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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 UK

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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 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 (OAC) therapy (discontinuation was defined as a gap in OAC therapy of >30 days); switched OAC within 30 days; discontinued and reinitiated 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. Reinitiation 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 reinitiations were with the index NOAC. Patients starting on dabigatran were more likely to switch OAC therapy than those starting on apixaban; ORs 4.28 (95% CI 3.24 to 5.65) for dabigatran and 1.89 (95% CI 1.49 to 2.39) for rivaroxaban. Severely reduced renal function was a predictor of any discontinuation, OR 1.77 (95% CI 1.28 to 2.44).

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

Strengths and limitations of this study

- ► Our study is the largest to evaluate non-vitamin K antagonist oral anticoagulant (NOAC) discontinuation rates among patients with non-valvular atrial fibrillation 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 generalisable 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 (OAC) therapy to mitigate risk.[3 4]

In the 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 in the long term is advocated in most patients.[7 8] NOACs have clear advantages over vitamin K antagonists (VKAs) such as warfarin. In addition to their favourable benefit-risk profile and fewer food-drug 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 body weight. 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 non-valvular atrial fibrillation (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]

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 the 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 was patients with NVAF, individuals were required to have a record of AF (online supplementary table 1) but with no record of valvular replacement (online supplementary table 2) or mitral stenosis (online 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 (online 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 (ie, 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 normalised 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_2VASc 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, previous major bleeding, age >65 years, medication use predisposing to bleeding and alcohol use), but omitted international normalised 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 estimated glomerular filtration rate (eGFR) expressed as mL/min/1.73 m^2 applying the Chronic Kidney Disease Epidemiology Collaboration equation,[27] but we omitted ethnicity because this is not systematically recorded in THIN. Patients with no recorded valid serum creatinine measurement were categorised as 'missing'. 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 (ie, 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 reinitiators, 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 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 reinitiators, switchers and non-reinitiators) were identified using unconditional logistic regression to estimate ORs with 95% 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 men than women in each cohort, and patients starting OAC therapy on apixaban were more likely to be OAC-naïve (55.0%) 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 in 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 (online supplementary table 5).

Less than 10% of patients 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 (53.0% (53/100)) for patients starting on apixaban, compared with 64.2% (113/176) for dabigatran and 57.1% (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

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)
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/1.73 m^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)

Continued

Table 1 Continued

	Apixaban n=3589	Dabigatran n=2003	Rivaroxaban n=5889	Total n=11 481
<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; eGFR, estimated glomerular filtration rate; NOAC, non-vitamin K oral anticoagulant; OAC, oral anticoagulant.

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) (online supplementary table 6).

Predictors of discontinuation

Associations between patient characteristics and discontinuation of NOAC therapy in the first year of treatment are shown in online 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 to 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 to 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 to 5.65), and those starting on rivaroxaban were twice as likely to switch (adjusted OR 1.89, 95% CI 1.49 to 2.39). Having a reduced renal function (<30 eGFR ml/min/1.73 m²) was associated with all three kinds of treatment discontinuation (table 4).

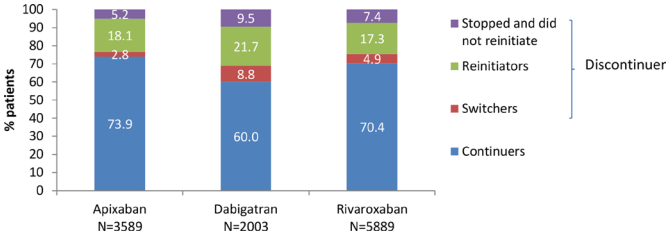

Figure 1 Patterns of NOAC use among first-time users of NOAC with NVAF (with >1 year of follow-up and using a 30-day treatment gap to define discontinuation). NOAC, non-vitamin K oral anticoagulant; NVAF, non-valvular atrial fibrillation.

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 long 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 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 patients with NVAF 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 analyse 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 were 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 to the eligibility criterion of requiring a year of available follow-up data after the index date.

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 (%).
*Restarted 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; VKA, vitamin K antagonist .

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 2871 patients with NVAF, Johnson *et al*[13] reported broadly similar, although 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 the 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 (eg, the inclusion of OAC-naïve users only). One-year NOAC discontinuation rates among patient populations with NVAF reported from claims database studies in USA 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] although not all,[22] studies. Most other studies on NOAC discontinuation have reported rates over shorter time periods.[34]

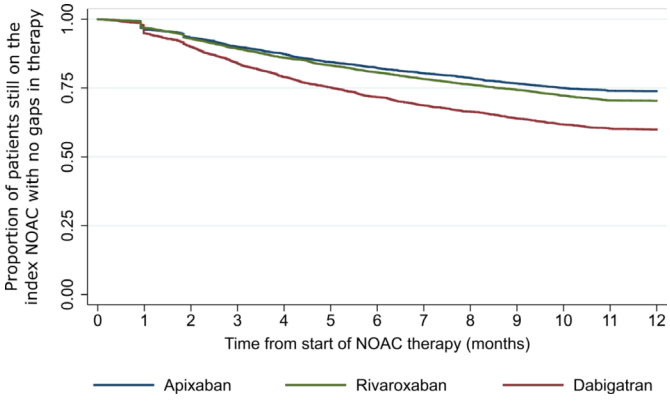

Figure 2 Kaplan-Meier plot showing time to NOAC discontinuation. NOAC, non-vitamin K antagonist oral anticoagulant.

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, patients 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 USA, who found that among 23 309 patients with NVAF starting NOAC therapy, patients treated with rivaroxaban were significantly less likely to discontinue therapy at 1 year, as well as at 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 patients with NVAF in our study

Table 3 Time to discontinuation of NOAC therapy among patients with NVAF 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 (ie, 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; VKA, vitamin K antagonist.

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 in another large US administrative database among 34 022 OAC-naïve patients with NVAF, 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 analyse 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 UK patients with NVAF initiating NOAC therapy, 7 (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 of 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 hospitalisation for a 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 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_2VASc Score. Observational data suggest that interruption of warfarin treatment in patients with AF is associated with an increased risk of thromboembolism,[38] as is poor adherence to NOACs.[39 40] 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 the number of patients with NVAF benefiting from NOAC-mediated stroke protection.

CONCLUSION

In conclusion, while the majority of patients with NVAF in the UK initiating NOAC treatment received continuous

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 (n=7997) versus discontinuers who reinitiated OAC therapy (n=2106)	Continuers (n=7997) versus discontinuers who switched OAC therapy (n=565)	Continuers (n=7997) versus discontinuers who did not reinitiate 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 to 0.99)	1.25 (1.03 to 1.53)	0.90 (0.76 to 1.07)
Age (years)			
<60	1.0 (reference)	1.0 (reference)	1.0 (reference)
60–69	0.74 (0.62 to 0.90)	0.95 (0.66 to 1.37)	0.33 (0.26 to 0.43)
70–79	0.74 (0.61 to 0.90)	0.93 (0.63 to 1.36)	0.27 (0.21 to 0.36)
≥80	0.72 (0.58 to 0.89)	0.68 (0.45 to 1.03)	0.35 (0.26 to 0.48)
Index NOAC			
Apixaban	1.0 (reference)	1.0 (reference)	1.0 (reference)
Dabigatran	1.36 (1.16 to 1.60)	4.28 (3.24 to 5.65)	2.19 (1.72 to 2.79)
Rivaroxaban	0.98 (0.87 to 1.09)	1.89 (1.49 to 2.39)	1.52 (1.26 to 1.83)
Year of first NOAC prescription			
2011–2013	1.0 (reference)	1.0 (reference)	1.0 (reference)
2014–2016	0.90 (0.79 to 1.02)	1.21 (0.97 to 1.50)	0.82 (0.68 to 0.99)
eGFR (mL/min/1.73 m^2)			
>50	1.0 (reference)	1.0 (reference)	1.0 (reference)
30–50	1.08 (0.93 to 1.26)	1.23 (0.95 to 1.59)	1.53 (1.22 to 1.91)
<30	1.51 (1.01 to 2.25)	2.21 (1.20 to 4.08)	2.25 (1.30 to 3.87)
Missing	1.31 (1.13 to 1.51)	1.28 (0.98 to 1.67)	1.30 (1.05 to 1.62)
OAC-naïve status			
Naïve	1.0 (reference)	1.0 (reference)	1.0 (reference)
Non-naïve	1.08 (0.97 to 1.19)	1.25 (1.04 to 1.50)	0.74 (0.64 to 0.87)
BMI (kg/m^2)			
<20	0.98 (0.74 to 1.31)	0.85 (0.50 to 1.44)	1.26 (0.86 to 1.85)
20–24	1.0 (reference)	1.0 (reference)	1.0 (reference)
25–29	0.94 (0.82 to 1.07)	1.01 (0.80 to 1.28)	0.90 (0.74 to 1.09)
≥30	0.89 (0.77 to 1.02)	0.78 (0.61 to 1.00)	0.67 (0.54 to 0.83)
Missing	0.94 (0.70 to 1.25)	0.99 (0.58 to 1.69)	1.37 (0.94 to 2.01)
Smoking			
Non-smoker	1.0 (reference)	1.0 (reference)	1.0 (reference)
Smoker	0.99 (0.82 to 1.19)	0.64 (0.43 to 0.96)	0.83 (0.62 to 1.10)
Ex-smoker	0.96 (0.86 to 1.07)	1.08 (0.90 to 1.30)	0.95 (0.81 to 1.12)
Missing	2.47 (0.40 to 15.21)	–	1.42 (0.11 to 18.04)
Alcohol (units/week)			
None	1.0 (reference)	1.0 (reference)	1.0 (reference)
1–9	1.03 (0.90 to 1.18)	1.13 (0.89 to 1.43)	0.87 (0.71 to 1.06)
10–20	1.13 (0.95 to 1.33)	0.92 (0.67 to 1.26)	1.11 (0.86 to 1.43)
21–41	1.19 (0.95 to 1.49)	1.32 (0.89 to 1.96)	0.85 (0.59 to 1.22)
≥42	1.75 (1.30 to 2.35)	1.10 (0.58 to 2.08)	1.24 (0.77 to 1.99)
Missing	1.12 (0.92 to 1.36)	0.93 (0.65 to 1.34)	0.77 (0.57 to 1.05)

Continued

Table 4 Continued

	Continuers (n=7997) versus discontinuers who reinitiated OAC therapy (n=2106)	Continuers (n=7997) versus discontinuers who switched OAC therapy (n=565)	Continuers (n=7997) versus discontinuers who did not reinitiate OAC therapy (n=813)
	Adjusted OR* (95% CI)	Adjusted OR* (95% CI)	Adjusted OR* (95% CI)
Frailty index			
Fit	1.0 (reference)	1.0 (reference)	1.0 (reference)
Mild frailty	0.87 (0.75 to 1.01)	0.91 (0.68 to 1.21)	0.63 (0.51 to 0.78)
Moderate frailty	1.05 (0.88 to 1.25)	1.24 (0.90 to 1.70)	0.85 (0.66 to 1.11)
Severe frailty	1.01 (0.82 to 1.24)	1.27 (0.88 to 1.85)	1.18 (0.87 to 1.60)
CHA_2DS_2VASc Score			
2	1.0 (reference)	1.0 (reference)	1.0 (reference)
3	0.91 (0.78 to 1.05)	1.02 (0.77 to 1.35)	0.69 (0.54 to 0.89)
4	0.85 (0.73 to 1.00)	1.03 (0.77 to 1.38)	0.80 (0.61 to 1.04)
HAS–BLED Score			
0	1.0 (reference)	1.0 (reference)	1.0 (reference)
2	0.99 (0.88 to 1.11)	0.85 (0.69 to 1.04)	0.88 (0.73 to 1.07)
3	0.94 (0.81 to 1.09)	0.79 (0.61 to 1.04)	0.79 (0.62 to 1.01)

*Adjusted for all the other variables in the table.
BMI, body mass index; eGFR, estimated glomerular filtration rate; NOAC, non-vitamin K antagonist oral anticoagulant; NVAF, non-valvular atrial fibrillation; OAC, oral anticoagulant.

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.

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Ethics approval 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 anonymised THIN data are used.

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Correction: *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 UK*

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This article was previously published with an error.

In table 1, the mean age of patients in the Rivaroxaban column should read 74.3 (10.5) and not 71.7 (14.4).

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