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# BMJ Open Evolving landscape of stroke prevention in atrial fibrillation within the UK between 2012 and 2016: a cross-sectional analysis study using CPRD

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## ABSTRACT

**Objective** To describe the changes in prescribing of oral anticoagulant (AC) and antiplatelet (AP) agents in patients with non-valvular atrial fibrillation (NVAF) in the UK and to identify the characteristics associated with deviation from guideline-based recommendations.

**Design** Five cross-sectional analyses in a large retrospective population-based cohort study.

**Setting** General practices contributing data to the UK Clinical Practice Research Datalink.

**Participants** The study included patients with a diagnosis of NVAF and eligible for anticoagulation (CHA<sub>2</sub>DS<sub>2</sub>-VASc score ≥2) on 1 April of 2012, 2013, 2014, 2015 and 1st January 2016.

**Results** The proportion of patients being treated with AC increased at each index date, showing an absolute rise of 16.7% over the study period. At the same time, the proportion of patients treated with an AP alone was reduced by half, showing an absolute decrease of 16.8%. The proportion of patients not receiving any antithrombotic (AT) treatment remained the same across the study period. A number of predictors were identified for AP alone or no treatment compared with AC treatment.

**Conclusion** Major improvements in the AT management of patients with NVAF for stroke prevention in the UK were observed between April 2012 and January 2016. Despite this, nearly 20% of at-risk patients still received AP alone and over 15% were on no AT agents in January 2016.

## INTRODUCTION

Atrial fibrillation (AF) is the most common cardiac arrhythmia,<sup>1</sup> estimated to affect up to 35 million people worldwide,<sup>2</sup> with 1.4 million people affected in England alone.<sup>3</sup> AF is an independent risk factor for stroke, increasing the risk five-fold.<sup>4</sup>

Approximately 20% of stroke cases in the UK are thought to have AF as a contributing factor, and AF-related strokes are more likely to be fatal or cause severe disability than non-AF related strokes.<sup>5 6</sup> However, AF-related strokes can be prevented and their impact minimised by effective management strategies including increased detection of

## Strengths and limitations of this study

- A large representative population of patients with all forms of atrial fibrillation (paroxysmal and chronic) studied in the 'real-world' using data obtained from general practitioner records in Clinical Research Practice Datalink (CPRD).
- Real-world data are more likely to reflect wider contemporary treatment practices than information obtained from registries.
- Although CPRD is regularly and extensively audited to ensure data quality, the study is limited by the accuracy of GP records.
- The completeness of the GP record is difficult to ascertain, and we may have not detected some individuals receiving anticoagulant prescriptions in secondary care.

AF, adherence to stroke prevention guidelines and anticoagulant (AC) use in at-risk patients.

Although AC use is effective in preventing strokes due to AF, evidence suggests AC therapy remains underused.<sup>7-13</sup> In 2010, Holt *et al*<sup>9</sup> showed that only 50.7% of patients with non-valvular AF (NVAF) at high risk of stroke in the UK were treated with oral AC. Opportunities to impact significantly on an important cause of cardiovascular morbidity and mortality are thereby frequently missed.

In 2012, a focused update of the 2010 European Society of Cardiology (ESC) guidelines for the management of AF was issued.<sup>14</sup> This update included three major changes based on new or strengthened evidence. First, the CHA<sub>2</sub>DS<sub>2</sub>-VASc score replaced the CHADS<sub>2</sub> score for the assessment of stroke risk. This was based on the accumulated evidence that the CHA<sub>2</sub>DS<sub>2</sub>-VASc score, which is inclusive of the most common risk factors for stroke<sup>15</sup> and has been validated in multiple cohorts,<sup>16</sup> is better at identifying patients at 'truly low

risk' of AF-related stroke.<sup>17–20</sup> Second, the use of aspirin therapy for stroke prevention in AF was restricted to those patients who refuse oral AC. Third, the use of non-vitamin K antagonist oral anticoagulants (Novel Oral ACs (NOACs) such as dabigatran, apixaban and rivaroxaban) was recommended in preference to vitamin K antagonists (VKAs such as warfarin) in most patients with a CHA<sub>2</sub>DS<sub>2</sub>-VASc score  $\geq 1$ .<sup>14</sup>

Despite these guidelines and the weight of evidence, national audit data from the UK showed that among patients with known AF admitted to hospital for stroke between January and March 2013, 38% were taking antiplatelet (AP) drugs alone.<sup>21</sup>

In 2014, when the National Institute for Health and Care Excellence (NICE) updated its AF clinical guidelines (CG180),<sup>22</sup> it recommended that NOACs should be considered as equal first-line options alongside warfarin for NVAf; furthermore, in a significant change to established practice stated that aspirin should not be used as monotherapy to prevent AF-related stroke. The Royal Colleges published a consensus statement reiterating this advice and emphasising the importance of ensuring patients are supported to make an informed choice of AC.<sup>23</sup>

It is not yet known whether the update of the ESC and NICE guidelines effectively impacted treatment practices in the UK. Therefore, this study aims to describe the changes in primary care prescribing of oral AC and AP agents in patients with NVAf eligible for anticoagulation during the years 2012–2016 and to identify clinical characteristics associated with deviation from guideline-based recommendations.

## METHODS

### Data source

Data were obtained from the UK Clinical Practice Research Datalink (CPRD).<sup>24</sup> The CPRD is an anonymised primary care database established in 1987 to collect longitudinal medical records data from general practitioner (GP) practices. As of April 2013, the CPRD covered 674 GP practices with 4.4 million active patients (ie, patients that are alive and registered), reflecting approximately 6.8% of the UK population. This active sample is representative of the UK population in terms of age, sex and ethnicity. The CPRD contains patient registration information as well as events that the GP records during routine clinical practice, including medical diagnoses, prescriptions issued, anthropometric measurements, diagnostic tests, lifestyle information (eg, smoking status and alcohol intake) and referrals to secondary care.

The CPRD has broad National Research Ethics Service Committee (NRES) ethics approval for purely observational research. This study protocol was approved by the Medicines and Healthcare products Regulatory Agency (MHRA) Independent Scientific Advisory Committee (protocol 14\_245R).

### Study population

All patients with a diagnosis of NVAf and eligible for anticoagulation according to ESC 2012<sup>14</sup> and NICE<sup>23</sup> guidance at index date (CHA<sub>2</sub>DS<sub>2</sub>-VASc score  $\geq 2$ ) were included in five cross-sectional analyses: on 1 April of 2012, 2013, 2014 and 2015 and 1 January of 2016 (index date for each year). Patients were further required to be at least 18 years old at the index date, have had at least one consultation with their GP in the last 12 months, have ongoing CPRD registration and have at least 12 months of computerised medical data prior to the index date. Patients were excluded from the study if they had a valvular condition (eg, rheumatic mitral or aortic valve disease, or prosthetic valve; codes used to identify patients are in the data supplement) or if their gender was unknown. **Figure 1** summarises the patient selection process.

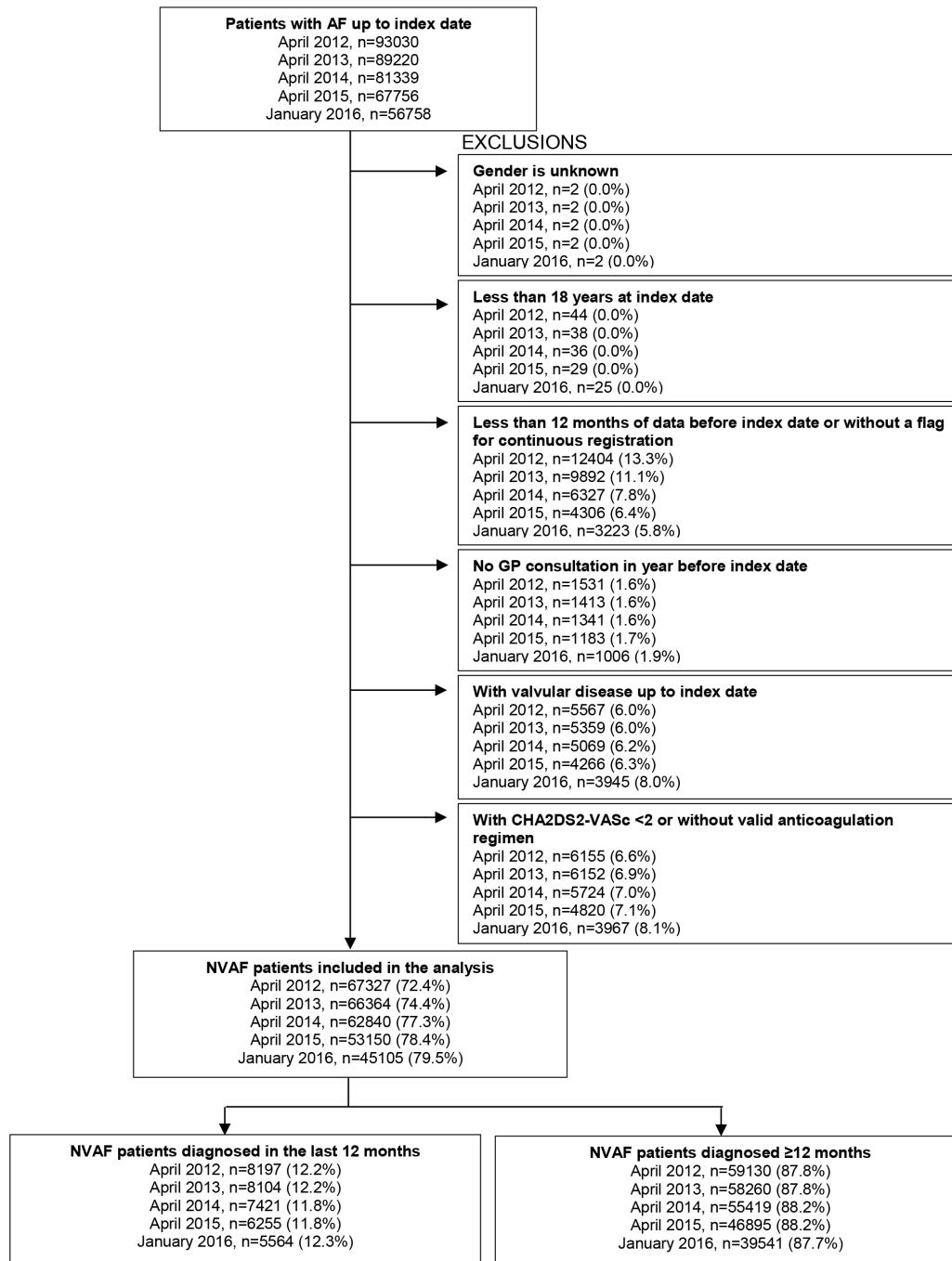
### Study variables

Exposure to AC was defined by the last anticoagulation prescription identified in the 90-day period preceding the index date. Three type of regimens were defined: AC, AP alone or no antithrombotic (AT) treatment. AC included VKAs, apixaban, rivaroxaban, dabigatran and parenteral AC. International normalised ratio (INR) measurements were treated as an indicator of VKA exposure and used to extend VKA exposure time. Exposure to AP alone was defined by an absence of AC prescription and the presence of at least one AP prescription in the 90-day period preceding the index date. No AT was defined by the absence of AC or AP prescription in the 90-day period preceding the index data. A 90-day period has been used in previous studies to identify recent treatment exposure.<sup>25</sup>

Demographic characteristics included age, gender and country of residence. Clinical characteristics were body mass index, smoking status, time since NVAf diagnosis, stroke risk factors (previous stroke, transient ischaemic attack (TIA) or other arterial thromboembolism, congestive heart failure (CHF), coronary artery disease, peripheral artery disease, hypertension or diabetes mellitus), other bleeding risk factors (previous bleeds, peptic ulcer, renal disease, liver disease, concomitant treatment with AP or non-steroidal anti-inflammatory drugs or high alcohol intake), falls, active cancer (at least one diagnosis related to cancer in the last 12 months) and number of concomitant treatments (prescribed in the last 90 days). The CHA<sub>2</sub>DS<sub>2</sub>-VASc score and a modified HAS-BLED score (excluding INR component as not consistently reported in CPRD, score range: 0–8) were calculated for all patients. All clinical diagnoses were identified using Readcode codes (codes lists provided in the data supplement). Diabetes and hypertension were also identified using the prescription of antidiabetic or antihypertensive treatments.

### Statistical analyses

The proportion of patients treated with each regimen (AC, AP alone or no AT) and their 95% CI were calculated



**Figure 1** Flow chart describing the sample used in each year. AF, atrial fibrillation; GP, general practitioner; NVAF, non-valvular atrial fibrillation.

at each index date. As the CPRD does not provide sample survey weights, it is only possible to estimate proportions as if the CPRD data is a simple random sample of approximately 8% of UK GPs/patients, so a finite population correction factor of 0.96 was applied to the standard errors of proportion estimates ( $FPCF = \sqrt{1-0.08} \sim 0.96$ ).

An interrupted time series analysis<sup>26</sup> was conducted to estimate the impact of the updated ESC guidance (published in August 2012) and NICE 2014<sup>23</sup> guidance (published in June 2014) on the evolution of the proportion of patients treated with each regimen, controlling for baseline level and trend. For this analysis, data from April

2011 to April 2015 were used, and month-by-month estimates were extracted to obtain 50 time-points (using the same inclusion criteria than for the five main cross-sectional analyses). The time series model was divided into three time periods: (1) pre-ESC guidelines, (2) post-ESC guidelines and (3) post-NICE guidelines. The statistical significance of the change in level (ie, the rapid drop in rates immediately after the intervention) and trend (ie, the gradual decline in rates over the remainder of the follow-up period) were tested for each time period. The slope in each time period was calculated by summing the change in trend observed in the time period and the



previous slope (in first period (pre-ESC), the baseline trend was equal to the slope).

These analyses of the evolution of the AT management over time were also run separately in newly diagnosed patients with NVAF (<12 months) and in patients with NVAF with a diagnosis for  $\geq 12$  months, as well as in each country of residence separately (England, Scotland, Wales and Northern Ireland; results by country provided in the data supplement).

Generalised estimating equations (GEEs) were used to identify demographic and clinical characteristics associated with AP treatment and with the absence of AT treatment (vs receiving AC) in April 2015 (date of the last planned cross-sectional analysis). The final models were obtained using a backward elimination until all variables were significantly associated with the outcome ( $p < 0.05$ ). Models were adjusted for clustering within individuals and within GP practices, and results are given as ORs and 95% CIs.

### Sensitivity analyses

To evaluate the proportion of patients that could have been misclassified as untreated, a sensitivity analysis was conducted, extending the exposure window used to classify patients to 180 days prior to index date. To assess the possible impact of GP sample modification, a second sensitivity analysis limiting the study sample to only those patients who were registered to a GP practice included in the CPRD throughout the study period.

All analyses were conducted using SAS software V.9.4.

## RESULTS

### Patient characteristics

The demographic and clinical characteristics of patients with NVAF eligible for anticoagulation according to ESC and NICE guidance ( $\text{CHA}_2\text{DS}_2\text{-VASc} \geq 2$ ) from April 2012 to January 2016 are provided in [table 1](#). The characteristics of the population were consistent across the study period: patients' mean age was 78 years, 52.4%–54.3% were male and more than 50% were either overweight or obese. Almost 20% had a history of stroke or TIA, around 30% had a history of coronary artery disease and most had hypertension (>97%). Approximately 12% had been diagnosed with NVAF within the preceding 12 months (newly diagnosed).

### Treatment patterns over time

The proportion of patients being treated with AC increased each year, showing an absolute rise of 16.7% over the study period (from 50.2% in April 2012 to 66.9% in January 2016) ([table 2](#)). At the same time, the proportion of patients treated with an AP alone was reduced by half, showing an absolute decrease of 16.8% (from 34.2% in April 2012 to 17.4% January 2016). The proportion of patients not receiving any AT treatment remained the same across the study period, at around 15% of all patients with NVAF.

Stratifying the population by time since diagnosis identified the reduction in the proportion of patients treated with AP alone was greater in newly diagnosed patients, relative to those who had been diagnosed for  $\geq 12$  months (26.8% vs 15.4%). In January 2016, only 11.3% of the newly diagnosed patients were treated with AP alone (vs 18.3% of those diagnosed  $\geq 12$  months). Similarly, the increase in the proportion of patients being prescribed AC was greater in those patients who were newly diagnosed compared with those diagnosed with NVAF for  $\geq 12$  months (25.3% vs 15.5%). In January 2016, 72.5% of the newly diagnosed patients were treated with AC (vs 66.1% of those diagnosed for  $\geq 12$  months).

In newly diagnosed patients, major changes in the type of oral AC prescribed were observed between April 2014 and January 2016. The proportion of patients initiated with VKA fell from 50.8% to 31.8% of all patients with NVAF, while the NOAC prescriptions rose from 9.8% to 40.6% (including 16.6% apixaban, 2.4% dabigatran and 21.5% rivaroxaban). No major change was observed in the NVAF population with a diagnosis for  $\geq 12$  months; VKA was prescribed in 50.9% of the population in January 2016 and NOACs in 15% (including 4.5% apixaban, 2.2% dabigatran and 8.3% rivaroxaban).

A sensitivity analysis using a time period of 180 days prior to index date was used to evaluate the proportion of patients that could have been misclassified as untreated. This analysis provided the same results, with only 2% difference in the proportion of untreated patients observed. Results were also unchanged when restricting only to those patients who were registered to a GP included in the CPRD throughout the study period.

### Impact of ESC and NICE guidelines publications on UK practice

The time series analysis stratified by time since NVAF diagnosis (<12 months or  $\geq 12$  months) showed that there was a significant trend for increasing AC treatment in both patient groups since April 2011 ([table 3](#)). However, a significant acceleration of this trend (increase of the slope) was observed after the updated ESC guidance publication (change in trend:  $\beta = +0.26$  in newly diagnosed,  $\beta = +0.18$  in patients diagnosed  $\geq 12$  months) and also after NICE guidance publication (change in trend:  $\beta = +0.12$  in newly diagnosed,  $\beta = +0.15$  in patients diagnosed  $\geq 12$  months).

Equally, a significant trend for decreasing AP use was observed since April 2011. A significant acceleration of this trend was observed after both ESC and NICE guidance publications. This change in trend was more marked after ESC for the newly diagnosed patients (post-ESC:  $\beta = -0.26$ , post-NICE:  $\beta = -0.10$ ) and after NICE for patients diagnosed  $\geq 12$  months (post-ESC:  $\beta = -0.15$ , post-NICE:  $\beta = -0.21$ ).

### Characteristics associated with the absence of AC therapy in April 2015

[Tables 4 and 5](#) present the results of the GEE models comparing demographic and clinical characteristics in

**Table 1** Demographic and clinical characteristics of patients with NVAf on each index date (data given as n, % unless stated otherwise)

	April 2012 (n=67 327)		April 2013 (n=66 364)		April 2014 (n=62 840)		April 2015 (n=53 150)		Jan 2016 (n=45 105)	
	n	%	n	%	n	%	n	%	n	%
Age (years) mean (SD)	78 (10)		78 (10)		78 (10)		78 (9.9)		78 (9.9)	
Gender: male	35277	52.4	35096	52.9	33477	53.3	28756	54.1	24495	54.3
Country										
England	51 055	75.8	49 721	74.9	45 422	72.3	36 910	69.4	28 226	62.6
Wales	7 193	10.7	7 168	10.8	7 658	12.2	6 791	12.8	7 088	15.7
Scotland	6 826	10.1	7 132	10.7	7 331	11.7	6 850	12.9	7 060	15.7
Northern Ireland	2 253	3.3	2 343	3.5	2 429	3.9	2 599	4.9	2 731	6.1
Smoking status										
Current smoker	4 685	7.0	4 500	6.8	4 087	6.5	3 305	6.2	2 877	6.4
Past smoker	34 297	50.9	34 019	51.3	32 258	51.3	27 389	51.5	23 119	51.3
Body mass index (kg/m <sup>2</sup> )										
Missing data	5 283	7.8	4 588	6.9	3 990	6.3	3 209	6.0	2 667	5.9
Median (Q1–Q3)	27.2 (24.1–31.1)		27.2 (24.1–31.2)		27.3 (24.2–31.2)		27.4 (24.3–31.4)		27.6 (24.3–31.5)	
GP consultation in the last year Median (Q1–Q3)	13 (8–22)		13 (8–22)		14 (8–23)		14 (8–23)		14 (8–22)	
Newly diagnosed NVAf	8 197	12.2	8 104	12.2	7 421	11.8	6 255	11.8	5 564	12.3
Stroke risk factors										
Previous stroke/TIA	13 136	19.5	12 966	19.5	12 312	19.6	10 393	19.6	8 986	19.9
Other arterial thromboembolism	281	0.4	267	0.4	243	0.4	207	0.4	182	0.4
Congestive heart failure	11 970	17.8	11 536	17.4	10 780	17.2	9 296	17.5	8 272	18.3
Coronary artery disease	21 158	31.4	20 213	30.5	18 691	29.7	15 383	28.9	12 892	28.6
Peripheral arterial disease	4 136	6.1	3 978	6	3 671	5.8	2 958	5.6	2 491	5.5
Hypertension	65 349	97.1	64 557	97.3	61 255	97.5	51 872	97.6	44 039	97.6
Diabetes mellitus	13 949	20.7	13 974	21.1	13 564	21.6	11 779	22.2	10 222	22.7
CHA <sub>2</sub> DS <sub>2</sub> -VAsC score Median (Q1–Q3)	4 (3–5)		4 (3–5)		4 (3–5)		4 (3–5)		4 (3–5)	
Modified HAS-BLED score* Median (Q1–Q3)	4 (3–4)		4 (3–4)		4 (3–4)		4 (3–4)		4 (3–4)	
Previous bleeding†	22 136	32.9	22 260	33.5	21 770	34.6	18 669	35.1	15 889	35.2
Intracranial	1 166	1.7	1 223	1.8	1 238	2.0	1 039	2.0	897	2.0
Gastrointestinal	7 755	11.5	7 700	11.6	7 575	12.1	6 536	12.3	5 677	12.6
Renal disease‡	23 367	34.7	23 003	34.7	21 391	34	17 796	33.5	15 061	33.4

Continued

Table 1 Continued

	April 2012 (n=67 327)		April 2013 (n=66 364)		April 2014 (n=62 840)		April 2015 (n=53 150)		Jan 2016 (n=45 105)	
	n	%	n	%	n	%	n	%	n	%
Liver disease	454	0.7	478	0.7	475	0.8	425	0.8	393	0.9
Number of concomitant treatments Median (Q1–Q3)	8 (5–11)		8 (5–11)		8 (5–11)		8 (5–11)		7 (5–11)	

\*Excluding INR component as not consistently reported in CPRD, score range: 0–8.

†Including intracranial, gastrointestinal, intraocular, pericardial, urinary, intra-articular, lung or other bleed. Gynaecological bleeds excluded.

‡Including any renal disease, chronic kidney disease stage 1–5.

CPRD, Clinical Research Practice Datalink; GP, general practitioner; INR, international normalised ratio; NVAF, non-valvular atrial fibrillation; TIA, transient ischaemic attack.

patients receiving either an AP alone or no AT, versus those receiving AC treatment in April 2015. Even after adjusting on CHA<sub>2</sub>DS<sub>2</sub>-VASc score, females and patients aged <65 or ≥85 (vs patients 65–74 years) were more likely to be prescribed an AP alone or no AT treatment, whereas patients with a history of stroke/TIA, CHF or hypertension were less likely to remain untreated. The likelihood of being treated with AP alone increased with time since diagnosis. Patients with coronary and peripheral artery disease were also more likely to be treated with an AP alone than AC. Importantly, CHA<sub>2</sub>DS<sub>2</sub>-VASc was associated with the absence of AT treatment, and patients with a score ≥3 were less likely to remain untreated than patients with a CHA<sub>2</sub>DS<sub>2</sub>-VASc score=2. To less extent, the same association was observed in patients treated with AP alone (vs AC). Patients who had a previous intracranial bleed were more likely to be treated with AP and even more likely to remain untreated. The absence of any AT was more frequent in patients with less than five comedications. Geographic variations were observed, with a higher proportion receiving AP alone or no AT in England and Scotland compared with Wales and Northern Ireland.

## DISCUSSION

A pronounced shift in AC management of patients with NVAF was observed in the UK between April 2012 and January 2016, coinciding with the update of ESC<sup>14</sup> and NICE<sup>22</sup> guidelines and with the availability of the NOACs as an alternative to VKAs. A substantial increase in the proportion of patients with NVAF at risk of stroke treated with AC was observed during this time (from 50.2% to 66.9%), as well as an important decrease of AP use (34.2% to 17.4%).

Whereas important increases in the proportion of patients with NVAF treated with AC were previously described in the UK between 1994 and 2003,<sup>7,8</sup> no significant changes were observed in the years 2007–2010 in patients with CHA<sub>2</sub>DS<sub>2</sub>-VASc ≥2, with AC use remaining low (around 50%) and AP alone widely used (36%). The high use of AP until March 2012 may have also partly reflected the recommendations of the Quality and Outcomes Framework of the National Health Service (NHS), which provided equal emphasis on AC and AP in stroke prevention in primary care at that time.<sup>13</sup>

The observed shift in treatment patterns in this study suggests a positive impact of both the ESC<sup>14</sup> and NICE<sup>22</sup> guidelines in driving changes in thromboprophylaxis strategy for patients with NVAF in the UK, most notably the move away from AP use. The release of the ESC guidance appeared to impact more significantly the management of recently diagnosed patients. This may reflect an earlier change in the practice of cardiologists who, in the UK, are typically more involved in the diagnosis and initial management of NVAF. Indeed, the publication of the NICE guidance had a greater impact on the decline in AP use among patients with a pre-existing diagnosis, which might reflect the higher impact of local guidance

**Table 2** Evolution of the proportion of patients treated with anticoagulants, with antiplatelet therapy alone or no antithrombotic therapy among patients with NVAF with CHA2DS2-VASc  $\geq 2$ 

	April 2012 % (95% CI)	April 2013 % (95% CI)	April 2014 % (95% CI)	April 2015 % (95% CI)	January 2016 % (95% CI)
Anticoagulation	50.2 (49.8 to 50.5)	53.2 (52.8 to 53.5)	57.5 (57.1 to 57.9)	62.9 (62.5 to 63.3)	66.9 (66.5 to 67.3)
Antiplatelet therapy alone	34.2 (33.9 to 34.5)	31.2 (30.8 to 31.5)	27.7 (27.3 to 28.0)	21.8 (21.5 to 22.2)	17.4 (17.1 to 17.8)
No antithrombotic therapy	15.6 (15.4 to 15.9)	15.7 (15.4 to 15.9)	14.8 (14.6 to 15.1)	15.3 (15.0 to 15.6)	15.7 (15.4 to 16.0)

on GPs who are more involved in the long-term management of patients.

Overall, the most marked improvement in stroke prevention in AF occurred in newly diagnosed patients, in whom AC prescriptions rose from 47.2% to 72.5% and the use of AP alone dropped to 11.3% in January 2016. At the time of diagnosis, patients are likely to be particularly engaged with their condition, more likely to be booked for further clinical assessment and physicians are obligated to make a decision regarding AC. Conversely,

patients with a long-standing diagnosis may be more resistant to changes in their treatment regimen, and thromboembolism prophylaxis may not be the focus of clinical appointments. As newly diagnosed patients represent only 20% of the NVAF population, this emphasises the potential impact on stroke prevention in the UK that could be achieved by effectively addressing thromboembolism prophylaxis strategy in patients with an established NVAF diagnosis. Ongoing educational activity and the use of specialist nurses and pharmacist-led anticoagulation

**Table 3** Time series analysis describing the trends in the evolution of the proportion of patients with NVAF treated with anticoagulants, aspirin or other AP therapy alone or without any antithrombotic treatment from April 2012 to April 2015 in the UK by time since NVAF diagnosis

	Pre-ESC*			Post-ESC†			Post-NICE†		
	$\beta$	SE	p Value	$\beta$	SE	p Value	$\beta$	SE	p Value
<b>A. Anticoagulation treatment</b>									
Diagnosed <12 months									
Level	43.09	0.26	<0.0001	0.28	0.35	0.418	0.10	0.49	0.846
Trend	0.34	0.02	<0.0001	0.26	0.03	<0.0001	0.12	0.09	0.171
Diagnosed $\geq 12$ months									
Level	49.01	0.07	<0.0001	0.00	0.10	0.981	-0.16	0.14	0.251
Trend	0.13	0.01	<0.0001	0.18	0.01	<0.0001	0.15	0.02	<0.0001
<b>B. Aspirin (ASA) or other AP only</b>									
Diagnosed <12 months									
Level	41.94	0.24	<0.0001	-0.20	0.31	0.518	-0.63	0.44	0.159
Trend	-0.36	0.02	<0.0001	-0.26	0.03	<0.0001	-0.10	0.08	0.226
Diagnosed $\geq 12$ months									
Level	35.05	0.06	<0.0001	0.03	0.08	0.737	-0.33	0.12	0.008
Trend	-0.12	0.01	<0.0001	-0.15	0.01	<0.0001	-0.21	0.02	<0.0001
<b>C. Without any antithrombotic treatment</b>									
Diagnosed <12 months									
Level	14.97	0.15	<0.0001	-0.08	0.19	0.6835	0.54	0.27	0.057
Trend	0.02	0.01	0.211	0.00	0.02	0.9262	-0.03	0.05	0.612
Diagnosed $\geq 12$ months									
Level	15.94	0.07	<0.0001	-0.03	0.10	0.789	0.49	0.14	0.001
Trend	-0.01	0.01	0.174	-0.03	0.01	0.000	0.06	0.02	0.015

\*Pre-ESC data are base level, base trend.

†Post-ESC and post-NICE data are change in level, change in trend.

AP, antiplatelet; ESC, European Society of Cardiology; NICE, National Institute for Health and Care Excellence; NVAF, non-valvular atrial fibrillation.



**Table 4** Factors associated with the prescription of aspirin or other antiplatelet for TE prevention in NVAF in April 2015 (vs AC): results of the GEE model

	Antiplatelet therapy alone n=11 609		Treated with AC n=33 413		OR (95% CI)	p Value
	n	%	n	%		
Patient age (years)						<0.0001
<65	890	7.7	2016	6.0	1.22 (1.10 to 1.35)	
65–74	2769	23.9	8780	26.3	Reference	
75–84	3842	33.1	14 363	43.0	0.94 (0.87 to 1.02)	
≥85	4108	35.4	8254	24.7	1.72 (1.58 to 1.87)	
Country						0.001
England	8065	69.5	22 909	68.6	Reference	
Wales	1383	11.9	4524	13.5	0.80 (0.70 to 0.91)	
Scotland	1590	13.7	4231	12.7	1.06 (0.96 to 1.19)	
Northern Ireland	571	4.9	1749	5.2	0.83 (0.72 to 0.97)	
Gender: male (reference=female)	5364	46.2	14 580	43.6	0.87 (0.81 to 0.93)	<0.0001
Time since NVAF diagnosis						<0.0001
<6 months	497	4.3	2121	6.3	Reference	
6–12 months	442	3.8	2175	6.5	0.96 (0.83 to 1.11)	
12–24 months	979	8.4	3886	11.6	1.24 (1.10 to 1.41)	
2–5 years since	3095	26.7	8496	25.4	1.89 (1.68 to 2.12)	
≥5 years	6596	56.8	16 735	50.1	2.17 (1.93 to 2.44)	
Previous oral AC treatment						<0.0001
No previous treatment	8093	69.7	21 189	63.4	Reference	
NOAC only	87	0.7	411	1.2	0.61 (0.46 to 0.81)	
VKA and NOAC	76	0.7	490	1.5	0.37 (0.29 to 0.47)	
VKA only	3353	28.9	11 323	33.9	0.65 (0.59 to 0.72)	
Previous stroke/TIA/arterial TE	2291	19.7	7341	22.0	0.83 (0.75 to 0.92)	0.0008
Congestive heart failure	1722	14.8	6685	20.0	0.61 (0.56 to 0.66)	<0.0001
Previous coronary artery disease	4535	39.1	9636	28.8	1.60 (1.50–1.71)	<0.0001
Peripheral arterial disease	833	7.2	1887	5.6	1.20 (1.10 to 1.31)	0.0001
Hypertension	11 308	97.4	32 869	98.4	0.59 (0.51 to 0.69)	<0.0001
CHA <sub>2</sub> DS <sub>2</sub> -VASc score						<0.0001
2	1425	12.3	3444	10.3	Reference	
3	2408	20.7	7482	22.4	0.69 (0.63 to 0.76)	

Continued

Table 4 Continued

	Antiplatelet therapy alone n=11 609		Treated with AC n=33 413		OR (95% CI)	p Value
	n	%	n	%		
4	3206	27.6	9656	28.9	0.56 (0.50 to 0.64)	
5	2306	19.9	6544	19.6	0.54 (0.46 to 0.64)	
≥6	2264	19.5	6287	18.9	0.52 (0.42 to 0.65)	
Previous bleed						<0.0001
No bleed	7522	64.8	21577	64.6	Reference	
Intracranial bleed	346	3.0	404	1.2	3.02 (2.56 to 3.56)	
Gastrointestinal bleed	1430	12.3	4001	11.8	0.96 (0.90 to 1.02)	
Other bleed	2311	19.9	7473	22.4	0.82 (0.77 to 0.87)	
History of fall	3474	29.9	8211	24.6	1.14 (1.08 to 1.20)	<0.0001
Renal disease	4106	35.4	11 542	34.5	0.94 (0.90 to 0.99)	0.0131
Liver disease	102	0.9	214	0.6	1.32 (1.03 to 1.70)	0.0414
Number of comedications						<0.0001
<5	1448	12.5	6879	20.6	Reference	
5–9	5040	43.4	14 825	44.4	1.71 (1.60 to 1.82)	
10–14	3169	27.3	7782	23.3	2.08 (1.93 to 2.26)	
15 or more	1952	16.8	3927	11.8	2.66 (2.43 to 2.91)	

AC, anticoagulant; GEE, generalised estimating equations; NOAC, novel oral anticoagulant; NVAf, non-valvular atrial fibrillation; TE, thromboembolism; TIA, transient ischaemic attack; VKA, vitamin K antagonist.

**Table 5** Factor associated with the absence of TE prevention (no antithrombotic therapy vs anticoagulation) in NVAF in April 2015: results of the GEE model

Parameter	No antithrombotic therapy n=8128		Treated with AC n=33413		OR (95% CI)	p Value
	n	%	n	%		
Patient age (years)						
<65	1299	16	2016	6.0	1.64 (1.47 to 1.83)	<0.0001
65–74	2214	27.2	8780	26.3	Reference	
75–84	2367	29.1	14 363	43.0	1.09 (0.99 to 1.20)	
≥85	2248	27.7	8254	24.7	1.86 (1.68 to 2.07)	
Gender: male (reference=female)	4450	54.7	14 580	43.6	0.51 (0.46 to 0.56)	<0.0001
Country						
England	5936	73.0	22 909	68.6	Reference	<0.0001
Wales	884	10.9	4524	13.5	0.80 (0.69 to 0.93)	
Scotland	1029	12.7	4231	12.7	1.09 (0.96 to 1.23)	
Northern Ireland	279	3.4	1749	5.2	0.69 (0.57 to 0.83)	
Time since NVAF diagnosis						<0.0001
<6 months	592	7.3	2121	6.3	Reference	
6–12 months	427	5.3	2175	6.5	0.71 (0.61 to 0.82)	
12–24 months	864	10.6	3886	11.6	0.82 (0.71 to 0.94)	
2–5 years	2086	25.7	8496	25.4	0.93 (0.82 to 1.06)	
≥5 years	4159	51.2	16 735	50.1	1.07 (0.94 to 1.23)	
Previous OAC treatment						<0.0001
No previous OAC	5137	63.2	21 189	63.4	Reference	
NOAC only	189	2.3	411	1.2	1.82 (1.36 to 2.43)	
VKA and NOAC	159	2.0	490	1.5	1.50 (1.23 to 1.84)	
VKA only	2643	32.5	11 323	33.9	0.97 (0.88 to 1.07)	
Previous stroke/TIA/arterial TE	968	11.9	7341	22.0	0.55 (0.48 to 0.64)	<0.0001
Congestive heart failure	889	10.9	6685	20.0	0.76 (0.69 to 0.84)	<0.0001
Previous coronary artery disease	1212	14.9	9636	28.8	0.76 (0.70 to 0.84)	<0.0001
Hypertension	7695	94.7	32 869	98.4	0.62 (0.53 to 0.72)	<0.0001
CHA <sub>2</sub> DS <sub>2</sub> -VASc score						<0.0001
2	2212	27.2	3444	10.3	Reference	
3	2034	25	7482	22.4	0.48 (0.43 to 0.54)	
4	2057	25.3	9656	28.9	0.33 (0.28 to 0.39)	

Continued

Table 5 Continued

Parameter	No antithrombotic therapy n=8128		Treated with AC n=33413		OR (95% CI)	p Value
	n	%	n	%		
5	987	12.1	6544	19.6	0.28 (0.22 to 0.35)	
≥6	838	10.27	6287	18.9	0.27 (0.20 to 0.36)	
Previous bleed						<0.0001
No bleed	5382	66.2	21577	64.6	Reference	
Intracranial bleed	289	3.6	404	1.2	8.03 (6.43 to 10.02)	
Gastrointestinal bleed	1016	12.5	4001	11.8	1.24 (1.14 to 1.35)	
Other bleed	1441	17.7	7473	22.4	0.91 (0.85 to 0.97)	
History of peptic ulcer	465	5.7	1743	5.2	1.36 (1.21 to 1.52)	<0.0001
History of anaemia	227	2.8	880	2.6	1.44 (1.24 to 1.67)	<0.0001
History of fall	2097	25.8	8211	24.6	1.20 (1.13 to 1.28)	<0.0001
Renal disease	2148	26.4	11542	34.5	0.90 (0.84 to 0.96)	0.0016
Liver disease	109	1.3	214	0.6	2.39 (1.87 to 3.05)	<0.0001
Active cancer	455	3.9	1367	4.1	1.19 (1.06 to 1.35)	0.0053
Number of comedications						<0.0001
<5	3384	41.6	6879	20.6	Reference	
5-9	2791	34.3	14825	44.4	0.49 (0.45 to 0.52)	
10-14	1271	15.6	7782	23.3	0.46 (0.43 to 0.50)	
≥15	682	8.4	3927	11.8	0.53 (0.48 to 0.59)	

GEE, generalised estimating equations; NOAC, novel oral anticoagulant; NVAf, non-valvular atrial fibrillation; OAC, oral anticoagulant; TE, thromboembolism; TIA, transient ischaemic attack; VKA, vitamin K antagonist.

clinics will play an important role in reaching this group of patients.

Importantly, the trend for increasing use of AC between 2012 and 2016 was associated with the growing use of NOACs (apixaban, rivaroxaban and dabigatran). This growth of NOAC use was mainly observed in newly diagnosed patients between 2014 and 2016, associated with a decrease of VKA initiation and coincided with the release of NICE guidance<sup>22</sup> and the Consensus Statement reiterating that NICE-approved treatments have to be made available for prescribing. This highlights the vital role of the NOACs as alternatives to VKA through addressing some of the limitations of VKA therapy and responding to individual patient needs. However, in patients who had been diagnosed for  $\geq 12$  months, no major changes in the proportion treated with VKA were observed, indicating significant VKA inertia in this group.

This growing trend in the use of NOACs in newly diagnosed patients with AF can be linked to a growing awareness raised through NICE guidance about the benefits of NOAC treatment and to an increased attentiveness to AF detection. Currently, only opportunistic screening for AF is implemented: NICE recommends an ECG to diagnose AF in patients who present with irregular pulse.<sup>22</sup> An expansion in AF screening would potentially result in the earlier detection of AF in asymptomatic patients and thus the early provision of prophylactic OAC treatment.

Although these data show that AC treatment patterns in NVAF have improved substantially over the last 5 years, rates of anticoagulation appear to lag behind those observed in contemporary European cohorts. For example, at the 2-year follow-up of the EurObservational Research Programme - Atrial Fibrillation (EORP-AF) registry in 2015, 79.2% of patients with AF were identified as receiving at least one oral AC (compared with 62.9% in 2015 in this study, [table 2](#)).<sup>27</sup> Rates of NOAC use however appear more comparable, with 13.7% of patients in EORP-AF receiving at least one NOAC (compared with 10.9% in this study in 2015). Baseline data from the European population of the Global Registry on Long-Term Oral Antithrombotic Treatment in Patients with Atrial Fibrillation (GLORIA-AF) registry, which includes only newly diagnosed AF patients, showed the majority (52.4%) were treated with NOACs, while 5.7% received AP therapy and only 4.1% remained untreated.<sup>28</sup> These data are comparable with the 9.8% receiving NOACs, 23.8% AP therapy and 15.2% untreated among patients diagnosed between 2013 and 2014 in our study ([figure 2](#)). Similarly, in the global Global Anticoagulant Registry in the Field - Atrial Fibrillation (GARFIELD-AF) registry of patients with very recently diagnosed NVAF (<6 weeks), over the period from 2010/2011 to 2014/2015, the proportion of patients treated with AC increased from 57.4% to 71.1% including a significant increase in the proportion receiving NOACs (4.2%–37.0%), while AP monotherapy declined from 30.2% to 16.6%.<sup>29</sup> It is encouraging that our data up to January 2016 continue to show AC use is increasing in the UK. Differences with European-based cohorts may, therefore, reflect a time lag associated with the later release of

NICE guidance in 2014<sup>22</sup> relative to the ESC guidance in 2012.<sup>14</sup> Other factors may also be involved. The time lag between guideline recommendation and routine clinical practice should be considered with the release of newer ESC guidance in 2016.<sup>30</sup>

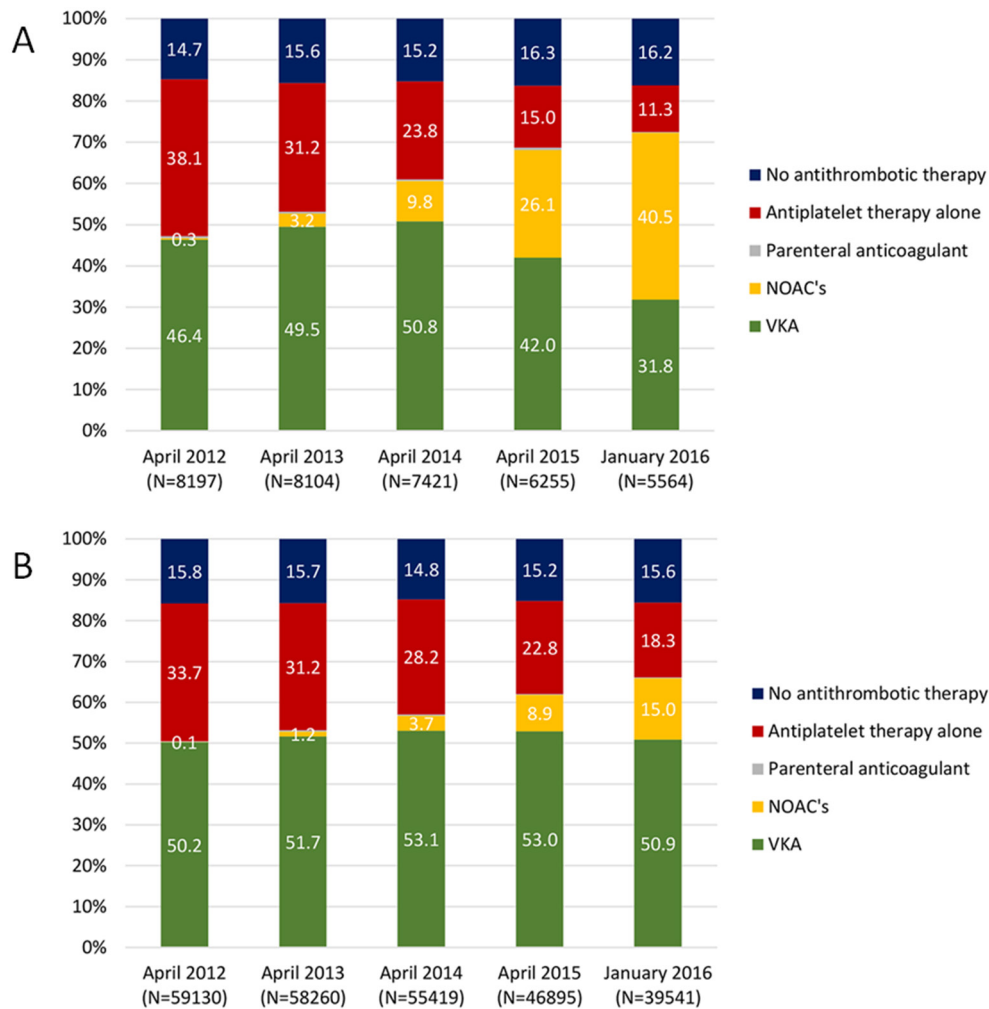
Whereas the striking decrease of AP use observed in this study is encouraging, the absence of any changes in the proportion of patients remaining untreated raises some concerns. These current data identify patient characteristics associated with remaining untreated. Younger patients (<65 years), patients taking fewer prescription medications (<5) and those with a CHA<sub>2</sub>DS<sub>2</sub>-VASc score of 2 were all more likely to remain untreated. We hypothesise that this could be secondary to a misperception of stroke risk by clinicians, but it may also be secondary to patient attitude. Furthermore for those patients <65 years of age, the monitoring requirements of VKAs may be regarded as incompatible with a working life, a barrier that could be overcome with the use of NOACs.

At the other end of the spectrum, elderly patients (>85 years) were found to be less likely to be prescribed AC therapy and more likely to be treated with AP alone. This observation is well documented<sup>8 12 13 31–35</sup> and may be secondary to an overestimation of bleeding risk despite unequivocal evidence of the benefits of AC in the elderly.<sup>36–39</sup>

Our findings clearly illustrate the risk–treatment paradox previously reported in AF management<sup>12</sup> that patients at higher risk of stroke who are more likely to benefit from AC therapy<sup>38</sup> are not receiving appropriate treatment, perhaps because of a perceived increased risk of bleeding. In fact, several bleeding risk factors such as falls, peptic ulcer disease, anaemia and previous risk of intracranial or gastrointestinal bleeds were found to also be associated with an increasing likelihood of remaining untreated. A survey of UK general practices from 2000 to 2009 showed that this underuse of AC therapy in the elderly is not adequately explained by either an increase in comorbidities or bleeding risk.<sup>40</sup>

In addition to age, female patients were found less likely to be treated with AC. This sex difference in prescribing has been previously observed in a UK study in AF.<sup>8</sup> Given that women with AF appear to lose their protection against sudden death including stroke<sup>41</sup> and may even have a higher mortality than men,<sup>42</sup> these lower AC rates are a cause for concern. AP alone was found to be prescribed more frequently in patients with coronary artery disease. This may highlight the lack of a definitive evidence base and clear guidance on the AT management of these patients, particularly in the initial period following an acute coronary syndrome.

Collectively, the results indicate a strong mandate to change current clinical practice to improve prescribing patterns among treating clinicians. This is further emphasised by the 2016 ESC guidelines, which state that aspirin monotherapy should not be used for stroke prevention in patients with AF regardless of stroke risk and may in fact cause harm.<sup>30</sup> Although the present study was conducted



**Figure 2** Evolution of the proportion of patients treated with each anticoagulant, with antiplatelet therapy alone or no antithrombotic therapy among patients with NVAF with  $\text{CHA}_2\text{DS}_2\text{-VASc} \geq 2$  separately in newly diagnosed patients (A) and patients diagnosed since 12 months or more (B). NOACs, novel oral anticoagulants; VKAs, vitamin K antagonists.

in the UK, the finding that a considerable number of patients with AF continue to be undertreated has wider implications for stroke prevention in AF, which remains a global issue.

### Strengths and limitations

This is a large study of a representative population of patients with NVAF managed in the UK. It includes patients with all forms of AF, including paroxysmal and chronic. The study may have not detected some individuals receiving AC prescriptions in secondary care. The National Patient Safety Agency has emphasised the importance of good communication between different bodies sharing responsibility for prescribing potentially interacting medication, and this has increased the use of codes in primary care to maintain awareness of AC therapy prescribed elsewhere.<sup>9 43</sup>

This study is based on a general practice database and is limited by the accuracy of GP records. Validation of the CPRD has shown high positive predictive value of some diagnoses and, where evaluated, comparisons of incidence with other UK data sources are also broadly similar.<sup>44</sup>

However, the completeness of the record is more difficult to ascertain. We acknowledge that the results reported in this study may under-represent comorbidities and, hence, overall stroke risk.

It is important to note that due to the falling number of GP practices involved in the CPRD, the number of eligible patients with NVAF also fell during the study period. However, a sensitivity analysis was conducted on the NVAF population who were registered to a GP practice included in the CPRD throughout the study period, and the results were unchanged. Therefore, the observed change in AT management cannot be attributed to the reduction in available GP data.

It is important to reflect on the differences in the nature of data collection and analysis between registry and real world healthcare records, whereby participation in a registry may influence treatment selection but allow more complete and accurate data collection, whereas real world datasets allow analysis of much larger cohorts that are more likely to reflect wider contemporary practice, although with less complete and well-validated data.

## CONCLUSION

Major improvements in the AC management of patients with NVAF for stroke prevention in the UK were observed between April 2012 and January 2016. Despite this, 20% of the at-risk population were still treated with AP alone and more than 15% of patients were on no AT agents in January 2016. However, if the trend of rapid reduction of AP use observed during the study period continues, then the use of AP alone for stroke prevention could essentially disappear in the next few years in the UK. The consistency observed over time in the proportion of patients not treated with any AT therapy represents the area of greatest concern. The clinical inertia seen in this group may be due to an underestimate of the risk of stroke in these patients who were found to be younger with less comorbidities, and the overestimation of bleeding risk in the elderly (>85 years). There remains a huge potential for reducing the stroke risk of the AF population by improving the thromboembolic risk assessment in NVAF in primary care and the identification of patients requiring AC.

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