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Discontinuation of Non-Vitamin K Antagonist Oral Anticoagulants in Patients with Non-Valvular Atrial Fibrillation: a Population-Based Cohort Study using Primary Care Data from The Health Improvement Network in the United Kingdom

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ABSTRACT

Objective: To determine discontinuation rates, patterns of use and predictors of discontinuation of non-vitamin K antagonist oral anticoagulants (NOACs) among patients with non-valvular atrial fibrillation (NVAF) in the first year of therapy.

Design: Population-based cohort study

Setting: United Kingdom (UK) primary care

Population: 11,481 patients with NVAF and a first prescription (index date) for apixaban, dabigatran or rivaroxaban (January 2012 to December 2016) with at least 1 year of follow-up and at least two prescriptions for the index NOAC in the year following the index date were identified. Rates and patterns of discontinuation in the year following the index date were described.

Primary and secondary outcome measures: Outcome measures were the percentage of patients who in the first year from starting NOAC therapy: discontinued with their oral anticoagulant therapy (OAC; discontinuation was defined as a gap in OAC therapy of >30 days); switched OAC within 30 days; discontinued and re-initiated OAC therapy. Predictors of discontinuation were also evaluated.

Results: One-year discontinuation rates were: apixaban 26.1%, dabigatran 40.0%, rivaroxaban 29.6%. 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, odds ratio (OR; 95% 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).

Conclusions: While the majority of NVAF patients in the UK initiating NOAC treatment received continuous therapy in the first year of treatment, a substantial proportion of patients experience gaps in treatment leaving them less protected against thromboembolism.

Strengths and limitations of the study

- Our study is the largest to evaluate NOAC discontinuation rates among patients with NVAF in the UK.
- The long study period enabled contemporary patterns of use between individual NOACs to be compared.
- The use of a validated primary care database representative of the UK demographic means our results are generalizable to the UK general population.
- We were unable to evaluate reasons for NOAC discontinuation/switching because this information is often entered as free text rather than as coded entries.

INTRODUCTION

Atrial fibrillation (AF) is a common cardiac arrhythmia encountered in clinical practice with an estimated prevalence of around 3% among adults aged 20 years or older.[1, 2] Left untreated, it is a significant risk factor for stroke and other morbidity, and therefore requires management with oral anticoagulant therapy (OAC) to mitigate risk.[3, 4]

In the United Kingdom (UK), the non-vitamin K antagonist oral anticoagulants (NOACs) – apixaban, edoxaban, dabigatran and rivaroxaban – are recommended as treatment options for stroke prevention in patients with AF,[4] and are now more commonly prescribed than warfarin in this patient population.[5, 6] Continuation with therapy long-term is advocated in most patients.[7, 8] Non-vitamin K antagonist oral anticoagulants have clear advantages over vitamin K antagonists (VKAs) such as warfarin. In addition to their favourable benefit–risk profile and fewer food– and drug-drug interactions, the fixed-dose and predictable pharmacokinetics of these medications removes the need for routine therapeutic coagulation monitoring (and thereby potentially fewer visits to healthcare professionals) or dose adjustment for bodyweight. However, less stringent monitoring requirements could mean that identification of patients discontinuing with treatment is more challenging,[9] and this is important because discontinuation of therapy among patients with AF is associated with an increased risk of stroke and all-cause mortality.[9, 10] Owing to the short half-life of NOACs,[11] their use should be uninterrupted to maintain the drug in the therapeutic range and thereby providing adequate thromboembolic protection.

Since the introduction of NOACs in clinical practice, many studies have evaluated patient discontinuation rates;[12-21] however, several have been limited in size and follow-up

duration and/or restricted to only one or two individual NOACs.[12, 13, 15, 18-20, 22] We conducted a large population-based cohort study to evaluate the frequency and predictors of discontinuation of NOACs among first-time NOAC users with NVAF, as well as subsequent detailed patterns of OAC therapy use during the first year of treatment in the UK between January 2012 and December 2016.

METHODS

Data sources

We used anonymised primary care electronic health records from The Heath Improvement Network (THIN) in the UK. As of January 2018, 3.1 million patients were registered with a general practice contributing patient data to THIN, corresponding to approximately 5% of the UK general population. The data held are those entered by the primary care practitioner (PCP) as part of routine patient care, and include clinical, demographic and lifestyle information, and all prescriptions issued. The database has been validated for pharmacoepidemiology research and is representative of the UK demographic in terms of age, sex and geographical distribution.[23, 24] The study protocol was approved by the Independent Scientific Research Committee for THIN (reference SRC 17THIN014).

Study population

The study population included all patients aged ≥18 years in THIN with a first prescription (index date) for apixaban, dabigatran or rivaroxaban (index NOAC) between 1 January 2012 and 31 December 2016. Although edoxaban has been recently licensed in the UK and recommended by The National Institute for Health and Care Excellence for stroke prevention in AF (June and September 2015, respectively)[25, 26] we did not expect

widespread use of this NOAC during the study period and, therefore, did not include patients starting treatment on edoxaban in the study. Patients were required to have at least 1 year of computerised data before the index date. Patients were followed up for 1 year after index date, and only patients with complete 1 year follow-up and at least two prescriptions for the index NOAC during this period were retained for analysis. To ensure our study population were patients with NVAF, individuals were required to have a record of AF but with no record of valvular replacement or mitral stenosis any time before the index date or within the 2 weeks after the index date. We also excluded patients with a record of deep vein thrombosis, pulmonary embolism, or hip/knee replacement surgery in the 3 months before the index date or in the week after the index date because these indications are associated with different posology and durations of NOAC use.

NOAC study cohorts

Three mutually exclusive study cohorts were identified based on the index NOAC. Patients with a first prescription for two different NOACs on the same index date were excluded, and those who qualified as a first-time user of more than one NOAC during the study period (i.e. they switched NOAC) were assigned to the cohort of the NOAC first prescribed. Patients with a prescription for a VKA before their index NOAC or a clinical entry implying previous use of a VKA, warfarin monitoring or international normalized ratio >2 were categorised as OAC non-naïve, otherwise they were considered to be OAC-naïve.

Patient characteristics

We extracted data on patient demographics and lifestyle variables (body mass index [BMI], smoking status, alcohol consumption) using the most recent recorded value/status before

the index date. We calculated patients' CHA_2DS_2-VASc score for stroke risk (based on the recorded history of congestive heart failure, hypertension, age, diabetes mellitus, vascular disease, and stroke or transient ischaemic attack), and HAS-BLED score for major bleeding risk (based on the recorded history of hypertension, renal disease, liver disease, stroke history, prior major bleeding, age >65 years, medication use predisposing to bleeding and alcohol use), but omitting international normalized ratio lability because this is not recorded for all patients in the database. Renal function was estimated using the closest valid serum creatinine value to the index date (within the year before) to estimate glomerular filtration rate (eGFR) expressed as mL/min/1.73m^2 applying the Chronic Kidney Disease Epidemiology Collaboration equation,[27] but omitting ethnicity because this is not systematically recorded in THIN. Patients with no recorded valid serum creatinine measurement were categorised as 'unknown'. Frailty was estimated using a frailty index based on a wide range of symptoms, signs, diseases, disabilities, abnormal laboratory values and social circumstances. developed for research using primary care databases,[28] categorising patients as fit, mildly frail, moderately frail or severely frail.

Follow-up and study outcomes

Follow-up of the three NOAC cohorts stopped 1 year after the index date. 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. In a sensitivity analysis, we changed the definition of discontinuation to require a treatment gap of 60 days (allowing for greater non-adherence) to assess the effect this had on study outcomes.

Statistical analysis

For each NOAC cohort, we described baseline characteristics using frequency counts and percentages for categorical variables, and means with standard deviation (SD) for continuous variables. To evaluate longitudinal patterns of NOAC use during the first year of treatment, we calculated the number and percentage of patients who continued/ discontinued their initial NOAC therapy, switched, reinitiated (with the index NOAC, a different NOAC, or a VKA), or stopped and did not reinitiate with any OAC therapy. Time to discontinuation and time to reinitiation, where appropriate, were calculated and expressed as mean time in days with SD and range (minimum to maximum). Patient characteristics associated with the likelihood of index NOAC discontinuation (all discontinuers as well as separately for re-initiators, switchers and non-reinitiators) were identified using unconditional logistic regression to estimate odds ratios (ORs) with 95% confidence intervals (CIs) adjusted for confounders.

Patient and public involvement

This was a descriptive study using routinely collected primary care data in the UK. There was no public or patient involvement in the conception of the research question, the design and implementation of the study, or the writing of the manuscript.

RESULTS

Baseline characteristics

In total, there were 11,481 patients with NVAF who were first-time NOAC users: 5889 (51.3%) started on rivaroxaban, 3589 (31.3%) on apixaban and 2003 (17.4%) on dabigatran. Baseline characteristics of the three study cohorts are shown in **Table 1**. 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 OAC therapy on apixaban were more likely to be OAC-naïve (55%) compared with those starting on dabigatran (44.0%) or rivaroxaban (48.0%).

Patterns of NOAC use

The percentage of patients who continued, switched, reinitiated or stopped and did not reinitiate OAC therapy is shown in **Figure 1** and **Table 2** by study cohort. Within the first year of treatment the majority of patients in each cohort were continuous users of their initial NOAC; discontinuers accounted for 26.1% of the apixaban cohort, 40.0% of the dabigatran cohort, and 29.6% of the rivaroxaban cohort. Some differences were seen among the percentage of patients discontinuing NOAC when restricting to those classified as OAC-naïve: apixaban 24.0%, dabigatran 40.9% and rivaroxaban 28.9%. In the sensitivity analysis (changing the definition of discontinuation to having a longer treatment gap of >60 days), the proportion of discontinuers was notably reduced: 13.5% for apixaban, 28.1% for dabigatran and 17.9% for rivaroxaban (**Supplementary Table 1)**.

Less than 10% in each cohort stopped NOAC therapy and did not reinitiate OAC therapy. 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), the vast majority (at least 93%) restarted on the index NOAC as opposed to another NOAC or a VKA: apixaban 97.7% (636/651), dabigatran 92.9% (403/434) and rivaroxaban 95.0% (970/1021). Only a small percentage of patients switched from their initial NOAC within 30 days of starting treatment, with a higher percentage of switchers seen in the dabigatran cohort (8.8%) compared with apixaban (2.8%) and rivaroxaban (4.9%). As shown in **Table 2**, more than half of switchers changed to a different NOAC rather than to a VKA (53% [53/100] for patients starting on apixaban, compared with 64% (113/176) for dabigatran and 57% (165/289) for rivaroxaban.

Time to discontinuation/reinitiation

As shown in **Table 3**, among discontinuers, the mean time to index NOAC discontinuation was 4.7 months (SD 3.0), ranging from 1 day to just under a year, with minimal differences between NOAC cohorts. Discontinuers who did not later reinitiate any OAC therapy had a slightly longer time to discontinuation (mean 5.5 months) than those who later reinitiated OAC therapy (either on the same NOAC, a different NOAC or a VKA; mean 4.6 months) or who switched treatment (4.6 months). Among OAC reinitiators, no noticeable difference was seen in the time to reinitiation between the NOAC cohorts (apixaban 1.9 months, dabigatran 2.1 months, and rivaroxaban 2.0 months) (**Table 4**).

Predictors of discontinuation

Associations between patient characteristics and discontinuation of NOAC therapy in the first year of treatment are shown in **Supplementary Table 2**. Younger age, impaired renal function, lower CHA_2DS_2-VASc score and high alcohol consumption were 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 of treatment (adjusted OR 1.81, 95% CI: 1.59–2.07), while patients starting on rivaroxaban had a possible small increased likelihood of discontinuing their anticoagulation treatment (adjusted OR 1.18, 95% CI: 1.08–1.30). As shown by a breakdown of this analysis by type of discontinuers (vs. continuers)(**Table 5**), compared with patients starting on apixaban, those starting on dabigatran were four times more likely to switch OAC therapy (adjusted OR 4.28, 95% CI: 3.24–5.65) and those starting on rivaroxaban were twice as likely to switch (adjusted OR 1.89, 95% CI: 1.49–2.39). Having a reduced renal function (<30 eGFR ml/min/1.73m^2) was associated with all three kinds of treatment discontinuation (**Table 5**).

DISCUSSION

Among patients with NVAF, continuation of NOAC therapy without interruption is important to gain the benefits of thromboembolic protection. In our study of 11,481 patients with NVAF prescribed a NOAC for the first time in UK primary care, the majority had continued treatment with their initial prescribed NOAC during the first year of therapy, yet a substantial percentage experienced gaps in treatment of more than a month.

Our study is the largest to evaluate NOAC discontinuation rates among patients with NVAF in the UK, and the longer study period including recent data enabled us to compare patterns of use between individual NOACs. Other strengths of our study include the large population-based sample of patients with NVAF from a validated primary care databases representative of the UK population as a whole. Also, by including patients with or without previous OAC

therapy use prior to starting NOAC therapy, we covered the whole spectrum of NVAF patients prescribed NOACs. In terms of limitations, although most NOAC prescriptions are issued in primary care, those prescribed in secondary care may not have been captured, leading to a degree of misclassification of NOAC use. In addition, we were able to analyze prescriptions issued, but some may not have been subsequently dispensed from pharmacies and/or taken by the patient. Missing data on clinical and lifestyle variables was low and did not differ substantially between index NOAC discontinuers and continuers (only for renal function was there a slightly higher level of missing data among discontinuers), therefore this is unlikely to have impacted on the risk estimates to identify predictors of discontinuation.

We are aware of only two previous UK studies in this area, both using electronic primary care data and among OAC-naïve patients. [12][13] In a study of among 2871 NVAF patients, Johnson *et al*[13] 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*,[12] 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 (apixaban was recommended by UK National Institute for Health and Care Excellence guidelines a year later than for dabigatran and rivaroxaban).[29-31]. Studies from other European countries have reported either highly comparable[32], notably higher[17] or lower[15, 18] 1-year NOAC discontinuation rates based on a 30-day treatment gap [18], 60-day treatment gap [17, 32] or other definition of discontinuation,[15] 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,[21, 33] yet are consistent with a trend of higher discontinuation for dabigatran compared with rivaroxaban or apixaban[13, 15, 17, 21, 22, 32, 33] and of rates lowest for apixaban in most,[13, 15, 17, 21, 33] albeit not all,[22] studies.

In our present study, after controlling for differences in patient characteristics (such as lifestyle factors, CHA_2DS_2-VASc score, HAS-BLED score and frailty index) between NOAC cohorts, those starting OAC therapy on rivaroxaban had only a small increased likelihood of discontinuing treatment, while those starting on dabigatran were twice as likely to discontinue, when compared with those starting on apixaban. This is in line with findings from other studies among American and European OAC naïve NVAF cohorts,[13, 15, 21] but contrasts with those reported by McHorney *et al*[22] in the US, who found that among 23,309 NVAF patients starting NOAC therapy, patients treated with rivaroxaban were significantly less likely to discontinue therapy at 1 year, as well as earlier time points, compared with those starting on apixaban or dabigatran. It should be noted that the higher level of discontinuation, seen for dabigatran both in our study and in others, could be partially explained by its longer market availability. Being the first NOAC to be introduced for stroke prevention in AF would mean that patients who started on dabigatran had greater opportunity to switch to a different (newer) NOAC as these became available. This is clearly shown by our finding that patients starting on dabigatran were four times more likely to switch OAC in the first month of therapy than patients starting on apixaban. Only 7% of NVAF patients in our study permanently discontinued NOAC therapy, which is

approximately half the rate seen in Italy [34] and approximately a third of that seen for rivaroxaban in Germany,[18] and this may be a reflection of the growing confidence of both physicians and patients about long-term use of NOACs.

As seen in Sweden,[15] 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,[14, 33] while another large US administrative database among 34,022 OAC naïve NVAF patients, nearly 20% switched medication.[35] 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*[32] found that 9.8% of patients starting rivaroxaban therapy switched to another OAC class, while in the UK, Martinez *et al* [12] reported a 6.6% NOAC-to-VKA switch rate.

We did not analyze reasons for discontinuation or switching in our study as this was beyond the scope of this study and these reasons are included in the free text comments entered by PCPs in THIN, which we did not access. In the study by Martinez *et al*,[12] among 914 NVAF UK patients initiating NOAC therapy, seven (0.8%) discontinued because of a bleeding event, while in Germany, 30% of all rivaroxaban discontinuations were due to bleeding complications, 24% due to side effects and 10% because a diagnosis of stable sinus rhythm. In a nationwide registry-based study in Denmark of 5206 patients with NVAF, 7.6% of patients who discontinued did so because of bleeding, while about quarter of both

discontinuations and of NOAC to VKA switches were preceded by a hospitalization for specific clinical event or procedure, cardioversion being the most common reason.[36] Cardioversion is another possible explanation for the higher discontinuation rate among patients starting NOAC therapy with dabigatran, having been approved for use in this patient population earlier.[37-40]

Identifying patients more likely to discontinue NOAC therapy may help target those for counselling regarding persistence with treatment, and in our current findings suggest that these might include patients at younger age when starting NOAC therapy as well as those with impaired renal function and lower CHA_2DS_2-VASc score. Observational data suggest that interruption of warfarin treatment in patients with AF is associated with an increased risk of thromboembolism,[41], as is poor adherence to NOACs.[42, 43] Studies are now needed to quantify the impact of interrupted NOAC therapy, including the length of interruption, on the risk of stroke and other thromboembolic events in well-designed large cohort studies. Efforts are also needed to increase uninterrupted and continued NOAC use in order to increase number of NVAF patients benefiting from NOAC-mediated stroke protection.

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Author contributions: LR and SF developed the concept for the research study. LR, SF, LAGR, AR, GB, PV, and YB planned the study. AR, LAGR and OF conducted the study. All authors interpreted the data, reviewed drafts of the manuscript, and approved the final version of the article for publication.

Data sharing: Data are available from the corresponding author upon reasonable request.

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Table 1. Baseline characteristics of the three NOAC study cohorts.

	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)

	Apixaban N=3589	Dabigatran N=2003	Rivaroxaban N=5889	Total N=11,481
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)
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)
CV / 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.

BMI, body mass index; CV, cardiovascular; NOAC, non-vitamin K oral anticoagulant; OAC, oral anticoagulant; SD, standard deviation, eGFR, estimated glomerular filtration rate

Table 2. Pattern of NOAC discontinuation (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 (9.5)	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.

NOAC, non-vitamin K antagonist oral anticoagulant; NVAF, non-valvular atrial fibrillation; OAC, oral anticoagulant

Table 3. Time to discontinuation of NOAC therapy among NVAF patients who discontinued their initial prescribed NOAC (index NOAC).

	Time to discontinuation* (months)		
	N	**Mean (months; SD)**	**Range (days, min–max)**
Among discontinuers by index NOAC			
Apixaban	937	4.7 (3.0)	3–356
Dabigatran	802	4.5 (3.0)	2–361
Rivaroxaban	1745	4.9 (3.1)	1–363
Among discontinuers by type of discontinuation			
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.

NOAC, non-vitamin-K antagonist oral anticoagulant; NVAF, non-valvular atrial fibrillation; OAC, oral anticoagulant

Table 4. Time to re-initiation of OAC therapy among NVAF patients who reinitiated OAC therapy after a gap of >30 days from treatment with the initial prescribed NOAC (index NOAC).

	Time to re-initiation*		
	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 a 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.

NOAC, non-vitamin K antagonist oral anticoagulant; NVAF, non-valvular atrial fibrillation; OAC, oral anticoagulant

Table 5. Associations between baseline characteristics of patients with NVAF (new users of a NOAC) and risk of discontinuation according to type of discontinuation.

	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**
	Adjusted OR* (95% CI)	**Adjusted OR* (95% CI)**	**Adjusted OR* (95% CI)**
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	1.0 (reference)	1.0 (reference)	1.0 (reference)
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			
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_EPI			
>50mL/min	1.0 (reference)	1.0 (reference)	1.0 (reference)
30–50 mL/min	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)

	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
	Adjusted OR* (95% CI)	**Adjusted OR* (95% CI)**	**Adjusted OR* (95% CI)**
BMI (kg/m²)			
<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_2VASc 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)

	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
	Adjusted OR* (95% CI)	**Adjusted OR* (95% CI)**	**Adjusted OR* (95% CI)**
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)

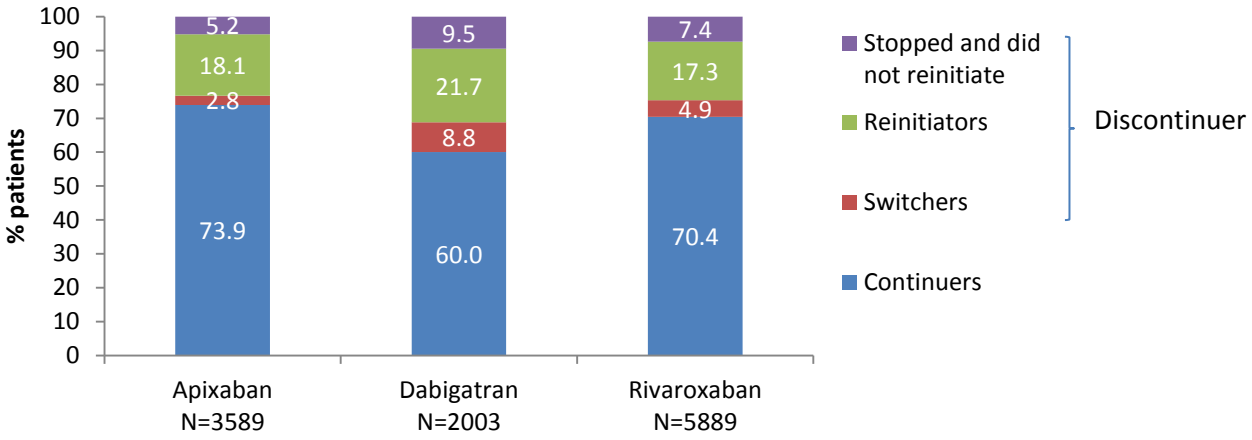
*Adjusted for all the other variables in the table.

BMI, body mass index; NOAC, non-vitamin K antagonist oral anticoagulant; OAC, oral anticoagulant; OR, odds ratio; SD, standard deviation; eGFR, estimated glomerular filtration rate.

FIGURE LEGEND

Figure 1. Patterns of NOAC use among first-time users of NOAC with NVAF (with >1 year of follow-up and using a 30-days treatment gap to define discontinuation).

NOAC, non-vitamin K oral anticoagulant; NVAF, non-valvular atrial fibrillation.



Supplementary Table 1. 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	**Dabigatran**	**Rivaroxaban**	**Total**
	N=3589	**N=2003**	**N=5889**	**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.

NOAC, non-vitamin-K antagonist oral anticoagulant; NVAF, non-valvular atrial fibrillation; OAC, oral anticoagulant

Supplementary Table 2. Associations between patient characteristics and discontinuation of NOAC therapy in the first year of treatment among patients with NVAF.

	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)

	Continuers N=7997	Discontinuers N=3484	Crude OR (95% CI)	Adjusted OR* (95% CI)
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)
eGFR_EPI				
>50mL/min	5857 (73.2)	2415 (69.3)	1.0 (reference)	1.0 (reference)
30–50 mL/min	1128 (14.1)	492 (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_2VASc 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)			
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.

BMI, body mass index; NOAC, non-vitamin K antagonist oral anticoagulant; NVAF, non-valvular atrial fibrillation; OAC, oral anticoagulant; OR, odds ratio; SD, standard deviation; eGFR, estimated glomerular filtration rate.

*Adjusted for all the other variables in the table.

†Frailty index (eFI): including a wide range of symptoms, signs, diseases, disabilities, abnormal laboratory values and social circumstances.

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract. **Page1 and 2**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found **Page 2**
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported. **Page 5 and 6**
Objectives	3	State specific objectives, including any prespecified hypotheses. **Page 6**
Methods		
Study design	4	Present key elements of study design early in the paper. **Page 6 and 7**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection **Page 6 and 7**
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up **Page 6 and 7**
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable. **Page 8 and 9**
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group **Page 7, 8, 9**
Bias	9	Describe any efforts to address potential sources of bias. **Page 6**
Study size	10	Explain how the study size was arrived at. **Page 6 and 7**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why. **Page 9**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding. **Page 9**
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) If applicable, explain how loss to follow-up was addressed
		(*e*) Describe any sensitivity analyses
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed. **Page 10**
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders. **Page 10 and Table 1**
		(b) Indicate number of participants with missing data for each variable of interest **Table 1**
		(c) Summarise follow-up time (eg, average and total amount)
Outcome data	15*	Report numbers of outcome events or summary measures over time
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders

		were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized. **Table 1**
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses. **Page 9**
Discussion		
Key results	18	Summarise key results with reference to study objectives. **Page 12**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias. **Page 13**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence. **Page 13 to 16**
Generalisability	21	Discuss the generalisability (external validity) of the study results. **Page 12**
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based. **Page 16**

*Give information separately for exposed and unexposed groups.

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

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Discontinuation of Non-Vitamin K Antagonist Oral Anticoagulants in Patients with Non-Valvular Atrial Fibrillation: a Population-Based Cohort Study using Primary Care Data from The Health Improvement Network in the United Kingdom

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Discontinuation of Non-Vitamin K Antagonist Oral Anticoagulants in Patients with Non-Valvular Atrial Fibrillation: a Population-Based Cohort Study using Primary Care Data from The Health Improvement Network in the United Kingdom

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ABSTRACT

Objective: To determine discontinuation rates, patterns of use and predictors of discontinuation of non-vitamin K antagonist oral anticoagulants (NOACs) among patients with non-valvular atrial fibrillation (NVAF) in the first year of therapy.

Design: Population-based cohort study

Setting: United Kingdom (UK) primary care

Population: 11,481 patients with NVAF and a first prescription (index date) for apixaban, dabigatran or rivaroxaban (January 2012 to December 2016) with at least 1 year of follow-up and at least one further NOAC prescription in the year following the index date were identified. 1-year rates and patterns of discontinuation were described.

Primary and secondary outcome measures: Outcome measures were the percentage of patients who in the first year from starting NOAC therapy: discontinued with their oral anticoagulant therapy (OAC; discontinuation was defined as a gap in OAC therapy of >30 days); switched OAC within 30 days; discontinued and re-initiated OAC therapy. Predictors of discontinuation were also evaluated.

Results: 1-year discontinuation rates according to the index NOAC were 26.1% for apixaban, 40.0% for dabigatran and 29.6% for rivaroxaban. Re-initiation rates were 18.1% for apixaban, 21.7% for dabigatran and 17.3% for rivaroxaban, and switching rates were 2.8% for apixaban, 8.8% for dabigatran and 4.9% for rivaroxaban. More than 93% of re-initiations were with the index NOAC. Patients starting on dabigatran were more likely to switch OAC therapy than those starting on apixaban; odds ratios 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, odds ratio 1.77 (95% CI: 1.28–2.44).

Conclusions: While the majority of NVAF patients in the UK initiating NOAC treatment received continuous therapy in the first year of treatment, a substantial proportion of patients experience gaps in treatment leaving them less protected against thromboembolism during these periods.

Strengths and limitations of the study

- Our study is the largest to evaluate NOAC discontinuation rates among patients with NVAF in the UK.
- The long study period enabled contemporary patterns of use between individual NOACs to be compared.
- The use of a validated primary care database representative of the UK demographic means our results are generalizable to the UK general population.
- We were unable to evaluate reasons for NOAC discontinuation/switching because this information is often entered as free text rather than as coded entries.

INTRODUCTION

Atrial fibrillation (AF) is a common cardiac arrhythmia encountered in clinical practice with an estimated prevalence of around 3% among adults aged 20 years or older.[1, 2] Left untreated, it is a significant risk factor for stroke and other morbidity, and therefore requires management with oral anticoagulant therapy (OAC) to mitigate risk.[3, 4]

In the United Kingdom (UK), the non-vitamin K antagonist oral anticoagulants (NOACs) – apixaban, edoxaban, dabigatran and rivaroxaban – are recommended as treatment options for stroke prevention in patients with AF,[4] and are now more commonly prescribed than warfarin in this patient population.[5, 6] Continuation with therapy long-term is advocated in most patients.[7, 8] Non-vitamin K antagonist oral anticoagulants have clear advantages over vitamin K antagonists (VKAs) such as warfarin. In addition to their favourable benefit–risk profile and fewer food– and drug-drug interactions, the fixed-dose and predictable pharmacokinetics of these medications removes the need for routine therapeutic coagulation monitoring (and thereby potentially fewer visits to healthcare professionals) or dose adjustment for bodyweight. However, less stringent monitoring requirements could mean that identification of patients discontinuing with treatment is more challenging,[9] and this is important because discontinuation of therapy among patients with AF is associated with an increased risk of stroke and all-cause mortality.[9, 10] Owing to the short half-life of NOACs,[11] their use should be uninterrupted to maintain the drug in the therapeutic range and thereby providing adequate thromboembolic protection.

Since the introduction of NOACs in clinical practice, many studies have evaluated patient discontinuation rates;[12-21] however, several have been limited in size and follow-up

duration and/or restricted to only one or two individual NOACs.[12, 13, 15, 18-20, 22] We conducted a large population-based cohort study to evaluate the frequency and predictors of discontinuation of NOACs among first-time NOAC users with NVAF, as well as subsequent detailed patterns of OAC therapy use during the first year of treatment in the UK between January 2012 and December 2016.

METHODS

Data sources

We used anonymised primary care electronic health records from The Heath Improvement Network (THIN) in the UK. As of January 2018, 3.1 million patients were registered with a general practice contributing patient data to THIN, corresponding to approximately 5% of the UK general population. The data held are those entered by the primary care practitioner (PCP) as part of routine patient care, and include clinical, demographic and lifestyle information, and all prescriptions issued. The database has been validated for pharmacoepidemiology research and is representative of the UK demographic in terms of age, sex and geographical distribution.[23, 24] The study protocol was approved by the Independent Scientific Research Committee for THIN (reference SRC 17THIN014).

Study population

The study population included all patients aged ≥18 years in THIN with a first prescription (index date) for apixaban, dabigatran or rivaroxaban (index NOAC) between 1 January 2012 and 31 December 2016. Although edoxaban has been recently licensed in the UK and recommended by The National Institute for Health and Care Excellence for stroke prevention in AF (June and September 2015, respectively)[25, 26] we did not expect

widespread use of this NOAC during the study period and, therefore, did not include patients starting treatment on edoxaban in the study. Patients were required to have at least 1 year of computerised data before the index date. Patients were followed up for 1 year after index date, and only patients with complete 1 year follow-up and at least two prescriptions for the index NOAC during this period were retained for analysis. To ensure our study population were patients with NVAF, individuals were required to have a record of AF (**Supplementary Table 1**) but with no record of valvular replacement (**Supplementary Table 2**) or mitral stenosis (**Supplementary Table 3**) any time before the index date or within the 2 weeks after the index date. We also excluded patients with a record of deep vein thrombosis, pulmonary embolism, or hip/knee replacement surgery (**Supplementary Table 4**) in the 3 months before the index date or in the week after the index date because these indications are associated with different posology and durations of NOAC use.

NOAC study cohorts

Three mutually exclusive study cohorts were identified based on the index NOAC. Patients with a first prescription for two different NOACs on the same index date were excluded, and those who qualified as a first-time user of more than one NOAC during the study period (i.e. they switched NOAC) were assigned to the cohort of the NOAC first prescribed. Patients with a prescription for a VKA before their index NOAC or a clinical entry implying previous use of a VKA, warfarin monitoring or international normalized ratio >2 were categorised as OAC non-naïve, otherwise they were considered to be OAC-naïve.

Patient characteristics

We extracted data on patient demographics and lifestyle variables (body mass index [BMI], smoking status, alcohol consumption) using the most recent recorded value/status before the index date. We calculated patients' CHA_2DS_2-VASc score for stroke risk (based on the recorded history of congestive heart failure, hypertension, age, diabetes mellitus, vascular disease, and stroke or transient ischaemic attack), and HAS-BLED score for major bleeding risk (based on the recorded history of hypertension, renal disease, liver disease, stroke history, prior major bleeding, age >65 years, medication use predisposing to bleeding and alcohol use), but omitting international normalized ratio lability because this is not recorded for all patients in the database. Renal function was estimated using the closest valid serum creatinine value to the index date (within the year before) to estimate glomerular filtration rate (eGFR) expressed as mL/min/1.73m^2 applying the Chronic Kidney Disease Epidemiology Collaboration equation,[27] but omitting ethnicity because this is not systematically recorded in THIN. Patients with no recorded valid serum creatinine measurement were categorised as 'unknown'. Frailty was estimated using a frailty index based on a wide range of symptoms, signs, diseases, disabilities, abnormal laboratory values and social circumstances developed for research using primary care databases,[28] categorising patients as fit, mildly frail, moderately frail or severely frail.

Follow-up and study outcomes

Follow-up of the three NOAC cohorts stopped 1 year after the index date. 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. In a sensitivity analysis, we changed the definition of discontinuation to require a treatment gap of 60 days (allowing for greater non-adherence) to assess the effect this had on study outcomes.

Statistical analysis

For each NOAC cohort, we described baseline characteristics using frequency counts and percentages for categorical variables, and means with standard deviation (SD) for continuous variables. To evaluate longitudinal patterns of NOAC use during the first year of treatment, we calculated the number and percentage of patients who continued/ discontinued their initial NOAC therapy, switched, reinitiated (with the index NOAC, a different NOAC, or a VKA), or stopped and did not reinitiate with any OAC therapy. Time to discontinuation and time to reinitiation, where appropriate, were calculated and expressed as mean time in days with SD and range (minimum to maximum). Kaplan–Meier survival analyses were performed to visualise the proportion of patients continuing treatment with the index NOAC during the 1-year follow-up period. Patient characteristics associated with the likelihood of index NOAC discontinuation (all discontinuers as well as separately for re-initiators, switchers and non-reinitiators) were identified using unconditional logistic regression to estimate odds ratios (ORs) with 95% confidence intervals (CIs) adjusted for confounders.

Patient and public involvement

This was a descriptive study using routinely collected primary care data in the UK. There was no public or patient involvement in the conception of the research question, the design and implementation of the study, or the writing of the manuscript.

RESULTS

Baseline characteristics

In total, there were 11,481 patients with NVAF who were first-time NOAC users: 5889 (51.3%) started on rivaroxaban, 3589 (31.3%) on apixaban and 2003 (17.4%) on dabigatran. Baseline characteristics of the three study cohorts are shown in **Table 1**. 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 OAC therapy on apixaban were more likely to be OAC-naïve (55%) compared with those starting on dabigatran (44.0%) or rivaroxaban (48.0%).

Patterns of NOAC use

The percentage of patients who continued, switched, reinitiated or stopped and did not reinitiate OAC therapy is shown in **Figure 1** and **Table 2** by study cohort while the proportion of patients continuing on the index NOAC during the 1-year follow-up period is shown in the **Supplementary Figure**. Within the first year of treatment the majority of patients in each cohort were continuous users of their initial NOAC; discontinuers accounted for 26.1% of the apixaban cohort, 40.0% of the dabigatran cohort, and 29.6% of the rivaroxaban cohort. Some differences were seen among the percentage of patients discontinuing NOAC when restricting to those classified as OAC-naïve: apixaban 24.0%, dabigatran 40.9% and

rivaroxaban 28.9%. In the sensitivity analysis (changing the definition of discontinuation to having a longer treatment gap of >60 days), the proportion of discontinuers was notably reduced: 13.5% for apixaban, 28.1% for dabigatran and 17.9% for rivaroxaban (**Supplementary Table 5)**.

Less than 10% in each cohort stopped NOAC therapy and did not reinitiate OAC therapy. 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), the vast majority (at least 93%) restarted on the index NOAC as opposed to another NOAC or a VKA: apixaban 97.7% (636/651), dabigatran 92.9% (403/434) and rivaroxaban 95.0% (970/1021). Only a small percentage of patients switched from their initial NOAC within 30 days of starting treatment, with a higher percentage of switchers seen in the dabigatran cohort (8.8%) compared with apixaban (2.8%) and rivaroxaban (4.9%). As shown in **Table 2**, more than half of switchers changed to a different NOAC rather than to a VKA (53% [53/100] for patients starting on apixaban, compared with 64% (113/176) for dabigatran and 57% (165/289) for rivaroxaban.

Time to discontinuation/reinitiation

As shown in **Table 3**, among discontinuers, the mean time to index NOAC discontinuation was 4.7 months (SD 3.0), ranging from 1 day to just under a year, with minimal differences between NOAC cohorts. Discontinuers who did not later reinitiate any OAC therapy had a slightly longer time to discontinuation (mean 5.5 months) than those who later reinitiated OAC therapy (either on the same NOAC, a different NOAC or a VKA; mean 4.6 months) or who switched treatment (4.6 months). Among OAC reinitiators, no noticeable difference

was seen in the time to reinitiation between the NOAC cohorts (apixaban 1.9 months, dabigatran 2.1 months, and rivaroxaban 2.0 months) (**Table 4**).

Predictors of discontinuation

Associations between patient characteristics and discontinuation of NOAC therapy in the first year of treatment are shown in **Supplementary Table 6**. Younger age, impaired renal function, lower CHA_2DS_2-VASc score and high alcohol consumption were 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 of treatment (adjusted OR 1.81, 95% CI: 1.59–2.07), while patients starting on rivaroxaban had a possible small increased likelihood of discontinuing their anticoagulation treatment (adjusted OR 1.18, 95% CI: 1.08–1.30). As shown by a breakdown of this analysis by type of discontinuers (vs. continuers)(**Table 5**), compared with patients starting on apixaban, those starting on dabigatran were four times more likely to switch OAC therapy (adjusted OR 4.28, 95% CI: 3.24–5.65) and those starting on rivaroxaban were twice as likely to switch (adjusted OR 1.89, 95% CI: 1.49–2.39). Having a reduced renal function (<30 eGFR ml/min/1.73m²) was associated with all three kinds of treatment discontinuation (**Table 5**).

DISCUSSION

Among patients with NVAF, continuation of NOAC therapy without interruption is important to gain the benefits of thromboembolic protection. In our study of 11,481 patients with NVAF prescribed a NOAC for the first time in UK primary care, the majority had continued

treatment with their initial prescribed NOAC during the first year of therapy, yet a substantial percentage experienced gaps in treatment of more than a month.

Our study is the largest to evaluate NOAC discontinuation rates among patients with NVAF in the UK, and the longer study period including recent data enabled us to compare patterns of use between individual NOACs. Other strengths of our study include the large population-based sample of patients with NVAF from a validated primary care databases representative of the UK population as a whole. Also, by including patients with or without previous OAC therapy use prior to starting NOAC therapy, we covered the whole spectrum of NVAF patients prescribed NOACs. In terms of limitations, although most NOAC prescriptions are issued in primary care, those prescribed in secondary care may not have been captured, leading to a degree of misclassification of NOAC use. In addition, we were able to analyze prescriptions issued, but some may not have been subsequently dispensed from pharmacies and/or taken by the patient. Missing data on clinical and lifestyle variables was low and did not differ substantially between index NOAC discontinuers and continuers (only for renal function was there a slightly higher level of missing data among discontinuers), therefore this is unlikely to have impacted on the risk estimates to identify predictors of discontinuation. Another limitation of our study is the limited data available for patients whose index NOAC prescription was in 2016. This was due the eligibility criterion of requiring a year of available follow-up data after the index date.

We are aware of only two previous UK studies in this area, both using electronic primary care data and among OAC-naïve patients. [12][13] In a study of among 2871 NVAF patients,

Johnson *et al*[13] 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*,[12] 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 (apixaban was recommended by UK National Institute for Health and Care Excellence guidelines a year later than for dabigatran and rivaroxaban).[29-31]. Studies from other European countries have reported either highly comparable[32], notably higher[17] or lower[15, 18] 1-year NOAC discontinuation rates based on a 30-day treatment gap [18], 60-day treatment gap [17, 32] or other definition of discontinuation,[15] 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,[21, 33] yet are consistent with a trend of higher discontinuation for dabigatran compared with rivaroxaban or apixaban[13, 15, 17, 21, 22, 32, 33] and of rates lowest for apixaban in most,[13, 15, 17, 21, 33] albeit not all,[22] studies. Most other studies on NOAC discontinuation have reported rates over shorter time periods.[34]

In our present study, after controlling for differences in patient characteristics (such as lifestyle factors, CHA_2DS_2-VASc score, HAS-BLED score and frailty index) between NOAC cohorts, those starting OAC therapy on rivaroxaban had only a small increased likelihood of discontinuing treatment, while those starting on dabigatran were twice as likely to discontinue, when compared with those starting on apixaban. This is in line with findings

from other studies among American and European OAC naïve NVAF cohorts,[13, 15, 21] but contrasts with those reported by McHorney *et al*[22] in the US, who found that among 23,309 NVAF patients starting NOAC therapy, patients treated with rivaroxaban were significantly less likely to discontinue therapy at 1 year, as well as earlier time points, compared with those starting on apixaban or dabigatran. It should be noted that the higher level of discontinuation, seen for dabigatran both in our study and in others, could be partially explained by its longer market availability. Being the first NOAC to be introduced for stroke prevention in AF would mean that patients who started on dabigatran had greater opportunity to switch to a different (newer) NOAC as these became available. This is clearly shown by our finding that patients starting on dabigatran were four times more likely to switch OAC in the first month of therapy than patients starting on apixaban. Only 7% of NVAF patients in our study permanently discontinued NOAC therapy, which is approximately half the rate seen in Italy [35] and approximately a third of that seen for rivaroxaban in Germany,[18] and this may be a reflection of the growing confidence of both physicians and patients about long-term use of NOACs.

As seen in Sweden,[15] 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,[14, 33] while another large US administrative database among 34,022 OAC naïve NVAF patients, nearly 20% switched medication.[36] 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*[32] found that 9.8% of patients starting rivaroxaban therapy switched to another OAC class, while in the UK, Martinez *et al* [12] reported a 6.6% NOAC-to-VKA switch rate.

We did not analyze reasons for discontinuation or switching in our study as this was beyond the scope of this study and these reasons are included in the free text comments entered by PCPs in THIN, which we did not access. In the study by Martinez *et al*,[12] among 914 NVAF UK patients initiating NOAC therapy, seven (0.8%) discontinued because of a bleeding event, while in Germany, 30% of all rivaroxaban discontinuations were due to bleeding complications, 24% due to side effects and 10% because a diagnosis of stable sinus rhythm. In a nationwide registry-based study in Denmark of 5206 patients with NVAF, 7.6% of patients who discontinued did so because of bleeding, while about quarter of both discontinuations and of NOAC to VKA switches were preceded by a hospitalization for specific clinical event or procedure, cardioversion being the most common reason.[37] Cardioversion is another possible explanation for the higher discontinuation rate among patients starting NOAC therapy with dabigatran, having been approved for use in this patient population earlier.[38–41]

Identifying patients more likely to discontinue NOAC therapy may help target those for counselling regarding persistence with treatment, and in our current findings suggest that these might include patients at younger age when starting NOAC therapy as well as those with impaired renal function and lower CHA_2DS_2-VASc score. Observational data suggest that interruption of warfarin treatment in patients with AF is associated with an increased risk of thromboembolism,[42], as is poor adherence to NOACs.[43, 44] Evaluating adherence

in our study population was beyond the scope of this individual study, yet is an area for future study in order to compare with the existing wide-ranging findings on this topic.[34] Studies are now needed to quantify the impact of interrupted NOAC therapy, including the length of interruption, on the risk of stroke and other thromboembolic events in well-designed large cohort studies. Efforts are also needed to increase uninterrupted and continued NOAC use in order to increase number of NVAF patients benefiting from NOAC-mediated stroke protection.

In conclusion, while the majority of NVAF patients in the UK initiating NOAC treatment received continuous therapy in the first year of treatment, a substantial proportion of patients experience gaps in treatment leaving them less protected against thromboembolism during these periods.

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Competing interests: LAGR, OF and AR work for the Spanish Centre for Pharmacoepidemiologic Research (Madrid, Spain), which has received research funding from Bayer AG. LAGR also declares honoraria for serving on advisory boards for Bayer AG. PV and YB, are employees of Bayer AG (Germany), the funder of the study; GB is an employee of Bayer AB, (Stockholm, Sweden); LR and SF are employees of Bayer PLC (Reading, UK). LR and SF declare shares in Bayer.

Author contributions: LR and SF developed the concept for the research study. LR, SF, LAGR, AR, GB, PV, and YB planned the study. AR, LAGR and OF conducted the study. All authors interpreted the data, reviewed drafts of the manuscript, and approved the final version of the article for publication.

Data sharing: Data are available from the corresponding author upon reasonable request.

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Table 1. Baseline characteristics of the three NOAC study cohorts.

	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)
Missing	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)
Missing	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)
Missing	338 (9.4)	198 (9.9)	571 (9.7)	1107 (9.6)

	Apixaban N=3589	Dabigatran N=2003	Rivaroxaban N=5889	Total N=11,481
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)
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)
Missing	473 (13.2)	227 (11.3)	719 (12.2)	1419 (12.4)
CV / 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.

BMI, body mass index; CV, cardiovascular; NOAC, non-vitamin K oral anticoagulant; OAC, oral anticoagulant; SD, standard deviation, eGFR, estimated glomerular filtration rate

Table 2. Pattern of NOAC discontinuation (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 (9.5)	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.

NOAC, non-vitamin K antagonist oral anticoagulant; NVAF, non-valvular atrial fibrillation; OAC, oral anticoagulant

Table 3. Time to discontinuation of NOAC therapy among NVAF patients who discontinued their initial prescribed NOAC (index NOAC).

	Time to discontinuation* (months)		
	N	**Mean (months; SD)**	**Range (days, min–max)**
Among discontinuers by index NOAC			
Apixaban	937	4.7 (3.0)	3–356
Dabigatran	802	4.5 (3.0)	2–361
Rivaroxaban	1745	4.9 (3.1)	1–363
Among discontinuers by type of discontinuation			
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.

NOAC, non-vitamin-K antagonist oral anticoagulant; NVAF, non-valvular atrial fibrillation; OAC, oral anticoagulant

Table 4. Time to re-initiation of OAC therapy among NVAF patients who reinitiated OAC therapy after a gap of >30 days from treatment with the initial prescribed NOAC (index NOAC).

	Time to re-initiation*		
	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 a 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.

NOAC, non-vitamin K antagonist oral anticoagulant; NVAF, non-valvular atrial fibrillation; OAC, oral anticoagulant

Table 5. Associations between baseline characteristics of patients with NVAF (new users of a NOAC) and risk of discontinuation according to type of discontinuation.

	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**
	Adjusted OR* (95% CI)	**Adjusted OR* (95% CI)**	**Adjusted OR* (95% CI)**
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	1.0 (reference)	1.0 (reference)	1.0 (reference)
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			
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)

	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
	Adjusted OR* (95% CI)	**Adjusted OR* (95% CI)**	**Adjusted OR* (95% CI)**
BMI (kg/m²)			
<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)
Missing	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)
Missing	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_2VASc 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)

	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
	Adjusted OR* (95% CI)	**Adjusted OR* (95% CI)**	**Adjusted OR* (95% CI)**
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)

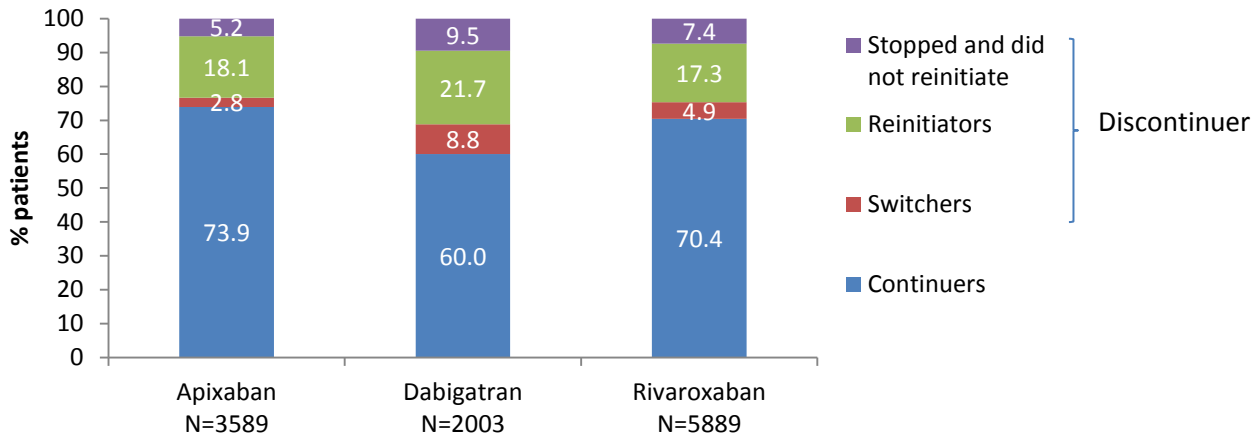
*Adjusted for all the other variables in the table.

BMI, body mass index; NOAC, non-vitamin K antagonist oral anticoagulant; OAC, oral anticoagulant; OR, odds ratio; SD, standard deviation; eGFR, estimated glomerular filtration rate.

FIGURE LEGEND

Figure 1. Patterns of NOAC use among first-time users of NOAC with NVAF (with >1 year of follow-up and using a 30-days treatment gap to define discontinuation).

NOAC, non-vitamin K oral anticoagulant; NVAF, non-valvular atrial fibrillation.



Supplementary Table 1. 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

Supplementary Table 2. 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

Supplementary Table 3. 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

Supplementary Table 4. Read codesfor pulmonary embolism, deep vein thrombosis and hip/knee replacement surgery.

Read code	Description PE
G401.00	Pulmonary embolism
G401100	Recurrent pulmonary embolism
G401000	Post operative pulmonary embolus
G402.00	Pulmonary infarct
G401.12	Pulmonary embolus
L096400	Pulmonary embolism following abortive pregnancy
L43..11	Obstetric pulmonary embolus
L43..00	Obstetric pulmonary embolism
L432.00	Obstetric blood-clot pulmonary embolism
L432000	Obstetric blood-clot pulmonary embolism unspecified
L432100	Obstetric blood-clot pulmonary embolism - delivered
L432300	Obstetric blood-clot pulmonary embolism + a/n complication
L432400	Obstetric blood-clot pulmonary embolism + p/n complication
L432z00	Obstetric blood-clot pulmonary embolism NOS
L43y.00	Other obstetric pulmonary embolism
L43y000	Other obstetric pulmonary embolism unspecified
L43y100	Other obstetric pulmonary embolism - delivered
L43y200	Other obstetric pulmonary embolism - delivered + p/n comp
L43y300	Other obstetric pulmonary embolism with antenatal comp
L43y400	Other obstetric pulmonary embolism with postnatal comp
L43yz00	Other obstetric pulmonary embolism NOS
L43z.00	Obstetric pulmonary embolism NOS
L43z000	Obstetric pulmonary embolism NOS, unspecified
L43z100	Obstetric pulmonary embolism NOS - delivered
L43z200	Obstetric pulmonary embolism NOS - delivered with p/n comp
L43z300	Obstetric pulmonary embolism NOS with antenatal complication
L43z400	Obstetric pulmonary embolism NOS with postnatal complication
L43zz00	Obstetric pulmonary embolism NOS
ZV12900	Personal history of pulmonary embolism

Read code	Description DVT
G801.00	Deep vein phlebitis and thrombophlebitis of the leg
G801.11	Deep vein thrombosis
G801.12	Deep vein thrombosis, leg
G801.13	DVT - Deep vein thrombosis
G801C00	Deep vein thrombosis of leg related to air travel
G801D00	Deep vein thrombosis of lower limb
G801E00	Deep vein thrombosis of leg related to intravenous drug use
G801F00	Deep vein thrombosis of peroneal vein
G801600	Thrombophlebitis of the femoral vein
G801700	Thrombophlebitis of the popliteal vein

G801800	Thrombophlebitis of the anterior tibial vein
G801900	Thrombophlebitis of the dorsalis pedis vein
G801A00	Thrombophlebitis of the posterior tibial vein
G801B00	Deep vein thrombophlebitis of the leg unspecified
G802000	Thrombosis of vein of leg
G80y.00	Other phlebitis and thrombophlebitis
G80y400	Thrombophlebitis of the common iliac vein
G80y500	Thrombophlebitis of the internal iliac vein
G80y600	Thrombophlebitis of the external iliac vein
G80y700	Thrombophlebitis of the iliac vein unspecified
G80y800	Phlebitis and thrombophlebitis of the iliac vein NOS
L414.12	Phlegmasia alba dolens - obstetric
L413.00	Antenatal deep vein thrombosis
L413.11	DVT - deep venous thrombosis, antenatal
L413000	Antenatal deep vein thrombosis unspecified
L413100	Antenatal deep vein thrombosis - delivered
L413200	Antenatal deep vein thrombosis with antenatal complication
L413z00	Antenatal deep vein thrombosis NOS
L414.00	Postnatal deep vein thrombosis
L414.11	DVT - deep venous thrombosis, postnatal
L414000	Postnatal deep vein thrombosis unspecified
L414100	Postnatal deep vein thrombosis - delivered with p/n comp
L414200	Postnatal deep vein thrombosis with postnatal complication
L414z00	Postnatal deep vein thrombosis NOS
SP12200	Post operative deep vein thrombosis
ZV12800	[V] Personal history deep vein thrombosis
ZV12811	[V] Personal history DVT- deep vein thrombosis
14A8100	H/O: Deep Vein Thrombosis
G82..00	Other venous embolism and thrombosis

Read code, Read range	**Description (hip/knee surgery)**
7K20.00 - 7K20z00	Total prosthetic replacement of hip joint using cement
7K21.00 - 7K21z00	Total prosthetic replacement of hip joint not using cement
7K22.00 - 7K22z00	Other total prosthetic replacement of hip joint
7K23.00 - 7K23z00	Prosthetic cemented hemiarthroplasty of hip
7K24.00 - 7K24z00	Prosthetic uncemented hemiarthroplasty of hip
7K25.00 - 7K25z00	Other prosthetic hemiarthroplasty of hip
7K2y.00	Other specified operations on hip joint
7K2z.00	Hip joint operations NOS
7K2..00	Hip joint operations
7K1D.00 - 7K1D01F	Primary open reduction fracture bone & intramedull fixation
7K1J000	Cls red+int fxn proximal femoral #+screw/nail device alone
7K1J011	Cl red intracaps frac neck femur fix-Garden cannulated screw
7K1J012	Cl red intracaps fract neck femur fix - Smith-Petersen nail

7K1J013	Cls red+int fxn prox femoral #+Richard's cannulat hip screw
7K6c.00 - 7K6cz00	Hybrid prosthetic replacement hip joint cemented acetab comp
7K6d.00 - 7K6dz00	Hybrid prosthetic replace hip joint cemented femoral compon
7K6e.00 - 7K6ez00	Hybrid prosthetic replacement of hip joint using cement
7K30.00- 7K30z00	Total prosthetic replacement of knee joint using cement
7K31.00 - 7K31z00	Total prosthetic replacement of knee joint not using cement
7K32.00 - 7K32z00	Other total prosthetic replacement of knee joint
7K37.00 - 7K37x00	Cemented unicompartmental knee replacement
7K38.00 - 7K38x00	Uncemented unicompartmental knee replacement
7K39.00 - 7K39x00	Hybrid unicompartmental knee replacement
7K3A.00	Unicompartmental knee replacement NOS
7K3y.00	Other specified operations on knee joint
7K3z.00	Knee joint operations NOS
7K3..00	Knee joint operations
7K30.1I	Manchester total replacement of knee joint using cement
7K3A.00	Unicompartmental knee replacement NOS
7K6q.00- 7K6qz00	Hybrid prosthetic replacement of knee joint using cement
7L06200 - 7L06017	Amputation leg

Supplementary Table 5. 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	**Dabigatran**	**Rivaroxaban**	**Total**
	N=3589	**N=2003**	**N=5889**	**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.

NOAC, non-vitamin-K antagonist oral anticoagulant; NVAF, non-valvular atrial fibrillation; OAC, oral anticoagulant

Supplementary Table 6. Associations between patient characteristics and discontinuation of NOAC therapy in the first year of treatment among patients with NVAF.

	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)

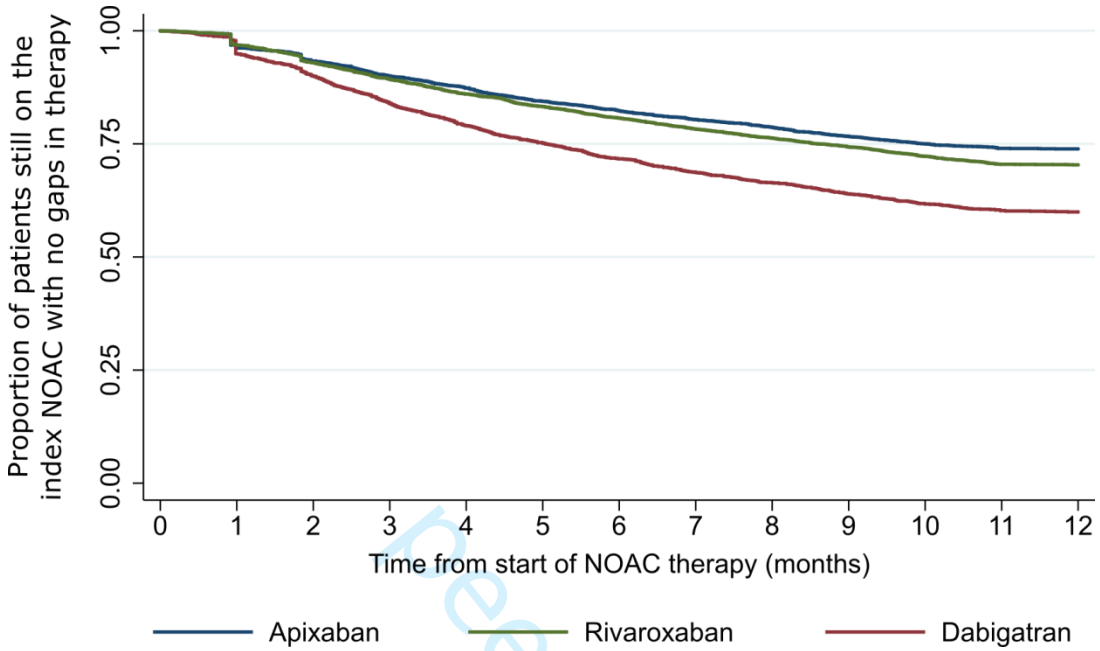
	Continuers N=7997	Discontinuers N=3484	Crude OR (95% CI)	Adjusted OR* (95% CI)
Moderate frailty	2435 (30.4)	1048 (30.1)	0.74 (0.66–0.84)	1.02 (0.88–1.18)
Severe frailty	1315 (16.4)	578 (16.6)	0.76 (0.66–0.87)	1.08 (0.91–1.29)
eGFR_EPI				
>50mL/min	5857 (73.2)	2415 (69.3)	1.0 (reference)	1.0 (reference)
30–50 mL/min	1128 (14.1)	492 (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_2VASc 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)			
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.

BMI, body mass index; NOAC, non-vitamin K antagonist oral anticoagulant; NVAF, non-valvular atrial fibrillation; OAC, oral anticoagulant; OR, odds ratio; SD, standard deviation; eGFR, estimated glomerular filtration rate.

*Adjusted for all the other variables in the table.

†Frailty index (eFI): including a wide range of symptoms, signs, diseases, disabilities, abnormal laboratory values and social circumstances.



Supplementary Figure. Kaplan–Meier plot showing time to NOAC discontinuation.

NOAC, non-vitamin K antagonist oral anticoagulant

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract. **Page1 and 2**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found **Page 2**
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported. **Page 5 and 6**
Objectives	3	State specific objectives, including any prespecified hypotheses. **Page 6**
Methods		
Study design	4	Present key elements of study design early in the paper. **Page 6 and 7**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection **Page 6 and 7**
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up **Page 6 and 7**
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable. **Page 8 and 9**
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group **Page 7, 8, 9**
Bias	9	Describe any efforts to address potential sources of bias. **Page 6**
Study size	10	Explain how the study size was arrived at. **Page 6 and 7**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why. **Page 9**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding. **Page 9**
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) If applicable, explain how loss to follow-up was addressed
		(*e*) Describe any sensitivity analyses
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed. **Page 10**
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders. **Page 10 and Table 1**
		(b) Indicate number of participants with missing data for each variable of interest **Table 1**
		(c) Summarise follow-up time (eg, average and total amount)
Outcome data	15*	Report numbers of outcome events or summary measures over time
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders

		were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized. **Table 1**
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses. **Page 9**
Discussion		
Key results	18	Summarise key results with reference to study objectives. **Page 12**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias. **Page 13**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence. **Page 13 to 16**
Generalisability	21	Discuss the generalisability (external validity) of the study results. **Page 12**
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based. **Page 16**

*Give information separately for exposed and unexposed groups.

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

BMJ Open

Discontinuation of Non-Vitamin K Antagonist Oral Anticoagulants in Patients with Non-Valvular Atrial Fibrillation: a Population-Based Cohort Study using Primary Care Data from The Health Improvement Network in the United Kingdom

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Discontinuation of Non-Vitamin K Antagonist Oral Anticoagulants in Patients with Non-Valvular Atrial Fibrillation: a Population-Based Cohort Study using Primary Care Data from The Health Improvement Network in the United Kingdom

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Word count: 3487

ABSTRACT

Objective: To determine discontinuation rates, patterns of use and predictors of discontinuation of non-vitamin K antagonist oral anticoagulants (NOACs) among patients with non-valvular atrial fibrillation (NVAF) in the first year of therapy.

Design: Population-based cohort study

Setting: United Kingdom (UK) primary care

Population: 11,481 patients with NVAF and a first prescription (index date) for apixaban, dabigatran or rivaroxaban (January 2012 to December 2016) with at least 1 year of follow-up and at least one further NOAC prescription in the year following the index date were identified. 1-year rates and patterns of discontinuation were described.

Primary and secondary outcome measures: Outcome measures were the percentage of patients who in the first year from starting NOAC therapy: discontinued with their oral anticoagulant therapy (OAC; discontinuation was defined as a gap in OAC therapy of >30 days); switched OAC within 30 days; discontinued and re-initiated OAC therapy. Predictors of discontinuation were also evaluated.

Results: 1-year discontinuation rates according to the index NOAC were 26.1% for apixaban, 40.0% for dabigatran and 29.6% for rivaroxaban. Re-initiation rates were 18.1% for apixaban, 21.7% for dabigatran and 17.3% for rivaroxaban, and switching rates were 2.8% for apixaban, 8.8% for dabigatran and 4.9% for rivaroxaban. More than 93% of re-initiations were with the index NOAC. Patients starting on dabigatran were more likely to switch OAC therapy than those starting on apixaban; odds ratios 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, odds ratio 1.77 (95% CI: 1.28–2.44).

Conclusions: While the majority of NVAF patients in the UK initiating NOAC treatment received continuous therapy in the first year of treatment, a substantial proportion of patients experience gaps in treatment leaving them less protected against thromboembolism during these periods.

Strengths and limitations of the study

- Our study is the largest to evaluate NOAC discontinuation rates among patients with NVAF in the UK.
- The long study period enabled contemporary patterns of use between individual NOACs to be compared.
- The use of a validated primary care database representative of the UK demographic means our results are generalizable to the UK general population.
- We were unable to evaluate reasons for NOAC discontinuation/switching because this information is often entered as free text rather than as coded entries.

INTRODUCTION

Atrial fibrillation (AF) is a common cardiac arrhythmia encountered in clinical practice with an estimated prevalence of around 3% among adults aged 20 years or older.[1, 2] Left untreated, it is a significant risk factor for stroke and other morbidity, and therefore requires management with oral anticoagulant therapy (OAC) to mitigate risk.[3, 4]

In the United Kingdom (UK), the non-vitamin K antagonist oral anticoagulants (NOACs) – apixaban, edoxaban, dabigatran and rivaroxaban – are recommended as treatment options for stroke prevention in patients with AF,[4] and are now more commonly prescribed than warfarin in this patient population.[5, 6] Continuation with therapy long-term is advocated in most patients.[7, 8] Non-vitamin K antagonist oral anticoagulants have clear advantages over vitamin K antagonists (VKAs) such as warfarin. In addition to their favourable benefit–risk profile and fewer food– and drug-drug interactions, the fixed-dose and predictable pharmacokinetics of these medications removes the need for routine therapeutic coagulation monitoring (and thereby potentially fewer visits to healthcare professionals) or dose adjustment for bodyweight. However, less stringent monitoring requirements could mean that identification of patients discontinuing with treatment is more challenging,[9] and this is important because discontinuation of therapy among patients with AF is associated with an increased risk of stroke and all-cause mortality.[9, 10] Owing to the short half-life of NOACs,[11] their use should be uninterrupted to maintain the drug in the therapeutic range and thereby providing adequate thromboembolic protection.

Since the introduction of NOACs in clinical practice, many studies have evaluated patient discontinuation rates;[12-21] however, several have been limited in size and follow-up

duration and/or restricted to only one or two individual NOACs.[12, 13, 15, 18-20, 22] We conducted a large population-based cohort study to evaluate the frequency and predictors of discontinuation of NOACs among first-time NOAC users with NVAF, as well as subsequent detailed patterns of OAC therapy use during the first year of treatment in the UK between January 2012 and December 2016.

METHODS

Data sources

We used anonymised primary care electronic health records (EHRs) from The Heath Improvement Network (THIN) in the UK. As of January 2018, 3.1 million patients were registered with a general practice contributing patient data to THIN, corresponding to approximately 5% of the UK general population. The data held are those entered by the primary care practitioner (PCP) as part of routine patient care, and include clinical, demographic and lifestyle information, and all prescriptions issued. The database has been validated for pharmacoepidemiology research and is representative of the UK demographic in terms of age, sex and geographical distribution.[23, 24] The study protocol was approved by the Independent Scientific Research Committee for THIN (reference SRC 17THIN014). Data collection for THIN was approved by the South East Multicentre Research Ethics Committee in 2003 and individual studies using THIN data do not require separate ethical approval if only anonymized THIN data is used.

Study population

The study population included all patients aged ≥18 years in THIN with a first prescription (index date) for apixaban, dabigatran or rivaroxaban (index NOAC) between 1 January 2012

and 31 December 2016. Although edoxaban has been recently licensed in the UK and recommended by The National Institute for Health and Care Excellence for stroke prevention in AF (June and September 2015, respectively)[25, 26] we did not expect widespread use of this NOAC during the study period and, therefore, did not include patients starting treatment on edoxaban in the study. Patients were required to have at least 1 year of computerised data before the index date. Patients were followed up for 1 year after index date, and only patients with complete 1 year follow-up and at least two prescriptions for the index NOAC during this period were retained for analysis. To ensure our study population were patients with NVAF, individuals were required to have a record of AF (**Supplementary Table 1**) but with no record of valvular replacement (**Supplementary Table 2**) or mitral stenosis (**Supplementary Table 3**) any time before the index date or within the 2 weeks after the index date. We also excluded patients with a record of deep vein thrombosis, pulmonary embolism, or hip/knee replacement surgery (**Supplementary Table 4**) in the 3 months before the index date or in the week after the index date because these indications are associated with different posology and durations of NOAC use.

NOAC study cohorts

Three mutually exclusive study cohorts were identified based on the index NOAC. Patients with a first prescription for two different NOACs on the same index date were excluded, and those who qualified as a first-time user of more than one NOAC during the study period (i.e. they switched NOAC) were assigned to the cohort of the NOAC first prescribed. Patients with a prescription for a VKA before their index NOAC or a clinical entry implying previous use of a VKA, warfarin monitoring or international normalized ratio >2 were categorised as OAC non-naïve, otherwise they were considered to be OAC-naïve.

Patient characteristics

We extracted data on patient demographics and lifestyle variables (body mass index [BMI], smoking status, alcohol consumption) using the most recent recorded value/status before the index date. We calculated patients' CHA_2DS_2-VASc score for stroke risk (based on the recorded history of congestive heart failure, hypertension, age, diabetes mellitus, vascular disease, and stroke or transient ischaemic attack), and HAS-BLED score for major bleeding risk (based on the recorded history of hypertension, renal disease, liver disease, stroke history, prior major bleeding, age >65 years, medication use predisposing to bleeding and alcohol use), but omitting international normalized ratio lability because this is not recorded for all patients in the database. Renal function was estimated using the closest valid serum creatinine value to the index date (within the year before) to estimate glomerular filtration rate (eGFR) expressed as mL/min/1.73m^2 applying the Chronic Kidney Disease Epidemiology Collaboration equation,[27] but omitting ethnicity because this is not systematically recorded in THIN. Patients with no recorded valid serum creatinine measurement were categorised as 'unknown'. Frailty was estimated using a frailty index based on a wide range of symptoms, signs, diseases, disabilities, abnormal laboratory values and social circumstances developed for research using primary care databases,[28] categorising patients as fit, mildly frail, moderately frail or severely frail.

Follow-up and study outcomes

Follow-up of the three NOAC cohorts stopped 1 year after the index date. 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. In a sensitivity analysis, we changed the definition of discontinuation to require a treatment gap of 60 days (allowing for greater non-adherence) to assess the effect this had on study outcomes.

Statistical analysis

For each NOAC cohort, we described baseline characteristics using frequency counts and percentages for categorical variables, and means with standard deviation (SD) for continuous variables. Patients with missing data on smoking, alcohol consumption, BMI or renal function (eGFR) were not excluded from the analyses but were placed in a separate category 'missing' for that variable. To evaluate longitudinal patterns of NOAC use during the first year of treatment, we calculated the number and percentage of patients who continued/ discontinued their initial NOAC therapy, switched, reinitiated (with the index NOAC, a different NOAC, or a VKA), or stopped and did not reinitiate with any OAC therapy. Time to discontinuation and time to reinitiation, where appropriate, were calculated and expressed as mean time in days with SD and range (minimum to maximum). Kaplan–Meier survival analyses were performed to visualise the proportion of patients continuing treatment with the index NOAC during the 1-year follow-up period. Patient characteristics associated with the likelihood of index NOAC discontinuation (all discontinuers as well as

separately for re-initiators, switchers and non-reinitiators) were identified using unconditional logistic regression to estimate odds ratios (ORs) with 95% confidence intervals (CIs) adjusted for confounders.

Patient and public involvement

This was a descriptive study using routinely collected primary care data in the UK. There was no public or patient involvement in the conception of the research question, the design and implementation of the study, or the writing of the manuscript.

RESULTS

Baseline characteristics

In total, there were 11,481 patients with NVAF who were first-time NOAC users: 5889 (51.3%) started on rivaroxaban, 3589 (31.3%) on apixaban and 2003 (17.4%) on dabigatran. Baseline characteristics of the three study cohorts are shown in **Table 1**. 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 OAC therapy on apixaban were more likely to be OAC-naïve (55%) compared with those starting on dabigatran (44.0%) or rivaroxaban (48.0%). Among all patients in the study, missing data were present as follows: BMI (3.6%), smoking (0.1%), alcohol consumption (9.6%), and renal function (12.4%).

Patterns of NOAC use

The percentage of patients who continued, switched, reinitiated or stopped and did not reinitiate OAC therapy is shown in **Figure 1** and **Table 2** by study cohort while the proportion

of patients continuing on the index NOAC during the 1-year follow-up period is shown in **Figure 2**. Within the first year of treatment the majority of patients in each cohort were continuous users of their initial NOAC; discontinuers accounted for 26.1% of the apixaban cohort, 40.0% of the dabigatran cohort, and 29.6% of the rivaroxaban cohort. Some differences were seen among the percentage of patients discontinuing NOAC when restricting to those classified as OAC-naïve: apixaban 24.0%, dabigatran 40.9% and rivaroxaban 28.9%. In the sensitivity analysis (changing the definition of discontinuation to having a longer treatment gap of >60 days), the proportion of discontinuers was notably reduced: 13.5% for apixaban, 28.1% for dabigatran and 17.9% for rivaroxaban (**Supplementary Table 5)**.

Less than 10% in each cohort stopped NOAC therapy and did not reinitiate OAC therapy. 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), the vast majority (at least 93%) restarted on the index NOAC as opposed to another NOAC or a VKA: apixaban 97.7% (636/651), dabigatran 92.9% (403/434) and rivaroxaban 95.0% (970/1021). Only a small percentage of patients switched from their initial NOAC within 30 days of starting treatment, with a higher percentage of switchers seen in the dabigatran cohort (8.8%) compared with apixaban (2.8%) and rivaroxaban (4.9%). As shown in **Table 2**, more than half of switchers changed to a different NOAC rather than to a VKA (53% [53/100] for patients starting on apixaban, compared with 64% (113/176) for dabigatran and 57% (165/289) for rivaroxaban.

Time to discontinuation/reinitiation

As shown in **Table 3**, among discontinuers, the mean time to index NOAC discontinuation was 4.7 months (SD 3.0), ranging from 1 day to just under a year, with minimal differences between NOAC cohorts. Discontinuers who did not later reinitiate any OAC therapy had a slightly longer time to discontinuation (mean 5.5 months) than those who later reinitiated OAC therapy (either on the same NOAC, a different NOAC or a VKA; mean 4.6 months) or who switched treatment (4.6 months). Among OAC reinitiators, no noticeable difference was seen in the time to reinitiation between the NOAC cohorts (apixaban 1.9 months, dabigatran 2.1 months, and rivaroxaban 2.0 months) (**Supplementary Table 6**).

Predictors of discontinuation

Associations between patient characteristics and discontinuation of NOAC therapy in the first year of treatment are shown in **Supplementary Table 7**. Younger age, impaired renal function, lower CHA_2DS_2-VASc score and high alcohol consumption were 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 of treatment (adjusted OR 1.81, 95% CI: 1.59–2.07), while patients starting on rivaroxaban had a possible small increased likelihood of discontinuing their anticoagulation treatment (adjusted OR 1.18, 95% CI: 1.08–1.30). As shown by a breakdown of this analysis by type of discontinuers (vs. continuers)(**Table 4**), compared with patients starting on apixaban, those starting on dabigatran were four times more likely to switch OAC therapy (adjusted OR 4.28, 95% CI: 3.24–5.65) and those starting on rivaroxaban were twice as likely to switch (adjusted OR 1.89, 95% CI: 1.49–2.39). Having

a reduced renal function (<30 eGFR ml/min/1.73m²) was associated with all three kinds of treatment discontinuation (**Table 4**).

DISCUSSION

Among patients with NVAF, continuation of NOAC therapy without interruption is important to gain the benefits of thromboembolic protection. In our study of 11,481 patients with NVAF prescribed a NOAC for the first time in UK primary care, the majority had continued treatment with their initial prescribed NOAC during the first year of therapy, yet a substantial percentage experienced gaps in treatment of more than a month.

Our study is the largest to evaluate NOAC discontinuation rates among patients with NVAF in the UK, and the longer study period including recent data enabled us to compare patterns of use between individual NOACs. Other strengths of our study include the large population-based sample of patients with NVAF from a validated primary care databases representative of the UK population as a whole. Also, by including patients with or without previous OAC therapy use prior to starting NOAC therapy, we covered the whole spectrum of NVAF patients prescribed NOACs. In terms of limitations, although most NOAC prescriptions are issued in primary care, those prescribed in secondary care may not have been captured, leading to a degree of misclassification of NOAC use. In addition, we were able to analyze prescriptions issued, but some may not have been subsequently dispensed from pharmacies and/or taken by the patient. Missing data on clinical and lifestyle variables was low and did not differ substantially between index NOAC discontinuers and continuers (only for renal function was there a slightly higher level of missing data among discontinuers), therefore this is unlikely to have impacted on the risk estimates to identify predictors of

discontinuation. Another limitation of our study is the limited data available for patients whose index NOAC prescription was in 2016. This was due the eligibility criterion of requiring a year of available follow-up data after the index date.

We are aware of only two previous UK studies in this area, both using electronic primary care data and among OAC-naïve patients. [12][13] In a study of among 2871 NVAF patients, Johnson *et al*[13] 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*,[12] 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 (apixaban was recommended by UK National Institute for Health and Care Excellence guidelines a year later than for dabigatran and rivaroxaban).[29-31]. Studies from other European countries have reported either highly comparable[32], notably higher[17] or lower[15, 18] 1-year NOAC discontinuation rates based on a 30-day treatment gap [18], 60-day treatment gap [17, 32] or other definition of discontinuation,[15] 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,[21, 33] yet are consistent with a trend of higher discontinuation for dabigatran compared with rivaroxaban or apixaban[13, 15, 17, 21, 22, 32, 33] and of rates lowest for apixaban in most,[13, 15, 17, 21, 33] albeit not all,[22]

studies. Most other studies on NOAC discontinuation have reported rates over shorter time periods.[34]

In our present study, after controlling for differences in patient characteristics (such as lifestyle factors, CHA_2DS_2-VASc score, HAS-BLED score and frailty index) between NOAC cohorts, those starting OAC therapy on rivaroxaban had only a small increased likelihood of discontinuing treatment, while those starting on dabigatran were twice as likely to discontinue, when compared with those starting on apixaban. This is in line with findings from other studies among American and European OAC naïve NVAF cohorts,[13, 15, 21] but contrasts with those reported by McHorney *et al*[22] in the US, who found that among 23,309 NVAF patients starting NOAC therapy, patients treated with rivaroxaban were significantly less likely to discontinue therapy at 1 year, as well as earlier time points, compared with those starting on apixaban or dabigatran. It should be noted that the higher level of discontinuation, seen for dabigatran both in our study and in others, could be partially explained by its longer market availability. Being the first NOAC to be introduced for stroke prevention in AF would mean that patients who started on dabigatran had greater opportunity to switch to a different (newer) NOAC as these became available. This is clearly shown by our finding that patients starting on dabigatran were four times more likely to switch OAC in the first month of therapy than patients starting on apixaban. Only 7% of NVAF patients in our study permanently discontinued NOAC therapy, which is approximately half the rate seen in Italy [35] and approximately a third of that seen for rivaroxaban in Germany,[18] and this may be a reflection of the growing confidence of both physicians and patients about long-term use of NOACs.

As seen in Sweden,[15] 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,[14, 33] while another large US administrative database among 34,022 OAC naïve NVAF patients, nearly 20% switched medication.[36] 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*[32] found that 9.8% of patients starting rivaroxaban therapy switched to another OAC class, while in the UK, Martinez *et al* [12] reported a 6.6% NOAC-to-VKA switch rate.

We did not analyze reasons for discontinuation or switching in our study as this was beyond the scope of this study and these reasons are included in the free text comments entered by PCPs in THIN, which we did not access. In the study by Martinez *et al*,[12] among 914 NVAF UK patients initiating NOAC therapy, seven (0.8%) discontinued because of a bleeding event, while in Germany, 30% of all rivaroxaban discontinuations were due to bleeding complications, 24% due to side effects and 10% because a diagnosis of stable sinus rhythm. In a nationwide registry-based study in Denmark of 5206 patients with NVAF, 7.6% of patients who discontinued did so because of bleeding, while about quarter of both discontinuations and of NOAC to VKA switches were preceded by a hospitalization for specific clinical event or procedure, cardioversion being the most common reason.[37] Cardioversion is another possible explanation for the higher discontinuation rate among

patients starting NOAC therapy with dabigatran, having been approved for use in this patient population earlier.[38–41]

Identifying patients more likely to discontinue NOAC therapy may help target those for counselling regarding persistence with treatment, and in our current findings suggest that these might include patients at younger age when starting NOAC therapy as well as those with impaired renal function and lower CHA_2DS_2-VASc score. Observational data suggest that interruption of warfarin treatment in patients with AF is associated with an increased risk of thromboembolism,[42], as is poor adherence to NOACs.[43, 44] Evaluating adherence in our study population was beyond the scope of this individual study, yet is an area for future study in order to compare with the existing wide-ranging findings on this topic.[34] Studies are now needed to quantify the impact of interrupted NOAC therapy, including the length of interruption, on the risk of stroke and other thromboembolic events in well-designed large cohort studies. Efforts are also needed to increase uninterrupted and continued NOAC use in order to increase number of NVAF patients benefiting from NOAC-mediated stroke protection.

CONCLUSION

In conclusion, while the majority of NVAF patients in the UK initiating NOAC treatment received continuous therapy in the first year of treatment, a substantial proportion of patients experience gaps in treatment leaving them less protected against thromboembolism during these periods.

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Author contributions: LR and SF developed the concept for the research study. LR, SF, LAGR, AR, GB, PV, and YB planned the study. AR, LAGR and OF conducted the study. All authors interpreted the data, reviewed drafts of the manuscript, and approved the final version of the article for publication.

Data sharing: Data are available from the corresponding author upon reasonable request.

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Table 1. Baseline characteristics of the three NOAC study cohorts.

	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)
Missing	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)
Missing	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)
Missing	338 (9.4)	198 (9.9)	571 (9.7)	1107 (9.6)

	Apixaban N=3589	Dabigatran N=2003	Rivaroxaban N=5889	Total N=11,481
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)
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)
Missing	473 (13.2)	227 (11.3)	719 (12.2)	1419 (12.4)
CV / 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.

BMI, body mass index; CV, cardiovascular; NOAC, non-vitamin K oral anticoagulant; OAC, oral anticoagulant; SD, standard deviation, eGFR, estimated glomerular filtration rate

Table 2. Pattern of NOAC discontinuation (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 (9.5)	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.

NOAC, non-vitamin K antagonist oral anticoagulant; NVAF, non-valvular atrial fibrillation; OAC, oral anticoagulant

Table 3. Time to discontinuation of NOAC therapy among NVAF patients who discontinued their initial prescribed NOAC (index NOAC).

	Time to discontinuation* (months)		
	N	**Mean (months; SD)**	**Range (days, min–max)**
Among discontinuers by index NOAC			
Apixaban	937	4.7 (3.0)	3–356
Dabigatran	802	4.5 (3.0)	2–361
Rivaroxaban	1745	4.9 (3.1)	1–363
Among discontinuers by type of discontinuation			
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.

NOAC, non-vitamin-K antagonist oral anticoagulant; NVAF, non-valvular atrial fibrillation; OAC, oral anticoagulant

Table 4. Associations between baseline characteristics of patients with NVAF (new users of a NOAC) and risk of discontinuation according to type of discontinuation.

	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**
	Adjusted OR* (95% CI)	**Adjusted OR* (95% CI)**	**Adjusted OR* (95% CI)**
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	1.0 (reference)	1.0 (reference)	1.0 (reference)
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			
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)

	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
	Adjusted OR* (95% CI)	**Adjusted OR* (95% CI)**	**Adjusted OR* (95% CI)**
BMI (kg/m²)			
<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)
Missing	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)
Missing	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_2VASc 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)

	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
	Adjusted OR* (95% CI)	**Adjusted OR* (95% CI)**	**Adjusted OR* (95% CI)**
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.

BMI, body mass index; NOAC, non-vitamin K antagonist oral anticoagulant; OAC, oral anticoagulant; OR, odds ratio; SD, standard deviation; eGFR, estimated glomerular filtration rate.

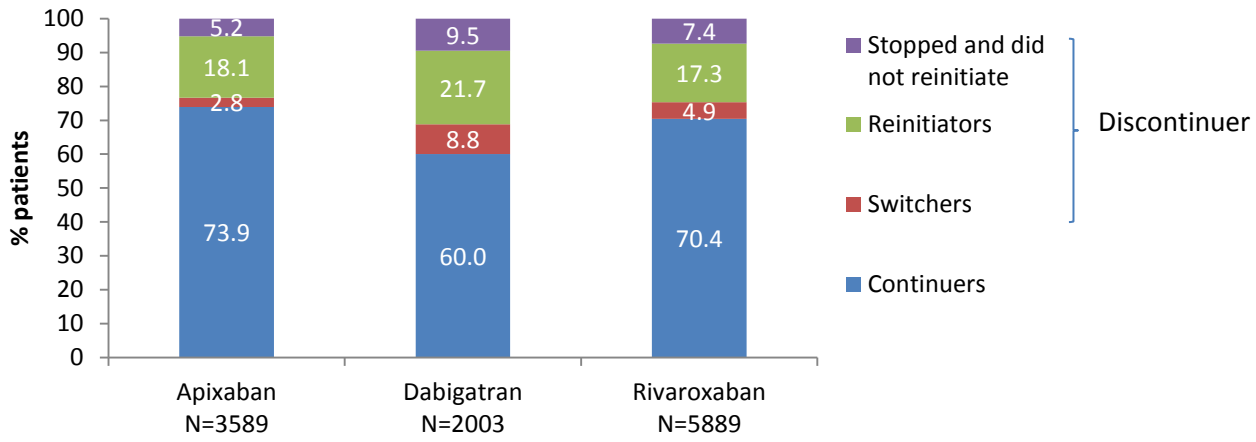
FIGURE LEGEND

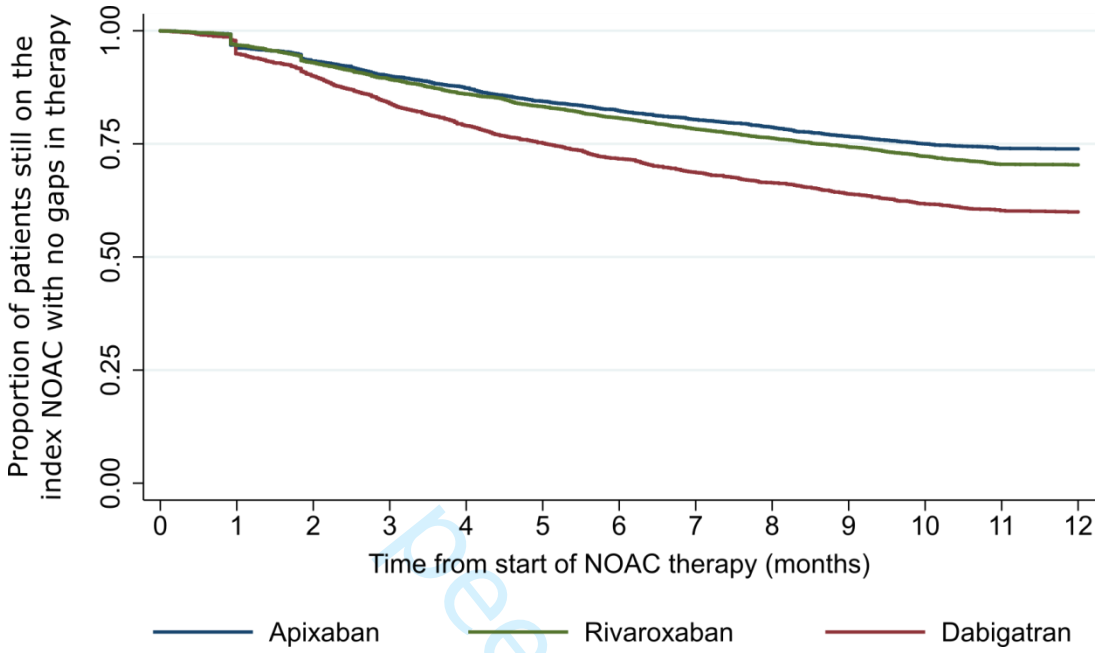
Figure 1. Patterns of NOAC use among first-time users of NOAC with NVAF (with >1 year of follow-up and using a 30-days treatment gap to define discontinuation).

NOAC, non-vitamin K oral anticoagulant; NVAF, non-valvular atrial fibrillation.

Figure 2. Kaplan–Meier plot showing time to NOAC discontinuation.

NOAC, non-vitamin K antagonist oral anticoagulant





Supplementary Table 1. 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

Supplementary Table 2. 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

Supplementary Table 3. 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

Supplementary Table 4. Read codes for pulmonary embolism, deep vein thrombosis and hip/knee replacement surgery.

Read code	Description PE
G401.00	Pulmonary embolism
G401100	Recurrent pulmonary embolism
G401000	Post operative pulmonary embolus
G402.00	Pulmonary infarct
G401.12	Pulmonary embolus
L096400	Pulmonary embolism following abortive pregnancy
L43..11	Obstetric pulmonary embolus
L43..00	Obstetric pulmonary embolism
L432.00	Obstetric blood-clot pulmonary embolism
L432000	Obstetric blood-clot pulmonary embolism unspecified
L432100	Obstetric blood-clot pulmonary embolism - delivered
L432300	Obstetric blood-clot pulmonary embolism + a/n complication
L432400	Obstetric blood-clot pulmonary embolism + p/n complication
L432z00	Obstetric blood-clot pulmonary embolism NOS
L43y.00	Other obstetric pulmonary embolism
L43y000	Other obstetric pulmonary embolism unspecified
L43y100	Other obstetric pulmonary embolism - delivered
L43y200	Other obstetric pulmonary embolism - delivered + p/n comp
L43y300	Other obstetric pulmonary embolism with antenatal comp
L43y400	Other obstetric pulmonary embolism with postnatal comp
L43yz00	Other obstetric pulmonary embolism NOS
L43z.00	Obstetric pulmonary embolism NOS
L43z000	Obstetric pulmonary embolism NOS, unspecified
L43z100	Obstetric pulmonary embolism NOS - delivered
L43z200	Obstetric pulmonary embolism NOS - delivered with p/n comp
L43z300	Obstetric pulmonary embolism NOS with antenatal complication
L43z400	Obstetric pulmonary embolism NOS with postnatal complication
L43zz00	Obstetric pulmonary embolism NOS
ZV12900	Personal history of pulmonary embolism

Read code	Description DVT
G801.00	Deep vein phlebitis and thrombophlebitis of the leg
G801.11	Deep vein thrombosis
G801.12	Deep vein thrombosis, leg
G801.13	DVT - Deep vein thrombosis
G801C00	Deep vein thrombosis of leg related to air travel
G801D00	Deep vein thrombosis of lower limb
G801E00	Deep vein thrombosis of leg related to intravenous drug use
G801F00	Deep vein thrombosis of peroneal vein
G801600	Thrombophlebitis of the femoral vein
G801700	Thrombophlebitis of the popliteal vein

G801800	Thrombophlebitis of the anterior tibial vein
G801900	Thrombophlebitis of the dorsalis pedis vein
G801A00	Thrombophlebitis of the posterior tibial vein
G801B00	Deep vein thrombophlebitis of the leg unspecified
G802000	Thrombosis of vein of leg
G80y.00	Other phlebitis and thrombophlebitis
G80y400	Thrombophlebitis of the common iliac vein
G80y500	Thrombophlebitis of the internal iliac vein
G80y600	Thrombophlebitis of the external iliac vein
G80y700	Thrombophlebitis of the iliac vein unspecified
G80y800	Phlebitis and thrombophlebitis of the iliac vein NOS
L414.12	Phlegmasia alba dolens - obstetric
L413.00	Antenatal deep vein thrombosis
L413.11	DVT - deep venous thrombosis, antenatal
L413000	Antenatal deep vein thrombosis unspecified
L413100	Antenatal deep vein thrombosis - delivered
L413200	Antenatal deep vein thrombosis with antenatal complication
L413z00	Antenatal deep vein thrombosis NOS
L414.00	Postnatal deep vein thrombosis
L414.11	DVT - deep venous thrombosis, postnatal
L414000	Postnatal deep vein thrombosis unspecified
L414100	Postnatal deep vein thrombosis - delivered with p/n comp
L414200	Postnatal deep vein thrombosis with postnatal complication
L414z00	Postnatal deep vein thrombosis NOS
SP12200	Post operative deep vein thrombosis
ZV12800	[V] Personal history deep vein thrombosis
ZV12811	[V] Personal history DVT- deep vein thrombosis
14A8100	H/O: Deep Vein Thrombosis
G82..00	Other venous embolism and thrombosis

Read code, Read range	**Description (hip/knee surgery)**
7K20.00 - 7K20z00	Total prosthetic replacement of hip joint using cement
7K21.00 - 7K21z00	Total prosthetic replacement of hip joint not using cement
7K22.00 - 7K22z00	Other total prosthetic replacement of hip joint
7K23.00 - 7K23z00	Prosthetic cemented hemiarthroplasty of hip
7K24.00 - 7K24z00	Prosthetic uncemented hemiarthroplasty of hip
7K25.00 - 7K25z00	Other prosthetic hemiarthroplasty of hip
7K2y.00	Other specified operations on hip joint
7K2z.00	Hip joint operations NOS
7K2..00	Hip joint operations
7K1D.00 - 7K1D01F	Primary open reduction fracture bone & intramedull fixation
7K1J000	Cls red+int fxn proximal femoral #+screw/nail device alone
7K1J011	Cl red intracaps frac neck femur fix-Garden cannulated screw
7K1J012	Cl red intracaps fract neck femur fix - Smith-Petersen nail

7K1J013	Cls red+int fxn prox femoral #+Richard's cannulat hip screw
7K6c.00 - 7K6cz00	Hybrid prosthetic replacement hip joint cemented acetab comp
7K6d.00 - 7K6dz00	Hybrid prosthetic replace hip joint cemented femoral compon
7K6e.00 - 7K6ez00	Hybrid prosthetic replacement of hip joint using cement
7K30.00- 7K30z00	Total prosthetic replacement of knee joint using cement
7K31.00 - 7K31z00	Total prosthetic replacement of knee joint not using cement
7K32.00 - 7K32z00	Other total prosthetic replacement of knee joint
7K37.00 - 7K37x00	Cemented unicompartmental knee replacement
7K38.00 - 7K38x00	Uncemented unicompartmental knee replacement
7K39.00 - 7K39x00	Hybrid unicompartmental knee replacement
7K3A.00	Unicompartmental knee replacement NOS
7K3y.00	Other specified operations on knee joint
7K3z.00	Knee joint operations NOS
7K3..00	Knee joint operations
7K30.1I	Manchester total replacement of knee joint using cement
7K3A.00	Unicompartmental knee replacement NOS
7K6q.00- 7K6qz00	Hybrid prosthetic replacement of knee joint using cement
7L06200 - 7L06017	Amputation leg

Supplementary Table 5. 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.

NOAC, non-vitamin-K antagonist oral anticoagulant; NVAF, non-valvular atrial fibrillation; OAC, oral anticoagulant

Supplementary Table 6. Time to re-initiation of OAC therapy among NVAF patients who reinitiated OAC therapy after a gap of >30 days from treatment with the initial prescribed NOAC (index NOAC).

	Time to re-initiation*		
	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 a 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.

NOAC, non-vitamin K antagonist oral anticoagulant; NVAF, non-valvular atrial fibrillation; OAC, oral anticoagulant

Supplementary Table 7. Associations between patient characteristics and discontinuation of NOAC therapy in the first year of treatment among patients with NVAF.

	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)

	Continuers N=7997	Discontinuers N=3484	Crude OR (95% CI)	Adjusted OR* (95% CI)
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)
eGFR_EPI				
>50mL/min	5857 (73.2)	2415 (69.3)	1.0 (reference)	1.0 (reference)
30–50 mL/min	1128 (14.1)	492 (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_2VASc 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)			
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.

BMI, body mass index; NOAC, non-vitamin K antagonist oral anticoagulant; NVAF, non-valvular atrial fibrillation; OAC, oral anticoagulant; OR, odds ratio; SD, standard deviation; eGFR, estimated glomerular filtration rate.

*Adjusted for all the other variables in the table.

†Frailty index (eFI): including a wide range of symptoms, signs, diseases, disabilities, abnormal laboratory values and social circumstances.

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract. **Page1 and 2**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found **Page 2**
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported. **Page 5 and 6**
Objectives	3	State specific objectives, including any prespecified hypotheses. **Page 6**
Methods		
Study design	4	Present key elements of study design early in the paper. **Page 6 and 7**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection **Page 6 and 7**
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up **Page 6 and 7**
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable. **Page 8 and 9**
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group **Page 7, 8, 9**
Bias	9	Describe any efforts to address potential sources of bias. **Page 6**
Study size	10	Explain how the study size was arrived at. **Page 6 and 7**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why. **Page 9**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding. **Page 9**
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) If applicable, explain how loss to follow-up was addressed
		(*e*) Describe any sensitivity analyses
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed. **Page 10**
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders. **Page 10 and Table 1**
		(b) Indicate number of participants with missing data for each variable of interest **Table 1**
		(c) Summarise follow-up time (eg, average and total amount)
Outcome data	15*	Report numbers of outcome events or summary measures over time
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders

		were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized. **Table 1**
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses. **Page 9**
Discussion		
Key results	18	Summarise key results with reference to study objectives. **Page 12**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias. **Page 13**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence. **Page 13 to 16**
Generalisability	21	Discuss the generalisability (external validity) of the study results. **Page 12**
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based. **Page 16**

*Give information separately for exposed and unexposed groups.

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