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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/after 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 CHA2DS2-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 (15.3-37.2) 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...
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. AF is an independent risk factor for stroke and thromboembolism, with an estimated 5-fold higher risk than in the normal population, and is predictive of premature mortality and heart failure. 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).

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. Despite the publication of numerous guidelines on AF management, a substantial proportion of eligible patients are undertreated. 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$_2$DS$_2$-VASc score ≥2 were also suboptimally treated, with seven of nine studies reporting treatment levels <70% (range 39.0%-92.3%) of optimal practice.

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. 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.

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 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.

## 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. 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), CHA2DS2-VASc score (stroke risk), HAS-BLED score (bleeding risk), comorbidities, medication use, and frailty.

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, out-patient 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.

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 was used to estimate mean healthcare costs per quarter per patient, up to 1 year after newly diagnosed AF, as confounding factors (baseline CHA2DS2-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), 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
≥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) CHA2DS2-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) CHA2DS2-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 CHA2DS2-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 (16.3% vs 23.1%, respectively, P < .0001). Similarly, the proportion of older 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 anti-platelet 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 CHA2DS2-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 CHA2DS2-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

FIGURE 1 Patient attrition in the linked HES-CPRD GOLD. *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
| Characteristic                  | All AF patients (N = 42 966) | Treatment-naïve patients with singular first treatment<sup>a</sup> | Patients without treatment of interest post-index |
|-------------------------------|-----------------------------|------------------------------------------------|-------------------|
|                               | 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 |
| Female                        | 20 452 | 47.6 | 2661 | 47.4 | 915  | 45.5 | 2490 | 48.6 | 354  | 54.6 | 1600 | 49.5 |
| **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  |
| 35-44                         | 568  | 1.3 | 88   | 1.6 | 29   | 1.4 | 61   | 1.2 | 3    | 0.5  | 14   | 0.4  |
| 45-54                         | 1771 | 4.1 | 308  | 5.5 | 132  | 6.6 | 257  | 5.0 | 12   | 1.9  | 58   | 1.8  |
| 55-64                         | 4420 | 10.3 | 756  | 13.5 | 291  | 14.5 | 758  | 14.8 | 53   | 8.2  | 145  | 4.5  |
| 65-74                         | 9889 | 23.0 | 1618 | 28.8 | 569  | 28.3 | 1364 | 26.6 | 139  | 21.5 | 522  | 16.2 |
| 74-84                         | 14 510 | 33.8 | 1946 | 34.6 | 640  | 31.8 | 1492 | 29.1 | 227  | 35.0 | 1126 | 34.8 |
| 85+                           | 11 508 | 26.8 | 876  | 15.6 | 345  | 17.2 | 1184 | 23.1 | 214  | 33.0 | 1357 | 42.0 |
| **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) | 78.9 (11.0) | 81.0 (10.8) | 74.5 (16.3) | 84.11 (92.0) |
| **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 |
| Asian                         | 496  | 1.2 | 48   | 0.9 | 6    | 0.3 | 51   | 1.0 | 6    | 0.9  | 38   | 1.2  |
| Black                         | 250  | 0.6 | 15   | 0.3 | 5    | 0.2 | 33   | 0.6 | 3    | 0.5  | 18   | 0.6  |
| Other                         | 2332 | 5.4 | 381  | 6.8 | 204  | 10.1 | 428  | 8.3 | 29   | 4.5  | 83   | 2.6  |
| **Year of first AF**          |     |     |     |     |     |     |     |     |     |     |     |     |
| 2011                          | 9415 | 21.9 | 1193 | 21.2 | 32   | 1.6 | 1692 | 33.0 | 148  | 22.8 | 682  | 21.1 |
| 2012                          | 9593 | 22.3 | 1294 | 23.0 | 109  | 5.4 | 1533 | 29.9 | 166  | 25.6 | 698  | 21.6 |
| 2013                          | 8738 | 20.3 | 1226 | 21.8 | 247  | 12.3 | 1088 | 21.2 | 138  | 21.3 | 642  | 19.9 |
| 2014                          | 7638 | 17.8 | 1119 | 19.9 | 537  | 26.7 | 568  | 11.1 | 115  | 17.7 | 586  | 18.1 |
| 2015                          | 6271 | 14.6 | 697  | 12.4 | 887  | 44.1 | 215  | 4.2 | 76   | 11.7 | 519  | 16.1 |
| 2016 Q1<sup>c</sup>           | 1311 | 3.1 | 89   | 1.6 | 199  | 9.9 | 32   | 0.6 | 5    | 0.8  | 105  | 3.2  |
| **Active registration<sup>d</sup> 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) | 13.0 (9.7-17.3) | 13.4 (10.0-17.3) | 13.1 (9.2-16.9) | 12.8 (8.2-16.4) |
| **Active registration post-index date, years** |     |     |     |     |     |     |     |     |     |     |     |     |
| 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**            |     |     |     |     |     |     |     |     |     |     |     |     |
| Current                       | 3504 | 8.2 | 377  | 6.7 | 140  | 7.0 | 364  | 7.1 | 43   | 6.6  | 319  | 9.9  |
| Ex                            | 14 208 | 33.1 | 1718 | 30.6 | 596  | 29.6 | 1513 | 29.5 | 203  | 31.3 | 1114 | 34.5 |
| Non                           | 7598 | 17.7 | 1065 | 19.0 | 393  | 19.5 | 972  | 19.0 | 109  | 16.8 | 492  | 15.2 |
| Unknown                       | 17 656 | 41.1 | 2458 | 43.8 | 882  | 43.9 | 2279 | 44.4 | 293  | 45.2 | 1307 | 40.4 |

(Continues)
TABLE 1

| Characteristic | All AF patients (N = 42,966) | Treatment-naïve patients with singular first treatment* | Patients without treatment of interest post-index |
|----------------|-------------------------------|--------------------------------------------------------|-----------------------------------------------|
|                | n | %  | n | %  | n | %  | n | %  | n | %  | n | %  | n | %  |
| Drinking status* | 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/m² | <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 | 1795 | 32.2 | 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 |
| CHA²DS²-VASc score<sup>e</sup> | 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<sup>e</sup> | 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)

| Characteristic                        | All AF patients (N = 42966) | Treatment-naïve patients with singular first treatment<sup>a</sup> | Patients without treatment of interest post-index | Not treatment naïve (n = 3232) | Treatment naïve (n = 9143) |
|---------------------------------------|-----------------------------|------------------------------------------------------------------|--------------------------------------------------|-------------------------------|---------------------------|
|                                       | n                           | %                   | n                           | %                   | n                           | %            | n                  | %             | n                  | %             |
| **Baseline comorbidity**              |                             |                     |                             |                     |                             |              |                   |                |                   |                |
| Myocardial infarction                 | 6120                        | 14.2                | 132                         | 2.3                 | 32                           | 1.6          | 155                | 3.0           | 50                | 7.7           |
| Cerebrovascular accident, stroke      | 5848                        | 13.6                | 174                         | 3.1                 | 87                           | 4.3          | 157                | 3.1           | 85                | 13.1          |
| Ischaemic                             | 3762                        | 8.8                 | 93                           | 1.7                 | 38                           | 1.9          | 84                 | 1.6           | 58                | 9.0           |
| Haemorrhagic                          | 131                         | 0.3                 | 6                            | 0.1                 | 6                            | 0.3          | 10                 | 0.2           | 2                 | 0.3           |
| Unspecified                           | 4225                        | 9.8                 | 119                          | 2.1                 | 59                           | 2.9          | 94                 | 1.8           | 52                | 8.0           |
| Periphal vascular disease             | 3374                        | 7.9                 | 142                          | 2.5                 | 34                           | 1.7          | 114                | 2.2           | 27                | 4.2           |
| CHF                                   | 4336                        | 10.1                | 246                          | 4.4                 | 81                           | 4.0          | 192                | 3.7           | 34                | 5.2           |
| Hypertension                          | 28871                       | 67.2                | 3363                         | 59.9                | 1167                         | 58.0         | 2894               | 56.4          | 429               | 66.2          |
| Diabetes                              | 8268                        | 19.2                | 732                          | 13.0                | 289                          | 14.4         | 613                | 12.0          | 112               | 17.3          |
| Moderate/severe liver disease         | 414                         | 1.0                 | 41                           | 0.7                 | 16                           | 0.8          | 27                 | 0.5           | 5                 | 0.8           |
| Renal disease                         | 11700                       | 27.2                | 1079                         | 19.2                | 337                          | 16.8         | 938                | 18.3          | 175               | 27.0          |
| Hospitalization due to               |                             |                     |                             |                     |                             |              |                    |                |                   |                |
| Malignancies                          | 5544                        | 12.9                | 556                          | 9.9                 | 194                          | 9.6          | 457                | 8.9           | 63                | 9.7           |
| GI bleeding                           | 2519                        | 5.9                 | 229                          | 4.1                 | 73                           | 3.6          | 214                | 4.2           | 43                | 6.6           |
| **Baseline treatment<sup>b</sup>**    |                             |                     |                             |                     |                             |              |                    |                |                   |                |
| Anticoagulants                        | 2337                        | 5.4                 | 24                           | 0.4                 | 8                            | 0.4          | 10                 | 0.2           | 2                 | 0.3           |
| Oral                                  | 2128                        | 5.0                 | 0                            | 0.0                 | 0                            | 0.0          | 0                  | 0.0           | 0                 | 0.0           |
| Other                                 | 310                         | 0.7                 | 24                           | 0.4                 | 8                            | 0.4          | 10                 | 0.2           | 2                 | 0.3           |
| Antiarrhythmics                       | 720                         | 1.7                 | 61                           | 1.1                 | 13                           | 0.6          | 27                 | 0.5           | 4                 | 0.6           |
| Statins                               | 17404                       | 40.5                | 1411                         | 25.1                | 499                          | 24.8         | 1132               | 22.1          | 177               | 27.3          |
| Antiplatelets                         | 15674                       | 36.5                | 0                            | 0.0                 | 0                            | 0.0          | 0                  | 0.0           | 0                 | 0.0           |
| Aspirin                               | 13483                       | 31.4                | 0                            | 0.0                 | 0                            | 0.0          | 0                  | 0.0           | 0                 | 0.0           |
| Clopidogrel                           | 3074                        | 7.2                 | 0                            | 0.0                 | 0                            | 0.0          | 0                  | 0.0           | 0                 | 0.0           |
| Other                                 | 681                         | 1.6                 | 0                            | 0.0                 | 0                            | 0.0          | 0                  | 0.0           | 0                 | 0.0           |
| Antidiabetics                         | 5487                        | 12.8                | 475                          | 8.5                 | 179                          | 8.9          | 356                | 6.9           | 73                | 11.3          |
| Oral                                  | 4814                        | 11.2                | 441                          | 7.8                 | 163                          | 8.3          | 320                | 6.2           | 66                | 10.2          |
| Insulin                               | 1373                        | 3.2                 | 85                           | 1.5                 | 33                           | 1.6          | 68                 | 1.3           | 16                | 2.5           |
| Other injectable                      | 107                         | 0.2                 | 9                            | 0.2                 | 6                            | 0.3          | 10                 | 0.2           | 1                 | 0.2           |
| Antihypertensives                     | 26793                       | 62.4                | 3177                         | 56.6                | 1086                         | 54.0         | 2567               | 50.1          | 355               | 54.8          |
| Beta-blockers                         | 10497                       | 24.4                | 907                          | 16.1                | 328                          | 16.3         | 687                | 13.4          | 117               | 18.1          |
| Diuretics                             | 6713                        | 15.6                | 152                          | 18.7                | 309                          | 15.4         | 875                | 17.1          | 110               | 17.0          |
| Calcium channel blockers              | 11596                       | 27.0                | 1481                         | 26.4                | 491                          | 24.4         | 1202               | 23.4          | 161               | 24.8          |
| ARB                                   | 5568                        | 13.0                | 745                          | 13.3                | 266                          | 13.2         | 485                | 9.5           | 76                | 11.7          |
| ACE inhibitors                        | 12318                       | 28.7                | 1359                         | 24.2                | 455                          | 22.6         | 1114               | 21.7          | 145               | 22.4          |
| Other (centrally-acting)              | 482                         | 1.1                 | 74                           | 1.3                 | 25                           | 1.2          | 52                 | 1.0           | 9                 | 1.4           |
| NSAIDs                                | 3218                        | 7.5                 | 533                          | 9.5                 | 181                          | 9.0          | 459                | 9.0           | 50                | 7.7           |

<sup>a</sup> Includes patients with singular treatment post-index.

<sup>b</sup> Includes patients with singular treatment post-index.

(Continues)
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\textsuperscript{2}DS\textsuperscript{2}-VASc scores had low rates of ischaemic stroke, irrespective of treatment post-index. Patients with intermediate CHA\textsuperscript{2}DS\textsuperscript{2}-VASc scores receiving OACs had lower rates of ischaemic stroke than those not receiving OACs.

### Table 1 (Continued)

| Characteristic | Treatment-naive patients with singular first treatment* | Patients without treatment of interest post-index |
|----------------|--------------------------------------------------------|--------------------------------------------------|

|                   | All AF patients (N = 42 966) | Warfarin (n = 5618) | NOACs (n = 2011) | Aspirin (n = 5128) | Other antiplatelet\textsuperscript{b} (n = 648) | Not treatment naïve (n = 3232) | Treatment naïve (n = 9143) |
|-------------------|-----------------------------|---------------------|------------------|------------------|------------------|-----------------|----------------------|
| 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         | 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

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
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.

Table 2

| Event          | NOAC | Incidence (95% CI) | Incidence (95% CI) | Incidence (95% CI) | Incidence (95% CI) |
|----------------|------|--------------------|--------------------|--------------------|--------------------|
| Ischaemic stroke |      | 9.4 (3.8-15.0)     | 10.4 (8.0-12.9)    | 20.1 (16.4-23.8)   | 21.3 (19.3-23.2)   |
| Major bleeding  |      | 35.0 (23.7-46.2)   | 32.1 (27.6-36.7)   | 29.1 (24.2-33.9)   | 21.3 (19.3-23.2)   |
| All-cause mortality | | 42.8 (31.4-54.3) | 55.1 (47.4-62.9) | 50.5 (45.2-52.4) | 50.5 (45.2-52.4) |

Abbreviations: AF, atrial fibrillation; CI, confidence interval; NOAC, novel oral anticoagulant; NVAF, non-valvular atrial fibrillation.

Survival probability

Figure 3 Continuous treatment after first AF diagnosis, by prescription type and year of diagnosis (n = 7766 patients). 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.

Figure 4 Treatment initiation and continuation after first AF diagnosis. 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.
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 \( \text{CHA}_2\text{DS}_2\text{-VASc} \) 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

| 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) |
|---|---|---|---|---|---|---|
| **Resource** | | | | | | |
| **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) |
| Admin, n (%) | 20 478 (99.1) | 602 (99.3) | 903 (99.6) | 1607 (99.3) | 5202 (90.4) | 1432 (92.1) |
| Staff | 20 302 (98.2) | 594 (98.0) | 897 (98.9) | 1570 (97.0) | 4703 (81.7) | 1321 (85.0) |
| Specialist referrals, n (%) | 17 467 (84.5) | 522 (86.1) | 825 (91.0) | 1356 (83.8) | 2657 (46.2) | 845 (54.3) |
| Laboratory tests (without INR), n (%) | 19 016 (92.0) | 564 (93.1) | 871 (96.0) | 1502 (92.8) | 3246 (56.4) | 1072 (68.9) |
| Prescriptions, n (%) | 19 950 (96.5) | 584 (96.4) | 890 (98.1) | 1517 (93.8) | 3789 (65.8) | 1140 (73.3) |
| HES inpatient admissions, n (%) | 16 244 (78.6) | 569 (93.9) | 884 (97.5) | 1612 (99.6) | 5591 (97.2) | 1553 (99.9) |
| HES inpatient procedures, n (%) | 13 014 (63.0) | 528 (87.1) | 821 (90.5) | 1561 (96.5) | 4269 (74.2) | 1453 (93.4) |
| 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) |

(Continues)
### TABLE 3 (Continued)

| Resource | 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) |
| A&E investigations, n (%) | 12 170 (58.9) | 503 (83.0) | 731 (80.6) | 1491 (92.2) | 4422 (76.9) | 1375 (88.4) |
| HES outpatient visits, n (%) | 17 449 (84.4) | 552 (91.1) | 826 (91.1) | 1435 (88.7) | 2799 (48.6) | 912 (58.6) |
| HES outpatient procedures, n (%) | 13 990 (67.7) | 457 (75.4) | 713 (78.6) | 1180 (72.9) | 2180 (37.9) | 740 (47.6) |

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.

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, adjusted by CHA₂DS₂-VASc score, HAS-BLED score, and frailty

| Time post-index | 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)               | £927 (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

| Time post-index | £211 (206) | £219 (254) | £411 (433) | £330 (355) | £328 (357) | £317 (356) |

Abbreviations: CI, confidence interval; NHS, National Health Service; NVAF, non-valvular atrial fibrillation.

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.

Costs are valued in 2015-2016 UK pounds.
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 CHA2DS2-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. Increased NOAC use was also reported in European patients in the GLORIA-AF registry with 52.4% receiving NOACs from 2.0% to 70.1%. Similar findings were reported in the GLORIA-AF registry in very recently diagnosed NVAF patients, with 52.4% receiving NOACs.

Increased NOAC use was also reported in European patients with low CHA2DS2-VASc scores, who are ineligible for AF treatment, 6320 patients (15%) remained without 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 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 CHA2DS2-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 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 CHA2DS2-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.

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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 CHA2DS2-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 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 CHA2DS2-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.

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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 2006.22 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 years26). 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 CHA2DS2-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 CHA2DS2-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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