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Real-world data on the incidence, mortality, and cost of ischaemic stroke and major bleeding events among non-valvular atrial fibrillation patients in England

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Abstract

Rationale, Aims, and Objectives: Several novel oral anticoagulants (NOACs) are licensed for atrial fibrillation (AF) treatment in the United Kingdom. We describe the incidence and mortality from ischaemic stroke and major bleeding in non-valvular atrial fibrillation (NVAF) patients in England, including treatment patterns before/following introduction of NOACs, healthcare resource utilization (HRU), and costs post-onset of these events.

Method: Data were extracted from the UK Clinical Practice Research Datalink linked to Hospital Episode Statistics secondary care and Office for National Statistics mortality data.

Results: Of 42 966 patients with a first AF record between 2011 and 2016, 9143 patients (21.3%) remained without AF (antiplatelets/antithrombotics) treatment post-index diagnosis. The proportion of patients receiving aspirin for ≥3 months post-index declined during the study (50.6%-5.5%), irrespective of CHA_2DS_2-VASc score, while the proportion prescribed NOACs increased (2.0%-70.1%). Rates of ischaemic stroke per 1000 patient-years (95% CI) were 9.4 (3.8-15.0) with NOACs, 10.4 (8.0-12.9) with warfarin, 20.1 (16.4-23.8) with aspirin, 21.3 (5.3-37.2) with other antiplatelets and 43.6 (39.3-47.8) in patients without AF prescription. Major bleeding occurred at a similar rate with different treatments. All-cause mortality rates were 42.8 (31.4-54.3) with NOACs, 46.3 (41.1-51.5) with warfarin, 56.5 (50.5-62.4) with aspirin, 102.2 (76.2-128.3) with

other antiplatelets and 412.8 (399.6-426.0) with no AF prescription. Mean annual National Health Service healthcare costs up to 1 year post-index were lowest in patients receiving aspirin plus other antiplatelets without an event (£6152), and highest in patients with an event without AF prescriptions (£17 957). By extrapolation, national AF HRU in the United Kingdom in 2016 was estimated at £8-16 billion annually.

Conclusions: These data provide temporal insights into AF treatment patterns and outcomes for NVAF patients in England and highlight the need to review higher stroke risk AF patients not receiving antiplatelet/antithrombotic prescriptions.

KEYWORDS

atrial fibrillation, bleeding, health economics, ischaemic stroke, real-world data

1 | INTRODUCTION

Atrial fibrillation (AF) is the most common form of cardiac arrhythmia, with an increasing prevalence due to improved survival rates from conditions such as ischaemic heart disease as well as an ageing population.[1] AF is an independent risk factor for stroke and thromboembolism, with an estimated 5-fold higher risk than in the normal population,[2] and is predictive of premature mortality[3] and heart failure.[4] The estimated direct cost of AF during 2000 in the United Kingdom, excluding hospitalizations with a secondary AF coding and nursing home costs, was £459 million (0.88% of the National Health Service [NHS] expenditure).[5]

Effective stroke prevention can be achieved with oral anticoagulant (OAC) treatment. In a study conducted using English electronic health records from 2006 to 2016, the prevalence of AF and OAC use increased, while rates of hospitalized AF-related stroke declined from 2011 and were significantly associated with the uptake of OACs.[6] Despite the publication of numerous guidelines on AF management, a substantial proportion of eligible patients are undertreated.[7] In a systematic review examining the underuse of OACs in AF, 25 of 29 studies described undertreatment, with 21 of these reporting treatment levels <60% (range 19.0%-81.3%) of optimal practice. Patients at increased risk for stroke with a CHA_2DS_2-VASc score ≥2 were also suboptimally treated, with seven of nine studies reporting treatment levels <70% (range 39.0%-92.3%) of optimal practice.[8]

Since 2012, a number of novel OACs (NOACs) have been licensed for AF treatment in the United Kingdom that, unlike warfarin, do not require prothrombin time/international normalized ratio (INR) monitoring. The risk of all-cause mortality was lower with NOACs compared with warfarin (INR 2.0-3.0) in a meta-analysis of 23 randomized trials involving 94 656 patients.[9] The risk of major/intracranial bleeding was also reduced with most of the NOACs relative to warfarin, although the NOACs were associated with substantial non-neurological bleeding risk. In the landmark phase III AF trials, the risk of gastrointestinal bleeding was higher with rivaroxaban, dabigatran, and edoxaban at some doses, and similar for apixaban, vs warfarin.[9]

Data on the long-term costs of ischaemic stroke or bleeding in non-valvular AF (NVAF), AF in the absence of rheumatic mitral stenosis, a mechanical or bioprosthetic heart valve or mitral valve repair[10] before and after introduction of NOACs and after guidance to dissuade mono-prescription of aspirin, have not been investigated. This retrospective study aimed to describe temporal trends in incidence and mortality from ischaemic stroke and major bleeding in NVAF patients in England, including patterns of treatment following availability of NOACs, healthcare resource utilization (HRU), and costs to the NHS after the onset of these events. This is an observational study and, given the risk of potential confounding from prescribing behaviour, between-treatment comparisons should be treated with caution and support hypothesis generation for further research or bring attention to patients potentially at increased risk. The value of our results is that they are nationally representative and take an objective approach to all treatment/non-treatment options, with unique data linkages that are unavailable in most healthcare settings.

2 | METHODS

2.1 | Data source

Data were extracted from the UK Clinical Practice Research Datalink (CPRD), an ongoing primary care database of anonymized general practitioner (GP) medical records representing ~7% of the UK population.[11] CPRD data were linked to English Hospital Episode Statistics (HES) secondary care data and Office for National Statistics (ONS) mortality data. Patients were identified using the CPRD GOLD database and HES admitted data. HRU data were collected from CPRD GOLD, HES admitted, outpatient and accident and emergency (A&E) files.

Prescribing data were recorded in CPRD GOLD, allowing analyses of the management of patients initially and over time. Over-the-counter medication use could not be formally captured. Patients were linked across the datasets using CPRD unique identifiers and the study team had access to anonymized records. The study protocols were approved by an independent Scientific Advisory Committee.

2.2 | Patients

For treatment and mortality, data from January 1, 2011 to June 30, 2016 were included. The AF index period ended on March 31, 2016, due to the limited availability of HES data. The index date was the first ever AF record in CPRD GOLD or HES (see supporting information 1).

Patient selection criteria included: a first record of AF during the study period, ≥364 days of active registration before the index date, ≥18 years of age on the index date and eligible for linkage with HES/ONS data. Patients with heart valve problems or replacement before, on or after the index date in CPRD GOLD or HES were excluded. For each outcome, the first ever record during follow-up after the index AF was identified.

2.3 | Endpoints

We described baseline patient characteristics, use of OACs and antiplatelets and the incidence of ischaemic stroke, major bleeding, and mortality. We also analysed HRU and healthcare costs to the NHS in patients with/without these events. Patient characteristics of interest, and potential confounding factors, were: age, sex, ethnicity, smoking and drinking status, body mass index (BMI), deprivation (Index of Multiple Deprivation), CHA_2DS_2-VASc score (stroke risk),[12] HAS-BLED score (bleeding risk),[12] comorbidities, medication use, and frailty.[13]

Use of OACs was assessed in OAC-naive patients (no exposure in the 364 days pre-index date) from the time of first AF record to first OAC prescription. Data of interest were: overall OAC use, OAC use by drug, calendar year, age, and OAC group (warfarin, NOACs, aspirin, or other antiplatelets).

Ischaemic stroke or major bleeding was defined as a hospital record in the HES or a primary care record after the first record of AF (index date). Mortality rates from ischaemic stroke and major bleeding from ONS mortality data were estimated overall and by age, sex, and OAC treatment. Cause of death was ascertained from death certification records from ONS and linked HES data. Ischaemic stroke and major bleeding within 10 days before death date were also recorded as cause of death.

HRU was measured by the number of GP visits, specialist referrals, laboratory tests, prescriptions, A&E visits and investigations, outpatient visits, and hospitalizations. Activity was captured using procedural and visit codes (OPCS codes/GP coding systems in CPRD) and frequency of visits in each category of interest. NHS costs were valued in 2015 to 2016 UK pounds using standard sources of unit costs.[14-16]

2.4 | Statistical analyses

Continuous variables were summarized as mean, SD, median and interquartile range (IQR). Categorical variables were reported as absolute count and percentage of counts in each category. Incidence rates per 1000 patient-years (PY) were estimated using a generalized linear model with Poisson distribution (log link), adjusting for age and sex. Results were stratified by baseline risk scores and the potentially confounding factors listed above. Mortality was estimated as the number of deaths divided by the total time at risk, adjusting for age and sex using a generalized linear model with Poisson distribution.

Altered Lin's regression[17] was used to estimate mean healthcare costs per quarter per patient, up to 1 year after newly diagnosed AF, as confounding factors (baseline CHA_2DS_2-VASc score, baseline HAS-BLED score, and frailty) needed to be controlled. Such methodology is applicable because detailed cost accumulation information is available during the follow-up period in the data. As most patients with an event had their first event within the first 3 months following NVAF diagnosis, we performed sensitivity analyses to compare results using different follow-up periods (see supporting information 2).

Different follow-up periods were used for incidence/mortality, HRU, and costs (HRU and cost analyses did not end at the outcomes of interest). For incidence/mortality, patients were followed from the index date until the earliest of one of the outcomes of interest, transfer out of the practice, last data collection or death, whichever occurred first. For HRU, patients were followed from the index date up to 3 years until transfer out of the practice, last data collection or death, whichever occurred first. For cost analyses, patients were followed from the index date up to 1 year until transfer out of the practice, last data collection or death, whichever occurred first.

Data are reported in-line with the STROBE checklist for observational studies (see supporting information 2).

3 | RESULTS

3.1 | Patients

In total, 131 814 patients had their first AF event recorded during 2011 to 2016 (Figure 1). The last day of follow-up was limited to the end of Q1 2016, due to incomplete HES-CPRD linkage for 2016. Overall, 62 238 patients (47.2%) were excluded, leaving 69 576 patients (52.8%) with ≥364 days of active registration before the index date. Applying the inclusion criteria of ≥18 years of age on index date, and the definition of NVAF on, before or after the index date, 42 966 patients were included in the study. As CPRD coverage represents ~7% of the UK population (based on the 2013 mid-year UK population[11]), extrapolation of this incidence rate would suggest there may have been 900 000 patients with a new diagnosis of NVAF that met our study inclusion criteria in the United Kingdom during the period 2011 to Q1 2016.

3.2 | First AF diagnosis

At the time of first AF diagnosis, the median age of patients included in our study was 78 years (IQR 69-85), with the majority aged

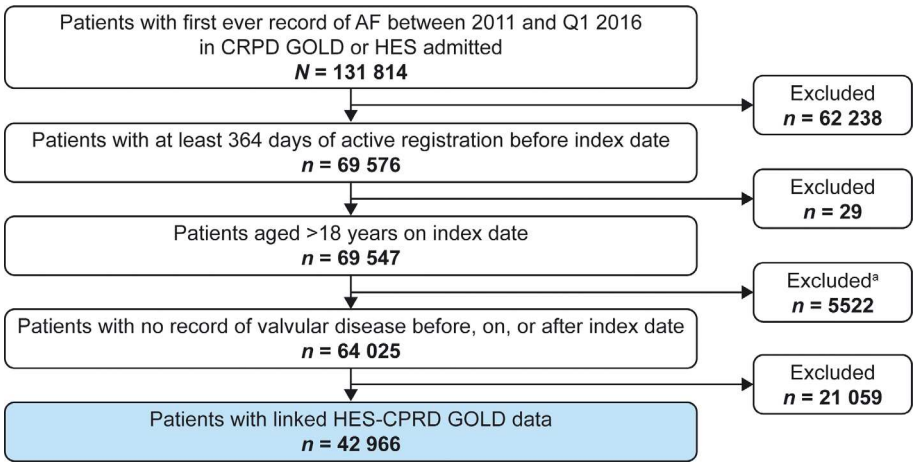

FIGURE 1 Patient attrition in the linked HES-CPRD GOLD. [a]Patients with at least one record of valvular disease before, on or after index date in CPRD GOLD or HES admitted. AF, atrial fibrillation; CPRD, UK Clinical Practice Research Datalink; HES, English Hospital Episode Statistics; Q, quarter

≥65 years (83.6%, n = 35 907; Table 1). The mean (SD) duration of active registration pre-index date was 13.0 (6.1) years. Most patients had no prior ischaemic stroke (91.2%, n = 39 204) or major bleeding (81.3%, n = 34 917) recorded and had high (≥3) CHA_2DS_2-VASc scores (45.2%, n = 19 437) with low (≤1) HAS-BLED scores (47.3%, n = 20 330). Most frequent baseline comorbidities were hypertension (67.2%, n = 28 871) and renal disease (27.2%, n = 11 700; Table 1). Commonly used medications were antihypertensives (62.4%, n = 26 793), statins (40.5%, n = 17 404) and antiplatelets (36.5%, n = 15 674). Overall, 5.4% of patients (n = 2337) had received anticoagulant treatment within 90 days prior to their first AF diagnosis.

Treatment-naïve patients with a singular first treatment of warfarin, NOACs, aspirin or other antiplatelet agent showed a similar distribution across the low (≤1), intermediate (2), and high (≥3) CHA_2DS_2-VASc score categories (Table 1). Most of the patients who did not receive any AF treatment of interest (warfarin, NOAC, aspirin or other antiplatelet) post-index (n = 12 375) had a high CHA_2DS_2-VASc score. Most patients within this group who were not treatment naïve (n = 3232) had intermediate (2) or high (≥3) HAS-BLED scores.

Table S1 shows patient characteristics by outcome of the index event, with notable differences observed between those who died vs survived. The proportion of females was significantly higher in the group of AF patients who died vs survived (52.3% vs 46.5%, respectively, $P < .0001$). Similarly, the proportion of white patients (95.3% vs 90.8%, respectively, $P < .0001$), frail patients (35.6% vs 19.9%, respectively, $P < .0001$), or patients with high CHA_2DS_2-VASc scores (57.8% vs 37.2%, respectively, $P < .0001$) was significantly higher among AF patients who died vs survived an event. The proportion of current drinkers was significantly lower in the group of AF patients who died compared with those who survived (16.3% vs 23.1%, respectively, $P < .0001$). Likewise, the proportion of obese patients (BMI ≥30; 20.6% vs 31.0%, respectively, $P < .0001$) or patients with low HAS-BLED scores (44.5% vs 55.5%, respectively, $P < .0001$) was significantly lower among AF patients who died vs survived an event. The proportion of patients with peripheral vascular disease, congestive heart failure, or renal disease who died following an event was higher compared with those who survived. There were similar proportions of aspirin-treated patients who died or survived.

3.3 | Treatment for first AF event

Approximately half of all patients (54.1%, n = 23 228) received no AF treatment within 364 days prior to index date, and around one-third (31.2%, n = 13 405) started singular AF treatment after index diagnosis (Figure 2). First singular AF prescriptions post-index consisted of warfarin (41.9%, n = 5618), aspirin (38.3%, n = 5128), NOACs (15.0%, n = 2011), and other antiplatelets (4.8%, n = 648). Overall, 9143 patients (21.3%) remained without any AF antithrombotic or antiplatelet treatment of interest prescriptions after index diagnosis during the follow-up period.

In patients who initiated treatment within 3 months after the index date and remained on treatment for ≥3 months, the proportion prescribed aspirin declined from 50.6% (n = 817) in 2011 to 5.5% (n = 9) in Q1 2016. Similar findings were seen in patients with low and intermediate/high CHA_2DS_2-VASc scores. A reduction in the proportion of patients being treated with warfarin was also noted, from 54.7% (n = 705) in 2014 to 22.6% (n = 37) in Q1 2016. Conversely, the proportion who were prescribed NOACs increased steadily from 2.0% (n = 33) in 2012 to 70.1% (n = 115) in Q1 2016 (Figure 3).

The proportion of patients receiving a first AF prescription who remained on that medication for ≥3 months ranged from 42.0% (n = 272) with other antiplatelets to 45.7% (n = 2344) with aspirin, 58.1% (n = 1168) with NOACs and 62.3% (n = 3502) with warfarin (Figure 4). Rates of prescription stasis were similar between patients with low or intermediate/high CHA_2DS_2-VASc scores.

3.4 | Incidence of adverse outcomes and mortality rates

Among patients who received continued AF treatment in the first 3 months post-index, the sex- and age-adjusted incidence of ischaemic stroke per 1000 PY (95% confidence interval [CI]) was 9.4 (3.8-15.0) in patients receiving NOACs, 10.4 (8.0-12.9) in those receiving warfarin, 20.1 (16.4-23.8) in patients receiving aspirin, 21.3 (5.3-37.2) in patients receiving antiplatelets and 43.6 (39.3-47.8) in those without AF prescription (Table 2). Mortality rates from

TABLE 1 Patient characteristics at the time of first AF diagnosis, by treatment status

			Treatment-naïve patients with singular first treatment[a]								Patients without treatment of interest post-index			
	All AF patients (N = 42 966)		Warfarin (n = 5618)		NOACs (n = 2011)		Aspirin (n = 5128)		Other antiplatelet[b] (n = 648)		Not treatment naïve (n = 3232)		Treatment naïve (n = 9143)	
Characteristic	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Sex														
Male	22 514	52.4	2957	52.6	1096	54.5	2638	51.4	294	45.4	1632	50.5	4203	46.0
Female	20 452	47.6	2661	47.4	915	45.5	2490	48.6	354	54.6	1600	49.5	4940	54.0
Age at first AF, years														
18-34	300	0.7	26	0.5	5	0.2	12	0.2	0	0.0	10	0.3	228	2.5
35-44	568	1.3	88	1.6	29	1.4	61	1.2	3	0.5	14	0.4	307	3.4
45-54	1771	4.1	308	5.5	132	6.6	257	5.0	12	1.9	58	1.8	625	6.8
55-64	4420	10.3	756	13.5	291	14.5	758	14.8	53	8.2	145	4.5	1104	12.1
65-74	9889	23.0	1618	28.8	569	28.3	1364	26.6	139	21.5	522	16.2	1584	17.3
74-84	14 510	33.8	1946	34.6	640	31.8	1492	29.1	227	35.0	1126	34.8	2337	25.6
85+	11 508	26.8	876	15.6	345	17.2	1184	23.1	214	33.0	1357	42.0	2958	32.4
Mean (SD)	76.0 (12.6)		73.0 (11.8)		72.9 (12.1)		74.3 (12.3)		78.9 (11.0)		81.0 (10.8)		74.5 (16.3)	
Median (IQR)	78 (69-85)		75 (66-82)		74 (65-82)		75 (66-84)		80 (71-87)		83 (75-89)		78 (65-87)	
Ethnicity														
White	39 888	92.8	5174	92.1	1796	89.3	4616	90.0	610	94.1	3093	95.7	8411	92.0
Asian	496	1.2	48	0.9	6	0.3	51	1.0	6	0.9	38	1.2	106	1.2
Black	250	0.6	15	0.3	5	0.2	33	0.6	3	0.5	18	0.6	72	0.8
Other	2332	5.4	381	6.8	204	10.1	428	8.3	29	4.5	83	2.6	554	6.1
Year of first AF														
2011	9415	21.9	1193	21.2	32	1.6	1692	33.0	148	22.8	682	21.1	1801	19.7
2012	9593	22.3	1294	23.0	109	5.4	1533	29.9	166	25.6	698	21.6	1843	20.2
2013	8738	20.3	1226	21.8	247	12.3	1088	21.2	138	21.3	642	19.9	1882	20.6
2014	7638	17.8	1119	19.9	537	26.7	568	11.1	115	17.7	586	18.1	1707	18.7
2015	6271	14.6	697	12.4	887	44.1	215	4.2	76	11.7	519	16.1	1512	16.5
2016 Q1[c]	1311	3.1	89	1.6	199	9.9	32	0.6	5	0.8	105	3.2	398	4.4
Active registration[d] pre-index date, years														
Mean (SD)	13.0 (6.1)		13.0 (6.0)		13.9 (6.5)		12.9 (5.9)		13.5 (5.9)		13.1 (6.2)		12.6 (6.3)	
Median (IQR)	13.0 (9.1-16.6)		13.0 (9.2-16.5)		14.2 (9.7-17.3)		12.7 (9.3-16.3)		13.4 (10.0-17.3)		13.1 (9.2-16.9)		12.8 (8.2-16.4)	
Active registration post-index date, years[e]														
Mean (SD)	1.7 (1.4)		2.2 (1.4)		1.3 (1.0)		2.4 (1.5)		2.0 (1.4)		0.3 (0.8)		1.0 (1.3)	
Median (IQR)	1.3 (0.4-2.6)		2.0 (1.0-3.1)		1.0 (0.5-1.7)		2.3 (1.2-3.5)		1.8 (0.9-3.1)		0.1 (0.0-0.2)		0.4 (0.1-1.6)	
Time to first treatment after AF index, days														
Mean (SD)	–		67.3 (160.8)		106.6 (243.8)		59.5 (147.7)		118.1 (234.9)		–		–	
Median (IQR)	–		18 (5-53)		25 (7-73)		14 (0-42)		31.5 (15-73)		–		–	
Smoking status[e]														
Current	3504	8.2	377	6.7	140	7.0	364	7.1	43	6.6	319	9.9	788	8.6
Ex	14 208	33.1	1718	30.6	596	29.6	1513	29.5	203	31.3	1114	34.5	2353	25.7
Non	7598	17.7	1065	19.0	393	19.5	972	19.0	109	16.8	492	15.2	1361	14.9
Unknown	17 656	41.1	2458	43.8	882	43.9	2279	44.4	293	45.2	1307	40.4	4641	50.8

(Continues)

TABLE 1 (Continued)

			Treatment-naïve patients with singular first treatment[a]								Patients without treatment of interest post-index			
	All AF patients (N = 42 966)		Warfarin (n = 5618)		NOACs (n = 2011)		Aspirin (n = 5128)		Other antiplatelet[b] (n = 648)		Not treatment naïve (n = 3232)		Treatment naïve (n = 9143)	
Characteristic	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Drinking status[e]														
Current	9222	21.5	1173	20.9	418	20.8	1009	19.7	101	15.6	632	19.6	1366	14.9
Ex	2849	6.6	285	5.1	85	4.2	247	4.8	37	5.7	273	8.4	479	5.2
Non	998	2.3	102	1.8	35	1.7	107	2.1	20	3.1	92	2.8	221	2.4
Unknown	29 897	69.6	4058	72.2	1473	73.2	3765	73.4	490	75.6	2235	69.2	7077	77.4
BMI, kg/m^2														
<18.5	1156	2.7	77	1.4	33	1.6	113	2.2	25	3.9	169	5.2	417	4.6
18.5 to < 25	12 432	28.9	1373	24.4	540	26.9	1463	28.5	220	34.0	1127	34.9	3102	33.9
≥25 to < 30	14 486	33.7	1975	35.2	658	32.7	1808	35.3	200	30.9	1003	31.0	2687	29.4
≥30	12 246	28.5	1869	33.3	666	33.1	1391	27.1	157	24.2	740	22.9	1994	21.8
Unknown	2646	6.2	324	5.8	114	5.7	353	6.9	46	7.1	193	6.0	943	10.3
Mean (SD)	27.9 (6.2)		28.8 (6.3)		28.6 (6.4)		28.0 (6.2)		26.9 (6.1)		26.7 (6.3)		26.7 (6.2)	
Median (IQR)	27.0 (23.8-30.9)		27.7 (24.7-31.9)		27.7 (24.3-32.0)		27.1 (23.9-30.8)		26.3 (22.6-30.1)		25.9 (22.6-29.8)		25.8 (22.6-29.8)	
Deprivation														
1 (least deprived)	7285	17.0	985	17.5	381	18.9	927	18.1	101	15.6	533	16.5	1598	17.5
2	8910	20.7	1198	21.3	440	21.9	1093	21.3	137	21.1	659	20.4	1893	20.7
3	9015	21.0	1288	22.9	417	20.7	1014	19.8	148	22.8	601	18.6	1932	21.1
4	8136	18.9	968	17.2	316	15.7	958	18.7	141	21.8	702	21.7	1756	19.2
5	9620	22.4	1179	21.0	457	22.7	1136	22.2	121	18.7	737	22.8	1964	21.5
Prior ischaemic stroke event														
No	39 204	91.2	5525	98.3	1973	98.1	5044	98.4	590	91.0	2704	83.7	8917	97.5
Yes	3762	8.8	93	1.7	38	1.9	84	1.6	58	9.0	528	16.3	226	2.5
Prior major bleeding event														
No	34 917	81.3	4796	85.4	1721	85.6	4364	85.1	517	79.8	2441	75.5	7480	81.8
Yes	8049	18.7	822	14.6	290	14.4	764	14.9	131	20.2	791	24.5	1663	18.2
CHA_2DS_2-VASc score[e]														
Low (≤1)	10 953	25.5	1927	34.3	740	36.8	1749	34.1	134	20.7	336	10.4	2823	30.9
Intermediate (2)	12 576	29.3	1736	30.9	597	29.7	1505	29.3	184	28.4	913	28.2	2311	25.3
High (≥3)	19 437	45.2	1955	34.8	674	33.5	1874	36.5	330	50.9	1983	61.4	4009	43.8
Mean (SD)	2.3 (1.3)		1.9 (1.2)		1.9 (1.2)		2.0 (1.2)		2.5 (1.3)		2.9 (1.3)		2.1 (1.3)	
Median (IQR)	2 (1-3)		2 (1-3)		2 (1-3)		2 (1-3)		3 (2-3)		3 (2-3)		2 (1-3)	
HAS-BLED score[e]														
Low (≤1)	20 330	47.3	4323	76.9	1569	78.0	3995	77.9	450	69.4	441	13.6	6716	73.5
Intermediate (2)	16 268	37.9	1107	19.7	378	18.8	965	18.8	146	22.5	1730	53.5	1945	21.3
High (≥3)	6368	14.8	188	3.3	64	3.2	168	3.3	52	8.0	1061	32.8	482	5.3
Mean (SD)	1.6 (0.9)		1.1 (0.7)		1.1 (0.7)		1.1 (0.7)		1.3 (0.8)		2.3 (0.9)		1.1 (0.8)	
Median (IQR)	2 (1-2)		1 (1-1)		1 (1-1)		1 (1-1)		1 (1-2)		2 (2-3)		1 (1-2)	
Frailty														
No	31 170	72.5	4769	84.9	1649	82.0	4158	81.1	474	73.1	1839	56.9	6170	67.5
Yes	11 796	27.5	849	15.1	362	18.0	970	18.9	174	26.9	1393	43.1	2973	32.5

TABLE 1 (Continued)

			Treatment-naïve patients with singular first treatment[a]								Patients without treatment of interest post-index			
	All AF patients (N = 42 966)		Warfarin (n = 5618)		NOACs (n = 2011)		Aspirin (n = 5128)		Other antiplatelet[b] (n = 648)		Not treatment naïve (n = 3232)		Treatment naïve (n = 9143)	
Characteristic	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Baseline comorbidity														
Myocardial infarction	6120	14.2	132	2.3	32	1.6	155	3.0	50	7.7	737	22.8	254	2.8
Cerebrovascular accident, stroke	5848	13.6	174	3.1	87	4.3	157	3.1	85	13.1	825	25.5	434	4.7
Ischaemic	3762	8.8	93	1.7	38	1.9	84	1.6	58	9.0	528	16.3	226	2.5
Haemorrhagic	131	0.3	6	0.1	6	0.3	10	0.2	2	0.3	13	0.4	23	0.3
Unspecified	4225	9.8	119	2.1	59	2.9	94	1.8	52	8.0	614	19.0	317	3.5
Peripheral vascular disease	3374	7.9	142	2.5	34	1.7	114	2.2	27	4.2	513	15.9	352	3.8
CHF	4336	10.1	246	4.4	81	4.0	192	3.7	34	5.2	605	18.7	622	6.8
Hypertension	28 871	67.2	3363	59.9	1167	58.0	2894	56.4	429	66.2	2526	78.2	4958	54.2
Diabetes	8268	19.2	732	13.0	289	14.4	613	12.0	112	17.3	827	25.6	1220	13.3
Moderate/severe liver disease	414	1.0	41	0.7	16	0.8	27	0.5	5	0.8	46	1.4	123	1.3
Renal disease	11 700	27.2	1079	19.2	337	16.8	938	18.3	175	27.0	1278	39.5	2041	22.3
Hospitalization due to														
Malignancies	5544	12.9	556	9.9	194	9.6	457	8.9	63	9.7	697	21.6	1541	16.9
GI bleeding	2519	5.9	229	4.1	73	3.6	214	4.2	43	6.6	262	8.1	634	6.9
Baseline treatment[f]														
Anticoagulants	2337	5.4	24	0.4	8	0.4	10	0.2	2	0.3	293	9.1	67	0.7
Oral	2128	5.0	0	0.0	0	0.0	0	0.0	0	0.0	252	7.8	0	0.0
Other	310	0.7	24	0.4	8	0.4	10	0.2	2	0.3	55	1.7	67	0.7
Antiarrhythmics	720	1.7	61	1.1	13	0.6	27	0.5	4	0.6	52	1.6	133	1.5
Statins	17 404	40.5	1411	25.1	499	24.8	1132	22.1	177	27.3	1707	52.8	1603	17.5
Antiplatelets	15 674	36.5	0	0.0	0	0.0	0	0.0	0	0.0	2117	65.5	0	0.0
Aspirin	13 483	31.4	0	0.0	0	0.0	0	0.0	0	0.0	1808	55.9	0	0.0
Clopidogrel	3074	7.2	0	0.0	0	0.0	0	0.0	0	0.0	375	11.6	0	0.0
Other	681	1.6	0	0.0	0	0.0	0	0.0	0	0.0	112	3.5	0	0.0
Antidiabetics	5487	12.8	475	8.5	179	8.9	356	6.9	73	11.3	546	16.9	752	8.2
Oral	4814	11.2	441	7.8	163	8.	320	6.2	66	10.2	462	14.3	650	7.1
Insulin	1373	3.2	85	1.5	33	1.6	68	1.3	16	2.5	160	5.0	181	2.0
Other injectable	107	0.2	9	0.2	6	0.3	10	0.2	1	0.2	8	0.2	9	0.1
Antihypertensives	26 793	62.4	3177	56.6	1086	54.0	2567	50.1	355	54.8	2207	68.3	3902	42.7
Beta-blockers	10 497	24.4	907	16.1	328	16.3	687	13.4	117	18.1	923	28.6	1126	12.3
Diuretics	6713	15.6	1052	18.7	309	15.4	875	17.1	110	17.0	416	12.9	1078	11.8
Calcium channel blockers	11 596	27.0	1481	26.4	491	24.4	1202	23.4	161	24.8	892	27.6	1676	18.3
ARB	5568	13.0	745	13.3	266	13.2	485	9.5	76	11.7	391	12.1	717	7.8
ACE inhibitors	12 318	28.7	1359	24.2	455	22.6	1114	21.7	145	22.4	1016	31.4	1621	17.7
Other (centrally-acting)	482	1.1	74	1.3	25	1.2	52	1.0	9	1.4	33	1.0	45	0.5
NSAIDs	3218	7.5	533	9.5	181	9.0	459	9.0	50	7.7	205	6.3	737	8.1

(Continues)

TABLE 1 (Continued)

			Treatment-naïve patients with singular first treatment[a]								Patients without treatment of interest post-index			
	All AF patients (N = 42 966)		Warfarin (n = 5618)		NOACs (n = 2011)		Aspirin (n = 5128)		Other antiplatelet[b] (n = 648)		Not treatment naïve (n = 3232)		Treatment naïve (n = 9143)	
Characteristic	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Corticosteroids	4496	10.5	552	9.8	188	9.3	394	7.7	55	8.5	520	16.1	1023	11.2
PPIs	14 536	33.8	1462	26.0	537	26.7	1171	22.8	213	32.9	1441	44.6	2723	29.8
HIV drugs	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Antifungals	759	1.8	69	1.2	25	1.2	52	1.0	8	1.2	121	3.7	204	2.2

Note: HAS-BLED score ranges from 0 to 8 as labile INR information was not available.
Abbreviations: ACE, angiotensin-converting-enzyme; AF, atrial fibrillation; ARB, angiotensin-2 receptor blocker; BMI, body mass index; CHF, congestive heart failure; GI, gastrointestinal; HIV, human immunodeficiency virus; INR, international normalized ratio; IQR, interquartile range; NOAC, novel oral anticoagulant; NSAID, non-steroidal anti-inflammatory drug; PPI, proton pump inhibitor; Q, quarter; SD, standard deviation.
[a]AF patients without any study treatments within 364 days prior to index and with at least one prescription of study treatment post-index.
[b]Including clopidogrel.
[c]AF index date is up to 2016 Q1, while treatment follow-up is up to 2016 Q2.
[d]Active registration is up to 2016 Q2.
[e]Within 364 days prior to index date.
[f]At least one prescription for treatment of interest within 90 days prior to index.

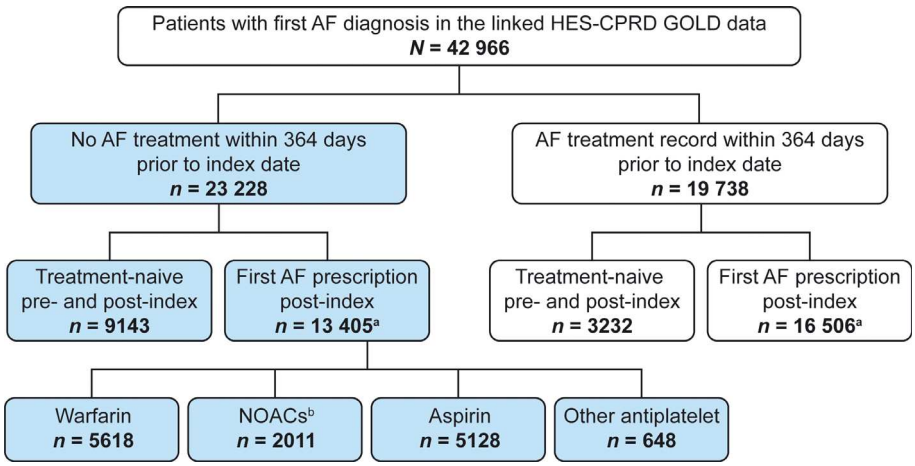

FIGURE 2 Patients with first AF diagnosis by treatment status. [a]Excludes 680 patients with multiple treatment in the first prescription. [b]NOACs include apixaban, dabigatran, edoxaban, and rivaroxaban. AF, atrial fibrillation; CPRD, UK Clinical Practice Research Datalink; HES, English Hospital Episode Statistics; NOAC, novel oral anticoagulant

ischaemic stroke were 1.1 (0.3-1.8) with warfarin, 1.4 (0.0-3.3) with NOACs, 2.5 (1.3-3.7) with aspirin, 5.1 (0.0-11.3) with other antiplatelets, and 19.5 (16.7-22.4) for patients without AF prescription.

The incidence rates of major bleeding per 1000 PY (95% CI) were 35.0 (23.7-46.2) in patients receiving NOACs, 32.1 (27.6-36.7) in patients receiving warfarin, 29.1 (24.2-33.9) in those on aspirin, 31.4 (14.2-48.5) in patients on antiplatelets, and 84.1 (77.4-90.8) in patients not prescribed any AF treatment during the first 3 months post-index. The risk of mortality from major bleeding was 11.0 (1.7-20.2) in patients on other antiplatelet therapy and 2.5 (0.00-5.4) in patients receiving NOACs (Table 2).

All-cause mortality rates per 1000 PY (95% CI) were 42.8 (31.4-54.3) with NOACs, 46.3 (41.1-51.5) with warfarin, 56.5 (50.5-62.4) with aspirin, 102.2 (76.2-128.3) in those on other antiplatelets, and 412.8 (399.6-426.0) in the cohort with no AF treatment for the first 3 months (Table 2).

Differences in baseline risk scores and confounding factors were addressed by stratified analysis of incidence rates (Figure 5). A fully adjusted model was not performed due to the very small number or zero events for some subgroups. Patients with low baseline CHA_2DS_2-VASc scores had low rates of ischaemic stroke, irrespective of treatment post-index. Patients with intermediate CHA_2DS_2-VASc scores receiving OACs had lower rates of ischaemic stroke than those not receiving OACs.

3.5 | Health resource utilization and costs

Up to 3 years after first AF diagnosis, 48.1% of patients (n = 20 668) survived without ischaemic stroke/major bleeding, 3.5% survived a

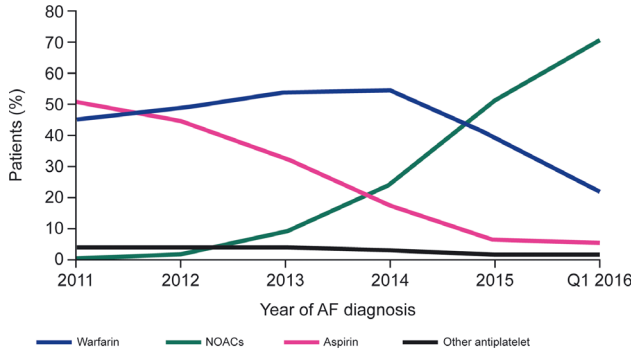

FIGURE 3 Continuous treatment after first AF diagnosis, by prescription type and year of diagnosis (n = 7286; patients who initiated treatment within 3 months after AF index and remained on treatment for ≥3 months). AF, atrial fibrillation; NOAC, novel oral anticoagulant

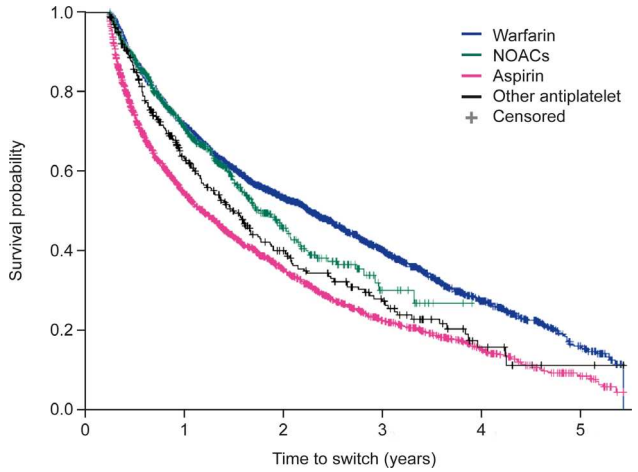

FIGURE 4 Treatment initiation and continuation[a] after first AF diagnosis. [a]Patients were considered to have remained on the same treatment if they had a prescription within 60 days of the final day of their previous prescription of the same treatment, without any other drugs in between. AF, atrial fibrillation; NOAC, novel oral anticoagulant

single event (n = 1513), 3.8% survived multiple events (n = 1618) and 17% (n = 7309) died (Figure 6). The mean (SD) time from index AF diagnosis to first event was similar for patients who survived a single ischaemic stroke [5.6 (9.0) months] or multiple events [5.2 (8.7) months], but this was almost doubled in patients who survived a single major bleed [10.4 (10.3) months] (Table 3).

HRU among AF patients with/without ischaemic stroke or major bleeding up to 3 years after index are shown in Table 3. HRU was higher in patients who died (due to index or other fatal event) compared with those surviving, when considering face-to-face consultations, doctors, laboratory tests, inpatient admissions, A&E investigations, and outpatient procedures. The mean (SD) monthly frequency count/patient for days spent in hospital (excluding day cases) was 9.0 (14.0) for those who survived a single ischaemic stroke vs 7.3 (10.9) for those who survived a single major bleed, 18.1 (23.8) for

TABLE 2 Sex- and age-adjusted incidence rate[a] of ischaemic stroke and major bleeding events in NVAF patients remaining on the same initial treatment for 3 consecutive months, by treatment status

Event	NOAC		Warfarin		Aspirin		Other antiplatelet		No AF prescription	
	Incidence (95% CI)	Events, n[b] (%)	Incidence (95% CI)	Events, n[b] (%)	Incidence (95% CI)	Events, n[b] (%)	Incidence (95% CI)	Events, n[b] (%)	Incidence (95% CI)	Events, n[b] (%)
Ischaemic stroke	9.4 (3.8-15.0)	11/1033 (1.1)	10.4 (8.0-12.9)	72/3240 (2.2)	20.1 (16.4-23.8)	117/2282 (5.1)	21.3 (5.3-37.2)	8/154 (5.2)	43.6 (39.3-47.8)	411/8917 (4.6)
Major bleeding	35.0 (23.7-46.2)	38/997 (3.8)	32.1 (27.6-36.7)	202/2975 (6.8)	29.1 (24.2-33.9)	141/1973 (7.1)	31.4 (14.2-48.5)	14/212 (6.6)	84.1 (77.4-90.8)	616/7480 (8.2)
All-cause mortality	42.8 (31.4-54.3)	55/1168 (4.7)	46.3 (41.1-51.5)	322/3502 (9.2)	56.5 (50.5-62.4)	355/2344 (15.1)	102.2 (76.2-128.3)	69/272 (25.4)	412.8 (399.6-426.0)	3821/9143 (41.8)
Death from ischaemic stroke	1.4 (0.0-3.3)	2/1168 (0.2)	1.1 (0.3-1.8)	8/3502 (0.2)	2.5 (1.3-3.7)	16/2344 (0.7)	5.1 (0.0-11.3)	3/272 (1.1)	19.5 (16.7-22.4)	186/9143 (2.0)
Death from major bleeding	2.5 (0.0-5.4)	3/1168 (0.3)	3.3 (1.9-4.6)	23/3502 (0.7)	3.7 (2.2-5.2)	23/2344 (1.0)	11.0 (1.7-20.2)	6/272 (2.2)	24.2 (21.0-27.5)	221/9143 (2.4)

Abbreviations: AF, atrial fibrillation; CI, confidence interval; NOAC, novel oral anticoagulant; NVAF, non-valvular atrial fibrillation.
[a]Incidence rate per 1000 patient-years of follow-up (reference: patients without event of interest at index diagnosis).
[b]Number of events among patients without event of interest at index diagnosis or first treatment.

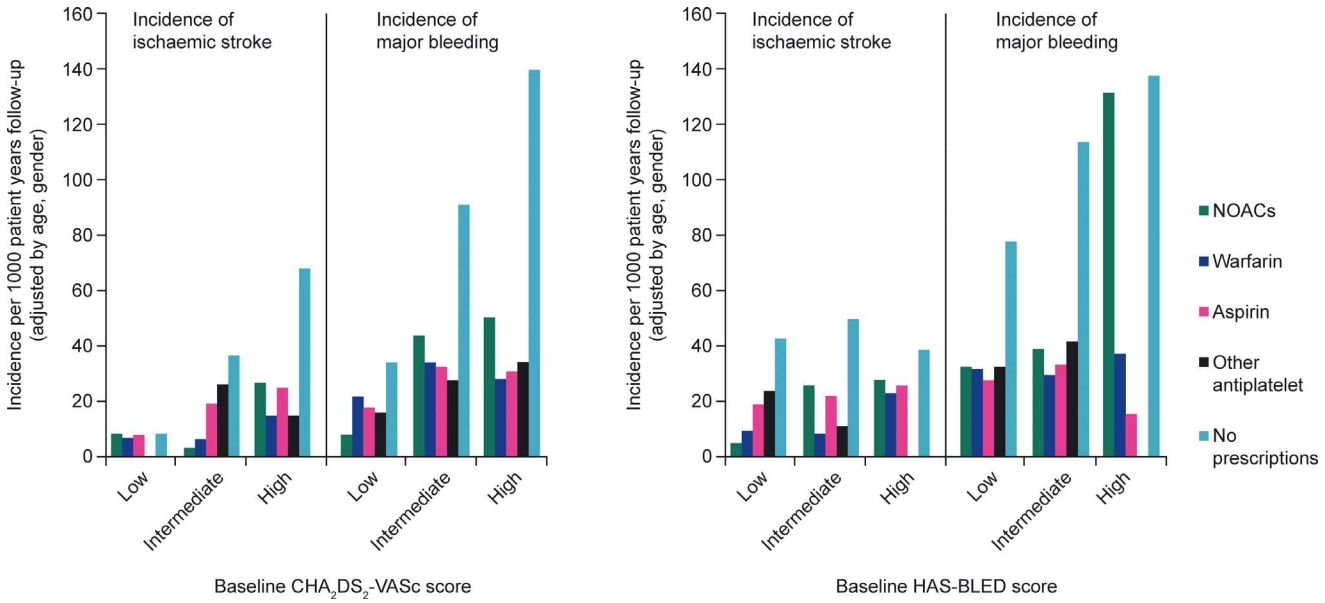

FIGURE 5 Event incidence rates by treatment and risk scores. NOAC, novel oral anticoagulant

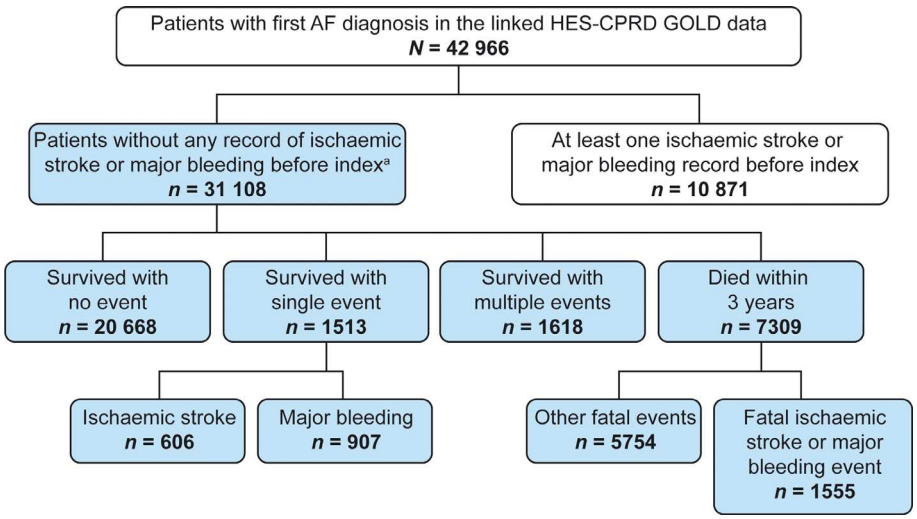

FIGURE 6 AF patients by event status up to 3 years after first diagnosis. [a]Excluded 987 patients with AF index date in 2016 due to lack of linked data in 2016. AF, atrial fibrillation; CPRD, UK Clinical Practice Research Datalink; HES, English Hospital Episode Statistics

those who survived multiple events and 16.8 (17.2) for those who died due to an event.

Total adjusted mean NHS costs were highest for AF patients up to 1 year post-index, with similar costs for patients incurring ischaemic stroke and major bleeding (Table 4). During this time, healthcare costs (95% CI) were highest overall for patients with fatal ischaemic stroke or major bleeding [£17 966 (17 427-18 614)] or other fatal events [£16 955 (16 497-17 337)], with costs mainly driven by inpatient admissions and procedures. Sensitivity analyses capturing costs across different follow-up periods (ie, from first event vs first NVAF diagnosis) revealed no statistically significant differences (data not shown). While most patients had their first index event within 3 months following index diagnosis, some events, specifically major bleeding, occurred after 12 months of follow-up and were not included in the cost comparisons.

By treatment group (adjusting for the confounders of baseline CHA_2DS_2-VASc score, baseline HAS-BLED score, and frailty only), mean annual NHS costs of healthcare (95% CI) up to 1 year post-index were lowest in AF patients receiving aspirin plus other antiplatelets without an event [£6152 (5820-6200)], and highest in AF patients without any prescribed AF treatment either with [£17 957 (16 927-18 270)] or without an event [£9803 (9542-10 080)] (Table 5). The number of patients with an event who did not receive AF treatment (n = 852) was considerably higher than the number of patients with an event who were treated with warfarin or a NOAC (n = 248) or aspirin or other antiplatelets (n = 206).

TABLE 3 Unadjusted resource utilization in NVAF patients with or without ischaemic stroke or major bleeding events up to 3 years from AF index date[a]

Resource	Resource use, monthly frequency count/patient; Mean (SD); Median (IQR)					
	Survived, no event (n = 20 668)	Survived, single ischaemic stroke event (n = 606)	Survived, single major bleeding event (n = 907)	Survived, multiple events (n = 1618)	Died, other fatal event (n = 5754)	Died, ischaemic stroke/major bleeding event (n = 1555)
Time from index AF diagnosis to first event						
Mean (SD)	—	5.6 (9.0)	10.4 (10.3)	5.2 (8.7)	—	4.2 (7.5)
Median (IQR)	—	0.2 (0.0-7.8)	7.4 (1.1-16.9)	0.0 (0.0-7.1)	—	0.0 (0.0-5.2)
Consultation						
Face-to-face, n (%)	20 443 (98.9)	601 (99.2)	901 (99.3)	1604 (99.1)	5138 (89.3)	1439 (92.5)
	2.3 (1.7)	2.3 (1.4)	2.6 (1.4)	2.6 (1.6)	4.5 (4.7)	3.6 (3.1)
	1.9 (1.2-2.9)	2.0 (1.3-3.0)	2.3 (1.5-3.4)	2.3 (1.5-3.4)	3.4 (1.7-5.9)	2.9 (1.7-4.8)
Admin, n (%)	20 478 (99.1)	602 (99.3)	903 (99.6)	1607 (99.3)	5202 (90.4)	1432 (92.1)
	3.2 (2.1)	3.4 (1.7)	3.7 (2.0)	3.9 (2.1)	5.7 (6.0)	4.7 (4.2)
	2.8 (1.9-4.1)	3.0 (2.2-4.4)	3.3 (2.3-4.6)	3.5 (2.4-4.9)	4.5 (2.5-7.3)	4.0 (2.3-6.2)
Staff						
Doctor, n (%)	20 302 (98.2)	594 (98.0)	897 (98.9)	1570 (97.0)	4703 (81.7)	1321 (85.0)
	1.8 (1.5)	1.8 (1.2)	2.1 (1.4)	2.1 (1.5)	3.8 (4.8)	2.9 (3.0)
	1.4 (0.9-2.3)	1.5 (1.0-2.5)	1.9 (1.2-2.7)	1.8 (1.1-2.8)	2.6 (1.0-5.0)	2.3 (1.1-4.0)
Staff, n (%)	17 467 (84.5)	522 (86.1)	825 (91.0)	1356 (83.8)	2657 (46.2)	845 (54.3)
	0.6 (0.9)	0.6 (0.7)	0.7 (0.8)	0.6 (0.9)	0.7 (1.8)	0.6 (1.2)
	0.3 (0.1-0.7)	0.3 (0.1-0.8)	0.4 (0.1-0.9)	0.3 (0.1-0.7)	0.0 (0.0-0.6)	0.1 (0.0-0.6)
Other, n (%)	20 505 (99.2)	603 (99.5)	903 (99.6)	1611 (99.6)	5372 (93.4)	1485 (95.5)
	3.4 (2.4)	3.7 (2.0)	3.9 (2.1)	4.2 (2.4)	7.1 (7.1)	5.8 (5.1)
	2.9 (2.0-4.3)	3.3 (2.3-4.6)	3.3 (2.5-5.0)	3.8 (2.6-5.3)	5.5 (3.2-8.9)	4.8 (2.9-7.4)
Specialist referrals, n (%)	13 869 (67.1)	413 (68.2)	731 (80.6)	1096 (67.7)	1987 (34.5)	667 (42.9)
	0.1 (0.2)	0.1 (0.1)	0.1 (0.2)	0.1 (0.1)	0.2 (0.8)	0.2 (0.8)
	0.1 (0.0-0.1)	0.1 (0.0-0.1)	0.1 (0.0-0.2)	0.1 (0.0-0.2)	0.0 (0.0-0.1)	0.0 (0.0-0.1)
Laboratory tests (without INR), n (%)	19 016 (92.0)	564 (93.1)	871 (96.0)	1502 (92.8)	3246 (56.4)	1072 (68.9)
	4.0 (8.1)	3.8 (3.1)	4.7 (3.9)	4.3 (4.1)	5.8 (21.0)	6.0 (32.4)
	2.9 (1.2-5.2)	3.2 (1.6-5.2)	3.9 (2.2-6.3)	3.5 (1.6-5.8)	0.8 (0.0-5.7)	2.1 (0.0-6.3)
Prescriptions, n (%)	19 950 (96.5)	584 (96.4)	890 (98.1)	1517 (93.8)	3789 (65.8)	1140 (73.3)
	6.3 (6.7)	6.9 (7.2)	7.0 (6.7)	8.1 (8.0)	7.4 (10.7)	7.3 (10.2)
	4.8 (2.6-7.8)	5.3 (3.1-8.3)	5.6 (3.3-8.6)	6.2 (3.5-9.9)	4.9 (0.0-10.5)	5.1 (0.0-9.8)
HES inpatient admissions, n (%)	16 244 (78.6)	569 (93.9)	884 (97.5)	1612 (99.6)	5591 (97.2)	1553 (99.9)
	0.2 (1.0)	0.2 (0.3)	0.3 (1.5)	0.3 (0.6)	2.5 (4.6)	1.8 (3.6)
	0.1 (0.0-0.2)	0.1 (0.1-0.2)	0.1 (0.1-0.3)	0.2 (0.1-0.3)	0.9 (0.3-2.5)	0.6 (0.3-1.6)
HES inpatient procedures, n (%)	13 014 (63.0)	528 (87.1)	821 (90.5)	1561 (96.5)	4269 (74.2)	1453 (93.4)
	0.4 (2.1)	0.5 (1.2)	0.5 (0.8)	1.0 (2.0)	6.2 (16.4)	6.8 (18.2)
	0.1 (0.0-0.3)	0.2 (0.1-0.5)	0.3 (0.1-0.6)	0.4 (0.2-1.0)	0.9 (0.0-4.9)	1.5 (0.4-5.3)
Days in hospital (excl. day cases), n (%)	12 555 (60.7)	525 (86.6)	768 (84.7)	1571 (97.1)	5405 (93.9)	1528 (98.3)
	5.7 (12.9)	9.0 (14.0)	7.3 (10.9)	18.1 (23.8)	13.3 (15.8)	16.8 (17.2)
	1.0 (0.0-6.5)	4.4 (1.5-10.0)	4.0 (1.0-9.0)	10.1 (4.0-23.0)	9.0 (4.0-17.0)	11.5 (6.0-21.6)

(Continues)

TABLE 3 (Continued)

Resource	Resource use, monthly frequency count/patient; Mean (SD); Median (IQR)					
	Survived, no event (n = 20 668)	Survived, single ischaemic stroke event (n = 606)	Survived, single major bleeding event (n = 907)	Survived, multiple events (n = 1618)	Died, other fatal event (n = 5754)	Died, ischaemic stroke/major bleeding event (n = 1555)
A&E attendances, n (%)	12 298 (59.5)	505 (83.3)	732 (80.7)	1495 (92.4)	4443 (77.2)	1376 (88.5)
	0.1 (0.7)	0.1 (0.2)	0.2 (1.5)	0.2 (0.3)	1.7 (4.0)	1.2 (3.0)
	0.0 (0.0-0.1)	0.1 (0.0-0.2)	0.1 (0.0-0.2)	0.1 (0.1-0.2)	0.4 (0.1-1.3)	0.3 (0.1-0.9)
A&E investigations, n (%)	12 170 (58.9)	503 (83.0)	731 (80.6)	1491 (92.2)	4422 (76.9)	1375 (88.4)
	0.6 (3.9)	0.6 (1.2)	0.7 (3.8)	0.9 (1.5)	7.8 (22.3)	5.7 (16.6)
	0.1 (0.0-0.4)	0.3 (0.1-0.7)	0.3 (0.1-0.6)	0.4 (0.2-1.1)	1.2 (0.1-5.4)	1.3 (0.4-3.8)
HES outpatient visits, n (%)	17 449 (84.4)	552 (91.1)	826 (91.1)	1435 (88.7)	2799 (48.6)	912 (58.6)
	0.5 (0.9)	0.6 (1.3)	0.6 (0.9)	0.7 (1.3)	0.7 (2.2)	0.7 (1.6)
	0.3 (0.1-0.7)	0.4 (0.2-0.7)	0.4 (0.2-0.8)	0.4 (0.2-0.8)	0.0 (0.0-0.7)	0.2 (0.0-0.7)
HES outpatient procedures, n (%)	13 990 (67.7)	457 (75.4)	713 (78.6)	1180 (72.9)	2180 (37.9)	740 (47.6)
	0.3 (0.8)	0.4 (1.3)	0.3 (0.4)	0.3 (0.6)	0.5 (1.9)	0.5 (1.6)
	0.1 (0.0-0.4)	0.2 (0.0-0.4)	0.2 (0.0-0.5)	0.2 (0.0-0.4)	0.0 (0.0-0.3)	0.0 (0.0-0.4)

Abbreviations: A&E, Accident & Emergency; AF, atrial fibrillation; HES, English Hospital Episode Statistics; INR, international normalized ratio; IQR, interquartile range; NVAF, non-valvular atrial fibrillation; SD, standard deviation.
[a]Patients are followed from index NVAF diagnosis up to 3 years, death or end of active registration.

TABLE 4 Mean NHS costs in NVAF patients with or without ischaemic stroke or major bleeding event up to 1 year post-index,[a] adjusted by CHA_2DS_2-VASc score, HAS-BLED score, and frailty

Time post-index	Mean cost/patient, £ (95% CI)[b]					
	Survived, no event (n = 20 668)	Survived, single ischaemic stroke event (n = 606)	Survived, single major bleeding event (n = 907)	Survived, multiple events (n = 1618)	Died, other fatal event (n = 5754)	Died, ischaemic stroke/major bleeding event (n = 1555)
0-3 mo	£3646 (3594-3692)	£4842 (4840-5250)	£4551 (4533-4929)	£7171 (6695-7182)	£9297 (9019-9587)	£9114 (8879-9564)
4-6 mo	£1369 (1345-1390)	£1697 (1660-1824)	£1963 (1810-2022)	£2323 (2139-2396)	£2711 (2607-2829)	£3319 (3103-3512)
7-9 mo	£1180 (1157-1201)	£1363 (1319-1452)	£1796 (1604-1858)	£1996 (1799-1999)	£2429 (2283-2522)	£2835 (2600-3046)
10-12 mo	£1123 (1098-1142)	£1302 (1163-1383)	£1565 (1408-1616)	£1941 (1848-2081)	£2519 (2316-2648)	£2698 (2397-2815)
Total	£7318 (7236-7386)	£9204 (8765-9688)	£9875 (9607-10 234)	£13 430 (12941-13 724)	16 955 (16497-17 337)	£17 966 (17427-18 614)
Prescriptions costs						
0-3 mo	£211	£206	£219	£254	£411	£330
4-6 mo	£217	£210	£266	£302	£355	£328
7-9 mo	£224	£203	£258	£305	£357	£317
10-12 mo	£229	£212	£269	£343	£356	£353
Total	£881	£831	£1012	£1204	£1478	£1327

[Correction added on 27 April 2020, after first online publication: Table 4 was amended as the alignment of 2 rows were incorrect. The data remains unchanged.]
Abbreviations: CI, confidence interval; NHS, National Health Service; NVAF, non-valvular atrial fibrillation.
[a]Patients are followed from index NVAF diagnosis up 1 year, death or end of active registration. As most patients with an event had their first event within the first 3 months post-NVAF diagnosis, we performed sensitivity analyses to compare results using different follow-up periods, but the findings were not significantly different.
[b]Costs are valued in 2015-2016 UK pounds.

TABLE 5 Mean NHS costs in NVAF patients by treatment group with or without ischaemic stroke or major bleeding event up to 1 year post-index,[a] adjusted by CHA_2DS_2-VASc score, HAS-BLED score, and frailty

	Mean cost/patient, £ (95% CI)[b]					
Time post-index	Warfarin + NOAC, no event (n = 3272)	Warfarin + NOAC, with event (n = 248)	Aspirin + other antiplatelet, no event (n = 1829)	Aspirin + other antiplatelet, with event (n = 206)	No treatment, no event (n = 6161)	No treatment, with event (n = 852)
0-3 mo	£2763 (2705-2848)	£3455 (3096-3665)	£2868 (2724-2960)	£3639 (3181-4050)	£6097 (5856-6311)	£10 873 (10217-11 445)
4-6 mo	£1332 (1288-1376)	£1905 (1587-1980)	£1179 (1085-1215)	£2313 (1946-2627)	£1508 (1446-1581)	£2713 (2338-3084)
7-9 mo	£1185 (1144-1243)	£1995 (1733-2246)	£1061 (988-1117)	£2002 (1717-2331)	£1143 (1091-1205)	£2038 (1707-2282)
10-12 mo	£1140 (1090-1196)	£1812 (1512-1964)	£1044 (970-1108)	£1615 (1226-1976)	£1055 (997-1114)	£2333 (1957-2659)
Total	£6421 (6344-6604)	£9167 (8188-9538)	£6152 (5820-6200)	£9569 (8943-10 546)	£9803 (9542-10 080)	£17 957 (16927-18 270)

Abbreviations: CI, confidence interval; NHS, National Health Service; NOAC, novel oral anticoagulant; NVAF, non-valvular atrial fibrillation.
[a]Patients are followed from index NVAF diagnosis up to 1 year, death or end of active registration. As most patients with an event had their first event within the first 3 months post-NVAF diagnosis, we performed sensitivity analyses to compare results using different follow-up periods, but the findings were not significantly different.
[b]Costs are valued in 2015-2016 UK pounds.

4 | DISCUSSION

Our retrospective study investigated treatment patterns, incidence, mortality, and long-term costs in a cohort of newly diagnosed NVAF patients representative of the United Kingdom population before and following uptake of the NOACs and reduction of aspirin monotherapy. Using linked HES-CPRD GOLD, we identified 42 966 patients [median age 78 years (IQR 69-85)] with a first AF event during the period 2011 to Q1 2016.

In line with treatment guidance, we identified a decline in patients receiving aspirin for ≥3 months post-index from 50.6% to 5.5%, irrespective of CHA_2DS_2-VASc score, with an increase in patients prescribed NOACs from 2.0% to 70.1%. Similar findings were reported in the GARFIELD-AF registry in very recently diagnosed NVAF patients.[18] Increased NOAC use was also reported in European patients in the GLORIA-AF registry, with 52.4% receiving NOACs from 2011 to 2014.[19] Similar trends, with a smaller proportion of untreated patients, were reported in a large cross-sectional report of NVAF patients eligible for OAC therapy during 2012 to 2016.[20]

Noting the methodological limitation that it is challenging in an observational dataset to fully adjust for prescribing behaviour confounders, we found that patients prescribed NOACs, warfarin, aspirin, or other antiplatelets had a markedly lower incidence of ischaemic stroke than patients not prescribed any AF treatment. The reasons for non-prescription of AF medication in a large number of patients (n = 9143; 21% of the study cohort) requires exploration. Specific baseline characteristics may have played a role in this, for example, patients not receiving AF treatment were concentrated in groups with high CHA_2DS_2-VASc scores, as previously reported.[8] Furthermore, within this group, those who were not treatment naïve tended to have intermediate/high HAS-BLED scores. While this may reflect older patients with considerable comorbidities, it could also represent patients on dialysis or with haematological or other malignancies (9%-10% with malignancies treated vs. 17% untreated patients). Excluding patients with low CHA_2DS_2-VASc scores, who are ineligible for AF treatment, 6320 patients (15%) remained without appropriate prescribed AF treatment following index diagnosis. The proportion of these patients steadily increased across each study year (2012, 19.2%; 2013, 21.5%; 2014, 22.3%; 2015, 24.1%). Over-the-counter recommendations to take aspirin could not be captured in our dataset and may also be a limiting factor.

Major bleeding occurred at a similar rate across the different OAC groups, but the highest incidence was in patients not prescribed any AF treatment during the first 3 months post-index (Table 2). It may be that the bleeding risk in these patients, for example, from gastrointestinal or cancer-related bleeding, contraindicated such treatments.

The high mortality rate observed in the untreated AF patients may suggest a potential health gain if selected subgroups were considered for appropriate OAC therapy. Within our study, ~15% of patients were not prescribed anticoagulants or antithrombotics in primary care, which could represent >90 000 patients if extrapolated nationally.

The use of propensity score matching to model costs within each treatment group was not planned in the study proposal, but the main drivers of treatment choice, or of no treatment (baseline CHA_2DS_2-VASc score, baseline HAS-BLED score and frailty), were included in the adjusted cost models. HRU was higher in patients who died compared with survivors. Healthcare costs were also highest for patients who died as a result of index/non-index events. The high cost was driven by inpatient admissions and procedures for both groups with fatal events. Mean NHS healthcare costs up to 1 year post-index were highest in

untreated AF patients with/without an event, again emphasizing the importance of focusing on this patient subgroup. Overall, total mean costs were highest for AF patients within the first 3 months post-index. If the prevalence of AF in the United Kingdom is considered to be 900 000 in 2016,[6] then the overall burden of management of AF patients with/without an event would relate to an annual cost between £9000 and £18 000, which would equate to between £8.1 and £16.2 billion, respectively, even without accounting for societal costs.

These findings add to published data on long-term HRU associated with stroke and bleeding. In 25 465 US NVAF patients studied between 1999 and 2009, the most significant costs of first ischaemic stroke/major bleeding occurred in the first year, but total healthcare costs remained elevated up to 3 years post-event.[21] The considerable economic burden of ischaemic stroke in AF patients was also highlighted in a systematic review including 16 studies of ischaemic stroke costs and HRU in patients with AF across nine countries.[22] In agreement with our results, the major component of overall costs was hospitalization.

The CPRD has been widely used to study incidence/mortality of AF in the United Kingdom.[20,23-25] Boggon et al described HRU and outcomes among 15 373 AF patients and age- and sex-matched controls from 2001 to 2006.[23] Gallagher et al examined the incidence of cardiovascular/bleeding outcomes and mortality among 16 513 patients with a first AF diagnosis between 2005 and 2010, before the launch of the NOACs.[24] Our study followed a similar design to the Gallagher trial; of note, the mean/median age at AF diagnosis increased by 2 years between the studies (mean 74 years, median 76 years[24]). More recently, Durham et al published findings of a cohort study of 23 018 AF patients treated from 2010 to 2014,[25] while Lacoin et al reported findings from a large cohort study of NVAF patients receiving OACs between 2012 and 2016.[20] In the Lacoin study, ~15% of patients were not offered any AF treatment within 90 days pre-index, which remained relatively stable across each study year. Their inclusion criteria differed from ours and they excluded patients with low CHA_2DS_2-VASc scores. Furthermore, they did not follow up patients after index or present HRU data, but focused on cross-sectional treatment pattern changes.

The size, breadth of data, representativeness of patient and practice characteristics, and long-term follow-up are key strengths of the CPRD, along with the recording of secondary care referrals, thereby providing a virtually complete medical history.[11] Strengths of our study include its size and duration of active registration pre-index [mean (SD) 13.0 (6.1) years]. As prescribing data were recorded, we were able to provide the first temporal data set relating to NOAC use in NVAF patients in England with relationships to outcomes and HRU. Our results were internally validated, with healthcare costs increasing as the number of events occurred, and the number of events increasing by CHA_2DS_2-VASc score, despite treatment. Additionally, unlike other registries specific to anticoagulation prescribing, our dataset includes AF patients on no treatment in significant proportion.

There are some limitations of the CPRD to consider. The quality of diagnoses represents real-world practice, which might not reflect the robustness of clinical trials or registry studies. Our analyses were not adjusted for all potential confounders, which means that comparison of outcomes between different treatments should be interpreted with caution. This is further emphasized by the fact that studies that attempted to adjust for multiple confounders found a significant proportion of patients were effectively excluded due to non-overlap of patient characteristics.[26,27] Results relating to the use of medication rely on an assumption that prescribed medications have complete adherence, which is unlikely. As the coding of outpatient and A&E operations and procedures is not mandatory in HES, these costs may have been poorly recorded. Furthermore, the extent of missing data is unknown, although GP records are expected to be of good quality. Cost analyses are based on applying the NHS reference unit costs to the HRU observed in the data and noting that non-NHS societal and private care costs are not captured.

In conclusion, data from this large, nationally representative study linking numerous datasets provide valuable insights into current treatment/non-treatment patterns and outcomes for NVAF patients and their economic impact, proving public health and policy makers ample examples of temporal changes over time. Our findings emphasize the major achievements in the United Kingdom of reducing antiplatelet prescriptions for high-risk AF patients with an increase in OAC use and the pressing need to review high-risk AF patients not receiving any antithrombotic or antiplatelet prescriptions for stroke reduction, as they have a disproportionately high adverse event rate and may benefit from a multidisciplinary review or be the subject of future prospective registries or trials.

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CONFLICT OF INTEREST

A.B. and M.S. have received consultancy fees from Roche Diagnostics; H.P. and Y.D. have received consultancy fees from Roche/Genentech; F.V. and C.W. are employees of Roche Diagnostics; N.F. was an employee of Roche Products Ltd during the course of this work.

AUTHOR CONTRIBUTIONS

All authors conceived and designed the research. Farnaz Vahidnia, Yingjie Ding, and Nadia Foskett acquired the data. Yingjie Ding performed statistical analyses. All authors had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors edited and approved the final manuscript for submission.

DATA ACCESSIBILITY

Access to CPRD, ONS, and HES data is subject to protocol review and approval from Independent Scientific Advisory Committee (ISAC).

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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