
Urogenital bleeding	1	25.0	27	8.7	246	14.7	434	12.7	742	14.1	636	13.8	1.00	0.86–1.17
Endocrine/metabolic disease														
Obesity	0	0.0	49	15.7	218	13.0	492	14.4	716	13.6	675	14.7	1.11	0.95–1.29
Diabetes mellitus	1	25.0	76	24.4	352	21.1	731	21.5	1132	21.5	1015	22.0	1.03	0.90–1.17
Respiratory disease														
COPD	1	25.0	40	12.8	217	13.0	421	12.4	681	13.0	583	12.7	0.97	0.83–1.14
Asthma	1	25.0	61	19.6	374	22.4	704	20.7	1152	21.9	959	20.8	0.94	0.82–1.06

	2011 N=4		2012 N=312		2013 N=1672		2014 N=3405		2015 N=5253		2016 N=4606		Crude OR 2016 (N=4606) vs. 2011–2013 (N=1988)	
	n	%	n	%	n	%	n	%	n	%	n	%	OR	95% CI
Gastrointestinal disease														
Liver disease	0	0.0	17	5.4	88	5.3	187	5.5	265	5.0	237	5.1	0.97	0.77–1.23
Pancreatic disease	0	0.0	6	1.9	27	1.6	47	1.4	75	1.4	59	1.3	0.77	0.50–1.18
Peptic ulcer disease	1	25.0	38	12.2	169	10.1	325	9.5	505	9.6	362	7.9	0.73	0.61–0.87
Other diseases														
Rheumatoid arthritis	0	0.0	13	4.2	61	3.6	129	3.8	242	4.6	218	4.7	1.28	0.98–1.68
Osteoarthritis	4	100.0	153	49.0	839	50.2	1573	46.2	2384	45.4	2074	45.0	0.82	0.73–0.91
Cancer	1	25.0	73	23.4	384	23.0	765	22.5	1258	23.9	1126	24.4	1.08	0.95–1.22
Severe renal failure	0	0.0	6	1.9	31	1.9	53	1.6	90	1.7	62	1.3	0.72	0.48–1.08
eGFR, ml/min/1.73m^2														
>50	3	75.0	221	70.8	1142	68.3	2355	69.2	3748	71.3	3230	70.1	1.0	–
30–50	1	25.0	48	15.4	306	18.3	568	16.7	781	14.9	685	14.9	0.82	0.71–0.94
<30	0	0.0	7	2.2	30	1.8	65	1.9	91	1.7	78	1.7	0.89	0.60–1.33
Unknown	0	0.0	36	11.5	194	11.6	417	12.2	633	12.1	613	13.3	1.13	0.96–1.33
Frailty index														
Fit	1	25.0	36	11.5	202	12.1	460	13.5	804	15.3	762	16.5	1.0	–
Mild frailty	2	50.0	101	32.4	534	31.9	1213	35.6	1776	33.8	1687	36.6	0.83	0.70–0.99
Moderate frailty	0	0.0	109	34.9	567	33.9	1064	31.2	1638	31.2	1340	29.1	0.62	0.52–0.74
Severe frailty	1	25.0	66	21.2	369	22.1	668	19.6	1035	19.7	817	17.7	0.59	0.49–0.71
Cardiovascular scores														
$CHADS_2$ score														
0	1	25.0	24	7.7	153	9.2	394	11.6	656	12.5	577	12.5	1.0	–
1	1	25.0	69	22.1	360	21.5	854	25.1	1371	26.1	1254	27.2	0.90	0.74–1.10
2	2	50.0	106	34.0	534	31.9	1029	30.2	1554	29.6	1438	31.2	0.69	0.57–0.84
≥3	0	0.0	113	36.2	625	37.4	1128	33.1	1672	31.8	1337	29.0	0.56	0.46–0.68

	2011 N=4		2012 N=312		2013 N=1672		2014 N=3405		2015 N=5253		2016 N=4606		Crude OR 2016 (N=4606) vs. 2011–2013 (N=1988)	
	n	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**OR**	**95% CI**
CHA_2DS_2-VASc score														
0–2	1	25.0	73	23.4	360	21.5	929	27.3	1515	28.8	1325	28.8	1.0	–
3	2	50.0	57	18.3	350	20.9	687	20.2	1075	20.5	1031	22.4	0.83	0.71–0.97
≥4	1	25.0	182	58.3	962	57.5	1789	52.5	2663	50.7	2250	48.8	0.64	0.57–0.73
HAS-BLED score														
0–1	2	50.0	135	43.3	576	34.4	1378	40.5	2362	45.0	2259	49.0	1.0	–
2	1	25.0	116	37.2	691	41.3	1378	40.5	1955	37.2	1654	35.9	0.65	0.57–0.73
≥3	1	25.0	61	19.6	405	24.2	649	19.1	936	17.8	693	15.0	0.47	0.41–0.54

Table 10. Medication use 1 year before the index date (not including the index date) among patients with NVAF newly prescribed apixaban (N=10,834) by calendar year.

	2011 N=0		2012 N=0		2013 N=291		2014 N=1888		2015 N=3773		2016 N=4882		Crude OR 2016 N=4882 vs. 2011–2013 N=291	
	n	%	n	%	n	%	n	%	n	%	n	%	OR	95% CI
Antiplatelet agents	–	–	–	–	162	55.7	1048	55.5	1883	49.9	2001	41.0	0.55	0.44–0.70
Aspirin	–	–	–	–	145	49.8	910	48.2	1584	42.0	1644	33.7	0.51	0.40–0.65
Clopidogrel	–	–	–	–	35	12.0	257	13.6	492	13.0	548	11.2	0.92	0.64–1.33
NSAIDs	–	–	–	–	47	16.2	272	14.4	459	12.2	566	11.6	0.68	0.49–0.94
Oral steroids	–	–	–	–	36	12.4	246	13.0	532	14.1	651	13.3	1.09	0.76–1.56
Anticoagulant drugs	–	–	–	–	110	37.8	576	30.5	1051	27.9	1437	29.4	0.69	0.54–0.88
Antiarrhythmic drugs	–	–	–	–	56	19.2	347	18.4	512	13.6	626	12.8	0.62	0.46–0.84
Antihypertensive drugs	–	–	–	–	262	90.0	1692	89.6	3294	87.3	4266	87.4	0.77	0.52–1.14
Beta-blockers	–	–	–	–	174	59.8	1097	58.1	2116	56.1	2759	56.5	0.87	0.69–1.11
ACE inhibitors	–	–	–	–	117	40.2	741	39.2	1421	37.7	1805	37.0	0.87	0.69–1.11
Diuretics	–	–	–	–	133	45.7	881	46.7	1712	45.4	2193	44.9	0.97	0.76–1.23
Statins	–	–	–	–	175	60.1	1088	57.6	2209	58.5	2748	56.3	0.85	0.67–1.09
Antidiabetic drugs	–	–	–	–	35	12.0	258	13.7	585	15.5	788	16.1	1.41	0.98–2.02
Oral contraceptives*	–	–	–	–	1	0.7	4	0.4	5	0.3	9	0.4	0.59	0.07–4.66
HRT*	–	–	–	–	2	1.3	21	2.3	24	1.4	29	1.3	0.95	0.22–4.01
PPIs	–	–	–	–	145	49.8	944	50.0	1776	47.1	2277	46.6	0.88	0.69–1.12
H_2-receptor antagonists	–	–	–	–	15	5.2	91	4.8	180	4.8	279	5.7	1.12	0.65–1.90
DMARDs	–	–	–	–	8	2.7	43	2.3	71	1.9	103	2.1	0.76	0.37–1.58
Antidepressants	–	–	–	–	61	21.0	424	22.5	841	22.3	1082	22.2	1.07	0.80–1.44
Antipsychotic drugs	–	–	–	–	26	8.9	182	9.6	334	8.9	415	8.5	0.95	0.63–1.43
Strong inhibitors of either cytochrome P450 3A4 or P-glycoprotein	–	–	–	–	1	0.3	4	0.2	6	0.2	8	0.2	0.48	0.06–3.82
Strong inducers of cytochrome P450 3A4	–	–	–	–	9	3.1	60	3.2	91	2.4	110	2.3	0.72	0.36–1.44

*Among 5075 women

Table 11. Medication use 1 year before the index date (not including the index date) among patients with NVAF newly prescribed dabigatran (N=4381) by calendar year.

	2011		2012		2013		2014		2015		2016		Crude OR 2016 (N=458 vs. 2011–2013 (N=2174)	
	N=76		N=838		N=1260		N=1010		N=739		N=458			
	N	%	n	%	n	%	n	%	n	%	n	%	OR	95% CI
Antiplatelet agents	42	55.3	474	56.6	713	56.6	505	50.0	363	49.1	181	39.5	0.50	0.41–0.62
Aspirin	33	43.4	434	51.8	636	50.5	446	44.2	314	42.5	157	34.3	0.51	0.41–0.63
Clopidogrel	15	19.7	109	13.0	147	11.7	110	10.9	72	9.7	33	7.2	0.55	0.37–0.79
NSAIDs	5	6.6	117	14.0	177	14.0	142	14.1	111	15.0	61	13.3	0.96	0.72–1.30
Oral steroids	12	15.8	111	13.2	152	12.1	141	14.0	92	12.4	62	13.5	1.08	0.80–1.45
Anticoagulant drugs	41	53.9	410	48.9	501	39.8	371	36.7	227	30.7	149	32.5	0.62	0.50–0.77
Antiarrhythmic drugs	21	27.6	198	23.6	263	20.9	178	17.6	105	14.2	63	13.8	0.56	0.42–0.74
Antihypertensive drugs	72	94.7	767	91.5	1125	89.3	879	87.0	642	86.9	405	88.4	0.82	0.59–1.12
Beta-blockers	47	61.8	519	61.9	762	60.5	580	57.4	431	58.3	256	55.9	0.81	0.66–0.99
ACE inhibitors	27	35.5	339	40.5	530	42.1	377	37.3	266	36.0	165	36.0	0.80	0.65–0.99
Diuretics	44	57.9	382	45.6	586	46.5	438	43.4	328	44.4	178	38.9	0.73	0.59–0.90
Statins	48	63.2	490	58.5	708	56.2	513	50.8	388	52.5	259	56.6	0.97	0.79–1.19
Antidiabetic drugs	9	11.8	104	12.4	169	13.4	142	14.1	97	13.1	48	10.5	0.79	0.57–1.09
Oral contraceptives*	0	0.0	1	0.3	4	0.8	0	0.0	1	0.3	0	0.0	–	–
HRT*	1	2.9	10	2.8	13	2.4	5	1.2	7	2.2	3	1.5	0.58	0.17–1.94
PPIs	39	51.3	370	44.2	551	43.7	433	42.9	322	43.6	187	40.8	0.87	0.71–1.07
H_2-receptor antagonists	2	2.6	29	3.5	59	4.7	35	3.5	31	4.2	19	4.1	1.00	0.60–1.66
DMARD	0	0.0	11	1.3	21	1.7	13	1.3	7	0.9	8	1.7	1.19	0.54–2.60
Antidepressants	17	22.4	164	19.6	236	18.7	180	17.8	135	18.3	87	19.0	0.99	0.76–1.28
Antipsychotic drugs	8	10.5	75	8.9	80	6.3	77	7.6	64	8.7	30	6.6	0.86	0.58–1.29
Strong inhibitors of either cytochrome P450 3A4 or P-glycoprotein	0	0.0	2	0.2	1	0.1	2	0.2	2	0.3	0	0.0	–	–
Strong CYP3A4 inducers	6	7.9	22	2.6	30	2.4	20	2.0	15	2.0	4	0.9	0.32	0.12–0.89

*Among 1858 women.

Table 12. Medication use 1 year before (not including the index date) among new users of rivaroxaban with NVAF (N=15,252) by calendar year.

	2011 N=4		2012 N=312		2013 N=1672		2014 N=3405		2015 N=5253		2016 N=4606		Crude OR 2016 N=4606 vs. 2011–2013 N=1988	
	n	%	n	%	n	%	n	%	n	%	n	%	OR	95%CI
Antiplatelet agents	3	75.0	137	43.9	928	55.5	1717	50.4	2342	44.6	1728	37.5	0.52	0.46–0.58
Aspirin	3	75.0	125	40.1	805	48.1	1520	44.6	1983	37.7	1467	31.8	0.53	0.47–0.59
Clopidogrel	0	0.0	28	9.0	219	13.1	347	10.2	560	10.7	401	8.7	0.67	0.57–0.80
NSAIDs	1	25.0	44	14.1	209	12.5	409	12.0	588	11.2	531	11.5	0.89	0.76–1.04
Oral steroids	1	25.0	37	11.9	254	15.2	472	13.9	813	15.5	653	14.2	0.96	0.83–1.1
Anticoagulant drugs	0	0.0	181	58.0	689	41.2	1264	37.1	1757	33.4	1470	31.9	0.60	0.54–0.67
Antiarrhythmic drugs	3	75.0	57	18.3	286	17.1	551	16.2	740	14.1	543	11.8	0.63	0.55–0.73
Antihypertensive drugs	2	50.0	287	92.0	1532	91.6	3040	89.3	4623	88.0	4033	87.6	0.65	0.54–0.77
Beta-blockers	0	0.0	191	61.2	1018	60.9	1997	58.6	2949	56.1	2533	55.0	0.79	0.71–0.88
ACE inhibitors	2	50.0	137	43.9	660	39.5	1325	38.9	2019	38.4	1641	35.6	0.82	0.74–0.92
Diuretics	0	0.0	170	54.5	864	51.7	1540	45.2	2337	44.5	1907	41.4	0.65	0.59–0.72
Statins	3	75.0	187	59.9	976	58.4	1891	55.5	2894	55.1	2490	54.1	0.83	0.75–0.92
Antidiabetic drugs	0	0.0	49	15.7	259	15.5	514	15.1	799	15.2	708	15.4	0.99	0.86–1.15
Oral contraceptives*	0	0.0	0	0.0	7	0.9	6	0.4	8	0.3	10	0.5	0.64	0.24–1.68
HRT*	0	0.0	2	1.5	9	1.2	25	1.6	34	1.4	24	1.2	0.97	0.47–2.00
PPIs	2	50.0	143	45.8	748	44.7	1522	44.7	2265	43.1	1975	42.9	0.92	0.83–1.02
H_2-receptor antagonists	0	0.0	18	5.8	93	5.6	172	5.1	277	5.3	201	4.4	0.77	0.61–0.98
DMARDs	0	0.0	8	2.6	37	2.2	60	1.8	112	2.1	99	2.1	0.95	0.66–1.35
Antidepressants	1	25.0	63	20.2	373	22.3	698	20.5	1084	20.6	931	20.2	0.90	0.79–1.02
Antipsychotic drugs	0	0.0	31	9.9	190	11.4	295	8.7	438	8.3	361	7.8	0.68	0.57–0.81
Strong inhibitors of either cytochrome P450 3A4 or P-glycoprotein	0	0.0	0	0.0	3	0.2	4	0.1	3	0.1	10	0.2	1.44	0.40–5.24
Strong CYP3A4 inducers	0	0.0	7	2.2	50	3.0	99	2.9	115	2.2	90	2.0	0.68	0.48–0.94

*Among 6878 women.

10.4.2 Patterns of NOAC use: dose posology

10.4.2.1 Dose posology (2011–2016)

Characteristics of the index prescription among the 10,834 NVAF patients starting NOAC therapy on apixaban are shown in **Table 13.** Approximately two thirds of these patients (65.2%) started on a daily dose of 10 mg. Among these 10,834 patients most received apixaban for a continuous period of at least 181 days, and of those with at least 12 months' follow-up, 69.9% had received apixaban for more than 365 days continuously, and 5.7% had a first continuous treatment period of ≤30 days.

Characteristics of the index prescription among the 4381 NVAF patients starting NOAC therapy on dabigatran are shown in **Table 14.** Among these patients, similar proportions were initially prescribed a tablet strength of 110 mg (48.7%) or 150 mg (47.5%), with only a few patients receiving the 75 mg tablet strength (3.8%); the dose frequency was twice daily in almost all patients (96.3%). Among patients with 12 months of follow up, 53.5% had received dabigatran continuously for more than 365 days and 13.3% had a first continuous treatment period of ≤30 days.

Characteristics of the index prescription among the 15,252 NVAF patients starting NOAC therapy on rivaroxaban are shown in **Table 15**. Among these patients, the majority (78.5%) started on a daily dose of 20 mg. Among these 15,252 patients most received rivaroxaban for a continuous period of at least 181 days, and of those with at least 12 months' follow-up, 64.4% had received rivaroxaban for more than 365 days continuously, and 5.7% had a first continuous treatment period of ≤30 days.

Table 13. Characteristics of the index prescription among patients with NVAF newly prescribed apixaban (N=10,834).

	N=10,834	
	n	**%**
Apixaban tablet strength		
2.5 mg	3638	33.6
5 mg	7196	66.4
Dose frequency per day		
Once daily	188	1.7
Twice daily	10646	98.3
Daily dose in first prescription of apixaban		
2.5 mg	53	0.5
5 mg	3720	34.3
10 mg*	7061	65.2
Length of first prescription of apixaban (days)		
1–15	562	5.2
16–30	8083	74.6
31–60	2119	19.6
61–90	64	0.6
≥91	6	0.1
Duration of first episode of apixaban use (days)†		
1–30	1001	9.2
31–60	881	8.1
61–90	791	7.3
91–180	2018	18.6
181–365	2721	25.1
>365	3422	31.6
Duration of first episode of apixaban use (days; restricting to patients with at least 1 year follow-up, N=4636)		
1–30	266	5.7
31–60	163	3.5
61–90	161	3.5
91–180	340	7.3
181–365	464	10.0
>365	3242	69.9

*Standard daily dose. †Duration of first episode of continuous treatment was computed until there was an interval free of use greater than 30 days (e.g. gap >30 days between end of supply of a prescription and the next prescription or no prescription thereafter).

Table 14. Characteristics of index prescription among patients with NVAF newly prescribed dabigatran.

	N=4381	
	n	**%**
Dabigatran tablet strength		
75 mg	167	3.8
110 mg	2134	48.7
150 mg	2080	47.5
Dose frequency per day		
Once daily	163	3.7
Twice daily	4218	96.3
Daily dose in first prescription of dabigatran		
75 mg	33	0.8
110 mg	68	1.6
150 mg	196	4.5
220 mg	2066	47.2
300 mg*	2018	46.1
Length of first prescription of dabigatran (days)		
1–15	250	5.7
16–30	3607	82.3
31–60	486	11.1
61–90	33	0.8
≥91	5	0.1
Duration of first episode of dabigatran use (days)†		
1–30	584	13.3
31–60	353	8.1
61–90	320	7.3
91–180	661	15.1
181–365	797	18.2
>365	1666	38.0
Duration of first episode of dabigatran use (days; restricting to patients with at least 1 year follow–up, N=3043)		
1–30	340	11.2
31–60	179	5.9
61–90	174	5.7
91–180	344	11.3
181–365	378	12.4
>365	1628	53.5

*Standard daily dose. †Duration of first episode of continuous treatment was computed until there was an interval free of use greater than 30 days (e.g. gap >30 days between end of supply of a prescription and the next one or no prescription thereafter).

Table 15. Characteristics of index prescription among patients with NVAF newly prescribed rivaroxaban (N= 15,252).

	N=15,252	
	n	**%**
Rivaroxaban tablet strength		
2.5 mg	50	0.3
10 mg	371	2.4
15 mg	2764	18.1
20 mg	12,067	79.1
Dose frequency per day (based on recorded posology for first prescription)		
Once daily	15,101	99.0
Twice daily	151	1.0
Daily dose in first prescription of rivaroxaban		
2.5 mg	13	0.1
5 mg	37	0.2
10 mg	340	2.2
15 mg	2691	17.6
20 mg*	12,091	79.3
30 mg	73	0.5
40 mg	7	0.0
Length of first prescription of rivaroxaban (days)		
1–15	886	5.8
16–30	10,587	69.4
31–60	3536	23.2
61–90	168	1.1
≥91	75	0.5
Duration of first episode of rivaroxaban use (days)†		
1–30	1361	8.9
31–60	1377	9.0
61–90	927	6.1
91–180	2665	17.5
181–365	3570	23.4
>365	5352	35.1
Duration of first episode of rivaroxaban use (days; restricting to patients with at least 1 year follow–up, N=7955)		
1–30	457	5.7
31–60	417	5.2
61–90	274	3.4
91–180	687	8.6
181–365	995	12.5
>365	5125	64.4

*Standard daily dose. †Duration of first episode of continuous treatment was computed until there was an interval free of use greater than 30 days (e.g. gap >30 days between end of supply of a prescription and the next one or no prescription thereafter).

A summary of the initial daily dose prescribed categorised as either standard dose, reduced dose or higher dose (for rivaroxaban only), among patients with NVAF newly prescribed a NOAC is shown in **Table 16.** The most common starting NOAC dose was the standard 10 mg for apixaban (65.2% of patients) and the standard 20 mg for rivaroxaban (79.3% of patients), while for dabigatran, the standard dose of 300 mg was not the most commonly prescribed dose, being slightly less frequently prescribed than a reduced dose of 220 mg (46.1% vs. 47.2%)

Table 16. Distribution of patients with NVAF newly prescribed a NOAC by dose at first prescription**.**

	n	%
Apixaban NVAF first time users (N=10,834)		
Apixaban standard dose (10 mg)	7061	65.2
Apixaban lower dose (2.5–5 mg)	3773	34.8
Dabigatran NVAF first time users (N=4381)		
Dabigatran standard dose (300 mg)	2018	46.1
Dabigatran lower dose (75–220 mg)	2363	53.9
Rivaroxaban NVAF first time users (N=15,252)		
Rivaroxaban standard dose (20 mg)	12,091	79.3
Rivaroxaban lower dose (2.5–15 mg)	3081	20.2
Rivaroxaban high dose (30–40 mg)	80	0.5

10.4.2.2 NOAC dose over the first 6 months of follow-up

Among patients with at least 180 days of available follow-up (**Table 17**) the percentage with at least 6 months of NOAC continuous NOAC use was: apixaban 88.5% (5898/6667), dabigatran 85.1% (2407/2827), and rivaroxaban 88.4% (8615/9750).

As shown in **Table 18,** among patients with at least 6 months of follow-up and still a current NOAC user at 6 months, the vast majority were prescribed the same dose as the index prescription: apixaban 95.4%, dabigatran 93.7% and rivaroxaban 95.0%.

Table 19 shows the dose of apixaban prescribed at 6 months among patients starting NOAC therapy on apixaban. Among these patients, most whose index prescription was for a 5 mg or 10 mg dose were prescribed the same dose 6 months later, whether they had been continuous users of apixaban at 6 months (91.8% and 97.5%, respectively) or non-continuous users of apixaban at 6 months (88.8% and 96.2%, respectively). Among patients whose index prescription was for a 2.5 mg dose, 21.7% of continuous users and 33.3% of non-continuous users were prescribed the same dose at 6 months, with almost all of the remaining patients shifting to a 5 mg dose after 6 months.

Table 20 shows the dose of dabigatran prescribed at 6 months among patients starting NOAC therapy on dabigatran. Among these patients, most whose index prescription was for a 220 mg or 300 mg dose were prescribed the same dose 6 months later, whether they had been continuous users of dabigatran at 6 months (97.8% and 96.0%, respectively) or non-

continuous users of dabigatran at 6 months (97.8% and 92.6%, respectively). Among patients whose index prescription was for a 2.5 mg dose, 21.7% of continuous users and 33.3% of non-continuous users were prescribed the same dose at 6 months, with almost all of the remaining patients shifting to a 5 mg dose after 6 months. Among patients with at least 6 months continuous use of dabigatran, only 58.5% of those with an index prescription for ≤110 mg and 53.7% of those with an index prescription for 150 mg were prescribed the same dose at 6 months, with most changes being to a higher dose. Among patients with non-continuous use of dabigatran at 6 months, less than half of those with an index prescription for ≤110 mg were prescribed the same dose at 6 months, with most changing to 220 mg.

Table 21 shows the dose of rivaroxaban prescribed at 6 months among patients starting NOAC therapy on rivaroxaban. Among rivaroxaban users who were still current users at 6 months, more than 94% of those whose index prescription was for a 15 mg or 20 mg dose, were prescribed the same dose 6 months later (whether continuous or non-continuous users). Among those whose index prescription was for ≤10 mg, about half were prescribed the same dose at 6 months (non-continuous users at 6 months, 46.9%; continuous users at 6 months 55.6%), with most changes being from a shift to 20 mg (non-continuous users at 6 months, 37.5%; continuous users at 6 months, 37.4%). Among the small number of patients with an index prescription for 30 mg, the majority shifted to a lower dose (20 mg) at 6 months.

Table 17. Distribution of continuous and non-continuous treatment among patients with NVAF with at least 180 days of follow-up and a current user at 6 months after the index prescription.

	Apixaban N=6667		Dabigatran N=2827		Rivaroxaban N=9750	
	n	%	n	%	n	%
Treatment duration since first prescription to 180 days after						
Non-continuous use*	769	11.5	420	14.9	1135	11.6
Continuous use	5898	88.5	2407	85.1	8615	88.4

*Non-continuous: users 180 days after first prescription with at least one gap between consecutive prescriptions greater than 30 days.

Table 18. NOAC daily dose variation over time among patients with NVAF with at least 180 days of follow-up and current users at 6 months after first prescription (row %)

	Dose 6 months after the index date					
	Lower dose than the index NOAC prescription		Same dose than the index NOAC prescription		Higher dose than the index NOAC prescription	
	n	%	n	%	n	%
Apixaban (N=6667)	129	1.9	6362	95.4	201	3.0
Dabigatran (N=2827)	72	2.5	2648	93.7	107	3.8
Rivaroxaban (N=9750)	325	3.3	9265	95.0	160	1.6

Table 19. Apixaban daily dose variation over time among current users after 6 months from index prescription (N=6667), by treatment duration (row %).

	Dose at 6 months						Total
	2.5 mg		5 mg		10 mg		
Non-continuous users at 6 months	**n=2**		**n=252**		**n=515**		**n=769**
Dose at index prescription	**n**	**%**	**n**	**%**	**n**	**%**	**n**
2.5 mg	1	33.3	2	66.7	0	0.0	3
5 mg	1	0.4	231	88.8	28	10.8	260
10 mg	0	0.0	19	3.8	487	96.2	506
Continuous users at 6 months	**n=8**		**n=1923**		**n=3967**		**n=5898**
Dose at index prescription	**n**	**%**	**n**	**%**	**n**	**%**	**N**
2.5 mg	5	21.7	17	73.9	1	4.3	23
5 mg	2	0.1	1810	91.8	160	8.1	1972
10 mg	1	0.0	96	2.5	3806	97.5	3903

Table 20. Dabigatran daily dose variation over time among current users after 6 months from index prescription (N=2827 by treatment duration (row %).

	Dose at 6 months								Total
	≤110mg		150 mg		220 mg		300 mg		
Non-continuous users at 6 months	**n=5**		**n=14**		**n=204**		**n=197**		**n=420**
Dose at index prescription	**%**	**n**	**%**	**n**	**%**	**%**	**n**	**%**	**N**
≤110 mg	4	40.0	0	0.0	6	60.0	0	0.0	10
150 mg	0	0.0	10	43.5	8	34.8	5	21.7	23
220 mg	0	0.0	1	0.5	179	97.8	3	1.6	183
300 mg	1	0.5	3	1.5	11	5.4	189	92.6	204
Continuous users at 6 months	**n=36**		**n=71**		**n=1152**		**n=1148**		**n=2407**
Dose at index prescription	**n**	**%**	**n**	**%**	**n**	**n**	**%**	**n**	**%**
≤110 mg	31	58.5	0	0.0	20	37.7	2	3.8	53
150 mg	1	0.9	58	53.7	11	10.2	38	35.2	108
220 mg	4	0.4	6	0.5	1083	97.8	14	1.3	1107
300 mg	0	0.0	7	0.6	38	3.3	1094	96.0	1139

Table 21. Rivaroxaban dose variation over time among current users after 6 months from the index prescription (N=9750), by treatment duration (row %).

	Dose at 6 months								
	≤ 10 mg		15 mg		20 mg		30 mg		Total
Non-continuous users at 6 months	**n=23**		**n=215**		**n=893**		**n=4**		**n=1135**
Dose at index prescription	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**%**
≤10 mg	15	46.9	4	12.5	12	37.5	1	3.1	32
15 mg	1	0.6	168	96.0	6	3.4	0	0.0	175
20 mg	7	0.8	42	4.6	871	94.7	0	0.0	920
30 mg	0	0.0	1	12.5	4	50.0	3	37.5	8
Continuous users at 6 months	**n=141**		**n=1668**		**n=6805**		**n=1**		**n=8615**
Dose at index prescription	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**%**
≤10 mg	119	55.6	15	7.0	80	37.4	0	0.0	214
15 mg	5	0.3	1426	96.8	41	2.8	1	0.1	1473
20 mg	17	0.2	219	3.2	6663	96.6	0	0.0	6899
30 mg	0	0.0	8	30.8	21	72.4	0	0.0	29

10.4.2.3 Dose, dose posology and duration of use stratified by renal function

Characteristics of the index NOAC and duration of use stratified by renal function is shown in **Table 22** for apixaban, **Table 23** for dabigatran and **Table 24** for rivaroxaban.

Among patients starting NOAC therapy on apixaban, 26.7% of those with normal renal function were prescribed a daily dose of 5 mg; among those with severe renal impairment, 90.0% received a daily dose of 5 mg. Among new users of apixaban with at least a year of follow-up, 57.7% of those with normal renal function had a first episode of use of at least 6 months compared with 47.1% of those with severe renal impairment.

Among patients starting NOAC therapy on dabigatran, 94.0% of those with normal renal function were prescribed a daily dose of either 220 mg or 300 mg; among those with severe renal impairment, 75.0% received a daily dose of 220 mg. Among new users of dabigatran with at least a year of follow-up, 67.5% of those with normal renal function had a first episode of continuous use of at least 6 months compared with 53.9% of those with severe renal impairment.

Among patients starting NOAC therapy on rivaroxaban, 89.2% of those with normal renal function were prescribed a daily dose of 20 mg. Among patients with severe renal impairment, 17.7% were prescribed a daily dose >20 mg/day. Among new users of rivaroxaban with at least 1 year of follow-up, 78.0% of those with normal renal function had a first episode of continuous use of at least 6 months compared with 68.9% of those with severe renal impairment.

Table 22. Characteristics of the index apixaban prescription and duration of use by degree of renal impairment among patients with NVAF newly prescribed apixaban.

	Normal renal function (eGFR >50 ml/min/1.73m^2) N=7291		Mild renal impairment (eGFR 30–50ml/min/1.73m^2) N=1819		Severe renal impairment (eGFR <30 ml/min/1.73m^2) N=230		Unknown N=1444	
	n	%	n	%	n	%	n	%
Tablet strength, mg								
2.5	1868	25.6	1114	61.2	254	90.7	402	27.8
5	5423	74.4	705	38.8	26	9.3	1042	72.2
Dose frequency per day								
Once	124	1.7	29	1.6	4	1.4	31	2.1
Twice	7167	98.3	1790	98.4	276	98.6	1413	97.9
Daily dose of first prescription, mg								
2.5	24	0.3	18	1.0	3	1.1	8	0.6
5	1944	26.7	1107	60.9	252	90.0	417	28.9
10	5323	73.0	694	38.2	25	8.9	1019	70.6
Length of first prescription of apixaban (days)								
1–15	329	4.5	126	6.9	19	6.8	88	6.1
16–30	5432	74.5	1393	76.6	227	81.1	1031	71.4
31–60	1483	20.3	288	15.8	34	12.1	314	21.7
61–90	43	0.6	10	0.5	0	0.0	11	0.8
≥90	4	0.1	2	0.1	0	0.0	0	0.0
Duration of first episode of use (days)								
1–30	651	8.9	159	8.7	41	14.6	150	10.4
31–60	584	8.0	151	8.3	25	8.9	121	8.4
61–90	506	6.9	159	8.7	19	6.8	107	7.4
91–180	1344	18.4	331	18.2	63	22.5	280	19.4
181–365	1817	24.9	474	26.1	62	22.1	368	25.5
>365	2389	32.8	545	30.0	70	25.0	418	28.9

	Normal renal function (eGFR >50 ml/min/1.73m^2) N=7291		Mild renal impairment (eGFR 30–50ml/min/1.73m^2) N=1819		Severe renal impairment (eGFR <30 ml/min/1.73m^2) N=230		Unknown N=1444	
Duration of first episode of use (days; restricting to patients with at least 1 year of follow-up (N=4636)								
1–30	175	5.5	35	5.0	8	8.0	48	7.7
31–60	106	3.3	19	2.7	2	2.0	36	5.8
61–90	99	3.1	25	3.5	3	3.0	34	5.5
91–180	228	7.1	52	7.4	12	12.0	48	7.7
181–365	322	10.0	63	8.9	11	11.0	68	10.9
>365	2277	71.0	513	72.6	64	64.0	388	62.4

Table 23. Characteristics of the index dabigatran prescription and duration of use by degree of renal impairment among patients with NVAF newly prescribed dabigatran.

	Normal renal function (eGFR >50 ml/min/1.73m^2) N=3256		**Mild renal impairment (eGFR 30–50ml/min/1.73m^2) N=574**		**Severe renal impairment (eGFR <30 ml/min/1.73m^2) N=20**		**Unknown N=528**	
	n	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Tablet strength, mg								
75	109	3.3	41	7.1	1	5.0	16	3.0
110	1481	45.4	417	72.6	15	75.0	221	41.9
150	1669	51.2	116	20.2	4	20.0	291	55.1
Dose frequency per day								
Once	111	3.4	34	5.9	0	0.0	18	3.4
Twice	3148	96.6	540	94.1	20	100.0	510	96.6
Daily dose of first prescription, mg								
75	23	0.7	9	1.6	0	0.0	1	0.2
110	44	1.4	19	3.3	0	0.0	5	0.9
150	130	4.0	38	6.6	1	5.0	27	5.1
220	1437	44.1	398	69.3	15	75.0	216	40.9
300	1625	49.9	110	19.2	4	20.0	279	52.8
Length of first prescription of dabigatran (days)								
1–15	165	5.1	57	9.9	2	10.0	26	4.9
16–30	2724	83.6	453	78.9	14	70.0	416	78.8
31–60	342	10.5	60	10.5	4	20.0	80	15.2
61–90	24	0.7	3	0.5	0	0.0	6	1.1
≥90	4	0.1	1	0.2	0	0.0	0	0.0
Duration of first episode of use (days)								
1–30	425	13.0	88	15.3	3	15.0	68	12.9
31–60	247	7.6	56	9.8	1	5.0	49	9.3
61–90	241	7.4	38	6.6	2	10.0	39	7.4
91–180	463	14.2	97	16.9	6	30.0	95	18.0

181–365	577	17.7	110	19.2	4	20.0	106	20.1
>365	1306	40.1	185	32.2	4	20.0	171	32.4
Duration of first episode of use (days; restricting to patients with at least 1 year of follow-up (N=3043)								
1–30	254	11.2	50	13.0	2	15.4	34	9.2
31–60	121	5.3	29	7.6	0	0.0	29	7.9
61–90	127	5.6	20	5.2	0	0.0	27	7.3
91–180	240	10.5	43	11.2	4	30.8	57	15.5
181–365	261	11.5	61	15.9	3	23.1	53	14.4
>365	1275	56.0	181	47.1	4	30.8	168	45.7

Table 24. Characteristics of the index rivaroxaban prescription and duration of use by degree of renal impairment among patients with NVAF newly prescribed rivaroxaban.

	Normal renal function (eGFR >50 ml/min/1.73m^2) N=10,699		**Mild renal impairment (eGFR 30–50 ml/min/1.73m^2) N=2389**		**Severe renal impairment (eGFR <30 ml/min/1.73m^2) N=271**		**Unknown N=1893**	
Tablet strength, mg								
2.5	32	0.3	9	0.4	0	0.0	9	0.5
10	242	2.3	62	2.6	12	4.4	55	2.9
15	899	8.4	1425	59.6	213	78.6	227	12.0
20	9526	89.0	893	37.4	46	17.0	1602	84.6
Dose frequency per day								
Once	10603	99.1	2359	98.7	269	99.3	1870	98.8
Twice	96	0.9	30	1.3	2	0.7	23	1.2
Daily dose of first prescription, mg								
2.5	9	0.1	2	0.1	0	0.0	2	0.1
5	23	0.2	7	0.3	0	0.0	7	0.4
10	218	2.0	61	2.6	12	4.4	49	2.6
15	855	8.0	1405	58.8	211	77.9	220	11.6
20	9547	89.2	892	37.3	46	17.0	1606	84.8
≥30	47	0.4	22	0.9	2	0.7	9	0.5
Length of first prescription of rivaroxaban (days)								
1–15	527	4.9	231	9.7	34	12.5	94	5.0
16–30	7396	69.1	1671	69.9	195	72.0	1325	70.0
31–60	2604	24.3	463	19.4	39	14.4	430	22.7
61–90	113	1.1	20	0.8	3	1.1	32	1.7
≥90	59	0.6	4	0.2	0	0.0	12	0.6
Duration of first episode of use (days)								
1–30	902	8.4	240	10.0	30	11.1	189	10.0
31–60	921	8.6	254	10.6	35	12.9	167	8.8
61–90	653	6.1	138	5.8	23	8.5	113	6.0

91–180	1811	16.9	416	17.4	55	20.3	383	20.2
181–365	2472	23.1	604	25.3	59	21.8	435	23.0
>365	3940	36.8	737	30.8	69	25.5	606	32.0
Duration of first episode of use (days; restricting to patients with at least 1 year of follow-up (N=7955)								
1–30	321	5.6	65	5.7	6	5.0%	65	6.7
31–60	267	4.7	78	6.8	13	10.9%	59	6.1
61–90	186	3.3	38	3.3	8	6.7	42	4.3
91–180	484	8.5	93	8.1	10	8.4	100	10.4
181–365	683	11.9	172	15.0	17	14.3	123	12.7
>365	3780	66.1	703	61.2	65	54.6	577	59.7

10.4.2.4 Trends in dose posology over time

The daily dose of the index NOAC and dose posology among patients with NVAF by study in **Table 25**, **Table 26** and **Table 27** by study year. Among new users of apixaban (**Table 25**), parameters of the index apixaban prescription were generally similar from 2013 (when data for apixaban became available) until the end of 2016. There was a decrease in the proportion of patients with a first apixaban prescription duration exceeding 61 days; however, this may be a reflection of the small sample sizes.

Among new users of dabigatran (**Table 26**) there was a shift towards the prescribing of a higher daily dose over time, with a daily dose of 300 mg prescribed to 23.7% of new users in 2011 (although the sample size was small) to 44.5% in 2012 and 47.6% in 2016. Almost all patients were prescribed a daily dose of either 220 mg (49.6%) or 300 mg (47.6%) by 2016.

Among new users of rivaroxaban (**Table 27**) there was a clear increase in the proportion of patients prescribed a daily dose of 20 mg, from 70.5% in 2012 to 80.3% in 2016. Just under a fifth of patients (17.9%) were prescribed a daily dose of 17.7 mg in 2016.

10.4.2.5 Trends in duration of use over time

As shown in **Table 25** and **Table 27**, among new users of either apixaban or rivaroxaban with at least 1 year of follow up, the percentage with at least 1 year of continuous NOAC use remained stable over study years. In contrast, the percentage of new users of dabigatran with at least 1 year of follow-up who had at least 1 year of continuous use increased over time from 35.9% in 2011, 51.7% in 2012 and 66.7% in 2016 (**Table 26**).

Table 25. Characteristics of the index prescription patients with NVAF newly prescribed apixaban.

	2011		2012		2013		2014		2015		2016	
	N=0		N=0		N=291		N=1888		N=3773		N=4882	
	n	%	n	%	n	%	n	%	n	%	n	%
Tablet strength, mg												
2.5	–	–	–	–	106	36.4	680	36.0	1265	33.5	1587	32.5
5	–	–	–	–	185	63.6	1208	64.0	2508	66.5	3295	67.5
Dose frequency per day												
Once	–	–	–	–	1	0.3	34	1.8	79	2.1	74	1.5
Twice	–	–	–	–	290	99.7	1854	98.2	3694	97.9	4808	98.5
Daily dose in first prescription of apixaban, mg												
2.5	–	–	–	–	0	0.0	8	0.4	21	0.6	24	0.5
5	–	–	–	–	107	36.8	698	37.0	1302	34.5	1613	33.0
10	–	–	–	–	184	63.2	1182	62.6	2450	64.9	3245	66.5
Length of first prescription of apixaban (days)												
1–15	–	–	–	–	12	4.1	86	4.6	202	5.4	262	5.4
16–30	–	–	–	–	234	80.4	1453	77.0	2838	75.2	3558	72.9
31–60	–	–	–	–	41	14.1	331	17.5	715	19.0	1032	21.1
61–90	–	–	–	–	4	1.4	17	0.9	18	0.5	25	0.5
≥91	–	–	–	–	0	0.0	1	0.1	0	0.0	5	0.1
Duration of first episode of use (days; restricted to patients with at least 1 year of follow-up, N=4636)												
1–30	–	–	–	–	15	6.0	86	5.6	164	5.8	1	2.9
31–60	–	–	–	–	8	3.2	54	3.5	101	3.6	0	0.0
61–90	–	–	–	–	10	4.0	52	3.4	97	3.4	2	5.7
91–180	–	–	–	–	19	7.6	108	7.1	210	7.4	3	8.6
181–365	–	–	–	–	24	9.6	146	9.6	291	10.3	3	8.6
>365*	–	–	–	–	175	69.7	1077	70.7	1964	69.5	26	74.3

*Very few users were at risk of presenting duration greater than 1 year among new users in 2016 due to the end of data collection.

Table 26. Characteristics of the index prescription patients with NVAF newly prescribed dabigatran.

	2011		2012		2013		2014		2015		2016	
	N=76		N=838		N=1260		N=1010		N=739		N=458	
	n	%	n	%	n	%	n	%	n	%	n	%
Dabigatran tablet strength, mg												
75	19	25.0	31	3.7	43	3.4	35	3.5	29	3.9	10	2.2
110	39	51.3	419	50.0	620	49.2	476	47.1	351	47.5	229	50.0
150	18	23.7	388	46.3	597	47.4	499	49.4	359	48.6	219	47.8
Dose frequency per day												
Once	2	2.6	42	5.0	44	3.5	40	4.0	31	4.2	4	0.9
Twice	74	97.4	796	95.0	1216	96.5	970	96.0	708	95.8	454	99.1
Daily dose in first prescription of dabigatran, mg												
75	0	0.0	9	1.1	11	0.9	5	0.5	8	1.1	0	0.0
110	2	2.6	18	2.1	13	1.0	18	1.8	14	1.9	3	0.7
150	19	25.0	37	4.4	52	4.1	47	4.7	30	4.1	11	2.4
220	37	48.7	401	47.9	607	48.2	458	45.3	337	45.6	226	49.3
300	18	23.7	373	44.5	577	45.8	482	47.7	350	47.4	218	47.6
Length of first prescription of dabigatran (days)												
1–15	4	5.3	72	8.6	58	4.6	65	6.4	36	4.9	15	3.3
16–30	59	77.6	679	81.0	1038	82.4	828	82.0	623	84.3	380	83.0
31–60	10	13.2	79	9.4	155	12.3	112	11.1	74	10.0	56	12.2
61–90	2	2.6	6	0.7	8	0.6	4	0.4	6	0.8	7	1.5
≥91	1	1.3	2	0.2	1	0.1	1	0.1	0	0.0	0	0.0
Duration of first episode of use (days; restricted to patients with at least 1 year of follow-up, N=3043)												
1–30	11	17.2	76	10.9	113	10.9	90	11.9	50	10.4	0	0.0
31–60	4	6.2	37	5.3	63	6.1	44	5.8	31	6.5	0	0.0
61–90	4	6.2	48	6.9	47	4.5	48	6.3	27	5.6	0	0.0
91–180	9	14.1	92	13.2	119	11.4	83	10.9	41	8.6	0	0.0
181–365	13	20.3	84	12.0	136	13.1	80	10.6	64	13.4	1	33.3
>365*	23	35.9	361	51.7	563	54.1	413	54.5	266	55.5	2	66.7

*Very few users were at risk of presenting duration greater than 1 year among new users in 2016 due to the end of data collection.

Table 27. Characteristics of the index prescription patients with NVAF newly prescribed rivaroxaban.

	2011		2012		2013		2014		2015		2016	
	N=4		N=312		N=1672		N=3405		N=5253		N=4606	
	n	%	n	%	n	%	n	%	n	%	n	%
Tablet strength, mg												
2.5	0	0.0	0	0.0	0	0.0	1	0.0	27	0.5	22	0.5
10	4	100.0	47	15.1	68	4.1	131	3.8	73	1.4	48	1.0
15	0	0.0	48	15.4	340	20.3	639	18.8	900	17.1	837	18.2
20	0	0.0	217	69.6	1264	75.6	2634	77.4	4253	81.0	3699	80.3
Dose frequency per day												
Once	4	100.0	307	98.4	1649	98.6	3375	99.1	5204	99.1	4562	99.0
Twice	0	0.0	5	1.6	23	1.4	30	0.9	49	0.9	44	1.0
Daily dose of first prescription , mg												
2.5	0	0.0	0	0.0	0	0.0	0	0.0	7	0.1	6	0.1
5	0	0.0	0	0.0	0	0.0	1	0.0	20	0.4	16	0.3
10	4	100.0	44	14.1	60	3.6	119	3.5	67	1.3	46	1.0
15	0	0.0	46	14.7	325	19.4	624	18.3	883	16.8	813	17.7
20	0	0.0	220	70.5	1272	76.1	2645	77.7	4255	81.0	3699	80.3
30	0	0.0	2	0.6	15	0.9	15	0.4	17	0.3	24	0.5
40	0	0.0	0	0.0	0	0.0	1	0.0	4	0.1	2	0.0
Length of first prescription of rivaroxaban (days)												
1–15	2	50.0	31	9.9	108	6.5	218	6.4	276	5.3	251	5.4
16–30	2	50.0	215	68.9	1157	69.2	2342	68.8	3674	69.9	3197	69.4
31–60	0	0.0	64	20.5	385	23.0	776	22.8	1228	23.4	1083	23.5
61–90	0	0.0	1	0.3	10	0.6	44	1.3	58	1.1	55	1.2
≥91	0	0.0	1	0.3	12	0.7	25	0.7	17	0.3	20	0.4
Duration of first episode of use (days; restricted to patients with at least 1 year of follow-up, N=7955)												
1–30	1	33.3	24	9.2	65	4.9	164	6.4	200	5.3	3	7.1
31–60	1	33.3	10	3.8	68	5.2	144	5.6	192	5.1	2	4.8
61–90	0	0.0	6	2.3	58	4.4	77	3.0	131	3.5	2	4.8
91–180	0	0.0	15	5.8	114	8.7	229	9.0	325	8.6	4	9.5
181–365	0	0.0	37	14.2	166	12.6	312	12.2	476	12.6	4	9.5

	2011		2012		2013		2014		2015		2016	
	N=4		N=312		N=1672		N=3405		N=5253		N=4606	
	n	%	n	%	n	%	n	%	n	%	n	%
>365*	1	33.3	168	64.6	844	64.2	1629	63.8	2456	65.0	27	64.3

*Very few users were at risk of presenting duration greater than 1 year among new users in 2016 due to the end of data collection.

10.4.3 Appropriateness of index NOAC prescription

10.4.3.1 Dose of index NOAC prescription by eligibility to receive a standard or reduced dose

Dose and dose posology of the index NOAC prescription according to whether patients were eligible to receive a standard or reduced dose NOAC or were contraindicated in **Table 28** for new users of apixaban, **Table 29** for new users of dabigatran and **Table 30** for new users of rivaroxaban. As shown in **Table 28**, among new users of apixaban eligible to receive the standard daily dose, three-quarters (74.5%) were prescribed the standard daily dose of 10 mg, and just under a quarter (25.2%) received a daily dose of 5 mg. Among those who were eligible for dose reduction, 89.5% were prescribed a reduced dose of 5 mg. There were a total of 255 patients who were prescribed apixaban despite having a contraindication; of these, 64.7% received a daily dose of 5 mg and 33.7% received a daily dose of 10 mg. As shown in **Table 29**, among new users of dabigatran eligible to receive the standard daily dose, 78.7% were prescribed a daily dose of 300 mg and 16.1% a daily dose of 220 mg. Among those who were eligible for dose reduction, 70.5% received a daily dose of 220 mg. There were a total of 234 patients who were prescribed dabigatran despite having a contraindication; of these, 49.6% received a daily dose of 220 mg 43.2% received a daily dose of 300 mg. Among new users of rivaroxaban (**Table 30**), almost all patients (88.5%) eligible to receive the normal recommended dose received a total daily dose of 20 mg; 10.7% received 15 mg or 10 mg (8.6% and 2.1%, respectively). Among the patients eligible to receive a reduced dose, 60.8% received a daily dose of 15 mg; however, 35.2% received a daily dose of 20 mg. There were only seven patients who received rivaroxaban despite having a contraindication.

As shown in **Table 31,** the majority of patients in the apixaban and rivaroxaban cohorts were eligible to receive the standard treatment dose, 84.9% (9194/10,834) for apixaban and 82.7% (12,608/15,252) for rivaroxaban, while in the dabigatran cohort less than half (40.9%; 1790/4381) were eligible for the standard dose. Among all patients eligible to receive a standard dose NOAC (N=23,592), the majority received the correct standard dose (82.3%); this percentage was highest for rivaroxaban (88.5%) followed by dabigatran (78.7%) and apixaban (74.5%). However, nearly a third of patients in the apixaban cohort (23.2%, 2344/10,098) who were eligible to receive the recommended standard daily dose were prescribed a reduced dose, compared with 21.3% (381/1790) of the dabigatran cohort and 11.0% (1390/12,608) of the rivaroxaban cohort. Among patients eligible for reduced dosing, the majority correctly received a reduced dose: apixaban (91.0%), dabigatran (78.4%) and rivaroxaban (63.9%).

Table 28. Description of characteristics of index NOAC prescription/dispensation among patients with NVAF newly prescribed apixaban according to the recommended dose.

	Normal recommended dose			Dose reduction recommended*			Contra-indicated†			Total
	N	Column %	Row %	N	Column %	Row %	N	Column %	Row %	N
Total	**9194**	**100.0**	**84.9**	**1385**	**100.0**	**12.8**	**255**	**100.0**	**2.4**	**10,834**
Apixaban tablet strength										
2.5 mg	2214	24.1	60.9	1256	90.7	34.5	168	65.9	4.6	3638
5 mg	6980	75.9	97.0	129	9.3	1.8	87	34.1	1.2	7196
Dose frequency per day										
Once daily	159	1.7	84.6	24	1.7%	12.8	5	2.0	2.7	188
Twice daily	9035	98.3	84.9	1361	98.3%	12.8	250	98.0	2.3	10646
Daily dose in first prescription of apixaban										
2.5 mg	29	0.3	54.7	20	1.4	37.7	4	1.6	7.5	53
5 mg	2315	25.2	62.2	1240	89.5	33.3	165	64.7	4.4	3720
10 mg	6850	74.5	97.0	125	9.0	1.8	86	33.7	1.2	7061
Length of first prescription of apixaban (days)										
1–15	423	4.6	75.3	115	8.3	20.5	24	9.4	4.3	562
16–30	6823	74.2	84.4	1078	77.8	13.3	182	71.4	2.3	8083
31–60	1884	20.5	88.9	186	13.4	8.8	49	19.2	2.3	2119
61–90	58	0.6	90.6	6	0.4	9.4	0	0.0	0.0	64
≥91	6	0.1	100.0	0	0.0	0.0	0	0.0	0.0	6
Duration of first episode of use (days)										
1–30	817	8.9	81.6	148	10.7	14.8	36	14.1	3.6	1001
31–60	731	8.0	83.0	129	9.3	14.6	21	8.2	2.4	881
61–90	652	7.1	82.4	122	8.8	15.4	17	6.7	2.1	791
91–180	1720	18.7	85.2	247	17.8	12.2	51	20.0	2.5	2018
181–365	2299	25.0	84.5	367	26.5	13.5	55	21.6	2.0	2721
>365	2975	32.4	86.9	372	26.9	10.9	75	29.4	2.2	3422

	Normal recommended dose			Dose reduction recommended*			Contra-indicated†			Total
	N	Column %	Row %	N	Column %	Row %	N	Column %	Row %	N
Duration of first episode of use (days; restricting to patients with at least 1 year follow-up, N=4636)										
	4016	**100.0**	**86.6**	**517**	**100.0**	**11.2**	**103**	**100.0**	**2.2**	**4636**
1–30	230	5.7	86.5	27	5.2	10.2	9	8.7	3.4	266
31–60	143	3.6	87.7	15	2.9	9.2	5	4.9	3.1	163
61–90	138	3.4	85.7	20	3.9	12.4	3	2.9	1.9	161
91–180	287	7.1	84.4	47	9.1	13.8	6	5.8	1.8	340
181–365	401	10.0	86.4	53	10.3	11.4	10	9.7	2.2	464
>365	2817	70.1	86.9	355	68.7	11.0	70	68.0	2.2	3242

*Apixaban reduced dose is recommended for patients with NVAF and at least two of the following characteristics: age ≥80 years, body weight ≤60 kg or serum creatinine ≥1.5 mg/dL. In patients with severe renal impairment (creatinine clearance 15–29 mL/min) the dose reduction is recommend.

†Apixaban is contraindicated in patients with hepatic disease associated coagulopathy, and in patients with creatinine clearance <15 mL/min, or in patients undergoing dialysis, there is no clinical experience therefore apixaban is not recommended.

Table 29. Description of characteristics of index NOAC prescription/dispensation among patients with NVAF newly prescribed dabigatran according to the recommended dose.

	Normal recommended dose			Dose reduction recommended*			Contra-indicated†			Total
	N	Column %	Row %	N	Column %	%	N	Column %	Row %	N
Total	**1790**	**100.0**	**40.9**	**2357**	**100.0**	**53.8**	**234**	**100.0**	**5.3**	**4381**
Dabigatran tablet strength										
75 mg	44	2.5	26.3	114	4.8	68.3	9	3.8	5.4	167
110 mg	302	16.9	14.2	1712	72.6	80.2	120	51.3	5.6	2134
150 mg	1444	80.7	69.4	531	22.5	25.5	105	44.9	5.0	2080
Dose frequency per day										
Once daily	57	3.2	35.0	96	4.1	58.9	10	4.3	6.1	163
Twice daily	1733	96.8	41.1	2261	95.9	53.6	224	95.7	5.3	4218
Daily dose in first prescription of dabigatran										
75 mg	8	0.4	24.2	23	1.0	69.7	2	0.9	6.1	33
110 mg	14	0.8	20.6	50	2.1	73.5	4	1.7	5.9	68
150 mg	71	4.0	36.2	114	4.8	58.2	11	4.7	5.6	196
220 mg	288	16.1	13.9	1662	70.5	80.4	116	49.6	5.6	2066
300 mg	1409	78.7	69.8	508	21.6	25.2	101	43.2	5.0	2018
Length of first prescription of dabigatran (days)										
1–15	32	1.8	12.8	202	8.6	80.8	16	6.8	6.4	250
16–30	1487	83.1	41.2	1929	81.8	53.5	191	81.6	5.3	3607
31–60	241	13.5	49.6	220	9.3	45.3	25	10.7	5.1	486
61–90	26	1.5	78.8	5	0.2	15.2	2	0.9	6.1	33
≥91	4	0.2	80.0	1	0.0	20.0	0	0.0	0.0	5
Duration of first episode of dabigatran use (days)										
1–30	204	11.4	34.9	347	14.7	59.4	33	14.1	5.7	584
31–60	137	7.7	38.8	200	8.5	56.7	16	6.8	4.5	353

	Normal recommended dose			Dose reduction recommended*			Contra-indicated†			Total
	N	Column %	Row %	N	Column %	%	N	Column %	Row %	N
61–90	134	7.5	41.9	161	6.8	50.3	25	10.7	7.8	320
91–180	279	15.6	42.2	343	14.6	51.9	39	16.7	5.9	661
181–365	337	18.8	42.3	414	17.6	51.9	46	19.7	5.8	797
>365	699	39.1	42.0	892	37.8	53.5	75	32.1	4.5	1666
Duration of first episode of use (days; restricting to patients with at least 1 year follow-up, N=3043)										
	1319	**100.0**	**43.3**	**1566**	**100.0**	**51.5**	**158**	**100.0**	**5.2**	**3043**
1–30	133	10.1	39.1	185	11.8	54.4	22	13.9	6.5	340
31–60	78	5.9	43.6	96	6.1	53.6	5	3.2	2.8	179
61–90	84	6.4	48.3	76	4.9	43.7	14	8.9	8.0	174
91–180	163	12.4	47.4	158	10.1	45.9	23	14.6	6.7	344
181–365	174	13.2	46.0	184	11.7	48.7	20	12.7	5.3	378
>365	687	52.1	42.2	867	55.4	53.3	74	46.8	4.5	1628

*Dabigatran reduced dose is recommended for patients with NVAF: age ≥80 years; patients who receive concomitant verapamil. Also special reduction is recommended for patients between 75–80 years, moderate renal impairment (creatinine clearance 30–50 mL/min), patients with gastritis, esophagitis or gastroesophageal reflux. †Dabigatran is contraindicated in patients with severe renal impairment (creatinine clearance <30 mL/min). Also not recommended in hepatic impairment or liver disease.

Table 30. Description of characteristics of index NOAC prescription/dispensation among patients with NVAF newly prescribed rivaroxaban according to the recommended dose.

	Normal Recommended dose			Dose reduction recommended*			Contra-indicated†			Total
	N	Column %	Row %	N	Column %	Row %	N	Column %	Row %	N
Total	**12,608**	**100.0**	**82.7**	**2637**	**100.0**	**17.3**	**7**	**100.0**	**0.0**	**15,252**
Rivaroxaban tablet strength										
2.5 mg	41	0.3	82.0	9	0.3	18.0	0	0.0	0.0	50
10 mg	297	2.4	80.1	74	2.8	19.9	0	0.0	0.0	371
15 mg	1133	9.0	41.0	1626	61.7	58.8	5	71.4	0.2	2764
20 mg	11,137	88.3	92.3	928	35.2	7.7	2	28.6	0.0	12,067
Dose frequency per day										
Once daily	12,489	99.1	82.7	2605	98.8	17.3	7	100.0	0.0	15,101
Twice daily	119	0.9	78.8	32	1.2	21.2	0	0.0	0.0	151
Daily dose in first prescription of rivaroxaban										
2.5 mg	11	0.1	84.6	2	0.1	15.4	0	0.0	0.0	13
5 mg	30	0.2	81.1	7	0.3	18.9	0	0.0	0.0	37
10 mg	267	2.1	78.5	73	2.8	21.5	0	0.0	0.0	340
15 mg	1082	8.6	40.2	1604	60.8	59.6	5	71.4	0.2	2691
20 mg	11,162	88.5	92.3	927	35.2	7.7	2	28.6	0.0	12,091
30 mg	51	0.4	69.9	22	0.8	30.1	0	0.0	0.0	73
40 mg	5	0.0	71.4	2	0.1	28.6	0	0.0	0.0	7
Length of first prescription of rivaroxaban (days)										
1–15	621	4.9	70.1	263	10.0	29.7	2	28.6	0.2	886
16–30	8734	69.3	82.5	1849	70.1	17.5	4	57.1	0.0	10,587
31–60	3037	24.1	85.9	498	18.9	14.1	1	14.3	0.0	3536
61–90	145	1.2	86.3	23	0.9	13.7	0	0.0	0.0	168
≥91	71	0.6	94.7	4	0.2	5.3	0	0.0	0.0	75

	Normal Recommended dose			Dose reduction recommended*			Contra-indicated†			Total
	N	Column %	Row %	N	Column %	Row %	N	Column %	Row %	N
Duration of first episode of use (days)										
1–30	1095	8.7	80.5	266	10.1	19.5	0	0.0	0.0	1361
31–60	1088	8.6	79.0	288	10.9	20.9	1	14.3	0.1	1377
61–90	767	6.1	82.7	160	6.1	17.3	0	0.0	0.0	927
91–180	2196	17.4	82.4	466	17.7	17.5	3	42.9	0.1	2665
181–365	2912	23.1	81.6	657	24.9	18.4	1	14.3	0.0	3570
>365	4550	36.1	85.0	800	30.3	14.9	2	28.6	0.0	5352
Duration of first episode of use (days; restricting to patients with at least 1 year follow–up N=7955)										
	6692	**100.0**	**84.1**	**1260**	**100.0**	**15.8**	**3**	**100.0**	**0.0**	**7955**
1–30	387	5.8	84.7	70	5.6	15.3	0	0.0	0.0	457
31–60	326	4.9	78.2	91	7.2	21.8	0	0.0	0.0	417
61–90	228	3.4	83.2	46	3.7	16.8	0	0.0	0.0	274
91–180	584	8.7	85.0	102	8.1	14.8	1	33.3	0.1	687
181–365	806	12.0	81.0	189	15.0	19.0	0	0.0	0.0	995
>365*	4361	65.2	85.1	762	60.5	14.9	2	66.7	0.0	5125

*Rivaroxaban reduced dose is recommended for patients with NVAF: patients with renal impairment eGFR 15–49 ml/min/1.73m^2 .

†Rivaroxaban is contraindicated in patients with severe renal impairment (eGFR <15 ml/min/1.73m^2).

Table 31. Prescribing of recommended daily dose of index NOAC (first NOAC prescription) by eligibility according to the EU label.

	Dosing eligibility			
Daily dose of index NOAC prescribed	**Standard dose**	**Reduced dose**	**Contraindicated**	**Total (any eligibility)**
Apixaban	**N=9194**	**N=1385**	**N=255**	**N=10,834**
Recommended	6850 (74.5)	1260 (91.0)	NA	8110 (74.9)
Lower than recommended	2344 (25.5)	0 (0)	NA	2344 (21.6)
Higher than recommended	0 (0)	125 (9.0)	NA	125 (1.1)
Prescribed a NOAC when contraindicated	NA	NA	255 (100)	255 (2.4)
Higher than recommended/contraindicated	0 (0)	125 (9.0)	255 (100)	380 (3.5)
Dabigatran	**N=1790**	**N=2357**	**N=234**	**N=4381**
Recommended	1409 (78.7)	1849 (78.4)	NA	3258 (74.4)
Lower than recommended	381 (21.3)	0 (0)	NA	381 (8.7)
Higher than recommended	0 (0)	508 (21.6)	NA	508 (11.6)
Prescribed a NOAC when contraindicated	NA	NA	234 (100)	234 (5.3)
Higher than recommended/contraindicated	0 (0)	508 (21.6)	234 (100)	742 (16.9)
Rivaroxaban	**N=12,608**	**N=2637**	**N=7**	**N=15,252**
Recommended	11,162 (88.5)	1686 (63.9)	NA	12,848 (84.2)
Lower than recommended	1390 (11.0)	0 (0)	NA	1390 (9.1)
Higher than recommended	56 (0.40)	951 (36.1)	NA	1007 (6.6)
Prescribed a NOAC when contraindicated	NA	NA	7 (100)	7 (0.05)
Higher than recommended/contraindicated	56 (0.40)	951 (36.1)	7 (100)	1014 (6)

10.4.3.2 Dosing by degree of renal impairment

The daily dose of the index NOAC prescription according to renal function is shown in **Figure 2** (approximately 1 in 8 patients in each cohort had unknown renal function). For all NOACs, there was a trend towards dose reduction with increasing renal impairment. Among patients with severe renal impairment (eGFR<30 ml/min/1.73m^2), most were prescribed a reduced daily dose: apixaban (91.1%, ≤5mg), dabigatran (80.0%, ≤200 mg) and rivaroxaban (83.0%, 15 mg). However, reduced doses were also prescribed to patients with no evidence of renal impairment, especially among the dabigatran cohort (50.1%, 1634/3259; mostly 220 mg/day) followed by apixaban (26.7% (1968/7291; nearly all 5 mg/day), and rivaroxaban (10.3%, 1105/10,699; mostly 15 mg/day) users.

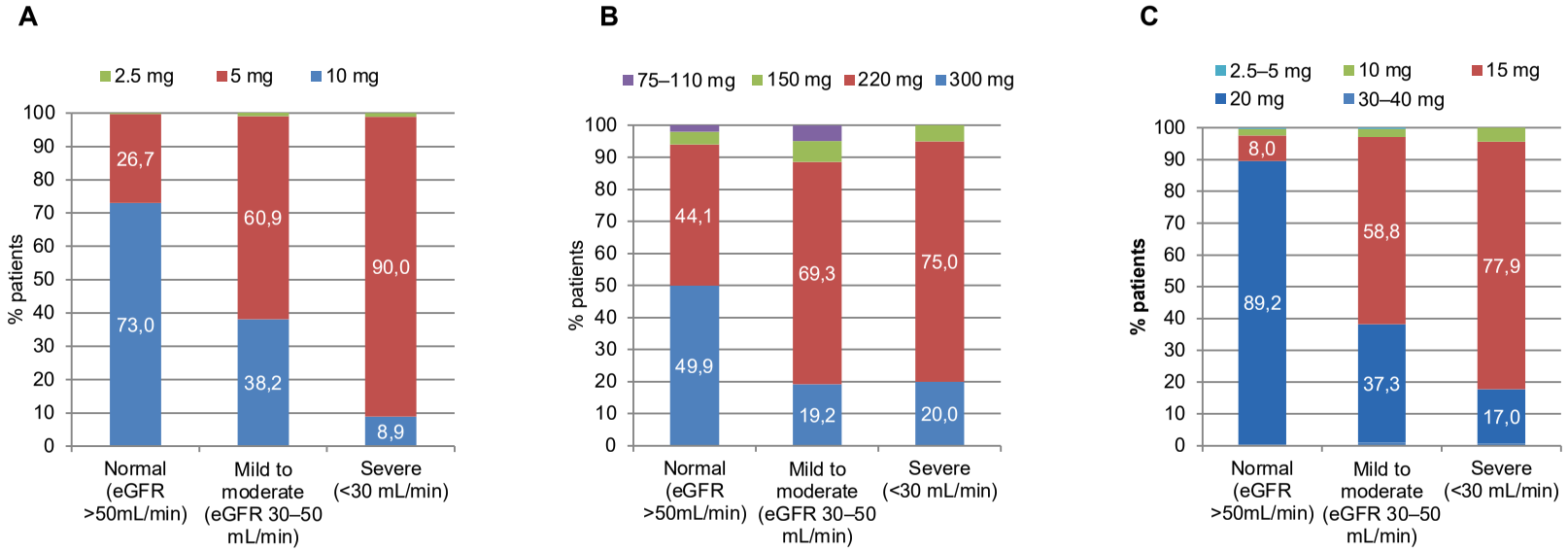

Figure 2. Daily dose at index prescription by degree of renal impairment* for (**A**) new users of apixaban, (**B**) new users of dabigatran and (**C**) new users of rivaroxaban, in patients with NVAF.

Note: Renal function was unknown in 13.6% of the apixaban cohort, 12.3% of the dabigatran cohort and 13.0% of the rivaroxaban cohort.*Estimated using the Chronic Kidney Disease Epidemiology Collaboration equation.

10.4.3.3 Overall appropriateness of initial NOAC daily dose

Figure 3 presents the percentage of patients appropriately dosed, underdosed and overdosed among all patients in each NOAC cohort. The majority of patients (79.5%) starting NOAC therapy were prescribed an appropriate dose; 74.9% of patients on apixaban, 74.4% on dabigatran and 84.2% on rivaroxaban. Underdosing was more frequent in the apixaban cohort (21.6% of patients) than in the dabigatran (8.7% of patients) and rivaroxaban (9.1%) cohorts. Overdosing, however, was more frequent in the dabigatran cohort (16.9%) than in the rivaroxaban (6.6%) or apixaban (3.5%) cohorts.

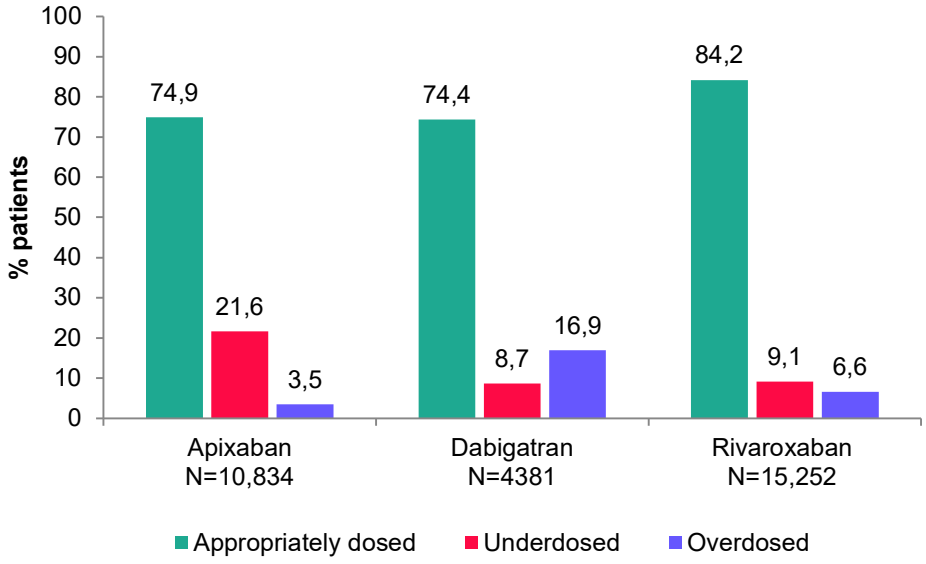

Figure 3. Overall dose appropriateness of index NOAC daily dose (first prescribed NOAC).

NOAC, non-vitamin K antagonist oral anticoagulant

10.4.3.3.1 Appropriateness of NOAC prescription among patients prescribed a standard or reduced dose

As shown in **Figure 4**, among patients starting NOAC therapy on a standard daily dose, this was appropriate for the vast majority of those in the apixaban cohort (97.0%) and rivaroxaban cohort (92.3%), but for fewer patients in the dabigatran cohort (69.8%). Among patients starting NOAC therapy on a reduced dose, there was a notable difference in the level of appropriate prescribing with a reduced dose being appropriate in only 11.2% of patients in the apixaban cohort compared with 78.2% of the dabigatran cohort and 54.7% of the rivaroxaban cohort (**Figure 4**).

Data from analyses of patient characteristics considered when determining eligibility for dose reduction (including age. bodyweight and renal function) according to initial dose prescribed are shown in **Table 32** for apixaban, **Table 33** for dabigatran and **Table 34** for rivaroxaban.

Among patients starting NOAC therapy with apixaban **Table 32**, patients prescribed either the 2.5 mg or 5 mg daily dose were predominantly over 80 years of age (81.1% and 75.6%, respectively). Severe renal failure – a contraindication for apixaban – was documented in 5.7% of patients prescribed a 2.5 mg daily dose, 4.0% of patients prescribed a 5 mg daily dose, and 0.5% of patients prescribed a 10 mg dose. Most patients prescribed 2.5 mg/day apixaban had a low bleeding risk (HAS-BLED score of 0–1; 75.5%), whereas more patients prescribed 5 mg/day apixaban (40.0%) or 10 mg/day apixaban (35.5%) had a moderate bleeding risk (HAS-BLED score of 2. Irrespective of daily dose of apixaban, about a quarter of patients had a history of bleeding. Only 1.9% of patients receiving a daily dose of 10 mg apixaban fulfilled the requisite criteria for dose reduction**.**

Among patients starting NOAC therapy with dabigatran (**Table 33**), 79.0% of those prescribed 300 mg/day were aged <75 years, whereas almost two-thirds (62.1%) of those prescribed 220 mg were aged ≥80 years. Less than 1% of patients receiving dabigatran had severe renal failure. The percentage of patients with each HAS-BLED score was broadly similar across the daily dose of dabigatran prescribed. Irrespective of the daily dose of the index dabigatran prescription, approximately a quarter of patients had a history of bleeding.

Among patients starting NOAC therapy with rivaroxaban (**Table 34**), just under half of patients (49.5%) whose index prescription was for 20 mg/day were aged <75 years, and almost a third (31.1%) were aged 80 years or more. The majority of patients (71.7%) who received a daily dose of 15 mg were aged 80 years or more. Although for rivaroxaban a dose reduction to 15 mg/day is recommended for those with moderate or severe renal impairment, 7.4% of patients prescribed 20 mg/day, 27.4% of those prescribed 30 mg/day and 28.6% of those prescribed 40 mg/day dose of rivaroxaban were classified as having moderate or severe renal impairment. The percentage of patients with each HAS-BLED score was broadly similar irrespective of the daily dose of the index rivaroxaban prescription, and between around a fifth to a quarter of patients had a history of bleeding.

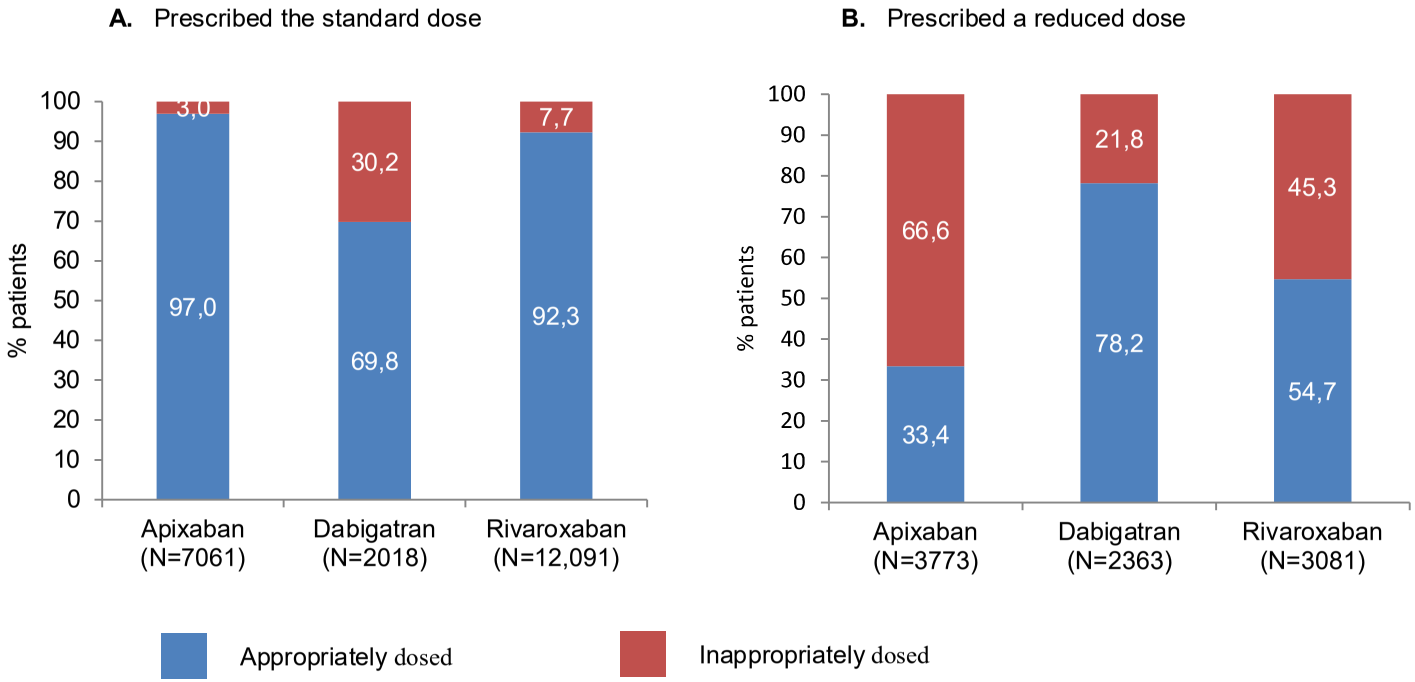

Figure 4. Appropriateness of daily dose of index NOAC among patients with NVAF who were prescribed (A) a standard dose and (B) a reduced dose.

Table 32. Daily dose of index prescription among patients with NVAF newly prescribed apixaban stratified by dose recommendation criteria.

	Daily dose of first apixaban prescription							
	2.5 mg		5 mg		10 mg		Total	
	N=53		N=3720		N=7061		N=10,834	
	n	%	n	%	n	%	n	%
Age (years)								
<75	7	13.2	446	12.0	4108	58.2	4561	42.1
75–79	3	5.7	460	12.4	1488	21.1	1951	18.0
≥80	43	81.1	2814	75.6	1465	20.7	4322	39.9
Sex								
Male	20	37.7	1468	39.5	4271	60.5	5759	53.2
Female	33	62.3	2252	60.5	2790	39.5	5075	46.8
Body weight, kg								
<50	5	9.4	258	6.9	55	0.8	318	2.9
50–60	6	11.3	684	18.4	269	3.8	959	8.9
>60	38	71.7	2678	72.0	6558	92.9	9274	85.6
Unknown	4	7.5	100	2.7	179	2.5	283	2.6
Liver disease	4	7.5	196	5.3	395	5.6	595	5.5
Hepatic disease with coagulopathy	1	1.9	17	0.5	49	0.7	67	0.6
Gastritis, esophagitis, GORD	1	1.9	85	2.3	150	2.1	236	2.2
Severe renal failure – CKD stage 4–5 or dialysis (by diagnostic READ codes)	3	5.7	147	4.0	37	0.5	187	1.7
eGFR, ml/min/1.73m^2								
>50	24	45.3	1944	52.3	5323	75.4	7291	67.3
30–50	18	34.0	1107	29.8	694	9.8	1819	16.8
29–15	3	5.7	242	6.5	23	0.3	268	2.5
<15	0	0.0	10	0.3	2	0.0	12	0.1
Unknown	8	15.1	417	11.2	1019	14.4	1444	13.3

	Daily dose of first apixaban prescription							
	2.5 mg		5 mg		10 mg		Total	
	N=53		N=3720		N=7061		N=10,834	
	n	%	n	%	n	%	n	%
Serum creatinine, mg/dL								
<1.5	33	62.3	2707	72.8	5839	82.7	8579	79.2
≥1.5	11	20.8	594	16.0	201	2.8	806	7.4
Unknown	9	17.0	419	11.3	1021	14.5	1449	13.4
HAS-BLED score								
0–1	15	28.3	1194	32.1	3251	46.0	4460	41.2
2	25	47.2	1489	40.0	2510	35.5	4024	37.1
≥3	13	24.5	1037	27.9	1300	18.4	2350	21.7
History of bleeding (intracranial, gastrointestinal, urogenital)	15	28.3	1051	28.3	1740	24.6	2806	25.9
Drug use (within a month of index prescription)								
Verapamil	0	0.0	72	1.9	220	3.1	292	2.7
ASA, NSAIDS, clopidogrel	22	41.5	1528	41.1	2836	40.2	4386	40.5
SSRIs, SNRIs	4	7.5	317	8.5	714	10.1	1035	9.6
Other factors that increase risk of bleeding*	50	94.3	3517	94.5	4789	67.8	8356	77.1
Categories for dose reduction†								
Age ≥80 years + body weight ≤60 kg	12	22.6	835	22.4	66	0.9	913	8.4
Age ≥80 years + SCr ≥1.5 mg/dL	7	13.2	390	10.5	43	0.6	440	4.1
Body weight ≤60 kg + SCr ≥1.5 mg/dL	0	0.0	13	0.3	3	0.0	16	0.1
Body weight ≤60 kg + age ≥80 years + SCr ≥1.5 mg/dL	1	1.9	59	1.6	2	0.0	62	0.6
Severe renal failure (CrCl <30 mL/min)	2	3.8	49	1.3	19	0.3	70	0.6
Remaining	31	58.5	2374	63.8	6928	98.1	9333	86.1

*Factors that increase bleeding risk: age ≥75 years, moderate renal impairment (creatinine clearance 30–50 mL/min), co-medication with P-gp inhibitors, low-dose aspirin ASA, NSAIDs, clopidogrel, SSRIs or SNRIs, congenital or acquired coagulation disorders, thrombocytopenia/ functional platelet defects, recent biopsy, bacterial endocarditis, esophagitis, gastritis/gastroesophageal reflux. †Dose reduction recommended with at least two of the following: age ≥80 years, body weight ≤60 kg, or serum creatinine ≥1.5 mg/dL.

Table 33. Daily dose of index prescription among patients with NVAF newly prescribed dabigatran stratified by dose recommendation criteria.

	Daily dose of first dabigatran prescription									
	75/110 mg		150 mg		220 mg		300 mg		Total	
	N=101		N=196		N=2066		N=2018		N=4381	
	n	%	n	%	n	%	n	%	n	%
Age (years)										
<75	34	33.7	91	46.4	374	18.1	1595	79.0	2094	47.8
75–79	15	14.9	50	25.5	410	19.8	353	17.5	828	18.9
≥80	52	51.5	55	28.1	1282	62.1	70	3.5	1459	33.3
Sex										
Male	50	49.5	116	59.2	977	47.3	1380	68.4	2523	57.6
Female	51	50.5	80	40.8	1089	52.7	638	31.6	1858	42.4
Body weight										
<50 kg	3	3.0	5	2.6	90	4.4	8	0.4	106	2.4
50–60 kg	6	5.9	12	6.1	253	12.2	64	3.2	335	7.6
>60 kg	89	88.1	175	89.3	1669	80.8	1875	92.9	3808	86.9
Unknown	3	3.0	4	2.0	54	2.6	71	3.5	132	3.0
Liver disease	5	5.0	9	4.6	96	4.6	97	4.8	207	4.7
Hepatic disease with coagulopathy	1	1.0	1	0.5	5	0.2	7	0.3	14	0.3
Gastritis, esophagitis, GORD	2	2.0	3	1.5	57	2.8	34	1.7	96	2.2
Severe renal failure – stages CKD 4–5 or dialysis (by diagnostic READ codes)	0	0.0	5	2.6	27	1.3	7	0.3	39	0.9
eGFR, ml/min/1.73m^2										
>50	67	66.3	130	66.3	1437	69.6	1625	80.5	3259	74.4
30–50	28	27.7	38	19.4	398	19.3	110	5.5	574	13.1
29–15	0	0.0	1	0.5	15	0.7	4	0.2	20	0.5
<15	6	5.9	27	13.8	216	10.5	279	13.8	528	12.1
Unknown	67	66.3	130	66.3	1437	69.6	1625	80.5	3259	74.4

	Daily dose of first dabigatran prescription									
	75/110 mg		150 mg		220 mg		300 mg		Total	
	N=101		N=196		N=2066		N=2018		N=4381	
	n	%	n	%	n	%	n	%	n	%
Serum creatinine, mg/dL										
<1.5	85	84.2	155	79.1	1753	84.8	1695	84.0	3688	84.2
≥1.5	10	9.9	14	7.1	96	4.6	43	2.1	163	3.7
Unknown	6	5.9	27	13.8	217	10.5	280	13.9	530	12.1
HAS-BLED score										
0–1	33	32.7	82	41.8	655	31.7	1016	50.3	1786	40.8
2	40	39.6	66	33.7	899	43.5	699	34.6	1704	38.9
≥3	28	27.7	48	24.5	512	24.8	303	15.0	891	20.3
History of bleeding (intracranial, gastrointestinal, urogenital)	23	22.8	54	27.6	563	27.3	425	21.1	1065	24.3
Drug use (within a month of index prescription)										
Verapamil	3	3.0	5	2.6	50	2.4	33	1.6	91	2.1
ASA, NSAIDS, clopidogrel	41	40.6	75	38.3	888	43.0	822	40.7	1826	41.7
SSRIs, SNRIs	7	6.9	17	8.7	187	9.1	143	7.1	354	8.1
Other factors that increase risk of bleeding*	85	84.2	154	78.6	1895	91.7	1130	56.0	3264	74.5

*Factors that increase bleeding risk: age ≥75 years, moderate renal impairment (creatinine clearance 30–50 mL/min), co-medication with P-gp inhibitors, low-dose aspirin ASA, NSAIDs, clopidogrel, SSRIs or SNRIs, congenital or acquired coagulation disorders, thrombocytopenia/ functional platelet defects, recent biopsy, bacterial endocarditis, esophagitis, gastritis/gastroesophageal reflux.

Table 34. Daily dose of index prescription among patients with NVAF newly prescribed rivaroxaban stratified by dose recommendation criteria.

	Daily dose of first rivaroxaban prescription											
	≤ 10 mg		15 mg		20 mg		30 mg		40 mg		Total	
	N=390		N=2691		N=12091		N=73		N=7		N=15,252	
	n	%	n	%	n	%	n	%	n	%	n	%
Age (years)												
<75	149	38.2	372	13.8	5987	49.5	25	34.2	3	42.9	6536	42.9
75–79	69	17.7	390	14.5	2342	19.4	15	20.5	2	28.6	2818	18.5
≥80	172	44.1	1929	71.7	3762	31.1	33	45.2	2	28.6	5898	38.7
Sex												
Male	205	52.6	1084	40.3	7042	58.2	39	53.4	4	57.1	8374	54.9
Female	185	47.4	1607	59.7	5049	41.8	34	46.6	3	42.9	6878	45.1
Body weight												
<50 kg	12	3.1	139	5.2	267	2.2	1	1.4	0	0.0	419	2.7
50–60 kg	47	12.1	386	14.3	858	7.1	6	8.2	1	14.3	1298	8.5
>60 kg	322	82.6	2114	78.6	10678	88.3	63	86.3	6	85.7	13,183	86.4
Unknown	9	2.3	52	1.9	288	2.4	3	4.1	0	0.0	352	2.3
Liver disease	20	5.1	109	4.1	661	5.5	4	5.5	0	0.0	794	5.2
Hepatic disease with coagulopathy	1	0.3	9	0.3	72	0.6	1	1.4	0	0.0	83	0.5
Gastritis, esophagitis, GORD	6	1.5	51	1.9	275	2.3	1	1.4	0	0.0	333	2.2
Severe renal failure – stages CKD4–5 or dialysis (by diagnostic READ codes)	14	3.6	148	5.5	66	0.5	1	1.4	1	14.3	230	1.5
eGFR, ml/min/1.73m^2												
>50	250	64.1	855	31.8	9547	79.0	44	60.3	3	42.9	10,699	70.1
30–50	70	17.9	1405	52.2	892	7.4	20	27.4	2	28.6	2389	15.7
29–15	12	3.1	206	7.7	44	0.4	2	2.7	0	0.0	264	1.7
<15	0	0.0	5	0.2	2	0.0	0	0.0	0	0.0	7	0.0
Unknown	58	14.9	220	8.2	1606	13.3	7	9.6	2	28.6	1893	12.4

	Daily dose of first rivaroxaban prescription											
	≤ 10 mg		15 mg		20 mg		30 mg		40 mg		Total	
	N=390		N=2691		N=12091		N=73		N=7		N=15,252	
	n	%	n	%	n	%	n	%	n	%	n	%
Serum creatinine												
<1.5	297	76.2	1863	69.2	10,264	84.9	59	80.8	4	57.1	12,487	81.9
≥1.5 mg/dL	34	8.7	605	22.5	213	1.8	7	9.6	1	14.3	860	5.6
Unknown	59	15.1	223	8.3	1614	13.3	7	9.6	2	28.6	1905	12.5
HAS–BLED score												
0–1	160	41.0	832	30.9	5684	47.0	34	46.6	2	28.6	6712	44.0
2	151	38.7	1154	42.9	4467	36.9	19	26.0	4	57.1	5795	38.0
≥3	79	20.3	705	26.2	1940	16.0	20	27.4	1	14.3	2745	18.0
History of bleeding (intracranial, gastrointestinal, urogenital)	77	19.7	760	28.2	3055	25.3	17	23.3	1	14.3	3910	25.6
Drug use (within a month of index prescription)												
Verapamil	8	2.1	36	1.3	317	2.6	1	1.4	1	14.3	363	2.4
ASA, NSAIDS, clopidogrel	150	38.5	1045	38.8	4427	36.6	30	41.1	3	42.9	5655	37.1
SSRIs, SNRIs	27	6.9	238	8.8	1048	8.7	10	13.7	0	0.0	1323	8.7
Other factors that increase risk of bleeding*	306	78.5	2575	95.7	8536	70.6	61	83.6	6	85.7	11,484	75.3

*Factors that increase bleeding risk: age ≥75 years, moderate renal impairment (creatinine clearance 30–50 mL/min), co-medication with P-gp inhibitors, low-dose aspirin ASA, NSAIDs, clopidogrel, SSRIs or SNRIs, congenital or acquired coagulation disorders, thrombocytopenia/ functional platelet defects, recent biopsy, bacterial endocarditis, esophagitis, gastritis/gastroesophageal reflux.

10.4.3.4 Dose variation over time among patients underdosed at index NOAC prescription

Among patients whose index NOAC prescription was underdosed and who also had at least 6 months of follow-up, the majority still received an underdosed prescription 6 months after their initial underdosed prescription: apixaban 90.2%, dabigatran 82.0% and rivaroxaban 84.6% (**Table 35**).

Table 35. NOAC daily dose 6 months after the index date among patients whose initial NOAC prescription was underdosed and who had at least 6 months of follow-up.

	Daily dose 6 months after the index date					
	Lower dose than the index NOAC prescription*		**Same dose than the index NOAC prescription**		**Higher dose than the index NOAC prescription**	
	n	**%**	**n**	**%**	**n**	**%**
Apixaban (N= 1427)	–	–	1242	87.0	185	13.0
Dabigatran (N=250)	1	0.4	205	82.0	44	17.6
Rivaroxaban (N=874)	2	0.2	739	84.6	133	15.2

*One patients prescribed dabigatran 220 mg at the index date was prescribed dabigatran 110 mg 6 months later. Two patients prescribed rivaroxaban 15 mg at the index date were prescribed rivaroxaban 10 mg 6 months later.

10.4.4 Predictors of inappropriate underdosing

Associations between baseline characteristics and inappropriate underdosing (vs. appropriate dosing) are shown in **Table 36** for patients starting NOAC therapy on apixaban, **Table 37** for those starting on dabigatran, and **Table 38** for those starting on rivaroxaban.

Older age (≥80 years vs. <60 years) was the strongest predictor of inappropriate apixaban underdosing (OR 7.9, 95% CI: 6.0–10.3). Other factors associated with an increased risk of inappropriate apixaban underdosing were a HAS-BLED score greater than zero, a history of intracranial bleeding, a CHA_2DS_2VASc score of ≥3 (vs. a score of zero), a $CHADS_2$ score ≥2 (vs. a score of zero), being moderately or severely frail, being overweight or obese, having moderate renal failure (eGFR 30–50 ml/min/1.73m^2), and being female. Being underweight was associated with a decreased risk of inappropriate apixaban underdosing.

Factors associated with an increased likelihood of inappropriate dabigatran underdosing were having a CHA_2DS_2VASc score of 1 or 2 (vs. a score of zero), having a HAS-BLED score of between 1 and

3 (vs. a score of zero), use of antiplatelets or antiarrhythmics, and very high alcohol consumption (≥42 units per week). Factors associated with a decreased likelihood of inappropriate dabigatran underdosing were having a $CHADS_2$ score of at least 2 (vs. a score of zero), and being obese. No association was seen between age and inappropriate dabigatran underdosing

As with apixaban, the strongest predictor of inappropriate rivaroxaban underdosing was older age (≥80 years vs. <60 years; OR 4.1, 95% CI: 3.0–5.4). other factors associate with an increased risk of inappropriate rivaroxaban underdosing were moderate or severe frailty, a history of IHD, being female, and being underweight. In contrast to what was observed for apixaban, being overweight or obese was associated with a decreased risk of inappropriate rivaroxaban underdosing.

Irrespective of the index NOAC, having the index NOA prescription in the later years of the study period (2014–2016) was associated with a lower likelihood of inappropriate underdosing (vs. 2011–2013).

10.4.5 Predictors of overdosing

As shown in **Table 39**, the strongest predictor of dabigatran overdosing (vs. appropriate dosing) was being aged 70–79 years (vs. <60 years; OR 7.8, 95% CI: 4.80–12.52). Other factors associated with an increased likelihood of dabigatran overdosing (vs. appropriate dosing) were being obese, a history of IHD, frailty, a CHA_2DS_2VASc score of ≥4 (vs. a score of zero), and a $CHADS_2$ score of at least 1 (vs. a score or zero). For rivaroxaban (**Table 40**), being aged ≥80 years was the strongest predictor of rivaroxaban overdosing (vs. appropriate dosing). Other factors associated with an increased likelihood of dabigatran overdosing (vs. appropriate dosing) were being aged >60 years, being female, being OAC non-naïve, having moderate or several renal failure, frailty especially severe frailty), a history of IHD< heart failure, hypertension or gastrointestinal bleeding, a CHA_2DS_2VASc score of ≥3 (vs. a score of zero), and a $CHADS_2$ score of at least 2 (vs. a score or zero), a HAS-BLED score of ≥1 (vs. a score of zero), use of antihypertensives, and being overweight or obese. Having moderate or high alcohol consumption was associated with a decreased likelihood of rivaroxaban overdosing.

Table 36. Association between baseline characteristics of patients with NVAF newly prescribed apixaban and inappropriate underdosing (reference group = appropriately dosed).

	Apixaban* N=10,520					
	Appropriately dosed N=8110 (69.8%)		**Inappropriately underdosed N=2344 (30.2%)**		**Age, sex and calendar year adjusted OR**	**95% CI**
Sex						
Male	4515	55.7	1079	46.0	1.0 (reference)	–
Female	3595	44.3	1265	54.0	1.12	(1.01–1.23)
Age (years)						
<60	822	10.1	60	2.6	1.0 (reference)	–
60–69	1880	23.2	165	7.0	1.19	(0.87–1.61)
70–79	2851	35.2	596	25.4	2.19	(2.12–3.69)
≥80	2557	31.5	1523	65.0	7.88	(6.00–10.33)
Mean (SD)	73.6 (11.0)		80.9 (8.4)			
OAC naïve status						
Naïve	4405	54.3	1216	51.9	1.0 (reference)	–
Non–naïve	3705	45.7	1128	48.1	0.98	(0.89–1.08)
Year of first NOAC prescription						
2011–2013	207	2.6	74	3.2	1.0 (reference)	–
2014–2016	7903	97.4	2270	96.8	0.75	(0.57–1.00)
BMI, kg/m^2						
<20 (underweight)	1866	23.0	536	22.9	0.49	(0.37–0.66)
20–24 (healthy weight)	361	4.5	63	2.7	1.0 (reference)	–
25–29 (overweight)	2775	34.2	954	40.7	1.55	(1.36–1.76)
≥30 (obese)	2825	34.8	654	27.9	1.35	(1.17–1.55)
Missing	283	3.5	137	5.8	2.25	(1.77–2.88)
Smoking						
Non-smoker	3371	41.6	1003	42.8	1.0 (reference)	–
Smoker	650	8.0	144	6.1	1.17	(0.95–1.44)
Ex-smoker	4081	50.3	1194	50.9	1.04	(0.93–1.15)
Unknown	8	0.1	3	0.1	1.57	(0.39–6.30)
Alcohol (units/week)						
None	1703	21.0	653	27.9	1.0 (reference)	–
1–9	3554	43.8	1007	43.0	0.89	(0.79–1.00)
10–20	1382	17.0	282	12.0	0.83	(0.70–0.98)
21–41	485	6.0	96	4.1	0.84	(0.65–1.09)
≥42	221	2.7	42	1.8	1.02	(0.71–1.46)
Unknown	765	9.4	264	11.3	1.08	(0.91–1.29)
CVD						
IHD	2328	28.7	765	32.6	1.01	(0.91–1.12)
Heart failure	1323	16.3	469	20.0	1.09	(0.97–1.24)
Hypertension	5267	64.9	1665	71.0	1.03	(0.93–1.15)
Ischaemic stroke	1211	14.9	469	20.0	1.19	(1.05–1.35)
History of bleeding disorders						
Intracranial bleeding	119	1.5	77	3.3	2.11	(1.55–2.87)

	Apixaban* N=10,520					
	Appropriately dosed N=8110 (69.8%)		**Inappropriately underdosed N=2344 (30.2%)**		**Age, sex and calendar year adjusted OR**	**95% CI**
GI bleeding	1101	13.6	365	15.6	1.11	(0.97–1.27)
Urogenital bleeding	1016	12.5	325	13.9	1.08	(0.94–1.25)
eGFR, ml/min/1.73m²						
>50 mL/min	5749	70.9	1441	61.5	1.0 (reference)	–
30–50 mL/min	1100	13.6	584	24.9	1.28	(1.13–1.45)
<30	167	2.1	0	0.0	–	–
Missing	1094	13.5	319	13.6	–	–
Frailty index						–
Fit	1324	16.3	167	7.1	1.0 (reference)	–
Mild frailty	3028	37.3	659	28.1	1.21	(0.93–1.36)
Moderate frailty	2371	29.2	875	37.3	1.36	(1.12–1.65)
Severe frailty	1387	17.1	643	27.4	1.37	(1.12–1.69)
CHA_2DS_2-VASc score						
0	425	5.2	25	1.1	1.0 (reference)	–
1	669	8.2	51	2.2	1.07	(0.64–1.79)
2	1430	17.6	222	9.5	1.45	(0.90–2.32)
3	1695	20.9	443	18.9	1.62	(1.01–2.60)
≥4	3891	48.0	1603	68.4	1.86	(1.16–2.99)
Mean (SD)		3.5 (1.8)		4.3 (1.7)		
$CHADS_2$ score						
0	1120	13.8	102	4.4	1.0 (reference)	–
1	2231	27.5	435	18.6	1.21	(0.96–1.54)
2	2287	28.2	773	33.0	1.36	(1.07–1.73)
≥3	2472	30.5	1034	44.1	1.48	(1.16–1.88)
Mean (SD)		1.9 (1.4)		2.5 (1.3)		
HAS-BLED score						
0	813	10.0	46	2.0	1.0 (reference)	–
1	2782	34.3	776	33.1	1.65	(1.16–2.36)
2	2943	36.3	950	40.5	1.68	(1.17–2.41)
3	1313	16.2	441	18.8	1.63	(1.12–2.36)
≥4	259	3.2	131	5.6	2.33	(1.53–3.53)
Mean (SD)		1.7 (1.0)		1.9 (0.9)		
Medications†						
Antiplatelets	3746	46.2	1148	49.0	1.05	(0.95–1.16)
Antiarrhythmics	1197	14.8	294	12.5	0.99	(0.85–1.14)
Antihypertensives	7054	87.0	2102	89.7	1.08	(0.92–1.26)

Data are n(%) unless otherwise stated.
*Patients receiving a higher than recommended dose of apixaban or any apixaban dose when contraindicated were not included. †Prescription in the year before the index date.

Table 37. Association between baseline characteristics of patients with NVAF newly prescribed dabigatran and inappropriate underdosing (reference group = appropriately dosed).

	Dabigatran N=3639					
	Appropriately dosed N=3258; 89.5%		**Inappropriately underdosed N=381; 10.5%**		**Age, sex and calendar year adjusted OR**	**95% CI**
Sex						
Male	1848	56.7	248	65.1	1.0 (reference)	–
Female	1410	43.3	133	34.9	0.89	0.71–1.13
Age years						
<60	351	10.8	62	16.3		
60–69	676	20.7	154	40.4	1.31	0.95–1.81
70–79	916	28.1	165	43.3	1.0 (reference)	0.73–1.39
≥80	1315	40.4	0	0.0	–	–
Mean age, SD	74.6	11.4	66.7	6.6	–	–
OAC naïve status						
Naïve	1383	42.4	167	43.8	1.0 (reference)	–
Non-naïve	1875	57.6	214	56.2	0.96	0.77–1.19
Year of first NOAC prescription						
2011–13	1578	48.4	218	57.2	1.0 (reference)	–
2014–16	1680	51.6	163	42.8	0.67	0.54–0.84
BMI, kg/m^2						
10–19 (underweight)	137	4.2	15	3.9	1.50	0.83–2.73
20–24 (healthy weight)	788	24.2	70	18.4	1.0 (reference)	
25–29 (overweight)	1185	36.4	140	36.7	1.17	0.86–1.59
≥30 (obese)	992	30.4	141	37.0	1.21	0.89–1.66
Unknown	156	4.8	15	3.9	0.89	0.49–1.61
Smoking						
Non-smoker	1351	41.5	147	38.6	1.0 (reference)	–
Smoker	215	6.6	43	11.3	1.47	1.00–2.14
Ex-smoker	1687	51.8	191	50.1	1.03	0.82–1.30
Unknown	5	0.2	0	0.0	–	–
Alcohol units/week						
None	590	18.1	56	14.7	1.0 (reference)	–
1–9	1496	45.9	149	39.1	0.91	0.65–1.28
10–20	532	16.3	82	21.5	1.19	0.81–1.75
21–41	219	6.7	32	8.4	0.98	0.60–1.60
≥42	84	2.6	22	5.8	1.83	1.03–3.25
Unknown	337	10.3	40	10.5	1.04	0.67–1.61
History of CVD						
IHD	825	25.3	98	25.7	1.19	0.93–1.54
Heart failure	535	16.4	51	13.4	0.90	0.66–1.24
Hypertension	2119	65.0	235	61.7	1.03	0.82–1.29
Ischaemic stroke	500	15.3	55	14.4	1.05	0.77–1.43

	Dabigatran N=3639					
	Appropriately dosed N=3258; 89.5%		Inappropriately underdosed N=381; 10.5%		Age, sex and calendar year adjusted OR	95% CI
History of bleeding						
Intracranial bleeding	48	1.5	10	2.6	2.15	1.06–4.36
GI bleeding	411	12.6	59	15.5	1.42	1.05–1.92
Urogenital bleeding	396	12.2	36	9.4	0.84	0.58–1.21
eGFR, ml/min/1.73m^2						
>50	2411	74.0	317	83.2	1.0 (reference)	–
30–50	439	13.5	0	0.0	–	–
<30	0	0.0	0	0.0	–	–
Unknown	408	12.5	64	16.8	1.14	0.85–1.53
Frailty index						
Fit	557	17.1	90	23.6	1.0 (reference)	
Mild frailty	1184	36.3	173	45.4	1.08	0.81–1.43
Moderate frailty	928	28.5	88	23.1	0.87	0.62–1.23
Severe frailty	589	18.1	30	7.9	0.54	0.34–0.86
CHA_2DS_2-VASc score						
0	205	6.3	28	7.3	1.0 (reference)	–
1	251	7.7	62	16.3	2.12	1.29–3.51
2	542	16.6	104	27.3	1.71	1.05–2.77
3	646	19.8	90	23.6	1.50	0.90–2.50
≥4	1614	49.5	97	25.5	0.74	0.44–1.25
Mean SD	3.5	1.9	2.6	1.5		
$CHADS_2$ score						
0	454	13.9	95	24.9	1.0 (reference)	–
1	822	25.2	151	39.6	1.01	0.75–1.35
2	946	29.0	73	19.2	0.50	0.36–0.71
≥3	1036	31.8	62	16.3	0.42	0.29–0.61
Mean SD	2.0	1.3	1.3	1.1		
HAS–BLED score						
0	293	9.0	41	10.8	1.0 (reference)	–
1	1100	33.8	132	34.6	1.50	1.01–2.25
2	1230	37.8	145	38.1	1.84	1.20–2.82
3	515	15.8	54	14.2	1.79	1.10–2.92
≥4	120	3.7	9	2.4	1.38	0.62–3.07
Mean SD	1.7	1.0	1.6	1.0		
Medications in prior 1y †						
Antiplatelets	1664	51.1	215	56.4	1.28	1.03–1.59
Antiarrhythmics	578	17.7	100	26.2	1.52	1.18–1.96
Antihypertensives	2876	88.3	334	87.7	1.02	0.73–1.42

Data are n(%) unless otherwise stated.
*Patients receiving a higher than recommended dose of dabigatran or any dabigatran dose when contraindicated were not included. †Prescription in the year before the index date.

Table 38. Association between baseline characteristics of patients with NVAF newly prescribed rivaroxaban and inappropriate underdosing (reference group = appropriately dosed).

	Rivaroxaban (N=14,238)*					
	Appropriate (n=12849; 90.2%)		Inappropriate underdosed (n=1389; 9.8%)		Age, sex and calendar year adjusted OR	95% CI
Sex						
Male	7324	57.0	590	42.5	1.0 (reference)	–
Female	5525	43.0	799	57.5	1.45	(1.29–1.62)
Age (years)						
<60	1238	9.6	53	3.8	1.0 (reference)	–
60–69	2688	20.9	136	9.8	1.14	(0.82–1.58)
70–79	4506	35.1	336	24.2	1.62	(1.20–2.18)
≥80	4417	34.4	8654	62.2	4.05	(3.04–5.39)
Mean age (SD)	74.3	(10.7)	80.3	(9.6)		
OAC naïve status						
Naïve	6136	47.8	655	47.2	1.0 (reference)	–
Non–naïve	6713	52.2	734	52.8	0.93	(0.83–1.05)
Year of first NOAC prescription						
2011–13	1628	12.7	221	15.9	1.0 (reference)	–
2014–16	11,221	87.3	1168	84.1	0.79	(0.67–0.92)
BMI, kg/m^2						
10–19 (underweight)	491	3.8	123	8.9	1.38	(1.10–1.73)
20–24 (healthy weight)	2899	22.6	441	31.7	1.0 (reference)	–
25–29 (overweight)	4496	35.0	436	31.4	0.75	(0.65–0.87)
≥30 (obese)	4479	34.9	339	24.4	0.69	(0.59–0.80)
Unknown	484	3.8	50	3.6	0.75	(0.54–1.02)
Smoking						
Non-smoker	5182	40.3	620	44.6	1.0 (reference)	–
Smoker	1068	8.3	86	6.2	0.99	(0.78–1.26)
Ex-smoker	6591	51.3	683	49.2	0.97	(0.86–1.09)
Unknown	8	0.1	0	0.0	–	
Alcohol (units/week)						
None	2487	19.4	333	24.0	1.0 (reference)	–
1–9	5820	45.3	671	48.3	1.01	(0.88–1.17)
10–20	2054	16.0	153	11.0	0.84	(0.68–1.04)
21–41	837	6.5	52	3.7	0.83	(0.61–1.14)
≥42	369	2.9	24	1.7	0.95	(0.61–1.48)
Unknown	1282	10.0	156	11.2	1.06	(0.86–1.30)
History of CVD						
IHD	3329	25.9	449	32.3	1.25	(1.11–1.41)
Heart failure	1995	15.5	260	18.7	1.10	(0.95–1.28)
Hypertension	8534	66.4	957	68.8	0.91	(0.80–1.03)
Ischaemic stroke	1734	13.5	230	16.5	1.07	(0.92–1.25)
History of bleeding						
Intracranial bleeding	147	1.1	28	2.0	1.65	(1.09–2.51)
GI bleeding	1698	13.2	184	13.2	0.98	(0.83–1.15)

	Rivaroxaban (N=14,238)*					
	Appropriate (n=12849; 90.2%)		Inappropriate underdosed (n=1389; 9.8%)		Age, sex and calendar year adjusted OR	95% CI
Urogenital bleeding	1744	13.6	192	13.8	0.99	(0.84–1.16)
eGFR, ml/min/1.73m²						
>50	9547	74.3	1105	79.6	1.0 (reference)	–
30–50	1478	11.5	6	0.4	0.02	(0.01–0.04)
<30	218	1.7	0	0.0	–	
Unknown	1606	12.5	278	20.0	1.66	(1.43–1.93)
Frailty index						
Fit	2124	16.5	115	8.3	1.0 (reference)	–
Mild frailty	4700	36.6	386	27.8	1.12	(0.90–1.40)
Moderate frailty	3841	29.9	515	37.1	1.39	(1.11–1.74)
Severe frailty	2184	17.0	373	26.9	1.47	(1.16–1.86)
CHA_2DS_2-VASc score						
0	606	4.7	23	1.7	1.0 (reference)	–
1	1109	8.6	56	4.0	1.29	(0.77–2.16)
2	2199	17.1	132	9.5	1.08	(0.66–1.77)
3	2754	21.4	270	19.4	1.28	(0.78–2.10)
≥4	6181	48.1	908	65.4	1.34	(0.81–2.19)
Mean (SD)	3.5	(1.8)	4.2	(1.7)		
$CHADS_2$ score						
0	1692	13.2	86	6.2	1.0 (reference)	–
1	3492	27.2	285	20.5	1.10	(0.85–1.42)
2	3827	29.8	471	33.9	1.12	(0.86–1.46)
≥3	3838	29.9	547	39.4	1.16	(0.89–1.51)
Mean (SD)	1.9	(1.3)	2.3	(1.3)		
HAS-BLED score						
0	1225	9.5	47	3.4	1.0 (reference)	–
1	4628	36.0	487	35.1	1.31	(0.91–1.88)
2	4789	37.3	581	41.8	1.37	(0.94–1.97)
3	1794	14.0	228	16.4	1.36	(0.92–2.00)
≥4	413	3.2	46	3.3	1.13	(0.71–1.82)
Mean (SD)	1.7	(1.0)	1.8	(0.9)		
Medications in prior 1y †						
Antiplatelets	5684	44.2	677	48.7	1.15	(1.03–1.29)
Antiarrhythmics	1843	14.3	191	13.7	1.07	(0.91–1.27)
Antihypertensives	11,327	88.2	1236	89.0	0.93	(0.78–1.11)

Data are n(%) unless otherwise stated.
*Patients receiving a higher than recommended dose of rivaroxaban or any rivaroxaban dose when contraindicated were not included. †Prescription in the year before the index date.

Table 39. Associations between baseline characteristics of patients with NVAF newly prescribed dabigatran and overdosing (reference group=appropriately dosed).

	Dabigatran N=3766					
	Appropriately dosed n=3258; 86.5		Overdosed* n=508; 13.5		Age, sex and calendar year adjusted OR	95% CI
Sex						
Male	1848	56.7	297	58.5	1	
Female	1410	43.3	211	41.5	0.92	0.75–1.13
Age years						
<60	351	10.8	19	3.7	1	
60–69	676	20.7	46	9.1	1.28	0.74–2.21
70–79	916	28.1	377	74.2	7.75	4.80–12.52
≥80	1315	40.4	66	13.0	0.96	0.56–1.63
Mean age SD	74.6	11.4	75.4	6.4		
OAC naïve status						
Naïve	1383	42.4	194	38.2	1	
Non–naïve	1875	57.6	314	61.8	1.18	0.96–1.45
Year of first NOAC prescription						
2011–13	1578	48.4	268	52.8	1	
2014–16	1680	51.6	240	47.2	0.91	0.75–1.11
BMI, kg/m^2						
10–19 (underweight)	137	4.2	13	2.6	0.77	0.41–1.45
20–24 (healthy weight)	788	24.2	104	20.5	1	
25–29 (overweight)	1185	36.4	183	36.0	1.06	0.80–1.39
≥30 (obese)	992	30.4	192	37.8	1.37	1.04–1.81
Unknown	156	4.8	16	3.1	0.88	0.49–1.58
Smoking						
Non-smoker	1351	41.5	199	39.2	1	
Smoker	215	6.6	28	5.5	0.81	0.52–1.27
Ex-smoker	1687	51.8	281	55.3	1.06	0.86–1.32
Unknown	5	0.2	0	0.0	—	
Alcohol units/week						
None	590	18.1	83	16.3	1.0 (reference)	–
1–9	1496	45.9	241	47.4	1.12	0.84–1.50
10–20	532	16.3	532	16.3	1.16	0.81–1.65
21–41	219	6.7	36	7.1	1.16	0.73–1.85
≥42	84	2.6	17	3.3	1.25	0.67–2.33
Unknown	337	10.3	41	8.1	1.02	0.67–1.55
History of CVD						
IHD	825	25.3	162	31.9	1.30	1.04–1.61
Heart failure	535	16.4	91	17.9	1.16	0.90–1.51
Hypertension	2119	65.0	347	68.3	1.12	0.90–1.39
Ischaemic stroke	500	15.3	89	17.5	1.11	0.85–1.44
History of bleeding						
Intracranial bleeding	48	1.5	10	2.0	1.52	0.72–3.19

GI bleeding	411	12.6	67	13.2	1.0	0.75–1.35
Urogenital bleeding	396	12.2	60	11.8	0.91	0.67–1.24
eGFR, ml/min/1.73m^2						
>50	2411	74.0	359	70.7	1.0 (reference)	–
30–50	439	13.5	107	21.1	2.18	1.66–2.86
<30	0	0.0	0	0.0	–	
Unknown	408	12.5	42	8.3	0.81	0.57–1.15
Frailty index						
Fit	557	17.1	46	9.1	1.0 (reference)	–
Mild frailty	1184	36.3	203	40.0	1.65	1.16–2.34
Moderate frailty	928	28.5	184	36.2	2.13	1.47–3.07
Severe frailty	589	18.1	75	14.8	1.81	1.18–2.77
CHA_2DS_2-VASc score						
0	205	6.3	10	2.0	1.0 (reference)	–
1	251	7.7	10	2.0	0.45	0.17–1.17
2	542	16.6	60	11.8	1.22	0.55–2.69
3	646	19.8	120	23.6	2.16	0.98–4.73
≥4	1614	49.5	308	60.6	2.78	1.27–6.11
Mean, SD	3.5	1.9	4.0	1.6		
$CHADS_2$ score						
0	454	13.9	22	4.3	1.0 (reference)	–
1	822	25.2	108	21.3	2.37	1.46–3.86
2	946	29.0	176	34.6	3.84	2.37–6.19
≥3	1036	31.8	202	39.8	4.38	2.70–7.09
Mean, SD	2.0	1.3	2.3	1.2		
HAS-BLED score						
0	293	9.0	13	2.6	1.0 (reference)	–
1	1100	33.8	140	27.6	1.36	0.69–2.67
2	1230	37.8	240	47.2	1.93	0.97–3.82
3	515	15.8	101	19.9	1.74	0.86–3.54
≥4	120	3.7	14	2.8	1.07	0.44–2.61
Mean SD	1.7	1.0	1.9	0.8		
Medications in prior 1y †						
Antiplatelets	1664	51.1	279	54.9	1.05	0.86–1.29
Antiarrhythmics	578	17.7	100	19.7	1.09	0.84–1.40
Antihypertensives	2876	88.3	460	90.6	1.25	0.89–1.74

Data are n(%) unless otherwise stated.
*Patients who were inappropriately underdosed or who received any dose of dabigatran when contraindicated where not included in this analysis.
†Prescription in the year before the index date.

Table 40. Association between baseline characteristics of patients with NVAF newly prescribed rivaroxaban and overdosing (reference group=appropriately dosed).

	Rivaroxaban N=13,856					
	Appropriately dosed N=12,849; 92.7%		Overdosed* N=1007;7.3%		Age, sex and calendar year adjusted OR	95% CI
Sex						
Male	7324	57.0	458	45.5	1.0 (reference)	–
Female	5525	43.0	549	54.5	1.26	1.11–1.44
Age years						
<60	1238	9.6	14	1.4	1.0 (reference)	–
60–69	2688	20.9	85	8.4	2.74	1.55–4.84
70–79	4506	35.1	294	29.2	5.54	3.23–9.51
≥80	4417	34.4	614	61.0	11.44	6.70–19.54
Mean age, SD	74.3	10.7	80.7	8.1	–	–
OAC naïve status						
Naïve	6136	47.8	413	41.0	1.0 (reference)	–
Non–naïve	6713	52.2	594	59.0	1.20	1.05–1.37
Year of first NOAC prescription						
2011–13	1628	12.7	138	13.7	1.0 (reference)	–
2014–16	11221	87.3	869	86.3	0.95	0.79–1.15
BMI, kg/m^2						
10–19 (underweight)	491	3.8	32	3.2	0.69	0.47–1.01
20–24 (healthy weight)	2899	22.6	228	22.6	1.0 (reference)	–
25–29 (overweight)	4496	35.0	363	36.0	1.21	1.02–1.45
≥30 (obese)	4479	34.9	346	34.4	1.43	1.19–1.71
Unknown	484	3.8	38	3.8	1.14	0.79–1.64
Smoking						
Non-smoker	5182	40.3	388	38.5	1.0 (reference)	–
Smoker	1068	8.3	52	5.2	0.99	0.73–1.34
Ex-smoker	6591	51.3	565	56.1	1.23	1.07–1.42
Unknown	8	0.1	2	0.2	4.21	0.82–21.51
Alcohol units/week						
None	2487	19.3	270	26.8	1.0 (reference)	–
1–9	5820	45.3	489	48.6	0.89	0.76–1.04
10–20	2054	16.0	94	9.3	0.60	0.46–0.77
21–41	837	6.5	31	3.1	0.56	0.38–0.83
≥42	369	2.9	12	1.2	0.54	0.30–0.99
Unknown	1282	10.0	111	11.0	0.92	0.73–1.16
History of CVD						
IHD	3329	25.9	351	34.9	1.37	1.19–1.57
Heart failure	1995	15.5	259	25.7	1.68	1.44–1.96
Hypertension	8534	66.4	788	78.3	1.46	1.25–1.71
Ischaemic stroke	1734	13.5	169	16.8	1.08	0.91–1.29
History of bleeding						
Intracranial bleeding	147	1.1	18	1.8	1.41	0.86–2.33

GI bleeding	1698	13.2	174	17.3	1.32	1.11–1.58
Urogenital bleeding	1744	13.6	150	14.9	1.04	0.87–1.25
eGFR, ml/min/1.73m^2						
>50	9547	74.3	47	4.7	1.0 (reference)	–
30–50	1478	11.5	905	89.9	156.7	114.03–215.44
<30	218	1.7	46	4.6	55.18	35.42–85.98
Unknown	1606	12.5	9	0.9	1.11	0.54–2.28
Frailty index						
Fit	2124	16.5	26	2.6	1.0 (reference)	–
Mild frailty	4700	36.6	226	22.4	2.91	1.93–4.40
Moderate frailty	3841	29.9	360	35.7	4.57	3.03–6.90
Severe frailty	2184	17.0	395	39.2	7.70	5.08–11.67
CHA_2DS_2-VASc score						
0	606	4.7	4	0.4	1.0 (reference)	–
1	1109	8.6	18	1.8	1.81	0.60–5.50
2	2199	17.1	56	5.6	2.10	0.73–6.06
3	2754	21.4	178	17.7	4.27	1.50–12.17
≥4	6181	48.1	751	74.6	6.46	2.27–18.39
Mean SD	3.5	1.8	4.5	1.6		
$CHADS_2$ score						
0	1692	13.2	27	2.7	1.0 (reference)	–
1	3492	27.2	132	13.1	1.66	1.08–2.54
2	3827	29.8	362	35.9	3.02	2.00–4.57
≥3	3838	29.9	486	48.3	3.67	2.42–5.55
Mean SD	1.9	1.3	2.6	1.2		
HAS–BLED score						
0	1225	9.5	10	1.0	1.0 (reference)	–
1	4628	36.0	315	31.3	2.97	1.50–5.86
2	4789	37.3	423	42.0	3.44	1.74–6.83
3	1794	14.0	201	20.0	4.14	2.07–8.29
≥4	413	3.2	58	5.8	5.03	2.41–10.47
Mean SD	1.7	1.0	2.0	0.9		
Medications in prior 1y †						
Antiplatelets	5684	44.2	490	48.7	1.13	0.99–1.29
Antiarrhythmics	1843	14.3	145	14.4	1.16	0.96–1.40
Antihypertensives	11327	88.2	947	94.0	1.79	1.37–2.34

*Patients who were inappropriately underdosed or who received any dose of rivaroxaban when contraindicated where not included in this analysis.
†Prescription in the year before the index date.
Data are n (%) unless otherwise stated.

10.4.6 Discontinuation of NOAC use

10.4.6.1 Baseline characteristics of patients in the THIN discontinuation analysis

In total, there were 11,481 patients with NVAF who were first-time users of a NOAC: 5889 patients (51.3%) started on rivaroxaban, 3589 (31.3%) started on apixaban and 2003 (17.4%) started on dabigatran. Baseline characteristics of the three study cohorts are shown in **Table 41**. Mean age, obesity, smoking status, alcohol consumption, frailty, CHA_2DS_2-VASc score and HAS-BLED score were all comparable across cohorts. There were slightly more males than females in each cohort, and patients starting therapy on apixaban were more likely to be OAC naïve (55%) compared with those starting on dabigatran (44.0%) or rivaroxaban (48.0%).

10.4.6.2 Discontinuation with index NOAC therapy during the first year of treatment

The percentage of patients who continued, switched, reinitiated or stopped and did not reinitiate OAC therapy is shown in **Figure 5** and **Table 42** by study cohort. The majority of patients in each cohort remained on their initial NOAC therapy (i.e. were continuous users) within the first year of treatment; 26.1% of the apixaban cohort, 40.0% of the dabigatran cohort, and 29.6% of the rivaroxaban cohort discontinued therapy within this time period. Among OAC naïve patients, minimal difference was seen among the percentage of patients discontinuing their index NOAC: apixaban (24.0%), dabigatran (40.9%) and rivaroxaban (28.9%). Around a fifth of patients in each cohort discontinued their initial NOAC therapy but reinitiated OAC treatment (after a gap in treatment of >30 days), while less than 10% in each cohort stopped OAC therapy and did not reinitiate it later in the first year of treatment.

Only a small percentage of patients switched from their initial NOAC within 30 days of starting treatment, with a higher percentage of switchers seen for dabigatran (8.8%) than for apixaban (2.8%) or rivaroxaban (4.9%). As shown in **Table 42**, most switchers changed to a different NOAC rather than to a VKA, and among patients who discontinued the index NOAC and later reinitiated OAC therapy, the vast majority re-started with the index NOAC: apixaban (79.7%, 636/651), dabigatran (92.6%, 403/434) and (95.0%, 970/1021). In a sensitivity analysis (**Table 43**), changing the definition of discontinuation to having a gap in treatment of >60 days, the proportion of substantially reduced the proportion of patients who discontinued NOAC therapy: 13.5% for apixaban, 28.1% for dabigatran and 17.9% for rivaroxaban.

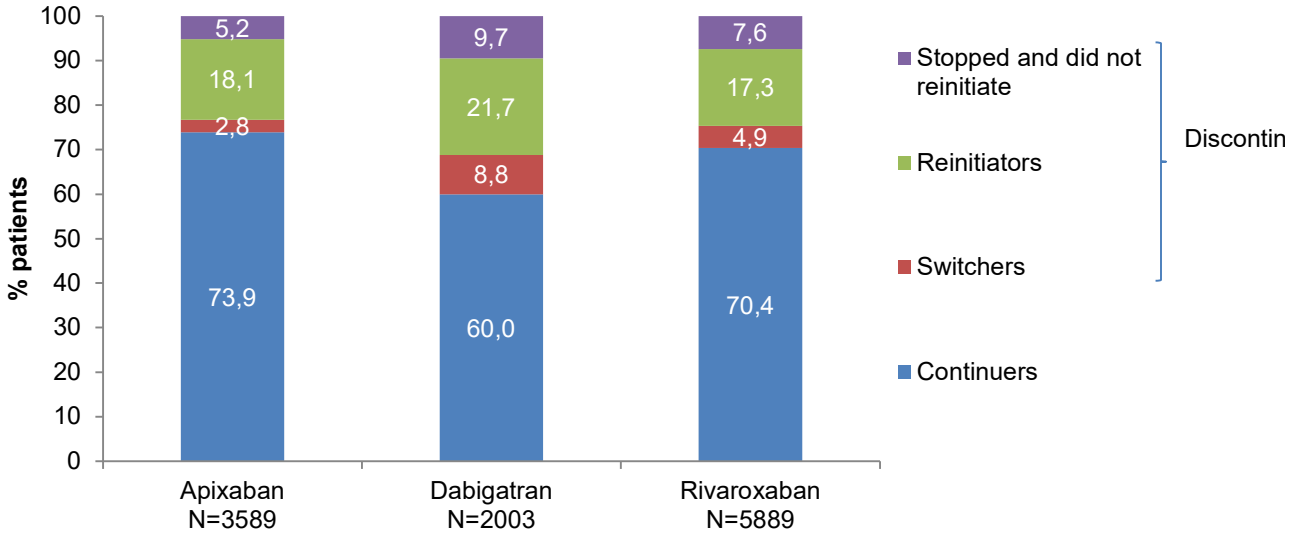

Figure 5. Patterns of NOAC use among new users of NOAC with NVAF (with >1 year of follow-up).

Table 41. Baseline characteristics of the three NOAC study cohorts (discontinuation analysis).

	Apixaban N=3589	Dabigatran N=2003	Rivaroxaban N=5889	Total N=11,481
Sex				
Male	1931 (53.8)	1187 (59.3)	3280 (55.7)	6398 (55.7)
Female	1658 (46.2)	816 (40.7)	2609 (44.3)	5083 (44.3)
Age (years)				
<60	332 (9.2)	239 (11.9)	541 (9.2)	1112 (9.7)
60–69	776 (21.6)	459 (22.9)	1249 (21.2)	2484 (21.6)
70–79	1201 (33.5)	713 (35.6)	2098 (35.6)	4012 (34.9)
≥80	1280 (35.7)	592 (29.6)	2001 (34.0)	3873 (33.7)
Mean age (SD)	74.2 (10.7)	72.9 (10.7)	71.7 (14.4)	74.0 (10.6)
OAC naïve status				
Naïve	1973 (55.0)	881 (44.0)	2826 (48.0)	5680 (49.5)
Non-naïve	1616 (45.0)	1122 (56.0)	3063 (52.0)	5801 (50.5)
Year of first NOAC prescription				
2011	0 (0.0)	40 (2.0)	2 (0.0)	42 (0.4)
2012	0 (0.0)	444 (22.2)	196 (3.3)	640 (5.6)
2013	186 (5.2)	704 (35.1)	984 (16.7)	1874 (16.3)
2014	1171 (32.6)	494 (24.7)	1823 (31.0)	3488 (30.4)
2015	2197 (61.2)	318 (15.9)	2845 (48.3)	5360 (46.7)
2016	35 (1.0)	3 (0.1)	39 (0.7)	77 (0.7)
BMI (kg/m^2)				
10–19	124 (3.5)	62 (3.1)	216 (3.7)	402 (3.5)
20–24	810 (22.6)	435 (21.7)	1298 (22.0)	2543 (22.1)
25–29	1276 (35.6)	737 (36.8)	2078 (35.3)	4091 (35.6)
≥30	1248 (34.8)	697 (34.8)	2090 (35.5)	4035 (35.1)
Unknown	131 (3.7)	72 (3.6)	207 (3.5)	410 (3.6)
Smoking				
Non-smoker	1519 (42.3)	844 (42.1)	2399 (40.7)	4762 (41.5)
Smoker	286 (8.0)	147 (7.3)	484 (8.2)	917 (8.0)
Ex-smoker	1783 (49.7)	1010 (50.4)	3003 (51.0)	5796 (50.5)
Unknown	1 (0.0)	2 (0.1)	3 (0.1)	6 (0.1)
Alcohol (units/week)				
None	851 (23.7)	330 (16.5)	1178 (20.0)	2359 (20.5)
1–9	1544 (43.0)	894 (44.6)	2677 (45.5)	5115 (44.6)
10–20	578 (16.1)	354 (17.7)	936 (15.9)	1868 (16.3)
21–41	195 (5.4)	160 (8.0)	367 (6.2)	722 (6.3)
≥42	83 (2.3)	67 (3.3)	160 (2.7)	310 (2.7)
Unknown	338 (9.4)	198 (9.9)	571 (9.7)	1107 (9.6)
Frailty index				
Fit	547 (15.2)	346 (17.3)	922 (15.7)	1815 (15.8)
Mild frailty	1338 (37.3)	771 (38.5)	2181 (37.0)	4290 (37.4)
Moderate frailty	1097 (30.6)	576 (28.8)	1810 (30.7)	3483 (30.3)

	Apixaban N=3589	Dabigatran N=2003	Rivaroxaban N=5889	Total N=11,481
Severe frailty	607 (16.9)	310 (15.5)	976 (16.6)	1893 (16.5)
eGFR, ml/min/1.73m^2				
>50	2488 (69.3)	1524 (76.1)	4260 (72.3)	8272 (75.1)
30–50	553 (15.4)	241 (12.0)	826 (14.0)	1620 (14.1)
<30	75 (2.1)	11(0.6)	84 (1.4)	170 (1.5)
Unknown	473 (13.2)	227 (11.3)	719 (12.2)	1419 (12.4)
Cardiovascular disease / bleeding risk score				
CHA_2DS_2-VASc, mean (SD)	3.6 (1.8)	3.4 (1.9)	3.6 (1.8)	3.5 (1.8)
HAS-BLED, mean (SD)	1.8 (1.0)	1.7 (1.0)	1.7 (1.0)	1.7 (1.0)

Data are n (%) unless otherwise specified.

Table 42. Pattern of NOAC use among discontinuers (gap of >30 days after the end of supply) of the index NOAC during the first year of use among patients with NVAF.

	Apixaban N=3589	Dabigatran N=2003	Rivaroxaban N=5889	Total N=11,481
Switched within 30 days of the index date	100 (2.8)	176 (8.8)	289 (4.9)	565 (4.9)
Switched to a different NOAC	53 (1.5)	113 (5.6)	165 (2.8)	331 (2.9)
Switched to a VKA	47 (1.3)	63 (3.1)	124 (2.1)	234 (2.0)
Reinitiated* OAC therapy	651 (18.1)	434 (21.7)	1021 (17.3)	2106 (18.3)
Reinitiated with the index NOAC	636 (17.7)	403 (20.1)	970 (16.5)	2009 (17.5)
Reinitiated with a different NOAC	8 (0.2)	14 (0.7)	21 (0.4)	43 (0.4)
Reinitiated with a VKA	7 (0.2)	17 (0.8)	30 (0.5)	54 (0.5)
Stopped and did not reinitiate OAC therapy	186 (5.2)	192 (9.6)	435 (7.4)	813 (7.1)
Total discontinuers	**937 (26.1)**	**802 (40.0)**	**1745 (29.6)**	**3484 (30.3)**

Data are n (%).

*Re-started OAC therapy after a gap of >30 days between the end of the last prescription for the index NOAC and the next prescription for an OAC.

Table 43. Sensitivity analysis: pattern of NOAC discontinuation (gap of >60 days after the end of supply) of the index NOAC during the first year of use among patients with NVAF.

	Apixaban N=3589	Dabigatran N=2003	Rivaroxaban N=5889	Total N=11,481
Switched within 60 days of the index date	104 (2.9)	201 (10.0)	327 (5.6)	632 (5.5)
Switched to a different NOAC	59 (1.6)	127 (6.3)	182 (3.1)	368 (3.2)
Switched to a VKA	45 (1.3)	74 (3.7)	145 (2.5)	264 (2.3)
Reinitiated* OAC therapy	189 (5.3)	153 (7.6)	323 (5.4)	665 (5.8)
Reinitiated with the index NOAC	178 (5.0)	133 (6.6)	296 (5.0)	607 (5.3)
Reinitiated with a different NOAC	6 (0.2)	13 (0.7)	12 (0.2)	31 (0.3)
Reinitiated with a VKA	5 (0.1)	7 (0.4)	15 (0.3)	27 (0.2)
Stopped and did not reinitiate OAC therapy	191 (5.3)	208 (10.5)	407 (6.9)	806 (7.0)
Total discontinuers	**484 (13.5)**	**562 (28.1)**	**1057 (17.9)**	**2103 (18.3)**

Data are n (%).

*Re-started OAC therapy after a gap of >60 days between the end of the last prescription for the index NOAC and the next prescription for an OAC.

10.4.6.3 Time to discontinuation/reinitiation

As shown in **Table 44**, among patients who discontinued treatment with their index NOAC, the mean time to discontinuation was 4.7 months (SD 3.0), and ranged from 1 days to just under a year, with minimal differences between NOAC cohorts. Patients who discontinued their index NOAC and did not later reinitiate with any OAC therapy had a slightly longer time to discontinuation (mean 5.5

months) than those who discontinued due to a switch in treatment (4.6 months) or who discontinued but later reinitiated OAC therapy (either on same NOAC, a different NOAC or a VKA; mean 4.6 years).

Table 44. Time to discontinuation of NOAC therapy among NVAF patients who discontinued their initial NOAC prescribed.

	Time to discontinuation* (months)		
	N	**Mean (months; SD)**	**Range (days, min–max)**
Apixaban	937	4.7 (3.0)	3–356
Dabigatran	802	4.5 (3.0)	2–361
Rivaroxaban	1745	4.9 (3.1)	1–363
Any NOAC: switchers	565	4.0 (3.0)	1–363
Any NOAC: discontinued and reinitiated†	2106	4.6 (2.9)	5–334
Any NOAC: stopped and did not restart any OAC therapy	813	5.5 (3.2)	10–334
Total (all NOACs)	**3484**	4.7 (3.0)	**1–363**

*Among patients who discontinued treatment with their index NOAC – had a break in treatment of >30 days between consecutive index NOAC prescriptions (i.e. between the end of supply of an index NOAC prescription and the date of the subsequent index NOAC prescription), or if they switched to another NOAC or a VKA during the treatment period with the index NOAC or within 30 days after the end of supply of the index NOAC prescription.
†Reinitiated with either the same NOAC, a different NOAC, or with a VKA.

Among patients who discontinued but later reinitiated OAC therapy, no difference was seen in the time to reinitiation of OAC therapy between NOAC cohorts (1.9 months for apixaban, 2.1 months for dabigatran and 2.0 months for rivaroxaban (**Table 45**).

Table 45. Time to reinitiation of OAC therapy among NVAF patients who reinitiated OAC therapy after a gap of >30 days from treatment with the initial NOAC prescribed.

	Time to reinitiation*		
	N	**Mean (months, SD)**	**Range (days, min–max)**
Apixaban	651	1.9 (1.3)	31–294
Dabigatran	434	2.1 (1.6)	31–329
Rivaroxaban	1021	2.0 (1.4)	31–322
Total (all NOACs)	**2106**	2.0 (1.4)	**31–329**

*Among patients who stopped their initial NOAC treatment and restarted with either the same or different OAC therapy (after a gap of >30 days between the end of the last prescription for the index NOAC and the next prescription for an OAC) within the first year of therapy.

10.4.6.4 Predictors of discontinuing therapy with the index NOAC during the first year of treatment

Associations between patient characteristics and discontinuation of NOAC therapy in the first year of treatment are shown in **Table 46**. Factors associated with a reduced likelihood of discontinuing NOAC therapy were being female, older age and having more comorbid conditions (renal impairment, being frail, higher CHA_2DS_2-VASc score, higher HAS-BLED score), whereas higher alcohol consumption as associated with an increased likelihood of discontinuation. Compared with patients starting NOAC therapy on apixaban, those starting therapy on dabigatran were almost twice as likely to discontinue their treatment during the first year (OR 1.89, 95% CI: 1.68–2.12), while there was no evidence that patients starting on rivaroxaban were either more or less likely to discontinue their anticoagulation treatment.

Associations between patient characteristics and different types of discontinuation among discontinuers of NOAC therapy in the first year of treatment are shown in **Table 47**. After controlling for differences in patients characteristics between NOAC cohorts, patients aged ≥60 years had an increased likelihood of discontinuing therapy than younger patients – this was observed for each three subtypes of discontinuers. Both discontinuers that reinitiated OAC therapy and those that did not reinitiate OAC therapy were more frequent in 2011–2013 than in 2014–2016. The opposite finding was seen for switching – higher in later years – coinciding with greater familiarity with NOAC therapy. Reduced renal function was found to be associated with an increased likelihood of discontinuation for all subtypes of discontinuers. Compared with patients starting on apixaban, those starting on dabigatran were twice as likely to completely discontinue OAC therapy (no reinitiation with any OAC therapy) while those starting on rivaroxaban had a small increased likelihood of discontinuing OAC therapy with no re-initiation.

Table 46. Baseline characteristics of the three NOAC study cohorts (discontinuation analysis).

	Continuers N=7997	Discontinuers N=3484	Crude OR (95% CI)	Adjusted OR* (95% CI)
Sex				
Male	4372 (54.7)	2026 (58.2)	1.0 (reference)	1.0 (reference)
Female	3625 (45.3)	1458 (41.8)	0.87 (0.80–0.94)	0.95 (0.87–1.04)
Age (years)				
<60	631 (7.9)	481 (13.8)	1.0 (reference)	1.0 (reference)
60–69	1737 (21.7)	747 (21.4)	0.56 (0.49–0.65)	0.61 (0.53–0.72)
70–79	2871 (35.9)	1141 (32.7)	0.52 (0.45–0.60)	0.59 (0.50–0.70)
≥80	2758 (34.5)	1115 (32.0)	0.53 (0.46–0.61)	0.58 (0.48–0.69)
Mean (SD)	74.5 (10)	72.8 (11.8)		
Index NOAC				
Apixaban	2652 (33.2)	937 (26.9)	1.0 (reference)	1.0 (reference)
Dabigatran	1201 (15.0)	802 (23.0)	1.89 (1.68–2.12)	1.81 (1.59–2.07)
Rivaroxaban	4144 (51.8)	1745 (50.1)	1.19 (1.09–1.31)	1.18 (1.08–1.30)
OAC naïve status				
Naïve	3990 (49.9)	1690 (48.5)	1.0 (reference)	1.0 (reference)
Non-naïve	4007 (50.1)	1794 (51.5)	1.06 (0.98–1.14)	1.02 (0.93–1.11)
Year of first NOAC prescription				
2011–2013	1661 (20.8)	895 (25.7)	1.0 (reference)	1.0 (reference)
2014–2016	6336 (79.2)	2589 (74.3)	0.76 (0.69–0.83)	0.93 (0.83–1.03)
BMI, kg/m^2				
<20	277 (3.5)	125 (3.6)	1.0 (0.79–1.25)	1.03 (0.82–1.30)
20–24	1750 (21.9)	793 (22.8)	1.0 (reference)	1.0 (reference)
25–29	2826 (35.3)	1265 (36.3)	0.99 (0.89–1.10)	0.95 (0.85–1.06)
≥30	2875 (36.0)	1160 (33.3)	0.89 (0.80–0.99)	0.83 (0.74–0.93)
Missing	269 (3.4)	141 (4.0)	1.16 (0.93–1.44)	1.05 (0.83–1.33)
Smoking				
Non-smoker	3303 (41.3)	1459 (41.9)	1.0 (reference)	1.0 (reference)
Smoker	631 (7.9)	286 (8.2)	1.03 (0.88–1.20)	0.90 (0.77–1.06)
Ex-smoker	4060 (50.8)	1736 (49.8)	0.97 (0.89–1.05)	0.98 (0.90–1.07)
Unknown	3 (0.0)	3 (0.1)	2.26 (0.46–11.2)	1.92 (0.36–10.12)
Alcohol (units/week)				
None	1693 (21.2)	666 (19.1)	1.0 (reference)	1.0 (reference)
1–9	3604 (45.1)	1511 (43.4)	1.07 (0.96–1.19)	1.01 (0.90–1.13)
10–20	1268 (15.9)	600 (17.2)	1.20 (1.05–1.37)	1.09 (0.95–1.26)
21–41	479 (6.0)	243 (7.0)	1.29 (1.08–1.54)	1.14 (0.94–1.38)
≥42	186 (2.3)	124 (3.6)	1.69 (1.33–2.16)	1.55 (1.19–2.01)
Unknown	767 (9.6)	340 (9.8)	1.13 (0.96–1.32)	1.01 (0.85–1.19)
Frailty index				
Fit	1148 (14.4)	667 (19.1)	1.0 (reference)	1.0 (reference)
Mild frailty	3099 (38.8)	1191 (34.2)	0.66 (0.59–0.74)	0.81 (0.71–0.92)
Moderate frailty	2435 (30.4)	1048 (30.1)	0.74 (0.66–0.84)	1.02 (0.88–1.18)
Severe frailty	1315 (16.4)	578 (16.6)	0.76 (0.66–0.87)	1.08 (0.91–1.29)

	Continuers N=7997	Discontinuers N=3484	Crude OR (95% CI)	Adjusted OR* (95% CI)
eGFR, ml/min/1.73m²				
>50	5857 (73.2)	(69.3)	1.0 (reference)	1.0 (reference)
30–50	1128 (14.1)		1.06 (0.94–1.19)	1.18 (1.05–1.34)
<30	106 (1.3)	64 (1.8)	1.46 (1.07–2.00)	1.77 (1.28–2.44)
Missing	906 (11.3)	513 (14.7)	1.37 (1.22–1.55)	1.30 (1.15–1.47)
CHA_2DS_2-VASc score				
2	2188 (27.4)	1185 (34.0)	1.0 (reference)	1.0 (reference)
3	1742 (21.8)	693 (19.9)	0.73 (0.66–0.82)	0.88 (0.77–1.00)
4	4067 (50.9)	1606 (46.1)	0.73 (0.67–0.80)	0.86 (0.75–0.98)
Mean (SD)	3.6 (1.8)	3.4 (1.9)		
HAS-BLED score				
0	3229	1570 (45.1)	11.0 (reference)	1.0 (reference)
2	3084 (38.7)	1262 (36.2)	0.84 (0.77–0.92)	0.94 (0.85–1.04)
3	1684 (21.1)	652 (18.7)	0.80 (0.71–0.89)	0.88 (0.78–1.00)
Mean (SD)	1.8 (1.0)	1.7 (1.0)		

Data are n (%) unless otherwise specified.

*Adjusted for all the other variables in the table.

Table 47. Association between baseline characteristics of patients with NVAF (new users of a NOAC) and risk of discontinuation according to type of discontinuation.

	OR (95% CI)		
	Continuers vs. discontinuers who re-initiated OAC therapy N=2106	**Continuers vs. discontinuers who switched OAC therapy N=565**	**Continuers vs. discontinuers who did not re-initiate OAC therapy N=813**
Sex			
Male	1.0 (reference)	1.0 (reference)	1.0 (reference)
Female	0.89 (0.79–0.99)	1.25 (1.03–1.53)	0.90 (0.76–1.07)
Age (years)			
<60			
60–69	0.74 (0.62–0.90)	0.95 (0.66–1.37)	0.33 (0.26–0.43)
70–79	0.74 (0.61–0.90)	0.93 (0.63–1.36)	0.27 (0.21–0.36)
≥80	0.72 (0.58–0.89)	0.68 (0.45–1.03)	0.35 (0.26–0.48)
Index NOAC			
Apixaban	1.0 (reference)	1.0 (reference)	1.0 (reference)
Dabigatran	1.36 (1.16–1.60)	4.28 (3.24–5.65)	2.19 (1.72–2.79)
Rivaroxaban	0.98 (0.87–1.09)	1.89 (1.49–2.39)	1.52 (1.26–1.83)
Year of first NOAC prescription	1.0 (reference)		
2011–2013	1.0 (reference)	1.0 (reference)	1.0 (reference)
2014–2016	0.90 (0.79–1.02)	1.21 (0.97–1.50)	0.82 (0.68–0.99)
eGFR, ml/min/1.73m^2			
>50	1.0 (reference)	1.0 (reference)	1.0 (reference)
30–50	1.08 (0.93–1.26)	1.23 (0.95–1.59)	1.53 (1.22–1.91)
<30	1.51 (1.01–2.25)	2.21 (1.20–4.08)	2.25 (1.30–3.87)
Missing	1.31 (1.13–1.51)	1.28 (0.98–1.67)	1.30 (1.05–1.62)
OAC naïve status			
Naïve	1.0 (reference)	1.0 (reference)	1.0 (reference)
Non-naïve	1.08 (0.97–1.19)	1.25 (1.04–1.50)	0.74 (0.64–0.87)
BMI (kg/m^2)			
<20	0.98 (0.74–1.31)	0.85 (0.50–1.44)	1.26 (0.86–1.85)
20–24	1.0 (reference)	1.0 (reference)	1.0 (reference)
25–29	0.94 (0.82–1.07)	1.01 (0.80–1.28)	0.90 (0.74–1.09)
≥30	0.89 (0.77–1.02)	0.78 (0.61–1.00)	0.67 (0.54–0.83)
Missing	0.94 (0.70–1.25)	0.99 (0.58–1.69)	1.37(0.94–2.01)

Smoking			
Non-smoker	1.0 (reference)	1.0 (reference)	1.0 (reference)
Smoker	0.99 (0.82–1.19)	0.64 (0.43–0.96)	0.83 (0.62–1.10)
Ex-smoker	0.96 (0.86–1.07)	1.08 (0.90–1.30)	0.95 (0.81–1.12)
Unknown	2.47 (0.40–15.21)	–	1.42 (0.11–18.04)
Alcohol (units/week)			
None	1.0 (reference)	1.0 (reference)	1.0 (reference)
1–9	1.03 (0.90–1.18)	1.13 (0.89–1.43)	0.87 (0.71–1.06)
10–20	1.13 (0.95–1.33)	0.92 (0.67–1.26)	1.11 (0.86–1.43)
21–41	1.19 (0.95–1.49)	1.32 (0.89–1.96)	0.85 (0.59–1.22)
≥42	1.75 (1.30–2.35)	1.10 (0.58–2.08)	1.24 (0.77–1.99)
Unknown	1.12 (0.92–1.36)	0.93 (0.65–1.34)	0.77 (0.57–1.05)
Frailty index			
Fit	1.0 (reference)	1.0 (reference)	1.0 (reference)
Mild frailty	0.87 (0.75–1.01)	0.91 (0.68–1.21)	0.63 (0.51–0.78)
Moderate frailty	1.05 (0.88–1.25)	1.24 (0.90–1.70)	0.85 (0.66–1.11)
Severe frailty	1.01 (0.82–1.24)	1.27 (0.88–1.85)	1.18 (0.87–1.60)
CHA_2DS_2-VASc score			
2	1.0 (reference)	1.0 (reference)	1.0 (reference)
3	0.91 (0.78–1.05)	1.02 (0.77–1.35)	0.69 (0.54–0.89)
4	0.85 (0.73–1.00)	1.03 (0.77–1.38)	0.80 (0.61–1.04)
HAS–BLED score			
0	1.0 (reference)	1.0 (reference)	1.0 (reference)
2	0.99 (0.88–1.11)	0.85 (0.69–1.04)	0.88 (0.73–1.07)
3	0.94 (0.81–1.09)	0.79 (0.61–1.04)	0.79 (0.62–1.01)

*Adjusted for all the other variables in the table.

10.4.7 Time trends in first-time users of NOAC (secondary objective results)

The cumulative incidence per 1000 patients of new users of apixaban, dabigatran and rivaroxaban among the eligible source population in THIN is shown in **Figure 6** by study year (2011–2016) and stratified by age and sex for the whole study period (2001–2016) in **Figure 7**. The graphs illustrate the increase in use of both apixaban and rivaroxaban over study years. The incidence of apixaban use for SPAF increased from 0.09 per 1000 persons in 2013 to 1.93 per 1000 persons in 2016 where it became the most commonly prescribed NOAC for this indication. The incidence of rivaroxaban for SPAF increased from 0.52 per 1000 persons in 2013 to 1.82 per 1000 persons in 2016 (just slightly lower than apixaban). The incidence of dabigatran fell from 0.39 per 1000 persons in 2013 to 0.18 in 2016. Incidence rates among males were higher than those among females for the same NOAC across all age groups and study years.

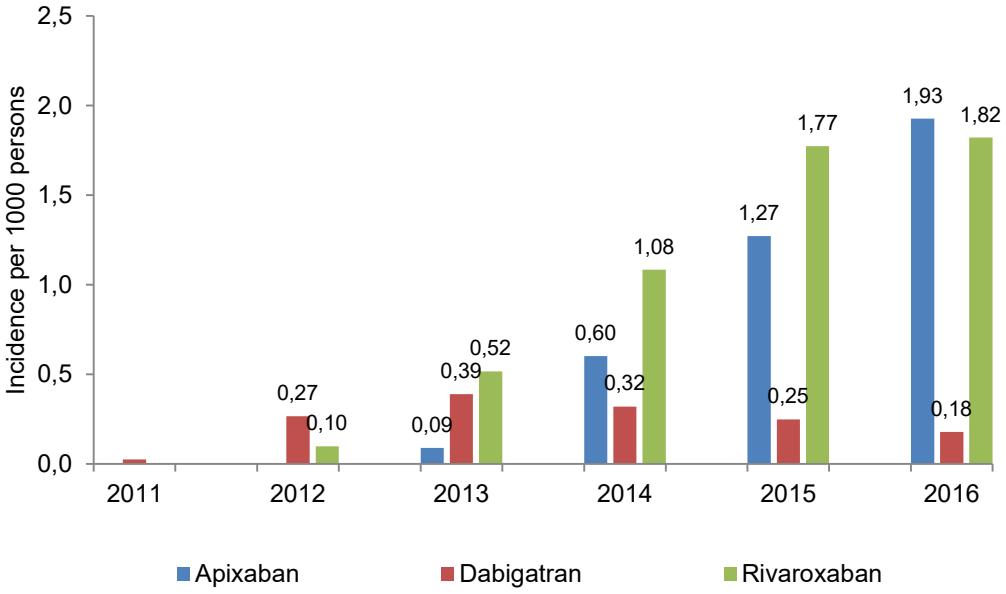

Figure 6. Incidence per 1000 patients of patients with NVAF newly prescribed a NOAC by study year (2011–2016).

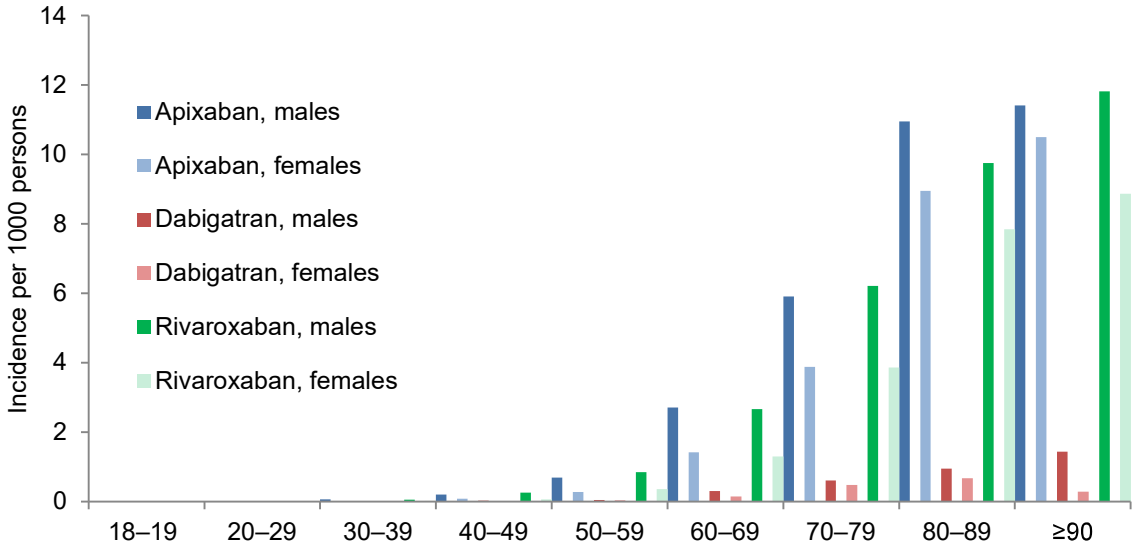

Figure 7. Cumulative incidence of patients with NVAF newly prescribed a NOAC in 2016 by age group and sex.

10.5 Other analyses

A sensitivity analysis was performed in which the definition of discontinuation was changed to require a treatment gap of 60 days between the end of a prescription and the start of the next, if any (allowing for greater non-adherence), to assess the effect this had on study outcomes.

10.6 Safety data (Adverse events/adverse reactions)

As per the EMA Guideline on Good Pharmacovigilance Practices (Module VI–Management and reporting of adverse reactions to medicinal products), for non-interventional study designs that are based on secondary use of data, individual reporting of adverse reactions is not required. No expedited reporting of adverse events or reactions is required.

11. Discussion

11.1 Key results

11.1.1 Patient characteristics and comparison with clinical trial populations

A total of 30,467 patients with NVAF starting OAC therapy on a NOAC: 15,252 (50.1%) patients started NOAC therapy on rivaroxaban, 10,834 (35.6%) on apixaban and 4381 (14.4%) on dabigatran. The majority of patients prescribed a reduced dose were aged 70 years or older (apixaban 93.6%, dabigatran 88.4%, rivaroxaban 91.4%), and were moderately or severely frail (apixaban, 70.2%, dabigatran 61.7%, rivaroxaban 74.0%)

Most patients in each cohort were male (apixaban 53.2%, dabigatran 57.6%, rivaroxaban 54.9%) yet the male-to-female ratio was more balanced than that among participants in the pivotal phase 3 NOAC trials for the SPAF indication, in which approximately two-thirds of patients were male: 64.5% of the apixaban arm in ARISTOTLE, (15) 64.3 years and 63.2 years in the 110 mg and 150 mg dabigatran arms, respectively in RE-LY, (16) and 60.3% in the rivaroxaban arm of ROCKET-AF. (17) Patients in this current study were slightly older than participants in the NOAC AF clinical trials; apixaban mean 75 years vs. median 70 years in ARISTOTLE, dabigatran mean 74 years vs. median 71 years in RE-LY, and rivaroxaban mean 75 years vs. median 73 in ROCKET-AF. Most patients in the apixaban cohort were OAC naïve (53% vs. 43% in ARISTOTLE), while less than half of patients in the dabigatran and rivaroxaban cohorts were OAC naïve (dabigatran 42% vs. 50% in RE-LY; rivaroxaban 47% vs. 38% in ROCKET-AF).

The most commonly comorbidity at the index date was hypertension, which was recorded in about two-thirds of patients in each NOAC cohort, and which is less than that seen among participants in ARISTOTLE (87%), RE-LY (79%) and ROCKET-AF (90%). Heart failure was notably less prevalent (approximately 17% in each cohort) than patients in the clinical trials (36% in ARISTOTLE, 32% in RE-LY and 63% in ROCKET-AF). Approximately a third of patients in each cohort were obese, while a little under a third each had IHD and hyperlipidaemia. Most patients had normal renal function (apixaban 67.3%, dabigatran 74.4%, rivaroxaban 70.1%), a medium risk of bleeding (HAS-BLED score of 1–3) and a high mean CHA_2DS_2-VASc score (comorbidity index) of between 3.5 and 3.7.

In terms of $CHADS_2$ score, the majority of patient in each cohort (approx. two-thirds) had a score of between 0 and 2, which is in line with the $CHADS_2$ scores of participants in the ARISTOTLE (69.8% with a score of 1 or 2) and RE-LY trials (~ 67% with scores of 0–2 across the two dabigatran arms). In ROCKET-AF, however, only 13% of the rivaroxaban arm had a $CHADS_2$ score of 2, while 72.2% had a score of 3 or 4, and 14.8% had a score of 5 or 6. This suggests that the population enrolled in ROCKET-AF had a higher risk of stroke at baseline compared with the other two pivotal NOAC trials and the study population in this current observational study. As expected from patients' comorbidity profile, the most frequently prescribed comedications were antihypertensives, statins, PPIs, antiplatelets and diuretics.

Irrespective of the index NOAC, the percentage of patients who were OAC naïve increased over the study years (comparing 2016 with 2011–2013). This was most evident among the dabigatran cohort (OR 1.48, 95% CI: 1.21–1.82) and rivaroxaban cohort (OR 1.70, 95% CI: 1.53–1.90). While there was an increase in the percentage of patients aged ≥80 years, the opposite was seen for rivaroxaban.

11.1.2 Dosing appropriateness

Among patients starting NOAC therapy on rivaroxaban, 17.3% were eligible to receive a reduced dose compared with 12.8% of patients starting on apixaban and 53.8% of patients starting on dabigatran. The majority of patients were prescribed an appropriate dose according to the EU labels: apixaban 74.9 %, dabigatran 74.4%, rivaroxaban 84.2%. There was a trend towards dose reduction with increasing renal impairment. Among patients with severe renal impairment, the majority received a reduced dose NOAC: apixaban 91.1%, dabigatran 80.0%, rivaroxaban 83.0%.

Potential underdosing

Underdosing occurred in 21.6% of patients starting NOAC therapy on apixaban compared with 8.7% starting on dabigatran and 9.1% starting on rivaroxaban. Potential underdosing of NOACs has been reported in moderate-to-large studies from the US, (18) as well as in smaller studies from Europe and North America.(16,17,35) Using data from 7925 patients with AF in the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation II (ORBIT-AF II) registry, Steinberg *et al*, (18) found that 57% (734/1289) of patients prescribed a reduced dose NOAC did not fulfill the Food and Drug Administration's (FDAs) recommended criteria for dose reduction. A larger administrative claims database study of 14,865 patients with AF initiating NOAC treatment reported a much lower level of underdosing with 13.3% (1781/13,392) of patients with no renal indication for dose reduction receiving a reduced dose;(19) although other criteria for dose reduction were not assessed. Studies from Europe have been small but also suggest that underdosing may be more prevalent for apixaban than rivaroxaban. In Germany, Bucholtz *et al* (20) found that among 268 patients with NVAF starting reduced dose apixaban therapy in 2016, 60.8% did not meet labelling criteria for dose reduction, while in a study of 899 patients with NVAF starting rivaroxaban therapy in the Netherlands, Pisters *et al* (21) reported that 3.1% received a label-discordant dose. In the study by Bucholtz *et al* (20) there were 163 apixaban patients who received a reduced dose despite being eligible for the higher dose, and among these a substantial percentage met either only one (57.1%) or no (42.9%) dose-reduction criteria, with these patients more often having ages, weights and serum creatinine levels close to the cut-off values compared with patients prescribed an appropriate dose. In our current observational study, the majority of patients (73.1%) who were inappropriately prescribed a reduced dose of apixaban met only one dose reduction criteria. The strongest predictor of in inappropriate underdosing in both the apixaban and rivaroxaban cohort was older age; frailty was also a notable predictor.

Potential overdosing

In this current study, potential overdosing was more frequent for dabigatran (16.9%) than for rivaroxaban (6.6%) or apixaban (3.5%). In the US, Yao *et al* (19) reported that 43% of patients with a renal indication for NOAC dose reduction did not receive a reduced dose, while Steinberg *et al* (18) found that 32% of NVAF patients eligible for dose reduction according to the FDA approved drug labels received a standard dose NOAC. This is similar to the level of potential rivaroxaban overdosing among patients eligible for a reduced dose in our study (36.1%).

11.1.3 Discontinuation of NOACs

In the discontinuation analysis (N=11,481), one-year discontinuation rates were: apixaban 26.1%, dabigatran 40.0%, rivaroxaban 29.6%. One-year re-initiation rates were: apixaban 18.1%, dabigatran 21.7%, rivaroxaban 17.3%; (≥93% of re-initiations were with the index NOAC). Switching rates were: apixaban 2.8%, dabigatran 8.8%, rivaroxaban 4.9%; discontinuation with no reinitiation was: apixaban 5.2%, dabigatran 9.6%, rivaroxaban 7.4%. Compared with patients starting on apixaban, ORs (% CIs) for discontinuation due to switching were 4.28 (95% CI: 3.24–5.65) for dabigatran and 1.89 (95% CI: 1.49–2.39) for rivaroxaban. Severely reduced renal function was a predictor of any discontinuation, OR 1.77 (95% CI: 1.28–2.44). Only 7% of NVAF patients in our study permanently discontinued OAC therapy (i.e. discontinued their index NOAC and did not reinitiate and type of OAC), which is approximately half the rate seen in Italy (22) and approximately a third of that seen for rivaroxaban in Germany.(23)

In a study of among 2871 NVAF patients, Johnson *et al* (24) reported broadly similar, albeit slightly higher, 1-year NOAC discontinuation rates to those found in our study using a 60-day treatment gap, with rates highest for dabigatran (33.3%) followed by rivaroxaban (26.9%) and apixaban (17.2%). A smaller study by Martinez *et al*,(25) reported much lower NOAC discontinuation rates to ours (17% at 1 year) with apixaban unable to be assessed due to short duration of available follow-up. Studies from other European countries have reported either highly comparable (26), notably higher (27) or lower (23, 28) 1-year NOAC discontinuation rates based on a 30-day treatment gap (23), 60-day treatment gap (26, 27) or other definition of discontinuation,(28) with differences possibly attributable to differences in study size, design and/or composition of the study population (e.g. the inclusion of OAC-naïve users only). One-year NOAC discontinuation rates among NVAF patient populations reported from claims database studies in the United States have been substantially higher,(29, 30) yet are consistent with a trend of higher discontinuation for dabigatran compared with rivaroxaban or apixaban (24, 26-31) and of rates lowest for apixaban in most,(24, 27-30) albeit not all, (31) studies.

As seen in Sweden,(28) we found that the vast majority of NOAC reinitiators in our study restarted with the index NOAC. Similarly, only a small proportion of patients (<5%) switched to another NOAC or a VKA, with more than half switching to a different NOAC. These findings suggest good

tolerability and confidence in this class of medication in the UK. Comparable NOAC switching rates have been reported in two large US claims database studies,(30, 32) while in another large US administrative database among 34,022 OAC naïve NVAF patients, nearly 20% switched medication.(33) Switching rates among other European NVAF cohorts starting NOAC therapy have been notably higher. In particular, using national healthcare databases in France, Maura *et al*(26) found that 9.8% of patients starting rivaroxaban therapy switched to another OAC class, while in the UK, Martinez *et al* (25) reported a 6.6% NOAC-to-VKA switch rate.

11.2 Limitations

Limitations of this study include:

- Missing data on comorbidities and lifestyle variables among some patients.
- Possibly some missing data if PCPs did not enter the hospitalization data, however, we expect that the vast majority of PCPs would record information on hospitalizations into patients' EHRs.
- Medications prescribed at hospital and those obtained over-the-counter may not have been captured in the database
- Incomplete data concerning medication adherence because drug use was based on prescriptions issued by the PCP and no information was available to confirm if the drug was actually taken by the patient.
- We evaluated the dose of the first NOAC prescription issued in primary care and not subsequent prescriptions; however, the majority of patients had continued on the same dose of the index NOAC 6 months after treatment initiation.
- A small degree of misclassification for renal function and bodyweight may have occurred due to inaccuracies in data recording, which may have affected our findings for a small number of patients.

- Potential overdosing may have been overestimated because patients may have split a prescribed standard dose over more than one day.
- Crude ORs used to compare trends over time were not adjusted for potential differences in baseline patient characteristics between NOACs cohorts leading to the possibility of confounding.

11.3 Interpretation

There are some differences between the profiles of patients with NVAF in this observational study and participants in the three NOAC pivotal phase 3 trials, upon whose data these medications were approved. These differences must be considered when comparing efficacy and safety outcomes between this real-world patient population and those enrolled in clinical trials.

Between 2011 and 2016, the majority of patients with NVAF starting therapy with a NOAC in UK primary care were prescribed an appropriate daily dose based on the approved EU label, according to the information recorded in THIN and CPRD-GOLD. However, some patients were underdosed, in particular those starting therapy on apixaban (21.6% underdosed). Inappropriate underdosing of NOACs has concerning clinical implications because patients may not receive the benefits of the recommended NOAC dose in protecting against stroke and systemic embolism. Data from the ORBIT-II registry suggest that patients receiving an inappropriately reduced NOAC dose have less favourable outcomes in terms of thromboembolic events and death. (18) Yao *et al* (19) found that among apixaban-treated patients with no renal justification for dose reduction, those receiving the reduced dose had a significantly higher risk of stroke with no significant change in the risk of bleeding when compared with those receiving the standard dose.

Reasons why PCPs prescribe reduced NOAC doses to patients with no justification for dose reduction are unclear, although some PCPs may be exercising caution among patients of advanced age and/or those that are frail, and in turn this could suggest that NOAC-related bleeding may be more concerning to physicians than reduced stroke prophylaxis. This study also showed some evidence of potential overdosing of NOACs is potentially concerning because studies have shown this can increase bleeding risk.(19)

Although the majority of NVAF patients in the UK initiating NOAC treatment received continuous therapy in the first year of treatment, yet a substantial proportion of patients experience gaps in treatment leaving them less protected against thromboembolism. Observational data suggest that interruption of warfarin treatment in patients with AF is associated with an increased risk of thromboembolism, (34) as is poor adherence to NOACs.(35, 36) The low switching rates, however, along with high NOAC reinitiation rates (mostly with the same NOAC) seen in this study is likely a reflection of the growing confidence of both physicians and patients about long-term use of NOACs.

11.4 Generalizability

The individuals in this study are representative of the UK as a whole in terms of gender and age distribution. The nature of the data source make selection bias unlikely, and overall the results of this study are likely to reflect routine clinical practice in the UK.

12. Other information

Not applicable.

13. Conclusion

Our findings highlight the importance of monitoring the prescribing of NOACs in the post-marketing period. Further research is warranted into reasons for inappropriate prescribing of reduced and standard dose NOACs in UK primary care, the impact this has on risks of clinical outcomes, including stroke, systemic embolism and major bleeding in this setting, and ways to improve levels of correct dosing to ensure patients receive maximum benefit from treatment. Efforts are needed to increase NOAC continuation rates in order to increase the number of NVAF patients benefitting from NOAC-mediated stroke protection, and well-designed large cohort studies are warranted to quantify the impact of interrupting NOAC therapy on thromboembolism risk. Our findings also underscore the importance of considering differences in characteristics when comparing outcomes between real-world populations prescribed NOACs for SPAF and NOAC-AF clinical trials.

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Appendices

Annex 1. Appendix Tables

Appendix Table 1. Recommended dosing criteria and contraindications for each NOAC (for the prevention of stroke and systemic embolism in patients with NVAF) that were applied in the study.

NOAC	Reduced dosing criteria	Contraindications
Apixaban[*] **standard or normal recommended daily dose = 10 mg**	2.5 mg taken orally twice daily in patients with NVAF and ≥ 2 of the following: • age ≥ 80 years • body weight ≤ 60 kg • serum creatinine ≥ 1.5 mg/dL (133 micromole/L). Or, severe renal impairment (CrCL 15–29 mL/min)	*Note*: In patients with CrCL < 15 ml/min or undergoing dialysis, there is no clinical experience therefore apixaban is not recommended.
Dabigatran[†] **standard or normal recommended daily dose = 300mg**	• age ≥ 80 years • concomitant use of verapamil Reduction for consideration when[§]: • patients between 75–80 years • patients with moderate renal impairment (CrCL 30–50 mL/min • patients with gastritis oesophagitis or gastrooesophagel reflux.	• Severe renal impairment (CrCL < 30ml/min) *Note*: Dabigatran is also not recommended in patients with hepatic impairment or liver disease
Rivaroxaban[‡] **standard or normal recommended daily dose = 20mg**	In patients with moderate/severe renal impairment (CrCL 15–49 ml/min)	• Severe renal impairment (creatinine clearance < 15 ml/min)

Sources from which our modified criteria were obtained.
[*]Eliquis. Summary of Product Characteristics. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002148/WC500107728.pdf. Accessed 7 September 2018.
[†]Pradaxa. Summary of Product Characteristics. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000829/WC500041059.pdf
[‡]Xarelto. Pradaxa. Summary of Product Characteristics. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000944/WC500057108.pdf [§]Patients meeting at least one of these criteria were considered eligible for dose reduction in our study.

Annex 2. Additional information

NOAC drug codes.

Multilex code	BNF-code	Generic Name	ATC	ATC name	BCD	BCD name
53246979	02.08.02.00	Apixaban 5mg tablets	B01A	ANTITHROMBOTIC AGENTS	60396	APIXABAN
53247979	02.08.02.00	Apixaban 5mg tablets	B01A	ANTITHROMBOTIC AGENTS	60396	APIXABAN
81167998	02.08.02.00	Apixaban 2.5mg tablets	B01A F02	APIXABAN	60396	APIXABAN
81168998	02.08.02.00	Apixaban 2.5mg tablets	B01A F02	APIXABAN	60396	APIXABAN
81214998	02.08.02.00	Dabigatran etex150mg cap	B01A E07	DABIGATRAN ETEXILATE	60278	DABIGATRAN
81215998	02.08.02.00	Dabigatran etexilate 150mg caps	B01A E07	DABIGATRAN ETEXILATE	60278	DABIGATRAN
83971998	02.08.02.00	Dabigatran etexilate 110mg caps	B01A E07	DABIGATRAN ETEXILATE	60278	DABIGATRAN
83972998	02.08.02.00	Dabigatran etexilate 75mg caps	B01A E07	DABIGATRAN ETEXILATE	60278	DABIGATRAN
83973998	02.08.02.00	Dabigatran etexilate 75mg caps	B01A E07	DABIGATRAN ETEXILATE	60278	DABIGATRAN
83974998	02.08.02.00	Dabigatran etexilate 110mg caps	B01A E07	DABIGATRAN ETEXILATE	60278	DABIGATRAN
59454978	02.08.02.00	Rivaroxaban 2.5mg tablets	B01A F01	RIVAROXABAN	60320	RIVAROXABAN
60767979	02.08.02.00	Rivaroxaban 20mg tablets	B01A F01	RIVAROXABAN	60320	RIVAROXABAN
60768979	02.08.02.00	Rivaroxaban 20mg tablets	B01A F01	RIVAROXABAN	60320	RIVAROXABAN
60769979	02.08.02.00	Rivaroxaban 15mg tablets	B01A F01	RIVAROXABAN	60320	RIVAROXABAN
60770979	02.08.02.00	Rivaroxaban 15mg tablets	B01A F01	RIVAROXABAN	60320	RIVAROXABAN

80953998	02.08.02.00	Rivaroxaban 20mg tablets	B01A F01	RIVAROXABAN	60320	RIVAROXABAN
80954998	02.08.02.00	Rivaroxaban 20mg tablets	B01A F01	RIVAROXABAN	60320	RIVAROXABAN
80955998	02.08.02.00	Rivaroxaban 15mg tablets	B01A F01	RIVAROXABAN	60320	RIVAROXABAN
80956998	02.08.02.00	Rivaroxaban 15mg tablets	B01A F01	RIVAROXABAN	60320	RIVAROXABAN
83418998	02.08.02.00	Rivaroxaban 10mg tablets	B01A F01	RIVAROXABAN	60320	RIVAROXABAN
83425998	02.08.02.00	Rivaroxaban 10mg tablets	B01A F01	RIVAROXABAN	60320	RIVAROXABAN

READ codes for atrial fibrillation.

READ	Description
3272.00	ECG: ATRIAL FIBRILLATION
3273.00	ECG: ATRIAL FLUTTER
3274.00	ECG: PAROXYSMAL ATRIAL TACHY.
7936A00	IMPLANT INTRAVENOUS PACEMAKER FOR ATRIAL FIBRILLATION
G570.00	PAROXYSMAL SUPRAVENTRICULAR TACHYCARDIA
G570000	PAROXYSMAL ATRIAL TACHYCARDIA
G573.00	ATRIAL FIBRILLATION AND FLUTTER
G573000	ATRIAL FIBRILLATION
G573100	ATRIAL FLUTTER
G573200	PAROXYSMAL ATRIAL FIBRILLATION
G573z00	ATRIAL FIBRILLATION AND FLUTTER NOS
14AN.00	H/O: ATRIAL FIBRILLATION
212R.00	Atrial fibrillation resolved
662S.00	Atrial fibrillation monitoring
6A9..00	Atrial fibrillation annual review
9hF..00	Exception reporting: atrial fibrillation quality indicators
9hF1.00	Excepted from atrial fibrillation qual indic: Inform dissent
9Os..00	Atrial fibrillation monitoring administration
9Os0.00	Atrial fibrillation monitoring first letter
9Os1.00	Atrial fibrillation monitoring second letter
9Os2.00	Atrial fibrillation monitoring third letter
9Os3.00	Atrial fibrillation monitoring verbal invite
9Os4.00	Atrial fibrillation monitoring telephone invite
G573300	Non-rheumatic atrial fibrillation

READ codes for mitral stenosis.

READ	Description
G11..11	Rheumatic mitral valve disease
G110.00	Mitral stenosis
G110.11	Rheumatic mitral stenosis
G112.00	Mitral stenosis with insufficiency
G112.12	Mitral stenosis with incompetence
G112.13	Mitral stenosis with regurgitation
G113.00	Nonrheumatic mitral valve stenosis
G130.00	Mitral and aortic stenosis
G131.00	Mitral stenosis and aortic insufficiency
G131.13	Mitral stenosis and aortic incompetence
G131.14	Mitral stenosis and aortic regurgitation
P65..00	Congenital mitral stenosis
P650.00	Congenital mitral stenosis, unspecified
P651.00	Fused commissure of the mitral valve
P65z.00	Congenital mitral stenosis NOS
P6yyC00	Fusion of mitral valve cusps

READ codes for valvular replacement.

READ	Description
7910.12	Replacement of mitral valve
7910000	Allograft replacement of mitral valve
7910100	Xenograft replacement of mitral valve
7910200	Prosthetic replacement of mitral valve
7910211	Bjork-Shiley prosthetic replacement of mitral valve
7910212	Bjork-Shiley prosthetic replacement of mitral valve
7910213	Carpentier prosthetic replacement of mitral valve
7910214	Edwards prosthetic replacement of mitral valve
7910300	Replacement of mitral valve NEC
7911.12	Replacement of aortic valve
7911000	Allograft replacement of aortic valve
7911100	Xenograft replacement of aortic valve
7911200	Prosthetic replacement of aortic valve
7911300	Replacement of aortic valve NEC
7911500	Transapical aortic valve implantation
7911600	Transluminal aortic valve implantation
7912.11	Replacement of tricuspid valve
7912000	Allograft replacement of tricuspid valve
7912100	Xenograft replacement of tricuspid valve
7912200	Prosthetic replacement of tricuspid valve
7912300	Replacement of tricuspid valve NEC
7913.12	Replacement of pulmonary valve
7913000	Allograft replacement of pulmonary valve
7913100	Xenograft replacement of pulmonary valve
7913200	Prosthetic replacement of pulmonary valve
7913300	Replacement of pulmonary valve NEC
7914.11	Replacement of unspecified valve of heart
7914000	Allograft replacement of valve of heart NEC
7914100	Xenograft replacement of valve of heart NEC
7914200	Prosthetic replacement of valve of heart NEC
7914211	Edwards prosthetic replacement of valve of heart
7914212	Starr prosthetic replacement of valve of heart
7914300	Replacement of valve of heart NEC
7914600	Replacement of truncal valve
7919600	Percutaneous transluminal pulmonary valve replacement
791C000	Aortic root replac us pul val auto ri vent pulm art val cond

791C100	Ao ro repl us pulm val auto ri vent pul art val cond aortov
791C200	Aortic root replacement using homograft
791C300	Aortic root replacement using mechanical prosthesis
791C400	Aortic root replacement
14S4.00	H/O: heart valve recipient
14T3.00	H/O: artificial heart valve
SP00200	Mechanical complication of heart valve prosthesis
SP00400	Infect and inflammatory reaction due to cardiac valve pros
SyuK611	[X] Embolism from prosthetic heart valve
TB01200	Implant of heart valve prosthesis + complication, no blame
ZV42200	[V]Heart valve transplanted
ZV43300	[V]Has artificial heart valve
ZV45H00	[V]Presence of prosthetic heart valve
ZVu6e00	[X]Presence of other heart valve replacement

Read codes for dialysis (renal impairment).

Read	Description
14V2.00	H/O: renal dialysis
14V2.11	H/O: kidney dialysis
4I29.00	Peritoneal dialysis sample
4N3..00	Peritoneal dialysis fluid cell count
4N4..00	Dialysis fluid potassium level
4N5..00	Dialysis fluid sodium level
7A60600	Creation of graft fistula for dialysis
7A61900	Ligation of arteriovenous dialysis fistula
7A61A00	Ligation of arteriovenous dialysis graft
7L1A.11	Dialysis for renal failure
7L1A000	Renal dialysis
7L1A011	Thomas intravascular shunt for dialysis
7L1A100	Peritoneal dialysis
7L1A200	Haemodialysis NEC
7L1A400	Automated peritoneal dialysis
7L1A500	Continuous ambulatory peritoneal dialysis
7L1A600	Peritoneal dialysis NEC
7L1B.11	Placement ambulatory dialysis apparatus - compens renal fail
7L1B000	Insertion of ambulatory peritoneal dialysis catheter
7L1B100	Removal of ambulatory peritoneal dialysis catheter
7L1B200	Flushing of peritoneal dialysis catheter
7L1C000	Insertion of temporary peritoneal dialysis catheter
7L1f000	Extracorporeal albumin haemodialysis
8882.00	Intestinal dialysis
SP05613	[X] Peritoneal dialysis associated peritonitis
SP06B00	Continuous ambulatory peritoneal dialysis associated perit
TA02.00	Accid cut,puncture,perf,h'ge - kidney dialysis/oth perfusion
TA02000	Accid cut,puncture,perf,h'ge - kidney dialysis
TA02011	Accidental cut/puncture/perf/haem'ge during renal dialysis
TA12000	Foreign object left in body during kidney dialysis
TA12011	Foreign object left in body during renal dialysis
TA22000	Failure of sterile precautions during kidney dialysis
TA22011	Failure of sterile precautions during renal dialysis
TA42000	Mechanical failure of apparatus during kidney dialysis
TA42011	Mechanical failure of apparatus during renal dialysis
TB11.00	Kidney dialysis with complication, without blame
TB11.11	Renal dialysis with complication, without blame
U611200	[X]Foreign obj accid left body dur kidney dialys/oth perfus
U612200	[X]Failure sterile precautions dur kidney dialys/other perf

U641.00	[X]Kidny dialysis caus abn reac pt/lat comp no misad at time
Z131500	Warming patient with warm haemodialysis
Z131600	Warming patient with warm peritoneal dialysis
Z1A2.00	Haemodialysis training
Z1A2.11	HD - Haemodialysis training
Z919.00	Care of haemodialysis equipment
Z919100	Priming haemodialysis lines
Z919200	Washing back through haemodialysis lines
Z919300	Reversing haemodialysis lines
Z91A.00	Peritoneal dialysis bag procedure
Z91A100	Putting additive into peritoneal dialysis bag
ZV45100	[V]Renal dialysis status
ZV56.00	[V]Aftercare involving intermittent dialysis
ZV56000	[V]Aftercare involving extracorporeal dialysis
ZV56011	[V]Aftercare involving renal dialysis NOS
ZV56100	[V]Preparatory care for dialysis
ZV56y00	[V]Other specified aftercare involving intermittent dialysis
ZV56y11	[V]Aftercare involving peritoneal dialysis
ZV56z00	[V]Unspecified aftercare involving intermittent dialysis
4N...00	Dialysis fluid examination
4N0..00	Dialysis fluid urea level
4N1..00	Dialysis fluid creatinine level
4N2..00	Dialysis fluid glucose level
SP01500	Mechanical complication of dialysis catheter
Z131400	Warming patient by dialysis therapy
Z132800	Cooling patient using cool peritoneal dialysis
Z1A..00	Dialysis training
Z1A1.00	Peritoneal dialysis training
Z1A1.11	PD - Peritoneal dialysis training
Z919400	Recirculation of the dialysis machine
ZVu3G00	[X]Other dialysis

Read codes for kidney transplant (renal impairment).

Read	Description
7B00.00	Transplantation of kidney
7B00000	Autotransplant of kidney
7B00100	Transplantation of kidney from live donor
7B00111	Allotransplantation of kidney from live donor
7B00200	Transplantation of kidney from cadaver
7B00211	Allotransplantation of kidney from cadaver
7B00300	Allotransplantation of kidney from cadaver, heart-beating
7B00400	Allotransplantation kidney from cadaver, heart non-beating
7B00500	Allotransplantation of kidney from cadaver NEC
7B00y00	Other specified transplantation of kidney
7B00z00	Transplantation of kidney NOS
7B01500	Transplant nephrectomy
7B01511	Excision of rejected transplanted kidney
7B06300	Exploration of renal transplant
7B0F.00	Interventions associated with transplantation of kidney
7B0F100	Pre-transplantation of kidney work-up, recipient
7B0F200	Pre-transplantation of kidney work-up, live donor
7B0F300	Post-transplantation of kidney examination, recipient
7B0F400	Post-transplantation of kidney examination, live donor
7B0Fy00	OS interventions associated with transplantation of kidney
7B0Fz00	Interventions associated with transplantation of kidney NOS
8L50.00	Renal transplant planned
SP08011	Det.ren.func.after ren.transpl
SP08300	Kidney transplant failure and rejection
TB00100	Kidney transplant with complication, without blame
ZV42000	[V]Kidney transplanted
14S2.00	H/O: kidney recipient

Read codes for chronic kidney disease.

Read	Description
CKD stage 1	
1Z10.00	Chronic kidney disease stage 1
1Z17.00	Chronic kidney disease stage 1 with proteinuria
1Z17.11	CKD stage 1 with proteinuria
1Z18.00	Chronic kidney disease stage 1 without proteinuria
CKD Stage 2	
1Z11.00	Chronic kidney disease stage 2
1Z19.00	Chronic kidney disease stage 2 with proteinuria
1Z19.11	CKD stage 2 with proteinuria
1Z1A.00	Chronic kidney disease stage 2 without proteinuria
1Z1A.11	CKD stage 2 without proteinuria
CKD Stage 3	
1Z12.00	Chronic kidney disease stage 3
1Z15.00	Chronic kidney disease stage 3A
1Z16.00	Chronic kidney disease stage 3B
1Z1B.00	Chronic kidney disease stage 3 with proteinuria
1Z1B.11	CKD stage 3 with proteinuria
1Z1C.00	Chronic kidney disease stage 3 without proteinuria
1Z1C.11	CKD stage 3 without proteinuria
1Z1D.00	Chronic kidney disease stage 3A with proteinuria
1Z1D.11	CKD stage 3A with proteinuria
1Z1E.00	Chronic kidney disease stage 3A without proteinuria
1Z1E.11	CKD stage 3A without proteinuria
1Z1F.00	Chronic kidney disease stage 3B with proteinuria
1Z1F.11	CKD stage 3B with proteinuria
1Z1G.00	Chronic kidney disease stage 3B without proteinuria
1Z1G.11	CKD stage 3B without proteinuria
CKD Stage 4-5	
K054.00	Chronic kidney disease stage 4
K055.00	Chronic kidney disease stage 5
1Z1a.00	CKD with GFR category G4 & albuminuria category A1
1Z1b.00	CKD with GFR category G4 & albuminuria category A2
1Z1c.00	CKD with GFR category G4 & albuminuria category A3
1Z1d.00	CKD with GFR category G5 & albuminuria category A1
1Z1e.00	CKD with GFR category G5 & albuminuria category A2
1Z1f.00	CKD with GFR category G5 & albuminuria category A3
1Z1H.11	CKD stage 4 with proteinuria
1Z1J.00	Chronic kidney disease stage 4 without proteinuria
1Z1J.11	CKD stage 4 without proteinuria

1Z1K.00	Chronic kidney disease stage 5 with proteinuria
1Z1K.11	CKD stage 5 with proteinuria
1Z1L.00	Chronic kidney disease stage 5 without proteinuria
1Z1L.11	CKD stage 5 without proteinuria
1Z13.00	Chronic kidney disease stage 4
1Z14.00	Chronic kidney disease stage 5

Annex 3 Signature pages

Signature page - Study conduct responsible and study epidemiologist

Title	Pattern of use of Direct Oral Anticoagulants in Non-valvular Atrial Fibrillation patients in UK general practices
Report version and date	v1.4, 21 MAY 2019
IMPACT study number	19330
Study type / Study phase	Observational, Phase IV
EU PAS register number	EUPAS18521
Medicinal product / Active substance /	Xarelto / Rivaroxaban
Comparator / Reference therapy	Apixaban and Dabigatran
Study Initiator and Funder	Bayer AG 51368 Leverkusen Germany

The undersigned confirms that s/he has read this report and confirms that to the best of her/his knowledge it accurately describes the conduct and results of the study.

Print Name: PPD

Epidemiology

Date, Signature: June 24, 2019 PPD

Signature page - study medical expert

Title	Pattern of use of direct oral anticoagulants in non-valvular atrial fibrillation patients in UK general practices
Report version and date	v1.4, 21 MAY 2019
IMPACT study number	19330
Study type / Study phase	Observational, Phase IV
EU PAS register number	EUPAS18521
Medicinal product / Active substance /	Xarelto / Rivaroxaban
Comparator / Reference therapy	Apixaban and Dabigatran
Study Initiator and Funder	Bayer AG 51368 Leverkusen Germany

The undersigned confirms that s/he has read this report and confirms that to the best of her/his knowledge it accurately describes the conduct and results of the study.

Print Name: PPD

Global Medical Affairs Thrombosis

Date, Signature: 29 July 2019 PPD

Signature page - study safety lead

Title	Pattern of use of direct oral anticoagulants in non-valvular atrial fibrillation patients in UK general practices
Report version and date	v1.4, 21 MAY 2019
IMPACT study number	19330
Study type / Study phase	Observational, Phase IV
EU PAS register number	EUPAS18521
Medicinal product / Active substance /	Xarelto / Rivaroxaban
Comparator / Reference therapy	Apixaban and Dabigatran
Study Initiator and Funder	Bayer AG 51368 Leverkusen Germany

The undersigned confirms that s/he has read this report and confirms that to the best of her/his knowledge it accurately describes the conduct and results of the study.

Print Name: PPD

Pharmacovigilance

Date, Signature: 11. June 2019

PPD

Signature page - study statistician

Title	Pattern of use of direct oral anticoagulants in non-valvular atrial fibrillation patients in UK general practices
Report version and date	v1.4, 21 MAY 2019
IMPACT study number	19330
Study type / Study phase	Observational, Phase IV
EU PAS register number	EUPAS18521
Medicinal product / Active substance /	Xarelto / Rivaroxaban
Comparator / Reference therapy	Apixaban and Dabigatran
Study Initiator and Funder	Bayer AG 51368 Leverkusen Germany

The undersigned confirms that s/he has read this report and confirms that to the best of her/his knowledge it accurately describes the conduct and results of the study.

Print Name: PPD

Statistics

Date, Signature: June 14, 2019 , PPD

Signature page - real life evidence strategy and outcomes data generation

Title	Pattern of use of direct oral anticoagulants in non-valvular atrial fibrillation patients in UK general practices
Report version and date	v1.4, 21 MAY 2019
IMPACT study number	19330
Study type / Study phase	Observational, Phase IV
EU PAS register number	EUPAS18521
Medicinal product / Active substance /	Xarelto / Rivaroxaban
Comparator / Reference therapy	Apixaban and Dabigatran
Study Initiator and Funder	Bayer AG 51368 Leverkusen Germany

The undersigned confirms that s/he has read this report and confirms that to the best of her/his knowledge it accurately describes the conduct and results of the study.

Print Name: PPD

Real World Evidence, Outcomes Data Generation

Date, Signature: 22 July 2019 , PPD

Signature Page - local study unit - medical affairs (Bayer UK)

Title	Pattern of use of direct oral anticoagulants in non-valvular atrial fibrillation patients in UK general practices
Report version and date	v1.4, 21 MAY 2019
IMPACT study number	19330
Study type / Study phase	Observational, Phase IV
EU PAS register number	EUPAS18521
Medicinal product / Active substance /	Xarelto / Rivaroxaban
Comparator / Reference therapy	Apixaban and Dabigatran
Study Initiator and Funder	Bayer AG 51368 Leverkusen Germany

The undersigned confirms that s/he has read this report and confirms that to the best of her/his knowledge it accurately describes the conduct and results of the study.

Print Name: PPD

Local Study Unit – Medical Affairs (Bayer UK)

Date, Signature: 21st July 2019, PPD

Signature page – medical advisor (Bayer UK)

Title	Pattern of use of direct oral anticoagulants in non-valvular atrial fibrillation patients in UK general practices
Report version and date	v1.4, 21 MAY 2019
IMPACT study number	19330
Study type / Study phase	Observational, Phase IV
EU PAS register number	EUPAS18521
Medicinal product / Active substance /	Xarelto / Rivaroxaban
Comparator / Reference therapy	Apixaban and Dabigatran
Study Initiator and Funder	Bayer AG 51368 Leverkusen Germany

The undersigned confirms that s/he has read this report and confirms that to the best of her/his knowledge it accurately describes the conduct and results of the study.

Print Name: PPD

Medical Advisor (Bayer UK)

Date, Signature: 8 July 2019 PPD

Signature page – Principal Investigator

Title	Pattern of use of direct oral anticoagulants in non-valvular atrial fibrillation patients in UK general practices
Report version and date	v1.4, 21 MAY 2019
IMPACT study number	19330
Study type / Study phase	Observational, Phase IV
EU PAS register number	EUPAS18521
Medicinal product / Active substance /	Xarelto / Rivaroxaban
Comparator / Reference therapy	Apixaban and Dabigatran
Study Initiator and Funder	Bayer AG 51368 Leverkusen Germany

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Print Name: PPD

Centro Español de Investigación Farmacoepidemiológica (CEIFE), Madrid, Spain

Date, Signature: 19 June 2019 PPD

Signature page – co-investigator

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Print Name: PPD

Centro Español de Investigación Farmacoepidemiológica (CEIFE), Madrid, Spain

Date, Signature: 19 June 2019, PPD